CHAPTER
6

The importance of serotonin in the treatment of functional dyspepsia

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ABSTRACT
Introduction: Functional dyspepsia (FD) is a gastrointestinal disorder of multifactorial etiology. Although present in about 20% of the world population, there is no satisfactory pharmacological treatment for these patients yet. Considering the fundamental role of serotonin in the pathogenesis of functional gastrointestinal disorders, the objective of this study was to review the literature related to the use of serotonergic drugs in the treatment of FD and assess their effectiveness. Method: We conducted a horizontal review in the PubMed® database on the treatment of FD and serotonin. Articles were selected using the PRISMA method, as well as the keywords "functional dyspepsia treatment" and "serotonin". Result: We retrieved 180 studies and after eliminating articles based on titles and abstracts, languages other than English and on pathophysiology, 16 studies remained. Discussion: Overall, treatment with prokinetic agents 5-HT4 antagonists cisapride and tegaserod showed improvement in symptoms in patients with FD compared to placebos, while the efficacy of mosapride is still highly questioned. Regarding antidepressants, tricyclics were effective in the treatment of FD, especially amitriptyline in patients with epigastric pain syndrome. Mirtazapine also showed benefits compared to placebo, especially in patients with FD and weight loss. On the other hand, serotonin and norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors were not effective in the treatment of FD, in addition to causing several adverse effects. The anxiolytics buspirone and tandospirone, responsible for relaxing the gastric fundus, have proven effective for the treatment of FD. Conclusion: Considering the treatment of FD based on serotonergic drugs, tricyclic antidepressants and anxiolytics were the most efficient and indicated in FD cases. The importance of serotonin in the treatment of FD and consequently, in the pathophysiology of the gastrointestinal disorder is demonstrated.

Keywords: Dyspepsia, Pharmacological treatment, Serotonin, Gastropathies, Tricyclic antidepressants, Anxiolytics.

1 INTRODUCTION

Dyspepsia is a set of symptoms referring to the gastroduodenal region of the upper gastrointestinal tract associated with a wide spectrum of diseases [1, 2]. The main cause of dyspeptic symptoms is functional dyspepsia (FD), a common functional gastrointestinal disorder affecting about 20% of the population [1, 3-5].

According to the Rome IV criteria published in 2016, FD is defined as the presence of one or more of the following symptoms: postprandial fullness, early satiety, and epigastric pain or burning without demonstration of structural or metabolic disease that could explain the origin of symptoms. The duration of symptoms should be at least three months [3, 4, 6, 7]. Confirmation of the diagnosis is based on the patient's history and exclusion of other diseases with similar presentations [4].

To help guide the FD therapy, two syndromes have been proposed according to the grouping of dyspeptic symptoms: epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). These two syndromes may also overlap [1, 4, 5-7].

Epigastric pain syndrome is the presence of pain or intermittent burning in the epigastric region [1, 6]. Postprandial distress syndrome is more common and characterized by the occurrence of bothersome postprandial fullness after normal-sized meals or by the presence of early satiety. Patients often report associated loss of appetite, nausea, belching, heartburn, vomiting and swelling [1, 4, 6, 7].

Although the exact mechanism is not well known, the pathophysiology of FD is complex and multifactorial [4, 5]. Macroscopic mechanisms include gastroesophageal reflux, impaired gastric accommodation, and delayed gastric emptying. Microscopic mechanisms include impaired barrier function, visceral hypersensitivity changes in the nervous system, and gastroduodenal inflammation. Furthermore, there may be a central processing of visceral stimuli of gastrointestinal tract sensations that can be altered by psychological factors such as anxiety and depression [1, 4, 5, 6, 8].

In turn, psychiatric comorbidities are more common in patients with FD compared to the control population [5]. Serotonin, the primary neurotransmitter involved in the regulation of psychological processes, is currently known to play a key role in the pathogenesis of functional gastrointestinal disorders [5].

The intestine is the main source of serotonin in the body: in addition to more than 90% being released by enterochromaffin cells of the intestinal mucosa, its molecules are also contained in intrinsic neurons of the gastrointestinal tract. In the gut, serotonin functions both as a neurotransmitter and as a mucosal signaling molecule [9].

Serotonin is involved in the gastrointestinal process from the moment food enters the body. The activation of taste cells on the tongue releases serotonin into sensory afferent nerves that transmit taste information to the central nervous system (CNS). Once food enters the gastrointestinal tract, it is propelled by peristaltic waves, which, like intestinal motility and secretion, are modulated by serotonin [10].

Serotonin also modulates pain perception and nociceptive processing at various levels in the CNS and peripheral nervous system, which may explain the higher pain perception in patients with mood disorders and the effectiveness of serotonergic drugs in treating pain disorders [10].

Functional dyspepsia can significantly impair patients' quality of life through physical and mental suffering [4, 6, 8]. Considering the limited amount of therapies available, the treatment of FD is directed to predominant symptoms [11]. Medical therapy is the basis of treatment, although most drug treatments have shown modest efficacy [11]. The commonly used drugs in the treatment of FD are: drugs to eradicate *Helicobacter pylori*, antacids, prokinetic agents and antidepressants [12].

Considering that serotonin is possibly an important component of the pathophysiology of FD and the substantial lack of medical therapies with satisfactory results, the objective of this study was to perform a literature review on the effectiveness of the various serotonergic drugs in the treatment of FD, covering the role of serotonin in the pathophysiology of the disease, a subject that needs clarification.

2 METHOD

PubMed® was the database chosen to perform this review. On March 15, 2021, we searched for articles using the words “functional dyspepsia treatment” and “serotonin”. A total of 180 articles were retrieved. Seven articles were manually added later.

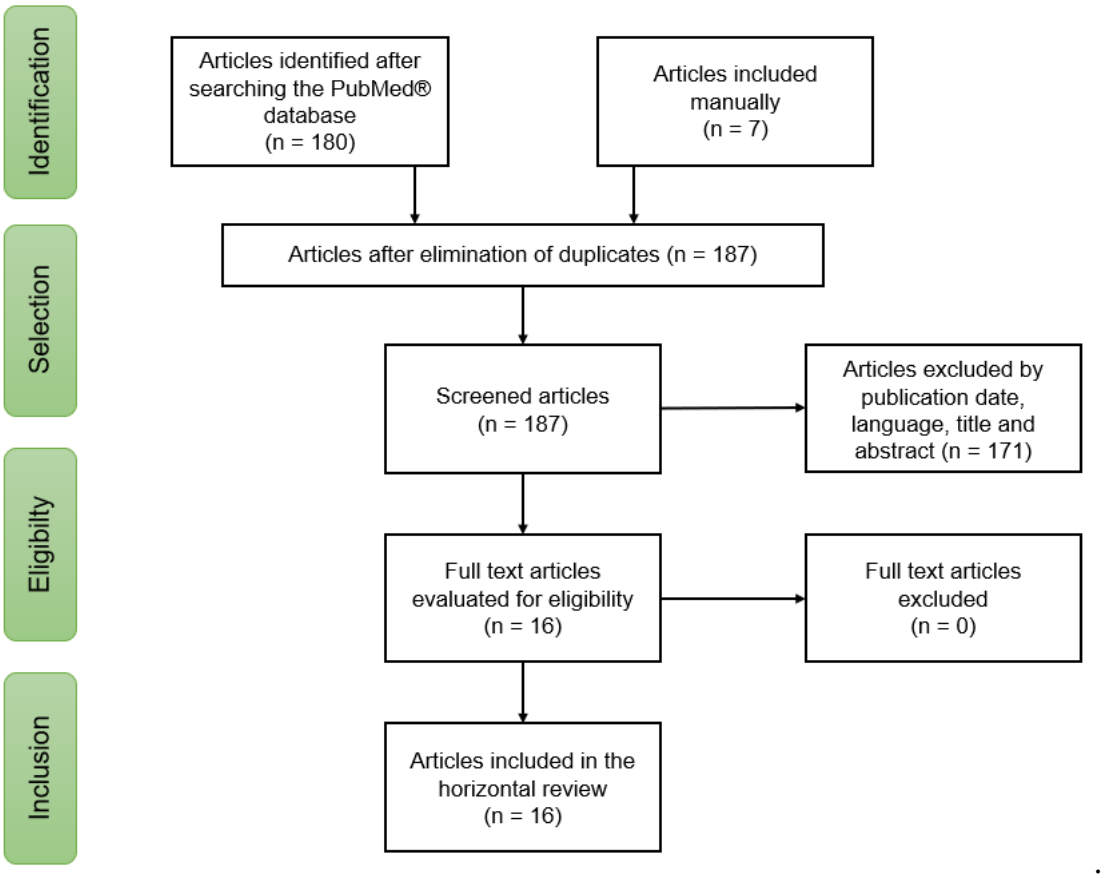
The inclusion criteria for studies in this horizontal review were: 1) compliance with eligibility criteria (articles on the effectiveness of serotonergic agents in the treatment of functional dyspepsia), 2) articles published between January 1, 2015 and March 15, 2021, and 3) articles in English. Exclusion criteria were: 1) comments and editorials, 2) articles on the pathophysiology of functional dyspepsia, genetic bases of drugs, studies in healthy individuals and in animals, 3) articles published before January 1, 2015, and 4) articles in languages other than English.

Of the total of 187 articles found, 149 were excluded in the initial analysis: 145 studies were published before January 1, 2015; four studies were in languages other than English.

The remaining 38 articles were evaluated. Of these, 14 were excluded by the title, as they addressed different topics from the one chosen for the study: treatment of FD with serotonergic agents. Finally, 24 articles were selected for abstract reading, of which eight were excluded as they did not specifically evaluate the effectiveness of serotonergic agents in individuals with FD. All 16 articles selected for full text reading were included in the horizontal review.

The analysis of articles was initially done by the author and the final choice also included a senior reviewer. Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram



3 RESULTS

The review consisted of 16 articles, four of which were literature reviews, two systematic reviews, four meta-analyses, three systematic reviews and meta-analyses, and three prospective studies. Table 1 summarizes the main results found in each article regarding the effectiveness of serotonergic agents in the treatment of FD.

Table 1. Main results on the effectiveness of serotonergic agents in the treatment of FD.

Reference	Year of publication	Type of study	Included articles/patients	Medication	Condition	Result
Talley [13]	2015	Randomized controlled clinical trial	292 patients	Amitriptyline	Relief of FD symptoms compared to escitalopram	Greater effectiveness
					Relief of FD symptoms in EDS patients compared to placebo	
					Improvement of abdominal pain and postprandial distress in FD patients with	Effective

					normal gastric emptying at baseline	
					Symptom relief in FD patients with mild delay in gastric emptying	30% response rate
					Relief of FD symptoms in patients with PDS	46% response rate
				Escitalopram	Use for the treatment of FD	Ineffective
Bang [14]	2015	Meta-analysis	13 articles	Mosapride	Therapeutic effect on overall FD symptoms compared to placebo or other control drugs	Not statistically significant effect
Lu [15]	2016	Systematic review and meta-analysis	8 articles	Tricyclics	Effective in treating FD in adults	Effective
				SSRI		Ineffective
Talley [16]	2016	Literature review	-	Buspirone	Efficacy in the treatment of FD compared to placebo	Greater effectiveness
				Tricyclics	Efficacy in the treatment of FD compared to placebo in patients with normal gastric emptying	
				SSRI	Efficacy in the treatment of FD compared to placebo	Ineffective
				SNRI		
Tack [17]	2016	Randomized controlled clinical trial	34 patients	Mirtazapine	Improvement of early satiety scores compared to placebo in patients with FD and weight loss	Greater effectiveness
					Decreased weight loss in patients with FD and weight loss	Effective
					Improvement of symptoms of nausea, epigastric pain and burning in patients with	Ineffective

					FD and weight loss	
Ford [18]	2017	Systematic review and meta-analysis	13 articles	Tricyclics	Efficacy in the treatment of FD compared to placebo	Effective
				SSRI		Ineffective
				SNRI		
				Tetracyclics		
Hojo [19]	2017	Systematic review	9 articles	Tandospirone	Efficacy in the treatment of FD compared to placebo	Effective
				Buspirone		
				Amitriptyline		
				Sertraline		Ineffective
				Venlafaxine		
				Tricyclics	Effect in FD patients who do not respond to first-line treatment	Beneficial effect
				Tetracyclics		
Lacy [20]	2017	Randomized controlled clinical trial	292 patients	Amitriptyline	Improvement of symptoms of abdominal pain, postprandial fullness, nausea and abdominal bloating in patients with FD	Effective
				Escitalopram		
				Amitriptyline	Improvement in global FD symptoms compared to escitalopram, SSRIs or placebo	Greater effectiveness
Yang [21]	2017	Meta-analysis	25 articles	Mosapride	Efficacy in the treatment of FD compared to itopride and acotiamide	Greater effectiveness
Quigley [22]	2017	Literature review	-	Mosapride	Efficacy in the treatment of FD	Ineffective
Pittayanon [23]	2018	Systematic review and meta-analysis	43 articles	Cisapride	Reduction of dyspeptic symptoms in patients with FD	Authors were unable to reach a conclusion
				Tegaserod		
				Cisapride	Improved quality of life for patients with FD	Ineffective
				Tegaserod		
Pittayanon [24]	2018	Systematic review and meta-analysis	38 articles	Cisapride	Reduction of dyspeptic symptoms in patients with FD	Effective
				Tegaserod		
				Cisapride	Improved quality of life for patients with FD	Ineffective
				Tegaserod		
Tack [25]	2018	Literature review	-	Amitriptyline	Improvement of FD symptoms in	Effective

					patients with EDS or normal gastric emptying	
				Tricyclics	Improvement of FD symptoms compared to placebo	Greater effectiveness
				Mirtazapine	Improvement of general symptoms, early satiety and nausea in patients with FD without depression or anxiety and with weight loss	Effective
Masuy [26]	2019	Literature review	-	Cisapride	Improvement of FD symptoms compared to placebo and other prokinetic agents	Greater efficacy according to some studies and no significant difference according to other studies
				Mosapride	Reduction of symptoms of gastric stasis and epigastric pain in patients with FD	Effective
					Improved quality of life for patients with FD	
					Improvement of FD symptoms compared to dopamine antagonists	Greater effectiveness
					Improvement of FD symptoms compared to placebo	Ineffective
				Tegaserod	Improvement of FD symptoms compared to placebo	Greater effectiveness
				Amitriptyline	Improvement of FD symptoms in patients with EDS	Effective

					Improvement of FD symptoms in patients with PDS	Ineffective
					FD symptom relief compared to escitalopram and placebo	Greater effectiveness
				Mirtazapine	Improvement of symptoms and quality of life of patients with FD without depression or anxiety and with weight loss compared to placebo	Greater effectiveness
				Venlafaxine	Improvement of FD symptoms	Ineffective
				SSRI		
				Buspirone	Improvement of gastric accommodation and gastrointestinal symptoms in patients with FD	Effective
				Tandospirone	Improvement of FD symptoms compared to placebo	Greater effectiveness
Vijayvargiya [27]	2019	Systematic review and meta-analysis	67 studies	Cisapride	Improvement in gastric emptying time and upper gastrointestinal symptoms in patients with FD	Effective
Jin [28]	2019	Meta-analysis	10 studies	Mosapride	Improvement of symptoms in patients with FD compared to placebo	Greater effectiveness

4 DISCUSSION

Different serotonin receptors have been described in the gastrointestinal tract, each with specific effects. They may be located in pre- and post-synaptic regions on neurons of intrinsic inhibitory and excitatory motor pathways and extrinsic afferent pathways to the CNS and smooth muscle cells. The effects on motility and sensitivity depend on the receptor that is activated [29].

5-HT1A receptors are located in the presynaptic region of cholinergic nerve endings and in the neuromuscular junction region. Their activation inhibits the release of acetylcholine, leading to smooth muscle relaxation [29].

As 5-HT3 receptors are located in postsynaptic excitatory motor neurons and vagal afferent neurons, they have been linked to gut-to-CNS communication and activation of smooth muscle cell contraction. Animal studies suggest that 5-HT3 receptors are excitatory mediators in visceral sensory pathways [29].

5-HT4 receptors are abundantly present in the intestine and activated in the nerve endings of intrinsic primary afferent neurons, stimulating peristalsis and the secretion of enteric substances [30, 31]. They are also present at the neuromuscular junction, so their activation increases the release of acetylcholine [29].

Serotonergic signaling is terminated by intracellular serotonin reuptake by SERT, a specific serotonin transporter. Then, the molecule undergoes enzymatic catabolic inactivation [32].

Therefore, serotonergic agents may result in symptomatic improvement as they act at various levels regulating motility, enteric reflexes, secretion and absorption [31]. Based on this background, the present review was performed to assess current evidence on the effectiveness of serotonergic drugs in the treatment of FD.

4.1 PROKINETICS

A meta-analysis containing ten studies showed significantly higher response rates and improvement in symptoms in patients with FD treated with 5-HT4 agonists such as cisapride, mosapride and tegaserod compared to the placebo group [28]. In another meta-analysis, the mean percentage of improvement in symptoms was 40% in the prokinetic group, compared to 26.1% in the placebo group, and cisapride and tegaserod were identified as effective individual prokinetic agents for the treatment of FD [24]. In a meta-analysis, no significant difference in efficacy between the prokinetics was found when studying metoclopramide, trimebutine, mosapride and domperidone, even though these showed better efficacy in the treatment of FD compared to itopride or acothiamide [21].

4.1.1 Cisapride

Cisapride, a 5-HT4 receptor agonist and 5-HT3 receptor antagonist, acts by increasing lower esophageal sphincter tone, increasing esophageal peristalsis, accelerating gastric emptying and increasing postprandial gastric accommodation [30]. Two systematic reviews reported the effectiveness of cisapride in reducing dyspeptic symptoms and that it was superior to placebo in the treatment of FD [23, 24]. A study in healthy individuals has shown that cisapride increases gastric

accommodation, while several studies have shown that cisapride improves the gastric emptying rate in patients with FD and has a treatment response rate of around 70%, showing superiority compared to placebos or other prokinetic agents [26].

A systematic review and meta-analysis evaluating changes in gastric emptying and upper gastrointestinal symptoms following the use of promotility agents demonstrated that cisapride resulted in clinically significant improvements in gastric emptying and upper gastrointestinal symptoms. Compared to domperidone and relamorelin, cisapride showed the greatest change in gastric emptying time, with an improvement of 39.5 minutes [27].

However, Masuy et. al concluded that the effects of cisapride on gastrointestinal symptoms remain debatable, as some studies have not shown significant differences between cisapride treatment compared to placebo [26]. Furthermore, in their two systematic reviews, Pittayanon et. al concluded that cisapride did not improve quality of life in patients with FD [23, 24].

Note that cisapride was withdrawn from the market in year 2000 after being associated with the occurrence of fatal cardiac arrhythmias due to QT interval prolongation [28, 33, 34].

4.1.2 Mosapride

Mosapride, also a 5-HT4 receptor agonist, acts by decreasing acid reflux and increasing esophageal motor function in patients with gastroesophageal reflux disease [30]. In their review, Masuy et. al found evidence that mosapride may be a useful therapy for FD. A randomized trial reported a 91% rate of reduction in FD symptoms in patients after treatment with mosapride, showing that the drug reduces gastric stasis and epigastric pain. A meta-analysis showed that mosapride is 6.7% more likely to produce a symptom response in patients with FD compared to dopamine antagonists. It was also found that mosapride can improve the quality of life in patients with FD [26].

However, a review concluded that mosapride showed no benefit in the treatment of FD, despite accelerating gastric emptying and increasing gastric accommodation [22]. In a European study, no beneficial effect of mosapride treatment over placebo was found [26]. In a meta-analysis, mosapride had no statistically significant therapeutic effect on overall symptoms compared to placebo and other control drugs [14]. Adverse events were reported in less than 5% of patients and include diarrhea, headache, and dry mouth [26].

4.1.3 Tegaserod

Tegaserod, a partial agonist of the 5-HT4 receptor, accelerates gastric emptying, increases gastric accommodation, intestinal secretions and peristaltic reflexes, and inhibits visceral afferent responses [32, 34]. In their review, Masuy et. al reported that the improvement of symptoms in patients

using tegaserod is possibly associated with the drug's effects on the increase in gastric accommodation and emptying and pain thresholds. A large randomized placebo-controlled trial showed a 4.6% rate of satisfactory symptom relief after six weeks of treatment with tegaserod. Another study in women with FD under treatment with proton pump inhibitors revealed a 69% rate of symptom relief after ten weeks of tegaserod treatment compared to baseline treatment [26].

However, two systematic reviews concluded that tegaserod is ineffective in improving the quality of life of patients with FD [23, 24] and in one of them, the authors were unable to reach a conclusion about the effectiveness of tegaserod in the treatment of FD [23].

In 2007, tegaserod was withdrawn from the market due to the increased incidence of cardiac ischemic events [32, 34].

4.2 ANTIDEPRESSANTS

4.2.1 Tricyclics

A meta-analysis and literature review concluded that tricyclics are effective in treating FD in adults [15, 18]. A systematic review showed that tricyclic drugs may have a beneficial effect in patients with FD who do not respond to first-line treatment [19] and two literature reviews reported their effectiveness in treating FD compared to placebo [16, 25].

4.2.1.1 Amitriptyline

According to Masuy et. al, amitriptyline improves FD symptoms, especially in EPS patients, although it has no significant effect on gastric function. A large randomized controlled clinical trial investigated the effects of amitriptyline on FD compared to escitalopram and placebo: appropriate symptom relief was achieved in 53% of patients after treatment with amitriptyline compared to 40% for placebo and 38% for escitalopram. However, amitriptyline was superior to placebo only in the treatment of EPS, but not in the treatment of patients with PDS [13, 25, 26]. The mean time to gastric emptying at baseline was similar between the three groups, even though modest treatment effects favored amitriptyline in improving postprandial fullness and early satiety [13]. In the group of EPS patients receiving amitriptyline, greater improvements in overall quality of life scores related to sleep and upper abdominal pain were observed in patients who did not experience delayed gastric emptying [13, 25].

In a prospective study, symptoms of abdominal pain, fullness, nausea, and abdominal distension improved in patients with FD who used amitriptyline. In the same study, amitriptyline was more effective in improving overall symptoms of FD compared to escitalopram, selective serotonin

reuptake inhibitors (SSRIs) and placebo [20]. In their systematic review, Hojo et. al found that amitriptyline was effective in the treatment of FD compared to placebo [19].

However, in a trial in patients with FD, treatment with amitriptyline did not affect the rate of gastric emptying and the maximum tolerated volume in drinking [26]. In their prospective study, Talley et. al obtained a response rate of only 30% of FD symptom relief in patients with mild delay in gastric emptying [13]. In a systematic review, drowsiness and rash were reported as side effects of using amitriptyline for the treatment of FD [19].

4.2.2 Tetracyclics

A systematic review showed that tetracyclic drugs may have a beneficial effect in patients with FD who do not respond to first-line treatment [19]. On the other hand, a meta-analysis found no significant difference between tetracyclics and placebo in the treatment of FD [18].

4.2.2.1 Mirtazapine

Masuy et. al included mirtazapine in their review. In patients with FD and weight loss, mirtazapine has been shown to improve symptoms, quality of life, anxiety and ingested volume tolerance compared to placebo after eight weeks of treatment [26].

A double-blind, placebo-controlled randomized clinical trial showed that mirtazapine has the potential to become the treatment of choice for patients with FD and weight loss. In that study, mirtazapine improved early satiety and nutrient tolerance scores compared to placebo. The symptomatic benefit of mirtazapine was more consistent for the early satiety symptom, to a lesser extent for nausea and absent for epigastric pain and burning, suggesting that the drug may be more beneficial for the PDS subgroup. Symptomatic benefit appears to occur from the third week of treatment. The symptoms that improved most consistently during treatment were early satiety and weight loss [17].

A review concluded that mirtazapine is effective in non-depressed, non-anxious FD patients with major weight loss, acting by improving not only body weight, but general symptoms, nausea, early satiety, and nutrient volume tolerance [25].

4.2.3 Serotonin and noradrenaline reuptake inhibitors (SNRIs)

Talley in his literature review, and Ford et. al in their systematic review and meta-analysis, concluded that SNRIs are ineffective in the treatment of FD compared to placebo [16, 18].

4.2.3.1 Venlafaxine

Masuy et. al reported a randomized placebo-controlled clinical trial that showed the ineffectiveness of venlafaxine in treating FD. However, the dose used in the study was low, insufficient to significantly inhibit noradrenaline reuptake [26]. In a systematic review, the superiority of treatment with venlafaxine was not found when compared to placebo. In addition, several adverse effects related to the use of venlafaxine for the treatment of FD were found, namely nausea, palpitations, sweating, sleep disturbances, dizziness and visual impairment [19].

4.2.4 Selective serotonin reuptake inhibitors (SSRIs)

SSRIs inhibit serotonin reuptake by SERT in crypt epithelial cells and enteric neurons, resulting in prolonged availability of physiologically released serotonin [29]. This way, SSRIs can improve central and visceral pain, in addition to treating anxiety or depression, when coexisting [35].

The same studies that found the effectiveness of tricyclics in the treatment of FD showed that patients who used SSRIs did not show improvement in FD symptoms [15, 18]. In their review, Masuy et al. included a meta-analysis that showed the ineffectiveness of SSRIs in treating FD [26], just as Talley found in his literature review that SSRIs are ineffective in treating FD compared to placebo [16].

4.2.4.1 Sertraline

A systematic review reported insomnia, constipation and restlessness as side effects for the use of sertraline in the treatment of FD, in addition to not finding a superiority of the drug in the treatment of FD compared to placebo [19].

4.2.4.2 Escitalopram

In a multicenter randomized trial, the outcome of treatment with escitalopram was comparable to placebo, and it did not support the use of escitalopram in FD [13]. On the other hand, in a prospective study, patients with FD who used escitalopram showed improvement in symptoms of abdominal pain, fullness, nausea and abdominal distension [20].

4.3 ANXIOLYTICS

4.3.1 Buspirone

In their review, Masuy et al. reported that buspirone, a 5-HT1A receptor agonist, demonstrated an improvement in gastric accommodation and gastrointestinal symptoms in patients with FD [26], just as Talley reported that buspirone relaxes the gastric fundus and therefore, may have a value in the treatment of FD [16]. In another systematic review, buspirone had a stronger effect than placebo in the

treatment of FD, even though nausea and abdominal discomfort were found as side effects. Buspirone possibly has the effect of relaxing the proximal stomach [19].

4.3.2 Tandospirone

Masuy et al. analyzed a four-week study in which tandospirone, another 5-HT1A agonist, was superior to placebo in eliminating FD symptoms [26]. Furthermore, the same meta-analysis that investigated the efficacy of 5-HT4 agonists in patients with FD also showed that patients treated with tandospirone had a significantly higher response rate to FD symptoms compared to placebo [28]. Likewise, a systematic review showed that tandospirone was superior to placebo in the treatment of FD. Like buspirone, tandospirone probably acts by relaxing the proximal stomach [19].

5 FINAL CONSIDERATIONS

The initial proposal of the work was to conduct a review about the role of serotonin in the pathophysiology of FD. As the scarcity of literature addressing the subject was an obstacle for this study, we chose to analyze the effectiveness of drugs acting on serotonergic pathways in the treatment of FD. We emphasize that despite the considerable amount of studies on the effectiveness of serotonergic agents in the treatment of FD, the role of serotonin in the pathophysiology of FD is still poorly understood and needs clarification.

6 CONCLUSION

In our review, we concluded that serotonergic agents can be effective in the treatment of FD, especially tricyclic antidepressants, highlighting amitriptyline and anxiolytic drugs. On the other hand, we observed that SNRI and SSRI are not indicated in the treatment of FD. Prokinetics and tetracyclics have shown good efficacy in the treatment of FD, although there is a lot of controversy in the analyzed literature.

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