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

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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

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.
than males.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[9]}

The best treatment approach for IBS is still a question as numerous patients resenting from IBS are unresponsive 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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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\textsuperscript{[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:

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

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

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.\textsuperscript{[13]}

\[ \text{IRCT20181118041691N1} \]**
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 were aware of the received treatments. The current study was conducted as a pilot one and we did not perform the 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\textsuperscript{b} 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](image-url)
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.

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.

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. 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.

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. 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: 0.51–0.94), 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
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 was evaluated using antidepressants. 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.

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.

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. Further studies considering the use of SSRI remedies presented uncertain outcomes. Studies of Vahedi et al. and Tack et al. demonstrated moderate improvement of IBS while two other studies performed by Kuiken et al. about the use of Fluoxetine and Talley et al. about the citalopram showed no positive effect.
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. 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

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### 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<sub>time</sub> | P<sub>time×group</sub> | P<sub>group</sub> |
|------------------------|-------|----------|----------------|----------------|-----------------|------------------------------------------|-----------|----------------|----------------|
| Frequency of abdominal pain or discomfort | Intervention | 5.8±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 | 1.3±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** | 0.71 | 0.01 | 0.03 | 0.03 | 0.62 | | | | |
| 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±0.56 | <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<sub>time</sub> | P<sub>time×group</sub> | P<sub>group</sub> |
|------------------------|---------|-------|----------|----------------|----------------|-----------------|------------------------------------------|-----------|----------------|----------------|
| 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 | <0.001 | | | | |
| 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

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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 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. [29] Outcomes of this study may indicate the possibility of venlafaxine use among those with diarrhea-dominant IBS. It should be mentioned that symptoms return following venlafaxine treatment cessation, depression, anxiety, stress, and QoL of patients with IBS. Further studies with larger sample size and longer treatment duration are recommended.

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.

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