Original Article

Effects of Duloxetine on Gastrointestinal Symptoms, Depression, Anxiety, Stress, and Quality of Life in Patients with the Moderate-to-Severe Irritable Bowel Syndrome

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Abstract

Background: Irritable bowel syndrome (IBS) is a chronic disease. There are very few studies on the Duloxetine efficacy in improving the gastrointestinal and psychological symptoms, in IBS. The current study attempted to evaluate the effectiveness of Duloxetine in symptoms and quality of life in moderate-to-severe IBS patients.

Materials and Methods: This is a double-blind placebo-controlled clinical trial in which the population is composed of 37 patients with moderate-to-severe IBS in Isfahan from March 2018 to March 2019. For the intervention group, Duloxetine was administered for three months, and the treatment protocol was the same for the control group but using a placebo. The severity of IBS symptoms, quality of life, and negative emotions such as depression, anxiety, and stress were assessed.

Results: Our data showed no significant difference between the two groups of the study for the severity of IBS symptoms (P value = 0.150); however, in the intervention group, it was significantly lower than controls after six, eight, and ten weeks of the intervention (P value = 0.023). Overall evaluation of the quality of life in patients indicated significantly higher quality of life in the Duloxetine group than the control group from the eighth week to the twelfth week after the intervention (P value <0.038). Anxiety and stress in the Duloxetine group were significantly lower than controls after the intervention (P value <0.05).

Conclusion: Duloxetine is probably helpful for reducing anxiety, stress, and the severity of symptoms in IBS patients. It also could increase the quality of life in patients.

Keywords: Anxiety, duloxetine, irritable bowel syndrome, quality of life, stress

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Introduction

Irritable bowel syndrome (IBS) is a disabling chronic disease which is one of the functional gastrointestinal disorders (FGIDs), presented with abdominal discomfort/pain and difficulties in excretion and intestinal functionality.[1] In Western countries, the prevalence of IBS has been reported as 9% to 22%, and in Iran, a prevalence of 6% has been reported.[2]

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IBS is often accompanied by psychological disorders such as anxiety and depression, problems in the life quality, disability as well as problems with job affairs and absence from work, and massive spending.[3,4] Although the psychologic factors are not a part of IBS by itself, it plays a critical role in

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disease progression and clinical consequences. It has also been declared that personality traits could be related to IBS. An instance, Sharbafchi and colleagues indicated that higher scores of extraversion, conscientiousness, openness, and agreeableness could be associated with lower risks of functional dyspepsia, and as a result, psychiatric consultations have high clinical importance in gastrointestinal diseases.[5] Stress, anxiety, and depression are strongly and commonly associated with the onset and intensity of signs and symptoms of IBS.[6,7]

IBS treatments included an appropriate patient–physician relationship, fostering the patient's assurance, proper diet, and removing the most frequent IBS symptoms (pain, diarrhea, and constipation). Antidepressants, in addition of their effects on mood, can act as analgesics in patients with chronic pain.[8]

The common antidepressants used for IBS are serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs).[9]

TCA or SNRIs have large benefits with reducing of pain and SSRIs can reduce anxiety, obsessiveness, or phobic behaviors. The TCAs may modify pain perception through a central mechanism. They also cause peripheral effects on motility, gut secretion, changes in visceral afferent signaling, and smooth muscle effects on viscera. However, treating comorbid anxiety and depressive disorders requires higher dosages of TCAs than are used to treat functional bowel disorders.[10] Significant and common side effects of the TCAs, such as cardiovascular effects and anticholinergic properties, may limit their tolerability in this population.

Duloxetine is an SNRI that has efficacy and FDA approval for generalized anxiety disorder (GAD), as well as in pain conditions such as diabetic neuropathic pain and fibromyalgia.[11]

Duloxetine is a slow-release drug that benefits from a reduced risk of severe nausea. It can be absorbed well and converted to numerous metabolites due to extensive metabolism in the liver. Urinary Duloxetine excretion rate is 70%, and of remained dose, 20% is exerted through the intestinal tract. Studies comparing the efficacy of Duloxetine with serotonin-specific inhibitors have suggested that Duloxetine is more efficacious in pain control. However, there are very few studies on the Duloxetine efficacy in improving signs and symptoms, the quality of life, depression, and anxiety in IBS patients. Also, they could not achieve a unified conclusion in this respect.[12]

Taking into account the role of serotonin in FGIDs pathophysiology, some evidence for SSRIs efficacy in the treatment of these groups of disease[8,9] and antidepressants administration by specialists empirically to treat IBS, the current study attempted to evaluate the effectiveness of Duloxetine in signs and symptoms and life quality in patients with moderate-to-severe symptoms.

Materials and Methods

This is a double-blind, randomized clinical trial in which the population is selected from all patients with moderate-to-severe IBS (both constipation and diarrhea) presented at Psychosomatic Clinics affiliated to medical university in Isfahan, from March 2018 to March 2019. The IBS diagnoses were based on the ROME III criterion by a specialist in gastrointestinal and hepatic disease. The inclusion criterion includes the ability to read and write (as a literate person); absence of depressive, anxiety, bipolar, and/or psychotic disorders (based on the diagnostic criterion of DSM-V); no serious suicidal thoughts or plans at baseline; no consumption of any psychotropic drugs within last two weeks; no pregnancy or breastfeeding; no contraindication of Duloxetine consumption; and informed consent for participating in the study.

However, the presence of any organic disease within the study course, lack of drug consumption regularly, uncompleted questionnaire, the incidence of severe side effects due to Duloxetine use, and discontinuing the participation in the study were of exclusion criteria.

A total of 78 individuals were screened, and 40 were included in the study. Using random allocation software, eligible subjects were allocated in a 1:1 ratio into two groups [Figure 1].

The baseline demographic data (including age, sex, educational level, duration of disease, and marital status) were recorded.

After the registration of baseline information for the intervention group, 30 mg/day Duloxetine was administered for the first week and continued from 4 to 7 days to minimal side effects (particularly nausea) can be reached. Afterward, a dose of 60 mg/day was administered for the rest of the study. The duration of treatment was three months for both groups. The treatment protocol was the same for the control group but using a placebo.

The study was blinded to the researcher and the patients. We used a placebo made of cornstarch in a similar shape and color to Duloxetine by the faculty of pharmacology. The two drugs are entitled A and B.

Standard medications that were initially taken by the patients continued, which include pharmacologic factors affecting intestines, anticholinergic drugs, and antidiarrheal drugs. Moreover, although the use of no diet can generally lead to the incidence of symptoms, some specific foods such as fatty foods, alcohol, coffee, and milk were eliminated from the diary of patients due to the potential of intensifying the symptoms. Thus, we informed that if any severity of symptoms due to the consumption of specific food was found, they need to benefit from the physician's recommendations for diet adjustment.

Before and through the intervention within the second, fourth, sixth, eighth, tenth, and twelfth weeks and in order for the long-term follow-up after six months of the intervention, the patients were present at the clinic to record the severity of IBS symptoms and any side effect and to fill out questionnaires.

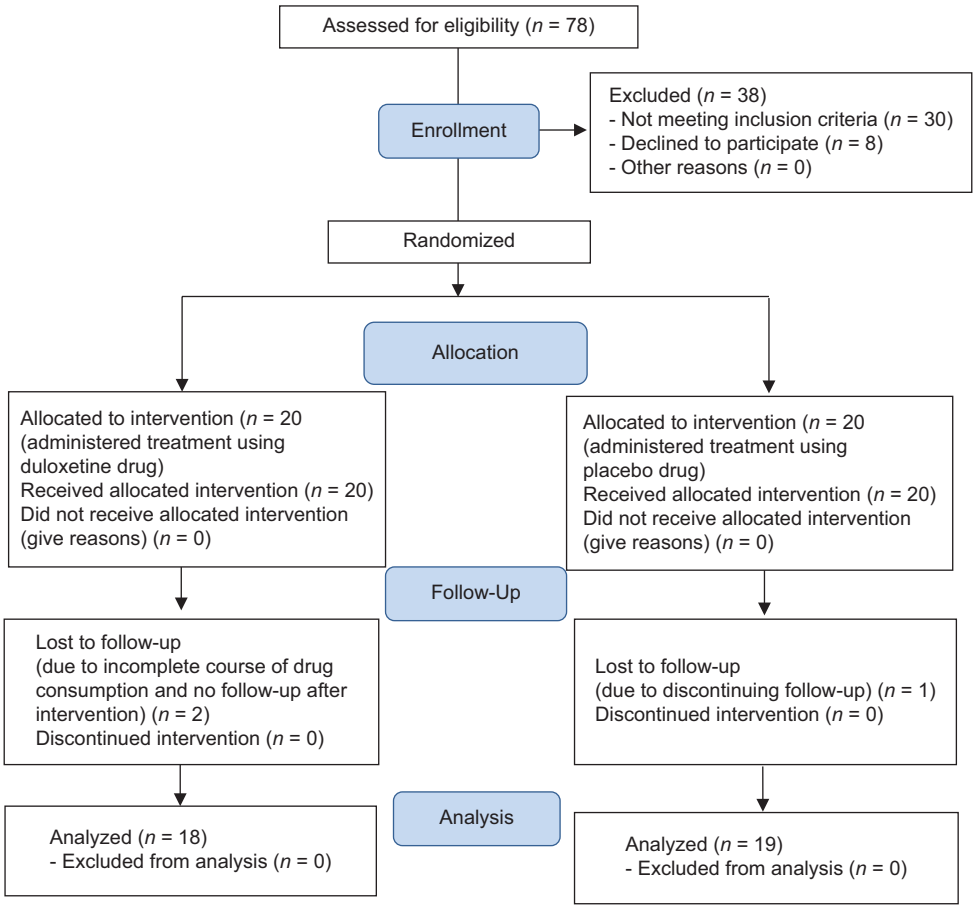

Figure 1: Consort flow diagram

At the end, medications were tapered gradually for two weeks and then discontinued.

To determine the severity of IBS symptoms, we applied the Irritable Bowel Syndrome Severity Scoring System (IBSSS) questionnaire and evaluated the quality of life by IBS Quality of Life (IBS-QOL) Scale and negative emotional manners such as depression, anxiety, and stress by depression, anxiety, and stress scale (DASS-21). Finally, pre-intervention findings were recorded.

Study instruments

The irritable bowel severity scoring system (IBSSS)

This self-report questionnaire consists of five sections that examines IBS symptoms including pain, defecation disorder, bloating, the effect of the disease on daily life activities, and extraintestinal symptoms using Visual Analog Scale (VAS). The maximum score of each section is 100, and the total score of the questionnaire equals 500. The questionnaire does not have a particular cutoff, but a higher score reflects more severe conditions. Mild, moderate, and severe cases are represented by scores of 75–174, 175–300, and ≥300, respectively. The aforementioned instrument had acceptable validity due to internal consistency of 0.69 and interclass correlation coefficient of 0.86.[13] The forward and back-translation method was used to ensure the validity of questionnaire based on World Health Organization (WHO) guidelines.[14]

The irritable bowel syndrome quality of life (IBS-QOL)

This questionnaire has been primarily proposed by Patrick *et al*. in 34 items assessing eight factors including dysphoria, interference with activity, interpersonal relations, food avoidance, social reactions, sexual concerns, body image, and health worry based on a five-score Likert scale. The total score ranges from 34 to 170, and the higher scores represent worse quality of life.[15] The Persian version of this questionnaire has been validated by Masaeli *et al*. with Cronbach's alpha of 0.95.[16]

Depression, anxiety, and stress scale (DASS)

This questionnaire is a set of three scales to measure negative emotional states in depression, anxiety, and stress. Each of the scales consists of 14 items, which are divided into two–five item subsets with same content. The 21-item short form of this questionnaire consists of seven items in each of the categories, and the scores are multiplied by two. The higher a score is, the worse the condition is. This short version of DASS has high Cronbach's alpha of 0.93.[17] The 21-item version of this questionnaire was translated and validated in Persian by Sahebi *et al*. which has Cronbach's alpha of 0.77, 0.79, and 0.78 for depression, anxiety, and stress scales, respectively.[18]

Finally, we analyzed the data using SPSS (ver. 19). Mean, standard deviation, and frequencies (in number and

percentage) as descriptive statistics and Chi-square, Mann–Whitney, and repeated measurement ANOVA (adjusted for confounders such as age, sex, and education) as inferential statistics were used. For all analyses, we considered a significance level of < 0.05.

Results

Two patients in the intervention group were excluded due to incomplete courses of drug consumption and no follow-up after intervention by the patient. In addition, one patient in the control group was excluded because of discontinuing follow-up by the patient. Finally, the study included 18 patients in Duloxetine group (men = 8 [44.4%] and women = 10 [55.6%]; mean age = 41.32 ± 11.54 yrs.) and 19 patients in control group (men = 7 [36.8%] and women = 12 [63.2%]; mean age = 37.85 ± 12.67 yrs.) (*P* value >0.05) [Table 1].

The pre-intervention IBS-SSS evaluation showed no significant difference between the two groups of the study (*P* value = 0.150). However, the IBS-SSS score of cases (Duloxetine group) was significantly lower than controls over time and after six, eight, and ten weeks of the intervention (*P* value <0.05). Although the follow-up, six months after the intervention, showed lower IBS-SSS in cases than controls, there was no significant difference between groups (*P* value = 0.179). The adjusted findings for age and sex showed that the treatment could play an essential role in the reduction of IBS-SSS over time (*P* value = 0.023) [Table 2].

However, the evaluation of depression, anxiety, and stress in patients suggested that there was no significant difference between the two groups in the baseline values of these three factors (*P* value >0.05). However, the levels of anxiety, depression, and stress in cases were significantly lower than those of controls from the sixth week to the twelfth week after the intervention (*P* value <0.05). Moreover, it indicated that the role of the intervention was not significant in the reduced depression adjusted for confounding variables (age and sex) (*P* value = 0.146), although this role was significant in anxiety and stress of the patients (*P* value <0.05) [Table 3].

Overall evaluation of the life quality in patients indicated significantly higher quality of life in the Duloxetine group than the control group from the eighth week to the twelfth week after the intervention (*P* value <0.05). In addition, the role of the intervention was significant when adjusted for confounding variables (age and sex) (*P* value = 0.038) [Table 4].

Table 1: Baseline characteristics of patients in the two groups

Characteristics		Duloxetine (*n*=18)	Control (*n*=19)	*P*
Sex	Male	8 (44.4%)	7 (36.8%)	0.743
	Female	10 (55.6%)	12 (63.2%)	
Age; mean year		41.32±11.54	37.85±12.67	0.391
Married status	Single	3 (16.7%)	8 (42.1%)	0.120
	Married	15 (83.3%)	10 (52.6%)	
	Widow	0 (0.0%)	1 (5.3%)	
Education	Elementary	5 (27.8%)	1 (5.3%)	0.165
	Diploma	5 (27.8%)	5 (26.3%)	
	Universal	8 (44.5%)	13 (68.4%)	
Smoking		7 (21.1%)	4 (21.1%)	0.295

Discussion

The present study showed that, administration of Duloxetine, up to the fourth week, had no significant effect on IBS symptoms based on the IBS-SSS criterion compared to the control group, but in the sixth, eighth, and tenth weeks, the mean of IBS-SSS was significantly lower.

However, the administration of Duloxetine was identified as an influential factor in controlling and reducing IBS symptoms in these patients by controlling the confounding variables such as age and sex. In addition, Duloxetine significantly reduced anxiety and stress in these patients, but it was associated with a decrease in depression, which difference was not significant.

In fact, it may be argued that this therapeutic intervention has indirectly reduced their symptoms of IBS by lowering anxiety and stress. It can also have an indirect effect on the improvement of IBS symptoms.

Table 2: Comparison of mean IBS-SSS score in two groups

Variable	Time	Duloxetine (*n*=18)	Control (*n*=19)	*P*[1]
IBS-SSS	Before intervention	323.28±63.96	359.84±84.93	0.150
	Second week	306.78±74.89	355.11±86.20	0.078
	Fourth week	304.11±67.76	340.21±106.39	0.229
	Sixth week	274.56±50.61	314.05±62.93	0.043
	Eighth week	288.28±67.08	238.05±63.80	0.025
	Tenth week	271.22±73.54	201.16±56.89	0.003
	Twelfth week	177.61±44.24	204.32±55.64	0.116
	Six months after the intervention	180.56±57.50	206.26±56.51	0.179
P[2]		0.023		

1. The significance level of the Mann–Whitney test resulted from the comparison of the mean value of the variable between two groups. 2. The significance level of repeated measurements ANOVA test adjusted for age, sex, and education to the evaluation of the role of the intervention in variable variations

Table 3: Comparison of mean DASS score in two groups

DASS	Time	Duloxetine (n=18)	Control (n=19)	P^1
Depression Score	Before intervention	8.50±3.07	8.53±1.81	0.975
	Second week	7.67±3.08	7.63±1.61	0.965
	Fourth week	7.17±2.83	7.79±1.69	0.419
	Sixth week	4.72±1.90	7.11±1.91	0.001
	Eighth week	4.56±2.12	6.95±1.61	<0.001
	Tenth week	4.44±2.23	6.68±1.92	0.002
	Twelfth week	4.06±1.89	6.11±2.35	0.006
	Six months after the intervention	4.00±2.09	5.53±2.74	0.066
P^2		0.146		
Anxiety Score	Before intervention	7.67±2.40	7.42±1.71	0.721
	Second week	7.33±2.11	7.53±1.77	0.765
	Fourth week	7.56±1.92	7.95±1.61	0.505
	Sixth week	6.06±1.95	6.42±1.89	0.567
	Eighth week	4.11±1.28	5.47±2.04	0.021
	Tenth week	3.28±1.53	4.79±2.32	0.026
	Twelfth week	2.72±1.41	4.53±2.19	0.006
	Six months after the intervention	3.94±2.31	5.21±2.51	0.120
P^2		0.047		
Stress Score	Before intervention	10.44±1.95	9.95±2.37	0.492
	Second week	10.06±1.55	9.47±2.19	0.361
	Fourth week	9.39±1.75	9.11±2.05	0.655
	Sixth week	9.06±1.39	8.74±1.97	0.575
	Eighth week	7.61±1.58	7.74±2.21	0.844
	Tenth week	5.44±1.76	6.79±1.82	0.028
	Twelfth week	4.89±1.28	6.79±1.90	0.001
	Six months after the intervention	4.11±1.02	6.05±1.58	<0.001
P^2		0.028		

1. The significance level of the Mann–Whitney test resulted from the comparison of the mean value of the variable between two groups. 2. The significance level of repeated measurements ANOVA test adjusted for age, sex, and education to the evaluation of the role of the intervention in variable variations

Table 4: Comparison of mean IBS-QOL score in two groups

Variable	Time	Duloxetine (n=18)	Control (n=19)	P^1
IBS-QOL	Before intervention	85.50±17.14	84.21±17.62	0.823
	Second week	81.00±18.52	80.42±19.90	0.928
	Fourth week	81.44±18.40	82.00±17.32	0.925
	Sixth week	78.33±17.48	74.16±19.05	0.493
	Eighth week	66.78±17.50	79.63±19.40	0.042
	Tenth week	57.17±17.63	71.63±23.12	0.040
	Twelfth week	52.94±17.70	69.84±22.47	0.016
	Six months after the intervention	66.06±19.28	72.42±20.32	0.336
P^2		0.038		

1. The significance level of the Mann–Whitney test resulted from the comparison of the mean value of the variable between two groups. 2. The significance level of repeated measurements ANOVA test adjusted for age, sex, and education to the evaluation of the role of the intervention in variable variations

According to Daghaghzadeh *et al*., Duloxetine not only reduced anxiety and depression in patients with inflammatory bowel disease (IBD), but also the severity of symptoms such as diarrhea frequency and pain declined following the treatment that was associated with the increase of QOL. In fact, Duloxetine not only can reduce anxiety but may also have primary effects on the severity of symptoms by anti-inflammatory effects.[19] In addition, other studies have showed that Duloxetine has an independent analgesic result, which supports the benefit of treatment for IBS patients, regardless of suffering from anxiety or depression.[20]

In line with the study by Kaplan *et al*., Duloxetine was shown to be effective in reducing the severity of IBS symptoms, with a significant effect from the sixth week onward. Though, it should be noted that an evaluation has been done in a similar long-term follow-up (six months after the intervention) and resulted in the good results of SNRI (Duloxetine) in patients with a generalized anxiety disorder (GAD) with IBS.[12]

Lewis-Fernández and colleagues declared that Duloxetine is a well-tolerable medicine and the use of this drug for 12 weeks resulted in significantly improved symptoms of both IBS and MDD. However, they did not include the placebo group and did not evaluate the QOL in patients.[21] In 2009, Brennan and others also showed that Duloxetine was associated with significant improvement in severity of illness, pain, QOL, anxiety, and work and family disability.[22] The important point of the current study was that we evaluated these symptoms among 40 patients with IBS and indicated significant results that were consistent with previous findings.

In a systematic and meta-analysis study, Ford *et al*. concluded that antidepressants reduced IBS symptoms in comparison with placebo, and this was independent of their impact on depression, anxiety, and sensory-motor function of the intestine.[23] However, the sample size in most of these studies was not sufficient for meta-analysis. Also, the duration of treatment in this study (six weeks) was shorter than the recommended time (8 to 12 weeks), and there was no follow-up.

Despite the widespread use of SNRIs by experienced professionals, their use has not been mentioned, and the results of all studies have not been the same. There have also been previous studies on the use of SSRIs in IBS patients. Based on a systematic review by Kułak-Bejda in 2017, SSRIs could significantly improve the IBS symptoms including pain, severity, bloating, and also QOL.[24] Talley *et al*. stated that neither citalopram nor imipramine did not have any effects on the initial goal, which was the improvement of IBS symptoms.[25] However, the limitations of the study must be carefully interpreted. In the current study, the sample size in the citalopram group (including 17 individuals, among whom 12 cases completed the study) was insufficient. Another study was conducted by Tack and colleagues in 2006 that evaluated the use of citalopram in 23 non-depressed IBS patients. Based on their results, citalopram significantly improved IBS symptoms, such as abdominal pain. It was also stated that the therapeutic effect was independent of effects on depression, anxiety, and sensorimotor function.[26] In 2017, Chen and colleagues also reported that antidepressants including benzodiazepines, TCAs, SSRI, and SNRIs have better effects in reducing symptoms and pain of IBS compared to conventional pain managing drugs.[27] These data were in line with the findings of our study showing the effectiveness of Duloxetine in IBS. There are also some paradoxical reports on the effectiveness of SSRIs in IBS. A meta-analysis was performed by Xie and others in 2015 that assessed the use of antidepressants in IBS. By evaluating 12 studies, it was indicated that TCAs may improve symptoms of irritable bowel syndrome, but there was no strong evidence to support the effectiveness of SSRIs in treatment of IBS.[9]

Psychological factors are considered to play a role in exacerbation of symptoms in IBS; therefore, antidepressants may be regarded as a type of IBS treatment and can significantly improve the patients' condition.[23] A preliminary study of Duloxetine on the patients with IBS indicated that this drug could result in lowering the pain, disease severity, and anxiety and improving QOL.[22] This could be another reason for the reduction of some symptoms after the use of antidepressants in patients with IBD, such as what was achieved in our study as the effect of 60 mg Duloxetine on symptoms and quality of life in moderate-to-severe IBS.

Evidence suggests that the clinical response to antidepressants does not increase with rising doses (up to the dose required to treat depression), and therefore lower doses of the mentioned drugs (with lower side effects) can be used to treat IBS.[28] The results will help to clarify the role of antidepressants in the treatment of FGIDs.

Because the gastrointestinal symptoms are a marker of anxiety, the IBS QOL has three indicators of physical, social, and mental health. The quality of life of these patients may be affected by gastrointestinal problems as well as psychological disorders. The present study showed that the patients' quality of life in the Duloxetine group was significantly higher than the control group.

QOL is essential in patients with gastrointestinal problems through the social challenges of this disease. In recent studies, psychological indicators such as anxiety and depression, as well as physical symptoms such as pain and bowel dysfunction, were reported as negative predictors of QOL.[29] Management of these factors can increase QOL in patients. In the study carried out by Daghaghzadeh *et al*., psychological, physical, and social parts of quality of life were increased by Duloxetine. This was associated with a decrease in psychological and physical symptoms (anxiety and depression), but environmental QOL did not increase significantly.[19] In another study by Brennan *et al*., the quality of life in IBS patients who were treated with Duloxetine was also improved considerably.[22]

Another study on IBS patients that assessed the psychological and physical aspects of patients was conducted by Sharbafchi and colleagues in 2020. This study evaluated the venlafaxine for depression, anxiety, stress, gastrointestinal symptoms, and quality of life in 33 patients with IBS. By using 37.5 mg/day venlafaxine, it was stated that significant improvement in IBS symptoms was achieved. They also showed significant progression in depression, anxiety, stress, and quality of life compared to controls.[30] As a result, we believe that selective serotonin and norepinephrine reuptake inhibitor antidepressant (SSNRI) drugs including Duloxetine and venlafaxine could have significant effects on patients with IBS.

In the current study, physical, psychological, and social dimensions of QOL were not evaluated, and only the general QOL was assessed. Although this variable has been enhanced by Duloxetine, it is advisable to measure its promotion in each QOL dimension as well. It seems Duloxetine is effective in reducing stress and anxiety in such patients, as well as

having the most significant impact on the psychological aspect of patients' quality of life. Depression, anxiety, and stress as dimensions of psychological aspect showed significant reduction in study group from sixth week of intervention, eighth week of intervention, and tenth week of intervention, respectively. Moreover, the remarkable improvement appeared in QOL of study group subjects from eighth week of intervention. Although, this impact lasts for six months after intervention only for depression and stress.

However, although the long-term follow-up in the present study (within six months after the intervention) has been one of the strength points of the current research, one of the major limitations of this study is the lack of adequate sample size. Thus, it is suggested to do future studies with a larger sample size. In addition, it should be noted that no unexpected adverse events have been reported in this study, which should be considered by the other researchers.

Conclusion

Duloxetine is probably effective for psychological symptoms such as anxiety and stress and the severity of IBS symptoms. It also could increase QOL in patients. This drug may be a good augmentation for treating IBS.

Ethics approval and consent to participate

The current study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and the ethics committee of Isfahan University of Medical Sciences approved it (code: IR.MUI.REC.1396.3.752). It has been registered on the Iranian Registry of Clinical Trials with identifier Number (IRCT20190404043159N1). Afterward, we obtained the written informed consent from all subjects and randomly assigned them into two groups using randomized allocation.

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Conflicts of interest

There are no conflicts of interest.

References

1. Pazhouh HK, Hosseini SMA, Taghipour A, Hamedi S, Noras M. Anti-irritable bowel syndrome syrup improves constipation-predominant irritable bowel syndrome: A randomized, placebo-controlled trial. Chin J Integr Med 2020;26:729-35.
2. Solhpour A, Pourhoseingholi MA, Soltani F, Zarghi A, Solhpour A, Habibi M, *et al*. Gastro-oesophageal reflux disease and irritable bowel syndrome: A significant association in an Iranian population. Eur J Gastroenterology Hepatol 2008;20:719-25.
3. Lacy BE, Pimentel M, Brenner DM, Chey WD, Keefer LA, Long MD, *et al*. ACG clinical guideline: Management of irritable bowel syndrome. Am J Gastroenterol 2021;116:17-44.
4. Zeeshan MH, Vakkalagadda NP, Sree GS, Anne KK, Devi S, Parkash O, *et al*. Irritable bowel syndrome in adults: Prevalence and risk factors. Ann Med Surg (Lond) 2022;81:104408. eCollection 2022 Sep.
5. Sharbafchi MR, Tabatabaiyan S, Haghighatdoost F, Afshar H, Keshteli AH, Feizi A, *et al*. Personality traits are related to functional dyspepsia in a large sample of Iranian adults. J Psychosom Res 2020;129:109912. Epub 2019 Dec 27.
6. Pellissier S, Bonaz B. The place of stress and emotions in the irritable bowel syndrome. Vitam Horm 2017;103:327-54.
7. Söderquist F, Syk M, Just D, Kurbalija Novicic Z, Rasmusson AJ, Hellström PM, *et al*. A cross-sectional study of gastrointestinal symptoms, depressive symptoms and trait anxiety in young adults. BMC Psychiatry 2020;20:535.
8. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol 2016;1:133-46.
9. Xie C, Tang Y, Wang Y, Yu T, Wang Y, Jiang L, *et al*. Efficacy and safety of antidepressants for the treatment of irritable bowel syndrome: A meta-analysis. PLoS One 2015;10:e0127815.
10. Kwon OY, Park SP. Depression and anxiety in people with epilepsy. J Clin Neurol 2014;10:175-88.
11. Huybrechts KF, Bateman BT, Pawar A, Bessette LG, Mogun H, Levin R, *et al*. Maternal and fetal outcomes following exposure to duloxetine in pregnancy: Cohort study. BMJ 2020;368:m237.
12. Kaplan A, Franzen MD, Nickell PV, Ransom D, Lebovitz PJ. An open-label trial of duloxetine in patients with irritable bowel syndrome and comorbid generalized anxiety disorder. Int J Psychiatry Clin Pract 2014;18:11-5.
13. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: A simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997;11:395-402.
14. Organization WH. Process of translation and adaptation of instruments. Available from: http://www who int/substance_abuse/research_tools/translation/en/.2009.
15. Patrick DL, Drossman DA, Frederick IO, Dicesare J, Puder KL. Quality of life in persons with irritable bowel syndrome (development and validation of a new measure). Dig Dis Sci 1998;43:400-11.
16. Masaeli N, Kheirabadi GR, Afshar H, Daghaghzadeh H, Maracy MR, Assadolahi F, *et al*. Validity, reliability, and factor analysis of Persian version of quality of life questionnaire for irritable bowel syndrome (IBS-QOL-34). J Res Med Sci 2013;18:492-6.
17. Parkitny L, McAuley JH. The depression anxiety stress scale (DASS). J Physiother 2010;56:204.
18. Sahebi A, Asghari MJ, Salari RS. Validation of Depression Anxiety and Stress Scale (DASS-21) for an Iranian Population. Scientific Journal Management System 2005;1:36-54.
19. Daghaghzadeh H, Naji F, Afshar H, Sharbafchi MR, Feizi A, Maroufi M, *et al*. Efficacy of duloxetine add on in treatment of inflammatory bowel disease patients: A double-blind controlled study. J Res Med Sci 2015;20:595-601.
20. Lipkovich IA, Choy EH, Van Wambeke P, Deberdt W, Sagman D. Typology of patients with fibromyalgia: Cluster analysis of duloxetine study patients. BMC Musculoskeletal Disord 2014;15:450.
21. Lewis-Fernández R, Lam P, Lucak S, Galfalvy H, Jackson E, Fried J, *et al*. An open-label pilot study of duloxetine in patients with irritable bowel syndrome and comorbid major depressive disorder. J Clin Psychopharmacol 2016;36:710-5.
22. Brennan BP, Fogarty KV, Roberts JL, Reynolds KA, Pope HG Jr, Hudson JI. Duloxetine in the treatment of irritable bowel syndrome: An open-label pilot study. Hum Psychopharmacol 2009;24:423-8.
23. Ford AC, Talley NJ, Schoenfeld PS, Quigley EMM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: Systematic review and meta-analysis. Gut 2009;58:367-78.
24. Kułak-Bejda A, Bejda G, Waszkiewicz N. Antidepressants for irritable bowel syndrome—A systematic review. Pharmacol Rep 2017;69:1366-79.
25. Talley NJ, Kellow JE, Boyce P, Tennant C, Huskic S, Jones M. Antidepressant therapy (imipramine and citalopram) for irritable bowel

syndrome: A double-blind, randomized, placebo-controlled trial. Dig Dis Sci 2008;53:108-15.
26. Tack J, Broekaert D, Fischler B, Van Oudenhove L, Gevers AM, Janssens J. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. Gut 2006;55:1095-103.
27. Chen L, Ilham SJ, Feng B. Pharmacological approach for managing pain in irritable bowel syndrome: A review article. Anesth Pain Med 2017;7:e42747.
28. Halpert A, Dalton CB, Diamant NE, Toner BB, Hu Y, Morris CB, *et al*. Clinical response to tricyclic antidepressants in functional bowel disorders is not related to dosage. Am J Gastroenterol 2005;100:664-71.
29. Rochelle TL, Fidler H. The importance of illness perceptions, quality of life and psychological status in patients with ulcerative colitis and Crohn's disease. J Health Psychol 2013;18:972-83.
30. Sharbafchi MR, Afshar H, Adhamian P, Feizi A, Daghaghzadeh H, Adibi P. Effects of venlafaxine on gastrointestinal symptoms, depression, anxiety, stress, and quality of life in patients with the moderate-to-severe irritable bowel syndrome. J Res Med Sci 2020;25:115.