Treatment of Esophageal (Noncardiac) Chest Pain: An Expert Review

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BACKGROUND & AIMS: Chest pain is a common and frightening symptom. Once cardiac disease has been excluded, an esophageal source is most likely. Pathophysiologically, gastroesophageal reflux disease, esophageal dysmotility, esophageal hypersensitivity, and anxiety disorders have been implicated. However, treatment remains a challenge. Here we examined the efficacy and safety of various commonly used modalities for treatment of esophageal (noncardiac) chest pain (ECP) and provided evidence-based recommendations.

METHODS: We reviewed the English language literature for drug trials evaluating treatment of ECP in PubMed, Cochrane, and MEDLINE databases from 1968–2012. Standard forms were used to abstract data regarding study design, duration, outcome measures and adverse events, and study quality.

RESULTS: Thirty-five studies comprising various treatments were included and grouped under 5 broad categories. Patient inclusion criteria were extremely variable, and studies were generally small with methodological concerns. There was good evidence to support the use of omeprazole and fair evidence for lansoprazole, rabeprazole, theophylline, sertraline, trazodone, venlafaxine, imipramine, and cognitive behavioral therapy. There was poor evidence for nifedipine, diltiazem, paroxetine, biofeedback therapy, ranitidine, nitrates, botulinum toxin, esophageal myotomy, and hypnotherapy.

CONCLUSIONS: Ideally, treatment of ECP should be aimed at correcting the underlying mechanism(s) and relieving symptoms. Proton pump inhibitors, antidepressants, theophylline, and cognitive behavioral therapy appear to be useful for the treatment of ECP. However, there is urgent and unmet need for effective treatments and for rigorous, randomized controlled trials.

Keywords: Esophageal Chest Pain; Noncardiac Chest Pain Treatment; Hypersensitivity; GERD; Behavioral Therapy.

Esophageal chest pain (ECP) is common, with global prevalence of 13%, and affects up to 30% of patients with chest pain. It is also described as noncardiac chest pain (NCCP) because patients describe recurrent retrosternal chest pain, and a cardiac source has been excluded. Because chest pain may herald life-threatening disease, if possible, an underlying mechanism should be identified. A lack of positive diagnosis leads to frequent emergency department visits, increasing disability, and loss of productivity and increased health care expenditure. In a large series of patients with ECP, 42% had gastroesophageal reflux disease (GERD), 7% of patients had motility disorder, 37% had esophageal hypersensitivity, and 14% were unexplained.

Although the precise cause or origin of ECP is not fully understood, mechanisms have been implicated, including GERD, dysmotility, hypersensitivity, altered cerebral processing of pain, autonomic dysregulation, panic disorder, and anxiety. Because of its heterogeneous nature, there are significant overlap and uncertainty regarding diagnostic criteria for ECP. The Rome III diagnostic criteria proposed that patients have ECP if they report symptoms for 3 months with symptoms beginning at least 6 months before diagnosis and include (1) midline chest pain or discomfort that is not burning quality, (2) absence of evidence that gastroesophageal reflux is the cause of the symptom, and (3) absence of histopathology-based esophageal motility disorders. However, chest pain is complex and may occur with or without acid reflux disease. Hence, the Rome III criteria may not encompass the heterogeneous nature of this illness.

The aim of this review was to critically examine the evidence for several proposed treatments for ECP and to provide perspectives regarding its management.
Methods

Literature Search

We conducted a search by using PubMed, MEDLINE, and Cochrane databases from 1968–April 2012. The search terms were “functional esophageal chest pain”, “non-cardiac chest pain” and “esophageal chest pain” and “treatment” and/or “management” or “drug therapy” or “therapeutics”. Full-text manuscripts written in English were included. Case reports were excluded. Included studies had at least 1 clinical end point of improvement for ECP. We mostly included randomized controlled trials (RCTs), but case-control studies for the treatment of ECP were also included when there was lack of high quality data for a particular treatment modality.

Qualitative Assessment of Study Methodology

The authors independently extracted data, and disagreements were resolved by consensus. The methodological quality was assessed by Jadad score. The quality scale ranged from 0–5 points with a low quality of 2 or less and high quality report of at least 3. Although data from published studies are described in the tables, only randomized controlled studies with a score of ≥3 were considered for treatment recommendations and were based on the U.S. Preventive Services Task Force recommendations.

The treatment of ECP is directed toward relieving symptoms and ameliorating the key mechanism(s). Because a mechanistic cause was not elucidated or described in many clinical trials, for the purposes of this review, we believed that the best approach would be to describe the treatments and to group them under 5 broad therapeutic categories. Also the literature contains terms such as unexplained chest pain, ECP, NCCP, irritable esophagus, and others; for the purposes of this review the terms ECP and/or NCCP have been used, largely on the basis of the original authors’ description of their studies.

1. Treatment of ECP related to GERD
2. Treatment of ECP related to esophageal spastic motility/dysmotility disorders
3. Treatment of ECP related to esophageal hypersensitivity
4. Treatment of ECP by using nonpharmacologic/behavioral approaches
5. Treatment of ECP by using surgery

Results

Our database search revealed 182 articles, of which 35 met our inclusion criteria, and 17 were excluded for cross-search, 41 for non-English language, 32 for being non-original, 30 for non-treatment-related, and 27 because of no outcome measures. Tables 1–4 provide details regarding study methodology and design, outcome measures, patient characteristics, including whether cardiac disease was excluded and presence/absence of GERD, results and safety analysis, as well as the quality assessment of these studies.

Treatment of Esophageal Chest Pain Related to Gastroesophageal Reflux Disease

Pathophysiology. ECP is often presumed to be due to GERD through activation of esophageal chemoreceptors. Demeester et al showed that 46% of patients with chest pain had acid reflux during ambulatory pH studies. The pH testing also yielded a combined positive symptom index and/or pathologic acid reflux in 50% of individuals. Others have shown that acid reflux may cause ECP in 30%–60% of patients. Nonacid reflux may also cause chest pain. In one study on and off proton pump inhibitor (PPI) therapy, heartburn decreased significantly but not regurgitation or chest pain, indicating that nonacid reflux caused ECP. Thus, both acid and nonacid reflux may be involved in the pathogenesis of ECP.

Treatment. Several PPIs have been tried including omeprazole, lanoprazole, and rabeprazole. However, the literature on GERD and ECP is inconsistent. In one study, ECP patients with acid reflux were more likely to respond to PPIs than those without reflux. Because nonerosive reflux represents 70% of the GERD population and approximately 50% of these individuals may experience heartburn without acid reflux, not all patients with ECP have abnormal acid reflux. At least one-third of patients have physiologically normal levels of acid reflux, and these individuals have either altered afferent receptor dysfunction or aberrant central modulation of pain.

Undoubtedly, acid reflux causes ECP, but it is only one of many components of a complex, multifactorial disorder. A recent systematic review that included 7 RCTs (Tables 1 and 5) found a therapeutic gain compared with placebo ranging from 56%–85% and relative risk of >50%, 4.3 (95% confidence interval [CI], 2.8–6.7; P < .001), in GERD-positive patients and only 0%–17% and relative risk of 0.4 (95% CI, 0.3–0.7; P < .0004) in GERD-negative patients. In another meta-analysis of 8 studies, pooled sensitivity, specificity, and diagnostic odds ratio for the PPI test versus 24-hour pH study and endoscopy were 80%, 74%, and 13.8% (95% CI, 5.48–34.91), respectively. The pooled risk ratio for continued chest pain was 0.54 (95% CI, 0.41–0.71). These data suggest that patients with acid reflux and ECP may improve with PPI, although numbers were small, and there was publication bias.
Table 1. PPI Treatment of ECP Related to GERD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods score</th>
<th>Intervention</th>
<th>Study design</th>
<th>Study size (N)</th>
<th>Mean age (y)</th>
<th>F/M</th>
<th>Duration</th>
<th>Outcome measures</th>
<th>Patient characteristics</th>
<th>Results</th>
<th>Safety analysis</th>
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</thead>
<tbody>
<tr>
<td>Fass et al14</td>
<td>5</td>
<td>Omeprazole 40 mg AM and 20 mg PM or placebo</td>
<td>Double-blind, placebo-controlled crossover</td>
<td>39</td>
<td>60</td>
<td>1/38</td>
<td>7 days, then crossover for 7 days</td>
<td>CPF and CPS on a VAS composite chest pain score, severity × frequency/wk</td>
<td>Positive and negative EGD and/or positive pH-metry, no manometry, negative cardiac angiogram or negative cardiac stress tests</td>
<td>Resolution: 52% vs 4% ○ Resolution: &gt;50% improvement: 26% vs 18% ○ Resolution: &lt;50% improvement: 18% vs 27% ○ No change: 4% vs 51%</td>
<td>1 diarrhea and 1 abdominal pain</td>
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<tr>
<td>Achem et al19</td>
<td>5</td>
<td>Omeprazole 20 mg twice a day or placebo</td>
<td>Double-blind, placebo-controlled</td>
<td>36</td>
<td>49</td>
<td>23/11</td>
<td>8 weeks</td>
<td>CPF and CPS (0–10); global chest pain rating (better, same, and worse)</td>
<td>Negative EGD (90%), positive pH-metry (100%), positive/ negative manometry, negative coronary angiography, or negative stress thallium test</td>
<td>CPF: decreased 39% (omeprazole) and 10% (placebo), P &lt; .006 ○ CPS: decreased 41% (omeprazole) and 15% (placebo), P &lt; .032 ○ Global severity: omeprazole better 81%, same 6%, worse 13% vs placebo 6%, 72%, and 22%, respectively (P &lt; .001)</td>
<td>Mild symptoms of headaches, abdominal pain, diarrhea, nausea, and rash</td>
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<td>Pandak et al20</td>
<td>5</td>
<td>Omeprazole 40 mg twice a day or placebo</td>
<td>Double-blind, placebo-controlled crossover</td>
<td>42</td>
<td>48</td>
<td>24/18</td>
<td>14 days, then crossover for 14 days</td>
<td>CPF and CPS improvement in 2 points from baseline VAS (0–10) and &gt;50% response</td>
<td>Positive and negative EGD and/or positive pH-metry, negative stress test</td>
<td>Overall response: 71% (omeprazole) and 18% (placebo) ○ Responders: GERD positive: 95% omeprazole vs 10% placebo GERD negative: 39% omeprazole</td>
<td>Not performed</td>
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<tr>
<td>Xia et al21</td>
<td>2</td>
<td>Lansoprazole 30 mg/day or placebo</td>
<td>Single-blind, placebo-controlled</td>
<td>68</td>
<td>58</td>
<td>26/42</td>
<td>4 weeks</td>
<td>CPF and CPS, severity × frequency/wk</td>
<td>Negative EGD, positive and negative pH-metry, no manometry, negative coronary angiography</td>
<td>Overall improvement 53% (lansoprazole) vs 34% (placebo), P &lt; .127 ○ Responders: GERD-positive: 92% (lansoprazole) vs 33% (placebo), P &lt; .001 GERD-negative: 33% (lansoprazole) vs 35% (placebo), P = NS</td>
<td>Not reported</td>
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<td>Study</td>
<td>Treatment</td>
<td>Study Design</td>
<td>Duration</td>
<td>Outcomes</td>
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<tr>
<td>Bautista et al22</td>
<td>Lansoprazole 60 mg AM and 30 mg PM or placebo</td>
<td>Double-blind, placebo-controlled crossover</td>
<td>40/54 9/31 7 days, then crossover for 7 days</td>
<td>CPF and CPS, VAS composite chest pain score, severity x frequency/wk Positive EGD and/or pH-metry, negative coronary angiogram or negative cardiac stress test</td>
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<tr>
<td>Dickman et al23</td>
<td>Rabeprazole 20 mg/day or placebo</td>
<td>Double-blind, placebo-controlled crossover</td>
<td>35/56 12/23 7 days</td>
<td>CPF and CPS improvement &gt;50% Positive and negative EGD and/or pH-metry, no manometry, negative coronary angiogram or negative stress test</td>
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<tr>
<td>Kim et al24</td>
<td>Rabeprazole 20 mg twice a day</td>
<td>Open-label trial, first week vs second week</td>
<td>42/54 17/25 2 weeks</td>
<td>CPF and CPS = &gt;50% improvement, composite score = severity x frequency/wk Positive and negative EGD and/or positive pH-metry, no manometry, negative stress test</td>
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- Lansoprazole response
  - GERD-positive vs GERD-negative
    - Resolution: 39% vs 0%
    - >50% improvement: 39% vs 9%
    - <50% improvement: 5% vs 50%
    - No change: 17% vs 41%
- Lansoprazole vs placebo
  - GERD-positive: 78% vs 22%, \( P = .01 \)
  - GERD-negative: 9% vs 36%, \( P = .7 \)
- Rabeprazole vs placebo:
  - >50% improvement
  - GERD-positive: 75% vs 11%
  - GERD-negative: 19% vs 21%
- Overall response, week 2: 81% (rabeprazole) and 27% (placebo)
- GERD-positive vs GERD-negative
  - Resolution: 45% vs 12%
  - >50% improvement: 38% vs 14%
  - <50% improvement: 6% vs 28%
  - No change: 11% vs 46%
- Week 1: GERD-positive vs GERD-negative = 8.5% vs 6.2%, \( P = NS \)

CPF, chest pain frequency; CPS, chest pain score (severity); EGD, esophagogastroduodenoscopy; negative, normal test; positive, abnormal test; VAS, visual analog scale.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Method score</th>
<th>Intervention</th>
<th>Study design</th>
<th>Study size (N)</th>
<th>Mean age (y)</th>
<th>F/M</th>
<th>Duration</th>
<th>Outcome measure</th>
<th>Patient characteristics</th>
<th>Results</th>
<th>Safety analysis</th>
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<tbody>
<tr>
<td>Richter et al (30)</td>
<td>4</td>
<td>Nifedipine 10–30 mg 3 times a day vs placebo</td>
<td>Double-blind crossover study</td>
<td>20</td>
<td>50</td>
<td>8/12</td>
<td>14 weeks</td>
<td>Peristaltic amplitude, CPF and CPS and chest pain index = frequency x severity</td>
<td>ECP and nutcracker esophagus (manometry), negative EGD or upper gastrointestinal x-ray, Bernstein test (14 negative, 6 positive), negative or nonobstructing coronary angiography or negative stress test</td>
<td>• Significant decrease in amplitude of peristalsis in distal esophagus with nifedipine, (P &lt; .005) • CPF and CPS, nifedipine vs placebo, no change • Chest pain index improved in nifedipine, 10.3 (14 wk) vs 3.2 (baseline), but no difference with placebo</td>
<td>Nifedipine &gt; placebo: facial flushing, edema, headaches, lightheadedness, nervousness</td>
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<td>Nasrallah et al (31)</td>
<td>2</td>
<td>Nifedipine 10 mg 3 times a day vs placebo</td>
<td>Double-blind crossover study</td>
<td>16</td>
<td>29–76</td>
<td>—</td>
<td>4 weeks</td>
<td>Global improvement in chest pain (0–10 scale)</td>
<td>ECP and achalasia, nutcracker, or spasm, hypertensive LES (manometry), negative EGD, no pH-metry, negative cardiac catheterization or negative stress test</td>
<td>• 13/16 improved with nifedipine vs 4/16 with placebo • Manometry, no change</td>
<td>Lightheadedness = 1, throbbing headache = 1, no change in blood pressure</td>
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<td>Davies et al (32)</td>
<td>4</td>
<td>Nifedipine vs placebo</td>
<td>Double-blind, placebo-controlled</td>
<td>8</td>
<td>39</td>
<td>4/4</td>
<td>6 weeks</td>
<td>Chest pain by using diary</td>
<td>ECP, dysphagia, esophageal spasm (manometry), EGD positive (2), no pH-metry, negative coronary angiography (?)</td>
<td>• No difference between nifedipine and placebo</td>
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<td>Study</td>
<td>Treatment</td>
<td>Type</td>
<td>Duration</td>
<td>ECP</td>
<td>Other Procedures</td>
<td>Chest Pain Improvement</td>
<td>Side Effects</td>
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<tr>
<td>Richter et al³³</td>
<td>Diltiazem 90 mg 4 times a day</td>
<td>Open-label study</td>
<td>10</td>
<td>6/4</td>
<td>8 weeks</td>
<td>Chest pain improved, $P &lt; .01$</td>
<td>Chest pain</td>
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<td>No effect on esophageal contractions</td>
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<td>Drenth et al³⁴</td>
<td>Diltiazem 16 mg 3 times a day</td>
<td>Double-blind crossover</td>
<td>8</td>
<td>40</td>
<td>2/6 weeks</td>
<td>CPF and CPS (intensity)</td>
<td>No side</td>
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<tr>
<td>Cattau et al³⁵</td>
<td>Diltiazem 60–90 mg 4 times a day</td>
<td>Double-blind crossover, per protocol analysis</td>
<td>22</td>
<td>–</td>
<td>8 weeks</td>
<td>CPS</td>
<td>Withdrawal</td>
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<td>8/22 (34%)</td>
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<td>Swamy et al³⁶</td>
<td>Short-acting NTG = 12, long-acting nitrate = 5/12</td>
<td>Open-label study</td>
<td>12</td>
<td>40–87</td>
<td>3/9 Short-acting $= &lt;6$ mo Long-acting $= 6$ mo–4 y</td>
<td>Chest pain</td>
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<td>ECP, esophageal spasm (manometry), positive/ negative pH-metry correlated to EGD, no cardiac tests</td>
<td>Side effects + in GERD patients</td>
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<td>Reference</td>
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<td>Intervention</td>
<td>Study design</td>
<td>Study size (N)</td>
<td>Mean age (y)</td>
<td>F/M</td>
<td>Duration</td>
<td>Outcome measure</td>
<td>Patient characteristics</td>
<td>Results</td>
<td>Safety analysis</td>
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<tr>
<td>Miller et al37</td>
<td>0</td>
<td>Botulinum toxin 100 IU injected</td>
<td>Open-label prospective</td>
<td>29</td>
<td>61</td>
<td>24/5</td>
<td>1–18 mo</td>
<td>CPS (0–4 Likert scale), &lt;50% in pain severity</td>
<td>ECP in non-achalasia, nonreflux motility disorders (manometry), negative PPI test or negative pH-metry, negative manometry, negative stress test or negative cardiac catheterization</td>
<td>Botulinum toxin reduced chest pain in 62% ($P &lt; .0001$), Mean duration (standard deviation) of response, 5.8 ± 4.8 mo Repeat Botox in 3 subjects</td>
<td>Not reported</td>
</tr>
<tr>
<td>Storr et al38</td>
<td>1</td>
<td>Botulinum toxin 100 IU injected at multiple sites 1- to 1.5-cm levels</td>
<td>Open-label prospective</td>
<td>9</td>
<td>71</td>
<td>3/6</td>
<td>6 mo</td>
<td>Total symptoms score, regurgitation score, dysphagia score, and NCCP score</td>
<td>ECP and DES (barium radiogram or manometry), negative EGD, negative pH-metry or PPI test, negative stress test, or negative cardiac angiography</td>
<td>Improvement in total symptom score and NCCP score in 89% at 4 weeks and up to 6 mo but required repeat injections</td>
<td>Slight chest pain (transient) &lt;2 h after procedure</td>
</tr>
<tr>
<td>Borjesson et al39</td>
<td>4</td>
<td>Lansoprazole 30 mg twice a day vs placebo 8 weeks</td>
<td>Double-blind crossover</td>
<td>19</td>
<td>58</td>
<td>9/10</td>
<td>8 weeks</td>
<td>CPF and CPS, esophageal manometry</td>
<td>Nutcracker esophagus (manometry) 12/19 had GERD (pH &lt;4 = &gt;4% of time) (pH-metry), negative cardiac tests (no details)</td>
<td>No difference in CPF or CPS between lansoprazole and placebo</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Eherer et al. 0 Patients: 
sildenafil 50 mg
Healthy subjects: 
sildenafil 50 mg vs placebo

Open-label study (patients) (double-blind RCT; healthy subjects only)

11 patients, 6 healthy subjects 26–30 in healthy subjects 7/4 patients, 0/6 healthy

Treatment up to 4 mo in patients, healthy subjects received once

Esophageal manometry (vector volume of LES, pressure amplitudes of esophageal body)

3 Achalasia, 2 hypertensive LES, 4 nutcracker esophagus, 2 esophageal spasm: (manometry) negative PPI test, No cardiac tests

- Patients: manometry improved in 9 after sildenafil
- Symptoms improved in 4/9 (1 NK, 1 hypertensive LES, 1 spasm), (2 improved with no side effects, 2 improved, had side effects, and discontinued sildenafil)
- Health subjects: LES pressure vector volume and pressure amplitudes reduced significantly in distal half of esophagus body

2 had sleep disturbances or feeling of tightness to the chest, 3 had dizziness and headache

CPF, chest pain frequency; CPS, chest pain (severity) score; EGD, esophagogastroduodenoscopy; LES, lower esophageal sphincter; negative, normal test; NTG, nitroglycerin; positive, abnormal test.
| Reference     | Method score | Intervention                              | Study design                     | Study size (N) | Mean age (y) F/M Duration | Outcome measure                                                                 | Patient characteristics                                                                 | Results                                                                 | Safety analysis                                                                 |
|---------------|--------------|-------------------------------------------|----------------------------------|----------------|---------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Cannon et al 49 | 4            | Clonidine 0.1 mg twice a day or imipramine 50 mg at every bedtime or placebo twice a day | Double-blind, placebo-controlled crossover | 60             | 50                        40/20 10 weeks | CPF and CPI Change in frequency (no. of episodes) and intensity from baseline | ECP, [manometry (54, 90% tested); 22 (41%) had motility disorder], no pH-metry, positive Bernstein test (41%), negative coronary angiogram, and negative stress test | • Imipramine decreased CPF in 52% and 1% placebo (P = .03) and 39% clonidine  
• CPI was lower in imipramine (P < .001) and in clonidine (P < .002) vs placebo | Imipramine: prolonged QT interval |
| Clouse et al 50 | 3            | Trazadone 100–150 mg every day or placebo every day | Double-blind, placebo-controlled | 29             | 48                        21/8 6 weeks | Global improvement in chest pain, residual distress, manometric changes | ECP, dysmotility (DES, nutcracker, IEM) (manometry) negative esophagogram, no pH test, negative stress test, or negative cardiac catheterization | • Trazadone improved global symptoms of chest pain vs placebo (P = .002)  
• No change on manometry vs placebo | Sedation |
| Varia et al 51 | 4            | Sertraline 50 mg every day or placebo     | Double-blind, placebo-controlled | 30             | —                         — 8 weeks | VAS, CPS, BDI, SF36 Change in VAS (baseline–end treatment) | ECP, GERD not ruled out (no pH test), no manometry, negative angiogram, and/or negative stress test | • Sertraline decreased daily pain in 20% (VAS) per week (P < .03)  
• No effect on BDI or SF36 | Sertraline: nausea, restlessness, decreased libido, delayed ejaculation (all mild) |
<p>| Keefe et al 52 | 5            | CST + sertraline, CST + placebo, sertraline alone, or placebo alone | Double-blind, placebo-controlled | 115            | 48                        77/38 34 weeks | CPS on VAS (0–100) BDI, rate of change in outcomes | ECP, GERD not ruled out (no pH test), no manometry, negative stress test or negative coronary angiogram | • CST + sertraline showed highest response (P &lt; .001) followed by CST (P &lt; .002) and sertraline alone (P &lt; .001). No differences in anxiety and catastrophizing | Dry mouth, diarrhea, sexual side effects, nausea, headache |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Design</th>
<th>Study Population</th>
<th>Duration</th>
<th>Endpoint</th>
<th>Methods</th>
<th>Adverse Events</th>
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</thead>
<tbody>
<tr>
<td>Lee et al &lt;sup&gt;53&lt;/sup&gt;</td>
<td>Venlafaxine 75 mg or placebo</td>
<td>Double-blind, placebo-controlled crossover</td>
<td>43</td>
<td>24</td>
<td>6/37 4 weeks</td>
<td>CPF and CPS composite score (frequency × severity) &gt;50% improvement, ECP, negative EGD, negative pH-metry, negative manometry, 4 weeks off PPI, negative cardiac stress test, negative coronary angiogram</td>
<td>Venlafaxine vs placebo &lt;br&gt; &gt;50% improvement: 52% vs 4% &lt;br&gt; SF 36 (bodily pain, emotional role) improved significantly (P &lt; .002 in venlafaxine group)</td>
</tr>
<tr>
<td>Doraiswamy et al &lt;sup&gt;54&lt;/sup&gt;</td>
<td>Paroxetine 10–50 mg daily vs placebo</td>
<td>Double-blind, placebo-controlled</td>
<td>50</td>
<td>53</td>
<td>42/8 8 weeks</td>
<td>Physician-rated clinical global impression scale + patient-rated score, Cardiac testing: NA</td>
<td>Patient-rated chest pain, no change, paroxetine vs placebo, NS &lt;br&gt; Physician-rated scale improved paroxetine vs placebo (P &lt; .05)</td>
</tr>
<tr>
<td>Spinhoven et al &lt;sup&gt;55&lt;/sup&gt;</td>
<td>Paroxetine 10–50 mg daily vs placebo</td>
<td>Randomized double-blind, placebo-controlled</td>
<td>95</td>
<td>55</td>
<td>48/47 16 weeks</td>
<td>NCCP and HADS ECP, no pH-metry, no manometry, no EGD, negative coronary angiography, or negative stress test, or negative cardiac history</td>
<td>Paroxetine was no more effective than placebo &lt;br&gt; Change in chest pain score, paroxetine vs placebo = 22 vs 24 (P = NS)</td>
</tr>
<tr>
<td>Prakash et al &lt;sup&gt;56&lt;/sup&gt;</td>
<td>Amitriptyline, imipramine, nortriptyline, desipramine (20–75 mg/day)</td>
<td>Open-label retrospective review</td>
<td>21</td>
<td>50</td>
<td>14/7 0.8–8.6 (mean 2.7) y Likert scale (0 = no improvement, 3 = clinical remission) responders ≥2 after treatment and 3 for remission, Chest pain index frequency × severity</td>
<td>ECP, use of tricyclic antidepressants and 6-mo follow-up, negative EGD, negative pH-metry, negative PPI response, no cardiac tests</td>
<td>Sedation, anticholinergic symptom</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method score</th>
<th>Intervention</th>
<th>Study design</th>
<th>Study size (N)</th>
<th>Mean age (y)</th>
<th>F/M</th>
<th>Duration</th>
<th>Outcome measure</th>
<th>Patient characteristics</th>
<th>Results</th>
<th>Safety analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rao et al57</td>
<td>1</td>
<td>Theophylline 150–250 mg twice a day</td>
<td>Open-label</td>
<td>12</td>
<td>46</td>
<td>10/2</td>
<td>12 weeks</td>
<td>CPF, CPI (VAS) Global chest pain improvement = &gt;50% improvement</td>
<td>ECP, negative EGD, negative pH-metry, negative manometry, positive EBDT, negative coronary angiography</td>
<td>• 8 completed study</td>
<td>Nausea, palpitation, tremor</td>
</tr>
<tr>
<td>Rao et al58</td>
<td>5</td>
<td>Theophylline SR 200 mg twice a day or placebo</td>
<td>Double-blind, placebo-controlled</td>
<td>25</td>
<td>46</td>
<td>18/7</td>
<td>8 weeks</td>
<td>Change in no. of days with chest pain, Global assessment (better, same, worse)</td>
<td>ECP, negative EGD, negative pH-metry, negative manometry, positive EBDT, negative stress test, or negative coronary angiography</td>
<td>• Median no. of days with chest pain was lower (P &lt; .014) and severity (P &lt; .03) decreased with theophylline vs placebo</td>
<td>Theophylline: nausea, insomnia, tremor, and lightheadedness; placebo: palpitations, insomnia</td>
</tr>
</tbody>
</table>

BDI, Beck Depression Inventory; CPF, chest pain frequency; CPI, chest pain intensity; CST, coping skills treatment; EBDT, esophageal balloon distention test; HADS, hospital anxiety and depression scale; IEM, ineffective esophageal motility; negative, normal test; positive, abnormal test; SF36, Short Form 36 quality of life measure; SR, slow release; TCA, tricyclic antidepressant; VAS, Visual Analogue Scale.
| Reference       | Methods score | Intervention                                | Study design                  | Study size (N) | Mean age (y) | F/M Duration | Outcome measure                                                                 | Patient characteristics                                                                 | Results                                                                 | Safety analysis |
|-----------------|---------------|---------------------------------------------|-------------------------------|----------------|--------------|--------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------|
| Jones et al61    | 3             | Hypnotherapy (12 sessions) or supportive    | Single-blind, randomized     | 28             | 57           | 18/10        | 12 weeks                                                                 | Global assessment of chest pain 7-point Likert scale Complete better or moderately better improvement | ECP negative pH-metry, negative EGD, no manometry, negative coronary angiogram           | None              |
| Klimes et al62   | 2             | CBT vs assessment control                   | Single-blind, controlled     | 35             | 41           | 15/20        | 12 weeks                                                                 | BDI, frequency chest pain and STAI > 50% improvement                                       | ECP (symptoms persistent 3 mo after negative cardiac evaluation), no pH test, no manometry, negative stress test | None              |
| Mayou et al63    | 3             | CBT vs standard clinical advice             | Single-blind, controlled     | 37             | 49           | 22/15        | 12 weeks                                                                 | CPF and CPS, improvement in mood, mental state                                            | ECP, no pH-metry or manometry, negative coronary angiography or negative outpatient cardiac evaluation (no details) | 33% dropout rate |

- Hypnotherapy decreased chest pain in 80% and 23% in supportive treatment group ($P < .008$) but no change in quality of life or anxiety
- 31% free of symptoms (chest pain) in CBT and 34% partial responders
- Improvement in depression and anxiety
- Improvement maintained 4- to 6-mo follow-up
- Decrease in pain severity at 3 mo and improvement of limitation of activities at 6 mo
- Significant clinical improvement 43%, some improvement 13%, modest improvement 31%, and no improvement 13%
<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods score</th>
<th>Intervention</th>
<th>Study design</th>
<th>Study size (N)</th>
<th>Mean age (y)</th>
<th>F/M</th>
<th>Duration</th>
<th>Outcome measure</th>
<th>Patient characteristics</th>
<th>Results</th>
<th>Safety analysis</th>
</tr>
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<tbody>
<tr>
<td>Van Peski et al&lt;sup&gt;64&lt;/sup&gt;</td>
<td>2</td>
<td>CBT vs usual care</td>
<td>Single-blind, controlled trial</td>
<td>65</td>
<td>49</td>
<td>36/29</td>
<td>12 weeks</td>
<td>CPF and duration, HADS</td>
<td>ECP, no pH-metry or manometry, gastrointestinal source excluded (no details), negative coronary angiography, negative exercise testing, or negative cardiac history</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Jonsbu et al&lt;sup&gt;66&lt;/sup&gt;</td>
<td>3</td>
<td>CBT or normal care by a general practitioner</td>
<td>Single-blind, controlled trial</td>
<td>40</td>
<td>52</td>
<td>26/14</td>
<td>3 sessions (every week)</td>
<td>Reduction of fear to body sensations CPF by using a 1 (daily) to 4 scale (no symptoms in last 6 mo), BDI, SF-36 (quality of life)</td>
<td>ECP (persistent symptoms after 6 months of negative cardiac evaluation, no details), no pH-metry and manometry</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Potts et al&lt;sup&gt;66&lt;/sup&gt;</td>
<td>1</td>
<td>Psychological treatment</td>
<td>Open-label trial</td>
<td>60</td>
<td>53</td>
<td>38/22</td>
<td>8 weeks</td>
<td>HADS, CPF, and severity scale: improvement, same, worse</td>
<td>ECP (symptoms ≥2/wk after negative coronary angiography or &lt;50% stenosed coronary arteries), no pH test, no manometry</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

- Decrease in frequency 1/week in CBT and 5/week in usual care
- Pain reduction = adequate awareness about source of pain; no influence in panic disorders
- Decrease in CPF
- Decrease of fear about body sensations (2.7 to 3.5; \( P < .007 \)), increase in physical activities, improvement in depression and quality of life; effective up to 12 mo
- 76% improved, 20% same, and 4% worse
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study Design</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Outcome Measures</th>
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<tbody>
<tr>
<td>Shapiro et al(^6)</td>
<td>Open-label study</td>
<td>22, FCP = 9, biofeedback = 6, standard care = 3</td>
<td>44</td>
<td>Functional heartburn = 13, biofeedback = 6, standard care = 7</td>
</tr>
<tr>
<td>Gasiorowska et al(^6)</td>
<td>Single-blind, controlled trial</td>
<td>39, Johrei = 21, wait-list control = 18</td>
<td>54.5</td>
<td>Daily symptoms assessment diary (symptom intensity score), SF-36, HADS, PSS, SCL-90R</td>
</tr>
</tbody>
</table>

**Results:**
- Biofeedback for non-GERD FCP vs standard care:
  - HADS and global assessment scale: free of symptoms (5 points), to no change/worse (1 point). Improvement = 3–5 points.
- Functional heartburn and FCP, negative EGD, negative pH-metry, negative coronary angiogram/stress-ECHO test.
- FCP = 3/8 free of symptoms; 2/9 partial responders (\(P = .048\)) vs standard care (0/3).
- 4/9 reported improved general well-being regardless of symptom response.
- Functional heartburn group = no improvement with biofeedback or standard care.

**Johrei treatment:**
- Single-blind, controlled trial
- 39, Johrei = 21, wait-list control = 18
- Improvement in symptom intensity score.
- No difference in HADS, PSS, SCL-90.
- Numerical higher increase in SF-36, not significant.
- Baseline vs end of treatment:
  - Johrei: 20.2 vs 7.0, \(P < .002\)
  - Control: 20.2 vs 23.1, \(P = \text{NS}\)
- No side effects.

**Instruments:**
- BDI, Beck Depression Inventory;
- CPF, chest pain frequency;
- CPI, chest pain intensity;
- ECHO, echocardiogram;
- FCP, functional chest pain;
- HADS, hospital anxiety and depression scale;
- negative, normal test;
- positive, abnormal test;
- PSS, perceived stress scale;
- SF-36, Short Form 36;
- SCL-90R, Symptom Checklist 90 Revised;
- STAI, State Trait Anxiety Inventory.
Omeprazole. Three studies showed that omeprazole was effective in treatment of ECP.14,19,20 Fass et al14 reported 65% improvement in ECP in 39 patients after one 1-week course of omeprazole 60 mg/day, but maximal benefit was noted in GERD-positive patients (52% vs 7%). They suggested that a 7-day PPI trial may serve as a diagnostic and cost-effective approach for GERD-related chest pain.14,20 The “omeprazole test” has a sensitivity of 87%, specificity of 85.7%, and positive predictive value of 90.9%. In summary, there is good evidence (Level I) for omeprazole in GERD-related chest pain, especially in those with esophagitis and/or abnormal 24-hour pHmetry.

For omeprazole, there were 3 double-blind, placebo-controlled trials14,19,20 with quality scores of 5, 5, 5. Evidence was good (Level I).

Lansoprazole. In a single-blind study, 92% patients with GERD and 33% without GERD improved (odds ratio, 22; P < .001). In the placebo group, there was no difference in response rates between GERD groups.21 The “lansoprazole test” had sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 92%, 67%, 58%, 94%, and 75%, respectively, for detection of GERD-related chest pain. In another randomized, double-blind, placebo-controlled crossover study of lansoprazole 60 mg AM and 30 mg PM for 7 days, 78% were responders (50% improvement in chest pain score) with lansoprazole and 22% with placebo (P < .0143) in GERD-positive patients and only 9% in GERD-negative patients.22 For lansoprazole, there was 1 double-blind and 1 single-blind controlled trial21,22 with quality scores of 2, 4. Evidence was fair (Level II).

Rabeprazole. In a double-blind, placebo-controlled crossover study of 35 patients, rabeprazole (40 mg) for 7 days showed a response rate of 75% in GERD-positive patients and 19% in GERD-negative.23 Importantly, majority of GERD-related responders (75%) had erosive esophagitis. Rabeprazole was mostly useful in GERD-related ECP. For rabeprazole, there was 1 double-blind, placebo-controlled trial23 and open-label trial24 with quality scores of 4, 0. Evidence was fair (Level II).

Ranitidine. The efficacy of ranitidine 150 mg 4 times a day was evaluated in 1 open-label trial of 13 patients,25 without cardiologic evaluation. All improved, but results were better in patients with positive symptom index on pHmetry. For ranitidine, there was 1 open-label trial with quality score of 1. Evidence was poor (Level III).

Treatment of Esophageal Chest Pain Related to Esophageal Spastic Motility/Dysmotility Disorders

Pathophysiology. Several motility disorders have been implicated in the pathogenesis of ECP including diffuse esophageal spasm (DES), nutcracker esophagus, achalasia, scleroderma, and nonspecific motility disorders,6,26 however, the evidence is conflicting. In one study, although 32% of patients had dysmotility, none experienced pain during the abnormal manometry.13 Another study of 10 patients with 24-hour endoluminal ultrasonography described sustained esophageal contractions during episodes of spontaneous chest pain.27 However, this activity, mediated by longitudinal muscle contractions, occurred only in a subset and only during some of the pain episodes and is probably due to heartburn and acid reflux.28 Esophageal spasm may cause ECP and may occur either spontaneously or as a result of noxious stimuli such as acid reflux29 and this formed the basis for testing with calcium channel blockers, nitrates, or botulinum toxin injection.

Treatment. Therapeutic trials for this category are summarized in Tables 2 and 6.

Nifedipine. Nifedipine, a calcium channel blocker, was tested in 3 RCTs.30–32 Twenty patients with ECP and nutcracker esophagus were randomized to receive nifedipine or placebo, 10–30 mg 3 times a day for 14 weeks.30 Nifedipine did not decrease chest pain frequency or intensity, but chest pain index (severity × frequency) decreased from 10.3 ± 2.0 to 3.2 ± 0.8 (P < .005). A second study compared nifedipine 10 mg 3 times a day with placebo in a 4-week randomized crossover study in 16 patients with esophageal motor disorders including achalasia, spasm, and nutcracker esophagus.31 Thirteen of 16 patients (81%) on nifedipine and 4 of 16 (25%) on placebo had >50% improvement in ECP. A third placebo-controlled study in 8 patients with esophageal spasm showed no differences.32 For nifedipine, there were 3 double-blind, placebo-controlled trials30–32 with quality score of 4, 2, 4. Evidence was fair (Level II).
Diltiazem. In an open-label study of 10 patients with nutcracker esophagus, diltiazem 90 mg 4 times a day showed improvement. However, in a 10-week randomized, double-blind crossover study of 8 patients with DES, diltiazem was not superior to placebo. In another double-blind, randomized crossover study of 8 weeks, the peristaltic amplitude decreased \((P < .05)\) and chest pain score decreased \((P < .05)\) in 14 patients with nutcracker esophagus. Generally, these were small studies with significant methodological issues, and GERD was not effectively ruled out. For diltiazem, there were 2 double-blind, placebo-controlled trials with quality score of 3, 3. Evidence was fair (Level II).

Nitrates. In an open-label trial of 12 patients who received nitroglycerine and long-acting nitrates, the 5 patients who did not have reflux responded well to treatment, whereas the 7 patients with acid reflux had poor response. There were significant methodological issues including subject selection. For nitrates, there was 1 open-label study with quality score of 0. Evidence was poor (Level III).

Botulinum toxin. In an open-label trial, botulinum toxin A was injected into the gastroesophageal junction in 29 patients; 72% responded with at least 50% reduction in chest pain. There was 79% reduction in the mean chest pain score (from 3.7 to 0.78, \(P < .0001\)). However, mean duration of response was 7.3 ± 4.1 months. In another small open-label study of 9 patients with DES and ECP, 100 IU botulinum toxin A was injected at every 1–1.5 cm above the gastroesophageal junction. After 4 weeks, 8 of 9 patients (89%) showed improvement in total symptom score for 6 months, and some required repeat injections. For botulinum toxin, there were 2 open-label prospective trials with quality score of 0, 1. Evidence was poor (Level III).

Lansoprazole. Lansoprazole 30 mg once a day for 8 weeks improved neither symptoms nor manometric changes in nutcracker esophagus. For lansoprazole, there was 1 double-blind, placebo-controlled trial with quality score of 4. Evidence was poor (Level III).

Phosphodiesterase inhibitors. Sildenafil, a phosphodiesterase-5 inhibitor, was examined in an uncontrolled small study of patients with spastic esophageal motor disorders, and the results were inconsistent; acid reflux and cardiac disease were not excluded. For sildenafil, there was 1 open-label study, not randomized, with quality score of 0 (Tables 2 and 6). Evidence was poor (Level III).

Treatment of Esophageal Visceral Hypersensitivity

Pathophysiology. Esophageal hypersensitivity is a key neurobiological mechanism that causes pain. Patients with ECP demonstrated 50% lower sensory thresholds when compared with controls, together with a hyperreactive and poorly compliant esophagus. Also, in 80% of patients their typical chest pain was reproduced. More significantly, smooth muscle relaxation with atropine did not improve sensory thresholds or chest pain. Likewise, esophageal hypersensitivity was seen in 90% of patients with nutcracker esophagus, suggesting sensory dysfunction. Together, these findings suggest that esophageal hypersensitivity rather than motor dysfunction is important in ECP. Furthermore, it explained why smooth muscle relaxants by themselves are generally ineffective.

Recent studies have suggested that pain perception in ECP patients may be due to central sensitization and that N-methyl-D-aspartate blockers may alter chest pain. In 1 controlled study of healthy subjects, citalopram, a selective serotonin reuptake inhibitor given intravenously, significantly increased sensory thresholds and prolonged the time for perception of heartburn after acid infusion, implying that ECP may be centrally mediated. Also, adenosine may play a key role in mediating pain; adenosine infusion decreased esophageal sensory thresholds in both healthy controls and ECP patients.

Treatment. Various classes of drugs including imipramine, trazodone, citalopram, sertraline, and theophylline have been tried and are summarized in Tables 3 and 7.

Imipramine. Cannon et al postulated a role for medistinal hypersensitivity in ECP. In a placebo-controlled
study, 60 patients were randomized for a 3-week trial. Chest pain decreased in 52%, 39%, and 1% of patients who received imipramine 50 mg 4 times a day, clonidine 0.1 mg 4 times a day, and placebo, respectively, but the reduction was significant (P < .03) only in the imipramine group. Also, the response was independent of esophageal dysfunction or psychiatric comorbidities.

For imipramine, there was 1 double-blind, placebo-controlled trial with quality score of 4. Evidence was fair (Level II).

Trazodone. Twenty-nine patients with chest pain and dysmotility completed a 6-week RCT of trazodone (100–150 mg/day)50. Trazodone group (n = 15) reported greater global improvement than placebo group (n = 14, P = .02). However, this was not related to manometric improvement, which was the primary end point. For trazodone, there was 1 double-blind, placebo-controlled trial with quality score of 3. Evidence was fair (Level II).

Sertraline. In a double-blind, placebo-controlled study, sertraline was titrated up to 200 mg daily in 30 patients for 8 weeks.51 Sertraline showed a significant reduction in pain (P < .02) when compared with placebo, but no differences were seen on Beck Depression Inventory.

Another study assessed whether a combination of psychological treatment (coping skills) plus sertraline, sertraline alone, coping skills alone, or placebo was effective in ECP.52 Although there was some benefit in each group, the highest response was seen in the combined therapy (coping skills plus sertraline). Also, anxiety and catastrophizing improved, suggesting that patients with higher levels of anxiety will benefit the most.52

A major drawback was that GERD was not excluded. These studies showed that psychiatric co-morbidity may influence the outcome of this treatment. For sertraline, there were 2 double-blind, placebo-controlled trials with quality scores of 4, 5. Evidence was fair (Level II).

Venlafaxine. In a 4-week randomized placebo-controlled study, 43 patients who received 75 mg venlafaxine showed a therapeutic response in 52% of subjects compared with 4% on placebo.53 Also, the venlafaxine group showed improvements in body pain and emotional role (P < .002).

For venlafaxine, there was 1 double-blind, placebo-controlled trial with quality score of 5. Evidence was fair (Level II).

Paroxetine. Fifty patients were randomized to paroxetine (10–50 mg daily, median dose 30 mg) or placebo for 8 weeks. Patients who received paroxetine showed improvement in the clinical global impression scale (physician-rated) but not in the patient-rated chest pain scale.54 In a second study, 69 patients were randomized to receive paroxetine, cognitive behavioral therapy (CBT), or placebo55 for 16 weeks; paroxetine was no more effective than placebo.

For paroxetine, there were 2 double-blind, placebo-controlled trials with quality score of 5, 5. Evidence was fair (Level II) against use.

In a retrospective study (mean follow-up, 2.7 years) of antidepressants for the treatment of chest pain, in 21 patients moderate symptom reduction was seen in 17 subjects (81.0%).56 Of these, 7 (41.2%) were successfully treated continuously, and 5 (29.4%) discontinued because of side effects.

Theophylline. After an open-label pilot study of 12 patients,57 an RCT showed that intravenous theophylline decreased esophageal hypersensitivity and wall reactivity and improved esophageal distensibility.58 In another randomized placebo-controlled crossover study of 25 patients with ECP, theophylline 200 mg orally twice a day improved chest pain (P < .03) in 58% of patients compared with 6% in placebo.58 Theophylline, whose effects are mediated by adenosine receptor antagonism, may act as visceral analgesic and smooth muscle relaxant.

For theophylline, there were 2 double-blind, placebo-controlled trials with quality score of 5. Evidence was fair (Level II).

Treatment of Esophageal Chest Pain by Using Nonpharmacologic/Behavioral Approaches

In one study, 21 of 25 patients (84%) with abnormal esophageal manometry had a psychiatric diagnosis compared with 8 subjects (31%) with normal manometry.59 Another study by Cannon et al59 showed that 38

| Table 7. Quality Assessment of Trials on Visceral Hypersensitivity for ECP |
|-----------------|---|---|---|---|---|
| Reference       | Randomization | Blinding | Statement on withdrawals | Total score |
| Cannon et al59  | 2             | 2         | 0                         | 4           |
| Clouse et al59  | 1             | 1         | 1                         | 3           |
| Varia et al52   | 1             | 2         | 1                         | 4           |
| Keefe et al52   | 2             | 2         | 1                         | 5           |
| Lee et al52     | 2             | 2         | 1                         | 5           |
| Spinov et al56  | 2             | 2         | 1                         | 5           |
| Prakash et al56 | 0             | 0         | 1                         | 1           |
| Rao et al58     | 2             | 2         | 1                         | 5           |
| Doraiswamy et al54 | 2          | 2         | 1                         | 5           |
of 60 patients (63%) with ECP had 1 or more psychiatric disorders, and their ECP responded to imipramine. In one study of 441 patients with functional chest pain, the prevalence of panic disorder was 24.5%. Whether psychological or psychiatric disorders cause ECP or are commonly associated with this condition remains controversial. A number of approaches have been tried and are summarized in Tables 4 and 8.

**Hypnotherapy.** In a single-blind RCT, 28 patients were randomized to receive hypnotherapy or supporting listening plus placebo medication. The hypnotherapy arm had greater improvement ($P = .008$) in chest pain and a greater reduction in pain intensity ($P = .046$) but not in frequency and in overall well-being when compared with supportive therapy.61

For hypnotherapy, there was 1 single-blind RCT61 with quality score of 3. Evidence was poor (Level III).

**Cognitive behavioral therapy.** In a small controlled study of CBT versus conventional treatment, 31% of subjects (5 of 17) were free of symptoms at 12 weeks, and 34% (6 of 17) were partial responders. Depression and anxiety also improved.62 In another study, 37 patients with persistent chest pain with heart disease excluded, but not reflux disease, received 12 sessions of CBT. Fifteen of 20 completed CBT treatment (75%) versus 10 of 17 (59%) in the control group. At 3 months, CBT group showed a decrease in pain severity and the number of pain-free days, and also at 6 months, physical and social impairment improved.63 Major drawbacks were the high dropout rate in both treatments, questioning the durability of CBT, and GERD was not excluded.

Another RCT compared CBT with usual care in 65 patients and showed significant reduction in chest pain frequency but no improvement in concurrent panic disorders.64

In another RCT, 40 patients received 3 weekly sessions of CBT. They showed greater improvement with regard to fear of bodily sensations and some domains of health-related quality of life.65 However, the unblinded allocation of patients into each therapy indicated significant bias.

An open-label study of psychological treatment “package” (breathing exercises, education, relaxation, and graded exposure to activity) in 60 patients with ECP showed significant reduction ($P < .01$) in median chest pain episodes from 6.5 to 2.5 per week. There were significant improvements in anxiety and depression scores ($P < .05$), disability rating ($P < .0001$), and exercise tolerance ($P < .05$) that were maintained for 6 months.66 This study was not blinded, and GERD and other sources of chest pain were not excluded.

For CBT, there were 4 single-blind RCTs62–65 with quality scores of 2, 3, 2, 3. Evidence was fair (Level II) (Tables 4 and 8).

**Biofeedback therapy.** Another study involved biofeedback (diaphragmatic exercises), breathing techniques, and self-control of stress by using galvanic skin resistance feedback. This technique improved symptoms in 5 of 9 patients with functional chest pain but not in patients with functional heartburn.67

For biofeedback therapy, there was 1 open-label trial67 with quality score of 1. Evidence was poor (Level III).

**Johrei treatment.** Thirty-nine patients with functional chest pain were randomized to receive 20 minutes of Johrei treatment (Spiritual Energy healing) for 6 weeks or weight-list control.68 When compared with baseline, there was significant reduction in chest pain symptom intensity score ($P < .0002$) in the Johrei group but not in the control group (20.2 vs 23.1, $P = NS$). This pilot study whose mechanism of action is unclear and did not include sham treatment needs further confirmation.

For Johrei therapy, there was 1 randomized, uncontrolled, non-sham study68 with a quality score of 3. Evidence was poor (Level III).

Although the aforementioned studies provide some evidence for the utility of CBT and other psychological approaches, the precise mechanism for improvement is unclear, and robust RCTs are lacking.

**Treatment of Esophageal Chest Pain by Using Surgery**

One study compared thoracoscopic versus laparoscopic myotomy in 49 patients (12%) with DES and 41 (10%) with nutcracker esophagus and showed no difference in outcome between the 2 techniques. Chest pain

<table>
<thead>
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<th>Randomization</th>
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improved in 80% of patients with DES but failed in patients with nutcracker esophagus. Several surgical approaches have been tried, particularly long esophageal myotomy, but RCTs are lacking.

For long esophageal myotomy, there were non-randomized, uncontrolled studies with quality scores of 0, 1. Evidence was poor (Level III).

Discussion

Although patients with ECP or NCCP are commonly encountered in family medicine, cardiology, and gastroenterological practices, with an annual incidence of 200,000 patients, with regard to its treatment, there is significant dearth of high quality, placebo-controlled,
randomized studies. We identified significant methodological problems including the selection of patients, inconsistent definition of ECP across studies, and typically small studies. Some have defined this condition as NCCP when a cardiac source has been excluded, others have either included or excluded GERD as a source of ECP, and yet others have excluded a cardiac source, GERD, and motility dysfunction. Likewise, the definition of clinical improvement was quite variable. Some have defined improvement that was based on changes in the frequency of chest pain episodes, few have defined this as ≥50% improvement in chest pain, and others have used improvement in the intensity of chest pain or a global improvement rate or other subjective parameters. Thus, a lack of clear inclusion/exclusion criteria and a lack of well-defined and standardized patient-reported outcome measure have hampered our ability to compare the efficacy and therapeutic usefulness of clinical trials on this topic. It is clear that no one drug or therapeutic modality is likely to work for ECP because it is caused by 1 or more pathophysiological mechanism(s).

Ideally, treatment of ECP should alleviate not only the symptom(s) but also remedy the underlying pathophysiological mechanism. An evidence-based summary of the efficacy and safety of therapeutic trials in ECP is presented in Tables 1–8. The quality of these studies was assessed by using criteria previously established to minimize bias and enhance validity of therapeutic trials.10

The following recommendations can be made for treatment of ECP that is based on current evidence summarized above and our clinical experience (Figure 1). After excluding a cardiac source for chest pain, it seems reasonable to begin with antireflux therapy (PPI, twice a day), because GERD affects at least one-third of patients with ECP.6,7 Omeprazole, lansoprazole, and rabeprazole appear to be safe and effective.14,18,20–23 If unhelpful, esophageal manometry, 24-hour ambulatory pH test, and esophageal balloon distention test should be considered and may identify an esophageal source for chest pain in more than 75% of patients.5 Alternatively, an empirical trial of theophylline 150–250 mg twice a day should be considered.57,58

If ineffective or patient has overlapping features of irritable bowel syndrome, functional dyspepsia, or anxiety,42 a trial of low-dose antidepressants such as imipramine, sertraline, or venlafaxine may be considered.49,51–53,56 If none of these approaches help, a psychology consultation together with CBT or hypnotherapy1481 should be considered. Surgical approaches such as long thoracoscopic myotomy have undesirable long-term consequences and are best avoided.

References


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September 25, 2014


True or False

1. Esophageal motility disorders account for <10% of cases of esophageal chest pain.

2. Acid reducing therapy improves esophageal chest pain in <40% of patients that have no pathologic acid reflux.

3. Calcium channel blockers produced contradictory data in poor quality studies.

4. A patient with a hypersensitive esophagus (no GERD, positive pain with balloon distention) should be tried on theophylline therapy.

5. Imipramine, trazodone, sertraline and venlafaxine, but not paroxetine may help with visceral hypersensitivity and decrease esophageal chest pain.

6. Theophylline was found to be ineffective in relieving esophageal chest pain.

7. There is lack of reliable, well designed clinical studies addressing the management of esophageal chest pain.

NOTE: It appears that figure 1 in the article has an error. The GERD positive and negative boxes appear to be switched.