ORIGINAL ARTICLE

Effects of venlafaxine on gastrointestinal symptoms, depression, anxiety, stress, and quality of life in patients with the moderate-to-severe irritable bowel syndrome

Mohammad Reza Sharbafchi[1], Hamid Afshar[1], Pardis Adhamian[1], Awat Feizi[2], Hamed Daghaghzadeh[3,4], Peyman Adibi[5]

[1]Department of Psychiatry, Psychosomatic Research Center, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Biostatistics and Epidemiology, Psychosomatic Research Center, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Integrative Functional Gastroenterology Research Center, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Psychosomatic Research Center, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [5]Integrative Functional Gastroenterology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder which its treatment is still a question. According to the literature, the use of antidepressants is common for IBS, while its efficacy in this regard is controversial. This study has been raised to assess the efficacy of venlafaxine in IBS patients. **Materials and Methods:** In this double-blind, randomized clinical trial, 33 patients with moderate-to-severe IBS were included and randomly divided into two groups by using permuted block randomization process of size 4 for each block to receive Venlafaxine or placebo. Venlafaxine in 37.5 mg/day for 2 weeks, followed by 75 mg/day for the next 2 weeks and then 150 mg/day until the end of the study was prescribed. Gastrointestinal symptoms severity, depression, anxiety, stress as main, and quality of life (QoL) as the secondary outcomes were evaluated at the study initiation, within 2, 6, and 12 weeks after treatment and 3 months after intervention cessation. **Results:** The gastrointestinal symptoms severity, depression, anxiety, stress, and QoL scores significantly improved in patients who received Venlafaxine but not in placebo group; although after treatment discontinuation they experienced relapse ($P < 0.05$). Patients treated with venlafaxine experienced significant improvement in IBS symptoms, all three psychological disorders and QoL than placebo group ($P < 0.01$). The frequency of observed side effects in venlafaxine group including vomiting, nausea, and sleep disturbance was higher than placebo. **Conclusion:** Venlafaxine could be considered as an effective treatment for improving gastrointestinal symptoms severity, depression, anxiety, stress, and QoL of patients with IBS. Further studies with larger sample size and longer treatment duration are recommended.

Key words: Anxiety, depression, irritable bowel syndrome, quality of life, stress, venlafaxine

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INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder diagnosed based on classical characteristics of abdominal pain plus habitual bowel changes over at least 3 months without any presentation of gastrointestinal alarm signs.[1] Although the pathophysiology of IBS is still a question, it seems that alterations in gastrointestinal motility and sensations responses are responsible for the occurrence of it. This disorder poses significant morbidities and decrease in quality of life (QoL).[1,2]

IBS has different prevalence worldwide ranges from 5% to 20% in the general population. This disorder is more common among 30–50 years old females

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Address for correspondence: Dr. Pardis Adhamian, Department of Psychiatry, Psychosomatic Research Center, School of Medicine, Isfahan University of Medical Sciences, PO Box 81465-1148, Isfahan, Iran. E-mail: adh276@yahoo.com

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than males.[3] Approximately 12% of patients with gastrointestinal presentations referring to general clinics and up to 25% of patients referring to tertiary clinics have presentations of IBS.[4]

Based on the literature, not only IBS is considerably associated with psychological situations such as stress, anxiety, and depression but also these factors can precipitate IBS initiation, progression, and flares.[5]

The best treatment approach for IBS is still a question as numerous patients resenting from IBS are irresponsive to usual remedies, and this fact causes patients intolerance, several visits for achieving best treatment and poses a significant burden on the health-care system.[6]

Antidepressant drugs in addition to their mood effects have analgesic effects. Therefore, these remedies have been used widely for IBS patients, as they are influential in both psychological conditions (e.g., depression and anxiety) and chronic abdominal pain. Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been used widely previously, and various outcomes have been presented.[7,8]

Recently, a novel group of drugs known as serotonin-norepinephrine reuptake inhibitors (SNRIs) has opened a new window in treating approach of IBS, as the previous successful use of this class in chronic pain such as fibromyalgia.[9]

Venlafaxine is an SNRI with different chemical structure, approved for depression and anxiety disorders treatment. Mechanism of this drug is serotonin, norepinephrine, and dopamine re-absorption inhibition. The individualized feature of venlafaxine is its lacking of effect on muscarinic, nicotinic, histaminergic, or adrenergic receptors and also it does not influence monoamine oxidase enzyme. Thus, venlafaxine can act more targeted in comparison to other antidepressants. Venlafaxine has gastrointestinal absorption with 3.5 h half-life of itself and 9 h half-life for its metabolites.[10,11]

Venlafaxine has been found to be more effective in the treatment of depression, and anxiety than SSRIs and IBS is strongly in association with these psychiatric symptoms in the literature.[7] By considering the fact that patients resenting from IBS mention deterioration of their symptoms following anxiety, depressive state, and anxiety and also a limited number of studies assessed outcomes of venlafaxine use in the treatment of IBS; this study evaluated venlafaxine efficacy on symptom severity and psychiatric symptoms in IBS patients.

MATERIALS AND METHODS

Study design and participants

This study is a double-blinded randomized clinical-trial conducted on patients with a documented diagnosis of IBS based on Rome III criteria[12] and by a gastrointestinal specialist who referred to psychosomatic clinic affiliated to Isfahan University of Medical Science (IUMS) in 2017. It has been registered on the Iranian Registry of Clinical Trials with identifier Number (IRCT20181118041691N1).

The current study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the Ethics Committee of Isfahan University of Medical Sciences (code: 396262). All participants provided written informed consent.

Inclusion criteria were as followed: (1) age between 18 and 65 years old, (2) presence of moderate to severe IBS symptoms, (3) having at least educational level of writing and reading, (4) lacking major psychiatric disorder (e.g., depressive disorders, bipolar and related disorders or psychotic disorders) and presence of suicidal thoughts or plans, and (5) no history of the administration of antidepressant or anti-anxiolytic medications within 2 weeks prior to study initiation.

Exclusion criteria include diagnosis of any other disease that inhibits authors from continuing the study, patients' pregnancy or lactation and patient's reluctance of using medications and fulfilling questionnaires. Furthermore, the presence of venlafaxine side effects which needs to stop using this medication and the patient's unwillingness to continue this study were exclusion criteria.

A total of 123 individuals screened to find at least 30 eligible participants according to:

$$n_{1repeated} = R\left[\frac{2(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2} + \frac{z^2_{1-\alpha/2}}{4}\right]$$

$$R = \left[\frac{1+(w-1)p}{w}\right] - \frac{vp^2}{1+(v-1)p}$$

At the screening visit, after providing demographic data, subjects received a physical examination, liver function tests, electrocardiography, and urine pregnancy test to ensure that the results did not preclude involving in the study. Psychiatric diagnoses were obtained using the Structured Clinical Interview for DSM-V.[13]

After screening, 65 patients did not have our inclusion criteria and 24 patients refused to participate in the study finally 34 patients agreed to participate in our study. Eligible subjects were allocated in a 1:1 ratio into two groups using random allocation software according to permuted block randomization of size blocks with size 4. Randomization codes were generated in blocks of constant size four. The assignment to the RCT groups was conducted in a double-blind manner, in which none of the patients and investigators aware of the received treatments. The current study was conducted as a pilot one and we did not power analysis for sample size determination.

The first group (intervention group, 17 subjects) received venlafaxine, and the second group (control group, 16 subjects) received placebo. Three patients dropped out in the study process; one in venlafaxine group because of vomiting, and two in the control group because of unwillingness to continue the study [Figure 1].

Procedures and variables assessment

Venlafaxine was prescribed in 37.5 mg/day for 2 weeks, followed by 75 mg/day for the next 2 weeks and then 150 mg/day until the end of the study. Placebo drugs, which were similar to venlafaxine tablets in shape, color, and package, were used in the same pattern. Both groups received their medications for 3 months. Abidi[R] company, Iran, prepared venlafaxine, and School of Pharmacy and Pharmaceutical Sciences of IUMS prepared placebo.

Demographic data including age, gender, marital status, educational level, patient's occupation, physical activity, and smoking were recorded in the study checklist.

Clinical features of patients including main outcomes, i.e., the Gastrointestinal Symptom, (2) The IBS Severity, (3) Depression, Anxiety and Stress, and (4) QoL Questionnaire in IBS patients (IBS-QOL) as the secondary outcome were evaluated using following questionnaires.

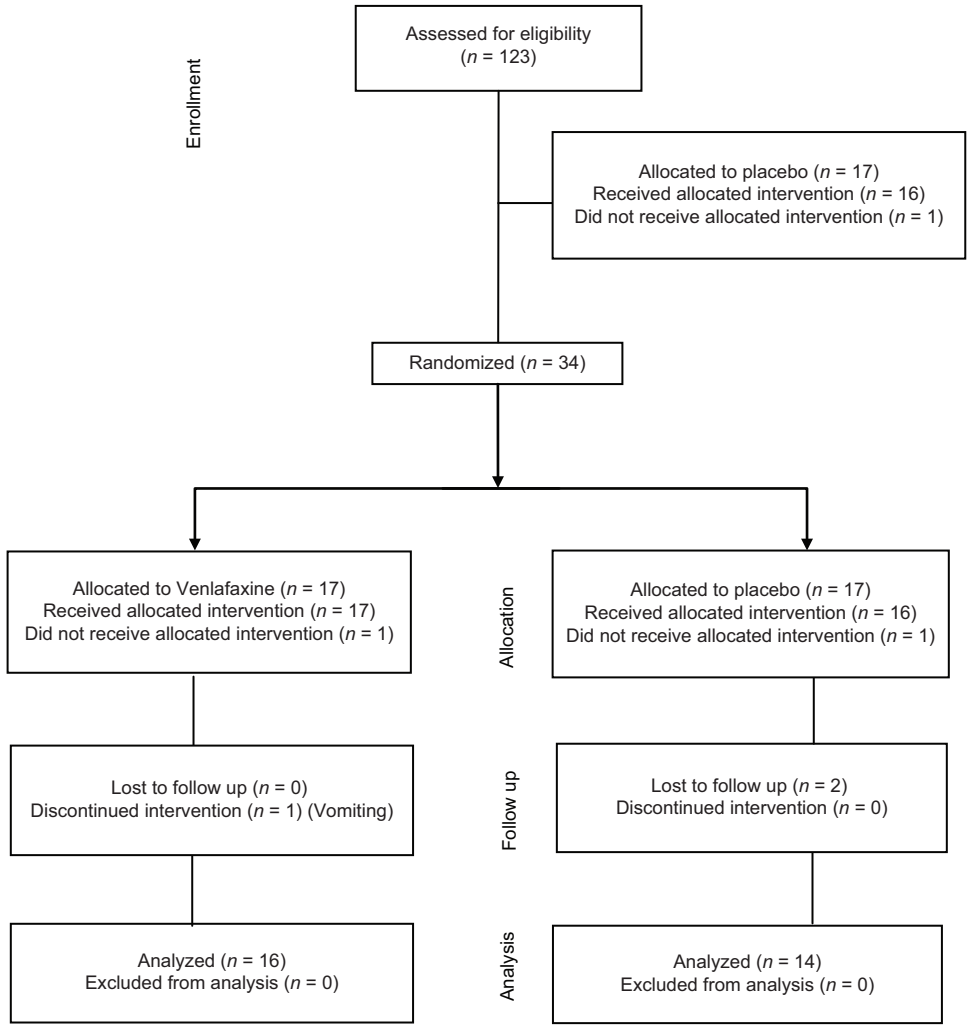

Figure 1: Consort diagram of the study population

For the assessment of all study outcomes, we used the Iranian validated version of questionnaires.

Study instruments

1. The Gastrointestinal Symptom Questionnaire consists of nine questions evaluating symptoms scoring 0–5 sorted based on the severity of symptoms from mild to severe. Questions were about the frequency of abdominal pain/discomfort, abdominal pain improvement after defecation, and association of frequency defecations with abdominal pain, an association of loose/hard stool with abdominal pain and frequency of having loose/hard stool during the past 3 past months. The validity and reliability of questionnaire have been assessed in the Iranian population[14]
2. IBSSS questionnaire consists of five parts evaluating IBS symptoms with visual analog scale (VAS). These symptoms include pain, impairments in defecations, the sensation of bloating, effects of disease on daily activity and extra-intestinal manifestations. Validity of the used questionnaire has been approved in Iranian patients population[15]
3. IBS-QOL is a questionnaire with 34 items that evaluate various entities of an IBS patient QoL. QoL analysis was performed reversely, thus means that higher scores are presenting a lower QoL.[16] The validity and reliability of IBS-QOL-34 has been approved in Iranian IBS patient's population. The reported value for total questions of questionnaire was 0.95 and for its subscales ranged from 0.65 to 90[17]
4. DASS questionnaire is a 42-item self-report instrument designed to measure three negative emotional statuses of depression, anxiety, and stress. Depression subscale of this scale evaluates dysphoria, hopelessness, devaluation of life, self-deprecation, and lack of interest/involvement, anhedonia, and inertia. Anxiety subtitle assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. Eventually, stress subtitle evaluates relaxing difficulty, nervous arousal, and being easily upset/agitated, irritable/over-reactive, and impatient. Scores for depression, anxiety, and stress were calculated, summing the scores of each subtitle. This reliability of Persian version of this questionnaire was evaluated in previous studies.[18] The Cronbach alpha for depression, anxiety, and stress scales were 0.85, 0.85, and 0.87, respectively. The test-retest period was 3 weeks. The intraclass correlation with absolute agreement between time 1 and time 2 assessment occasions for depression, anxiety, and stress scales was 0.77 (95% confidence interval [CI]: 0.56–0.88), 0.89 (95% CI: 0.81–0.94) and 0.85 (95% CI: 051–0.94), respectively.

Patient's follow-up

All patients were visited by a particular gastroenterologist and received IBS medications based on standard protocol and guidelines except psychotropic medications. All of the patients received diet consultations to avoid consumption of nutrition that is in correlation with symptoms exacerbation.

Before study initiation, within 2 and 6 weeks following treatment initiation and at the end of 3 months, patients referred to the clinic and were asked to complete all questionnaires. At the end of the study, medications were tapered for 2 weeks and then discontinued. Then, after 3 months from treatment cessation, patients were asked to refer again and answer questionnaires for the last time.

Statistical analysis

Quantitative and categorical data were presented as mean ± standard deviation and frequency (percentage), respectively. Normality of quantitative variables has been evaluated using the Kolmogorov–Smirnov test and Q-Q plot. Basic quantitative and categorical data between the two study groups were compared using independent samples *t*-test and Chi-square test, respectively. Repeated measures analysis of variance (ANOVA) used to evaluate the change over time in each study group and between groups. Mauchly's test of sphericity was used in assessing the compound symmetry assumption in repeated measure ANOVA and when it was not satisfied with the multivariate ANOVA . The data analysis was conducted in per-protocol approach. All statistical analysis was conducted using SPSS software version 15 (SPSS Inc., Chicago, USA).

RESULTS

Demographic data (age, gender, marital status, occupation, and physical activity) were not significantly different between two groups ($P > 0.05$) while the frequency of work shifts was significantly higher in the control group ($P = 0.04$) [Table 1].

Repeated measure ANOVA showed a statistically significant decrease in mean frequency of all IBS's symptoms, except pain relief by defecation, in venlafaxine group ($P < 0.001$) while no statistically significant changes were observed in the control group. At the end of the intervention, a significant difference was seen between two study groups in which the patients in venlafaxine experienced significantly lower frequency of IBS's symptoms, except pain relief by defecation. However, at the end of the follow-up period, i.e., at the end of 3 months from treatment cessation, the differences between two groups was disappeared and not statistically significant ($P > 0.05$), [Table 2].

In the IBSSS questionnaire, repeated measure ANOVA showed a statistically significant decrease in mean frequency of abdominal pain, abdominal distention, the satisfaction of defecation and impaired daily activity in venlafaxine

Table 1: Demographic data of participants in intervention and control groups

Variables	Intervention, *n* (%)	Control, *n* (%)	*P**
Age (years), mean±SD	37.68±9.70	36.75±6.93	0.64
Gender			
Male	2 (12.5)	2 (14.8)	0.62
Female	14 (87.5)	12 (83.2)	
Marital status			
Single	7 (43.8)	2 (14.3)	0.08
Married	8 (50)	12 (85.7)	
Widow	1 (6.2)	0 (0)	
Educational status (years)			
0-5	1 (6.3)	2 (14.3)	0.46
6-12	3 (18.8)	3 (21.4)	
>12	12 (74.9)	9 (64.3)	
Having job			
No	10 (62.5)	10 (71.4)	0.60
Yes	6 (37.5)	4 (28.6)	
Shift work			
Yes	0 (0)	5 (35.7)	0.04
No	16 (100)	9 (64.3)	
Physical activity			
Never	3 (18.8)	3 (21.4)	0.83
Sometimes	8 (50)	8 (57.1)	
Regular	5 (31.3)	3 (21.4)	

*Resulted from independent samples *t*-test and Chi-square for continuous and categorical data, respectively. Intervention: Venlafaxine. SD=Standard deviation

group ($P < 0.001$). In the control group, just abdominal distention showed a statistically significant decrease and no statistically significant changes were observed in other symptoms ($P > 0.05$). At the end of the intervention, a significant difference was seen between two study groups in which the patients in venlafaxine experienced significantly lower frequency symptoms ($P < 0.001$). At the end of the follow-up period, repeated measure tests showed a significant association between time and intervention ($P < 0.001$) [Table 3].

The mean score of stress, anxiety, and depression score decreased statistically significant during 3 months of treatment in venlafaxine group ($P < 0.001$). No statistically significant different were observed in the control group except the mean score of stress, which was significantly increased during 3 months of treatment ($P < 0.05$). At the end of the intervention, a significant difference was observed between two study groups in which the patients in venlafaxine experienced significantly more decrease in stress, depression, and anxiety ($P < 0.05$). The mean score of stress and depression in the 6th and 12th week after intervention and the mean score of anxiety in the 12th week after intervention initiation were significantly different between the two groups. Repeated measure test showed a significant correlation between time and intervention ($P < 0.001$) [Table 4].

The mean score of QoL significantly decreased (mean increasing in QoL) within the duration of treatment in venlafaxine group ($P < 0.05$), while no statistically significant changes were observed in the control group. Repeated measures ANOVA regarding the evaluation of the QoL changes showed a significant more improvement in venlafaxine group than patients in placebo group ($P < 0.001$) [Table 5].

The adverse effects of this study were as followed: nausea (50%; $n = 8$), headache (37.5%; $n = 6$), sleep disturbances (25%; $n = 4$), and vomiting (6.3%; $n = 1$) in intervention group and nausea (7.1%, $n = 1$) in placebo group. The incidence of nausea, sleep disturbance, and headache was significantly higher in the intervention group ($P < 0.05$) the incidence of vomiting was not significantly different between groups ($P = 0.34$).

DISCUSSION

In the current study, the efficacy and safety of venlafaxine on gastrointestinal, psychological and QoL of IBS patients were evaluated and its efficacy for symptoms and severity of IBS as well as depression, anxiety, and stress have been proved. It also demonstrated significant efficacy on improving of QOL of patients. Some adverse events have been observed more in patients treated with venlafaxine than placebo, need to be highlighted.

Evidence in literature has presented a satisfactory clinical improvement of IBS utilizing antidepressant remedies. A meta-analysis conducted by Ford *et al*. showed that the prescription of antidepressants caused IBS symptoms reduction independent of the effects of these medications on anxiety, depression, and sensory-motor functions.[8] In two other meta-analysis conducted by Ford *et al*. in 2009 and 2018, IBS symptoms improved using antidepressants. They concluded in both studies that use of these remedies was accompanied with improvement of mood disorders and after that IBS symptom. It is notifying that both studies recommended further studies considering the better quality of evidence.[19,20]

Another study on IBS patients that evaluated the effect of citalopram, imipramine, and placebo on improving IBS symptoms, reported that neither citalopram nor imipramine was superior to placebo and each other. These results may have been achieved because of a small number of population members follow-up.[21] Further studies considering the use of SSRI remedies presented uncertain outcomes. Studies of Vahedi *et al*.[22] and Tack *et al*.[23] demonstrated moderate improvement of IBS while two other studies performed by Kuiken *et al*. about the use of Fluoxetine,[24] and Talley *et al*.[25] about the citalopram showed no positive effect.

Table 2: Gastrointestinal symptoms of participants in intervention and control groups

		Study follow up points							
	Group	Baseline	Within 2 weeks	Within 6 weeks	Within 12 weeks	Within 3 months after treatment cessation	P_{time}*	$P_{time\times group}$*	P_{group}*
Frequency of abdominal pain or discomfort	Intervention	5.81±1.42	5.62±1.71	4.31±1.25	3.87±0.96	5.25±1.18	0.001	<0.001	0.99
	Control	5.00±1.47	5.00±1.47	5.00±1.47	4.93±1.54	4.93±1.54	0.34		
	*P***	0.09	0.16	0.26	0.03	0.45			
Pain relief by defecation	Intervention	2.57±0.85	2.57±0.85	2.57±0.85	2.64±0.93	2.57±0.85	0.23	0.34	0.59
	Control	2.50±1.09	2.50±0.89	2.93±0.85	3.12±0.96	2.69±0.95	0.34		
	*P***	0.64	0.86	0.20	0.15	0.77			
Onset of pain in association with increased stool frequency	Intervention	2.75±1.69	2.94±1.34	1.56±0.89	1.31±0.48	2.69±1.35	<0.001	<0.001	0.83
	Control	2.21±1.19	2.21±1.19	2.14±1.10	2.14±1.03	2.14±1.03	0.40		
	*P***	0.43	0.13	0.12	0.01	0.28			
Onset of pain in association with decreased stool frequency	Intervention	2.25±1.24	3.25±1.00	1.56±0.51	1.56±0.63	2.37±0.96	<0.001	<0.001	0.91
	Control	2±0.91	2.23±1.01	2.38±1.12	2.31±1.03	2.23±1.01	0.23		
	*P***	0.71	0.01	0.03	0.03	0.62			
Onset of pain in association with looser stool	Intervention	2.56±1.55	2.94±1.29	1.31±0.60	1.25±0.44	2.62±1.31	0.002	0.001	0.42
	Control	2.50±1.34	2.50±1.34	2.43±1.28	2.43±1.22	2.43±1.22	0.40		
	*P***	0.91	0.30	0.003	0.001	0.66			
Onset of pain in association with firmer stool	Intervention	1.75±0.93	3.12±0.96	1.62±0.50	1.50±0.51	2.37±0.88	<0.001	<0.001	0.60
	Control	2.07±0.92	2.21±1.05	2.36±1.15	2.28±1.07	2.14±0.95	0.43		
	*P***	0.27	0.02	0.07	0.03	0.45			
Hard stool frequency	Intervention	2.13±1.19	3.53±0.83	2.13±0.64	1.53±0.52	2.53±1.06	<0.001	<0.001	0.45
	Control	2.57±1.02	2.57±1.16	2.71±1.07	2.64±1.01	2.57±1.02	0.64		
	*P***	0.32	0.04	0.10	0.005	0.93			
Watery stool frequency	Intervention	2.57±1.50	2.78±0.80	1.36±0.50	1.36±0.50	1.43±0.51	0.001	<0.001	0.11
	Control	2.50±1.02	2.50±1.02	2.43±1.02	2.43±1.02	1.86±0.86	0.17		
	*P***	0.86	0.93	0.002	0.002	0.57			

**P*-values resulted from repeated measures ANOVA, Intervention: Venlafaxine; **Resulted from independent samples *t*-test

Table 3: The severity of irritable bowel syndrome symptoms in intervention and control groups

		Study follow up points							
Symptom	Group	Baseline	Within 2 weeks	Within 6 weeks	Within 12 weeks	3 months after treatment cessation	P_{time}*	$P_{time\times group}$*	P_{group}*
Abdominal pain	Intervention	57.50±28.63	56.87±30.71	31.87±18.34	25.01±12.65	52.5±21.13	<0.001	<0.001	0.002
	Control	43.64±16.89	47.27±20.04	42.73±17.37	41.66±16.96	41.66±17.49	0.47		
	*P***	0.10	0.30	0.04	0.01	0.10			
Abdominal distension	Intervention	75.33±18.85	69.33±21.54	40±11.95	30.01±16.90	64.67±9.90	<0.001	<0.001	<0.001
	Control	70.77±19.35	69.46±24.30	67.92±24.89	63.78±27.10	63.78±26.81	0.008		
	*P***	0.38	0.98	0.002	0.001	0.63			
Bowel habit satisfaction	Intervention	66.87±25.75	65.62±30.10	34.62±17.76	28.75±11.47	60.62±19.48	<0.001	<0.001	<0.001
	Control	70.71±16.40	71.43±17.03	69.28±15.91	65.42±24.18	60.71±20.18	0.55		
	*P***	0.91	0.95	<0.001	<0.001	0.98			
Discomfort related to daily life	Intervention	80±23.66	76.87±27.01	44.50±15.27	35.01±18.97	66.25±22.47	<0.001	<0.001	<0.001
	Control	56.43±5.60	57.85±25.17	55±24.42	55.01±24.10	56.43±24.68	0.42		
	*P***	0.01	0.04	0.15	0.01	0.29			

**P*-values resulted from repeated measures ANOVA, Intervention: Venlafaxine; **Resulted from independent samples *t*-test

SNRIs are among newer antidepressants that limited studies about the administration of this group for the treatment of IBS have been performed previously. In a pilot study about the use of duloxetine, a member of SNRI drugs, in patients with concurrent IBS and anxiety disorders, acceptable outcomes were achieved.[26] Duloxetine was also shown to be useful for reducing depression, anxiety, and severity of physical symptoms and increasing the physical, psychological, and social QoL in patients with inflammatory bowel disease.[27]

Studies in the literature about the use of venlafaxine are mostly about its effect on pain control besides studies about

Table 4: The mean score of stress, anxiety, and depression in intervention and control groups

Symptom	Group	Baseline	Within 2 weeks	Within 6 weeks	Within 12 weeks	3 months after treatment cessation	P_{time}*	$P_{time\times group}$*	P_{group}*
Stress	Intervention	17.06±5.07	17.01±4.56	9.62±1.96	9.73±4.18	17.37±3.87	<0.001	<0.001	0.05
	Control	16.86±5.33	16.71±5.45	16.93±5.28	16.92±5.28	17.21±5.22	<0.001		
	*P***	0.85	0.72	<0.001	<0.001	0.93			
Anxiety	Intervention	14.56±5.04	13.43±4.44	9.87±2.27	9.53±3.96	12.87±4.19	0.007	0.002	<0.001
	Control	12.50±4.16	12.71±3.99	12.29±4.25	12.71±4.84	12.43±4.20	0.33		
	*P***	0.31	0.86	0.13	0.02	0.86			
Depression	Intervention	15.18±6.47	13.37±5.52	7.80±1.04	8.73±5.36	13.12±3.79	<0.001	<0.001	0.05
	Control	14.86±5.64	14.86±5.64	14.50±5.85	14.64±6.07	14.78±5.66	0.40		
	*P***	0.96	0.41	<0.001	<0.001	0.46			

**P*-values resulted from repeated measures ANOVA; ***Resulted from independent samples *t*-test , Intervention: Venlafaxine

Table 5: The mean score of quality of life in intervention and control groups

Quality of life score	Group	Baseline, mean±SD	After 2 weeks, mean±SD	After 6 weeks	After 12 weeks, mean±SD	3 months after treatment cessation, mean±SD	P_{time}*	$P_{time\times group}$*	P_{group}*
	Intervention	90.50±31.56	87.12±30.05	55.19±13.10	54.87±24.67	85.31±26.08	0.003	0.001	<0.001
	Control	85.86±28.21	85.93±28.24	85.01±27.66	84.28±28.20	85.28±28.23	0.17		
	P#	0.67	0.93	0.001	0.001	>0.99			

**P*-values resulted from repeated measures ANOVA; #Resulted from independent samples *t*-test, Intervention: Venlafaxine. SD=Standard deviation

its efficacy in managing psychiatric disorders. Studies in this regard have shown that chronic pain, neuropathic ones, in particular, can be acceptably controlled using venlafaxine.[28] Furthermore, the use of venlafaxine for the treatment of fibromyalgia was accompanied by successful outcomes.[29] Further studies administered this remedy for chronic pain control in patients resenting from concurrent depression.[10] Considering the results of mentioned studies favorable of venlafaxine use for chronic pain control made this hypothesis that this drug may be useful in pain control of patients resenting from IBS.[10,11]

Furthermore, the use of venlafaxine among healthy individuals showed that venlafaxine prescription was accompanied with altered colon tonicity and activity lead to reduces defecation sensation during colon relaxations.[30] Outcomes of this study may indicate the possibility of venlafaxine use among those with diarrhea-dominant IBS. It should be mentioned that in the research of Van Kerkhoven *et al*. on functional dyspepsia, venlafaxine was not superior to placebo.[11]

CONCLUSION

In this study, the frequency of the patient's pain has not changed among members of the intervention group, while its severity reduced significantly. This reduction in severity can improve other aspects such as QoL, depression, and anxiety. Of the strength points of this study are its novelty and also, we assessed our patients for 3 further months after treatment discontinuation. Notably, we found that by the discontinuation of venlafaxine treatment, patients complained from their symptoms that have been presented before study initiation. This fact may strongly have confirmed that venlafaxine use in the treatment of IBS was accompanied by acceptable outcomes. On the other hand, it should be mentioned that symptoms return following venlafaxine treatment cessation means a requirement of another efficient remedy rather than venlafaxine that preserves its effect for a longer duration or further continuing of venlafaxine.

One of the limitations of this is its small sample size and short duration of follow-up that restricts us for generalizing it to the IBS patients' population. Venlafaxine could be considered as an effective treatment for improving gastrointestinal symptoms severity, depression, anxiety, stress, and QoL of patients with IBS. Further studies with larger sample size and longer treatment duration are recommended.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. Gastroenterology 2002;123:2108-31.

2. Sharbafchi MR, Afshar H, Hassanzadeh-Keshteli A, Roohafza H, Daghaghzadeh H, Salehi M, *et al*. Comparison of stress profiles among individuals with and without functional dyspepsia. Int J Body Mind Culture 2016;3:46-54.
3. 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 Gastroenterol Hepatol 2008;20:719-25.
4. Jamieson DJ, Steege JF. The prevalence of dysmenorrhea, dyspareunia, pelvic pain, and irritable bowel syndrome in primary care practices. Obstet Gynecol 1996;87:55-8.
5. North CS, Hong BA, Alpers DH. Relationship of functional gastrointestinal disorders and psychiatric disorders: Implications for treatment. World J Gastroenterol 2007;13:2020-7.
6. Moayyedi P, Ford AC, Quigley EM, Foxx-Orenstein AE, Chey WD, Talley NJ, *et al*. The American College of Gastroenterology irritable bowel syndrome monograph: Translating systematic review data to clinical practice. Gastroenterology 2010;138:789-91.
7. Dekel R, Drossman DA, Sperber AD. The use of psychotropic drugs in irritable bowel syndrome. Expert Opin Investig Drugs 2013;22:329-39.
8. Ford AC, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, *et al*. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: Systematic review and meta-analysis. Am J Gastroenterol 2014;109:1350-65.
9. Gilron I, Chaparro LE, Tu D, Holden RR, Milev R, Towheed T, *et al*. Combination of pregabalin with duloxetine for fibromyalgia: A randomized controlled trial. Pain 2016;157:1532-40.
10. Barkin RL, Barkin S. The role of venlafaxine and duloxetine in the treatment of depression with decremental changes in somatic symptoms of pain, chronic pain, and the pharmacokinetics and clinical considerations of duloxetine pharmacotherapy. Am J Ther 2005;12:431-8.
11. van Kerkhoven LA, Laheij RJ, Aparicio N, De Boer WA, Van den Hazel S, Tan AC, *et al*. Effect of the antidepressant venlafaxine in functional dyspepsia: A randomized, double-blind, placebo-controlled trial. Clin Gastroenterol Hepatol 2008;6:746-52.
12. Koloski N, Jones M, Young M, Talley N. Differentiation of functional constipation and constipation predominant irritable bowel syndrome based on Rome III criteria: A population-based study. Aliment Pharmacol Ther 2015;41:856-66.
13. Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: Classification and criteria changes. World Psychiatry 2013;12:92-8.
14. Adibi P, Keshteli AH, Esmaillzadeh A, Afshar H, Roohafza H, Bagherian-Sararoudi R, *et al*. The study on the epidemiology of psychological, alimentary health and nutrition (SEPAHAN): Overview of methodology. J Res Med Sci 2012;17:S291-7.
15. 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.
16. Drossman DA, Patrick DL, Whitehead WE, Toner BB, Diamant NE, Hu Y, *et al*. Further validation of the IBS-QOL: A disease-specific quality-of-life questionnaire. Am J Gastroenterol 2000;95:999-1007.
17. 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.
18. Asghari A, Saed F, Dibajnia P. Psychometric properties of the Depression Anxiety Stress Scales-21 (DASS-21) in a non-clinical Iranian sample. Int J Psychol 2008;2:82-102.
19. Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: Systematic review and meta-analysis. Gut 2009;58:367-78.
20. Ford AC, Lacy BE, Harris LA, Quigley EMM, Moayyedi P. Effect of Antidepressants and Psychological Therapies in Irritable Bowel Syndrome: An updated systematic review and meta-analysis. Am J Gastroenterol 2019;114:21-39.
21. Kilkens TO, Honig A, Fekkes D, Brummer RJ. The effects of an acute serotonergic challenge on brain-gut responses in irritable bowel syndrome patients and controls. Aliment Pharmacol Ther 2005;22:865-74.
22. Vahedi H, Merat S, Rashidioon A, Ghoddoosi A, Malekzadeh R. The effect of fluoxetine in patients with pain and constipation-predominant irritable bowel syndrome: A double-blind randomized-controlled study. Aliment Pharmacol Ther 2005;22:381-5.
23. 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.
24. Kuiken SD, Tytgat GN, Boeckxstaens GE. The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable bowel syndrome: A double blind, randomized, placebo-controlled study. Clin Gastroenterol Hepatol 2003;1:219-28.
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. 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.
27. 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.
28. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev 2007 oct 17;(4): CD005454.
29. Zijlstra T, Barendregt P, van De Laar M, editors. Venlafaxine in fibromyalgia: Results of a randomized, placebo-controlled, double-blind trial. Wiley-Liss DIV John Wiley and Sons INC, 605 third AVE, NEW YORK, NY 10158-0012 USA: Arthritis and Rheumatism; 2002.
30. Chial HJ, Camilleri M, Ferber I, Delgado-Aros S, Burton D, McKinzie S, *et al*. Effects of venlafaxine, buspirone, and placebo on colonic sensorimotor functions in healthy humans. Clin Gastroenterol Hepatol 2003;1:211-8.