

## REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

## Functional Dyspepsia

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**D**YSPEPSIA IS A CONSTELLATION OF SYMPTOMS REFERABLE TO THE GASTRODUODENAL region of the upper gastrointestinal tract. Functional dyspepsia, a relapsing and remitting disorder, is the most common cause of these symptoms. The current standard for the diagnosis of functional dyspepsia is the Rome III criteria, developed by the Rome III Committees, a multinational group of experts in the field, first convened in 1990, that meets regularly to review and revise the diagnostic criteria for all functional gastrointestinal disorders.

The Rome III criteria for functional dyspepsia consist of a sensation of pain or burning in the epigastrium, early satiety (inability to finish a normal-sized meal), fullness during or after a meal, or a combination of these symptoms (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Symptoms must be chronic, occurring at least weekly and over a period of at least 6 months, in the absence of an organic explanation.<sup>1</sup> The global prevalence of functional dyspepsia in the community according to this definition is between 5% and 11%.<sup>2</sup>

Up to 40% of persons who have functional dyspepsia consult a physician,<sup>3</sup> and the condition negatively affects attendance and productivity in the workplace.<sup>4</sup> Functional dyspepsia has substantial financial implications for patients, health care organizations, and society as a whole; costs associated with the condition in the United States in 2009 were in excess of \$18 billion.<sup>5</sup> It is therefore important that physicians be able to recognize functional dyspepsia, use investigations and diagnostic tests judiciously, and recommend effective treatments, in order to minimize the potential adverse social and economic effects of the condition.

## DIAGNOSIS OF FUNCTIONAL DYSPEPSIA

Symptoms do not reliably distinguish between organic and functional forms of the disease,<sup>6,7</sup> so the challenge for the physician evaluating a patient with dyspepsia lies in discriminating between functional dyspepsia and organic conditions of the stomach or duodenum that may provoke similar symptoms (Table 1). In most cases, the cause can be clarified by means of upper gastrointestinal endoscopy, a test that generally shows that less than 10% of patients with dyspepsia have a peptic ulcer, less than 1% have gastroesophageal cancer, and more than 70% have functional dyspepsia.<sup>8</sup> Celiac disease is the great mimic of many gastrointestinal disorders, but its frequency is not significantly increased among persons who report dyspepsia.<sup>9</sup> The patient's medication history should be reviewed, but medication is not usually implicated in causing the dyspepsia.<sup>10</sup>

Given that upper gastrointestinal endoscopy is associated with a relatively low rate of identification of organic disease, it is neither desirable nor realistic to perform this test in all patients with dyspepsia. A primary care-based study showed that the cost of detecting each case of upper gastrointestinal cancer among patients

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**Table 1. Possible Underlying Causes of Symptoms of Dyspepsia.**

Functional dyspepsia
Peptic ulcer disease and infection with <i>Helicobacter pylori</i>
Gastroesophageal cancer
Gastroparesis
Gallstones, sphincter of Oddi dysfunction, biliary dyskinesia, or gallbladder cancer
Drugs (e.g., nonsteroidal antiinflammatory drugs, iron, calcium antagonists, angiotensin-converting-enzyme inhibitors, methylxanthines, and glucocorticoids)
Chronic pancreatitis or pancreatic cancer
Parasites (e.g., <i>Giardia lamblia</i> , strongyloides, and anisakis)
Hepatocellular carcinoma
Chronic mesenteric ischemia
Crohn's disease
Infiltrative diseases (e.g., eosinophilic gastroenteritis and sarcoidosis)

**Table 2. Alarm Symptoms of an Underlying Upper Gastrointestinal Cancer.**

Age >55 yr with new-onset dyspepsia*
Evidence of overt gastrointestinal bleeding including melena or hematemesis
Dysphagia, especially if progressive, or odynophagia
Persistent vomiting
Unintentional weight loss
Family history of gastric or esophageal cancer
Palpable abdominal or epigastric mass or abnormal adenopathy
Evidence of iron-deficiency anemia after blood testing

\* In regions with a high background prevalence rate of gastric cancer, such as Southeast Asia, a lower age threshold should be considered.

with dyspepsia was more than \$80,000,<sup>11</sup> which provides support for a selective approach. Guidelines recommend that patients with dyspepsia who report so-called alarm symptoms (Table 2), which may indicate an underlying gastroesophageal cancer, be referred urgently for upper gastrointestinal endoscopy<sup>12</sup>; however, only a small percentage of patients who undergo this test have such a cancer, which indicates that alarm symptoms have only modest predictive capability.<sup>13</sup>

For patients with simple dyspepsia who do not have alarm symptoms, in whom the likeliest diagnosis is functional dyspepsia, the requirement for any further diagnostic testing depends on the background prevalence of *Helicobacter pylori* infection. In populations in which the prevalence of infection is at least 10%, noninvasive testing for *H. pylori*, with either carbon-13-labeled urea

breath testing or stool antigen testing, is recommended.<sup>12</sup> In practice, however, because it is unlikely that the physician will be aware of the local prevalence of *H. pylori*, it is reasonable to use one of these tests as a first-line strategy, given that the testing is neither invasive nor prohibitively expensive.

Functional dyspepsia may be confused with other gastrointestinal conditions outside the gastroduodenal region, including other functional disorders.<sup>14</sup> In the past 20 years, there has been a concerted effort to standardize the definitions of functional dyspepsia, in part to minimize the likelihood of overlap with other functional gastrointestinal disorders. For the most part, this goal has been achieved by excluding from the definition of functional dyspepsia persons with symptoms suggestive of gastroesophageal reflux disease (GERD), such as retrosternal burning pain, regurgitation of acid into the mouth, or the irritable bowel syndrome, which is characterized by lower abdominal pain or discomfort associated with a change in stool form or frequency.<sup>1</sup> Despite this effort, in one study, more than 50% of the patients who met the criteria for functional dyspepsia and who had normal 48-hour pH studies reported heartburn and regurgitation, which were the predominant symptoms in 30% of these patients.<sup>15</sup> Common underlying mechanisms, such as failure of the gastric fundus to relax properly, may account for such symptoms in patients with overlapping functional dyspepsia and heartburn.<sup>16</sup> In a factor-analysis study, the presence of lower gastrointestinal symptoms, such as diarrhea and constipation, increased the ability of physicians to discriminate between people with functional dyspepsia and those without it.<sup>17</sup>

There is also overlap between symptoms of functional dyspepsia and those of gastroparesis. More than one in four patients with functional dyspepsia have evidence of delayed gastric emptying,<sup>18</sup> and in one study 86% of the patients with gastroparesis met the criteria for functional dyspepsia,<sup>19</sup> which suggests that these conditions share similar pathophysiological features; the degree of overlap of symptoms also means that the capacity of diagnostic tests such as gastric scintigraphy to discriminate between functional dyspepsia and gastroparesis is limited.<sup>20</sup> The usefulness of ultrasonography in detecting relevant organic pancreatobiliary disease in pa-

tients with dyspepsia who have normal results on upper gastrointestinal endoscopy was less than 5% in one primary care–based study.<sup>21</sup>

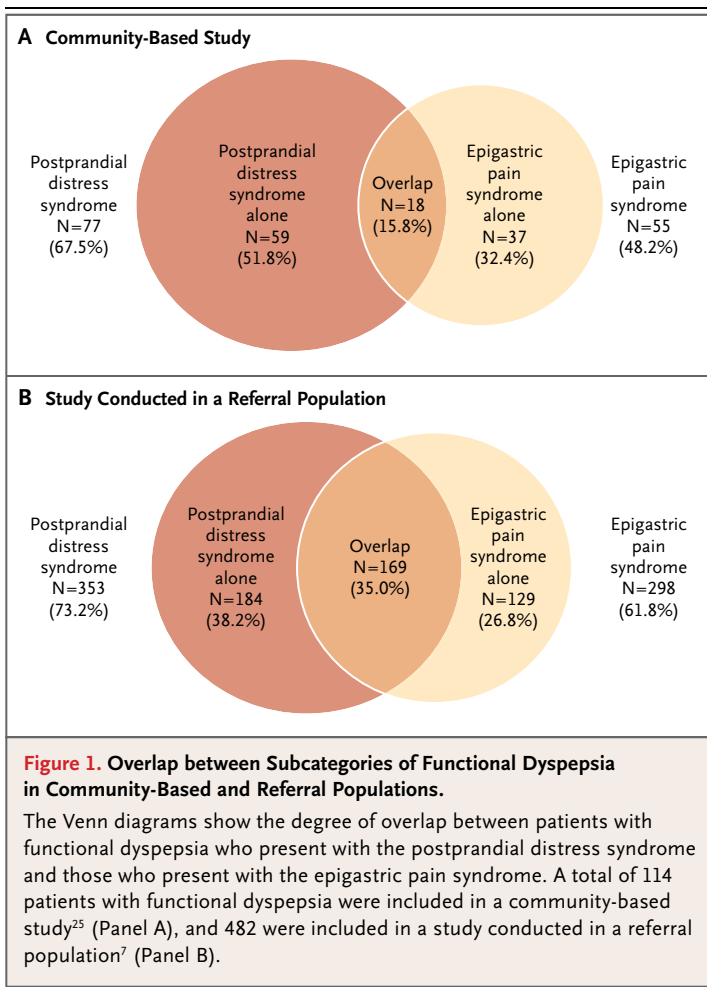
#### CLASSIFICATION OF FUNCTIONAL DYSPEPSIA

In the past 10 years, the terminology used to describe functional dyspepsia has changed, moving away from grouping patients according to the predominant reported symptom as having ulcer-like, reflux-like, or dysmotility-like functional dyspepsia and instead describing them as having one of two newly defined syndromes, the epigastric pain syndrome and the postprandial distress syndrome. The epigastric pain syndrome consists of intermittent pain or burning in the epigastrium, occurring at least once per week, and the postprandial distress syndrome is marked by the occurrence at least several times per week of bothersome postprandial fullness occurring after normal-sized meals or by early satiety that prevents the person from finishing a regular meal (Table S1 in the Supplementary Appendix).<sup>1</sup>

These two syndromes were proposed because as many as 80% of persons with dyspepsia report that their symptoms are aggravated by the ingestion of a meal.<sup>22</sup> The definitions were also based on factor analysis that showed the grouping of dyspeptic symptoms into three or four clusters,<sup>23,24</sup> with the epigastric pain syndrome and the postprandial distress syndrome appearing consistently in several different studies. Subsequent community-based cross-sectional surveys, which showed good separation between these two subgroups, support this approach.<sup>25</sup> Studies in referral populations are less convincing, however, with a greater degree of overlap evident between the epigastric pain syndrome and the postprandial distress syndrome (Fig. 1).<sup>7,26</sup> The rationale for assigning patients into these two syndrome subtypes in the clinic is that the classification may help guide therapy.

#### PATHOPHYSIOLOGICAL FEATURES OF FUNCTIONAL DYSPEPSIA

Psychological distress, particularly anxiety, is associated with functional dyspepsia and may precede the onset of the disorder in some persons.<sup>27</sup> In others, the gut symptoms occur before



the onset of anxiety, which suggests that a gut-driven brain disorder may explain some cases.<sup>28</sup> Central pain processing may be abnormal in persons with functional dyspepsia,<sup>29</sup> although whether it is caused by gut disturbances or is a primary symptom is uncertain.<sup>30</sup> Genetic factors have also been implicated in functional dyspepsia, but the associations remain weak.<sup>31</sup>

Functional dyspepsia has conventionally been attributed to a disturbance of gastric physiologic factors, such as slow gastric emptying, failure of the gastric fundus to relax after a meal (fundic disaccommodation, which is a vagal reflex), or gastric hypersensitivity with distention of the stomach.<sup>32</sup> Some patients with functional dyspepsia have none of these abnormalities, and any link with specific symptoms is unconvincing, except possibly for the inability to finish a normal meal and fundic failure.<sup>18,22</sup> Gastric accommodation failure is also linked to transient

relaxations of the lower esophageal sphincter that occur in GERD and may, in part, explain the overlap of GERD with functional dyspepsia.<sup>16</sup> Duodenal hypersensitivity to acid or distention has also been reported in patients with functional dyspepsia.<sup>33</sup>

Infections may cause functional dyspepsia, but Koch's postulates have not yet been fulfilled for any microbe. The occurrence of a postinfectious irritable bowel syndrome is well established; however, gastroenteritis can also lead to functional dyspepsia or to a persistent combination of functional dyspepsia and symptoms of the irritable bowel syndrome. Salmonella, *Escherichia coli* O157, *Campylobacter jejuni*, *Giardia lamblia*, and norovirus may induce functional dyspepsia; risk factors include genetic factors and smoking.<sup>34</sup> It is conceivable that functional dyspepsia arises when the proximal small intestine or stomach becomes inflamed after an enteric infection, whereas the irritable bowel syndrome may arise from involvement of the distal small intestine or colon; if both the proximal and distal small intestine are inflamed, an overlap syndrome (the irritable bowel syndrome and functional dyspepsia) may be likely,<sup>35</sup> although this hypothesis needs formal testing.

Duodenal inflammation has been observed in up to 40% of patients with functional dyspepsia, particularly subtle duodenal eosinophilia with, in some cases, excess clusters of eosinophils and eosinophil degranulation adjacent to nerves (Fig. S1 in the Supplementary Appendix).<sup>36-38</sup> Duodenal eosinophilia has been linked to smoking and to symptoms of early satiety and pain; barrier disruption and increased duodenal permeability have been documented.<sup>36,39</sup> In some cases, mast cells that can recruit eosinophils have also been observed in functional dyspepsia, but the patient population that was studied included patients with both functional dyspepsia and the irritable bowel syndrome.<sup>39</sup> Further evidence linking intestinal inflammation to functional dyspepsia is provided by the finding of enhanced small-bowel homing T lymphocytes that are positive for both  $\alpha_4\beta_7$  integrin and chemokine receptor 9 in patients with functional dyspepsia — a finding that has been significantly associated with the release of cytokines (including tumor necrosis factor  $\alpha$ ), a greater severity of symptoms, and delayed gastric emptying,<sup>40</sup> thus implicating the duodenum in gastric disorders.<sup>41</sup>

Together, these findings suggest that some

patients with functional dyspepsia may have an organic mechanism for their symptoms. Another likely infectious cause is *H. pylori*. Although *H. pylori* infection is usually asymptomatic, in a small subgroup of patients with functional dyspepsia the eradication of infection leads to the long-term resolution of symptoms.<sup>42</sup> The role of other components of the microbiome in functional dyspepsia is unknown.<sup>43</sup>

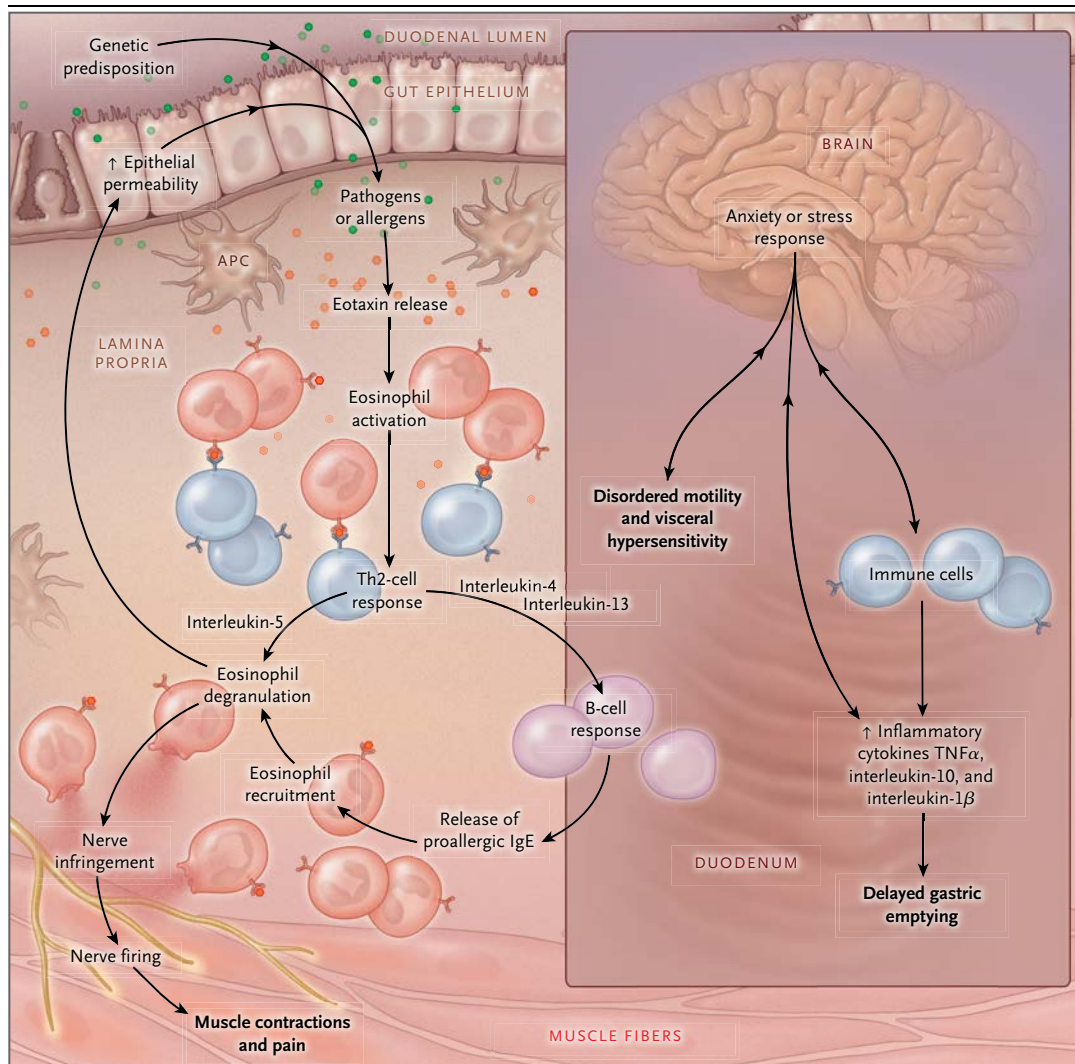
Functional dyspepsia is most often a meal-induced syndrome.<sup>22,44</sup> A high-fat meal, for example, can alter gastroduodenal physiology by means of altered gut-hormone responses,<sup>45</sup> including by raising cholecystokinin levels.<sup>46</sup> Food intolerance or allergy may play a direct role in functional dyspepsia, but this possibility has been poorly studied.<sup>47</sup>

An overarching disease model postulates that, in genetically predisposed persons, an allergen or infection leads to antigen presentation, barrier disruption, immune activation, and a type 2 helper T-cell response in functional dyspepsia, in which eosinophils are recruited that degranulate in some patients (Fig. 2).<sup>48</sup> In some patients, this process can lead to tissue injury and symptoms, whereas in others eosinophils may be protective and promote healing. An inflamed duodenum may be sensitive to acid and induce reflex responses and cytokine release that alter gastroduodenal function and result in meal-related symptoms. If this hypothesis is correct, then some patients with functional dyspepsia may have a response to therapy targeted at immune activation, but this remains to be established; however, preliminary data in children suggest that montelukast, a leukotriene-receptor antagonist, reduces symptoms.<sup>49</sup>

## TREATMENT OF FUNCTIONAL DYSPEPSIA

### PLACEBO OR REASSURANCE

The rate of response to placebo in trials involving patients with functional dyspepsia is 30% to 40%,<sup>42,50</sup> but factors that influence this rate have not been analyzed systematically. A randomized clinical trial that compared placebo with no treatment in patients with the irritable bowel syndrome<sup>51</sup> showed a significantly greater likelihood of adequate relief of symptoms with placebo, but we are unaware of any similar trials involving patients with functional dyspepsia. There have also been no randomized trials of



**Figure 2. An Overarching Disease Model of Functional Dyspepsia.**

In the presence of a background genetic disposition, a type 2 helper T (Th2)–cell response may be activated in the duodenum, possibly by allergens or pathogens, which cross through the gut epithelium. Resident and recruited eosinophils may be activated by eotaxin, which is expressed constitutively in the lamina propria, and act as antigen-presenting cells to Th2 lymphocytes, which in turn express interleukin-5. This process can lead to eosinophil degranulation that impinges on nerve fibers, which may then fire, inducing muscle contraction or pain. Duodenal feedback by means of interleukin-4 and interleukin-13, also expressed by Th2 cells, may promote immunoglobulin class switching to proallergic IgE antibody expression by B cells, further recruiting eosinophils and leading to degranulation with increased epithelial permeability. The cytokines tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin-10, and interleukin-1 $\beta$  can then be released into the blood and invoke an anxiety or stress response, which in turn may lead to disordered motility and visceral hypersensitivity in the stomach and duodenum. Gut-homing T cells may also increase in number and produce excess inflammatory cytokines that could then delay gastric emptying. APC denotes antigen-presenting cell.

reassurance as a treatment strategy in patients with functional dyspepsia, although this approach is often used by physicians. It should be pointed out that any reassurance derived from investigations that have ruled out organic disease is minimal.<sup>52</sup>

#### **H. PYLORI ERADICATION THERAPY**

Although 5% of the cases of dyspepsia in the community are attributable to infection with *H. pylori*,<sup>53</sup> the effect of eradication therapy on the symptoms of functional dyspepsia is modest. In a meta-analysis of 17 randomized trials,

involving 3566 patients, the relative risk of persistent symptoms was 0.90 (95% confidence interval [CI], 0.86 to 0.94), with a number needed to treat of 15.<sup>42</sup> Nevertheless, economic modeling that was based on these data suggests that eradication therapy is a cost-effective strategy for managing functional dyspepsia.<sup>54</sup> Evidence continues to accumulate that such therapy is beneficial.<sup>55</sup> A trial assessing the effect of eradication therapy according to individual symptoms reported by the patient<sup>56</sup> showed a significant effect on epigastric pain and burning but not on early satiety or postprandial fullness. These data suggest that the benefit of eradication therapy may be more pronounced in patients with the epigastric pain syndrome than in others.

#### ACID-SUPPRESSION THERAPY

Despite evidence of impaired duodenal clearance of gastric acid and duodenal hypersensitivity to infused gastric acid in persons with functional dyspepsia,<sup>33</sup> the efficacy of acid-suppressive drugs such as proton-pump inhibitors (PPIs) or histamine H<sub>2</sub>-receptor antagonists is modest. A Cochrane meta-analysis of 10 randomized trials of PPIs, involving 3347 patients, reported a relative risk of persistent symptoms of 0.87 (95% CI, 0.80 to 0.96) and a number needed to treat of 10.<sup>50</sup> For histamine H<sub>2</sub>-receptor antagonists, the effect was more pronounced than with PPIs (relative risk, 0.77; 95% CI, 0.65 to 0.92; number needed to treat, 7), but the quality of the trials was lower. The majority of these trials were completed before the Rome III classification of functional dyspepsia, and subgroup analyses were therefore conducted according to the predominant symptoms reported by the patients rather than according to whether the patients had the epigastric pain syndrome or the postprandial distress syndrome.

The meta-analysis showed that PPIs were effective in patients reporting reflux-like or ulcer-like functional dyspepsia but not in patients with dysmotility-like functional dyspepsia.<sup>12</sup> However, a recent trial conducted in Japan that confirmed the efficacy of the PPI rabeprazole in patients with functional dyspepsia did not show any difference in the effect of treatment according to whether patients met the criteria for the epigastric pain syndrome or the postprandial distress syndrome.<sup>57</sup> A trial of acid suppression seems to be a worthwhile strategy in most patients with functional dyspepsia, particularly in those who

have negative results on *H. pylori* testing or in those with positive results on *H. pylori* testing in whom eradication therapy has not improved symptoms. Antacids, bismuth, and sucralfate are not efficacious in functional dyspepsia.<sup>12</sup>

#### PROKINETIC AGENTS

A substantial proportion of patients with functional dyspepsia have abnormalities in gastric motility and fundal accommodation.<sup>58</sup> Existing prokinetic agents, including cisapride, domperidone, and itopride, have all been tested in functional dyspepsia and have been shown to be more effective than placebo in a meta-analysis of 24 randomized trials.<sup>50</sup> Cisapride was withdrawn because of its increased risk of adverse cardiac events, including sudden death due to a prolonged QT interval, and itopride was no more effective than placebo in two large trials published after this meta-analysis.<sup>59</sup> Metoclopramide is not recommended routinely because of its uncertain efficacy and side effects (including irreversible tardive dyskinesia), and the prescription of domperidone in the United States requires an Investigational New Drug application to the Food and Drug Administration.<sup>60</sup>

Partly as a result of the lack of efficacy of these drugs, new agents have been developed and tested in recent years. Acotiamide is an acetylcholinesterase inhibitor that accelerates gastric emptying and enhances gastric accommodation.<sup>61</sup> In a double-blind, placebo-controlled trial involving 897 patients with functional dyspepsia in Japan, symptoms improved in 52% of those assigned to active therapy, as compared with 35% of those assigned to placebo ( $P < 0.001$ ).<sup>62</sup> When the effect of acotiamide on individual dyspeptic symptoms was studied, significant improvements were identified in postprandial fullness, upper abdominal bloating, and early satiety but not in upper abdominal pain or discomfort. The drug has now been approved for the treatment of the postprandial distress syndrome in Japan, and phase 3 trials are ongoing in Western populations.

Drugs such as buspirone and tandospirone, which act on the 5-hydroxytryptamine-1<sub>A</sub> receptor, leading to relaxation of the gastric fundus, have also been tested in functional dyspepsia. A randomized crossover trial of buspirone in 17 patients with functional dyspepsia showed that the drug was effective in relaxing the gastric fundus and reduced bloating and postprandial

fullness.<sup>63</sup> In a double-blind, placebo-controlled study involving 144 patients, the response rate after 4 weeks of treatment with tandospirone was 31.5%, as compared with 12.7% with placebo ( $P=0.002$ ).<sup>64</sup>

#### ANTIDEPRESSANTS

Because of the potential role of the brain–gut axis and abnormal central pain processing in functional dyspepsia,<sup>29,30</sup> antidepressants have been suggested as a second-line or third-line therapy for many years, but it is only in the past decade that their efficacy has been tested in large, rigorously designed clinical trials. A trial of venlafaxine in 160 patients with functional dyspepsia showed no benefit after 8 weeks of treatment (37% of the patients were symptom free with venlafaxine, as compared with 39% with placebo).<sup>65</sup> In a placebo-controlled trial of sertraline in 193 patients in China, 28% of the patients randomly assigned to the active drug had complete relief of their symptoms, as compared with 28% of those assigned to placebo.<sup>66</sup>

Mirtazapine has also been assessed in 34 patients with functional dyspepsia and weight loss<sup>67</sup>; significant improvements were seen in early satiety and quality of life at 8 weeks in the patients assigned to mirtazapine, as compared with those assigned to placebo. More recently, in a large North American multicenter trial, 292 patients with functional dyspepsia were assigned to amitriptyline, escitalopram, or placebo.<sup>68</sup> The rate of response after 10 weeks was 53% with amitriptyline, 38% with escitalopram, and 40% with placebo ( $P=0.05$  for the three-way comparison). Taken together, these data suggest that tricyclic antidepressants, such as amitriptyline, should be preferred over selective serotonin-reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors for the treatment of functional dyspepsia.

#### PSYCHOLOGICAL THERAPY

The use of psychological therapy in functional dyspepsia remains an under-studied area. A Cochrane review published 10 years ago identified only four studies and highlighted the need for more research addressing this issue.<sup>69</sup> Few studies have been published since this review, although a recent trial involving 158 patients with functional dyspepsia in Spain randomly assigned participants to receive conventional medical treatment or conventional medical treatment plus

psychotherapy.<sup>70</sup> There were significant improvements in dyspepsia-related quality-of-life and symptom scores at 10 weeks with psychotherapy, and these effects persisted for as long as 6 months after the end of treatment. However, these data should be regarded as preliminary.

More studies will be required before the place of psychological therapy in the treatment of functional dyspepsia is known. That said, such treatment should probably be considered for patients who have not had any improvement in their symptoms with conventional medical therapies, particularly in those with coexisting impairment of mood.

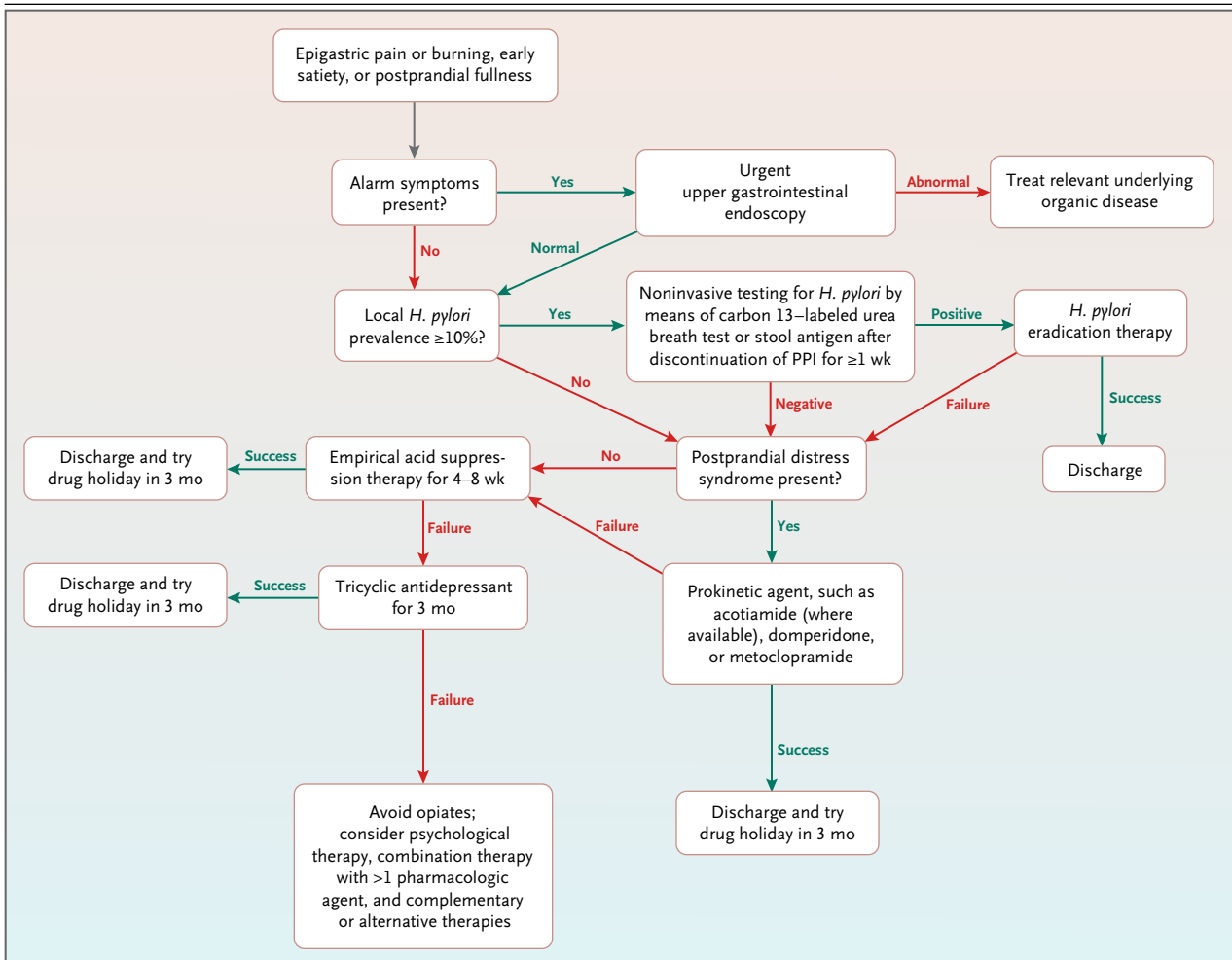
#### COMPLEMENTARY AND ALTERNATIVE THERAPY

Given the limited efficacy of the majority of conventional medical therapies, it is not surprising that up to 50% of patients with functional dyspepsia seek out other forms of treatment<sup>71</sup>; in one study, nearly 50% of the patients were willing to accept a 12.7% risk of sudden death with a drug that offered a 99% chance of cure,<sup>72</sup> in the hope of improving their symptoms and quality of life. However, consistent evidence of the efficacy of acupuncture, homeopathy, or probiotics in functional dyspepsia is lacking.

Some patients may find herbal supplements, such as the nine-herb combination product *iberogast* (also known as STW5),<sup>73</sup> beneficial, and STW5 has been observed to relax the gastric fundus.<sup>74</sup> Capsaicin, a component of red pepper, was superior to placebo in terms of the reduction in symptom scores in one small trial,<sup>75</sup> but more studies are needed before any definitive conclusions can be drawn. Disordered sleep is more common in patients with functional dyspepsia than in healthy controls without functional dyspepsia, and it appears to be correlated with the severity of symptoms,<sup>76</sup> but no intervention studies have been performed.

#### MANAGEMENT OF FUNCTIONAL DYSPEPSIA

All patients with functional dyspepsia should be offered a positive diagnosis after targeted investigation, reassurance that the disorder does not negatively affect survival,<sup>77</sup> and an explanation of the probable origin of symptoms. Attention to stress reduction and lowering of anxiety is important, and dietary advice should be provided (e.g., ingestion of small, regular, low-fat meals and avoidance of foods that precipitate symptoms, if possible). However, there is no evidence



**Figure 3. Recommended Treatment Algorithm for Patients with a Provisional Diagnosis of Functional Dyspepsia.**

This treatment algorithm can be applied in patients who present with epigastric pain or burning, early satiety, or postprandial fullness. In the case of treatment failure, the clinician should reevaluate and reconsider the diagnosis at each step by means of further investigations, such as upper gastrointestinal endoscopy if the procedure has not been performed within the past 5 years; ultrasonography of the abdomen, particularly if the patient has severe, intermittent episodes of pain; serologic testing for celiac disease; and gastric scintigraphy or carbon-13–labeled octanoic or spirulina (*Arthrospira platensis*) breath test to assess gastric emptying if the symptoms are severe or resistant to treatment or if the patient has vomiting and prominent weight loss. There are no data from randomized trials in support of using metoclopramide to treat patients with the postprandial distress syndrome; we suggest starting the drug at a low dose owing to the potential for cardiac and neurologic toxic effects. PPI denotes proton-pump inhibitor.

to support the screening of all patients with functional dyspepsia for anxiety or for treating those in whom it is present with an anxiolytic. A treatment algorithm is presented in Figure 3.

#### MANAGEMENT OF REFRACTORY FUNCTIONAL DYSPEPSIA

In patients whose symptoms do not respond to standard medical therapy, treatment is empirical. In our experience, histamine  $H_2$ -receptor antagonists may help even if PPIs have failed.

The combination of acid suppression with a prokinetic agent appears to benefit some other patients. The combination of peripheral drug therapy with psychological treatment is promising.<sup>70</sup>

If pain is the predominant symptom despite these strategies, the physician should consider other options, although these are empirical and not evidence-based.<sup>78</sup> Approaches that may be helpful include adjusting the dose of a tricyclic antidepressant to the full antidepressant level, prescribing an antipsychotic drug such as levo-



sulpiride,<sup>79</sup> or adding an anxiolytic (e.g., buspirone) to a tricyclic antidepressant. The combination of an antidepressant with pregabalin or gabapentin is yet another option that appears to relieve pain. Opioids have no therapeutic role in the management of functional dyspepsia and should be avoided because of the risk of dependence, the frequent failure of analgesia, and possibility of the narcotic bowel syndrome.<sup>80</sup>

#### PROGNOSIS IN FUNCTIONAL DYSPEPSIA

In most patients with functional dyspepsia, the natural history is chronic and fluctuating, with periods of time when the patient is asymptomatic followed by episodes of symptom relapse. Data from population-based studies suggest that, during extended follow-up, approximately 15 to 20% of people with functional dyspepsia have persistent symptoms and 50% have resolution of symptoms; in the remaining 30 to 35% of patients symptoms will fluctuate and meet the criteria for another functional gastrointestinal

disorder.<sup>81</sup> Despite the chronic nature of functional dyspepsia, there is no evidence to suggest that it is associated with decreased survival.<sup>77</sup>

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#### REFERENCES

- Tack J, Talley NJ, Camilleri M, et al. Functional gastroduodenal disorders. *Gastroenterology* 2006;130:1466-79.
- Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. *Gut* 2015;64:1049-57.
- Ford AC, Forman D, Bailey AG, Cook MB, Axon ATR, Moayyedi P. Who consults with dyspepsia? Results from a longitudinal 10-yr follow-up study. *Am J Gastroenterol* 2007;102:957-65.
- Sander GB, Mazzoleni LE, Francesconi CF, et al. Influence of organic and functional dyspepsia on work productivity: the HEROBS-DIP study. *Value Health* 2011;14:Suppl 1:S126-S129.
- Lacy BE, Weiser KT, Kennedy AT, Crowell MD, Talley NJ. Functional dyspepsia: the economic impact to patients. *Aliment Pharmacol Ther* 2013;38:170-7.
- Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. The Rome III criteria for the diagnosis of functional dyspepsia in secondary care are not superior to previous definitions. *Gastroenterology* 2014;146:932-40.
- Fang YJ, Liou JM, Chen CC, et al. Distinct aetiopathogenesis in subgroups of functional dyspepsia according to the Rome III criteria. *Gut* 2015;64:1517-28.
- Ford AC, Marwaha A, Lim A, Moayyedi P. What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia? Systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2010;8:830-7.
- Ford AC, Ching E, Moayyedi P. Meta-analysis: yield of diagnostic tests for coeliac disease in dyspepsia. *Aliment Pharmacol Ther* 2009;30:28-36.
- Hallas J, Bytzer P. Screening for drug related dyspepsia: an analysis of prescription symmetry. *Eur J Gastroenterol Hepatol* 1998;10:27-32.
- Vakil N, Talley NJ, van Zanten SV, et al. Cost of detecting malignant lesions by endoscopy in 2741 primary care dyspeptic patients without alarm symptoms. *Clin Gastroenterol Hepatol* 2009;7:756-61.
- Talley NJ, Vakil NB, Moayyedi P. American Gastroenterological Association technical review on the evaluation of dyspepsia. *Gastroenterology* 2005;129:1756-80.
- Vakil N, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. *Gastroenterology* 2006;131:390-401.
- Pleyer C, Bittner H, Locke GR III, et al. Overdiagnosis of gastro-esophageal reflux disease and underdiagnosis of functional dyspepsia in a USA community. *Neurogastroenterol Motil* 2014;26:1163-71.
- Vakil N, Halling K, Ohlsson L, Wernersson B. Symptom overlap between postprandial distress and epigastric pain syndromes of the Rome III dyspepsia classification. *Am J Gastroenterol* 2013;108:767-74.
- Pauwels A, Altan E, Tack J. The gastric accommodation response to meal intake determines the occurrence of transient lower esophageal sphincter relaxations and reflux events in patients with gastroesophageal reflux disease. *Neurogastroenterol Motil* 2014;26:581-8.
- Matsuzaki J, Suzuki H, Asakura K, et al. Classification of functional dyspepsia based on concomitant bowel symptoms. *Neurogastroenterol Motil* 2012;24(4):325-e164.
- Sarnelli G, Caenepeel P, Geypens B, Janssens J, Tack J. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. *Am J Gastroenterol* 2003;98:783-8.
- Parkman HP, Yates K, Hasler WL, et al. Clinical features of idiopathic gastroparesis vary with sex, body mass, symptom onset, delay in gastric emptying, and gastroparesis severity. *Gastroenterology* 2011;140:101-15.
- Stanghellini V, Tack J. Gastroparesis: separate entity or just a part of dyspepsia? *Gut* 2014;63:1972-8.
- Heikkinen M, Räsänen H, Färkkilä M. Clinical value of ultrasound in the evaluation of dyspepsia in primary health care. *Scand J Gastroenterol* 2005;40:980-4.
- Bisschops R, Karamanolis G, Arts J,

- et al. Relationship between symptoms and ingestion of a meal in functional dyspepsia. *Gut* 2008;57:1495-503.
23. Piessevaux H, De Winter B, Louis E, et al. Dyspeptic symptoms in the general population: a factor and cluster analysis of symptom groupings. *Neurogastroenterol Motil* 2009;21:378-88.
  24. Camilleri M, Dubois D, Coullie B, et al. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. *Clin Gastroenterol Hepatol* 2005;3:543-52.
  25. Zagari RM, Law GR, Fuccio L, et al. Epidemiology of functional dyspepsia and subgroups in the Italian general population: an endoscopic study. *Gastroenterology* 2010;138:1302-11.
  26. van Kerkhoven LA, Laheij RJ, Meineche-Schmidt V, Veldhuyzen-van Zanten SJ, de Wit NJ, Jansen JB. Functional dyspepsia: not all roads seem to lead to Rome. *J Clin Gastroenterol* 2009;43:118-22.
  27. Aro P, Talley NJ, Johansson SE, Agréus L, Ronkainen J. Anxiety is linked to new-onset dyspepsia in the Swedish population: a 10-year follow-up study. *Gastroenterology* 2015;148:928-37.
  28. Koloski NA, Jones M, Kalantar J, Weltman M, Zaguirre J, Talley NJ. The brain-gut pathway in functional gastrointestinal disorders is bidirectional: a 12-year prospective population-based study. *Gut* 2012;61:1284-90.
  29. Vandenberghe J, Dupont P, Van Oudenhove L, et al. Regional cerebral blood flow during gastric balloon distention in functional dyspepsia. *Gastroenterology* 2007;132:1684-93.
  30. Wilder-Smith CH, Li X, Shen L, Cao Y, Ho KY, Wong RK. Dysfunctional endogenous pain modulation in patients with functional dyspepsia. *Neurogastroenterol Motil* 2014;26:489-98.
  31. Oshima T, Toyoshima F, Nakajima S, Fukui H, Watari J, Miwa H. Genetic factors for functional dyspepsia. *J Gastroenterol Hepatol* 2011;26:Suppl 3:83-7.
  32. Carbone F, Tack J. Gastrointestinal mechanisms underlying functional gastric disorders. *Dig Dis* 2014;32:222-9.
  33. Samsom M, Verhagen MA, vanBerge Henegouwen GP, Smout AJ. Abnormal clearance of exogenous acid and increased acid sensitivity of the proximal duodenum in dyspeptic patients. *Gastroenterology* 1999;116:515-20.
  34. Futagami S, Itoh T, Sakamoto C. Systematic review with meta-analysis: post-infectious functional dyspepsia. *Aliment Pharmacol Ther* 2015;41:177-88.
  35. Spiller R. Postinfectious functional dyspepsia and postinfectious irritable bowel syndrome: different symptoms but similar risk factors. *Gastroenterology* 2010;138:1660-3.
  36. Walker MM, Aggarwal KR, Shim LS, et al. Duodenal eosinophilia and early satiety in functional dyspepsia: confirmation of a positive association in an Australian cohort. *J Gastroenterol Hepatol* 2014;29:474-9.
  37. Futagami S, Shindo T, Kawagoe T, et al. Migration of eosinophils and CCR2-/CD68-double positive cells into the duodenal mucosa of patients with postinfectious functional dyspepsia. *Am J Gastroenterol* 2010;105:1835-42.
  38. Talley NJ, Walker MM, Aro P, et al. Non-ulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. *Clin Gastroenterol Hepatol* 2007;5:1175-83.
  39. Vanheel H, Vicario M, Vanuytsel T, et al. Impaired duodenal mucosal integrity and low-grade inflammation in functional dyspepsia. *Gut* 2014;63:262-71.
  40. Liebrechts T, Adam B, Bredack C, et al. Small bowel homing T cells are associated with symptoms and delayed gastric emptying in functional dyspepsia. *Am J Gastroenterol* 2011;106:1089-98.
  41. Azpiroz F, Feinle-Bisset C, Grundy D, Tack J. Gastric sensitivity and reflexes: basic mechanisms underlying clinical problems. *J Gastroenterol* 2014;49:206-18.
  42. Moayyedi P, Soo S, Deeks J, et al. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2006;2:CD002096 [Withdrawn: Cochrane Database Syst Rev 2011 February 16].
  43. Walker MM, Talley NJ. Review article: bacteria and pathogenesis of disease in the upper gastrointestinal tract — beyond the era of *Helicobacter pylori*. *Aliment Pharmacol Ther* 2014;39:767-79.
  44. Farré R, Vanheel H, Vanuytsel T, et al. In functional dyspepsia, hypersensitivity to postprandial distention correlates with meal-related symptom severity. *Gastroenterology* 2013;145:566-73.
  45. Bharucha AE, Camilleri M, Burton DD, et al. Increased nutrient sensitivity and plasma concentrations of enteric hormones during duodenal nutrient infusion in functional dyspepsia. *Am J Gastroenterol* 2014;109:1910-20.
  46. Feinle-Bisset C, Azpiroz F. Dietary lipids and functional gastrointestinal disorders. *Am J Gastroenterol* 2013;108:737-47.
  47. Zuo XL, Li YQ, Li WJ, et al. Alterations of food antigen-specific serum immunoglobulins G and E antibodies in patients with irritable bowel syndrome and functional dyspepsia. *Clin Exp Allergy* 2007;37:823-30.
  48. Walker MM, Powell N, Talley NJ. Atopy and the gastrointestinal tract — a review of a common association in unexplained gastrointestinal disease. *Expert Rev Gastroenterol Hepatol* 2014;8:289-99.
  49. Friesen CA, Schurman JV, Colombo JM, Abdel-Rahman SM. Eosinophils and mast cells as therapeutic targets in pediatric functional dyspepsia. *World J Gastrointest Pharmacol Ther* 2013;4:86-96.
  50. Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2006;4:CD001960.
  51. Kaptchuk TJ, Friedlander E, Kelley JM, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One* 2010;5(12):e15591.
  52. van Kerkhoven LA, van Rossum LG, van Oijen MG, Tan AC, Laheij RJ, Jansen JB. Upper gastrointestinal endoscopy does not reassure patients with functional dyspepsia. *Endoscopy* 2006;38:879-85.
  53. Moayyedi P, Forman D, Braunholtz D, et al. The proportion of upper gastrointestinal symptoms in the community associated with *Helicobacter pylori*, lifestyle factors, and nonsteroidal anti-inflammatory drugs. *Am J Gastroenterol* 2000;95:1448-55.
  54. Moayyedi P, Soo S, Deeks JJ, et al. Systematic review and economic evaluation of *Helicobacter pylori* eradication treatment for non-ulcer dyspepsia. *BMJ* 2000;321:659-64.
  55. Mazzoleni LE, Sander GB, Francesconi CF, et al. *Helicobacter pylori* eradication in functional dyspepsia: HEROES trial. *Arch Intern Med* 2011;171:1929-36.
  56. Lan L, Yu J, Chen YL, et al. Symptom-based tendencies of *Helicobacter pylori* eradication in patients with functional dyspepsia. *World J Gastroenterol* 2011;17:3242-7.
  57. Iwakiri R, Tominaga K, Furuta K, et al. Randomised clinical trial: rabeprazole improves symptoms in patients with functional dyspepsia in Japan. *Aliment Pharmacol Ther* 2013;38:729-40.
  58. Thumshirn M, Camilleri M, Saslow SB, Williams DE, Burton DD, Hanson RB. Gastric accommodation in non-ulcer dyspepsia and the roles of *Helicobacter pylori* infection and vagal function. *Gut* 1999;44:55-64.
  59. Talley NJ, Tack J, Ptak T, Gupta R, Giguère M. Itopride in functional dyspepsia: results of two phase III multicentre, randomised, double-blind, placebo-controlled trials. *Gut* 2008;57:740-6.
  60. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013;108:18-37.
  61. Kusunoki H, Haruma K, Manabe N, et al. Therapeutic efficacy of acotiamide in patients with functional dyspepsia based on enhanced postprandial gastric accommodation and emptying: randomized controlled study evaluation by real-time ultrasonography. *Neurogastroenterol Motil* 2012;24:540-5.
  62. Matsueda K, Hongo M, Tack J, Saito Y, Kato H. A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. *Gut* 2012;61:821-8.
  63. 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;10:1239-45.
64. Miwa H, Nagahara A, Tominaga K, et al. Efficacy of the 5-HT<sub>1A</sub> agonist tansospirone citrate in improving symptoms of patients with functional dyspepsia: a randomized controlled trial. *Am J Gastroenterol* 2009;104:2779-87.
65. van Kerkhoven LA, Laheij RJ, Aparicio N, et al. Effect of the antidepressant venlafaxine in functional dyspepsia: a randomized, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol* 2008;6:746-52.
66. Tan VP, Cheung TK, Wong WM, Pang R, Wong BC. Treatment of functional dyspepsia with sertraline: a double-blind randomized placebo-controlled pilot study. *World J Gastroenterol* 2012;18:6127-33.
67. Ly HG, Carbone F, Holvoet L, et al. Mirtazapine improves early satiation, nutrient intake, weight recovery and quality of life in functional dyspepsia with weight loss: a double-blind, randomized, placebo-controlled pilot study. *Gastroenterology* 2013;144:S37.
68. Talley NJ, Locke GR, Saito YA, et al. Effect of amitriptyline and escitalopram on functional dyspepsia: a multi-center, randomized, controlled study. *Gastroenterology* 2015;149:340-9.
69. Soo S, Moayyedi P, Deeks JJ, Delaney B, Lewis M, Forman D. Psychological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2005;2:CD002301.
70. Orive M, Barrio I, Orive VM, et al. A randomized controlled trial of a 10-week group psychotherapeutic treatment added to standard medical treatment in patients with functional dyspepsia. *J Psychosom Res* 2015;78:563-8.
71. Lahner E, Bellentani S, Bastiani RD, et al. A survey of pharmacological and nonpharmacological treatment of functional gastrointestinal disorders. *United European Gastroenterol J* 2013;1:385-93.
72. Lacy BE, Yu J, Crowell MD. Medication risk-taking behavior in functional dyspepsia patients. *Clin Transl Gastroenterol* 2015;6:e69.
73. von Arnim U, Peitz U, Vinson B, Gundermann KJ, Malfertheiner P. STW 5, a phytopharmakon for patients with functional dyspepsia: results of a multicenter, placebo-controlled double-blind study. *Am J Gastroenterol* 2007;102:1268-75.
74. Pilichiewicz AN, Horowitz M, Russo A, et al. Effects of iberogast on proximal gastric volume, antropyloroduodenal motility and gastric emptying in healthy men. *Am J Gastroenterol* 2007;102:1276-83.
75. Bortolotti M, Coccia G, Grossi G, Miglioli M. The treatment of functional dyspepsia with red pepper. *Aliment Pharmacol Ther* 2002;16:1075-82.
76. Lacy BE, Everhart K, Crowell MD. Functional dyspepsia is associated with sleep disorders. *Clin Gastroenterol Hepatol* 2011;9:410-4.
77. Ford AC, Forman D, Bailey AG, Axon ATR, Moayyedi P. Effect of dyspepsia on survival: a longitudinal 10-year follow-up study. *Am J Gastroenterol* 2012;107:912-21.
78. Törnblom H, Drossman DA. Centrally targeted pharmacotherapy for chronic abdominal pain. *Neurogastroenterol Motil* 2015;27:455-67.
79. Arienti V, Corazza GR, Sorge M, et al. The effects of levosulpiride on gastric and gall-bladder emptying in functional dyspepsia. *Aliment Pharmacol Ther* 1994;8:631-8.
80. Drossman D, Szigethy E. The narcotic bowel syndrome: a recent update. *Am J Gastroenterol* 2014;2:22-30.
81. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Bjornsson E, Thjodleifsson B. Natural history of functional gastrointestinal disorders: comparison of two longitudinal population-based studies. *Dig Liver Dis* 2012;44:211-7.

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