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Comparison of the Effect of Duloxetine and Imipramine in the Treatment of Patients with Diarrhea Dominant Irritable Bowel Syndrome

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ABSTRACT

Background & Objective: Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by changes in bowel movements and abdominal pain in the absence of structural disorders. Although effective treatment for irritable bowel syndrome is not yet available. One of the treatments is the low-dose antidepressants, depending on the type and severity of the disease. This study was performed to compare the effect of selective serotonin-norepinephrine reuptake inhibitors including duloxetine and imipramine from a tricyclic antidepressant

Materials & Methods: forty-eight definitively diagnosed IBS patients (based on Rome III criteria) were examined in 2 groups of men and women. Patients in the control group were treated with Dicyclomine and Imipramine while the case group received dicyclomine and duloxetine. The outcomes were measured before and 3 months after treatment to determine and compare the improvement in responses (mainly diarrhea).

Results: Duloxetine could significantly improve the symptoms such as abdominal pain in females (P-value: 0.01) and males (P-value: 0.001), bloating in females (P-value: 0.004) and incomplete defecation in females (P-value: 0.001) and in males (P-value: 0.007). The side effects of this drug were, however, higher than Imipramine. The introduction of more appropriate treatment requires further studies on a larger sample size to assess the symptoms and the side effects.

Conclusion: Based on the effect of duloxetine on this clinical results, it is recommended as an effective treatment in controlling of abdominal pain, bloating, and incomplete defecation.

Keywords: Irritable bowel syndrome, diarrhea, Duloxetine hydrochloride, Imipramine, Abdominal pain

Introduction

Gastrointestinal diseases are among the most important and common chronic non-communicable diseases which can impose a great deal of economic burden and stress on society and the health care system. Among the various gastrointestinal disorders, recurrent abdominal pain and irritable bowel syndrome (IBS) have received the highest attention due to their prevalence according to community-based studies (1). Irritable bowel syndrome is one of the most common gastrointestinal diseases affecting people with a wide range of gastrointestinal and non-gastrointestinal symptoms (2). Chronic abdominal pain and defecation changes are the most common complaints in these patients (3, 4). As IBS is not a life-threatening disorder and does not require surgery or reduce patient survival, its potential impact may be underestimated as a real health problem capable of seriously affecting the patient's daily activities and quality of life (5, 6).

The prevalence of this disease is higher in young people, although community-based studies have shown that the prevalence of this syndrome increases with age (7). In most studies, the ratio of women to men is 3 to 1 with equal prevalence in white and black races. The most documented risk factor for IBS is the female sex which has been shown to have a probability ratio of 1.67. The prevalence of IBS decreases with age (over 50 years). However, the treatment of this disease has not been fully determined (8). Different treatment methods, mostly symptomatic, have been employed based on the patient's symptoms (9, 10). The current research aimed to compare the effect of selective serotonin-norepinephrine reuptake inhibitors including duloxetine with imipramine from the

tricyclic antidepressant class. These drugs inhibit the reuptake of serotonin from the presynaptic terminal and increase the concentration of serotonin in the synaptic space.

In a pilot study by Roberto Lewis-Fernández et al., the administration of duloxetine was evaluated in patients with IBS and depression for 12 weeks. Duloxetine managed to significantly reduce the symptoms of IBS and depression (11). A study by Alicia J Kaplan et al., revealed that 12-week administration of duloxetine can significantly reduce the symptoms of IBS and GAD (12). Brain P. Brennan et al., showed that duloxetine improved the pain and symptoms of IBS loose stools and emergency bowel movements, but did not affect hard stools (13). Megan Friedrich et al., reported conflicting evidence about the effectiveness of antidepressants in patients with IBS and comorbid depression (14). Xie C et al. showed that TCA can significantly improve IBS symptoms, while SSRI had no strong positive influence on IBS treatment (15). Prakash S. Masand et al. showed the effectiveness of paroxetine in improving abdominal pain and IBS symptoms (16). Keshavarz et al. found a better effect of doxepin, a new generation of antidepressant drugs, on IBS compared to fluoxetine (17). J Tack et al. reported that citalopram significantly reduced the symptoms of IBS including abdominal pain compared to placebo (18). Madhusudan Grover et al. reported the efficacy of antidepressants in patients with IBS along with depression or anxiety (19). Mihaela Fadgyas-Stanculete et al. reported an association between some mental disorders such as anxiety and mood disorders with IBS (20). Vahedi H et al. reported that Fluoxetine was more effective than placebo at reducing abdominal discomfort and bloating, increasing the number of bowel movements, and reducing stool consistency. The overall symptom rating decreased from 10.7 to 2.8 in the fluoxetine-receiving group and from 10.5 to 6.7 in the control group ($P < 0.001$), implying that fluoxetine is an effective and short-term treatment. It is tolerable for patients with IBS with overcoming pain and constipation (21).

Forootan Hosseini et al. conducted a clinical trial study on 173 IBS patients in Tehran. The diagnosis was based on Rome's criteria. Patients were randomly divided into three groups which were separately treated with fluoxetine 20 mg daily, amitriptyline 25 mg overnight, and neurotriptyline 25 mg overnight. They reported the effectiveness of fluoxetine in increasing the frequency of defecation in constipated patients ($P < 0.02$) but it showed no effect on reducing the frequency of defecation in diarrhea patients. Amitriptyline improved bowel movements in constipated ($P < 0.01$) and diarrhea ($P < 0.01$) patients. Nortriptyline was also effective in improving bowel movements in constipated ($P < 0.01$) and diarrhea ($P < 0.01$) patients. Fluoxetine and TCAs significantly improved patients' pain, bloating, and general function showing no superiorities over each other. The side effects of amitriptyline were significantly higher than those of fluoxetine and nortriptyline ($P < 0.01$), but there was no significant difference in the side effects of nortriptyline and fluoxetine. This study concluded that fluoxetine is more effective and less complicating in patients with constipation as compared to TCAs. But fluoxetine was not effective in patients suffering from the predominant form of diarrhea (22).

In the present study, the effect of duloxetine was compared with imipramine on the improvement of diarrhea in IBS outpatients with diarrhea predominance. In this regard, the following items were addressed: 1. Determining the therapeutic effect of duloxetine on diarrhea and other symptoms such as abdominal pain and bloating in IBS patients; 2. Determining the therapeutic effects of imipramine on diarrhea and other symptoms such as abdominal pain and bloating in IBS patients; 3. Determining the therapeutic effects of duloxetine on diarrhea and other symptoms of patients with IBS considering the factor of age; 4. Determining the therapeutic effects of imipramine on diarrhea and other symptoms of patients with IBS considering the factor of age; 5. Determining the therapeutic effects of duloxetine on diarrhea and other symptoms of IBS patients considering the factor of sex; and 6. Determining the therapeutic effect of imipramine on diarrhea and other symptoms of IBS patients considering the factor of sex. The research hypotheses included: 1. Duloxetine will be helpful in IBS patients with predominant symptoms of diarrhea and abdominal pain; 2. Imipramine will be helpful in patients with IBS with predominant symptoms of diarrhea and abdominal pain, and 3. In IBS patients with predominant symptoms of diarrhea and abdominal pain, age and sex do not affect the efficacy of fluoxetine and duloxetine.

Materials and Methods

Overview of Procedure

This study examined forty-eight IBS diarrhea dominant patients with the age range of 19-48 years who submit normal TSH,ESR,CRP, S/E×3, Anti-TTG (IgA) ,Ca,Alb,CBC tests (to exclude other diagnoses) during the referr to Valiasr Hospital in Zanjan. All patients were visited and examined and their detailed histories were recorded, as well as the symptoms such as bleeding, weight loss, nocturnal diarrhea, inflammatory bowel disease, and severe awakening abdominal pain. All eligible patients underwent total colonoscopy by gastroenterologist to rule out the possible remaining disease such as colon cancer, inflammatory and atypic colitis. Pregnant and lactating women, cases with a history of gastrointestinal surgery other than an appendectomy, cases who received any medication in the past two months, and diabetic patients were excluded from the study. After obtaining the patients' consent, a questionnaire was passed to collect demographic information (age, sex, etc.) as well as the frequency of diarrhea per day, the severity of abdominal pain before and after taking the drug, the severity of bloating the day before and after taking the drug, the feeling of urgency in defecation and incomplete excretion before and after taking the drug, history of disease and surgery, as well as

complications after taking the drug. No special diet was recommended to patients. Randomization was performed in two groups based on Permutation Block Randomization and quadruple blocks. The patients in the control group were treated with dicyclomine and imipramine. Imipramine was started with a dose of 10 mg for patients and increased to 25 mg within two weeks if, the patient did not respond to the treatment. For case group, inconjuction with dicyclomin,duloxetin was started with 20 mg and increased to 60 mg if there was no response within two weeks. Patients' outcomes were measured before and 3 months after treatment. The rate of improvement in outcomes (mainly diarrhea) was compared between the two groups.

Educate and follow up of patients

Before recommending the drugs, questions were asked on the history of drug allergies, liver problems, use of other drugs, history of heart disease, decision to become pregnant and breastfeeding, and symptoms of intestinal obstruction. The patients were counseled to take their medications regularly and keep them out of reach of children. During this period, patients were followed up by phone or in person to continue the treatment process and record any possible complications such as abdominal pain, blood in the stool, exacerbation of diarrhea, or severe constipation**.**

Study population, sample size, and calculation and sampling methods

The sample size of IBS patients with diarrhea in the age range of 19 to 48 years was calculated as follows:

n= 〖{Z_(1-α/2) √((2p)¯(1-p¯))+Z_(1-β) √(p_1 (1-p_1)+p_2 (1-p_2))}〗 ^2/ 〖(p_1-p_2)〗 ^2

p_1=0.263

p_2=0.633

α =0.05

β =0.2

n=24

Subgroup Analysis

Subgroup analysis was performed according to *Leishmania* species (*L. major, L. amazonesis, L.*

Result

Of the 48 patients registered in this study, 56.2% of them were female and 43.8% were male. They were between 19 and 48 years old and with a mean age of 30. None of the patients had any disease other than IBS. The number of patients in both groups was equal (24). In the group that received duloxetine, 13 were women and 11 were men with a mean age of 29.7; while 14 women and 10 men comprised the 24 members of the imipramine groups with a mean age of 30.2.

The sample size was determined based on the implications of previous studies following the evaluation of similar drugs to improve diarrhea.

Inclusion criteria and exclusion criteria of samples:

Patients with IBS with predominant diarrhea in the age range of 19 to 48 years according to ROME III criteria were included in this research. Patients with the following conditions were excluded from the study : pregnancy, lactation, history of any gastrointestinal surgery except appendectomy, taking drugs for gastrointestinal diseases, reluctance to continue the study, any signs of inflammatory bowel disease, atypic colitis and celiac disease patients , cases with drug interactions, or allergies to imipramine and duloxetine. Criteria for leaving patients: Failure to take regular and timely medication or discontinuation of medication by patients, side effects for patients.

Data collection

In this study, two types of data collection tools were used. The first tool was a checklist prepared based on the view of experts and an extensive search of relevant literature. In addition to demographic data including age, sex, level and of education, this checklist recorded the frequencies of bowel movements and emergency defecations as well as the severity of the symptoms such as pain and bloating. The second tool is the IBS Severity Score Questionnaire, which was used to assess the severity of IBS.

Data analysis method

Data were entered into SPSS software after allocating appropriate codes and analysis. Continuous quantitative data were reported as mean and standard deviation while qualitative and nominal data were recorded as frequency percentages in the form of tables and graphs. The K-square test was used to determine the relationship between the groups. The effect of potentially confounding variables was evaluated using multivariate models. The significance level in all was considered 0.05.

Ethical considerations

Patients were enrolled in the study based on informed consent. This study was registered in the clinical trial database and patients had the right to leave the research at any stage of the study. In addition, it was possible to end the study as soon as possible in case of any significant complication that could be attributed to the intervention. This research was registered in the system in Feb 2019 with the code IRCT20190703044084N1.

Defecation rate before and after treatment with duloxetine and imipramine

The frequency of defecation by the drug can be found in Figure 1. No significant relationship was detected between duloxetine and imipramine consumption and frequency of defecation (P> 0.05). The frequency data according to age was also investigated. (Data not shown)

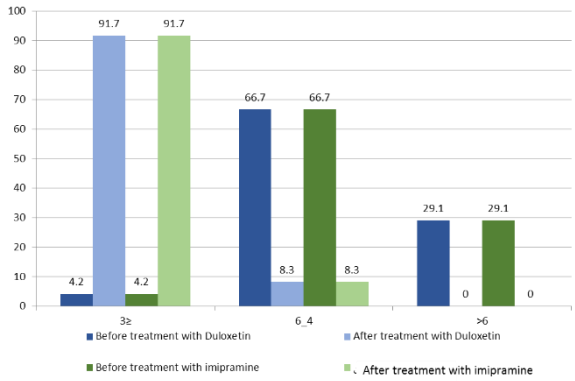

Figure 1. Comparison of frequency percentage of defecation before and after treatment with duloxetine and imipramine

Intensity of the pain in patients before and after treatment with duloxetine and imipramine

The frequency of abdominal pain is depicted in Figure (2). Duloxetine and imipramine significantly affected the pain intensity (P <0.05). (Data in terms of gender is not presented here).

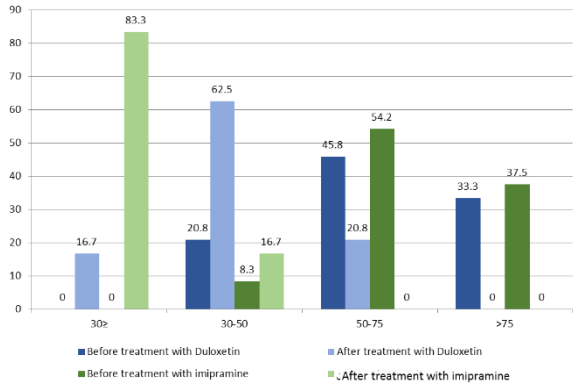

Figure 2. Comparison of frequency of patients by severity of abdominal pain before and after administration of duloxetine and imipramine

Bloating before and after treatment with duloxetine and imipramine

The frequency of bloating is presented in Figure 3. The severity of swelling before and after drug administration in terms of gender and age, was also investigated. Duloxetine and imipramine consumption was significantly related to the severity of bloating (P <0.05). (Data not shown)

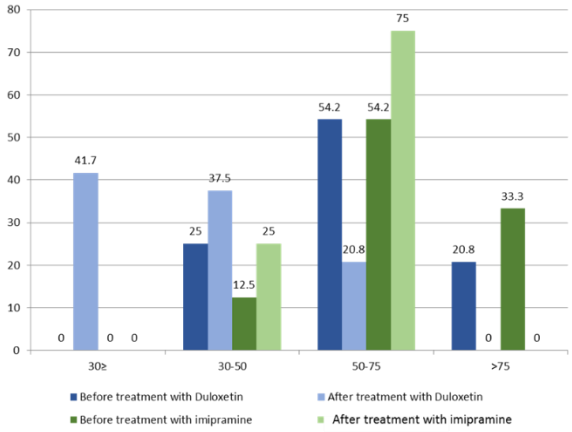

Figure 3. Comparison of the frequency of patients with the severity of bloating before and after administration of duloxetine and imipramine

Urgent need for defecation before and after treatment with duloxetine and imipramine

The frequency of urgency of defecation is presented in Figure (4). The degree of urgency in excretion, before and after drug administration was investigated by gender and age, respectively. No significant relationship was observed between duloxetine and imipramine consumption and the degree of urgency in excretion (P> 0.05). (Data not shown)

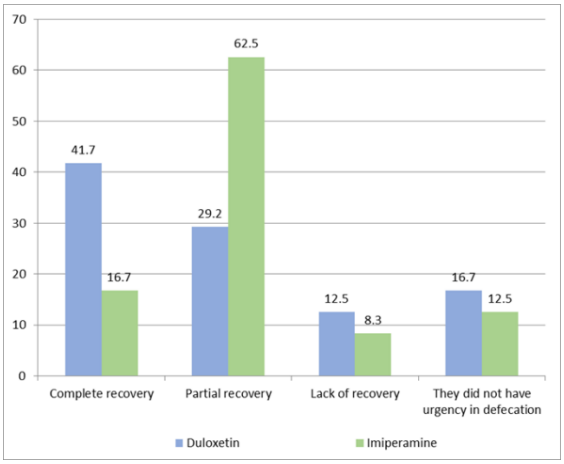

Figure 4. Percentage of patients in terms of immediate recovery in defecation after administration of duloxetine and imipramine

Incomplete defecation before and after treatment with duloxetine and imipramine. Duloxetine and imipramine consumption showed a significant relationship with incomplete defecation P <0.05). (Data regarding sex is not described here).

Side effects

The side effects of the studied drugs can be seen in Figure (5). Patients without side effects were more in the imipramine group. The most common side effects were nausea in the duloxetine group and dry mouth in the imipramine group. A significant relationship was

also observed between the type of drug and some side effects.

It should be noted that one patient in the duloxetine group and two patients in the imipramine group had a history of appendectomy. All three patients had an urgent bowel movement. The patient in the duloxetine group also suffered from bloating and severe pain, which improved by duloxetine.

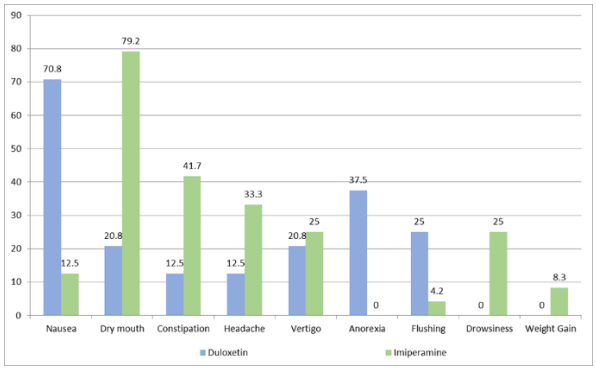

Figure 5. Percentage of side effects of duloxetine and imipramine

Discussion

In this study, the effect of imipramine and duloxetine treatment was investigated in diarrhea predominance IBS patients. One group of patients received imipramine while the other was treated with duloxetine. In general, the rate of improvement of abdominal pain and bloating as well as complete recovery of symptoms such as incomplete defecation was higher in the duloxetine group. However, the improvement of defecation rate was the same in both duloxetine and imipramine groups (91.7%). Concerning the frequency of defecation before taking the drug, out of 24 patients in the duloxetine group, 1 patient had a low rate of defecation; 16 patients had moderate rate while 7 patients reported sever defecation rate. After treatment with duloxetine, 22 patients reported daily defecation frequencies below 3 times while 2 cases (males) reported defecation frequency of 4 to 6 times a day. In the imipramine group before taking the drug; 1 patient had a low, 16 patients moderate bowel movements and 7 patients had strong bowel movements. 2 cases reported 4 to 6 times a day and no significant relationship was observed between the two drugs.

In the duloxetine group and before treatment, 2 patients had moderate pain, 13 patients reported moderate to severe pain while severe pain was reported by 9 patients. After treatment, twenty patients had mild pain and 4 patients had moderate pain. Concerning the pain level before treatment in the imipramine group, 5 patients had moderate pain, 11 patients had moderate to severe pain, and 8 patients had severe pain. After taking imipramine; 4 patients had mild pain, 15 patients reported moderate pain while 5 patients suffered from moderate to severe pain. Out of 24 patients in the duloxetine group, 83.3% of patients reported a significant reduction in the severity of IBS-induced pain.

Brennan et al. 2009 and Lewis-Fernández 2016 (11, 13), found that duloxetine reduced heartburn by 56%. Kaplan et al. 2013 reported that duloxetine improved anxiety symptoms and IBS in 13 patients suffering from stress and IBS (12). The frequency of bloating before taking duloxetine was moderate in 6 patients, 13 patients had moderate to severe bloating and 5 patients reported severe bloating. After Duloxetine consumption; 10 patients had mild bloating, 9 patients had moderate to severe bloating and 5 patients reported moderate to severe bloating. Before taking imipramine, 3 patients had moderate bloating, 13 patients reported moderate to severe bloating while 8 patients suffered from severe bloating. After taking this drug, 6 patients had moderate bloating and 18 patients reported moderate to severe bloating. The association between duloxetine and imipramine was significant in these patients and it seems that duloxetine was more effective in improving bloating. Duloxetine and other antidepressants may exert their anti-IBS effect through 5-HT and NE neurotransmission, corticotrophin-releasing factor regulation, and other mediators of central and intestinal pain, intestinal motility, intestinal secretion, visceral sensitivity, and stress response (11).

The mechanism of action of imipramine and TCAs in IBS is unclear, but these drugs appear to modulate the nerve axis of the brain and intestines. Another possible mechanism for these drugs could be the modulation of intestinal motility by acting on peripheral muscarinic receptors or ATP-sensitive potassium channels in Cajal interstitial cells (23). Xie et al. showed that TCA significantly improved IBS symptoms, while SSRI had no strong evidence (15). Abdul-Baki et al. studied 59 IBS patients for 12 weeks and reported that imipramine may be effective in treating IBS patients as well as improving their quality of life. Careful patient selection, low-dose initiation, and gradual increase in drug dose, and monitoring of side effects can further enhance the therapeutic response (23). A study on 51 IBS patients with diarrhea showed that imipramine failed to improve the pain associated with the syndrome. This study showed that imipramine can improve the symptoms (24). Trinkley K.E. revealed that imipramine was not effective in treating these patients (25).

In terms of age, the results of the present study showed that the frequency of evacuation in the duloxetine group was 30-30 years older than the other age groups. Two cases had bowel movements more than 6 times a day, with the use of duloxetine, 11 cases reported bowel movements less than 3 times a day. The frequency of excretion in the imipramine group was higher in the age group of 20-30 years, which was

achieved in 11 patients after treatment with imipramine.

Pain intensity was higher in the age group of 20-30 years. The pain was significantly reduced after taking duloxetine. In the imipramine group, severe pain was reported in the age group of years, which also showed a significant reduction after medication. The highest rate of bloating was related to the age group of 20-30 years.Seven cases were completely cured after taking duloxetine. In the imipramine group, the highest rate of bloating was in the age group of 20-30 years .The highest rate of emergency defecation was in the age group of 20-30 years (in both drug groups); 3 patients in the duloxetine group achieved complete recovery and 3 patients in the imipramine also achieved complete recovery.

All patients in the duloxetine group had incomplete excretion. In patients under 20 years, 1 case had complete recovery, while 7, 8, and 1 case in age ranges of 20-30, 30-40, and 40-50 years old reported a complete recovery, respectively. Also, in the age group of 20-30 years, 5 patients had a relative recovery. In the age groups of 30-40 and 40-50, 1 patient reported relative recovery. In the imipramine group, in the age group of 20-30 years, 9 people, 7-30 years old, 7 people and 2-40 years old, 2 people had incomplete excretion, of which only one person reported complete recovery by taking imipramine. The results of this group for age subgroups of below 20 years and 40-50 years were a little thought-provoking due to the smaller number of patients which requires further study.

In the present study, side effects of duloxetine-receiving patients included anorexia (37.5%), hot flashes (25%), nausea (70.8%), dry mouth (20.8%), and constipation (12.5%). Dizziness (20.8%) and headache (12.5%) were also observed. Brennan et al. reported the effectiveness of dolesteine on 15 IBS patients although it had side effects such as constipation in patients (13). Lewis-Fernández et al. reported dizziness (7.1%) dry mouth (7.1%) night sweats (7.1%), and tremors (7.1%) after administration of duloxetine (11).

In this study, side effects of imipramine-receiving patients reported nausea (12.5%), drowsiness (25%), weight gain (8.3%), dry mouth (79.2%), hot flashes (4.2%), constipation (41.7%), headache (33.3%), and dizziness (25%). Abdul-Baki H et al. revealed that side effects such as sleep disorders, urological symptoms, palpitations, constipation, anxiety, dry mouth, dizziness, hot flashes, and sweating may motivate the patients to stop the medication (23).

As mentioned earlier, the rate of improvement in abdominal pain, bloating, and complete recovery from symptoms such as incomplete defecation was higher in the duloxetine group. Imipramine, however, exhibited lower side effects (nausea and hot flashes) compared to duloxetine. Since IBS is a common disease, whose severe cases can be disabling and affect a person's normal life, the results of the present study can help physicians and therapists choose the best treatment in clinical practice. However, this study had some limitations such as the follow-up duration. Since IBS is a chronic disease and there is no definitive cure, it can be expected that patients' symptoms return after a limited treatment period, necessitating longer clinical trials. The long-term effects of these drugs should be also addressed. Other limitations of this study include the absence of a control group with placebo administration, so it is recommended to compare the drugs with the control group. Another limitation of this study is the small sample size (less than 200), which reduces the ability of the study to detect differences or the relationship between predictor variables and outcomes. The lack of Para Kinetic criteria for diagnosing or evaluating the improvement of patients' condition should be also considered.

Conclusion

The results of this study showed the higher effectiveness of duloxetine in improving symptoms such as abdominal pain, bloating, and incomplete defecation, although the side effects of this drug were greater than imipramine group. It should be noted that the choice of appropriate treatment for this disease requires further study of the symptoms and side effects of these drugs on larger sample sizes. Importantly, the cost of imipramine was much lower than that of duloxetine, depending on the length of treatment. A detailed clinical history and a more obvious patient complaint can help in prescribing the drug. For example, duloxetine is the preferred option of an IBS patient with diarrhea predominance and pronounced complaints of abdominal pain and bloating.

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Authors' Contribution

NMP and SKM drafted the article. NMP provided critical revision of the article. SJ carried out native editing. NMP, SKM and SJ developed the theory to investigate a specific aspect and supervised the findings of the work, as well as conceived the presented idea. All authors discussed the results and contributed to the final manuscript submitted for publication.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval and consent to participate

Written and informed consent was obtained from all participants for their participation in the present study and also for the publication of this report.

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