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Original Article

Comparing the Effect of Aripiprazole with Nortriptyline on Severity of Irritable Bowel Syndrome

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ABSTRACT

Background:
Neuropsychiatric factors play important roles in symptoms of irritable bowel syndrome (IBS). Mood disorders such as bipolar disorder are prevalent among patients with IBS. Antidepressants are used traditionally for management of IBS symptoms but antibipolar agents have not been studied. Aripiprazole, an antibipolar agent, was selected because of having the least anticholinergic side effects.

Materials and Methods:
147 patients with diagnosis of IBS were included in the study. Randomly selected 74 patients took nortriptyline 10 mg/day and 73 patients received aripiprazole 5 mg/day. Birmingham IBS Symptom Questionnaire for assessing the severity of IBS symptoms and Mood Disorder Questionnaire for diagnosis of bipolar mood disorder were filled by all the patients in the base time and then by 52 and 41 patients in month 1 and 40 and 28 patients in month 3, respectively. Two groups and subgroups of bipolar and non-bipolar disorders were compared in regard to the severity of IBS during follow-up visits.

Results:
Decreases in mean scores were significant in both aripiprazole and nortriptyline groups during follow-up visits, but comparing the groups, the changes were more in aripiprazole group compared with nortriptyline group, although the differences were not significant ($p > 0.05$). The decrease in mean score was significant in both bipolar and non-bipolar subgroups during the follow-up visits, but the changes were only significant in bipolar subgroup of aripiprazole group ($p < 0.05$).

Conclusion:
Overall, aripiprazole has the same efficacy of nortriptyline in decreasing IBS symptoms but it is significantly more efficient in subgroup of patients with bipolar disorder. More and larger studies are needed for confirming the results of this study.

Keywords: Aripiprazole, Nortriptyline, Irritable bowel syndrome, Bipolar disorder

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INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder, which presents with chronic abdominal pain or discomfort in association with changed bowel habit and disorder in defecation (1). IBS is diagnosed after ruling out the causes of organic diseases in developing symptoms. The affected patients have symptoms such as abdominal pain or discomfort, diarrhea, frequent loose stool, constipation, need to strain to pass stool, incomplete defecation, rectal mucus discharge, abdominal pain or discomfort after eating, urgency, and

improving abdominal pain after defecation (2,3). IBS is classified to the following subtypes:

1. IBS with predominant constipation, which the patient usually has constipation.
2. IBS with predominant diarrhea, which patient usually has diarrhea.
3. IBS with mixed bowel habits, which patient has both constipation and diarrhea (more than one-fourth of all abnormal bowel movements have constipation and more than one-fourth have diarrhea).
4. IBS unclassified, which cannot be accurately categorized into the above subtypes.

IBS is a common disease. The overall prevalence is 11.5% (4). Neuropsychiatric factors play an important role in IBS symptoms (5-7). Chronic stress is associated with the onset or exacerbation of symptoms and non-pharmacological and pharmacological interventions targeted on stress-related alterations, such as antidepressants, antipsychotics, 5-Hydroxytryptamine (5-HT) synthesis inhibitors, selective 5-HT reuptake inhibitors, and specific 5-HT receptor antagonists or agonists have shown a major role in IBS management (8,9). In a study, researchers observed that patients with IBS had increased mood disorders, anxiety, phobia, and somatization. They concluded that psychiatric assessment and treatment might be useful in the course of IBS (10). Mood disorders are prevalent in IBS. Many patients with IBS are hypertalkative, hyperactive, and irritable. They have elevated mood, and decreased concentration. They are also more self-confident and more social and outgoing, the symptoms that indicate bipolar disorder. In a study in Taiwan, 4689 patients with IBS and 18756 participants as controls were followed up for 5.92 and 5.94 years, separately from 2000 to 2008. The incidence rate for depressive disorder (4.70 vs. 1.74 per 1,000 person-years, respectively), anxiety disorder (4.00 vs. 1.39 per 1,000 person-years, respectively), sleep disorder (2.94 vs. 1.19 per 1,000 person-years, respectively), and bipolar disorder (0.32 vs. 0.13 per 1,000 person-years, respectively) were all significantly higher in the patients with IBS than in the comparison cohort (depressive disorder: risk ratio [RR] = 2.70, 95% confidence interval [CI] = 2.28 – 3.19; anxiety disorder: RR = 2.88, 95% CI = 2.40 – 3.46; sleep disorder: RR = 2.01, 95% CI = 1.73 – 2.34; bipolar disorder: RR = 2.44, 95% CI = 1.25 – 4.61). In this study the risks of mood disorders were higher in patients with IBS than the controls and the increase in hazard ratios (HR) in bipolar disorder (HR = 2.44) was similar to depressive disorder (HR = 2.71) (11). Antidepressants are used traditionally for the management of IBS symptoms but antibipolar agents have not been studied. A small randomized controlled trial (RCT) was done using the combination of citalopram and olanzapine in patients with IBS. Although significant improvement in IBS symptoms and a trend toward better results in combination therapy compared with placebo were observed, no significant difference was observed between the intervention and placebo groups (12). We decided to investigate the effects of antibipolar drugs on IBS symptoms. Aripiprazole, an antibipolar agent, was selected because of having the least anticholinergic side effects and that it can be prescribed in patients with constipation (13). Aripiprazole is one of the second-generation antipsychotics, also known as atypical antipsychotics that have lower extrapyramidal side effects and tardive dyskinesia compared with first-generation antipsychotics such as haloperidol. It partially blocks post-synaptic brain dopamine D2 receptors and blocks or has partial agonist activity at muscarinic, alpha-adrenergic, and histaminic 1 receptors, with resultant anticholinergic, hypotensive, sedative, and metabolic side effects. This agent is used for the management of bipolar I disorder and as adjunctive to antidepressants for depression disorder. However pharmacokinetics of this drug is complex and differs from patient to patient. The present study was aimed to compare the effect of aripiprazole with nortriptyline on severity of IBS.

MATERIALS AND METHODS

This is a prospective randomized controlled trial carried out in Isfahan, Iran. The protocol of the study was registered at the "Iranian Registry of Clinical Trials" center (IRCT ID: IRCT2017012227682N1). Ethics Committee of Isfahan University of Medical Sciences (Ethic code: IR.MUI.REC.1395.4.068), Poursina Hakim Research Center and Medical Students' Research Committee (Project code: 195163) approved the protocol of the study.

The study was done among 210 consecutive

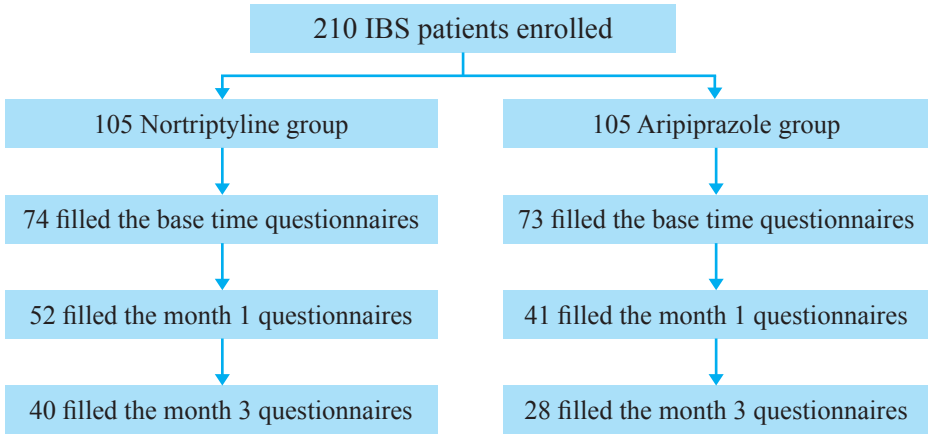

Fig. 1: Flowchart of questionnaires

patients with IBS who were enrolled in the study in 2017 and were randomly assigned to receive nortriptyline (105) or aripiprazole (105). 74 and 73 patients of the both groups participated in the study after obtaining written informed consents, respectively.

Inclusion criteria were all patients with the diagnosis of IBS by gastroenterologists based on Rome IV Diagnostic Criteria for IBS who came to either Poursina Hakim Clinic or a gastroenterologist office in Isfahan, Iran.

Exclusion criteria were patients with major depression and severe bipolar disorder who needed specific psychological treatments and patients who consumed psychotropic drugs. The exclusion of patients with major depression or diagnosis of the severity of bipolar disorder were done clinically by the psychiatrist in the clinic after referring all the patients enrolled in the study to her. Ten patients with major depressive and two patients with severe bipolar disorders were excluded from the study after consulting with the psychiatrist.

After obtaining written informed consents, 74 randomly selected patients received nortriptyline 10 mg/day and 73 received aripiprazole 5 mg/day. Baseline data were recorded and self-administered and validated Birmingham IBS Symptom Questionnaire for assessing the severity of IBS symptoms (14) and the Mood Disorder Questionnaire (MDQ) for diagnosis of bipolar mood disorder (15,16) were filled by all patients. The Birmingham IBS Symptom Questionnaire includes 11 questions about discomfort or pain in abdomen, troubling with loose, mushy, or watery bowel motions, diarrhea, troubling with hard bowel motions, need to strain to pass stool, troubling with constipation, pain, or discomfort in abdomen after eating, abdominal pain preventing from sleeping or awaking during the night, leaking or soiling him/herself, urgency, passing mucus or slime in stools, over the last 4 weeks in six scales of symptoms severity from none, a little, some, a good bit, most, and all the time and the scales in the analysis were scored from 0 to 5, respectively.

MDQ includes 15 questions about bipolar symptoms and a criteria for diagnosing the presence or absence of mild, moderate, or severe bipolar disorder. We also evaluated the general satisfaction of patients in all follow-up visits in five scales; very bad, bad, moderate, good, and very good with scoring 1 to 5, respectively.

In the second follow-up, 1 month later, the questionnaires were again filled by the patients and if the response to the drugs were unsatisfied, the doses of noritriptyline and aripiprazole increased to 25 mg and 10 mg, respectively. The third follow-up was 3 months after the initial visit, with filling the questionnaires (Figure 1).

After collecting data and entering to SPSS software, descriptive and analytical analyses were done in manners of intention to treat analysis (ITTA) and per protocol analysis (PPA) using descriptive analysis and Fisher's exact, Chi-square, paired and independent t tests and the groups of patients on nortriptyline and aripiprazole as well as subgroups with bipolar and non-bipolar disorders were compared

Table 1: Baseline data of patients

Variables		Nortriptyline (N = 52)	Aripiprazole (N = 41)	*P* value
Sex	Male N (%)	29 (55.8%)	17 (41.5%)	0.17
	Female N (٪)	23 (44.2%)	24 (58.5%)	
Age (year)		38.52 ± 10.425	39.95 ± 8.994	0.48
Education	Under high school diploma N (٪)	10 (20.4%)	13 (34.2%)	0.19
	High school diploma N (٪)	21 (42.9%)	17 (44.7%)	
	Bachelor and higher N (٪)	18 (36.7%)	8 (21.1%)	
Smoking habit	Yes N (%)	5(10.0%)	3 (8.3%)	0.79
	No N (%)	45 (90.0%)	33 (91.7%)	
Alcohol Use	Yes N (%)	3 (6.0%)	0 (0.0%)	0.26
	No N (%)	47 (94.0%)	36 (100.0%)	
Underlying diseases	Yes N (%)	25 (48.1%)	25 (61.0%)	0.21
	No N (%)	27 (51.9%)	16 (39.0%)	
Drug use	Yes N (%)	26 (50.0%)	21 (51.2%)	0.90
	No N (%)	26 (50.0%)	20 (48.8%)	

Table 2: Comparing nortriptyline and aripiprazole groups based on the Birmingham IBS Symptom score in follow-ups

Type of analysis	Group	Number	Base time (mean score ± SD)	Month 1 (mean score ± SD)	Month 3 (mean score ± SD)
ITTA	Nortriptyline	52	24.44 ± 9	16.79 ± 6.74	11.63 ± 7.23
	Aripiprazole	41	23.56 ± 10.80	15.34 ± 6.93	9.43 ± 6.04
	P value	-	0.66	0.31	0.19
PPA	Nortriptyline	40	24.38 ± 9.22	16.80 ± 7.06	11.36 ± 7.23
	Aripiprazole	28	23.14 ± 12.09	14.46 ± 7.08	9.43 ± 6.04
	P value	-	0.63	0.18	0.19

ITTA: Intention to treat analysis, PPA: Per protocol analysis

in regard to the severity of IBS in the follow-ups. The level of significance was set at $p < 0.05$.

RESULT

Of the 147 patients, 74 received nortriptyline and 73 received aripiprazole. 52 and 41 patients of the both groups referred for the second follow-up and 40 and 28 patients referred for the third follow up, respectively. The major reasons for loss to follow ups in 34 patients that we could contact them, were discontinuing the drugs because of the fear of psychological agents in nine vs. five patients in aripiprazole group compared with nortriptyline group and ineffective drugs for symptoms improvement (two vs. eight), respectively. Other reasons were drugs side effects (one vs. seven) and not believing in drug efficacy (one vs. one), respectively.

Baseline data of patients are presented in table 1. In nortriptyline and aripiprazole groups 55.8% and 44.2%, and 41.5% and 48.5% were men and women, respectively. The mean age of the patients in nortriptyline and aripiprazole groups were 38.52 ± 10.425 and 39.95 ± 8.994 years, respectively. The patients were matched in terms of sex, age, education, smoking habits, alcohol use, underlying diseases, and drug use.

Two groups of nortriptyline and aripiprazole were compared based on the Birmingham IBS Symptom score in cross-sectional times at follow-ups using ITTA and PPA (table 2). No significant differences were seen ($p > 0.05$).

In the next step, two groups of nortriptyline and aripiprazole were compared based on the changes in the Birmingham IBS Symptom score and the changes

Table 3: Comparing nortriptyline and aripiprazole groups based on the changes in the Birmingham IBS Symptom score and changes percent in follow-ups

Type of analysis	Group	Number	Diff = IBS1-IBS0* (mean score ± SD)	*P* value	Change percent	Effect size	Diff = IBS3-IBS0** (mean score ± SD)	*P* value	Change percent	Effect size
ITTA	Nortriptyline	52	-7.65 ± 6.17	< 0.001	-31%	0.96	-12.81 ± 7.56	< 0.001	-52%	1.56
	Aripiprazole	41	-8.21 ± 10.07	< 0.001	-34%	0.90	-14.31 ± 12.57	< 0.001	-60%	1.61
	P value	-	0.74	-	-	-	0.69	-	-	-
PPA	Nortriptyline	40	-7.57 ± 5.93	< 0.001	-31%	0.92	-12.75 ± 7.56	< 0.001	-52%	1.53
	Aripiprazole	28	-8.67 ± 11.31	< 0.001	-37%	0.87	-13.71 ± 12.57	< 0.001	-59%	1.43
	P value	-	0.63	-	-	-	0.71	-	-	-

ITTA: Intention to treat analysis, PPA: Per protocol analysis
* Diff = IBS1-IBS0: mean score in the month 1 – mean score in the base time
**Diff = IBS3-IBS0: mean score in the month 3 – mean score in the base time

Table 4: General satisfaction of nortriptyline and aripiprazole groups based on the Birmingham IBS Symptom score in the follow-ups

Type of analysis	Group	Number	Base time (mean score ± SD)	Month 1 (mean score ± SD)	Month 3 (mean score ± SD)	*P* value
ITTA	Nortriptyline	52	2.81 ± .90	3.29 ± 0.84	3.60 ± .81	< 0.001
	Aripiprazole	41	2.46 ± 1	3.34 ± 1.08	3.79 ± 1.03	< 0.001
	P value	-	0.08	0.79	0.40	-
PPA	Nortriptyline	40	2.95 ± .84	3.40 ± 0.81	3.60 ± .81	< 0.001
	Aripiprazole	28	2.39 ± 1.06	3.32 ± 1.12	3.79 ± 1.03	< 0.001
	P value	-	0.025	0.47	0.22	-

ITTA: Intention to treat analysis, PPA: Per protocol analysis

percent during follow-ups using ITTA and PPA (table 3). The decreases in mean scores were significant in both groups during follow-ups, but the changes were more in aripiprazole group compared with nortriptyline group, although the differences were not significant ($p > 0.05$). In PPA, the changes percent were -31% vs -37%, from the base time to month 1, in nortriptyline and aripiprazole groups, respectively. These values were -52% vs. 59%, respectively from the base time to month 3. The effect sizes were more than 0.8 in both groups.

The general satisfaction of patients in nortriptyline and aripiprazole groups were assessed using ITTA and PPA based on the Birmingham IBS Symptom score in follow-ups (table 4). The increases in scores (more satisfying) were seen significant in both groups during follow-ups ($P < 0.05$). No significant differences were seen between the groups in months 1 and 3 ($p > 0.05$).

Nortriptyline and aripiprazole groups were divided in two subgroups in regard to having bipolar disorder (BPD) or non-bipolar disorder (non-BPD). 29 out of 147 patients had BPD (19.7%) and 118 had non-BPD (80.3 %). Then the subgroups in each nortriptyline and aripiprazole groups were compared based on the changes of Birmingham IBS Symptom score and the changes percent in follow-ups using ITTA and PPA (table 5). The decrease in mean scores were significant in both BPD and non-BPD subgroups during follow-ups ($p < 0.05$), but comparing them the changes were more and significant only in BPD subgroup of aripiprazole group ($p < 0.05$). In PPA, the changes percent toward the decrease in scores were obviously more in BPD compared with non-BPD subgroups of aripiprazole group from the base time to month 1 (-58% vs. -17%, respectively) and from the base time to month 3 (-77% vs. -42%, respectively). The effect sizes were more than 0.8 in both groups.

DISCUSSION

The case and control groups were match in terms of confounding factors include sex, age, education, smoking habit, alcohol use, underlying diseases, and drug use. Although the exact effects of these factors in IBS have not yet been studied, some data indicate that

Table 5: Comparing the subgroups of BPD and non-BPD of nortriptyline and aripiprazole groups based on the changes in the Birmingham IBS Symptoms scores and changes percent in follow-ups

Type of analysis	Group	Subgroups	Number in month 1	Diff = IBS1-IBS0* (mean score)	*P* value	Change percent	Effect size	Number in month 3	Diff = IBS3-IBS0** (mean score)	*P* value	Change percent	Effect size
ITTA	Nortriptyline	BPD	9	-9.33 ± 7.01	0.004	-42%	1.11	6	-17.33 ± 7.14	< 0.001	-52%	1.62
		Non-BPD	43	-7.30 ± 6.01	< 0.001	-31%	0.94	34	-11.94 ± 7.44	< 0.001	-52%	1.55
	P value	-		0.37	-				0.10	-		
	Aripiprazole	BPD	13	-17.69 ± 12.26	< 0.001	-56%	1.77	10	-24.13 ± 14.40	< 0.001	-77%	2.51
		Non-BPD	28	-3.82 ± 4.48	< 0.001	-19%	0.80	18	-9.28 ± 5.89	< 0.001	-46%	1.30
	P value	-		0.002	-				0.005	-		
PPA	Nortriptyline	BPD	6	-11.83 ± 6.21	0.005	-37%	1.49	6	-17.33 ± 7.14	0.002	-55%	1.99
		Non-BPD	34	-6.82 ± 5.64	< 0.001	-29%	.85	34	-11.94 ± 7.44	< 0.001	-51%	s1.48
	P value	-		0.055	-				0.10	-		
	Aripiprazole	BPD	10	-18.50 ± 13.43	0.002	-58%	1.79	10	-24.50 ± 14.40	< 0.001	-77%	2.46
		Non-BPD	18	-3.22 ± 4.41	0.007	-17%	0.80	18	-7.72 ± 5.89	< 0.001	-42%	1.01
	P value	-		0.006	-				0.005	-		

ITTA: Intention to treat analysis, PPA: Per protocol analysis, BPD: Bipolar disorder, Non-BPD: Non-bipolar disorder
* Diff=IBS1-IBS0: mean score in the month 1 – mean score in the base time
**Diff=IBS3-IBS0: mean score in the month 3 – mean score in the base time

these factors may play roles in IBS symptoms. For example smoking and alcohol use may play role in developing or symptoms exacerbation of IBS (17-19).

According to our results, patients who received aripiprazole had overall more effects albeit non-significant on decreasing IBS symptoms than nortriptyline. After 3 months about 59% and 52% decreases in IBS symptoms were observed, respectively and both of them had more general satisfaction from treatment during 3 months. In a study it has been observed that patients with IBS compared with placebo using low dose tricyclic antidepressants, had improvement in abdominal pain in 54% versus 37% (Number Need to Treat (NNT) = 5), global assessment (59% vs. 39%, NNT = 4) and symptom score (53% vs. 26%, NNT = 4) (20). Interestingly, in our study patients in BPD subgroups receiving aripiprazole responded significantly to the drug compared with those in non-BPD and 77% and 42% decrease in their IBS symptoms were observed, respectively. About 20% of our patients had BPD. Thus, the major effect of aripiprazole on IBS symptoms belonged to BPD subgroup of patients with IBS. However aripiprazole had significant decreasing effects on IBS symptoms in patients with non-BPD.

This is the first study indicated the significant efficacy of aripiprazole on improving IBS symptoms. The mechanism by which aripiprazole can affect IBS symptoms is unknown. In many studies tricyclic antidepressants (TCA) have made improvement in IBS symptoms such as abdominal pain and pooled relative risk of 1.93 for clinical improvement with TCA therapy and odds ratio was 4.2 (21-23). Some studies have shown that the effects of TCA on IBS symptoms may be attributed to the analgesic properties of TCA independent of their mood effects (24), but this pathophysiology has not yet been proven. The role of neuropsychiatric factors in IBS has been taken into consideration. The brain-gut axis points that gut content and enteric neuromuscular apparatus as well as neural and psychological factors such as behavior and cognition are involved in causing IBS symptoms (5-7). The gastrointestinal receptors transmit signals via afferent neural pathways to the dorsal horn of the spinal cord and from them to the brain. Patients with IBS have increased visceral hypersensitivity. It has not been elucidated that the increased colonic sensitivity is due to receptor hypersensitivity, cerebral cortical activity, or psychological tendency to report pain and urgency (25-28). The role of psychological factors in inducing or exacerbating IBS has been the subject of many studies. Chronic stress is associated with the onset and exacerbation of symptoms of IBS and non-pharmacological and pharmacological interventions

targeted on stress-related alterations, such as antidepressants, antipsychotics, 5-HT synthesis inhibitors, selective 5-HT reuptake inhibitors, and specific 5-HT receptor antagonists or agonists have shown a major role in IBS management (8,9). In a study the patients with IBS had increased mood disorders compared with the controls and the increase in hazard ratios in bipolar disorder (HR = 2.44) was similar to depressive disorder (HR = 2.71) (10,11). In our study the BPD was prevalent and about 20%. The effects of aripiprazole as an antibipolar agent on IBS is suspected to be due to inhibitory effects on the brain-gut axis, but it is not known in which level the drug exerts its efficacy. Aripiprazole partially block dopamine D2 receptors and blocks or has partial agonist activity at muscarinic, alpha-adrenergic, and histaminic 1 receptors. These receptors are located in the central and peripheral nervous system and many organs include muscles, vessels, heart, and lungs. This can be the subject of research in the future.

TCAs have relatively common side effects most known as anticholinergic activity of drugs such as dry mouth, blurry vision, constipation, urinary retention, cognitive and/or memory impairment, increased body temperature, drowsiness, anxiety, sexual dysfunction, weakness, nausea and vomiting, hypotension, tachycardia, and rarely, irregular heart rhythms (29,30). Because many of patients with IBS have constipation or alternate constipation and diarrhea, the anticholinergic effects of TCAs make problems in the management of these patients due to exacerbation of constipation. On the other hand antidepressants alone should not be prescribed in bipolar disorder, as they have mood-elevating effect and there are concerns about switching patients from depression to mania/ hypomania and induction of rapid cycling (31,32). Based on our study, aripiprazole is a suitable drug for management of patients with IBS. It has mildly better efficacy on improvement of IBS symptoms compared with nortriptyline and has significant efficacy on IBS symptoms in bipolar subgroup of patients with IBS. On the other hand aripiprazole has the least anticholinergic side effects (13) and can be prescribed in patients with constipation or mixed bowel habits. More and larger studies are needed for confirming the results of this study.

CONCLUSION

Overall, aripiprazole has the same efficacy of nortriptyline in decreasing IBS symptoms but it is significantly more efficient in subgroup of patients with bipolar disorder. Aripiprazole is a suitable drug for more studies because of lower anticholinergic side effects in patients with IBS especially in predominant constipation or mixed bowel habits and if confirmed, probable substituting to Nortriptyline, as our study showed better efficacy in bipolar subgroups of IBS. More and larger studies are needed for confirming the results of this study.

Contributions:

Dr. Hojjatollah Rahimi- conception and design, acquisition of data, interpretation of data, literature review and preparing manuscript (corresponding author)

Dr. Mohammad hasan Emami- conception and design

Dr. Emad Fayyazi- acquisition of data

Dr. Niloofar Sadat Mirdamadi- acquisition of data

Dr. Rana Gharahkhani- acquisition of data

Dr. Omid Mirmosayyeb- literature review

Dr. Alireza Fahim- acquisition of data

Dr. Maryam Poorbafrani- psychiatrist, patients' consultant, conception and design, acquisition of data

Mrs. Najmeh Tavakol- analysis and interpretation of data

Dr. Mehdi Serati- acquisition of data

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CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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