Neuromodulating agents in functional dyspepsia: a comprehensive review

L. Bosman[1], L. Wauters[2], T. Vanuytsel[2]

(1) Faculty of Medicine, KULeuven, Leuven, Belgium; (2) Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium.

Abstract

Background and study aims: **Functional dyspepsia is a common chronic condition with upper abdominal symptoms in the absence of an organic cause. The first line treatment consists of proton-pomp inhibition or Helicobacter pylori eradication. However, this approach often does not provide enough symptom relief. Neuromodulating agents are commonly used in clinical practice but only tricyclic antidepressant (TCAs) are mentioned in European and American and Canadian guidelines.**

Methods: **We performed a comprehensive review of the literature in Pubmed for full-text randomized controlled trials in English with adult participants (>18 years) who met the Rome II, III or IV criteria or were diagnosed by a physician with a negative upper endoscopy and that compared a neuromodulating agent with placebo.**

Results: **The search strategy identified 386 articles of which 14 articles met the eligibility criteria. TCAs like amitriptyline and imipramine have been shown to be effective in the treatment of functional dyspepsia whereas other neuromodulating agents like tetracyclic antidepressants, levosulpiride and anxiolytics might be beneficial but conclusive evidence is lacking. serotonin and noradrenaline reuptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI) have not shown benefit in patients with functional dyspepsia.**

Conclusion: **Selected neuromodulators have an established efficacy in functional dyspepsia. The best supporting evidence is available for TCAs with a potential role for tetracyclic antidepressants, levosulpiride and anxiolytics.** (Acta gastroenterol. belg., **2023,** 86, **49-57**).

Keywords: Functional gastrointestinal disorders; neuromodulators; antidepressants; antipsychotics; anti-anxiety agents

Introduction

Functional Dyspepsia (FD) is a gastrointestinal disorder that is defined by the Rome IV criteria as recurring or persistent dyspeptic symptoms for the last 3 months with symptom onset at least 6 months prior to diagnosis with no evidence of an organic cause on routine testing, including upper endoscopy (1,2). The symptoms include bothersome postprandial fullness, early satiation, epigastric pain and/or epigastric burning (1). FD can be divided into 2 subtypes: postprandial distress syndrome (PDS), with the main symptoms being postprandial fullness and early satiation, and epigastric pain syndrome (EPS) characterized by epigastric pain or burning (1).

The worldwide prevalence in a large-scale multi-national survey was shown to be 7.2% and is higher in women, NSAIDs users and H. Pylori-positive individuals (3,4). Psychosocial factors, including anxiety and depression are also associated with FD (5). FD impairs quality of life and work productivity (6,7) .

The management of FD, after excluding H. pylori infection or an organic cause, depends on the subtype (8). For EPS, the first line therapy consists of acid suppression which helps to reduce the symptoms in 30-70% of the patients (9). For PDS prokinetic agents, which may improve disordered motility, are classically used as first line, although supportive evidence is scarce and PPIs may be equally effective (2,9). However, the quality of the supporting evidence for PPI and prokinetics in functional dyspepsia is low (2). In case of insufficient symptom control, the American and Canadian guidelines suggest that patients not responding to proton pomp inhibitor or H. pylori eradication therapy, should be treated with a tricyclic antidepressant (10).

The pathophysiology of functional dyspepsia consists of various interacting mechanisms including impaired accommodation, delayed emptying and hypersensitivity of the stomach and hypersensitivity of the duodenum to acid and/or lipids and duodenal low-grade inflammation mainly characterized by eosinophil infiltration (1,11,12). It is commonly assumed that PDS and EPS have a different pathophysiology and therefore the treatment should be different, but this is not supported by the scientific evidence as the prevalence of delayed gastric emptying, impaired accommodation and hypersensitivity is similar across the subgroups (11). Therefore the European guidelines recommend PPI therapy as initial treatment in both EPS and PDS (2). Abnormalities in the brain-gut axis have also been shown to play a role in generating the symptoms of FD (11). The brain-gut axis is a bidirectional neurohumoral communication system between the brain and the gut (5). Neuromodulators including antidepressants and anxiolytics have various pain-modulating properties at various levels of the brain-gut axis and are therefore suggested in the treatment of FD (9). In this comprehensive review we will focus on neuromodulating agents and their efficacy in the management of FD. We will provide a detailed discussion of the individual studies regarding the treatment outcome and adverse events.

Correspondence to: Tim Vanuytsel, Dienst Maag-Darm-Leverziekten, UZ Leuven, Herestraat 49, 3000 Leuven.
Email: tim.vanuytsel@uzleuven.be

Submission date: 19/08/2022
Acceptance date: 29/01/2023

Methods

The first author searched for full-text randomized controlled trials in English using the Pubmed database. We used the term 'Dyspepsia' as MESH term and free text term. This was combined with the set operator AND with studies found with the terms 'psychotropic drugs' (as MESH and free text terms), 'Antidepressive Agents' (as MESH and free text), 'Antipsychotic Agents' (as MESH terms and free text terms) and desipramine, doxepin, dothiepin, amitriptyline, amitryptiline, paroxetine, sertraline, fluoxetine, citalopram, trimipramine, desipramine, imipramine, nortriptyline, venlafaxine, duloxetine, escitalopram, sulpiride, levosulpiride, mirtazapine, buspirone, tandospirone as free text terms. The addition of the individual antidepressants was based on a consensus between the first and the last author and these were selected based on the most commonly used antidepressants in clinical practice.

RCTs with adult participants (>18 years) that met the Rome II, III or IV criteria or were diagnosed by a physician with a negative upper endoscopy were eligible. The outcome had to be a neuromodulating drug, or combination of one or more neuromodulating agents, compared to placebo. No publication date restriction was applied and only articles published in English were eligible. The reference lists of the individual articles were also searched for additional literature.

Results

Results of search strategy

The search strategy identified 386 articles of which 363 articles were excluded based on title, abstract and article type, resulting in 23 possible eligible articles. These 23 articles were assessed in full text and 14 articles met the eligibility criteria and 9 articles were excluded due to various reasons as shown in figure 1.

Four trials evaluated tricyclic antidepressants (TCA) (13-16), one trial a selective serotonin reuptake inhibitor (SSRI) (17), one trial SSRIs vs. TCAs (18), one trial a selective serotonin and noradrenalin reuptake inhibitor (SNRI) (19), two trials tetracyclic antidepressants (20,21), two trials antipsychotic drugs (22,23), one trial a combination of an antipsychotic drug and a tetracyclic antidepressant (24) and two trials anxiolytic agents (25,26). Table 1 gives an overview of the characteristics of the included articles.

Tricyclic antidepressant

Cheong *et al.* performed a randomized controlled trial in 107 patients, examining the effect of imipramine (13). The patients received imipramine at a dose of 25 mg for the first 2 weeks, and thereafter a dose of 50 mg with a total duration of treatment of 12 weeks. Patient-reported overall satisfactory relief of global dyspepsia symptoms

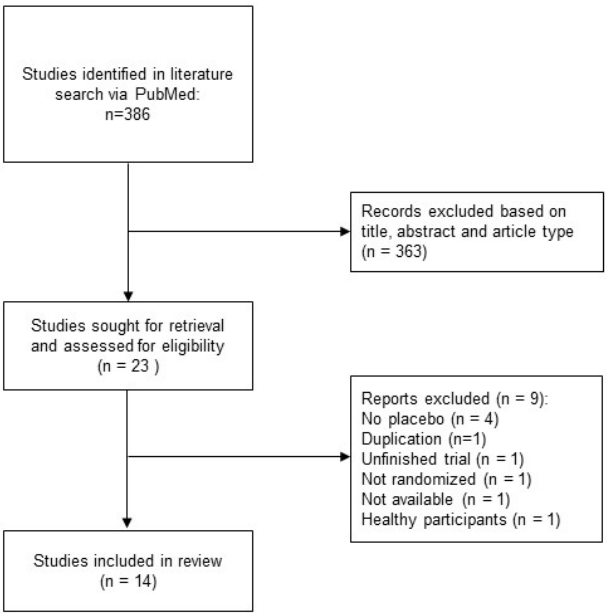

Figure 1. — Flowchart of literature search.

at week 12 occurred significantly more frequent in the imipramine group compared to the placebo arm (63.6% (95%CI 50.4%-75.1%) vs. 36.5% (95%CI 24.8%-50.1%) respectively; p = 0.0051, number needed to treat (NNT) 4). Patients in the imipramine arm showed significant reductions in total dyspepsia symptom score, as well as epigastric pain, bloating, postprandial fullness, early satiety and vomiting scores compared with baseline. Mood and anxiety scores improved at the end of the study period.

Another study using a tricyclic antidepressant was performed by Kaosombatwattane *et al.* and investigated the effect of nortriptyline in 61 Thai patients with refractory functional dyspepsia (15). This study showed no statistically significant difference in the response rate, defined as having a >50% reduction of dyspepsia symptom score from baseline. Also the quality of life scores were similar in both groups.

One of the more commonly used neuromodulators is amitriptyline, which was studied in two RCTs and one head-to-head comparison trial against SSRI. Braak *et al.* studied the effect of 25 mg amitriptyline on a nutrient drinking test and symptoms in 38 patients with functional dyspepsia (14). The study showed no difference for the nutrient challenge or post-prandial symptoms provoked by the drinking test between amitriptyline and placebo. However, the total symptoms score and nausea were significantly reduced by amitriptyline compared with placebo.

The second study evaluating amitriptyline was a small randomized controlled cross-over trial performed by Mertz *et al.* in 7 patients with a focus on sleep quality assessed by the amount of REM sleep and sleep efficacy measured by electrophysiological monitoring and by video monitoring (16). The patients were randomized to a treatment with amitriptyline 50 mg once a day for

Table 1. — **Characteristics of eligible RCTs in functional dyspepsia**

Author and date	Country	Diagnostic criteria for FD	Intervention (number of patients)	Comparison (number of patients)	Treatment duration	Outcomes and summary of results
Cheong *et al*., 2018 (14)	UK, Hong Kong	Rome II criteria and negative investigations	Imipramine 50mg od (first 2 weeks 25 mg once daily) (n=55)	placebo (n=52)	12 weeks	Overall satisfactory relief of dyspepsia: + Total and individual dyspepsia symptom scores: + Sleep: - Mood and anxiety scores: + Side effects for Imipramine: dry mouth, constipation, drowsiness, insomnia, palpitations, blurred vision
Tack *et al*., 2015 (21)	Belgium	Rome III criteria, weight loss >10%, negative investigations	Mirtazapine 15 mg od for 8 weeks (n = 17)	Placebo (n= 17)	8 weeks	Dyspepsia symptom severity: + at week 4, - at week 8 Early satiation: + Other cardinal functional dyspepsia symptoms: - Weight: + Nutrient tolerance after drinking challenge: + Gastric emptying: - Quality of life: + Anxiety and depression: - Gastrointestinal-specific anxiety: +
Talley *et al*., 2015 (19)	USA	Rome II criteria and normal upper endoscopy within 5 years	Amitriptyline 25 mg od for the first 2 weeks, then 50 mg once daily (n = 97) Or escitalopram 10 mg for 12 weeks (n = 98)	Placebo (n = 97)	12 weeks	Adequate relief: Amitriptyline: + (3x greater odds of reporting adequate relief in ulcer-like FD) Escitalopram: - Nutrient drink test: - for both amitriptyline and escitalopram Daily diary symptoms: Upper abdominal pain, nausea and bloating: - Fullness and early satiety: + for amitriptyline, - for escitalopram Dyspepsia-specific quality of life: + for both amitriptyline and escitalopram Side effects for amitriptyline and escitalopram: dizziness, drowsiness/somnolence Side effect for amitriptyline: suicidal thoughts
Van Kerkhoven *et al.*, 2008 (20)	The Netherlands	Clinical diagnoses and negative investigations	Venlafaxine 75 mg od for the first 2 weeks, then 150 mg once daily for 4 weeks, then 75 mg once daily for the last 2 weeks (n = 80)	Placebo (n = 80)	8 weeks	Dyspepsia symptoms: - Anxiety and depression: - Quality of life: -
Braak *et al*., 2011 (15)	The Netherlands	Rome III criteria and negative investigations	Amitriptyline 25mg od (n = 18)	Placebo (n = 20)	8 weeks	Nutrient drink test: Maximal ingested volume: - Postprandial symptoms : - Total symptoms score: + Nausea: + Side effects for amitriptyline: drowsiness, dry mouth, dizziness
Kaosombatwattana *et al.,* 2018 (16)	Thailand	Rome III criteria and negative investigations	Nortriptyline 10 mg od (n = 28)	Placebo (n = 33)	8 weeks	Dyspepsia symptoms - Quality of life - Side effects: dizziness, dry mouth, constipation, fatigue
Tanum *et al.*, 1996 (22)	Norway	Diagnosis by a gastroenterologist and negative investigations	Mianserin 120 mg od (n = 25)	Placebo (n = 22)	7 weeks	Dyspepsia symptoms: + Functional disability: + Side effects for mianserin: mild and transient sedation, dizziness
Hashash *et al.*, 2008 (25)	Lebanon	Rome III criteria and negative investigations	Flupenthixol 0.5 mg + melitracen 10 mg BID (n = 13 in group receiving F+M first, n = 11 in the group receiving placebo first)	Placebo (n = 13 in group receiving F+M first, n = 12 in the group receiving placebo first)	2 weeks, then 2 week wash-out, then cross-over for another 2 weeks	Dyspepsia symptom relief: + Subjective global symptom relief: + Disease-specific quality of life: + Side effects for F+M: insomnia, generalized discomfort, diarrhea, new symptom of heartburn
Tan *et al.*, 2012 (18)	Hong Kong, China	Rome II criteria and negative investigations	Sertraline 50mg od (n = 98)	Placebo (n = 95)	8 weeks	Dyspepsia symptoms: - Quality of life: - Subjective global symptom resolution: - Depression and anxiety: - Side effects: insomnia, constipation, agitation
Mertz *et al.*, 1998 (17)	U.S.A.	Clinical diagnosis and negative investigations	Amitriptyline 50 mg od (n = NA)	Placebo (n = NA)	4 weeks, then 3 week wash-out, then cross-over for another 4 weeks	Abdominal symptoms after 4 weeks: + Weekly rating of abdominal symptoms: - Sleep quality: - Sleep studies: Relative and absolute REM time: + Other parameters of sleep: - Response to gastric distension: -
Song *et al.*, 1998 (24)	Korea	Clinical diagnosis and negative investigations	Levosulpiride 25 mg od (n = 17)	Placebo (n = 15)	3 weeks	Dyspeptic symptoms: + Gastric emptying: + Side effects for levosulpiride: mild somnolence

Arienti *et al.*, 1994 (23)	Italy	Clinical diagnosis and negative investigations	Levosulpiride 25 mg TID (n = 15)	Placebo (n = 15)	20 days	Dyspeptic symptoms: + Gastric and gall-bladder emptying: +
Tack *et al.*, 2012 (26)	Belgium	Rome II criteria and negative investigations	Buspirone 10 mg TID (n = 7 in group receiving buspirone first, n = 10 in the group receiving placebo first)	Placebo (n = 7 in group receiving buspirone first, n = 10 in the group receiving placebo first)	4 weeks, then 2 week wash-out, then cross-over for another 4 weeks	Dyspepsia symptom severity: + (borderline; p = 0.5) Severity of postprandial fullness: + Gastric emptying rates: - Meal-related symptoms: Total symptom scores: - Fullness: + Bloating: + Gastric barostat studies: Preprandial intraballon volumes: - Postprandial intraballon volumes: + Gastric accommodation: +
Miwa *et al.*, 2009 (27)	Japan	Rome II criteria and negative investigations	Tandospirone 10 mg TID (n = 75)	Placebo (n = 75)	4 weeks	Total abdominal symptom scores: + Individual abdominal symptom scores: Upper abdominal pain: + Discomfort: + State-trait anxiety index: - Quality of life: - Adverse events for tandospirone: faintness, dizziness, sleepiness, headache, diarrhea

OD, once daily; BID, twice a day; TID, three times a day; NA, not available. +: significant ($p < 0,05$) positive effect for treatment group compared to placebo.
-: no significant effect between treatment group and placebo.

4 weeks or placebo and after a 3 week wash-out period, both groups crossed-over to the other treatment for 4 more weeks. Patients in the amitriptyline phase reported significantly less severe gastrointestinal symptoms after 4 weeks ($p = 0.016$) and had a significant reduction in absolute ($p = 0.037$) and relative ($p = 0.016$) amounts of REM sleep compared to placebo. Other parameters related to non-regenerative sleep showed no significant difference between amitriptyline and placebo. There were also no differences in the perceptual responses to gastric balloon distention after 4 weeks of amitriptyline compared to placebo.

Side effects

The side effects reported for imipramine were dry mouth, constipation, drowsiness, insomnia, palpitations and blurred vision but there was no significant difference in quantity of adverse events compared with placebo (13). For nortriptyline, the most frequent side effects included dizziness, dry mouth, constipation (15). In the RCT by Braak *et al.*, patients receiving amitriptyline reported significantly more side effects, including drowsiness, compared with placebo (14).

Tricyclic antidepressant vs. selective serotonin reuptake inhibitor

A randomized controlled study performed by Talley *et al.* evaluated the effect of amitriptyline vs. escitalopram as treatment options in functional dyspepsia (18). Patients with Rome II defined functional dyspepsia were randomized to groups receiving placebo, 50 mg amitriptyline, or 10mg escitalopram for 10 weeks. The rates for adequate relief were 40% for the placebo arm, 53% for amitriptyline and 38% for escitalopram, indicating a difference ($p = 0.05$) between the 3 treatment arms. Patients in the amitriptyline arm tended to respond better than the placebo arm (odds ratio = 1.1 (95%CI: 0.6-2.1)) and the escitalopram arm was comparable with placebo. The subjects with ulcer-like dyspepsia, generally corresponding to the Rome IV defined EPS group, who received amitriptyline, showed a 3-fold greater odds of reporting adequate relief compared with placebo (OR = 3.1 (95%CI: 1.1-9.0)). The treatment response was otherwise similar among the 3 treatment arms in those with dysmotility-like FD, similar to Rome IV defined PDS. The nutrient drink test showed no significant results. Both amitriptyline and escitalopram improved quality of life ($p = 0.02$). There were no serious adverse events reported. Dizziness and drowsiness or somnolence was more common in both antidepressant arms ($p=0.01$).

Selective serotonin reuptake inhibitor

Tan *et al.* analyzed the effect of sertraline in 193 patients with functional dyspepsia in a double-blind randomized placebo-controlled pilot study (17). They received sertraline 50 mg once daily for 8 weeks. In the per protocol analysis, they found that at week 8 the sertraline group had a statistically significant improvement in the mean Hong Kong dyspepsia index (HKDI) score compared to the placebo group ($p=0.02$). However, there was no improvement in the intention to treat analysis. No differences in measures of quality of life, subjective global symptom resolution and depression and anxiety were found. The observed adverse events included insomnia, constipation and agitation but there was no significant difference between both groups.

Selective serotonin and noradrenalin reuptake inhibitor

Van Kerkhoven *et al.* analyzed the effect of the antidepressant venlafaxine in 160 patients with functional dyspepsia in a randomized, double-blind, placebo-controlled trial (19). They received venlafaxine

extended-release 75 mg once daily during the first 2 weeks, 150 mg once daily for the next 4 weeks and again 75 mg once daily during the last 2 weeks. After 8 and 20 weeks there was no significant difference in proportions of symptom-free patients between the venlafaxine arm and the placebo arm. There was also no improvement in individual symptoms and no significant difference in symptom severity, mean symptom number, anxiety and depression scores or Health-Related Quality of Life scores between the 2 treatment arms at any of the measurement times.

Tetracyclic antidepressant

A randomized, placebo-controlled trial performed by Tack *et al.* evaluated the effect of mirtazapine in a dose of 15 mg during 8 weeks in 34 patients with functional dyspepsia and weight loss without psychiatric comorbidity (20). Compared to placebo, mirtazapine significantly reduced dyspepsia symptom severity scores at week 4, but not at week 8. There was a significant improvement in early satiation for the mirtazapine group compared to placebo. However, these significant effects were not found for other cardinal FD symptoms, including fullness. Mirtazapine significantly increased weight and nutrient volume tolerance during a nutrient drink challenge test. There were no significant effects on gastric emptying quantified by an octanoic acid breath test. Quality of life was improved by mirtazapine as well as gastrointestinal-specific anxiety but anxiety and depression score were not significantly altered by mirtazapine.

Tanum *et al.* evaluated mianserin as a possible treatment option for functional gastrointestinal disorders, i.e. irritable bowel syndrome and non-ulcer dyspepsia, in 49 patients (22). They received a dose of 30 mg the first week, building up to a dose of 120 mg, which they received from week 2 to week 7 and from week 8 they received a dose on gradual withdrawal. The study found an efficacy of mianserin for all outcome variables. Treatment with mianserin resulted in a significantly higher improvement in abdominal pain and in symptoms of abdominal distress compared to the placebo group ($p < 0.001$). According to the VAS criterion for pain, significantly more patients in the mianserin group were classified as responders ($p < 0.001$), which was defined as a 50% improvement from baseline. Moreover, there was also a significant improvement of functional disability evaluated by the Disability Scale in the mianserin group compared to the placebo group in the categories work, social life and family life. The side effects of mild and transient sedation or dizziness were registered by more patients in the mianserin group than in the placebo group (80% vs. 14%).

Combination therapy: flupenthixol and melitracen

A Lebanese study analyzed the effect of a combination therapy with flupenthixol and melitracen (F+M), an anti-psychotic and tricyclic antidepressant respectively, in 25 patients in a randomized controlled cross-over design (24). The study design consisted of a 2 week period with F+M or placebo, then a washout period of 2 weeks after which each group received the other treatment for another 2 weeks. The study showed a significant improvement in subjective global symptom relief in the patients receiving F+M compared to the patients receiving placebo ($p=0.001$). When looking at quality of life measured by the Nepean Dyspepsia Index, patients receiving F+M showed a more significant drop in scores than placebo. The side effects were insomnia, generalized discomfort, diarrhea and new symptom of heartburn reported in the F+M group and constipation, constant fatigue and somnolence in the placebo group. The side effects reported in both study arms showed no significant difference between both groups ($p = 0.221$).

Antipsychotic drugs

Both studies evaluating an antipsychotic drug used levosulpiride as a possible treatment drug for functional dyspepsia.

In a study performed by Song *et al.*, the effect of 25 mg levosulpiride once daily was analyzed in 32 eligible patients with functional dyspepsia (23). Compared to placebo, patients in the levosulpiride group reported a significantly higher improvement in total symptom score ($p = 0.001$) and a greater efficacy in relieving the dyspeptic symptoms in the groups of dysmotility-like ($p = 0.02$) and non-specified functional dyspepsia ($p = 0.01$) as compared to other subgroups ($p = 0.16$). The levosulpiride groups showed a greater reduction of gastric emptying time than the placebo group ($p = 0.01$) which correlated significantly with the improvement in symptom scores ($r = 0.47$, $p = 0.01$). Mild somnolence was reported by the levosulpiride group.

A study performed by Arienti *et al.* evaluated the effect of levosulpiride on gastric and gall-bladder emptying in 30 patients with functional dyspepsia (22). Levosulpiride reduced dyspeptic symptoms compared to placebo with particularly a reduction in upper abdominal pain, upper abdominal bloating, early satiety, nausea and vomiting. Furthermore, compared to placebo, levosulpiride significantly reduced the mean half-emptying gastric time of liquids ($p < 0.05$), accelerated gastric emptying ($p < 0.001$ at 180 min; $p < 0.05$ at 240 min) by one hour and also accelerated gall-bladder emptying ($p < 0.05$ at 60 min and 120 min) by one hour. There were no side effects reported during treatment.

Anxiolytic agents

Tack *et al.* compared buspirone with placebo in 17 patients in a randomized, double-blind, placebo-controlled, crossover study (25). Dyspepsia symptom severity was only borderline significantly reduced by buspirone compared to placebo. When compared to

baseline, buspirone showed a significant effect on liquid gastric emptying and total meal-related symptoms severity scores. However, when comparing to placebo, there was no significant effect. Nevertheless, buspirone significantly lowered postprandial fullness and bloating of the individual meal-related symptom severity scores. The gastric barostat studies showed a significant effect on postprandial intraballoon volumes indicating enhanced gastric accommodation after buspirone compared to placebo.

In a double-blind, randomized controlled trial by Miwa *et al.*, the effect of tandospirone was studied in 150 FD patients (26). There was a significant improvement in total symptoms scores at week 1, 2 and 4 for the tandospirone group compared to placebo. When looking at the individual abdominal symptom scores, there was a significant improvement seen in upper abdominal pain and discomfort in the tandospirone arm compared to placebo. The state-trait anxiety index and SF-8, questioning quality of life, did not show any significant differences between tandospirone and placebo patients. The side effects for tandospirone included faintness, dizziness, sleepiness, headache, diarrhea with similar incidence of individual events between the two arms.

Discussion

Functional dyspepsia has a significant impact on quality of life with important economic impact (6,7). Depression and anxiety are known comorbidities in patients with functional dyspepsia. The current management of FD involves PPI and H. pylori eradication as first line treatment options (2,9). Prokinetics are also used as treatment in PDS patients (2). However, there is no conclusive evidence and in a large part of the patients with FD the dyspeptic symptoms are not adequately resolved by this first line treatment (9). Neuromodulating agents are widely used in clinical practice and are included in the American and Canadian guidelines as a recommended treatment option for PPI and H. pylori eradication refractory patients, even before the use of prokinetics (10). Furthermore, in the European guidelines there is no full consensus about the efficacy of neuromodulating agents in functional dyspepsia (2). Only the use of TCAs in EPS-type patients was agreed upon by 78% of the experts in a recent Delphi consensus guideline (2).

Looking at the various working mechanisms of neuromodulating agents, a beneficial effect on functional dyspepsia can be expected. First, there is a well-known anxiolytic effect of antidepressants which works by the mechanism of a rapid boost of the monoaminergic neurotransmission followed by a slower adaptive down-regulation and desensitization of post-synaptic monoamine receptors (27). Therefore, neuromodulators with anxiolytic properties such as SSRIs can still be advocated in patients with FD and comorbid anxiety even if the effect on dyspeptic symptoms is limited. Secondly, antidepressants have analgesic effects via the brain-gut axis which is the basis of visceral pain perception (27). Thirdly antidepressants exert neuroplastic effects by increasing brain-derived neurotrophic factor and thus increasing precursor neuronal growth (27). Finally, by boosting serotonergic and noradrenergic neurotransmission, antidepressants have beneficial effects on peripheral GI physiology (27).

Summary of results

In this review we investigated the current evidence for the effectiveness of different types of neuromodulating agents in the treatment of functional dyspepsia. The neuromodulating agents reviewed include tricyclic antidepressants, tetracyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, tetracyclic antidepressants, antipsychotics and a combination of a tricyclic antidepressant and an antipsychotic.

Tricyclic antidepressants were the best investigated neuromodulating agents for functional dyspepsia. We found 5 randomized controlled trials using a TCA of which there was one head-to-head trial that compared a TCA to a SSRI (13-16,18). Tricyclic antidepressants have antidepressant properties via a combination of 5-hydroxytryptamine (serotonin; 5-HT) and noradrenalin (NA) reuptake inhibition and most TCAs have additional receptor affinities (27). This is one of the reasons that TCAs have a more potent analgesic effect than antidepressants that target only one monoamine system such as SSRIs (27). However, this also means that TCAs are likely to give more side effects (27). Among the tricyclic antidepressants, amitriptyline was evaluated in 3 RCTs and thus the agent with the best evidence. Mertz *et al.* were the first to analyze the effect of amitriptyline in patients with FD showing that amitriptyline is an effective treatment for improving abdominal symptoms and reducing the amount of time in REM sleep in patients with functional dyspepsia (16). However, it did not reduce subjective ratings for sleep and was also not associated with a change in perceptual responses to gastric distention. The beneficial effect of amitriptyline on dyspepsia symptoms was confirmed by Braak *et al.* (14). This study showed that amitriptyline was mostly effective in improving nausea but had no beneficial effect on the postprandial symptoms and on the drinking test capacity. Also, in the head-to-head study by Talley *et al.*, amitriptyline was effective and superior to escitalopram in patients with functional dyspepsia but mostly in patients with the ulcer-like subtype FD, a category comparable to the Rome IV defined EPS group (18). This suggest that amitriptyline can be a helpful treatment option for improving abdominal pain in patients with functional dyspepsia. Also, imipramine was shown to be effective in patients that had not responded to either PPIs or prokinetics in a RCT by Cheong *et al.* (13). However not all TCAs were shown to be effective. Nortriptyline

was not superior to placebo in improving dyspeptic symptoms and physical or mental aspects of quality of life in patients with functional dyspepsia refractory to PPIs and prokinetics (15).

The reported side effects for TCAs were drowsiness and dizziness for amitriptyline(14,18); dry mouth, constipation, drowsiness, insomnia, palpitations, blurred vision for imipramine (13); dizziness, dry mouth, constipation and fatigue for nortriptyline (15).

The selective serotonin reuptake inhibitors sertraline and escitalopram did not have a significant improving effect in patients with functional dyspepsia compared to placebo (17,18). SSRIs work by selectively boosting 5-HT neurotransmission, without noradrenergic effects which makes SSRIs more beneficial for treating anxiety disorders rather than chronic painful conditions (27). This can explain the lack of efficacy for SSRIs on functional dyspepsia. The reported side effects include insomnia, constipation and agitation for sertraline and dizziness for escitalopram. Nevertheless, SSRIs can still be useful in case of psychological comorbidity such as anxiety disorders (27).

Similar to SSRIs, the serotonin and norepinephrine reuptake inhibitor venlafaxine appeared to be not efficient in the treatment of functional dyspepsia shown in a RCT by Van Kerkhoven *et al.* (19). However, only one study evaluated SNRIs which makes it difficult to make assumptions about the true effect in this population. SNRIs work by blocking both 5-HT and NA reuptake (27). This makes SNRIs an indicated agent for treating painful somatic disorders and they are also commonly used for treating visceral pain (28). This mode of action is similar to TCAs with comparable pain reduction but with less side effects (28). A possible explanation for the lack of effectiveness for venlafaxine is that Van Kerkhoven *et al.* used venlafaxine in a dose of 150 mg while NA reuptake inhibition only applies for doses of 225 mg or more, reducing its central action to 5-HT blockage only (27). Duloxetine, another SNRI with NA reuptake inhibition effects at therapeutic doses, is often used in clinical practice, although there is no supportive evidence in the literature.

Atypical antidepressants like mianserin and mirtazapine could be useful in treating functional dyspepsia (20,21). Mirtazapine showed to improve early satiation, quality of life, gastro-intestinal-specific anxiety, nutrients tolerance and weight loss (20). Symptoms of epigastric pain and burning were not affected in contrary to symptoms of early satiation and to a lesser extent nausea. This suggests that mirtazapine may be most effective for the PDS subgroup. Tetracyclic antidepressants work by blocking the presynaptic α2 noradrenergic receptors on NA and 5-HT neurons which inhibits NA and 5-HT release from these neurons and thereby boosting 5-HT and NA neurotransmission (27). They possess an additional 5-HT3 antagonist property which induces some side effects like reduction in nausea, diarrhea and pain that can be favorable in functional dyspepsia patients. Mirtazapine has also histamine-1 (H1) and 5-HT_{2C} antagonist properties which explain the frequently observed weight gain and increased appetite that can be useful in functional dyspepsia as well.

Levosulpiride is the active form of sulpiride that blocks Dopamine 2 (D_2) dopaminergic receptors and has partial D_2 agonist properties when used in lower doses (27). Dopamine induces fundus relaxation and reduces the tone and contractility of the gastric antrum (22). Thus, blockage of dopamine results in stimulation of gastric motor activity during the digestive phase along with its central, anti-emetic actions (22,23). Levosulpiride accelerated both gastric and gallbladder emptying accompanied by improvement of dyspeptic symptoms in a study by Arienti *et al.* (22). This effect of levosulpiride on the gastric motor activity was confirmed by the study of Song *et al.* (23). Levosulpiride showed to be effective in the treatment of functional dyspepsia in patient with delayed gastric emptying (23). The only side effect reported in those studies was mild somnolence.

Even if less used for functional dyspepsia in clinical practice in Belgium, the combination of flupenthixol and melitracen, an antipsychotic and a tricyclic antidepressant, might be an effective short-term treatment of functional dyspepsia shown by a cross-over trial by Hashahs *et al.* (24).

Both the anxiolytic agents tandospirone and buspirone showed to be a possible effective treatment for functional dyspepsia by decreasing dyspepsia symptoms (25,26). When regarding to anxiety and quality of life, there were no significant results for tandospirone (26). Buspirone showed a significant effect on gastric accommodation compared to placebo but not on gastric emptying rate (25). They are known as non-benzodiazepine anxiolytics and work through their agonistic action on the pre- and post-synaptic 5-HT_{1A} receptors centrally, around the amygdala, as well as peripherally, at gastrointestinal level (27).

A systematic review and meta-analysis by Ford *et al.*, showed that neuromodulating agents could be effective for functional dyspepsia but the effectiveness of psychotropic drugs was reserved to only antipsychotics and tricyclic antidepressants (29). In a more recent systematic review and network meta-analysis, they confirmed this statement and showed that antipsychotics and secondly TCAs were superior to other treatment options like histamine-2 receptor antagonists, standard- and low-dose PPIs, itopride and acotiamide (30). An earlier Japanese systematic review by Hojo *et al.* classified anxiolytics and antidepressants as second-line treatment options for functional dyspepsia (31). In our review, we found a similar conclusion of TCAs and antipsychotics being superior to placebo as well as tetracyclic antidepressants. However, we did not perform a (network) meta-analysis because of the variable outcome measures used in the study and hence did not differentiate the effect of neuromodulating agents with other treatment options for functional dyspepsia and thus

cannot make a statement about the relative position of neuromodulating agents in a treatment plan. Previously mentioned systematic reviews also noted the relatively low quality of the individual studies and lack of hard evidence precluding a firm conclusion on efficacy (29-31). The added value of the current review lies in the detailed discussion of the individual studies highlighting also the variable outcome measures used in the studies.

Limitations

There are some limitations to our review. 1/ The study population was small in most RCTs. In total there were 1,205 patients included with the smallest study population being 7 and the largest being 292. 2/ This review was also challenging because of the multiple outcomes measured in the RCTs. There is no full consensus for the way of measuring dyspeptic symptoms. In addition, some RCTs evaluated more objective outcomes like gastric emptying or REM-sleep time of which the impact on symptoms is unclear, while others focused mainly on subjective symptom scores which makes it hard to compare the RCTs to each other. 3/ All the RCTs studied the short-term effect of neuromodulating agents. Little is known about the effects of these agents on the long term even though functional dyspepsia is a chronic disease that usually needs a long term treatment. 4/ Because most RCTs look at the short term treatment effect of these neuromodulating agents, there is little information about the side effects on long term. It has to be taken into account that there could be long term side effects caused by neuromodulating agents, some of which are more dangerous, like major cardiovascular adverse events for TCAs that occur at higher risk with longer duration of treatment (32). Although neuromodulating agents are mostly used in low doses for functional dyspepsia and thus have less side effects burden, possible long term side effects need to be evaluated in future studies. Finally, the current review was performed using one database (Pubmed) and only one researcher performed the initial search.

Conclusion

Tricyclic antidepressants, like amitriptyline and imipramine, seem to be effective in the treatment of functional dyspepsia. Also, tetracyclic antidepressants, antipsychotics and anxiolytic agents were shown to have a beneficial tendency but there is not sufficient evidence to make a well-founded recommendation. SNRIs and SSRIs do not seem to be effective in patients with functional dyspepsia. In the future, further research is necessary to provide adequate evidence for the use of certain neuromodulating agents in the treatment of functional dyspepsia. There is need for long term, large scale, head-to-head randomized controlled trials where 2 or more neuromodulating agents are compared, as well as network meta-analyses.

Conflict of interest

None

Financial disclosure

TV is supported by a senior clinical research fellowship of the Flanders Research Foundation (FWO Vlaanderen).

References

1. STANGHELLINI V., CHAN F.K.L., HASLER W.L., MALAGELADA J.R., SUZUKI H., TACK J., *et al.* Gastroduodenal Disorders. *Gastroenterology*, 2016, **150**(6): 1380-92.
2. WAUTERS L., DICKMAN R., DRUG V., MULAK A., SERRA J., ENCK P., *et al.* United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on functional dyspepsia. *Neurogastroenterol Motil.* 2021, **33**(9): e14238.
3. FORD A.C., MARWAHA A., SOOD R., MOAYYEDI P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. *Gut*, 2015, **64**(7): 1049-57.
4. SPERBER A.D., BANGDIWALA S.I., DROSSMAN D.A., GHOSHAL U.C., SIMREN M., TACK J., *et al.* Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. *Gastroenterology*, 2021, **160**(1): 99-114.e3.
5. VAN OUDENHOVE L., AZIZ Q. The role of psychosocial factors and psychiatric disorders in functional dyspepsia. *Nat Rev Gastroenterol Hepatol*., 2013, **10**(3): 158-67.
6. TALLEY N.J., LOCKE G.R., LAHR B.D., ZINSMEISTER A.R., TOUGAS G., LIGOZIO G., *et al.* Functional dyspepsia, delayed gastric emptying, and impaired quality of life. *Gut*, 2006, **55(7)**: 933-9.
7. LACY B.E., WEISER K.T., KENNEDY A.T., CROWELL M.D., TALLEY N.J. Functional dyspepsia: the economic impact to patients. *Aliment Pharmacol Ther.*, 2013, **38(2)**: 170-7.
8. CAMILLERI M., STANGHELLINI V. Current management strategies and emerging treatments for functional dyspepsia. *Nat Rev Gastroenterol Hepatol.*, 2013, **10(3)**: 187-94.
9. MASUY I., VAN OUDENHOVE L., TACK J. Review article: treatment options for functional dyspepsia. *Aliment Pharmacol Ther*., 2019, **49(9)**: 1134-72.
10. MOAYYEDI P., LACY B.E., ANDREWS C.N., ENNS R.A., HOWDEN C.W., VAKIL N. ACG and CAG Clinical Guideline: Management of Dyspepsia. *Am J Gastroenterol.*, 2017, **112(7)**: 988-1013.
11. VANHEEL H., FARRÉ R. Changes in gastrointestinal tract function and structure in functional dyspepsia. *Nat Rev Gastroenterol Hepatol*., 2013, **10(3)**: 142-9.
12. WAUTERS L., TALLEY N.J., WALKER M.M., TACK J., VANUYTSEL T. Novel concepts in the pathophysiology and treatment of functional dyspepsia. *Gut*, 2020, **69(3)**: 591-600.
13. CHEONG P.K., FORD A.C., CHEUNG C.K.Y., CHING J.Y.L., CHAN Y., SUNG J.J.Y., *et al.* Low-dose imipramine for refractory functional dyspepsia: a randomised, double-blind, placebo-controlled trial. *Lancet Gastroenterol Hepatol*., 2018, **3(12)**: 837-44.
14. BRAAK B., KLOOKER T.K., WOUTERS M.M., LEI A., VAN DEN WIJNGAARD R.M., BOECKXSTAENS G.E. Randomised clinical trial: the effects of amitriptyline on drinking capacity and symptoms in patients with functional dyspepsia, a double-blind placebo-controlled study. *Aliment Pharmacol Ther*., 2011, **34(6)**: 638-48.
15. KAOSOMBATWATTANA U., PONGPRASOBCHAI S., LIMSRIVILAI J., MANEERATTANAPORN M., LEELAKUSOLVONG S., TANWANDEE T. Efficacy and safety of nortriptyline in functional dyspepsia in Asians: A randomized double-blind placebo-controlled trial. *J Gastroenterol Hepatol*., 2018, **33(2)**: 411-7.
16. MERTZ H., FASS R., KODNER A., YAN-GO F., FULLERTON S., MAYER E.A. Effect of amitriptyline on symptoms, sleep, and visceral perception in patients with functional dyspepsia. *Am J Gastroenterol*., 1998, **93(2)**: 160-5.
17. TAN V.P.Y., CHEUNG T.K., WONG W.M., PANG R., WONG B.C.Y. Treatment of functional dyspepsia with sertraline: a double-blind randomized placebo-controlled pilot study. *World J Gastroenterol.*, 2012, **18(42)**: 6127-33.
18. TALLEY N.J., LOCKE G.R., SAITO Y.A., ALMAZAR A.E., BOURAS E.P., HOWDEN C.W., *et al.* Effect of Amitriptyline and Escitalopram on Functional Dyspepsia: A Multicenter, Randomized Controlled Study. *Gastroenterology*, 2015, **149(2)**: 340-349.e2.

19. VAN KERKHOVEN L.A.S., LAHEIJ R.J.F., APARICIO N., DE BOER W.A., VAN DEN HAZEL S., TAN A.C.I.T.L., *et al.* Effect of the antidepressant venlafaxine in functional dyspepsia: a randomized, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol*., 2008, **6(7)**: 746-52; quiz 718.
20. TACK J., LY H.G., CARBONE F., VANHEEL H., VANUYTSEL T., HOLVOET L., *et al.* Efficacy of Mirtazapine in Patients With Functional Dyspepsia and Weight Loss. *Clin Gastroenterol Hepatol*., 2016, **14(3)**: 385-392.e4.
21. TANUM L., MALT U.F. A new pharmacologic treatment of functional gastrointestinal disorder. A double-blind placebo-controlled study with mianserin. *Scand J Gastroenterol*., 1996, **31(4)**: 318-25.
22. ARIENTI V., CORAZZA G.R., SORGE M., BORIANI L., UGENTI F., BIAGI F., *et al*. The effects of levosulpiride on gastric and gall-bladder emptying in functional dyspepsia. *Aliment Pharmacol Ther.*, 1994, **8(6)**: 631-8.
23. SONG C.W., CHUN H.J., KIM C.D., RYU H.S., CHOE J.G., HYUN J.H. Effects of levosulpiride in patients with functional dyspepsia accompanied by delayed gastric emptying. *Korean J Intern Med*., 1998, **13(1)**: 15-21.
24. HASHASH J.G., ABDUL-BAKI H., AZAR C., ELHAJJ I.I., EL ZAHABI L., CHAAR H.F., *et al.* Clinical trial: a randomized controlled cross-over study of flupenthixol + melitracen in functional dyspepsia. *Aliment Pharmacol Ther*., 2008, **27(11)**: 1148-55.
25. TACK J., JANSSEN P., MASAOKA T., FARRÉ R., VAN OUDENHOVE L. Efficacy of buspirone, a fundus-relaxing drug, in patients with functional dyspepsia. *Clin Gastroenterol Hepatol*., 2012, **10(11)**: 1239-45.
26. MIWA H., NAGAHARA A., TOMINAGA K., YOKOYAMA T., SAWADA Y., INOUE K., *et al.* Efficacy of the 5-HT1A agonist tandospirone citrate in improving symptoms of patients with functional dyspepsia: a randomized controlled trial. *Am J Gastroenterol.*, 2009, **104(11)**: 2779-87.
27. DROSSMAN D.A., TACK J., FORD A.C., SZIGETHY E., TÖRNBLOM H., VAN OUDENHOVE L. Neuromodulators for Functional Gastrointestinal Disorders (Disorders of Gut-Brain Interaction): A Rome Foundation Working Team Report. *Gastroenterology*, 2018, **154(4)**: 1140-1171.e1.
28. SOBIN W.H., HEINRICH T.W., DROSSMAN D.A. Central Neuromodulators for Treating Functional GI Disorders: *A Primer. Am J Gastroenterol.*, 2017, **112(5)**: 693-702.
29. FORD A.C., LUTHRA P., TACK J., BOECKXSTAENS G.E., MOAYYEDI P., TALLEY N.J. Efficacy of psychotropic drugs in functional dyspepsia: systematic review and meta-analysis. *Gut*, 2017, **66(3)**: 411-20.
30. FORD A.C., MOAYYEDI P., BLACK C.J., YUAN Y., VEETTIL S.K., MAHADEVA S., *et al.* Systematic review and network meta-analysis: efficacy of drugs for functional dyspepsia. *Aliment Pharmacol Ther.*, 2021, **53(1)**: 8-21.
31. HOJO M., NAGAHARA A., ASAOKA D., SHIMADA Y., SASAKI H., MATSUMOTO K., *et al.* A Systematic Review of the Effectiveness of Antianxiety and Antidepressive Agents for Functional Dyspepsia. *Intern Med*., 2017, **56(23)**: 3127-33.
32. JANG H.Y., KIM J.H., SONG Y.-K., SHIN J.-Y., LEE H.-Y., AHN Y.M., *et al*. Antidepressant Use and the Risk of Major Adverse Cardiovascular Events in Patients Without Known Cardiovascular Disease: A Retrospective Cohort Study. *Front Pharmacol*., 2020, **11**: 594474.