Drotaverine in the Symptomatic Treatment of Irritable Bowel Syndrome

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Overview

Functional gastrointestinal disorders (FGIDs) encompass a heterogeneous group of disorders, with indistinct underlying pathophysiology. These disorders are considered to result from the interaction of altered gut physiology and psychological factors through the brain-gut axis, where brain and gut symptoms are reciprocally influencing each other's expression. The presence of chronic gastrointestinal symptoms in absence of any organic pathology is the hallmark of FGIDs. Bowel is the most commonly involved part of the gastrointestinal tract (functional bowel disorders), and abdominal pain or discomfort are among the most evident manifestations. FGIDs are highly prevalent and pose a sizeable burden on health care and society, and impact patients' quality of life.[1-3]

The new and updated ROME IV classification[4] has redefined functional gastrointestinal disorders as 'disorders of gut-brain interaction (DGBI),' and classified them into eight broad categories (Table 1), including the functional bowel disorders (category C) that are further subcategorized into the following: irritable bowel syndrome (IBS); functional constipation; functional diarrhea; functional abdominal bloating/distension; unspecified functional bowel disorder, and; opioid-induced constipation.

IBS is the most extensively studied and prototypical pain-associated DGBI. It is an important health care concern as it greatly affects patients' quality of life and imposes a considerable financial burden to the health care system.[5-7]

Table 1: Rome IV Classification of the Functional Gastrointestinal Disorders–Disorders of Gut-Brain Interaction (DGBI)

Category	Disorders
A	Esophageal disorders
B	Gastroduodenal disorders
C	Bowel disorders
D	Centrally mediated disorders of gastrointestinal pain
E	Gallbladder and sphincter of Oddi disorders
F	Anorectal disorders
G	Childhood functional gastrointestinal disorders: neonate/toddler
H	Childhood functional gastrointestinal disorders: child/adolescent

Clinical Presentation of Irritable Bowel Syndrome

Irritable bowel syndrome displays a wide range of symptoms of gastrointestinal dysmotility and visceral hypersensitivity.[6] Abdominal pain and altered bowel habits are the cardinal symptoms of IBS. Besides, it also exhibits extraintestinal symptoms.[7,8] Box 1 illustrates the gastrointestinal and extraintestinal symptoms of IBS. The intensity and frequency of these symptoms usually vary among patients. This variation in clinical presentation, together with the fact that many patients with IBS do not seek medical opinion, suggests that patients with symptoms related to IBS should be approached with a high level of clinical suspicion.[9]

The New Rome IV Diagnostic Criteria for Irritable Bowel Syndrome

The new Rome IV has introduced certain changes in the Rome III criteria. The Rome III criteria used to characterized IBS on the basis of abdominal pain or discomfort associated with defecation or changes in bowel habit, and with features of disordered defecation. Moreover, pain or discomfort onset had to be related with other two criteria: onset associated with a change in frequency of stools and

Box 1: Clinical presentation of irritable bowel syndrome

Gastrointestinal symptoms

- Chronic abdominal pain with variable intensity and periodic exacerbations
- Altered bowel habits ranging from diarrhea, constipation, alternating diarrhea and constipation, or normal bowel habits alternating with either diarrhea and/or constipation
- Diarrhea characterized by frequent loose stools of small to moderate volume
- Prolonged constipation with interludes of diarrhea or normal bowel function with often hard, pellet-shaped stools and a sense of incomplete evacuation even when the rectum is empty

Extraintestinal symptoms

- Impaired sexual function
- Dysmenorrhea
- Dyspareunia
- Increased urinary frequency and urgency
- Fibromyalgia symptoms

Table 2: Changes in diagnostic criteria in Rome III and Rome IV

Rome III	Rome IV
Recurrent abdominal pain or discomfort (defined as an uncomfortable sensation not described as pain) for at least three days/month in the last three months, associated with two or more of the following:	Recurrent abdominal pain on average at least one day per week in the last three months, associated with two or more of the following criteria:
1. Improvement with defecation	1. Related to defecation
2. Onset associated with a change in the frequency of stool	2. Associated with a change in the frequency of stool
3. Onset associated with a change in the form (appearance) of stool	3. Associated with a change in the form (appearance) of stool

onset associated with a change of form (appearance) of stool. However, the new Rome IV now requires that patients have abdominal pain and the term discomfort is now eliminated. The reasons for this change are as follows: Discomfort is considered nonspecific and ambiguous term and eliminating discomfort from the criteria brings the diagnostic criteria into closer alignment with the US FDA's guidance on evaluating IBS. As such, only abdominal pain is now included that should be present at least one day per week during the previous three months, whereas only 3 days per month were required in Rome III. Moreover, because not in every patient abdominal pain coincide with stools changes, onset is now deleted from the Rome IV (Table 2).[4,7,10,11]

In Rome III, the division of IBS into diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed (IBS-M), and unspecified (IBS-U) subtypes was based on the proportion of All bowel movements (BMs) that were loose/watery or hard/lumpy. However, subsequent studies demonstrated that IBS subtyping was more reliable if based only on the proportion of abnormal BMs that were loose/watery or hard/lumpy and this was adopted for Rome IV (Table 3).[4,10]

Table 3: Rome IV Irritable Bowel Syndrome–Subtypes Criteria

IBS Subtype	Criteria
IBS-C	More than one-fourth (25%) of bowel movements with Bristol Stool Scale Types 1–2 (hard or lumpy stools) and less than one-fourth (25%) with Types 6–7 (loose or watery stools)
IBS-D	More than one-fourth (25%) of bowel movements with Bristol Stool Scale Types 6–7 loose or watery stools) and less than one-fourth (25%) with Types 1–2 (hard or lumpy stools)
IBS-M	More than one-fourth (25%) of bowel movements with Bristol Stool Scale Types 1–2 (hard or lumpy stools) and more than one-fourth (25%) with Types 6–7 (loose or watery stools)
IBS-U	Patients meet diagnostic criteria for IBS but their bowel habits (stool consistency) cannot be accurately categorized in any of the above subtypes

Abbreviations: IBS, irritable bowel syndrome; IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; IBS-M, IBS with mixed bowel habits; IBS-U, unclassified IBS.

Burden of Irritable Bowel Syndrome

IBS is among the most prevalent adult FGIDs worldwide.[7] Although regional variation exists, it has been estimated that IBS affects 9% to 23% of the worldwide population.[11-17] Conventionally, IBS has been known to impose considerable health burden in the Western countries; however, its prevalence appears to be increasing in Asian countries, which is a cause of concern. Studies have reported the prevalence of IBS ranging from 3.7% to 22% in Asian population, with some studies reporting the prevalence to be as much as 24%.[8,18]

Although there is not much epidemiological data on IBS in Indian subcontinent, few Indian studies have evaluated its prevalence in India. Based on a symptomatic diagnosis, IBS prevalence in India has been found to be about 4.2%.[15] In India, the Task Force of the Indian Society of Gastroenterology (ISG)[19] attempted to investigate profile of IBS in Indian population, and observed IBS to be predominantly present in men. This finding was in contrast to the female predominance observed in the Western population. In a subsequent Indian study,[20] conducted in

a rural community in Northern India, the prevalence of IBS was found to be 4%. Contrary to the prior study (of the Task Force of the ISG), this latter analysis reported IBS to be common in women, similar to that reported in the Western population.

Pathogenesis of Irritable Bowel Syndrome

The pathophysiology of IBS is complex and is considered to be due to combination of several factors. The key pathophysiological aspect of IBS is supposed to be the communication between the gastrointestinal brain (the enteric-nervous system; ENS), and the central nervous system (CNS). Several factors implicated to be involved in the pathogenesis of IBS include: motor abnormalities, such as increased frequency and irregularity of luminal contractions, prolonged transit time with constipation predominance, and an exaggerated motor response to cholecystokinin and meal ingestion with prominent diarrhea symptoms; visceral hypersensitivity; increased sensation in various receptors in the gut wall increased risk associated with viral, bacterial, protozoan, and helminth infections; malabsorption; antibiotic use; changes in gut microbiota; small intestinal bacterial overgrowth (SIBO); and stress, increased anxiety, depression, and phobias.[8,21-24] It is believed that these multiple factors together or individually contribute to the symptom complex experienced by individuals with IBS.[25]

Diagnostic Approach in Irritable Bowel Syndrome

The absence of abdominal pain renders the diagnosis of IBS untenable. IBS is essentially a clinical diagnosis that can be made by performing a careful review of the patient's symptoms, taking a detailed history (diet, medication, medical, surgical, and psychological history), evaluating the patient for the presence of warning signs, performing a guided physical examination, and using the Rome IV criteria. In most cases with typical symptoms, detailed diagnostic investigations, including colonoscopy, are generally not required to make a diagnosis, especially if there are no "red flag" signs (patients aged >50 years; unintentional weight loss; nocturnal symptoms; symptoms of short duration; hematochezia, anemia or a family history of colorectal cancer or inflammatory bowel disease).[7,9]

It is important to exclude these "red flag" signs during the diagnostic work-up since their presence would indicate other differential diagnosis.[9] An appropriate approach in a patient with typical symptoms of IBS and without any "red flag" signs is thus to take a thorough history and perform a thorough clinical examination. Since many patients with suspected IBS symptoms present in primary care practice, it is prudent to identify diagnostic tests which may be appropriate in select cases. Often, these tests mainly aim to rule out other differential diagnosis of IBS, and include: full blood count; erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); tissue transglutaminase/ endomysial antibody (celiac disease serology); thyroid function tests (TFTs); and stool test for parasites.[26,27]

Management Approaches for Irritable Bowel Syndrome

Management approaches for IBS, similar to its pathophysiology, are also multifactorial. Treating IBS can be particularly demanding since symptoms often are recurrent and resistant to therapy. A positive patient-physician interaction is associated with fewer return visits for IBS and is a key factor in the treatment of these patients. The primary goals of treatment are symptom relief and improved quality of life, rather than disease modification or cure. Essentially, the management starts with patient education and counseling on dietary and lifestyle modifications, and stress relief.[26,28]

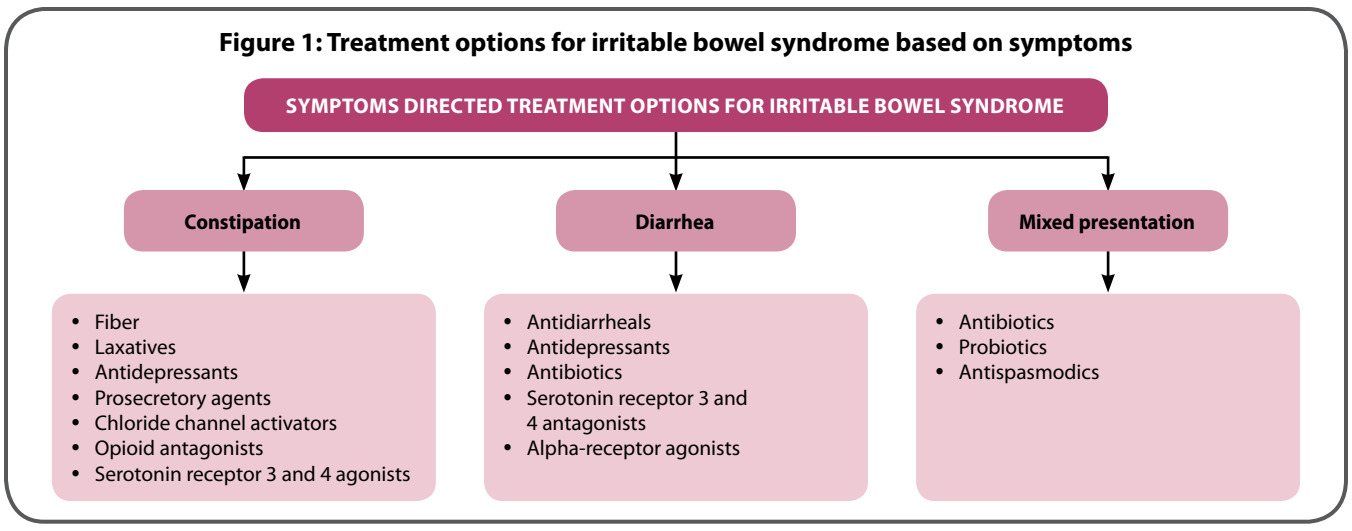
Dietary Intervention

Diet modification is one of the most frequently used interventions for patients with IBS. Increasing fiber intake has traditionally been considered one of the first-line treatment approaches advocated in patients with IBS. Fiber's beneficial effects may reflect colonic fermentation with production of short-chain fatty acids or its action as a prebiotic. However, it is important to note that while soluble fibers improve symptoms of IBS, including abdominal pain; insoluble fibers are usually ineffective and may even exacerbate symptoms.[8,29,30]

Pharmacological Interventions

IBS presents as a complex of symptoms ranging from intestinal inflammation to psychological dysfunction. Therefore, it is important to address the predominant symptoms first. In fact, treating the various symptoms of IBS is a challenge and drug targets vary. Peripherally-acting therapeutic options for IBS are based on the predominant symptoms and IBS subtype. Existing drug therapies are administered based on a diagnosis of either diarrhea-

Figure 1: Treatment options for irritable bowel syndrome based on symptoms



predominant IBS or constipation-predominant IBS. As follows, in patients presenting with diarrhea-predominant IBS, antidiarrheals (such as loperamide) can be used; whereas in those with constipation-predominant IBS, use of laxatives (such as polyethylene glycol) and bulking agents may be used to ameliorate the symptoms.[8,26] Treatment options for IBS are based on the symptoms as illustrated in Figure 1.[8] Table 4 depicts the various possible pharmacotherapeutic approaches, which may be considered in select patients with IBS, dependent on the primary symptom.[26,29-39]

Role of Chronic Abdominal Pain in Identifying IBS

Chronic abdominal pain is one of the most common clinical complaints seen in general practice that may have both organic and functional causes. It is also one of the most frequent reasons why people seek medical care. The importance of this vital symptom can be elucidated by the fact that although patients with chronic abdominal pain often undergo several diagnostic tests, in almost 40% cases no specific cause can be identified. These findings resonate in patients with FGIDs; in fact, in patients with IBS, abdominal pain is considered the most bothersome symptom and also the most common reasons of seeking medical care. Recurrent abdominal pain is the central feature of pain-associated FGIDs such as IBS. In a report by the Indian Society of Gastroenterology Task Force, it has been shown that as much as 70% of patients with IBS have abdominal pain or discomfort that considerably affects the patient's quality of life. This functional association is particularly important in the setting where chronic abdominal pain is associated with abnormality in stool consistency and frequency. The underlying cause of abdominal pain in IBS has been traditionally been ascribed to smooth muscle spasm, and it generally keeps recurring.[5,40-42]

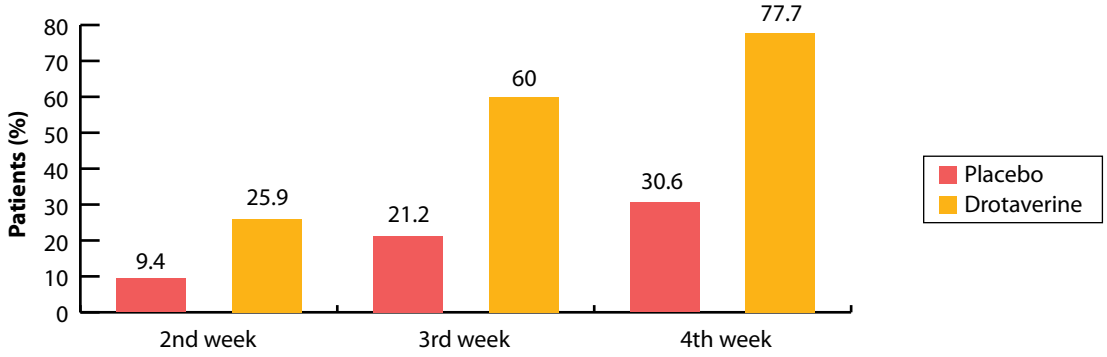
Table 4: Possible pharmacotherapeutic approaches in patients with irritable bowel syndrome

Therapeutic category	Examples
Antispasmodics	• Drotaverine • Dicyclomine • Hyoscyamine
Antidiarrheals	• Loperamide
Antidepressants	• Tricyclic antidepressants (diarrhea-predominant IBS) • Selective serotonin reuptake inhibitors (constipation-predominant IBS)
Probiotics	• Bifidobacteria • Lactobacilli
Antibiotics	• Rifaximin
Drugs modulating serotonin (5HT) receptors	• Romastron (diarrhea-predominant IBS) • Alosetron (in women with severe diarrhea-predominant IBS with chronic symptoms)
Other potential agents	• Lubiprostone, a highly selective activator of type 2 chloride channels in gastrointestinal tract • Linaclotide, a synthetic guanylate cyclase C agonist

Role of Antispasmodics in Abdominal Pain: Focus on Drotaverine

Considering the role of smooth muscle spasm in the etiology of abdominal pain, it is reasonable to use antispasmodic drugs in patients with IBS; in fact,

Figure 2: Patients experiencing reduction in pain frequency with drotaverine versus placebo



antispasmodic drugs have been and remain the main stay of therapy and these agents have demonstrated good symptom relief.[42] Drotaverine is one such antispasmodic agent that has been shown to exert a good relaxing effect on intestinal smooth muscle, resulting in pain alleviation. Importantly, drotaverine does not have side effects similar to anticholinergics.[42,43] Another significant advantage of drotaverine is that, unlike other conventional antispasmodics, it does not mask the symptoms of acute abdomen or interfere with diagnostic precision while providing optimum pain control. In humans, the drug exhibits quick absorption, with half-life of absorption 12 minutes after oral dosing, and reaching maximum plasma concentrations within 45 minutes of administration.[44]

Drotaverine, an isoquinoline derivative, is a potent spasmolytic or antispasmodic drug which acts directly on the smooth muscles by inhibiting phosphodiesterase IV enzyme and calmodulin, which is considered to regulate the smooth muscle relaxation of the gastrointestinal tract. Drotaverine directly normalizes the dysmoltility of intestinal tract. It suits all subset of IBS patients, the diarrhea predominant as well as the constipation predominant. Drotaverine is well tolerated and provides global relief from abdominal pain in IBS. In several studies, drotaverine has shown significant improvement in stool frequency, consistency, urgency, and flatulence. It also displays efficacy against spastic and motility disorders of the gastrointestinal smooth muscle as shown in multiple clinical studies.[31,45,46]

Xue XC *et al*[18] conducted a study to assess the efficacy and safety of drotaverine hydrochloride in patients with IBS. A total of 144 patients with IBS were included in the study and they were randomized into treatment group and placebo group in a 1:1 ratio. Patients were administered either drotaverine, or placebo 80-mg tablet, 3 times daily for a total of 4 weeks. It was observed that drotaverine can reduce the severity of pain evaluated by the visual analog scale (VAS) scale ($p<0.01$), and also decrease the stool frequency ($p<0.01$), as well as the Bristol score ($p<0.01$) compared with placebo at the end of the 4-week treatment. In a nutshell, this study suggests that drotaverine is a promising therapeutic agent to alleviate symptoms of irritable bowel syndrome.

In another randomized placebo-controlled study, Rai RR and colleagues[42] evaluated the efficacy and tolerability of drotaverine hydrochloride (80 mg tablet, TID) in 180 patients with IBS, and observed a significant decrease in both the pain frequency and pain severity scores. The results revealed that 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 week, 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 to placebo [26 (30.6%)] after 4 weeks. There was a statistically significant ($p < 0.01$) global relief in abdominal pain as perceived by the patient (85.9% vs 39.5%, respectively) and the clinician (82.4% vs 36.5%, respectively) in the drotaverine group as compared to placebo group (Figure 3). Moreover, drotaverine group was found to exhibit marked improvement in the stool frequency than the placebo group. The drug was well tolerated without any substantial adverse effects. Therefore, this study suggested that treatment of abdominal symptoms related to IBS with drotaverine HCl 80 mg given three times daily for 4 weeks is more effective than placebo.

Figure 3: Global relief in abdominal pain with drotaverine versus placebo

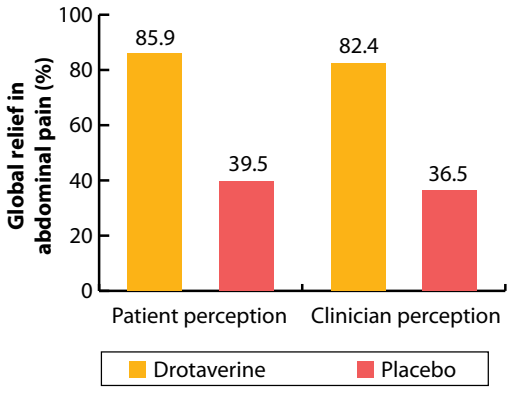
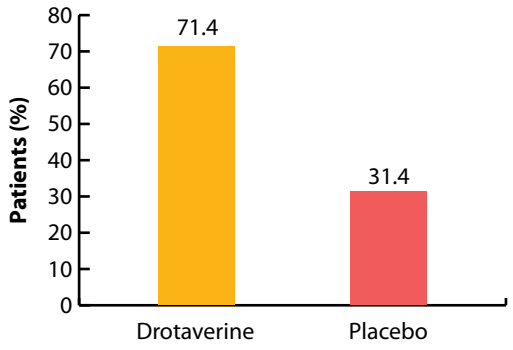


Figure 4: Proportion of patients with decrease in pain severity scores with drotaverine versus placebo



Similar findings were observed in another prospective double blind, randomized study conducted by Misra *et al*,[31] wherein a total of 70 patients with IBS were recruited. The patients (aged between 18 and 60 years) were randomly prescribed either drotaverine (80 mg TID) or placebo over a 4-week treatment period followed by a 4-week follow-up phase. The results of the study revealed a decrease in pain frequency in 11 (31.4%) patients in the drotaverine group versus 2 (5.7%) in the placebo group after 2 weeks. After 4 weeks of therapy, 25 (71.4%) patients in the drotaverine group experienced reduction in pain frequency, compared to 11 (31.4%) patients in the placebo group. In addition, a decrease in pain severity scores was also noted, with 25 (71.4%) in the drotaverine group and only 11 (31.4%) with placebo at 4 weeks (Figure 4). When compared to placebo, drotaverine also showed global improvement in abdominal pain (74.2% vs. 37.7%) and stool frequency (25.7% vs. 2.8%) without any overall effect on the bowel movements. Therefore, this study demonstrated that drotaverine produces global improvement in abdominal pain in patients with IBS.

In another study[19] conducted among 144 patients with IBS who were randomly prescribed either drotaverine tablet 80 mg or placebo, three times daily for a total of four weeks, it was observed that visual analog scale (VAS), stool frequency, and Bristol score were significantly better in the treatment group than in the placebo group ($p<0.01$ for all). The results of this study substantiate the efficacy of drotaverine in improving the symptoms of patients with IBS.

Likewise, in a prospective, self-control, multicentre clinical trial[47] conducted among 217 patients with IBS also demonstrated that drotaverine is well-tolerated and effective in treating all subtypes of IBS. In the study, the patients were treated with oral drotaverine tablets 80 mg TID for 2 weeks. Results of the study revealed that compared with those before treatment, the average weekly score for abdominal pain in patients with IBS was considerably decreased, and the overall efficacy rate was 77.9%; the average daily stool frequency was markedly decreased in IBS-D group, while markedly increased in IBS with constipation IBS-C group. In both groups (IBS-C and IBS-D), stool form and feeling of incomplete defecation, straining and urgency were improved in varying extents. The treatment was well-tolerated and no severe adverse events were observed.

Conclusion

Irritable bowel syndrome is one of the several highly prevalent functional gastrointestinal disorders displaying symptoms of gastrointestinal dysmotility and visceral hypersensitivity. With a wide array of symptoms, IBS often manifests with abdominal pain, discomfort such as cramping, bloating, gas, diarrhea, and/or constipation. Current management strategies aim for symptomatic relief mainly rather than curing the disease, with treatment selection dependent on individual patient symptoms. Considering that recurrent abdominal pain is the central feature of IBS, use of smooth muscle relaxants is deemed beneficial. In this context, drotaverine, a phosphodiesterase IV inhibitor that relaxes the gut smooth muscles, has been shown to exert a good relaxing effect on intestinal smooth muscle, resulting in pain alleviation in all subtypes of IBS. The drug exhibits quick absorption, and has a quick onset

of action. Drotaverine directly normalizes the dysmoltility of intestinal tract. It suits all subset of IBS patients, the diarrhea predominant as well as the constipation predominant. Drotaverine is well tolerated and provides global relief from abdominal pain in IBS. It does not have side effects similar to anticholinergics. A large pool of studies has substantiated the effectiveness of drotaverine in improving the abdominal symptoms related to irritable bowel syndrome, such as stool frequency, consistency, urgency, and flatulence.

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