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ORIGINAL ARTICLE

Comparison of the potency of nortriptyline and mirtazapine on gastrointestinal symptoms, the level of anxiety and depression in patients with functional dyspepsia

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ABSTRACT

Aim: In the current clinical trial study, the potency of mirtazapine and nortriptyline was compared in patients with Functional Dyspepsia (FD) who had anxiety or depression.

Background: FD usually accompanies other psychosocial disorders. According to previous studies, among these disorders, anxiety and depression have the most correlation.

Methods: This randomized clinical trial was organized in Taleghani hospital (Tehran, Iran). In two parallel groups, 42 patients were treated for 12 weeks, with 22 patients receiving 7.5 mg of mirtazapine and 20 patients receiving 25 mg of nortriptyline per day. To gain robust results, the patients with a positive history of antidepressant therapy, organic diseases, alcohol abuse, pregnancy, and major psychiatric disorders were excluded from the study. The subjects were examined by three questionnaires, including Nepean and Hamilton questionnaires. The patients were asked to answer the questions three times during the study: once before the onset of the treatment, second during the treatment, and third at the end of the treatment.

Results: Based on Gastrointestinal (GI) manifestations, mirtazapine, in comparison to nortriptyline could significantly suppress the signs and symptoms of FD, including epigastric pains (P=0.02), belching (P=0.004), and bloating (P=0.01). Although the results from the use of mirtazapine compared to the use of nortriptyline (P=0.002) showed a lower mean depression score on the Hamilton questionnaire, no significant differences were found between the effects of these drugs on the anxiety scale of patients (P=0.091).

Conclusion: Mirtazapine is more effective for GI symptoms related to gastric emptying. Considering the level of anxiety, mirtazapine, compared to nortriptyline, revealed better outcomes in FD patients suffering from depression.

Keywords: Functional dyspepsia (FD), Depression, Anxiety, Mirtazapine, Nortriptyline.

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Introduction

Functional dyspepsia (FD) is characterized by epigastric pain or discomfort without organic diseases (1). Although FD is not numbered as a life-threatening dysfunction, it causes a huge burden on the healthcare system (2). According to previous studies, the burden of this disease has been estimated at $18 million per year. This prevalence is about 21% worldwide (1). Furthermore, the disorder exhibits periodic characteristics, making it impossible to find an absolute cure for it (3). The prevalence of FD in the Iranian population has been estimated about 3-30%.

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Additionally, epidemiological studies with a large population in Iran have revealed a high prevalence of anxiety and depression in Iranian patients with FD (4). Recently, the correlation between FD and psychosocial issues has become bold. Several concomitant psychosocial issues in FD patients have been introduced, among which anxiety and depression are included as the most common psychosocial stressors associated with FD (5).

The usual accepted first-line treatments for FD include the eradication of Helicobacter Pylori and anti-acid agents such as PPIs and prokinetics. Recently, detecting the accompaniments of psychosocial issues in FD patients shows the role of antidepressant agents in treating FD has been shown (6). Several studies emphasized that synchronous psychotherapy and routine medical treatments could boost the outcome in these patients (1). Tricyclic antidepressants (TCAs) and tetracycline agents are two main antidepressant groups widely noticed in this field. TCAs suppress the pain and discomfort of FD cases by inhibiting the reuptake of serotonergic and noradrenaline transmissions. Tetracycline agents such as mirtazapine cause better fundus relaxants that reduce the discomfort caused by FD and result in better food tolerance. However, the results of the studies are conflicting. In a small Japanese study, amitriptyline as a TCA agent could not improve FD patients. Another multicenter study in a population of children and a small single-center study on adults represented no benefits of TCAs in FD cases (7). Furthermore, a limited number of studies compared the potency of these drugs with each other (8). Herein, it is attempted to estimate the potency of mirtazapine and nortriptyline on patients who suffered from FD and presented psychiatric issues, including anxiety and depression. Also, the researcher managed to compare these two drugs to reduce the gastrointestinal and psychiatric manifestations of the patients.

Methods

Study overview

Through the collaboration of the psychiatric and gastroenterology departments of Taleghani Hospital, this single-center randomized clinical trial has been organized. In the herein study, the effectiveness of two drugs, namely, mirtazapine and nortriptyline, were evaluated in two separate parallel groups for 12 weeks.

Moreover, the impact of both drugs on patients suffering from FD was compared to each other regarding GI symptoms, anxiety, and depression improvements. The study commenced on February 2019, with the last patient randomized on 10th November 2019. Ultimately, the study ended within the first week of February 2020. No changes in the results of trials were made. All authors had access to the study data. Therefore, they all reviewed and approved the final manuscript.

Subject and study design

The target population of the study consisted of adult patients with an age range of 18-70 years old. The patients suffered from FD as indicated by the Rome IV criteria administrated in the gastrointestinal clinic of Taleghani hospital. Also, FD was diagnosed from an interview at the baseline visit. If the patient had no history of upper GI Endoscopy in the last five years, he/she could participate in the study. The inclusion criteria were: the educational level of at least a diploma degree, the ability to participate actively in answering the questionnaires, no history of antidepressant treatments, absence of esophagitis or peptic ulcer or other organic diseases related to the digestive system, alcohol abuse, pregnancy, and no major systemic diseases or any major mental disorders. The exclusion criteria included: the occurrence of severe drug side effects and unwillingness to continue participating in the project. Eventually, 43 participants were included in the study. The 42 participants who suffered from FD were randomly divided into two groups.

Procedure

The study was conducted by allocating two doses of the chosen drugs to the patients. Thus, 23 patients were randomly administered 7.5 mg of daily mirtazapine, and 20 other patients were administered with 25 mg of daily nortriptyline. In addition to receiving mirtazapine and nortriptyline, all patients were also treated with domperidone and esomeprazole. The treatments for each group continued for three months uninterruptedly. Moreover, the participants were examined by three questionnaires: the Nepean and the Hamilton questionnaires. The patients were asked to answer the questions three times during the period of the study; once before the onset of the treatment, second, during the treatment (six weeks after starting the treatment),

and third, at the end of the treatment (12 weeks after starting the treatment).

2) Common drug side effects include sedation, drowsiness, and dry mouth. The improvement of GI symptoms was evaluated with the Nepean questionnaire. Simultaneously, the anxiety and depression of the patients were evaluated with Hamilton questionnaires. Furthermore, each of the important GI symptoms, including abdominal pain, epigastric pain, retrosternal burning, bloating, nausea, vomiting, and belching, were evaluated before, during, and after treatment in each group. It is worth noting that all patients adhered to the intention-to-treat method all through the treatment.

Definition

All patients were selected according to Rome IV criteria. According to the criteria, the FD definition includes all of the following:

1- Sense of solid and/or liquid foods sticking, lodging, or passing abnormally through the esophagus.
2- A sensation of abnormal transit in the absence of esophageal mucosal or structural abnormalities.
3- Absence of evidence that gastroesophageal reflux or eosinophilic esophagitis is the cause of the symptom.
4- Absence of major esophageal motor disorders. Not only must the patient present three months of symptoms during six months, but also, other organic disorders should be ruled out.

Evaluation of anxiety and depression

The following study, anxiety, and depression were determined with the Hamilton rating scale. Hamilton Rating Scale for Anxiety (HRSA) is a clinical, self-scored questionnairethat evaluates anxious mood, tension, fears, insomnia, depressed mood, somatic features, intellectual parameters, and sensory items. Other factors evaluated by the scale are cardiovascular, gastrointestinal, genitourinary, and autoimmune factors, and observed behavior. According to the questionnaire, scores higher than 17 are considered mild anxiety, scores between 25-30 are considered moderate anxiety, and scores above 30 are categorized as severe anxiety.

Evaluation of gastrointestinal symptoms

Nepean Dyspepsia Index (NDI) was used to calculate the quality of life in patients who suffer from FD. The questionnaire comprises five components: interference, knowledge/control, eating/drinking, sleep disturbance, and work/study. The questionnaire ranges from 0-100. In addition to NDI, the gastrointestinal symptoms were evaluated by a questionnaire designed by the researcher. The researcher-designed questionnaire assessed eight indexes: epigastric pain, dysphagia, retrosternal burning, vomiting, nausea, belching, and bloating. These indexes have been scaled from 0-3, with 0 indicating null; 1 indicating mild; 2 indicating moderate, and 3 indicating severe.

Ethical considerations

After explaining the study procedure and objectives to the patients, they were asked to provide written consent. Also, the study received ethical approval from the ethics committee of Shahid Beheshti University of Medical Sciences (ethic code: IR.SBMU.MSP.REC.1398.246). Each questionnaire was completed individually and independently by each participant. IRCT code: IRCT20190312043036N2

Statistical analysis

Statistical analyses were performed using simple randomization of all subjects. One-way Repeated Measures and the Friedman test were used to investigate the effects of gastrointestinal symptoms along with some anxiety and depression measures during the time in patients with FD. In the Repeated Measures design, Mauchly's test was used to examine the sphericity assumption. According to the estimated Epsilon, the Huynh-Feldt statistics should be used if the assumption scored more than 0.75. Otherwise, the Greenhouse Geisser would be implemented. Comparisons of the effects of mirtazapine and nortriptyline on gastrointestinal symptoms and anxiety measures within 3 months were made by independent samples t-test and Mann-Whitney U test.

In addition, baseline measurements for the Hamilton anxiety rating scale (HAM-A), Hamilton rating scale for depression (HRSD), and Nepean dyspepsia index (NDI) were considered confounders; while measurements three months after that were considered as responses. Ultimately, comparing mean demographic characteristics including sex (male and female), age (<30, 31-40, 41-50, 51-60,

and >61), and level of education (illiterate, elementary, diploma, higher diploma, bachelors, and masters) were performed by Analysis of Covariance. The significance level was considered to be 5% in all analyses. All analyses of the study were performed using R version 3.6.3 software.

Results

Eventually, the study enjoyed 42 participants who followed the treatments until the end of the third month. The participants were divided based on the type of drugs they received through the research. 22 participants were assigned to the nortriptyline arm, and 20 patients were assigned to the mirtazapine group. The patients in the nortriptyline arm consisted of 14 females and 8 males. Conversely, the mirtazapine arm included 16 female and 4 male participants. The mean age of patients who participated in the study was 40.19±12.43.

The impact of nortriptyline and mirtazapine on GI symptoms

The impact(s) of mirtazapine (7.5 mg) and nortriptyline (25 mg) were individually estimated on each GI symptom (vomiting, nausea, retrosternal pain, epigastric pain, dysphagia, bloating, and belching). The results gained from the researcher-designed questionnaire revealed that after three months, mirtazapine could significantly suppress retrosternal pain (P=0.001), epigastric pain (P<0.001), dysphagia (P=0.004), bloating (P<0.001), and belching (P<0.001). Equally, nortriptyline significantly decreased the prevalence of retrosternal pain (P0.020), nausea (P<0.001), epigastric pain (P<0.001), and dysphagia (P<0.001) after 12 weeks of treatment. On the next step, the impact of these drugs on each of the mentioned GI manifestations was compared with each other. It was found that mirtazapine compared to nortriptyline, had a significantly better effect on reducing epigastric pain (P=0.020), belching (P=0.004),

Table 1. The statistical analysis of depression, anxiety, and gastrointestinal symptoms of FD patients treated with nortriptyline or mirtazapine.

Indexes	Group	Mean	STD
HRSA1*	Mirtazapine	26.60	12.91
	Nortriptyline	32.27	6.37
HRSA2*	Mirtazapine	21.72	13.47
	Nortriptyline	24.31	5.29
HRSA3*	Mirtazapine	19.10	11.57
	Nortriptyline	24.82	5.72
HRSD1**	Mirtazapine	18.35	5.95
	Nortriptyline	24.23	4.92
HRSD2**	Mirtazapine	14.47	7.73
	Nortriptyline	19.04	5.83
HRSD3**	Mirtazapine	12.55	7.76
	Nortriptyline	19.68	5.69
NDI1***	Mirtazapine	25.97	8.36
	Nortriptyline	26.00	3.37
NDI2***	Mirtazapine	20.13	9.39
	Nortriptyline	19.40	3.85
NDI3***	Mirtazapine	18.40	9.34
	Nortriptyline	20.65	4.52

*HRSA: Hamilton Rating Scale Anxiety, **HRSD: Hamilton Rating Scale Depression, ***NDI: Nepean Dyspepsia Index.

Table 2. The comparison between the efficacy of mirtazapine and nortriptyline therapy among patients with Functional Dyspepsia (FD) diagnosis.

Index	(I) Time	(J) Time	Mean Difference (I-J)	P-value****
HRSA*	3	1	-7.47	0.001
	3	2	-1.06	0.200
HRSD**	3	1	-5.17	0.001
	3	2	-0.64	0.48
NDI ***	3	1	-6.45	0.001
	3	2	-0.23	1.000

* HRSA: Hamilton Rating Scale Anxiety, **HRSD: Hamilton Rating Scale Depression, ***NDI: Nepean Dyspepsia Index, ****P value < 0.05 is significant.

and bloating (P=0.01). On the other hand, nortriptyline was more effective than mirtazapine in reducing nausea after three months of treatment (P<0.001).

According to the Nepean scoring scale, mirtazapine is more effective at improving gastrointestinal signs than nortriptyline. At the onset of treatment, the score of gastrointestinal features of FD (according to the Nepean scoring scale) was 26±3.37. But, after six weeks, a significant improvement was observed in the gastrointestinal features of the patients (P=0.001). In addition, at the end of the three-month treatment, Nepean Score declined to 20.65±4.52. Treatment with 12 weeks of mirtazapine led to significant differences compared to baseline and six weeks of therapy (P=0.000 and 0.004, respectively). Before therapy onset, the Nepean score of the nortriptyline group was

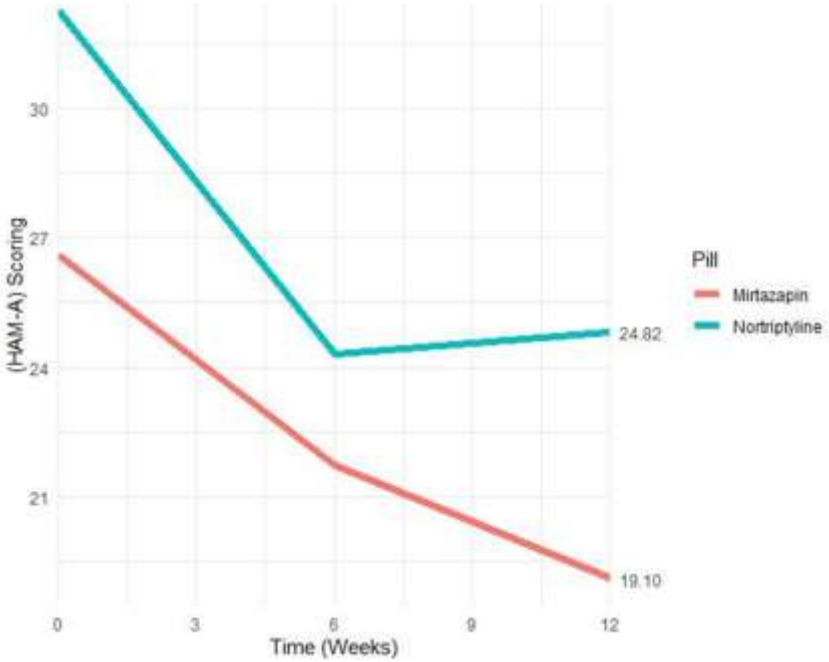

Figure 1. Hamilton anxiety rating getting smaller during the time by following the patients over 12 weeks.

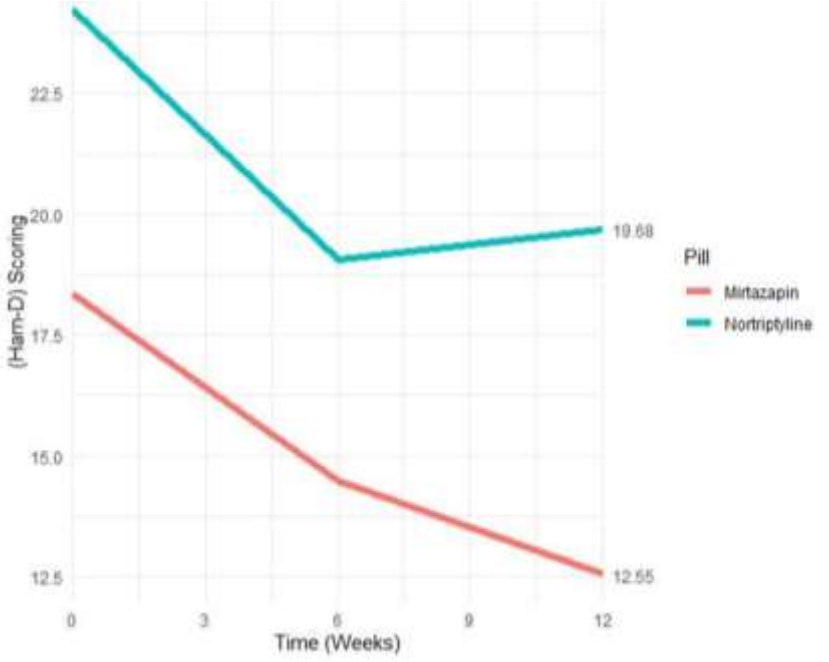

Figure 2. Hamilton depression rating getting smaller during the time by following the patients over 12 weeks.

about 26.00±3.37. But, after 12 weeks of treatment, it reached 20.65±4.52 (Table 1). The data analysis on the value of the treatment across different times demonstrated significant improvements in GI features after 3 months (P<0.001) and 1.5 months of receiving nortriptyline (P<0.001).

Furthermore, the three months of mirtazapine therapy compared to 12 weeks of nortriptyline treatment revealed more significant outcomes (P<0.001) (Table 2). However, after six weeks of treatment, mirtazapine showed no better efficacy than six weeks of nortriptyline therapy (P=1.000) (Table 2) (Figure 1).

The impact of nortriptyline and mirtazapine on depression

The effects of receiving 7.5 mg of mirtazapine and 25 mg of nortriptyline and their potency in decreasing the depression presentation in FD patients, were individually evaluated and compared. Before the onset of the treatment, the mean score of depression in the mirtazapine group was calculated as 18.35±5.95. After 12 weeks, the results were better, such that the score of depression reached 12.55±7.76. Based on the results, 12 weeks of treatment, compared to baseline, improved the depression score (P=0.002). In the nortriptyline arm, the baseline depression score was estimated as 24.23±4.92; in the middle of therapy, it dropped to 19.04±5.83; and after three months of drug receiving, it increased to 19.68±5.69. The obtained results show that both completed treatments (P<0.01) and the six-week treatments (P<0.01) led to significant developments in the parameters of depression. The results at the end of the treatment revealed that mirtazapine with the lower mean score led to better results than nortriptyline (P=0.002) (Figure 2).

The impact of nortriptyline and mirtazapine on anxiety

In the mirtazapine group, the baseline anxiety score was 26.61±12.91. After 12 weeks of treatment, this number declined to 19.1±11.57, indicating that this therapy could significantly reduce anxiety among patients suffering from FD (P=0.02). However, in our study population, mirtazapine was ineffective in reducing anxiety after six weeks of treatment (P=0.11). In the nortriptyline group, the mean anxiety score was 32.27±6.37. Also, after completing the treatment period, the mean anxiety score declined to 24.82±5.72. The six weeks of treatment (P<0.010) and 12 weeks of therapy (P<0.010) resulted in a significant reduction in the anxiety score compared to the baseline values. There were no differences between 12 weeks (three months) of treatment and six weeks of treatment with

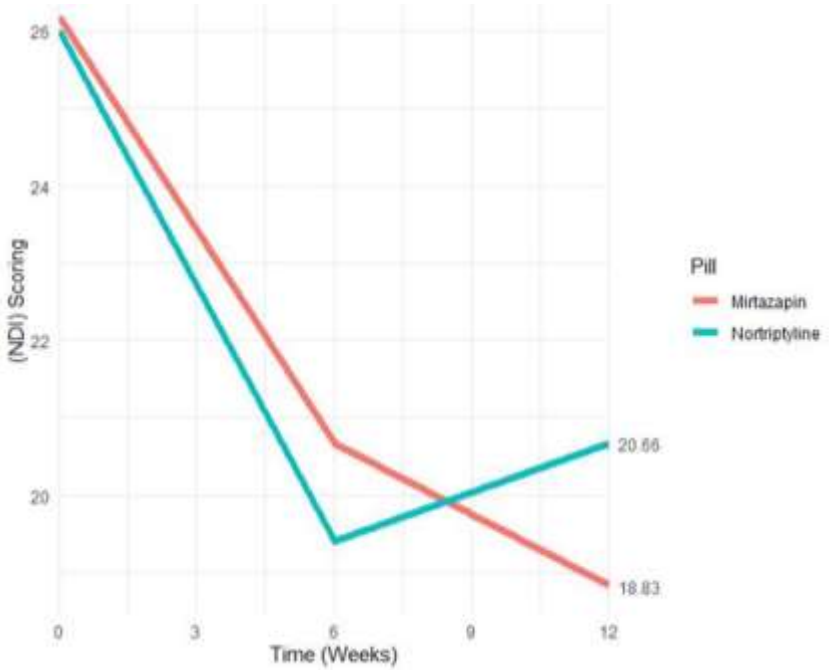

Figure 3. Nepean dyspepsia index rating getting smaller during the time by following the patients over 12 weeks.

nortriptyline (P=1.000). Finally, the potency of these two drugs was compared between the two arms during the study period. Surprisingly, there are no significant differences between the potential effects of these drugs on the anxiety scale of patients with FD (P=0.091) (Figure 3).

The effect of demographic factors in the course of treatment

During the treatment, the role of age and gender were analyzed individually for each group. Data analysis showed that age (P=0.520) and gender (P=0.220) differences did not affect the gastrointestinal symptoms in the nortriptyline arm (Table 3). The only outcome found was the significant effect of gender on the level of anxiety (P=0.020) in the mirtazapine group. It seems that female patients affected by anxiety respond significantly better to treatments with mirtazapine. However, no significant effects of age (P=0.970) or gender (0.400) were detected on gastrointestinal symptoms in the mirtazapine group (Table 3).

Discussion

In the current study, the potency of receiving 7.5 mg of daily mirtazapine and 25 mg of nortriptyline was evaluated in two separate groups for three months. Then, their impacts were determined and compared to each other. According to results, mirtazapine compared to nortriptyline could more significantly reduce bloating, belching, and epigastric pain. Also, based on the Nepean scoring scale, which was used to evaluate gastrointestinal symptoms, mirtazapine was more effective than nortriptyline. Furthermore, depression was significantly reduced by both therapies in the study population. However, it appears that mirtazapine was more effective. Although both of these treatments effectively improved the "anxiety" outcomes, no significant difference was observed between the potency of these drugs on anxiety reduction.

Compared to peptic ulcer, functional dyspepsia has a poorer outcome as the psychosocial triggers have a major role in FD cases (5). The accompanying depression and anxiety in functional dyspepsia leads to a decrease in quality of life (5, 9, 10). The anti-acid agents and prokinetics are considered the first-line treatments of FD. Patients who have hyperacidity in duodenum have received more benefit from PPIs. But, the main issue is that hyperacidity has been found only in a small group of patients with FD (11). Due to the simultaneous psychosocial stressors in patients with FD, the role of antidepressants in FD treatment has become notable. The pathophysiology of the antidepressants' role in FD symptoms is yet unclear (12). However, some factors are likely to be responsible for their effectiveness which is as follows:

1. These drugs could reduce psychosocial issues, including anxiety and depression.
2. The agents affect the brain-gut axis and modulate sensation, motility, and food tolerance.
3. The drugs have anti-inflammatory and immunomodulatory potency, as well (6).

Furthermore, a dual gut-brain link was obtained in FD cases. Accordingly, anxiety increases FD symptoms. Contrarily, FD's gastrointestinal features lead to anxiety onset in these patients (13). TCAs are nearly the accepted group of antidepressants in FD patients such that they are considered the second line of treatment after PPIs failure (11). Nortriptyline belongs to the tricyclic antidepressant group. Since these agents act non-selective, they may inhibit amine reuptake and enhance serotonin and noradrenaline levels. However, the definite pathway of these agents in improving the FD features is yet unclear (14). Our data represented

Table 3. The evaluation of the role of age and gender in treatments with mirtazapine and nortriptyline.

Treatment	Symptom	Gender		Age		Education	
		F-Statistics	Sig.	F-Statistics	Sig.	F-Statistics	Sig.
Mirtazapine	HRSA*	6.07	0.025	0.94	0.472	0.46	0.716
	HRSD**	0.71	0.411	0.65	0.636	0.55	0.659
	NDI***	0.72	0.406	0.12	0.974	2.15	0.134
Nortriptyline	HRSA*	0.54	0.474	2.71	0.094	0.45	0.719
	HRSD**	2.77	0.113	0.14	0.872	0.31	0.815
	NDI***	1.55	0.228	0.67	0.523	0.44	0.73

*HRSA: Hamilton Rating Scale Anxiety, **HRSD: Hamilton Rating Scale Depression, ***NDI: Nepean Dyspepsia Index.

that nortriptyline significantly improved the gastrointestinal features of FD. According to our investigation, it appears that the low doses of TCAs is sufficient for optimal efficacy. Hopefully, although there are limited data on the role of different groups of antidepressants in FD, most of them are related to the effects of TCAs in patients with FD. One of the first studies in this field was done by Linda M Herrick et al. (15). They revealed the improved gastrointestinal features of FD through amitriptyline therapy. It appears amitriptyline reveals pain syndromes, including IBS or neuropathic pain (16). Kaosombatwattana et al., in RCT, evaluated the efficacy of nortriptyline in FD. The target population in this study included patients who did not respond to routine treatments, including prokinetics and PPIs. They compared nortriptyline 10 mg with a placebo after eight weeks of treatment. Finally, they reported no significant differences between these two arms (17). However, almost all related studies reported that the low doses of TCAs (up to 25 mg/day) were more effective than high doses of this agent (25 mg/day-100mg/day) in reducing the FD signs and symptoms (18). Mirtazapine is a tetracycline agent with serotonergic and noradrenergic effects. It could block α2 adrenergic receptors presynaptically. In the postsynaptic area, this drug blocks 5-HT2c and 5-HT3 receptors. These mechanisms increase norepinephrine and serotonergic neurotransmission. In this study, the potency of mirtazapine was investigated in an arm with 23 allocable participants with accompanying anxiety and depression. All participants were treated with a low dose of mirtazapine (7.5 mg/day) for about three months. The effect of mirtazapine on the gastrointestinal features of FD was achieved very quickly after six weeks of treatment. Mirtazapine could significantly improve retrosternal pain, epigastric pain, dysphagia, bloating, and belching. This drug seems to have a positive effect on gastro-sensorimotor functions (19). Tetracycline agents could successfully help the fundus relaxants in FD patients to mitigate the pain and discomfort (20). One of the recent clinical trials on the effects of mirtazapine in patients with FD indicated that a low-dose treatment of mirtazapine (15 mg/day) for a month significantly reduced the gastrointestinal features of this disorder. Hopefully, their results showed that mirtazapine leads to a better quality of life. This agent, by helping the fundus relaxant, seems to lead to weight gain and meal tolerance. Furthermore, they reported that Mirtazapine, through the gut-brain link mechanism, declines anxiety and depression levels in FD patients (21). Other retrospective cohort studies with a large population compared the potency of mirtazapine against citalopram as an SSRI. They reported that the low dose of these agents is sufficient for optimal efficacy achievement (22). One of the biggest shortcomings of previous studies is their limited clinical trials for comparing the different groups of antidepressants with each other (22). There is a few studies that compared the efficacy of TCAs with other groups of antidepressants (13). Unfortunately, the researchers found few comparable studies between TCAs and tetracycline agents in FD patients. One of these studies was done by R.S CHOUNG et al. (23). In a double-blind study; they compared the potencies of mirtazapine, nortriptyline, and placebo with each other. Compared to the placebo group, they observed no significant improvements in gastric motor or post-nutrient discomfort, neither in mirtazapine nor the Nortriptyline arm. In the current study, we could not achieve an improved outcome in the anxiety and depression fields as quickly as gastrointestinal features. In this regard, after 12 weeks of treatment, significant improvements in anxiety and depression were observed in both groups. Although, both treatments had significant effects on decreasing anxiety and depression, mirtazapine, compared to nortriptyline, was found to be more effective in the improvement of patients who suffer from depression. Based on the results of the current study, mirtazapine, in comparison to TCAs, could effectively suppress the GI symptoms related to gastric emptyings, like bloating and belching. This therapy has significantly more potency in pain reduction. Although mirtazapine, compared to nortriptyline, seems to improve more numbers of FD presentations, it is without a doubt that none of these two therapies could resolve all GI symptoms in FD patients. However, the study is not without limitations. The results could have been more robust if the research was not affected by time constraints and could afford a larger population.

Conclusion

In the current study, we compared the potency of nortriptyline as a TCA agent with mirtazapine as a tetracycline agent. Our results advocated the efficacy of mirtazapine over nortriptyline in reducing the depression score. Nevertheless, both treatments could significantly improve anxiety and quality of life in FD patients. In addition, it appears that mirtazapine is more effective in improving the GI symptoms related to gastric emptyings, such as bloating and belching.

Conflict of interests

The authors declare that they have no competing interests.

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