Noncardiac chest pain (NCCP) is a very common disorder of international proportions. In the United States, nearly 70 million patients (23% of the population) suffer from NCCP. Population-based studies have also reported similar figures in: Australia, 33%; South China, 21%; Argentina, 24%; and Spain, 8% to 28%. Patients with NCCP represent a significant economic impact. They account for 2% to 5% of all emergency room evaluations and are one of the most frequent causes of hospital admission in the western world. A United States household survey of functional gastrointestinal disorders found that NCCP patients are usually gainfully employed and lose an average of 13 days of work each year.

The pathophysiology of NCCP is complex and poorly understood. Several mechanisms have been identified as possible sources of pain, including gastroesophageal reflux (GER), visceral hyperalgesia, esophageal motility disorders, psychiatric dysfunction, abnormal biomechanical properties of the esophageal wall, sustained esophageal contractions, abnormal cerebral processing of visceral stimulation, and disrupted autonomic activity. Treatment of NCCP is challenging due to the heterogeneous nature of this disorder. It is also possible that many patients suffer from more than one condition. Selection of therapy is frequently aimed at the suspected underlying process. The purpose of this article is to provide a focused review of available treatment modalities for this challenging disorder.

GASTROESOPHAGEAL REFLUX

GER is the most common cause of NCCP, and the best studied. The benefits of acid inhibition in NCCP have been demonstrated during short- (1 day–2 weeks) and long-term (6–8 weeks) trials. Tables 1 and 2 summarize the studies that have examined the impact of acid-inhibitory therapy in NCCP. These trials underscore the favorable effect of acid suppression in NCCP. Table 1 shows that for long-term therapy, only two studies were double blind and placebo controlled; and one is available only as an abstract. Table 2 shows that for short-term therapy, five studies were placebo controlled and two studies (available only as an abstract) were not. Overall, sample size is
small: 12 to 36 subjects for long-term studies (with the exception of Flook’s17 study, an abstract containing 599 subjects) and 17 to 68 subjects in short-term trials.

In contrast to the robust data available comparing medical to surgical therapies for the treatment of typical forms of GER, there is limited information regarding the surgical outcome for extra-esophageal GER, particularly NCCP. Furthermore, there are no randomized surgical trials. Six studies have addressed the effects of anti-reflux surgery on NCCP (Table 3).25–30 All are retrospective, uncontrolled studies. The results of these investigations found that between 41% and 100% of these patients obtain symptom relief. Patient selection has not been described, though it is likely to be highly selective. Complications were uncommon, but when they occurred, some were serious. All studies come from academic centers experienced in esophageal surgery, thus it is unknown how these results apply to community centers. Well-designed, prospective, controlled trials are needed to determine the efficacy of anti-reflux surgery in patients with GER related NCCP.

These studies suggest that in approaching patients with NCCP, an initial medical trial of acid suppression provides effective chest pain relief in the majority of the patients. Furthermore, the data from short-term therapeutic trials (Table 2) indicate that a brief course of high-dose proton pump inhibitor (PPI) therapy has the potential to serve as both a diagnostic and therapeutic approach to identify patients with GER-related chest pain.

VISCERAL HYPERALGESIA

Patients with NCCP show a heightened sensitivity to a variety of experimental esophageal stimuli such as pharmacologic provocation with cholinergic agonists,
### Table 2
Short-course PPI trials as a diagnostic test in noncardiac chest pain

<table>
<thead>
<tr>
<th>Author, Reference, Year</th>
<th>Number of Cases</th>
<th>Medication and Dosage</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young et al, 1992 (abstract)</td>
<td>30</td>
<td>Omeprazole, 80 mg/d for 1 day</td>
<td>90</td>
<td>80</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Squillace et al, 1993 (abstract)</td>
<td>17</td>
<td>Omeprazole, 80 mg/d for 1 day</td>
<td>69</td>
<td>75</td>
<td>90</td>
<td>43</td>
</tr>
<tr>
<td>Fass et al, 1998</td>
<td>37</td>
<td>Omeprazole, 40 mg/AM 20 mg/PM versus placebo for 7 days</td>
<td>78</td>
<td>86</td>
<td>90</td>
<td>71</td>
</tr>
<tr>
<td>Pandak et al, 2002</td>
<td>37</td>
<td>Omeprazole, 40 mg/bid versus placebo for 2 weeks</td>
<td>90</td>
<td>67</td>
<td>73</td>
<td>92</td>
</tr>
<tr>
<td>Xia et al, 2003</td>
<td>68</td>
<td>Lansoprazole, 30 mg/d versus placebo for 4 weeks</td>
<td>92</td>
<td>67</td>
<td>58</td>
<td>94</td>
</tr>
<tr>
<td>Bautista et al, 2004</td>
<td>40</td>
<td>Lansoprazole, 60 mg/AM 30 mg/PM versus placebo for 7 days</td>
<td>78</td>
<td>80</td>
<td>88</td>
<td>83</td>
</tr>
<tr>
<td>Dickman et al, 2005</td>
<td>35</td>
<td>Rabeprazole, 20 mg/bid versus placebo for 7 days</td>
<td>75</td>
<td>90</td>
<td>83</td>
<td>75</td>
</tr>
</tbody>
</table>

**Abbreviations:** NA, not available; NPV, negative predictive value; PPV, positive predictive value.

*Data from Achem SR. Treatment of noncardiac chest pain. Dis Month 2008;54:642–70.*
hydrochloric acid, and intraesophageal balloon distension. Studies have shown that 60% of patients with NCCP have an increased perception to esophageal distension, a phenomenon observed in only 20% of healthy controls. This increased reactivity has been termed visceral hyperalgesia and has also been described in subjects with irritable bowel syndrome during rectal balloon distension studies. Although the mechanisms responsible for visceral hyperalgesia remains unclear, several pharmacologic agents that reduce chest pain are believed to act by diminishing visceral sensitivity or inducing “visceral analgesia.” For instance, imipramine, when compared with baseline, was found to be effective in improving chest pain threshold induced during esophageal balloon distension studies in healthy males. In addition to tricyclic antidepressants (TCA), imipramine and trazodone, recent information suggests that the serotonin-uptake inhibitors (SSRIs) may also play an important role in visceral pain. The SSRIs, sertraline and paroxetine, have been studied in NCCP and compared with placebo showing favorable effects. The clinical trials that have examined the outcome of these therapeutic compounds (TCA and SSRI), on NCCP are summarized in Table 4. These studies suggest that visceral analgesics are effective in the

<table>
<thead>
<tr>
<th>Author, Reference, Year</th>
<th>Number of Cases</th>
<th>Improvement</th>
<th>Follow-up Time</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeMeester et al, 1982</td>
<td>11</td>
<td>100%</td>
<td>2–3 years</td>
<td>Symptom index at pH predicted improvement</td>
</tr>
<tr>
<td>So et al, 1998</td>
<td>12</td>
<td>48%</td>
<td>Median 22 months (12–36)</td>
<td>Previous improvement with histamine 2 receptor antagonists blockers or PPI predicted improvement</td>
</tr>
<tr>
<td>Chen et al, 2000</td>
<td>11</td>
<td>13% symptom free, 41% some improvement, 46% no improvement</td>
<td>1–5 years</td>
<td>Patients with atypical symptoms had less response than those with typical GER</td>
</tr>
<tr>
<td>Farrell et al, 2001</td>
<td>62</td>
<td>55% improved, 45% resolved</td>
<td>13 months</td>
<td>More improvement seen in patients with typical than atypical symptoms</td>
</tr>
<tr>
<td>Patti et al, 2002</td>
<td>165</td>
<td>65% (of those with no SI correlation), 79% of those with ≤ 40% SI correlation, 96% with ≥ 40% SI correlation</td>
<td>13 months</td>
<td>Highest improvement based on symptom index correlation</td>
</tr>
</tbody>
</table>
| Rakita et al, 2006       | 158             | 81%         | 50 months ± 83 months | Data from Achem SR. Treatment of noncardiac chest pain. Dis Month 2008;54:642–70.
treatment of NCCP when compared with placebo. Interestingly, all these trials are of relatively small sample size, a problem similar to that observed with antisecretory therapy trials. There are no head-to-head comparative studies. Potential side effects such as drowsiness, prostatic retention, and arrhythmias may limit the use of the TCAs, imipramine, and trazodone. Trazodone has also been associated with priapism. Decreased libido or ejaculation dysfunction may limit the use of SSRIs, sertraline, and paroxetine.

**PSYCHIATRIC DISORDERS**

Psychiatric conditions are common in NCCP. Several studies have noted a variable prevalence of panic disorders (24%–70%), anxiety (33%–50%), and major depression (11%–22%). Management of these patients is difficult because physicians may not critically screen for these conditions. Treatment is further complicated by the patient’s unwillingness to accept their psychiatric comorbidity and the lack of timely referral. The treatment may also be hampered by insufficient access to or availability of specially trained or interested therapists. Finally, it is unknown what therapeutic options are best suited to treat NCCP; whether pharmacologic intervention, cognitive therapy or other forms of intervention combined or alone yield the best treatment outcomes.

**Table 4**

<table>
<thead>
<tr>
<th>Author, Reference, Year</th>
<th>Number of Cases</th>
<th>Type of Trial</th>
<th>Medication and Dosage</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clouse et al, 1987</td>
<td>30 (15 received trazodone and 15 placebo)</td>
<td>Placebo-controlled for 6 weeks</td>
<td>Trazodone, 100–150 mg</td>
<td>Trazodone improved chest pain</td>
</tr>
<tr>
<td>Cannon et al, 1994</td>
<td>60 (20 patients in each arm of trial)</td>
<td>Double-blind, placebo-controlled for 3 weeks</td>
<td>Imipramine, 50 mg at night time; Clonidine, 0.2 mg or placebo</td>
<td>Imipramine induced significant improvement</td>
</tr>
<tr>
<td>Prakash and Clouse, 1999</td>
<td>21</td>
<td>Open-label, long-term up to 3 years</td>
<td>Several tricyclic antidepressant</td>
<td>Tricyclic antidepressant produced 75% improvement at 3 years</td>
</tr>
<tr>
<td>Varia et al, 2000</td>
<td>25</td>
<td>Single-blind, placebo-controlled for 9 weeks</td>
<td>Sertaline, 50–200 mg adjusted dose to response</td>
<td>Sertaline improved chest pain</td>
</tr>
<tr>
<td>Doraiswamy et al, 2006</td>
<td>50 (27 paroxetine and 23 placebo)</td>
<td>Double-blind, placebo-controlled</td>
<td>10 mg for 1 wk and titrated upward weekly up to 50 mg; median dose was 30 mg (range 5–50 mg)</td>
<td>Paroxetine induced improvement on a physician-rated scale, but not on self-rated pain scores</td>
</tr>
</tbody>
</table>
A typical approach has been to offer patients reassurance and education about the “benign nature” of NCCP and good prognosis in comparison to the prognosis of patients with chest pain and coronary artery disease. Despite a favorable medical prognosis, patients with NCCP continue to experience chest pain symptoms (50%–70%), occupational (19%–51%) and functional impairment (46%–100%), and high levels of chest pain–related medical use; including hospitalization and use of inappropriately prescribed cardiac medications (27%–79%). The goals of therapy should be to reduce unnecessary use of emergency services and other medical resources, to decrease the incidence and severity of chest pain symptoms, and improve patients’ quality of life.

A number of psychologic techniques have been employed for the treatment of NCCP. Cognitive therapy (CT) is based on the model of attribution approach. After cardiac tests deem chest pain as noncardiac, patients undergo several treatment sessions (7–16 sessions, 8–38 hours). The goal of treatment is to correct the misattributions regarding physical symptoms (ie, chest pain) as being harmful. Patients must adopt the belief that psychologic factors cause chest pain; and attribute the chest pain to panic attacks, anxiety, and psychologic factors. Three general principles are used during CT: (1) offer an alternative, noncardiac, explanation for the patient’s symptoms by addressing the problem as a combination of physical, cognitive, and behavioral factors, while challenging any catastrophic interpretation of patient’s symptoms; (2) teach patients how to cope with their symptoms using behavioral interventions such as relaxation and controlled breathing; and (3) address the potential problems that perpetuate symptoms such as stress, family, work, or other personal issues. Randomized, controlled trials of these treatments for NCCP demonstrate that these relatively lengthy treatments are effective in reducing psychologic distress, chest pain episodes, and decreasing functional impairment (Cott and colleagues, unpublished, 1990). Table 5 summarizes several trials of CT in NCCP and their outcomes. Overall, most published studies have shown a favorable outcome for CT. In a Cochrane analysis that involved eight studies of CT, Kisely and colleagues reported a significant benefit on chest pain parameters with CT.

Esler and Bock provide persuasive arguments to consider alternative psychologic management strategies to CT for NCCP, such as the biopsychosocial model. This approach is based on the following principles: (1) most illness, whether physical or psychiatric, is influenced and determined by biological, psychologic, and social phenomena; (2) biological, psychologic, and social variables influence the predisposition, onset, course, and outcome of most illnesses; and (3) better patient outcomes are achieved when therapeutic interventions are based on evaluation of the relationship between biological, psychologic, and social variables. Even if there is not a clinically-significant psychiatric disorder present, evaluating and managing psychologic and social variables is still critical. The biopsychosocial model allows the physician to admit uncertainty and retain the possibility of cardiac etiology, while still recognizing and treating psychiatric problems such as anxiety. The biopsychosocial model does not force an “either-or” view of the patient’s condition: medical versus psychologic. This model allows for the co-occurrence of biological, psychologic, and social factors, which influence the course, and outcome of distressing symptoms. This model has been used in the treatment of other chronic pain syndromes. Its proponents believe that because it requires shorter intervention time (such as one session in hospital while patient is having structural studies and two or three telephone follow-up sessions), it is more practical and faster, while also allowing for continued medical evaluation. It also allows for additional forms of treatment such as pharmacologic intervention. Controlled clinical trials are needed to evaluate the results of this type of therapy.
OTHER INTERVENTIONS

Hypnotherapy

A recent study examined the effects of hypnotherapy in NCCP. During a small trial, 28 patients were assigned to receive hypnotherapy (12 sessions) or supportive therapy plus placebo medication for a 17-week period. The hypnotherapy group experienced significantly more chest pain reduction (global and intensity, but not frequency). Hypnotherapy did not affect anxiety or depression scores.64

Biofeedback

Biofeedback has been used in a small trial of 70 patients with a variety of functional disorders, including NCCP (the precise number of patients with NCCP was not specified). Thirty patients were randomized to a control period, and 40 to active therapy. The authors reported symptom reduction and lowered costs for the treatment group compared with the control.65 Clearly, more studies are needed to determine whether this technique is effective in the treatment of NCCP.

Transcutaneous Nerve Stimulation

Transcutaneous nerve stimulation (TENS) has been used to treat diverse types of pain,66 including pain resulting from gastrointestinal tract distension.67 TENS has also been shown to exert important effects on esophageal motility parameters in achalasia and sphincter of Oddi dysfunction.68 During acute esophageal balloon distension studies in 18 patients with NCCP, TENS resulted in decreased perception of pain evoked by acute esophageal stimulation.69 This was not a blinded study with respect to the treatment given, and the patients could differentiate between the two TENS modes offered. However, the patients were not aware which of the stimulation sites was supposed to be active. It is unclear whether the use of TENS may have systemic effects (such as those potentially induced by placebo application). In a recent nonblinded, small trial of 24 patients with NCCP using either TENS or spinal cord stimulation, de Vries and colleagues70 found a greater than 50% improvement in pain parameters and nitroglycerin consumption during a mean follow-up time of five years. Thus, it appears that further research is warranted to evaluate the potential role of TENS in the treatment of NCCP.

Anxiolytics

The high prevalence of anxiety disorders in NCCP suggests that anxiety may amplify, trigger, or perpetuate NCCP. Although it is not known whether anxiety is a cause or an effect in NCCP, effective management of anxiety may have a favorable impact on chest pain. Benzodiazepines reduce the levels of peripheral catecholamines. Two small studies have suggested the potential benefit of anxiolytic agents in NCCP. In one nonblinded trial of 20 patients with NCCP and panic disorder, Beitman and colleagues71 showed that Alprazolam improved panic frequency but had no substantive benefit on chest pain parameters. In a second study, Clonazepan, at dosages of 1 to 4 mg/d for 6 weeks, was compared with placebo in 27 patients with NCCP and panic disorder. There was a significant reduction in panic attacks in the treated group compared with the control. However, the effects on chest pain were not described.72 Concern with drug dependence mandates caution in the use of these agents, particularly for patients with chronic chest pain.
<table>
<thead>
<tr>
<th>Author, Reference, Year</th>
<th>Type of Trial</th>
<th>Number and Type of Cases</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klimes et al,\textsuperscript{53} 1990</td>
<td>Cognitive therapy: controlled, clinical trial; randomized to immediate treatment or wait control; then control was crossed over</td>
<td>31 NCCP</td>
<td>Significant reductions in chest pain, disruption of daily life, autonomic symptoms, distress and psychologic morbidity in the treated group. The assessment-only group were treated subsequently showing similar improvement.</td>
<td>Improvements maintained by both treated groups at four–six months follow-up</td>
</tr>
<tr>
<td>Cott et al,\textsuperscript{54} 1992</td>
<td>Cognitive therapy: individual, group, self-monitoring or wait control</td>
<td>14 NCCP versus 90 with mitral valve prolapse</td>
<td>Group or individual treatment in NCCP and mitral valve prolapse improved short and long-term follow-up (6–12 months).</td>
<td>Functional improvement was independent of reduction of symptoms</td>
</tr>
<tr>
<td>De Guire et al,\textsuperscript{55} 1996</td>
<td>Paced diaphragmatic breathing</td>
<td>10 NCCP</td>
<td>Decrease in frequency of pain at 3 year follow-up</td>
<td>Improvement in respiratory rates and end-tidal carbon dioxide levels</td>
</tr>
<tr>
<td>Mayou et al,\textsuperscript{56} 1997</td>
<td>Cognitive therapy: treatment or assessment only control group.</td>
<td>37 NCCP</td>
<td>At 3 months, significant differences between the treatment group and the control on key outcome measures of symptoms, mood, and activity</td>
<td>At 6 months, there were fewer differences but significant advantages of treatment in terms of limitation of activities and worry about physical symptoms.</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Sample Size</td>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>-------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>van Peski-Oosterbaan et al, 1997</td>
<td>Cognitive therapy</td>
<td>10 NCCP</td>
<td>Significant improvement in intensity and duration of chest pain, anxiety, and functional limitations</td>
<td></td>
</tr>
<tr>
<td>van Peski-Oosterbaan et al, 1999</td>
<td>Cognitive therapy: patients randomized to active treatment or wait control</td>
<td>72 NCCP (37 to therapy, 35 control); 65 completed trial</td>
<td>15 (48%) of the 31 patients in the treatment group were pain free at 12-month follow-up, compared with 4 (13%) of the 33 patients in the control group (P = .002)</td>
<td></td>
</tr>
<tr>
<td>Potts et al, 1999</td>
<td>Cognitive therapy: comparing active group to waiting list control</td>
<td>56 NCCP</td>
<td>Treatment significantly reduced chest pain scores; anxiety and depression maintained for 6 months</td>
<td></td>
</tr>
<tr>
<td>Esler et al, 2001</td>
<td>Cognitive therapy: randomized controlled trial; controls received education and usual medications</td>
<td>36 NCCP with complete follow-up (of 59 randomized)</td>
<td>Study did not find significant chest pain improvement compared with control</td>
<td></td>
</tr>
<tr>
<td>Tyni-Lenne et al, 2002</td>
<td>Cognitive therapy: single-blinded, randomized to 3 groups: (1) physical training, (2) relaxation and (3) control.</td>
<td>24 female patients with Syndrome X</td>
<td>Patients benefited from physical training in terms of exercise capacity and quality of life and from relaxation therapy in terms of quality of life</td>
<td></td>
</tr>
</tbody>
</table>

Note: NCCP = Noncardiac chest pain.
ESOPHAGEAL MOTILITY DISORDER

Esophageal motility disorders such as diffuse esophageal spasm (DES), nutcracker esophagus, and hypertensive lower-esophageal sphincter may be found in 28% to 30% of patients with NCCP. Although it is not clear whether these motility disorders are the cause of NCCP or an epiphenomenon, several pharmacologic trials aimed at reducing the abnormal esophageal motility in these patients have produced mixed results. Unfortunately, most of these trials have considerable flaws including small sample size (1–22 patients) and open-label, uncontrolled study designs. The few studies with a placebo control are hampered by small sample size (14 was the largest) and fail to provide convincing evidence that improvement in esophageal motility parameters results in symptom reduction. A number of pharmacologic agents have been employed to treat NCCP in the setting of abnormal esophageal motility. Despite inconsistent outcomes and the concerns mentioned above, clinicians continue to use many of these pharmacologic agents. Nitrates and calcium blockers are the most commonly employed agents to treat patients with NCCP and abnormal esophageal motility, with variable degrees of success. Clearly, better-designed, placebo-controlled investigations of appropriate sample size are needed to better understand the role of these agents in the treatment of spastic esophageal disorders. The available studies and their outcome using these compounds are summarized in Tables 6–8.

Of note, GER may coexist in patients with spastic motility disorders. This is important since treatment of acid reflux in patients with nutcracker esophagus and DES coexisting with GER has resulted in chest pain reduction; and nitrates and calcium blockers are better avoided in these individuals for fear they may worsen coexisting GER.

Nitric Oxide

Nitric oxide (NO) is a major inhibitory nonadrenergic and noncholinergic neurotransmitter in the gastrointestinal tract. NO is synthesized by the activation of neuronal synthase (nNOS) in the myenteric plexus. Abundant concentrations of nNOS

<table>
<thead>
<tr>
<th>Author, Reference</th>
<th>Year</th>
<th>Number of Cases</th>
<th>Trial</th>
<th>Medication and Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlando and Bozymski</td>
<td>1973</td>
<td>1</td>
<td>Open</td>
<td>Erythritol tetra nitrate, 10 mg tid</td>
</tr>
<tr>
<td>Swamy</td>
<td>1977</td>
<td>12</td>
<td>Open</td>
<td>Isosorbate dinitrate (Isordil), 15–30 mg qid</td>
</tr>
<tr>
<td>Shafran et al</td>
<td>1979</td>
<td>5</td>
<td>Open</td>
<td>Nitroglycerin, 0.4 mg (sublingual)</td>
</tr>
<tr>
<td>Parker and Mackinon</td>
<td>1981</td>
<td>1</td>
<td>Open</td>
<td>Isosorbate dinitrate (Isordil), 5 mg before meals</td>
</tr>
<tr>
<td>Mellow</td>
<td>1982</td>
<td>5</td>
<td>Open</td>
<td>Isosorbide 20 mg tid dose</td>
</tr>
<tr>
<td>Millaire et al</td>
<td>1989</td>
<td>22</td>
<td>Open</td>
<td>Nitroglycerin spray, 0.8 mg</td>
</tr>
<tr>
<td>Konturek</td>
<td>1995</td>
<td>5</td>
<td>Open</td>
<td>Glyceryl trinitrate, 100 to 200 micrograms/kg/h intravenously</td>
</tr>
</tbody>
</table>

containing neurons have been identified in the human esophagus. In the smooth circular muscle of the human esophagus it regulates the latency and contraction amplitude of esophageal peristalsis. Murray and colleagues and Konturek and colleagues have shown that the experimental removal of NO in humans induces a pattern of simultaneous contractions similar to DES. Therefore, pharmacologic agents that result in the augmentation of NO may improve the clinical and manometric patterns of patients with diffuse esophageal spasm. At present time there are no available NO compounds for clinical use, but there is ongoing research to synthesize these agents.

**Phosphodiesterase 5 (PD-5) inhibitors** are important regulator of smooth muscle contraction that increase the availability of NO. Recent preliminary studies in small number of patients offer promising results for the treatment of spastic motility disorders. These studies suggest that the commercially available PD-5 inhibitors: sildenafil, vardenafil and tadalafil may be of potential therapeutic value. Certainly large, placebo-controlled, dose-finding clinical trials are needed before recommending the use of these agents.

**Botulinum Toxin**

Botulinum toxin (Botox) has been used successfully to treat achalasia, although its effects are temporary. Botox binds irreversibly to cholinergic nerve terminals blocking acetylcholine-mediated neuromuscular transmission, reducing LES pressures in animal models and humans. Several studies in patients with motility disorders have shown beneficial effects of Botox. Table 9 summarizes the published experience with Botox in patients with diverse nonachalasia esophageal motility

<table>
<thead>
<tr>
<th>Author, Reference</th>
<th>Year</th>
<th>Study Design</th>
<th>Number of Cases</th>
<th>Dosage</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackwell et al</td>
<td>1981</td>
<td>Open-label</td>
<td>6</td>
<td>20 mg tid</td>
<td>3/6 improved</td>
</tr>
<tr>
<td>Davies et al</td>
<td>1982</td>
<td>Double-blind, placebo</td>
<td>10</td>
<td>10-40 mg tid</td>
<td>Short-term improvement</td>
</tr>
<tr>
<td>Nasrallah et al</td>
<td>1982</td>
<td>Open-label</td>
<td>1</td>
<td>10 mg tid</td>
<td>Improved</td>
</tr>
<tr>
<td>Nasrallah et al</td>
<td>1985</td>
<td>Open-label</td>
<td>4</td>
<td>10 mg tid</td>
<td>Improved</td>
</tr>
<tr>
<td>Thomas et al</td>
<td>1986</td>
<td>Open-label</td>
<td>6</td>
<td>10–20 mg tid</td>
<td>Improvement of dysphagia</td>
</tr>
<tr>
<td>Davies et al</td>
<td>1987</td>
<td>Placebo-controlled (a single- and a double-blinded phase)</td>
<td>8</td>
<td>10–30 mg tid (mean 64 mg)</td>
<td>No response (treatment for up to 3 months)</td>
</tr>
<tr>
<td>Banciu et al</td>
<td>1990</td>
<td>Open-label</td>
<td>12</td>
<td>10–20 mg</td>
<td>Acute “improvement of radiologic appearance”</td>
</tr>
</tbody>
</table>

* Patients defined radiologically.

disorders (mostly DES and hypertensive lower esophageal sphincter). These trials have shown positive benefits in approximately 72% of the patients treated. Unfortunately, these studies are also hampered by small sample, lack of placebo control and some are available only as an abstract. The short-lived duration of the benefits of Botox injection remains problematic. Properly designed, controlled trials are sorely needed to determine whether Botox is effective in the treatment of NCCP.

RECENT PHARMACOLOGIC DEVELOPMENTS

Treatment of NCCP remains difficult. The multi-factorial nature of the disorder and the insufficient understanding of the putative sensory mechanism(s) are some of the factors challenging us in finding an ideal therapeutic modality. Recent studies suggest that adenosine plays a role in esophageal sensory processing.\textsuperscript{118} Infusion of adenosine induces chest pain in patients with chest pain and coronary artery disease as well as in healthy controls and in patients with NCCP (without triggering ischemic or EKG changes in the later two groups).\textsuperscript{119} However, there is an enhanced pharmacologic reactivity to adenosine in NCCP when compared with the other two groups.

**Table 8**

<table>
<thead>
<tr>
<th>Author, Reference</th>
<th>Year</th>
<th>Study Design</th>
<th>Number of Cases</th>
<th>Dosage</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richter et al\textsuperscript{93}</td>
<td>1984</td>
<td>Open-label, 8 weeks</td>
<td>10 (NE)</td>
<td>90 mg tid</td>
<td>Improved</td>
</tr>
<tr>
<td>Cattau et al\textsuperscript{94}</td>
<td>1991</td>
<td>Double-blind, placebo-controlled, 8 weeks</td>
<td>14 (NE)</td>
<td>60–90 mg tid</td>
<td>Improved</td>
</tr>
<tr>
<td>Drenth et al\textsuperscript{95}</td>
<td>1990</td>
<td>Double-blind, cross-over, 10 weeks</td>
<td>8 (DES)</td>
<td>60 mg tid</td>
<td>No significant improvement</td>
</tr>
</tbody>
</table>

*Abbreviations: DES, diffuse esophageal spasm; NE, nutcracker esophagus.*  

**Table 9**

<table>
<thead>
<tr>
<th>Author, Reference</th>
<th>Year</th>
<th>Number and Type of Cases</th>
<th>Publication Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller\textsuperscript{111}</td>
<td>1996</td>
<td>15 DES and other spastic disorders</td>
<td>Full paper</td>
</tr>
<tr>
<td>Cassidy\textsuperscript{112}</td>
<td>1996</td>
<td>10 DES</td>
<td>Abstract</td>
</tr>
<tr>
<td>Jones\textsuperscript{113}</td>
<td>1996</td>
<td>1 HLES</td>
<td>Letter to the editor</td>
</tr>
<tr>
<td>Nebendahl\textsuperscript{114}</td>
<td>1999</td>
<td>9 DES</td>
<td>Abstract</td>
</tr>
<tr>
<td>Storr\textsuperscript{115}</td>
<td>2001</td>
<td>9 DES</td>
<td>Full paper</td>
</tr>
<tr>
<td>Miller\textsuperscript{116}</td>
<td>2002</td>
<td>29 DES and other Spastic disorders</td>
<td>Full paper</td>
</tr>
<tr>
<td>Lacy\textsuperscript{117}</td>
<td>2002</td>
<td>1 HLES</td>
<td>Case report</td>
</tr>
</tbody>
</table>

*Abbreviations: DES, diffuse esophageal spasm; HLES, hypertensive lower-esophageal sphincter.*  
Patients with NCCP developed chest pain at much lower doses of adenosine than the other two groups. Melcher and Sylven triggered chest pain after acute infusion of adenosine, but failed to identify significant effects of adenosine infusion on esophageal peristalsis in healthy controls, suggesting that the effects of this drug on visceral pain are not mediated by esophageal spasm. Theophylline (a nonselective adenosine receptor antagonist) reduces chest pain significantly, suggesting that pain triggered by adenosine is, at least to some degree, dependant on activation of theophylline-sensitive receptors.

Rao and colleagues reported data from consecutive patients with recurrent NCCP who failed an eight-week therapeutic trial of double-dose PPI, or had a negative 24-hour pH testing. They found that intravenous infusion of theophylline, an adenosine receptor antagonist, but not placebo, improved the biomechanical and sensory properties of the esophageal wall. In a long-term study, 19 patients with esophageal hypersensitivity, randomized to receive oral theophylline 200 mg, twice a day, for 4 weeks in a crossover design, experienced significant improvement in pain parameters when compared with placebo. Unfortunately, theophylline has significant toxicity. Thus, it is unlikely that it will used for the treatment of NCCP. However, the findings of the above study suggest that research involving newer selective adenosine receptor agents may offer new opportunities for the treatment of NCCP.

SUMMARY

Treatment of NCCP remains difficult. In great part, this is due to the heterogeneous nature of the disorder. Available information indicates that GER is a very common problem in these patients and that PPI therapy is effective in reducing chest pain for the majority of patients with GER-related NCCP. Furthermore, a short trial of high-dose PPI may help identify those patients with GER-related NCCP.

On the other hand, the widespread use of PPI therapy has led to the recognition of a group of patients with persistent NCCP who fail to respond to PPI therapy. For these patients, therapeutic approaches are frequently directed at improving suspected visceral hyperalgesia with the aid of TCAs or SSRIs. Esophageal motility testing should also be considered to exclude the occasional patient with achalasia presenting with NCCP, since specific therapy for this condition is readily available.

For patients without achalasia and non-GER–related NCCP who do not respond to visceral analgesics, psychiatric evaluation and treatment should be considered. Depression, anxiety, or somatization may amplify or contribute to NCCP. Cognitive therapy and appropriate management of potential associated psychologic disorders may be very valuable in reducing chest pain for patients refractory to other pharmacologic interventions and those who have coexisting psychologic morbidity.

Nitrates and calcium blockers, and even Botox, are commonly used in the treatment of patients with non-GER–related esophageal motility disorders. However, the outcome of treatment with these compounds is inconsistent and there is a lack of randomized, controlled trials to support the use of this approach.

New research into additional mechanisms involved in visceral pain, such as adenosine receptors, appears promising. Future studies using improved selective adenosine receptor antagonists and other therapeutic interventions are needed. Further studies should take into account that the goals of therapy are to identify better strategies to decrease pain, diminish recurrent diagnostic evaluations and health care use, improve quality of life, and attenuate the disability of this challenging condition.
REFERENCES


