Effects of Antidepressants in Patients With Functional Esophageal Disorders or Gastroesophageal Reflux Disease: A Systematic Review

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BACKGROUND & AIMS: Patients with functional esophageal disorders present with symptoms of chest pain, heartburn, dysphagia, or globus in the absence of any structural abnormality. Visceral hypersensitivity is a feature of these functional disorders, and might be modulated by antidepressant therapy. We evaluated evidence for the efficacy of antidepressant therapy for symptoms associated with esophageal visceral hypersensitivity in patients with functional esophageal disorders or gastroesophageal reflux disease (GERD).

METHODS: We performed a systematic search of the Cochrane Comprehensive Trial Register, MEDLINE, and EMBASE (through February 2014). We analyzed relevant randomized, placebo-controlled trials reporting the effect of antidepressant therapy on experimentally induced esophageal sensation or intensity, or frequency of heartburn, chest pain, dysphagia, or globus.

RESULTS: The search strategy identified 378 articles; 15 described randomized controlled trials that were eligible for inclusion. In addition, 1 conference abstract and 2 case reports were included, providing the best available evidence on specific symptoms. Esophageal pain thresholds increased by 7% to 37% after antidepressant therapy. Antidepressant therapy reduced functional chest pain over a range from 18% to 67% and reduced heartburn in patients with GERD over a range of 23% to 61%. One study included patients with globus and none of the studies included patients with functional heartburn or functional dysphagia.

CONCLUSIONS: Based on a systematic review, antidepressants modulate esophageal sensation and reduce functional chest pain. There is limited evidence that antidepressants benefit a subgroup of patients with GERD. More controlled trials are needed to investigate the effects of antidepressants on functional esophageal disorders.

Keywords: Functional Gastrointestinal Disorders; Visceral Nociception; Pain Modulation; Esophagus.
46% of healthy individuals, and globus amounts to up to 4% of new ear, nose, and throat consultations.6 Functional dysphagia seems the least common symptom, but dysphagia was reported by 7% to 8% of healthy subjects.7

In all functional gastrointestinal disorders visceral hypersensitivity is regarded as an important pathophysiological factor.8 Visceral hypersensitivity is the enhanced perception of gastrointestinal stimuli, and is mediated by the sensitization of afferent nerves, the sensitization of spinal dorsal neurons, and alterations in psychoneuroimmune interactions. In the esophagus, visceral hypersensitivity contributes to symptom generation not only in the context of functional esophageal disorders, but also in gastroesophageal reflux disease (GERD).9 Within the GERD spectrum, several subgroups have been defined based on endoscopic appearance, esophageal acid exposure, and symptom association.10 The GERD patients in whom visceral hypersensitivity is thought most prominent are patients with a so-called hypersensitive esophagus. In these patients no erosions are present and esophageal acid exposure is low, but their symptoms clearly are associated with acid or nonacid reflux episodes and their esophageal perception of reflux seems enhanced.10 Therefore, although the exclusion of GERD is necessary for the diagnosis of any functional esophageal disorder, esophageal visceral hypersensitivity seems a shared pathophysiological phenomenon between GERD patients and patients with functional esophageal disorders.

Low-dose antidepressants are thought to attenuate visceral nociception in addition to treating co-existing anxiety or depression. It has been shown that they have a beneficial effect in functional gastrointestinal disorders such as irritable bowel syndrome (IBS) and in neuropathic pain syndromes such as diabetic neuropathy.11,12 Therefore, one might expect a similar beneficial effect of antidepressants in the treatment of symptoms related to esophageal hypersensitivity, both in functional esophageal disorders as well as in GERD. This systematic review aims to provide a comprehensive overview of all available evidence for the use of antidepressant therapy for symptoms associated with esophageal visceral hypersensitivity, both in the context of functional esophageal disorders and in GERD.

Methods

Search Strategy

We conducted a comprehensive search of MEDLINE (1966–2013), the Cochrane Comprehensive Trial Register (1997–2013), and EMBASE (1980–2013) databases up until February 2014 to identify relevant articles. The search terms included the following terms as text words and medical subject headings where possible: functional heartburn, dysphagia, chest pain, non-cardiac chest pain, globus, gastroesophageal reflux disease, non-erosive reflux disease, heartburn, hypersensitive esophagus, acid-sensitive esophagus, and the most commonly prescribed antidepressant: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin–norepinephrin reuptake inhibitors (Supplementary Table 1). The reference lists of relevant articles also were searched for additional appropriate articles. Studies reported in a language other than English were excluded.

Study Selection

We included all randomized, placebo-controlled, clinical trials reporting the effect of antidepressant therapy on experimentally induced esophageal sensation, for instance, after balloon distension or acid perfusion; and intensity or frequency of heartburn, chest pain, dysphagia, or globus. If no randomized controlled trial (RCT) was identified for a specific disorder, the best available evidence was reported.

Data Extraction

Data were extracted using a standardized data extraction form, collecting information on publication year, country, study design, diagnostic criteria used for disorder, total sample size, number of patients, number of controls, type and dose of antidepressants, and reduction in symptoms. The quality of the studies was assessed using the Jadad scoring system.13 A score of 0 to 5 was given depending on the article’s randomization description, blinding method description, and whether drop-outs were described adequately.

Because of the considerable clinical heterogeneity of the included trials (differences in patient definition, antidepressants, methods of symptom evaluation, outcome definition), a meta-analysis of outcome data was not performed.

Results

Eligible Studies

The search identified 378 citations that met the search criteria. Figure 1 shows the flowchart of the selection of retrieved studies. Ultimately, 15 RCTs were included for data extraction. One additional RCT was published as only a conference abstract. For the specific disorders in which no RCT was available, the best available evidence was described, resulting in the description of an additional 2 case reports. The quality of the selected studies was high, with a Jadad score of 3 or more for all full articles (Tables 1–3).

Experimentally Induced Esophageal Sensation

The effect of antidepressants on experimentally induced esophageal pain was evaluated in 3 studies. All studies included healthy volunteers without a history of
anxiety or depression, and the protocols used for balloon distension protocols were similar. Two studies investigated the effect of a TCA and 1 study investigated the effect of an SSRI; all studies were placebo-controlled (Table 1).14–16 Gorelick et al14 studied the effect of amitriptyline on both somatic and visceral sensitivity in 14 healthy subjects. Treatment with 50 mg of amitriptyline ante nocte for 3 weeks did not change the thresholds of perception or pain after mechanical distension of the esophagus. In contrast, amitriptyline significantly increased the threshold of perception and pain during cutaneous electrical stimulation. In a similar study the use of 75 mg of imipramine during 12 days slightly but significantly increased the threshold for pain during esophageal distension with a balloon. Imipramine only altered the threshold for pain and did not affect the threshold for the initial perception of distension.15 Finally, Broekaert et al16 studied the effect of a single intravenous dose of citalopram, an SSRI, on esophageal sensitivity in 10 healthy subjects with established esophageal hypersensitivity. Citalopram significantly increased balloon volumes leading to first perception and discomfort during mechanical distension. It also prolonged the time to perception and discomfort during esophageal acid perfusion compared with placebo. In none of these studies was the decreased esophageal sensitivity to mechanical distension associated with changes in compliance of the esophageal wall.

**Functional Chest Pain of Presumed Esophageal Origin**

Functional chest pain of presumed esophageal origin is defined in the Rome III criteria as midline chest pain or discomfort that is not of burning quality. A cardiac etiology and gastroesophageal reflux must be excluded, as well as other histopathology-based motility disorders

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**Table 1. Characteristics of RCTs Examining the Effect of Antidepressants on Experimentally Induced Esophageal Pain**

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Design</th>
<th>Jadad score</th>
<th>Subjects</th>
<th>N</th>
<th>Female, %</th>
<th>Mean age, y</th>
<th>Drug class</th>
<th>Drug</th>
<th>Dose, mg</th>
<th>Therapy duration</th>
<th>Stimulus</th>
<th>Therapy duration</th>
<th>Therapy duration</th>
<th>Pain thresholds</th>
<th>Drug</th>
<th>Drug</th>
<th>%</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peghini et al,15 1998</td>
<td>Cross-over</td>
<td>5</td>
<td>Healthy</td>
<td>15</td>
<td>0</td>
<td>36</td>
<td>TCA</td>
<td>Imipramine</td>
<td>25–75</td>
<td>12 d</td>
<td>Balloon distension</td>
<td>23.5 mL</td>
<td>21.0 mL</td>
<td>122 mL</td>
<td>12%</td>
<td>a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gorelick et al,14 1998</td>
<td>Parallel</td>
<td>4</td>
<td>Healthy</td>
<td>14</td>
<td>50</td>
<td>Unreported TCA</td>
<td>Amitriptyline</td>
<td>50</td>
<td>21 d</td>
<td>Balloon distension</td>
<td>7% increase vs basal</td>
<td>6.3 mL</td>
<td>8.6 mL</td>
<td>4% increase vs basal</td>
<td>15%</td>
<td>a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broekaert et al,16 2006</td>
<td>Cross-over</td>
<td>4</td>
<td>Asymptomatic but hypersensitive</td>
<td>30</td>
<td>25</td>
<td>SSRI</td>
<td>Citalopram</td>
<td>20</td>
<td>Single IV dose</td>
<td>Balloon distension</td>
<td>9.9 mL</td>
<td>16.7 min</td>
<td>12.2 min</td>
<td>37%</td>
<td>a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study, year</td>
<td>Design</td>
<td>Jadad score</td>
<td>Total</td>
<td>Patients</td>
<td>Controls</td>
<td>Female, %</td>
<td>Mean age, y</td>
<td>Drug class</td>
<td>Drug</td>
<td>Dose</td>
<td>Duration, wk</td>
<td>Symptom evaluation</td>
<td>Symptom reduction</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cannon et al, 18 1994</td>
<td>Parallel</td>
<td>3</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>73</td>
<td>49.5</td>
<td>TCA</td>
<td>Imipramine</td>
<td>25-50 mg</td>
<td>3</td>
<td>Diary</td>
<td>52%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cox et al, 23 1998</td>
<td>Cross-over</td>
<td>3</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>100</td>
<td>53</td>
<td>TCA</td>
<td>Imipramine</td>
<td>50 mg</td>
<td>5</td>
<td>Diary</td>
<td>11 episodes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21 episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Varia et al, 19 2000</td>
<td>Parallel</td>
<td>4</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>Unreported</td>
<td>Unreported</td>
<td>SSRI</td>
<td>Sertraline</td>
<td>50-200 mg</td>
<td>8</td>
<td>VAS</td>
<td>62.6%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15.4%</td>
<td></td>
<td></td>
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<tr>
<td>Spinhoven et al, 21 2010</td>
<td>Parallel</td>
<td>3</td>
<td>46</td>
<td>23</td>
<td>23</td>
<td>48</td>
<td>57.4</td>
<td>SSRI</td>
<td>Paroxetine</td>
<td>10-40 mg</td>
<td>16</td>
<td>VAS</td>
<td>18.6%</td>
<td>18.6%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Keefe et al, 24 2011</td>
<td>Parallel</td>
<td>5</td>
<td>58</td>
<td>30</td>
<td>28</td>
<td>67</td>
<td>Unreported</td>
<td>SSRI</td>
<td>Sertraline</td>
<td>50-200 mg</td>
<td>10</td>
<td>Diary</td>
<td>67.2%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al, 22 2010</td>
<td>Cross-over</td>
<td>5</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>14</td>
<td>23.5</td>
<td>SNRI</td>
<td>Venlafaxine</td>
<td>75 mg</td>
<td>4</td>
<td>Diary</td>
<td>52% had &gt;50% reduction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4% had &gt;50% reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clouse et al, 17 1987</td>
<td>Parallel</td>
<td>4</td>
<td>19</td>
<td>11</td>
<td>8</td>
<td>76</td>
<td>48</td>
<td>SARI</td>
<td>Trazodone</td>
<td>100 mg</td>
<td>3</td>
<td>Likert scale</td>
<td>Exact data not extractable</td>
<td>Exact data not extractable</td>
<td></td>
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<td></td>
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<tr>
<td>Doraiswamy et al, 20 2006</td>
<td>Parallel</td>
<td>3</td>
<td>50</td>
<td>27</td>
<td>23</td>
<td>42</td>
<td>53.3</td>
<td>SSRI</td>
<td>Paroxetine</td>
<td>5-50 mg</td>
<td>8</td>
<td>VAS</td>
<td>Exact data not extractable</td>
<td>Exact data not extractable</td>
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</tbody>
</table>

SARI, serotonin antagonist and reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; VAS, visual analogue scale.

<sup>a</sup>P < .05 vs placebo.
such as achalasia. We identified 8 randomized, placebo-controlled trials evaluating antidepressant therapy for noncardiac chest pain, of which 6 trials were discussed extensively in a systematic review by Nguyen et al.17–25 The primary outcome measures in these 8 trials varied considerably, but in all trials the frequency, intensity, or duration of chest pain was evaluated. Although currently a part of the Rome III diagnostic criteria, exclusion of GERD was performed in only 2 studies, by Lee et al.22 and Clouse et al. Favorable results were obtained in 5 studies, whereas in the other 3 studies no beneficial effect was observed compared with placebo (Table 2). Treatment with imipramine,18 sertraline,19 and venlafaxine22 all had significant beneficial effects on chest pain severity or frequency compared with placebo, reducing symptoms by more than 50%. In 2 trials the data regarding the intensity or frequency of chest pain were analyzed longitudinally during the entire treatment period using diaries. In a cross-over trial by Cox et al.23 patients on 50 mg imipramine had significantly fewer chest pain episodes during the entire active treatment period than during the placebo regimen, however, imipramine had no effect on overall quality of life. A study by Keefe et al.24 randomized patients with noncardiac chest pain to treatment with sertraline, placebo, or a treatment strategy including coping skills therapy. Sertraline, coping skills training, and a combination of both all significantly improved chest pain intensity throughout the 34-week treatment period, although an initial reduction of chest pain after placebo was not maintained. In contrast, 2 studies evaluating treatment with paroxetine showed a similar reduction in chest pain duration or intensity in the paroxetine and placebo groups.20,21 Similar results were obtained with trazodone, reducing chest pain but not leading to a significant advantage over placebo.17

Functional Heartburn

Functional heartburn is defined as the presence of burning retrosternal discomfort in the absence of evidence for a GERD diagnosis. Our systematic search did not identify any RCTs evaluating the use of antidepressants for this disorder, or any case reports or conference abstracts.

Heartburn in Gastroesophageal Reflux Disease Patients

The effect of antidepressants on heartburn in GERD patients was investigated by 4 studies, of which 1 was published only in abstract form (Table 3).26–29 Viazis et al.26 identified 75 patients with a hypersensitive esophagus among a group of 252 patients with proton pump inhibitor (PPI)-refractory reflux symptoms. Although these patients showed physiological acid exposure during a 24-hour pH-impedance measurement,
their reported symptoms were associated with reflux (Symptom Index, >50%). By using the current Rome criteria these patients were no longer classified as having a functional esophageal disorder but they were considered to be part of the GERD spectrum, which is supported by the fact that these patients generally benefit from antireflux surgery.20 In a randomized, double-blind study, 6 months of treatment with 20 mg citalopram once a day was significantly more efficient in treating reflux symptoms than placebo because 38.5% of patients using citalopram reported remaining symptoms vs 66.7% of patients using placebo.26 The most frequently remaining symptom was heartburn, followed by regurgitation and chest pain. A limitation of this study was that the presence of symptoms was not assessed using validated questionnaires or diaries but was based on physician reports. Recently, Ostovaneh et al29 included 144 patients with PPI refractory symptoms and a normal upper endoscopy and treated them with fluoxetine, omeprazole, or placebo. Six weeks of fluoxetine resulted in a significantly higher percentage of heartburn-free days compared with placebo and omeprazole, 37% vs 7% and 7%, respectively. Interestingly, a subgroup analysis showed that this difference was attributed completely to the patients with physiological acid exposure during 24-hour pH monitoring, a group composed of patients with functional heartburn and patients with a hypersensitive esophagus.

Besides these 2 positive studies, we also retrieved 2 studies that reported negative results. In a study by Forcelini et al,28 20 patients with nonerosive reflux disease were evaluated after treatment with nortriptyline (10 mg/d for 1 week, followed by 25 mg/d for 2 weeks) and placebo in a cross-over randomized fashion. Both nortriptyline and placebo significantly improved symptoms assessed using a validated heartburn questionnaire. However, the decrease of heartburn was similar for nortriptyline and placebo in a cross-over randomized fashion. Both nortriptyline and placebo significantly improved symptoms assessed using a validated heartburn questionnaire. However, the decrease of heartburn was similar for nortriptyline and placebo. A conference abstract by Hershcovici et al27 reported the effect of 3 treatment strategies in 140 patients with refractory GERD. All patients had a normal endoscopy but information on the severity of acid exposure or symptom association in the included study population was lacking. Patients were randomized to treatment with single-dose PPI in combination with 50 mg nortriptyline, to double-dose PPI, or to single-dose PPI with placebo. Complete heartburn resolution was the primary outcome and was achieved in 23.1% of patients treated with PPI in combination with nortriptyline. This was not superior to single-dose PPI with placebo (27.1%; odds ratio, 0.81; 95% confidence interval [CI], 0.3–2.2) or double-dose PPI (26.4%). The number of heartburn-free days also was similar.

**Functional Dysphagia**

Functional dysphagia is defined as the sense of foods sticking, lodging, or passing through the esophagus abnormally in the absence of GERD, an esophageal motility disorder, esoinophilic esophagitis, or obstructive lesions of the esophagus. Our systematic search did not identify any RCTs describing the use of antidepressants in the context of functional dysphagia, or any other evidence for the use of antidepressants for dysphagia.

**Globus**

Globus is defined as the nonpainful sensation of a lump or a foreign body in the throat occurring between meals and in the absence of dysphagia or odynophagia. GERD and other motility disorders have to be excluded. No placebo-controlled trials evaluating the treatment of globus with antidepressants were available. Our search identified 1 controlled trial in which 30 globus patients were randomized between 25 mg amitriptyline once daily and 40 mg pantoprazole once daily.31 After 4 weeks, a significantly higher percentage of patients in the amitriptyline group responded to treatment compared with the pantoprazole group, 75% and 36%, respectively. In addition, we identified 2 case reports. Brown et al32 described the resolution of globus symptoms with antidepressants in 3 patients with globus as the main presenting symptom. It must be acknowledged that these patients were treated in the context of depression. A second case report also described the complete resolution of globus symptoms after electroconvulsive therapy and maintenance treatment with clomipramine in a patient with severe depression.33

**Discussion**

Our aim was to review all available data regarding the use of antidepressant therapy for symptoms associated with esophageal visceral hypersensitivity, both in the context of functional esophageal disorders and in GERD. The retrieved literature suggests that antidepressants reduce esophageal sensitivity to experimentally induced pain, and reduce chest pain in patients with functional chest pain of unknown origin. Although the evidence is limited, SSRIs also might be effective for the treatment of heartburn in a subset of GERD patients. No conclusion can be drawn regarding the response of globus and functional dysphagia to antidepressant therapy.

The ratio to use low-dose antidepressants for the modulation of esophageal sensation is supported by studies showing that these drugs are effective in the treatment of several neuropathic pain disorders and IBS.11,12 In a large Cochrane review including all studies performed in patients with different types of neuropathies, treatment with TCAs was associated with a relative risk for moderate improvement of symptoms of 2.1 (95% CI, 1.8–2.5) vs placebo, with a number needed to treat of 4.12 Similarly, the meta-analysis performed by Ford et al11 reported a relative risk of persistent IBS...
symptoms during TCA or SSRI treatment of 0.66 (95% CI, 0.57–0.78) vs placebo, also with a number needed to treat of 4. The observed significant benefit of antidepressants over placebo in these disorders suggests their use in esophageal disorders associated with visceral hypersensitivity. In the literature identified by this systematic search, the percentage of symptom reduction ranged from 18% to 67% for the treatment of functional chest pain. For the treatment of heartburn this percentage ranged from 23% to 61%. Unfortunately, considerable differences between the selected studies regarding the patient definition, outcome definition, and the method of symptom analysis hampered the meta-analysis of the data presented.

The effect of antidepressants on heartburn was investigated in 4 studies. All studies included patients with GERD, whereas no study was performed on patients with functional heartburn in whom GERD was excluded. Two studies reported a beneficial effect of antidepressant therapy, whereas 1 published study and 1 conference abstract reported no benefit of nortriptyline on heartburn scores. Differences in medication and patient selection between these studies may explain the observed differences. Both negative studies used nortriptyline, a TCA, whereas the positive studies used citalopram or fluoxetine, both SSRIs. Both types of drugs showed similar efficacy in the treatment of depression and IBS. However, TCAs have been shown to prolong orocecal transit times, in contrast to the accelerating effect of SSRIs on orocecal transit. A prolonged presence of content in the stomach theoretically facilitates a prolonged time window for reflux to occur because stomach content and the acid pocket in particular are the main sources of refluxate. A second possible explanation is the significant difference in the included study populations. The positive studies strictly selected patients with physiological esophageal acid exposure, whereas both negative studies included patients without prior pH monitoring. The latter studies possibly included patients with severe esophageal acid exposure, in whom excessive exposition of the esophageal mucosa to reflux already had led to ultrastructural changes of the mucosa. These ultrastructural changes have been associated with an increased sensitivity to acid, which might not be overcome by the central effect of an antidepressant. A final explanation for the opposite outcomes might be a difference in treatment duration. In the negative study by Forcelini et al patients were treated for 3 weeks, whereas in the positive studies patients were treated for 6 weeks or longer. Although it has been claimed that the analgesic effect of a TCA already becomes apparent after only a couple of days, it is advised to treat new patients with neuropathic pain for at least 6 to 8 weeks. The success of antidepressant treatment for patients with heartburn seems to depend on a careful selection of eligible patients, a long-term treatment regimen, and possibly the choice of medication. Because no study is available that strictly included patients with functional heartburn, the earlier statement applies only to patients with heartburn in the context of GERD. However, because both conditions are associated with visceral hypersensitivity of the esophagus, a similar beneficial effect might be expected. Interestingly, in the study by Ostovaneh et al patients were included based on acid exposure time and no symptom association was used to differentiate between hypersensitive esophagus and functional heartburn. The heartburn-modulating effect of fluoxetine they observed in their pH-negative group therefore might be generalized to both hypersensitive esophagus and functional heartburn patients. Recently, modulation of esophageal sensation also was attempted by antagonizing the transient receptor potential vanilloid 1, a receptor responsive to heat and acid and present in esophageal mucosa. Although the transient receptor potential vanilloid 1 antagonist altered pain thresholds in healthy volunteers, no beneficial effect was observed in patients with nonerosive reflux disease.

Very limited data were identified regarding the effect of antidepressants on globus. The only available evidence was from a recent trial comparing low-dose amitriptyline with a PPI in 30 globus patients. Amitriptyline reduced globus symptoms assessed with a validated questionnaire more efficiently than PPI, and also improved quality of life. Furthermore, 2 case reports described antidepressant therapy for globus but these included patients with severe depression, making it questionable whether the observed response of globus symptoms was in fact a result of the resolution of their depression. Finally, no literature was available on the effect of antidepressants in patients with functional dysphagia. Besides the paucity of data on treatment with antidepressants for this disorder, there are no data on other medical treatments either. Therefore, sensible management could consist of reassurance, advice to chew foods carefully, and to avoid symptom-eliciting foods. Other treatment options for dysphagia such as botulinum toxin injection or pneumatic dilation should be used only in the case of specific motility disorders such as esophageal spasm or achalasia.

In summary, the results of the trials included in this systematic review provide modest evidence that both TCAs and SSRIs modulate esophageal sensation and reduce functional chest pain. Limited evidence suggests that SSRIs are beneficial for patients with heartburn, physiological acid exposure, and positive symptom association. Most importantly, this review emphasizes the lack of controlled trials investigating the effect of antidepressants on other esophageal symptomatic disorders. Future trials are warranted to address the question of whether antidepressants are indeed useful in the treatment of the sizeable group of patients with functional heartburn, dysphagia, and globus. These trials preferably should use validated questionnaires to assess symptoms and should select patients adequately by excluding motility disorders such as achalasia and GERD with functional testing.
Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2014.06.025.

References


### Supplementary Table 1. EMBASE Search Strategy

1. Clinical trial/
2. Randomized controlled trial/
3. Randomization/
4. Single-blind procedure/
5. Double-blind procedure/
6. Cross-over procedure/
7. Placebo/
8. Randomized controlled trial$.tw.
11. Randomly allocated.tw.
16. ((treble or triple) adj (blind$).tw.
17. Placebo$.tw.
18. Prospective study/
19. Or/1–18
20. Case study/
22. Abstract report/ or letter/
23. Or/20–22
24. 19 not 23
25. Exp gastroesophageal reflux
26. Gastroesophageal reflux.ti,ab,kw
27. Gastro oesophageal reflux.ti,ab,kw
28. Gastrooesophageal reflux.ti,ab,kw
29. GORD .ti,ab,kw
30. GERD.ti,ab,kw
31. NERD.ti,ab,kw
32. Nonerosive reflux disease.ti,ab,kw
33. Exp heartburn
34. Heartburn.ti,ab,kw
35. Pyrosis.ti,ab,kw
36. Esophagus .ti,ab,kw
37. Hypersensitive esophagus .ti,ab,kw
38. Acid-sensitive esophagus .ti,ab,kw
39. Functional heartburn .ti,ab,kw
40. Dysphagia.ti,ab,kw
41. Functional dysphagia .ti,ab,kw
42. Chest pain .ti,ab,kw
43. Functional chest pain .ti,ab,kw
44. Noncardiac chest pain .ti,ab,kw
45. Unexplained chest pain .ti,ab,kw
46. Globus .ti,ab,kw
47. Or/ 25 – 46
48. Amitriptyline.ti,ab,kw
49. Amitriptylinoxide.ti,ab,kw
50. Butriptyline.ti,ab,kw
51. Clomipramine.ti,ab,kw
52. Demexiptiline.ti,ab,kw
53. Desipramine.ti,ab,kw
54. Dibenzepin.ti,ab,kw
55. Dimetacrine.ti,ab,kw
56. Dosulepin.ti,ab,kw
57. Dothiepin.ti,ab,kw
58. Doxepin .ti,ab,kw
59. Imipramine .ti,ab,kw
60. Imipraminoxide .ti,ab,kw
61. Lofepramine .ti,ab,kw
62. Melitracen .ti,ab,kw
63. Metapramine .ti,ab,kw
64. Nitroxazepine .ti,ab,kw
65. Nortriptyline .ti,ab,kw
66. Noxiptiline .ti,ab,kw
67. Pipofezine .ti,ab,kw
68. Propizepine .ti,ab,kw
69. Protriptyline .ti,ab,kw
70. Quinupramine .ti,ab,kw
71. Citalopram .ti,ab,kw
72. Dapoxetine .ti,ab,kw
73. Escitalopram .ti,ab,kw
74. Fluoxetine .ti,ab,kw
75. Fluvoxamine .ti,ab,kw
76. Indalpine .ti,ab,kw
77. Paroxetine .ti,ab,kw
78. Sertraline .ti,ab,kw
79. Zimelidine .ti,ab,kw
80. Venlafaxine.ti,ab,kw
81. Desvenlafaxine.ti,ab,kw
82. Duloxetine.ti,ab,kw
83. Milnacipran.ti,ab,kw
84. Levomilnacipran.ti,ab,kw
85. Sibutramine.ti,ab,kw
86. Bicifadine.ti,ab,kw
87. Or/ 48 – 86
88. 24 and 47 and 87

### Supplementary Table 1. Continued

66. Noxiptiline .ti,ab,kw
67. Pipofezine .ti,ab,kw
68. Propizepine .ti,ab,kw
69. Protriptyline .ti,ab,kw
70. Quinupramine .ti,ab,kw
71. Citalopram .ti,ab,kw
72. Dapoxetine .ti,ab,kw
73. Escitalopram .ti,ab,kw
74. Fluoxetine .ti,ab,kw
75. Fluvoxamine .ti,ab,kw
76. Indalpine .ti,ab,kw
77. Paroxetine .ti,ab,kw
78. Sertraline .ti,ab,kw
79. Zimelidine .ti,ab,kw
80. Venlafaxine.ti,ab,kw
81. Desvenlafaxine.ti,ab,kw
82. Duloxetine.ti,ab,kw
83. Milnacipran.ti,ab,kw
84. Levomilnacipran.ti,ab,kw
85. Sibutramine.ti,ab,kw
86. Bicifadine.ti,ab,kw
87. Or/ 48 – 86
88. 24 and 47 and 87