Approach to Functional Gastrointestinal Disorders Associated with Abdominal Pain

Reviewed by:
Dr Neeraj Tulara
MBBS, MD, DNB (General Medicine)
Post Graduate Diploma in Infectious Disease
Dr. L. H. Hiranandani Hospital
Powai, Mumbai

Abdominal Pain and Functional Gastrointestinal Disorders

Abdominal pain is a common complaint and reason for primary consultation.[1] Organic causes usually are differentiated in patients with abdominal pain and treatment is administered in accordance with the causes; however, in many cases, patients have functional disorders with no obvious abnormal findings obtained with many routine diagnostic tests.[2] In primary care, about half of the patients seen with abdominal complaints have functional gastrointestinal disorders (FGID); the most common FGID being irritable bowel syndrome (IBS) that is characterized by abdominal pain or discomfort and alteration of bowel habits in the absence of an organic disorder. The quality of life of patients with chronic FGID is far worse than in the general population, and is even significantly lower than in patients with many other chronic illnesses.[3-5]

The term 'functional' is usually applied to disorders where the body's normal activities in terms of the movement of the intestines, the sensitivity of the nerves of the intestines, or the way in which the brain controls some of these functions is impaired. However, there are no structural or biochemical abnormalities that can be evaluated by routine medical tests, such as endoscopy, x-ray, CT scan, or blood tests. Thus, FGIDs are usually diagnosed following exclusion of organic pathologies and by symptom concordance with defined parameters, published as the Rome IV criteria for FGIDs.[6-8]

What Is New in Rome IV: Disorders of Gut–Brain Interaction

The new Rome IV mirrors a multicultural rather than a Western-culture focus and identifies FGIDs as disorders of gut-brain interaction (DGBI) that are classified by gastrointestinal symptoms related to any combination of motility disturbances, visceral hypersensitivity, altered mucosal and immune function, gut microbiota, and/or central nervous system processing. The Rome IV classifies FGID/DGBI into eight broad categories (Figure 1); including the functional bowel disorders

Figure 1: Classification of the functional gastrointestinal disorders–disorders of gut-brain interaction: Rome IV

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

Table 1: Changes in diagnostic criteria in Rome III and Rome IV

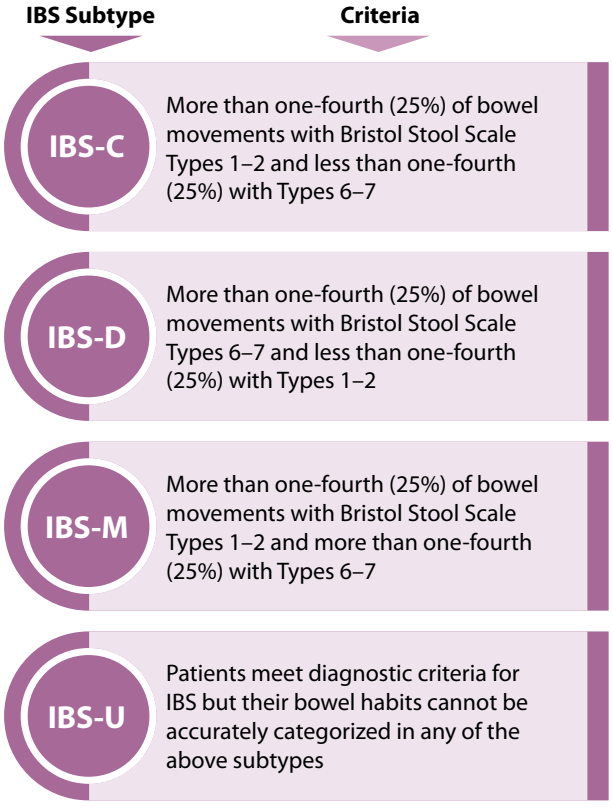
Rome III	Rome IV
• Recurrent abdominal pain or discomfort (defined as an uncomfortable sensation not described as pain) for at least three days/month in the last three months, associated with two or more of the following: » Improvement with defecation » Onset associated with a change in the frequency of stool » Onset associated with a change in the form (appearance) of stool	• 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: » Related to defecation » Associated with a change in the frequency of stool » Associated with a change in the form (appearance) of stool

(category C) that are further subclassified into the following: irritable bowel syndrome (IBS); functional constipation; functional diarrhea; functional abdominal bloating/distension; unspecified functional bowel disorder, and; opioid-induced constipation.[9]

The new Rome IV has introduced certain changes in the Rome III criteria. The Rome III criteria used to characterize IBS by occurrence of abdominal pain or discomfort associated with defecation or changes in bowel habit, and with features of disordered defecation. In addition, pain or discomfort onset had to be related with other two criteria: onset associated with a change in frequency of stools and onset associated with a change of form (appearance) of stool. However, the new Rome IV now requires, for IBS, only abdominal pain and the term discomfort is now eliminated. The reasons for this change are as follows:

- Discomfort is considered nonspecific and ambiguous term, having different meanings in different languages, 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.
- Moreover, because not in every patient abdominal pain coincide with stool changes, onset is now deleted from the Rome IV (Table 1).

Figure 2: Irritable bowel syndrome–subtypes criteria: Rome IV



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.

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.

In Rome IV, the subtypes of IBS include constipation-predominant IBS, diarrhea-predominant IBS, and IBS with predominant irregular (mixed diarrhea/constipation) bowel habits (Figure 2).

Functional bowel disorders (functional diarrhea, functional constipation, IBS with predominant diarrhea [IBS-D], IBS with predominant constipation [IBS-C], and IBS with mixed bowel habits) are considered to be on a continuum rather than as independent entities.[9-12]

Table 2: Symptom severity of functional gastrointestinal disorders		
Mild symptoms	**Moderate symptoms**	**Severe symptoms**
• Approximately 40% of the patients • Minimal pain • No comorbid physical symptoms • Usually no dominant psychiatric diagnoses • Good quality of life	• 30-35% of the patients • Intermittent disruptions in activity • Multiple physical or psychological comorbidities	• 20-25% of the patients • Refractory symptoms with psychological comorbidities such as anxiety and depression • Impaired daily functioning • Catastrophizing behavior • May have a history of major loss or abuse

Clinical Evaluation of Patients with Functional Gastrointestinal Disorders Associated with Abdominal Pain

As regards the clinical evaluation of patients with FGID associated with abdominal pain, a careful history should be taken that takes into account not only the chronology of pain events, but attention should also be paid to the emphasis and style with that these are described by the patient. The clinical features of FGID are the cumulative outcome of all the etiopathological aspects including gastrointestinal dysmotility, visceral hypersensitivity, altered CNS regulation, mucosal permeability, and immune dysregulation.[4,13]

The symptoms are primarily gastrointestinal-related and include constipation, diarrhea, abdominal pain, bloating, nausea, and vomiting, along with symptoms specifically associated with the structures affected. The intensity and frequency of these symptoms usually vary among patients and with each FGID, depending on the structural localization, with potential overlapping of site-specific symptoms of multiple FGIDs which may occur at the same time (Table 2). This variation in clinical presentation, along with the fact that many patients with FGID associated with abdominal pain do not seek medical opinion, suggests that a high level of clinical suspicion should be kept when approaching such patients.[13,14]

Management Strategies for Abdominal Pain

Chronic abdominal pain is one of the most common clinical complaints seen in general practice that may be attributable to both organic and functional causes. The significance of this important symptom typically lies in the fact that patients with chronic abdominal pain often undergo several diagnostic tests, though in almost 40% cases no specific cause can be identified. This seems consistent with its existence in patients with functional gastrointestinal disorders; in fact, in IBS patients, abdominal pain is considered the most distressing symptom and also the most frequent reasons for seeking medical care. 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 especially pertinent 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 conventionally attributed to smooth muscle spasm, and it generally keeps recurring.[15-18]

Role of Antispasmodics in Abdominal Pain: Focus on Drotaverine

As smooth muscle contractions account for important symptoms of IBS, in particular abdominal pain, antispasmodic drugs have been used in patients with IBS, and have demonstrated symptom relief. Drotaverine is one such antispasmodic agent that exerts a good relaxing effect on intestinal smooth muscle, resulting in pain alleviation; and possesses advantage of absence of anticholinergic side-effects in comparison to some other commonly used antispasmodic agents, such as hyoscyamine, dicyclomine, propantheline, and mebeverine.[18,19] 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.[20]

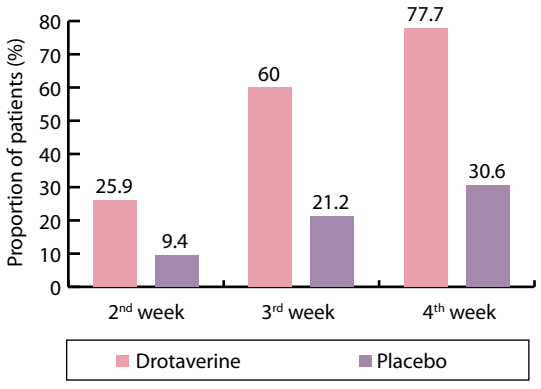
Table 3: Guidelines suggesting the use of drotaverine for irritable bowel syndrome

Guidelines	Recommendations/ Comments
• American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome, 2018	• It is suggested to use certain antispasmodics (Drotaverine, otilonium, pinaverium, hyoscine, cimetropium, and dicyclomine) for overall symptom improvement in IBS patients
• Guidelines on the Management of Irritable Bowel Syndrome, 2018 (Poland)	• It is suggested to use certain antispasmodics, the efficacy of which in IBS has been confirmed, such as hyoscine and drotaverine rather than antispasmodics as a group
• Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome (IBS) 2019	• Subanalyses of individual antispasmodics demonstrated significant benefits compared with placebo for drotaverine, otilonium, pinaverium bromide, hyoscine bromide, and cimetropium bromide

Drotaverine is a highly potent spasmolytic agent, suited for oral administration, and capable of relieving or preventing smooth muscle spasm of various organs. In fact, it contributes very effectively in relieving painful spasms in a large variety of diseases, including those of gastroenterological origin. Drotaverine directly normalizes the dysmotility of intestinal tract by relaxing distal muscles and sphincters participating in peristaltic reflex. Essentially, drotaverine would help in prolonging the pain-relief, and is efficacious for the maintenance of spasmolysis. Moreover, the drug is free of the side-effects associated with anti-cholinergic antispasmodics, such as hyoscyamine, dicyclomine, propantheline, and mebeverine, and may be given safely over long-term. 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.[21-23]

Drotaverine, owing to its clinical efficacy and well-tolerability, has also been recommended by various international guidelines for symptomatic improvement in patients with IBS (Table 3).[24-26]

Figure 3: Proportion of patients experiencing reduction in pain frequency with drotaverine versus placebo



Evidence-based Efficacy

Rai and colleagues[18] conducted a multicentric, randomized, double-blind, placebo-controlled parallel group study to evaluate the efficacy and safety of drotaverine hydrochloride (80 mg tablet, TID) in the symptomatic relief of patients with IBS. A total of 180 patients who fulfilled the criteria of IBS were randomly assigned to drotaverine and placebo treatment groups. Abdominal pain and stool frequency were assessed every week in both the groups for all the 4 weeks of treatment duration whereas Subject Global Assessment of Relief (SGA) of IBS symptoms was evaluated at study end. The results revealed a significant decrease in pain frequency ($p<0.01$) 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 to 8 (9.4%), 18 (21.2%), and 26 (30.6%) patients, respectively in the placebo group (Figure 3). Also, there were significant reductions in pain severity scores in the drotaverine group [66 (77.7%)] as compared with 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 4). Furthermore, drotaverine group was found to exhibit marked improvement in the stool frequency than the placebo group. The drug was well-tolerated without

Figure 4: Global relief in abdominal pain with drotaverine versus placebo

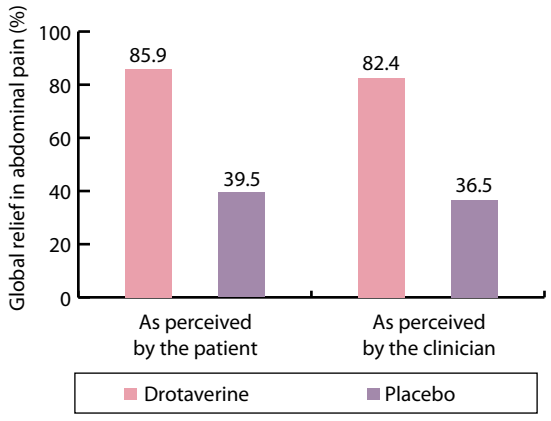
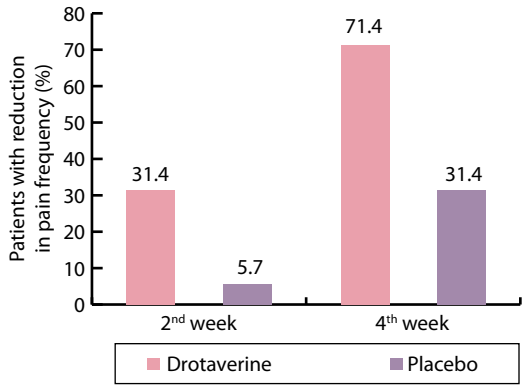


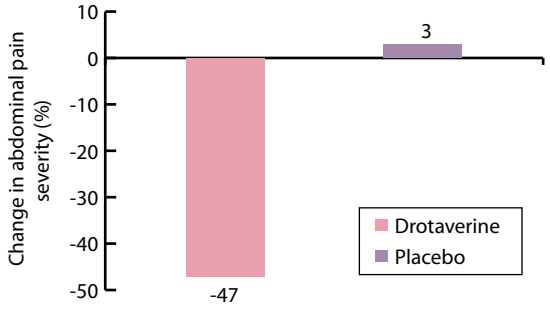
Figure 5: Reduction in pain frequency with drotaverine versus placebo in patients with IBS



any substantial adverse effects. This study demonstrated that a 4-week treatment with drotaverine significantly ameliorates abdominal symptoms in patients with IBS.

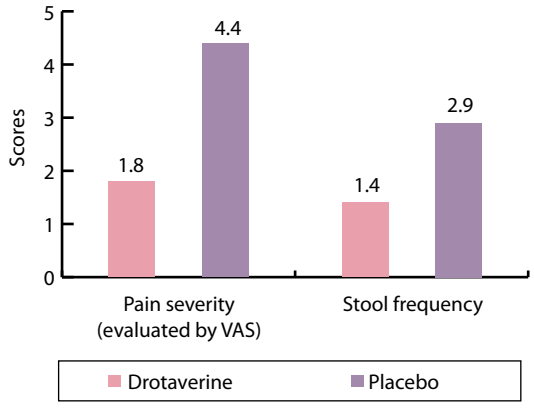
Similar outcomes were seen in another prospective double blind, randomized study performed by Misra *et al*,[23] wherein a total of 70 patients with IBS (aged between 18 and 60 years) were randomized to receive either drotaverine (80 mg TID) or placebo over a 4-week treatment period followed by a 4-week follow up. All patients reported abdominal pain of at least three months duration, occurring at least thrice a week and interfering in normal activity. The results of the study showed that after 2 weeks, pain frequency decreased in 11 (31.4%) patients in the drotaverine group versus 2 (5.7%) in the placebo group. 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 (Figure 5). In addition, a significant decrease in pain severity score was also noted in the drotaverine group [25 (71.4%)] as compared to placebo [11 (31.4%)] at 4 weeks. As compared to placebo, the drotaverine group demonstrated global improvement in abdominal pain as perceived by the patient and the clinician (74.2% versus 37.1%). Also, there was improvement in stool frequency in the drotaverine group (25.7%) in comparison to placebo group (2.8%) without any overall effect on the bowel movements. The study thus showed that drotaverine produces global improvement in abdominal pain in patients with IBS.

Figure 6: Change in abdominal pain severity with drotaverine versus placebo in patients with IBS



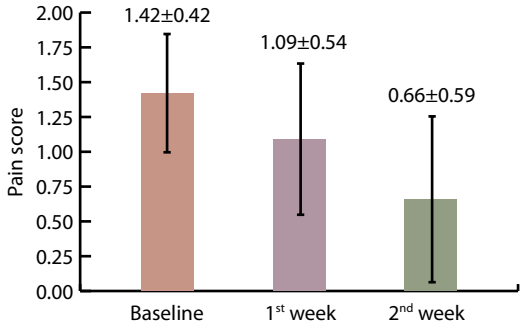
In another double blind, randomized, placebo controlled study conducted among 62 patients (53 females, 9 males, mean age 50.8±14.2 years) with IBS and constipation, Pap and colleagues[27] demonstrated that drotaverine can effectively diminish abdominal pain and bloating in IBS. The investigators categorized the patients into two groups; patients in one group were treated with 3×2 tablets (3×80mg) of drotaverine (n=30) and those in the other group were treated with 3×2 tablets of placebo (n=32). It was observed that 8 weeks of treatment with drotaverine (n=30) significantly reduced the abdominal pain by 47% while in the placebo group (n=32), severity of pain increased by 3% (Figure 6). There was also a fair reduction in bloating. According to the opinion of the patients and physicians, the active treatment was effective

Figure 7: Pain severity and stool frequency at the end of 4-week therapy with drotaverine versus placebo



Abbreviation: VAS, visual analog scale

Figure 8: Pain scores before and after drotaverine therapy in patients with IBS



in 15/24 (62.5%) and 17/24 (71%) cases, respectively. No significant adverse events were documented during the treatment period. This study suggested that drotaverine can effectively diminish abdominal pain and bloating in patients with IBS.

Xue XC *et al*[28] 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. The primary outcome consisted of abdominal pain, measured by the visual analog scale (VAS), and weekly stool frequency. It was observed that drotaverine can reduce the severity of pain evaluated by the 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 (Figure 7). In a nutshell, this study suggests that drotaverine is a promising therapeutic agent to alleviate symptoms of irritable bowel syndrome.

Another prospective, self-controlled, multicentre clinical trial[29] also demonstrated that drotaverine is well-tolerated and effective in treating all subtypes of IBS. A total of 217 patients with IBS were enrolled in the study and treated with oral drotaverine tablets 80 mg TID for 2 weeks. Abdominal pain, feeling of incomplete defecation, straining and urgency, as well as the stool frequency and stool form were recorded daily. The results revealed that the average weekly score for abdominal pain was significantly decreased (0.66±0.59) in patients following drotaverine therapy as compared to those before treatment (1.42±0.42), with an overall efficacy rate of 77.9% (Figure 8). The average daily stool frequency was significantly decreased in IBS with diarrhea (IBS-D) group, while significantly increased in IBS with constipation (IBS-C) group. In both groups, stool form and feeling of incomplete defecation, straining and urgency were improved in different extents. The treatment was well-tolerated and no severe adverse events were observed.

Conclusion

Chronic abdominal pain is one of the most common clinical complaints seen in general practice that may be attributable to both organic and functional causes, the latter being accountable for functional gastrointestinal disorders. Irritable bowel syndrome is the most common functional gastrointestinal disorder characterized by abdominal pain or discomfort and alteration of bowel habits in the absence of an organic disorder. The underlying cause of abdominal pain in functional gastrointestinal disorders has been conventionally attributed to smooth muscle spasm, and it generally keeps recurring. Current management strategies are mostly directed toward symptomatic relief rather than curing the disease, with treatment selection dependent on individual patient symptoms. In particular, since spasmodic abdominal pain is one of the most commonly encountered and vexing symptoms of functional gastrointestinal disorders, use of smooth

muscle relaxants is considered 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 patients with functional gastrointestinal disorders. The drug exhibits quick absorption, and has a quick onset of action. Drotaverine directly normalizes the dysmotility of intestinal tract and provides global relief from abdominal pain in IBS. Furthermore, it is well-tolerated and is devoid of anticholinergic side-effects. 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.

References

1. Viniol A, Keunecke C, Biroga T, *et al*. Studies of the symptom abdominal pain-a systematic review and meta-analysis. *Fam Pract.* 2014; 31(5):517-29.
2. Ryu HS, Choi SC. [Clinical Approach to Abdominal Pain as Functional Origin]. *Korean J Gastroenterol.* 2018;71(2):89-93.
3. Filipović B, Forbes A, Tepeš B. Current Approaches to the Functional Gastrointestinal Disorders. *Gastroenterol Res Pract.* 2017;2017:4957154.
4. Matthews PJ, Aziz Q. Functional abdominal pain. *Postgrad Med J.* 2005; 81(957):448–455.
5. Guthrie E, Thompson D. Abdominal pain and functional gastrointestinal disorders. *BMJ.* 2002;325:701.
6. Chopra J, Patel N, Basude D, *et al*. Abdominal pain-related functional gastrointestinal disorders in children. *Br J Nurs.* 2017;26(11):624-631.
7. Functional GI Disorders. Available at: https://www.iffgd.org/functional-gi-disorders.html. Accessed on 11-09-2019.
8. Question: What is a Functional GI disorder? Available at: https://www.med.unc.edu/ibs/files/2017/10/What-Is-Functional-GI.pdf. Accessed on 11-09-2019.
9. Schmulson MJ, Drossman DA. What Is New in Rome IV. *J Neurogastroenterol Motil.* 2017;23(2):151–163.
10. Lacy BE, Patel NK. Rome Criteria and a Diagnostic Approach to Irritable Bowel Syndrome. Weber HC, ed. *Journal of Clinical Medicine.* 2017;6(11):99.
11. Whitehead WE, Palsson OS, Simrén M. Irritable bowel syndrome: What do the new Rome IV diagnostic guidelines mean for patient management? *Expert Rev Gastroenterol Hepatol.* 2017;11(4):281-283.
12. Longstreth GF, Thompson WG, Chey WD, *et al*. Functional bowel disorders. *Gastroenterology* 2006;130:1480-1491.
13. Chandran S, Prakrithi SN, Mathur S, *et al*. A review of functional gastrointestinal disorders: A primer for mental health professionals. *Arch Ment Health.* 2018;19:70-81.
14. El-Salhy M. Irritable bowel syndrome: diagnosis and pathogenesis. *World J Gastroenterol.* 2012;18(37):5151-63.
15. Kovacic K. Current concepts in functional gastrointestinal disorders. *Curr Opin Pediatr.* 2015;27(5):619-24.
16. El-labban GM, Hokkam EN. The efficacy of laparoscopy in the diagnosis and management of chronic abdominal pain. *J Minim Access Surg.* 2010; 6(4): 95-99.
17. Grover M. When is irritable bowel syndrome not irritable bowel syndrome? Diagnosis and treatment of chronic functional abdominal pain. *Curr Gastroenterol Rep.* 2012;14(4):290-6.
18. Rai RR, Dwivedi M, Kumar N. Efficacy and Safety of Drotaverine Hydrochloride in Irritable Bowel Syndrome: A Randomized Double-Blind Placebo-Controlled Study. *Saudi Journal of Gastroenterology.* 2014; 20(6):378-382.
19. Mishra SC, Gupta K, Chatterjee N. Drotaverine in irritable bowel syndrome: A clinical review. *Gastroenterology Today.* 2001;5(4):186-188.
20. Blasko G. Pharmacology, mechanism of action and clinical significance of a convenient antispasmodic agent. *JAMA India.* 2001;4(12):55-6.
21. Pap A, Hamvas J, Filiczky I, *et al*. Beneficial effect of drotaverine in irritable bowel syndrome (IBS). *Gastroenterology.* 1998;114(Suppl 1):A818.
22. Abdullah M, Firmansyah MA. Diagnostic approach and management of acute abdominal pain. *Acta Med Indones.* 2012;44(4):344-50.
23. Misra SC, Pandey RM. Efficacy of drotaverine in irritable bowel syndrome: a double blind, randomized, placebo-controlled clinical trial. *Am J Gastroenterol.* 2000; 95 (9):2544.
24. Ford AC, Moayyedi P, Chey WD, *et al*; ACG Task Force on Management of Irritable Bowel Syndrome. American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome. *Am J Gastroenterol.* 2018;113(Suppl 2):1-18.
25. Pietrzak A, Skrzydło-Radomańska B, Mulak A, *et al*. Guidelines on the management of irritable bowel syndrome: In memory of Professor Witold Bartnik. *Prz Gastroenterol.* 2018;13(4):259-88.
26. Moayyedi P, Andrews CN, MacQueen G, *et al*. Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome (IBS). *Journal of the Canadian Association of Gastroenterology.* 2019;2(1):6-29.
27. Pap A, Hamvas J, Filiczky I, *et al*. Beneficial effect of drotaverine in irritable bowel syndrome (IBS). *Gastroenterology.* 1998;114(Suppl 1):A818.
28. Xue X, Qi XX, Wan XY. Randomized controlled study of efficacy and safety of drotaverine hydrochloride in patients with irritable bowel syndrome. Pany. S, ed. *Medicine.* 2017;96(51):e9235.
29. Sun J, Yuan Y, Gao J, *et al*. Treatment of irritable bowel syndrome with drotaverine hydrochloride: A multicentre clinical trial. *Chinese Journal of Gastroenterology.* 2010; 15(12):735-7.