Management of noncardiac chest pain in women

Raghubinder S Gill[1], Jo S Collins[1] & Nicolas J Talley*

Noncardiac chest pain (NCCP) is very prevalent in the community. Although mortality remains low, morbidity and the financial implications are high. Women, especially those of middle age, should be thoroughly investigated as per current guidelines for coronary artery disease before labeling their chest pain as NCCP. Gastroesophageal reflux disease is the most common cause of NCCP; however other esophageal pathology including esophageal hypersensitivity, neuromuscular disease and eosinophilic esophagitis may also cause NCCP. Proton pump inhibitors are commonly used initially to manage NCCP, although patients who do not respond to this therapy require further investigation and differing treatment regimes. This article will focus on current knowledge regarding GI tract-related NCCP management strategies.

Medscape: Continuing Medical Education Online

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Medscape, LLC and Future Medicine Ltd. Medscape, LLC is accredited by the ACCME to provide continuing medical education for physicians.

Medscape, LLC designates this Journal-based CME activity for a maximum of **1 AMA PRA Category 1 Credit(s)™**. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

All other clinicians completing this activity will be issued a certificate of participation. To participate in this journal CME activity: (1) review the learning objectives and author disclosures; (2) study the education content; (3) take the post-test with a 70% minimum passing score and complete the evaluation at www.medscape.org/journal/wh; (4) view/print certificate.

Release date: 1st March 2012; Expiration date: 1st March 2013

Learning objectives

Upon completion of this activity, participants should be able to:

- Analyze the epidemiology of noncardiac chest pain among women
- Assess outcomes of coronary artery disease among women
- Evaluate the role of gastroesophageal reflux disease in noncardiac chest pain
- Compare different treatments for gastroesophageal reflux disease in the setting of noncardiac chest pain

[1]Gosford Hospital, Division of Gastroenterology, New South Wales, Australia
*Author for correspondence:
Faculty of Health, University of Newcastle, New South Wales, Australia
Tel.: +61 2 4921 6378
nicholas.talley@newcastle.edu.au

Future Medicine part of **fsg**

Authors and Disclosures (cont.)

Nicolas J Talley, Faculty of Health, University of Newcastle, New South Wales, Australia.

Disclosure: Nicolas J Talley has disclosed the following relevant financial relationships:

Funding received from: Janssen and Takeda.

Editor

Elisa Manzotti, Editorial Director, Future Science Group, London, UK.

Disclosure: Elisa Manzotti has disclosed no relevant financial relationships.

Noncardiac chest pain (NCCP) is defined as recurring substernal chest pain of noncardiac origin. It may be of musculoskeletal, pulmonary, gastroenterological, psychosomatic or neurological etiology. As the symptoms can be indistinguishable from ischemic heart disease, a thorough cardiological evaluation is required. Up to 30% of coronary angiograms performed in the USA are normal or have an insignificant degree of obstruction [1].

NCCP is very common, with an observed prevalence varying from 14 to 33% in different population-based studies [2–4]. NCCP affects both genders; middle-aged women have a significantly higher prevalence of NCCP compared with men [3]. Caucasians are more likely to report chest pain symptoms when compared with African–Americans [5]. NCCP patients are younger, consume more alcohol, smoke more often and are more likely to suffer from anxiety [6]. A recent study observed that women have increased NCCP symptoms during pregnancy (9%) as opposed to the year before conceiving (2%) [7].

NCCP patients frequently utilize healthcare resources, resulting in a high economic burden [8]. Patients are often not reassured by investigations; in a study of patients suffering from NCCP, 44% believed they had heart disease in spite of a normal angiogram [9]. There is some evidence that the process of investigation itself may entrench the mistaken idea of cardiac disease [10]. NCCP causes a high personal economic and psychological toll as a half of the patients remain or become unemployed, a half remains on cardiac medications and approximately 75% continue to experience pain [11]. NCCP has a significant negative impact on patients' quality of life and social well being [12].

Chest pain & coronary artery disease in women

Coronary artery disease (CAD) is the leading cause of death among women in the USA, with 233,886 deaths recorded in 2003 [13]. The risk for in-hospital mortality in women with postacute myocardial infarction (MI) was 20% greater than for men after adjusting for covariates [14]. Clinical trials commonly under-represent women and there may be gender differences in therapeutic

responses that need to be further investigated in trials involving a larger representation of women [15]. In a recent large study of 125,161 patients in the USA, of which 50,162 (40%) were female, women aged 40–60 years had a 3.5% longer time to presentation than men despite adjusting for possible confounders. This demonstrates a significant gender gap remaining despite national awareness campaigns in the USA for women [16].

Typical chest pain from CAD is more often identified in middle-aged men with risk factors for atherosclerosis; however, women, patients with diabetes mellitus and the elderly may not present with classical symptoms. For example, in a retrospective study of 94 patients admitted to a hospital with MI, 32% presented with 'atypical' symptoms, particularly women above 65 years of age when compared with men of the same age group [17]. Elderly women who are diagnosed with a 'nonspecific chest pain' are potentially at higher risk of cardiac morbidity [18]. 'Atypical' chest pain is a term best avoided as it heightens the risk of a misdiagnosis in women, the elderly, patients who have long-standing diabetes and those with a MI presenting with symptoms such as dyspnea or postprandial epigastric pain.

Coronary artery dissection is a rare, but often deadly cause of MI that mainly affects otherwise healthy, young females [19]. The etiology is unknown, and most patients presenting with this entity do not have risk factors for coronary heart disease.

Cardiac syndrome X is a syndrome of angina-like, nongastrointestinal chest pain associated with normal epicardial coronary arteries and a positive response to exercise testing. However, this syndrome may still reflect coronary insufficiency [20]. There is no direct association with gastroesophageal reflux disease (GERD) [21] and the syndrome is most commonly found in premenopausal women and has been associated with underlying panic disorder [22].

Over 30% of patients with CAD suffer from persistent chest pain caused by extracardiac sources overlapping or mimicking precordial symptoms originating in the heart [23,24]. These result primarily from the coexistence of gastroesophageal reflux, aspirin-induced GI

tract damage and musculoskeletal or panic disorders [24–28].

A large multicenter US study, Internet Tracking Registry for Acute Coronary Syndromes (i*trACS), prospectively collected data on 17,737 patients with chest pain [29]. They concluded that when the initial impression is NCCP, high-risk features such as traditional cardiovascular risk factors or a history of CAD are still associated with adverse cardiac events. If patients present with these features, the treating physicians should consider further investigations before diagnosing patients with NCCP [30].

It should be noted that in patients with CAD, both cardiac and noncardiac causes of chest pain may exist concurrently. In any patient presenting with chest pain, cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, obesity and smoking should always be managed appropriately.

Approach to NCCP

NCCP has a broad differential (Figure 1). A prospective study of 399 episodes of chest pain in patients seen in multiple outpatient centers over a 1-year period noted the following prevalence of various causes of chest pain [31]:

- Approximately 60% of chest pain diagnoses were not 'organic' in origin (i.e., not due to cardiac, gastrointestinal or pulmonary disease);

- Musculoskeletal chest pain accounted for 20% of all diagnoses, with costochondritis (diagnosed by the history and physical exam) accounting for 13%, as did reflux esophagitis at 13%;

- Stable angina pectoris was responsible for 10% of chest pain episodes in patients presenting with chest pain to primary healthcare

physicians; unstable angina or MI occurred in only 1.5% of patients [31].

These findings are compatible with other reports of the frequency of etiologies of chest pain in primary care practice [32–36]. Pulmonary causes of NCCP include disease of the pulmonary vasculature, lung parenchyma or pleura.

Factors that likely contribute to NCCP include GERD, esophageal motility disorders, visceral hyperalgesia and psychiatric conditions (Figure 2). GERD has been reported to be by far the most common esophageal cause of NCCP; the prevalence of GERD based on prolonged esophageal pH monitoring ranges from 21 to 60% of patients with NCCP [37]. The underlying mechanism of GERD inducing NCCP is poorly understood; however, studies have shown that 50% of patients presenting with NCCP have abnormal acid exposure based on pH testing [38]. Others may have nonacid reflux, which is a reflux of gastric contents with a pH >4.0. In a study of 168 patients with reflux symptoms, Mainie et al. observed that a total of 49 patients suffered from NCCP, out of which 14 had evidence for nonacid reflux chest pain [39]. In a recent study using ambulatory pH monitoring indicators of GERD, including acid exposure time, evidence of relevant acid reflux was present in almost two-thirds of NCCP patients and this predicted a response to medical therapy [40]. It should be noted that the presence of Helicobacter pylori does not appear to influence reflux symptoms and therefore detection of the bacteria and eradication therapy is not a focus of management of NCCP [41,42]. A great number of patients (~60%) with typical reflux symptoms have no evidence of erosive esophagitis at endoscopy [43]; such patients are usually considered to have nonerosive reflux disease [44].
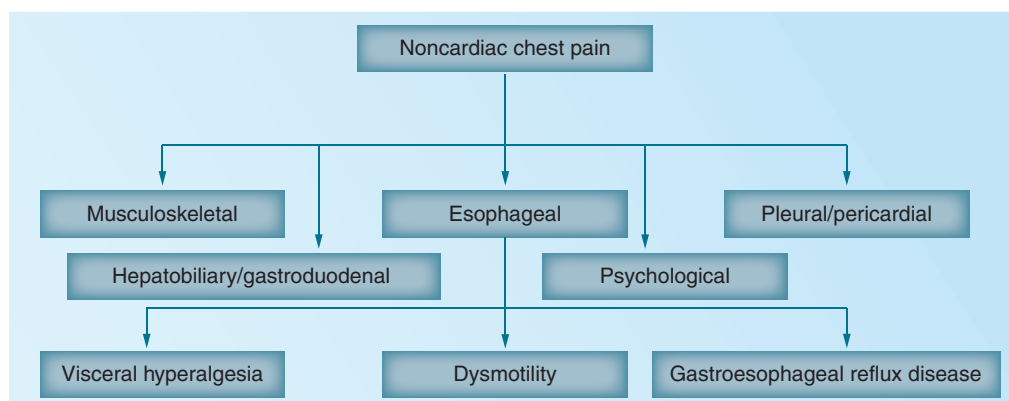

Figure 1. Differential diagnosis of noncardiac chest pain in adults.
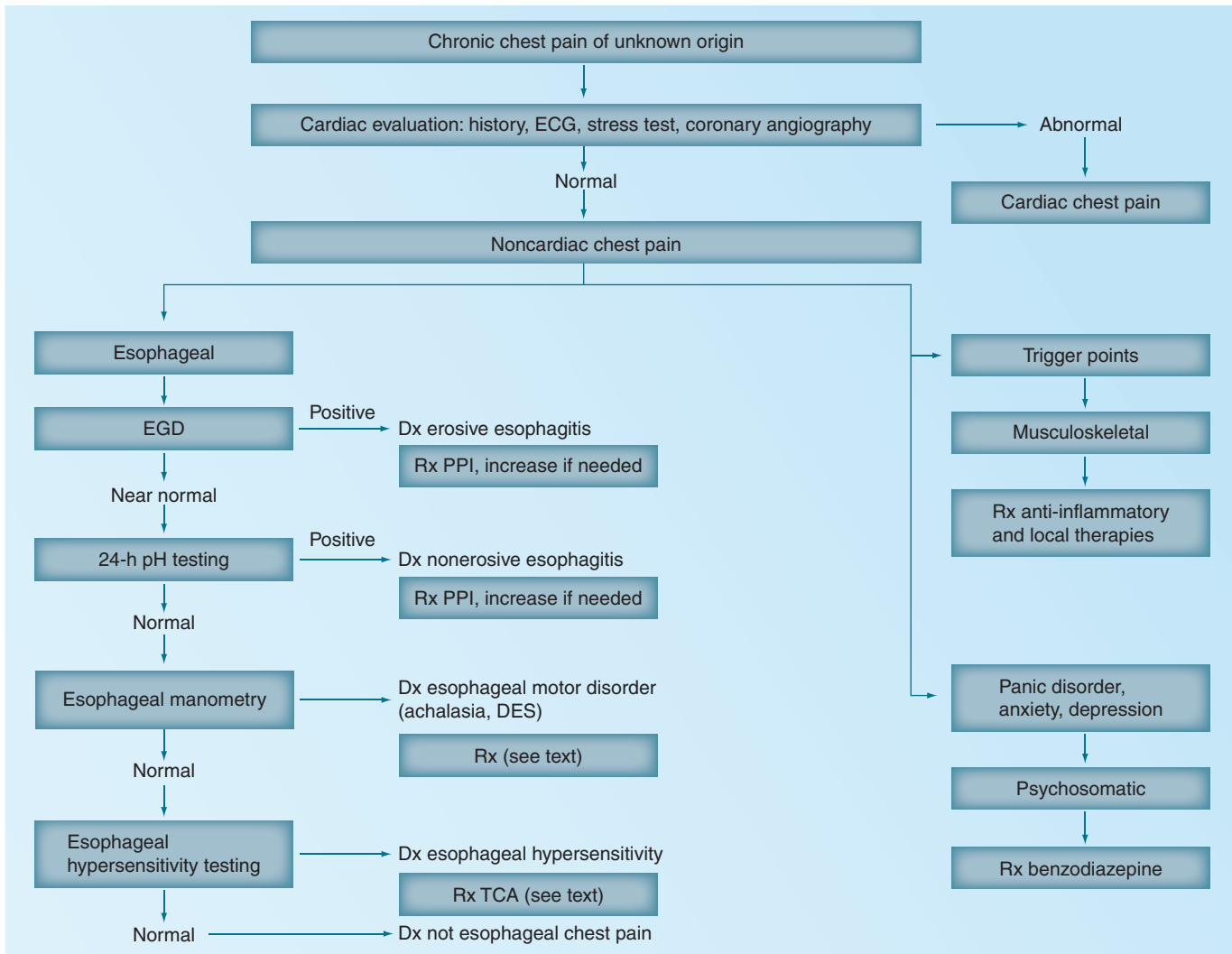Adapted with permission from [120].

www.manaraa.com

Figure 2. Approach to patient with chest pain. Algorithm outlining an approach to the patient with unexplained chest pain.
DES: Diffuse esophageal spasm; Dx: Diagnosis; EGD: Esophagogastroduodenoscopy; PPI: Proton pump inhibitor; Rx: Prescription;
TCA: Tricyclic antidepressant.
Reproduced with permission from [121].

Patients who have non-GERD-related NCCP are considered to have functional chest pain of presumed esophageal origin [45]. Possible mechanisms include esophageal mechano-physical abnormalities, central and peripheral hypersensitivity and sustained contractions of the esophageal longitudinal muscle [46,47]. Balaban *et al.* observed a strong temporal correlation between an esophageal motor event, sustained esophageal contraction, and both spontaneous and provoked esophageal chest pain. [46]. Hobson *et al.* observed that NCCP patients with esophageal hypersensitivity may be classified into distinct phenotypic subdivisions, namely the sensitized afferents phenotype group and the hypervigilant phenotype group, based on sensory responsiveness and objective neurophysiologic profiles [47].

In a recent study it was observed that an abnormal eosinophilic infiltrate was present in 14% of patients undergoing endoscopic evaluation for NCCP, suggesting that eosinophilic esophagitis should be considered in the differential diagnosis of NCCP [48].

Psychiatric evaluation of patients with NCCP has suggested a significant portion may meet the criteria for panic disorder, while others may suffer from depression [49,50]. There is an overlap with other mechanisms of NCCP such as esophageal mechano–physical abnormalities in these patients [49]. Therapy should be aimed towards the potential underlying disorder.

Prognosis
A prospective 4-year cohort study of patients presenting to a referral hospital in Sydney, Australia,

with chest pain was conducted [51]. The study observed that the majority of patients with NCCP continue to have unexplained chest pain over time and there was no significant difference with regard to mortality, continued chest pain and quality of life between patients presenting with cardiac and NCCP [51]. Further, it was observed that the mortality rate for those either initially diagnosed as having chest pain of cardiac or noncardiac origin at baseline was not significantly different, suggesting that presentation to hospital with acute chest pain that is diagnosed as noncardiac and normally considered nonfatal confers the same likelihood of death within a 2-year period from a cardiac cause as someone who presents with cardiac chest pain [51]. This study had limitations, including a relatively small sample size and patient selection from one hospital practice, so more data are needed.

Treatment
GERD-related NCCP
Background
GERD is the most common esophageal-related cause of NCCP, occurring in up to 60% of patients [52]. NCCP is the most common atypical symptom of reflux disease [53]; hence, empiric treatment of GERD remains the first-line management. Initial options for management include lifestyle modification and use of acid-suppressing medications. Proton pump inhibitors (PPIs) are considered to be the foundation of GERD management, with up to 90% of patients demonstrating improvement in symptoms with their use [54]. Those patients who fail to have an adequate response to antisecretory drugs may progress to surgical alternatives if GERD is confirmed. These surgical procedures are not without significant potential complications and response to surgery is less optimal in patients who fail an adequate PPI trial [55]. A new focus of interest has been the effect of GABA agonists in suppressing reflux. Developments are also being made in endoscopic treatments of GERD. Few studies examining the sole issue of NCCP have been performed; therefore, the following treatment of GERD has been extrapolated as a suggested management plan of NCCP by association; however, it is clear that more research is required to fully explore NCCP in its entirety.

Lifestyle modifications
In the current management of GERD, and its symptoms such as NCCP, there is a plethora of medications and interventions available to clinicians. Simple lifestyle adjustments such as weight loss, cessation of smoking, avoidance of alcohol and coffee, and elevation of the head of the bed have become overshadowed as primary therapies. However, these modifications are consistent with an understanding of the pathophysiology of reflux disease. As such, lifestyle modification may be a useful adjunct in the treatment of GERD, but is not strongly evidence based and usually is not efficacious enough to be the sole therapy utilized [56].

PPIs
PPIs (e.g., omeprazole, rabeprazole, lansoprazole and dexlansoprasole) are a mainstay treatment of the management of GERD-associated NCCP by suppressing acid production in the stomach. Many recent studies have focused on the diagnostic value and the role of an empirical trial of PPIs in NCCP [53,53,57–61]. Debate still exists over the required duration of a 'PPI test', with Bautista *et al.* suggesting that a trial of 2 days of lansoprazole 60 mg every morning and 30 mg every night may be sufficient to diagnose over 85% of GERD-associated NCCP [57], whereas Kim and colleagues found that the optimal duration of PPI trial was 14 days, using rabeprazole 20 mg twice daily [52]. Dickman *et al.* observed that a trial of rabeprazole at the same dosage was highly sensitive and specific for diagnosing gastroesophageal etiology of NCCP, as well as being a very cost-effective diagnostic strategy [53]. Fass *et al.* suggested GERD-related NCCP patients may require more than 2 months of PPI therapy at double the standard dose for optimal symptom control. Once NCCP control is achieved, dose tapering to the lowest symptom-controlling dose has been shown to be a highly effective management strategy [62]. In nonerosive reflux disease, PPI is also the mainstay of treatment [63]. A PPI trial is a simple and sensitive method of diagnosing GERD-related NCCP [53].

Histamine-2 receptor antagonists
The usage of histamine-2 receptor antagonists (H-2RA) has declined in the management of GERD-related NCCP and, as such, limited recent studies have been performed. Nagahara and colleagues compared the effects of a PPI (rabeprazole) and an H-2RA (lafutidine). They found that total reflux symptom scoring only improved with the use of rabeprazole [64]. Another study reported that cimetidine in conjunction with antacid use was only effective in 42% of GERD-associated NCCP patients [65]. Thus, H-2RAs have been superseded by the use of the more efficacious PPIs.

GABA agonists

Recent studies have focused on reducing transient lower esophageal sphincter relaxation (TLESR), a mechanism that is responsible for the majority of reflux episodes [66]. TLESRs are modulated by GABA acting on GABAB receptors [67]. Baclofen is a GABAB receptor agonist, and recent studies have shown that baclofen reduces the number of TLESRs, and thus the number of reflux episodes, and well as increasing the basal tone of the lower esophageal sphincter (LES) [66,67]. Other GABAB receptor agonists such as lesogaberan and AZD9343 have also demonstrated these effects, with lesogaberan reducing the number of TLESRs by 36% [67,68]. However, a significant side-effect profile is noted with these medications: drowsiness and incidences of short-acting paraesthesia have been reported [68]. A recent study by Gerson *et al.* evaluated arbaclofenplacarbil, a prodrug of baclofen [69]. This study found a significant decrease of 17% in reflux episodes when using arbaclofenplacarbil compared with placebo, with a reduction in the number of heartburn events reported. The study also showed that this medication was well tolerated by the trial group, with few adverse effects recorded. Drugs acting upon the GABAB receptors show a great deal of promise as a new mechanism to counter reflux disease and its symptoms but a benefit in NCCP has yet to be studied.

Surgery

Laparoscopic nissen fundoplication (LNF) is the most common antireflux surgery performed, with the laparoscopic approach being the procedure of choice [70]. Controlled trials of surgery in NCCP are lacking. Patti *et al.* demonstrated a reduction of chest pain in 85% of their study population [71]. Two case series of 90 and 324 patients, respectively, have demonstrated that those patients who display atypical symptoms such as NCCP have improvement of these symptoms; however, full resolution only occurred in approximately 50% [72,73]. Rakita *et al.* show satisfactory improvement in NCCP in 81% of patients post LNF [74]. LNF appears to be an effective treatment in improving GERD-related NCCP, although complete resolution of symptoms is difficult to achieve. As this is an invasive procedure, it is associated with morbidity and mortality risks. Therefore, LNF should only be considered when medical management options have been exhausted.

Endoscopic gastroplication

Endoscopic gastroplication is an emerging treatment for gastroesophageal reflux disease but is not yet US FDA approved for this indication and has not been studied in NCCP. There is a need for randomized, controlled trials to assess the effectiveness of this intervention; however, initial studies appear promising. Schwartz *et al.* report 41% of patients to be free from reflux pain at 12 months postendoscopic gastroplication, with a reduced usage of acid-inhibitory drugs [75]. Liao and colleagues showed that patients had significantly reduced heartburn scores postintervention, with improved quality of life. It was reported that 48% of their trial group of patients had discontinued antisecretory medication at 24 months of follow-up [76]. Minimal adverse effects were recorded. These studies suggest that endoscopic gastroplication is a relatively safe and possibly effective intervention for GERD symptoms; however, further trials are required to full assess its long-term efficacy.

Non-GERD-related NCCP

Introduction

Nonreflux-associated NCCP is often attributable to esophageal motor disorders. These disorders are often difficult to manage; however, current options include muscle relaxants, pain modulation therapy, endoscopic botulism treatment and consideration of psychological management. Recent areas of interest include the use of phosphodiesterase type 5 (PD-5) inhibitors, theophylline, tricyclic antidepressants (TCAs), selective-serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine-reuptake inhibitors (SNRIs). The choice of pharmacotherapy depends on the suspected etiology of the esophageal disorder. Other therapies such as the use of octreotide have been investigated in the past; however, no recent research has been conducted and as such they have not been included in this review.

Muscle relaxants

Nitrates

Previous studies have suggested that nitric oxide (NO) plays a significant role in esophageal motility and the regulation of esophageal wall smooth muscle contraction [77]. It was postulated that the administration of nitrates could alleviate esophageal spasm, and thus reduce the NCCP in these patients. There are no recent data available, as prior studies demonstrated that while sublingual nitroglycerin causes a statistically significant reduction in LES pressure, it is only a transient effect [78]. The effect was not reproducible with topical nitroglycerin or with the administration of isosorbide dinitrate. Another study showed

that a glyceryltrinitrate infusion can reduce symptoms [79]; however, this is an impractical long-term therapy. The administration of nitrates is not an effective therapy for long-term management of NCCP, although its transient effect on esophageal relaxation explains why it may have an effect on acute chest pain, and response to its administration cannot be used to differentiate between cardiac and NCCP.

Calcium channel blockers

Calcium channel blockers have been shown to relax gastrointestinal smooth muscle and lower the LES pressure in patients with achalasia, nutcracker esophagus or diffuse esophageal spasm [80–82]. Studies have shown variable effects of differing calcium channel blockers in addition to conflicting results. Allen *et al.* demonstrated that LES pressure was significantly reduced with usage of nifedipine, but was not affected by verapamil or diltiazem [80]. By contrast, Cattau *et al.* found that diltiazem administered over an 8-week period was associated with lower contraction pressures and resultant reduction of NCCP in patients with nutcracker esophagus [83]. Other studies have shown nifedipine to be no more effective than placebo for relief of NCCP in patients with esophageal spasm and nutcracker esophagus [84,85]. In addition, the use of calcium channel blockers has been shown to increase the incident of GERD due to relaxation of the LES, thus increasing the risk of patients experiencing NCCP via a differing mechanism [86–88]. Inconsistent results, increased risk of reflux disease and the side-effect profile of calcium channel blockers such as pedal edema and hypotension suggest that these medications have a very limited role in the management of chest pain related to esophageal motility disorders.

PD-5 inhibitor

As previously discussed, NO causes the relaxation of esophageal smooth muscle by increasing cellular concentrations of cGMP. PD-5 terminates this action of cGMP. By opposing the action of PD-5 using inhibitors such as sildenafil, relaxation of smooth muscle cells occurs [89]. Several studies have conclusively demonstrated that sildenafil decreases LES pressure and also lowers the amplitude of esophageal peristaltic contractions [89–94]. It has therefore been suggested that PD-5 inhibitors could be used to relieve pain associated with spastic esophageal motor disorders caused by a defect in NO neuromuscular communication, such as nutcracker esophagus, achalasia and hypertensive LOS [89,91,92]. One patient with

achalasia in the study by Eherer *et al.* did not demonstrate any response to sildenafil administration. It was proposed that this may have occurred because of the nature of the disease, as there was no longer any intrinsic NO activity and thus no activation of the NO–cGMP pathway [92]. Therefore, it appears that PD-5 inhibitors will only have an effect in those patients who retain an element of this pathway. Bortolotti and colleagues showed that the effect of sildenafil on lowering LES tone lasted for up to 1 h [93]; however, Eherer *et al.* demonstrated an effect lasting up to 8 h in healthy volunteers [92]. However, side effects have been noted with the use of sildenafil such as sleep disturbances, dizziness and headache. It has also been postulated that this may decrease its antireflux action owing to the relaxation of the LES, leading to the development or exacerbation of GERD in susceptible patients [93], although Kim *et al.* found no such increase in gastroesophageal reflux [94]. PD-5 inhibitors show promise as a therapeutic agent for the relief of chest pain associated with spastic esophageal motor disease.

Antidepressants

TCAs

TCAs, such as imipramine, have been shown to have an effect in reducing NCCP [95]. The proposed mechanism of action is modulation of visceral pain perception [96]; however, it has also been suggested that they have a muscle-relaxant effect via the inhibition of calcium channels [97]. Imipramine has been shown to decrease pain response in a study of 20 healthy male volunteers [98] and it was also demonstrated to decrease esophageal pain in the presence of distension, supporting a visceral analgesia effect [96]. Cannon *et al.* also found that imipramine improved the symptoms of patients with chest pain and normal coronary angiograms [99]. However, Gorelick *et al.* did not demonstrate any difference between amitriptyline and placebo in the perception of esophageal distension [100]. This may suggest that there is variable action of differing drugs within the class of TCAs on decreasing NCCP; however, this will need to be further evaluated.

SSRIs

A recent randomized trial of sertraline and pain coping skills training in patients with NCCP demonstrated decreased pain intensity and pain unpleasantness. The combination of coping skills training with sertraline produced significantly greater changes in pain catastrophizing and anxiety when compared with placebo [101]. Another

randomized study with paroxetine-treated patients exhibited improvements in the Clinical Global Impressions Scale, but not pain, when compared with placebo [102]. The role of SSRIs in symptom management for patients with NCCP therefore remains to be fully clarified but they may be worth considering in clinical practice.

SNRIs

A small randomized, placebo-controlled, double-blind crossover trial of venlafaxine 75 mg versus placebo in 50 young patients with functional chest pain demonstrated significant symptom improvement in 52% of patients, with minimal side effects [103]. Further studies will need to be performed to confirm these findings.

Other pain-modulating therapy

Benzodiazepines

Little recent evidence is available regarding the efficacy of benzodiazepines in the treatment of panic disorder in patients presenting with chest pain. Studies have reported that benzodiazepines, such as alprazolam and clonazepam, produced a significant drop in episodes of chest pain [104,105], although the sample size was limited. One of these studies reported eight out of 12 chest pain patients with panic disorders and normal coronary arteries halved the frequency of panic attacks within 4 weeks of clonazepam administration [104]. Further research is required to provide definitive evidence of their efficacy. In clinical practice, a trial of a benzodiazepine in patients with chest pain related to panic disorder may be of value.

Theophylline

It has been suggested that theophylline may ameliorate esophageal chest pain by reducing visceral pain response via its actions on adenosine receptors [106]. An uncontrolled, open-label trial suggested that theophylline could be an effective treatment in functional chest pain [106]. A randomized control trial of intravenous and oral theophylline versus placebo was performed to further explore these results, and a reduction of symptoms such as number of episodes, duration and severity of chest pain episodes was shown in 58% of patients [107].

Transcutaneous electrical nerve stimulation

Borjesson et al. demonstrated a reduction in esophageal pain sensitivity in response to distension with the use of transcutaneous electrical nerve stimulation and suggested that it may be a useful treatment for NCCP of esophageal origin [108].

These results need to be corroborated by further investigation; however, the use of transcutaneous electrical nerve stimulation may hold promise as a future treatment.

Endoscopic treatment

Botulinum toxin

Botulinum toxin (botox) causes muscle relaxation by inhibiting the release of acetylcholine from neurons at the neuromuscular junction. Therefore, botox may not only reduce esophageal muscle activity and thus the related symptoms of dysphagia and regurgitation, but also chest pain by reducing signaling in nociceptive (pain) pathways. A small uncontrolled study in patients with nonachalasia spastic esophageal disorders demonstrated reduction of chest pain in the majority of patients [109]. However, the first randomized, placebo-controlled, double-blinded study in 22 patients with nonachalasia esophageal hypermotility disorder established that botox injections significantly improved dysphagia symptoms but had no significant effect on chest pain [110].

Psychological treatment

Primary psychological causes of NCCP should be considered after negative evaluation of all organic causes. However, it is not uncommon for patients with NCCP to suffer from anxiety, depression and panic disorder. Psychological therapy could be of particular value in such patients [8,111,112] and early intervention might prevent these symptoms from becoming chronic. This is usually done using a behavioral framework, applying cognitive behavioral psychotherapy. A problem with many of the cognitive behavioral psychotherapy trials has been high attrition rates [113]. A recent study of manualized cognitive behavioral psychotherapy, including exposure to physical activity, showed it was an effective treatment for NCCP and benign palpitations over a 12-month follow-up but it was limited by its small sample size [114]. A small study of 28 patients with NCCP demonstrated that hypnotherapy helped alleviate pain intensity with improvement in overall well being [115]. Another study of 39 patients with functional chest pain, in which 21 patients were in the Johrei (a process of transmission of healing energy) group and 18 in the wait-list group, suggested that Johrei induced a significant reduction in symptoms. However, the authors concluded that further studies are needed to compare Johrei treatment with sham Johrei and supportive care [116]. Overall, it is still unclear whether it is of value to offer patients with NCCP psychological treatment and at what stage this should be considered.

www.manaraa.com

Conclusion

NCCP is common, and places a relatively high financial burden on the healthcare system [8,117,118]. Generally the prognosis of patients with NCCP is positive [119], but certain subgroups of patients such as middle-aged women may be at increased risk of misdiagnosis as they may not present with classical symptoms of CAD [17]. As GERD is the most common cause of NCCP, antireflux therapy plays an important role in diagnosis and treatment.

In non-GERD-related NCCP targeted treatment of visceral hyperalgesia and esophageal motility disorders is required. Many patients with NCCP have psychiatric conditions requiring psychological treatment.

Future perspective

The mechanisms inducing chest pain from the esophagus are now more readily identified in practice using pH-impedance, high-resolution manometry and, in specialized centers, endoscopic ultrasound evaluation of motor contractions. There are currently several proposed treatments that may be further developed for NCCP that is refractory to PPI therapy. The use of GABAB agonists reflects a different approach to the traditional management of decreasing acid secretion and aims to improve the effectiveness of the lower esophageal sphincter. Initial trials into this class of drug have shown a significant reduction in reflux episodes, and provided the adverse effect profile of these medications is limited, then GABAB agonists may offer a new management strategy for GERD. Further development of this class of medication is currently ongoing. PD-5 inhibitors have shown promise in the management of spasmodic esophageal disorders, with effective reduction of symptoms in trials to date. The development of long-acting forms of this medication may allow this to become a viable treatment option. A new target of therapy for treatment of non-GERD-related NCCP has been in the region of pain modulation. There are several pharmacological approaches for which preliminary studies have shown a reduction of symptoms. Theophylline and some TCAs have been demonstrated to have pain-modulating effects, via their action on receptors. Studies into the effect of SNRIs, SSRIs and psychological therapy have also found a reduction in symptoms and, although the mechanism of the symptom improvement is unclear and may be related to improved coping skills and anxiety relief, initial research nonetheless, shows a clear reduction in symptoms. Recent technological advances have allowed the expansion of endoscopic therapy. Gastroplication is one possible approach to reduce usage of antisecretory drugs in GERD-related NCCP. Further investigation is required to assess the long-term efficacy of these treatments; however, preliminary studies have shown positive results. The endoscopic administration of botox has shown a reduction in non-GERD-related chest pain in some studies, although the research to date has been of small patient samples and there have been inconsistent results and, additionally, the efficacy of the treatment is short lived. These therapies may have the potential to change current management of NCCP, and deserve further development and exploration in properly conducted clinical trials.

Executive summary

Background

- Noncardiac chest pain (NCCP) is very prevalent in the community and has high financial implications.

Chest pain & coronary artery disease in women

- Coronary artery disease is the leading cause of death in women; patients should be thoroughly investigated for coronary artery disease before being diagnosed with NCCP.

Approach to NCCP

- Proposed causes of NCCP include gastroesophageal reflux disease (GERD), esophageal motility disorders, visceral hyperalgesia, psychiatric conditions and uncommonly eosinophilic esophagitis.

Prognosis

- Generally good but some evidence suggests there is no significant difference with regards to mortality, continued chest pain and quality of life between patients presenting with cardiac and NCCP.

Treatment

- GERD is common and treatable; proton pump inhibitor treatment remains the mainstay of therapy in GERD-related NCCP.
- Visceral sensation secondary to acid sensitization deserves further attention.
- Combined reduction of both acid reflux and pain sensation may be the best hope for proton pump inhibitor failures.

References

Papers of special note have been highlighted as:
• of interest

1. Nevens F, Janssens J, Piessens J *et al.* Prospective study on prevalence of esophageal chest pain in patients referred on an elective basis to cardiac unit for suspected myocardial ischemia. *Dig. Dis. Sci.* 36, 229–235 (1991).

2. Fass R, Navarro-Rodriguez T. Noncardiac Chest Pain. *J. Clin. Gastroenterol.* 42, 636–646 (2008).

3. Wong WM, Lam KF, Cheng C *et al.* Population based study of noncardiac chest pain in southern Chinese: prevalence, psychosocial factors and health care utilization. *World J. Gastroenterol.* 10, 707–712 (2004).

4. Eslick GD, Jones MP, Talley NJ. Non-cardiac chest pain: prevalence, risk factors, impact and consulting – a population-based study. *Aliment. Pharmacol. Ther.* 17, 1115–1124 (2003).

5. Klingler D, Green-Weir R, Nerenz D *et al.* Perceptions of chest pain differ by race. *Am. Heart J.* 144, 51–59 (2002).

6. Tew R, Guthrie E, Creed FH *et al.* A long-term follow-up study of patients with ischemic heart disease versus patients with nonspecific chest pain. *J. Psychosom. Res.* 39, 977–985 (1995).

7. Rey E, Rodríguez-Artalejo F, Herraiz MA, Álvarez-Sánchez A, Escudero M, Díaz-Rubio M. Atypical symptoms of gastro-esophageal reflux during pregnancy. *Rev. Esp. Enferm. Dig.* 103(3), 129–132 (2011).

8. Eslick GD, Coulshed DS, Talley NJ. Review article: the burden of illness of non-cardiac chest pain. *Aliment. Pharmacol. Ther.* 16, 1217–1223 (2002).

9. Ockene IS, Shay M, Alpert J, Weiner BH, Dalen JE. Unexplained chest pain in patients with normal coronary angiograms: a follow study of functional status. *N. Engl. J. Med.* 303, 1249–1252 (1980).

10. Warwick H. Assessment of hypochondriasis. *Behav. Res. Ther.* 33, 845–853 (1995).

11. Chambers J, Bass C. Chest pain with normal coronary anatomy: a review of natural history and possible etiologic factors. *Prog. Cardiovasc. Dis.* 33, 161–184 (1990).

12. Eslick GD, Talley NJ. Non-cardiac chest pain: predictors of health care seeking, the types of health care professional consulted, work absenteeism and interruption of daily activities. *Aliment. Pharmacol. Ther.* 20, 909–915 (2004).

13. Thom T, Haase N, Rosamond W *et al.* Heart disease and stroke statistics – 2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 113(6), e85–e151 (2006).

• Shows the morbidity and mortality rates of heart disease in the community.

14. Maynard C, Every N, Martin JS, Kudenchuk PJ, Weaver WD. Association of gender and survival in patients with acute myocardial infarction. *Arch. Intern. Med.* 157(12), 1379–1384 (1997).

15. Graham I, Atar D, Borch-Johnsen K *et al.* European guidelines on cardiovascular disease prevention in clinical practice. *Eur. J. Cardiovasc. Prev. Rehabil.* 14(Suppl. 2), S1–S113 (2007).

16. Diercks DB, Owen KP, Kontos MC *et al.* Gender differences in time to presentation for myocardial infarction before and after a national women's cardiovascular awareness campaign. *Am. Heart J.* 160(1), 80–87.e3 (2010).

17. Lusiani L, Perrone A, Pesavento R, Conte G. Prevalence, clinical features, and acute course of atypical myocardial infarction. *Angiology* 45, 49–55 (1994).

18. Robinson JG, Wallace R, Limacher M *et al.* Elderly women diagnosed with nonspecific chest pain may be at increased cardiovascular risk. *J. Womens Health (Larchmt)* 15, 1151–1160 (2006).

19. Lodha A, Mirsakov N, Malik B, Shani J. Spontaneous coronary artery dissection: case report and review of literature. *South. Med. J.* 102, 315–317 (2009).

20. Lanza GA, Buffon A, Sestito A *et al.* Relation between stress-induced myocardial perfusion defects on cardiovascular magnetic resonance and coronary microvascular dysfunction in patients with cardiac syndrome X. *J. Am. Coll. Cardiol.* 4, 466–472 (2008).

21. Phan A, Shufelt C, Merz CN. Persistent chest pain and no obstructive coronary artery disease. *J. Am. Med. Ass.* 301, 1468–1474 (2009).

22. Kaski JC, Rosano GM, Collins P *et al.* Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. *J. Am. Coll. Cardiol.* 25, 807–814 (1995).

23. Dobrzycki S, Baniukiewicz A, Korecki J *et al.* Does gastroesophageal reflux provoke the myocardial ischemia in patients with CAD? *Int. J. Cardiol.* 104, 67–72 (2005).

24. Budzyński J, Kłopocka M, Pulkowski G *et al.* The effect of double dose of omeprazole on the course of angina pectoris and treadmill stress test in patients with coronary artery disease-a randomised, double-blind, placebo controlled, crossover trial. *Int. J. Cardiol.* 127, 233–239 (2008).

25. Van Rossum LG, Laheij RJ, Vlemmix F, Jansen JB, Verheugt FW. Health related quality of life in patients with cardiovascular disease – the effect of upper gastrointestinal symptom treatment. *Aliment. Pharmacol. Ther.* 19, 1099–1104 (2004).

26. Husser D, Bollmann A, Kühne C, Molling J, Klein HU. Evaluation of noncardiac chest pain: diagnostic approach, coping strategies and quality of life. *Eur. J. Pain* 10, 51–55 (2006).

27. Dickman R, Mattek N, Holub J, Peters D, Fass R. Prevalence of upper gastrointestinal tract findings in patients with noncardiac chest pain versus those with gastroesophageal reflux disease (GERD)-related symptoms: results from a national endoscopic database. *Am. J. Gastroenterol.* 102, 1173–1179 (2007).

28. Dickman R, Fass R. Noncardiac chest pain. *Clin. Gastroenterol. Hepatol.* 4, 558–563 (2006).

29. Lindsell CJ, Anantharaman V, Diercks D *et al.* The Internet Tracking Registry of Acute Coronary Syndromes (i*trACS): a multicenter registry of patients with suspicion of acute coronary syndromes reported using the standardized reporting guidelines for emergency department chest pain studies. *Ann. Emerg. Med.* 48(6), 666–677 (2006).

30. Miller CD, Lindsell CJ, Khandelwal S *et al.* Is the initial diagnostic impression of 'noncardiac chest pain' adequate to exclude cardiac disease? *Ann. Emerg. Med.* 44(6), 565–574 (2004).

31. Klinkman MS, Stevens D, Gorenflo DW. Episodes of care for chest pain: a preliminary report from MIRNET. Michigan Research Network. *J. Fam. Pract.* 38, 345–352 (1994).

32. Martina B, Bucheli B, Stotz M *et al.* First clinical judgment by primary care physicians distinguishes well between nonorganic and organic causes of abdominal or chest pain. *J. Gen. Intern. Med.* 12, 459–465 (1997).

33. Svavarsdóttir AE, Jónasson MR, Gudmundsson GH, Fjeldsted K. Chest pain in family practice. Diagnosis and long-term outcome in a community setting. *Can. Fam. Phys.* 42, 1122–1128 (1996).

34. Buntinx F, Knockaert D, Bruyninckx R. Chest pain in general practice or in the hospital emergency department: is it the same? *Fam. Pract.* 18, 586–589 (2001).

35. An exploratory report of chest pain in primary care. A report from ASPN. *J. Am. Board. Fam. Pract.* 3, 143–150 (1990).

36. Bösner S, Becker A, Haasenritter J *et al.* Chest pain in primary care: epidemiology and pre-work-up probabilities. *Eur. J. Gen. Pract.* 15, 141–146 (2009).

www.manaraa.com

37. Liuzzo JP, Ambrose JA. Chest pain from gastroesophageal reflux disease in patients with coronary artery disease. *Cardiol. Rev.* 13, 167–173 (2005).

38. Fass R, Naliboff B, Higa L *et al.* Differential effect of long-term esophageal acid exposure on mechanosensitivity and chemosensitivity in humans. *Gastroenterol*ogy 115, 1363–1373 (1998).

39. Mainie I, Tutuian R, Shay S *et al.* Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. *Gut* 55, 1398–1402 (2006).

40. Kushnir VM, Sayuk GS, Gyawali CP. Abnormal GERD parameters on ambulatory pH monitoring predict therapeutic success in noncardiac chest pain. *Am. J. Gastroenterol.* 105, 1032–1038 (2010).

41. Nam SY, Choi IJ, Ryu KH, Kim BC, Kim CG, Nam BH. Effect of *Helicobacter pylori* infection and its eradication on reflux esophagitis and reflux symptoms. *Am. J. Gastroenterol.* 105, 2153–2162 (2010).

42. Chey WD, Wong BC. American College of Gastroenterology Guideline on the management of *Helicobacter pylori* infection. *Am. J. Gastroenterol.* 102, 1808–1825 (2007).

43. Ronkainen J, Aro P, Storskrubb T *et al.* High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand. J. Gastroenterol.* 40, 275–285 (2005).

44. Drossman DA, Corazziari E, Delvaux M *et al.* [Appendix B: Rome III diagnostic criteria for functional gastrointestinal disorders.] *Rev. Gastroenterol. Mex.* 75(4), 511–516 (2010).

45. Drossman D, Corazziari R, Talley N *et al.* *Rome II – The Functional Gastrointestinal Disorders, 2nd Edition.* Drossman DA, Corazziari E, Talley NH, Thompson WG, Whitehead WE. Degnan Associates (2002).

46. Balaban DH, Yamamoto Y, Liu J *et al.* Sustained esophageal contraction: a marker of esophageal chest pain identified by intraluminal ultrasonography. *Gastroenterol*ogy 116, 29–37 (1999).

47. Hobson AR, Furlong PL, Sarkar S *et al.* Neurophysiologic assessment of esophageal sensory processing in noncardiac chest pain. *Gastroenterol*ogy 130, 80–88 (2006).

48. Achem SR, Almansa C, Krishna M *et al.* Oesophageal eosinophilic infiltration in patients with noncardiac chest pain. *Aliment. Pharmacol. Ther.* 33, 1194–1201 (2011).

49. Cannon RO, Quyyumi AA, Mincemoyer R *et al.* Imipramine in patients with chest pain despite normal coronary angiograms. *N. Engl. J. Med.* 330, 1411–1417 (1994).

50. Cannon RO 3rd. Can measures of coronary dynamics explain chest pain without coronary artery disease? *Circulation* 96, 3251–3254 (1997).

51. Eslick GD, Talley NJ. Natural history and predictors of outcome for non-cardiac chest pain: a prospective 4-year cohort study. *Neurogastroenterol. Motil.* 20, 989–997 (2008).

• **Interesting study on prognosis of noncardiac chest pain.**

52. Kim JH, Sinn DH, Son HJ, Kim JJ, Rhee JC, Rhee PL. Comparison of one-week and two-week empirical trial with a high-dose rabeprazole in non-cardiac chest pain patients. *J. Gastroenterol.Hepatol.* 24, 1504–1509 (2009).

53. Dickman R, Emmons S, Cui H *et al.* The effect of a therapeutic trial of high-dose rabeprazole on symptom response of patients with non-cardiac chest pain: a randomized, double-blind, placebo-controlled, crossover trial. *Aliment. Pharmacol. Ther.* 22, 547–555 (2005).

• **Double-blinded, randomized, placebo-controlled crossover study showing increased sensitivity and specificity of proton pump inhibitor in the diagnosis of gastroesophageal reflux disease-related noncardiac chest pain.**

54. Arts J, Sifrim D, Rutgeerts P, Lerut A, Janssens J, Tack J. Influence of radiofrequency energy delivery at the gastroesophageal junction (the Stretta procedure) on symptoms, acid exposure, and esophageal sensitivity to acid perfusion in gastroesophageal reflux disease. *Dig. Dis. Sci.* 52, 2170–2177 (2007).

55. Coron E, Sebille V, Cadiot G *et al.* Clinical trial: radiofrequency energy delivery in proton pump inhibitor-dependent gastro-oesophageal reflux disease patients. *Aliment. Pharmacol. Ther.* 28, 1147–1158 (2008).

56. Kitchin LI, Castell DO. Rationale and efficacy of conservative therapy for gastroesophageal reflux disease. *Arch. Intern. Med.* 151, 448–454 (1991).

57. Bautista J, Fullerton H, Briseno M, Cui H, Fass R. The effect of an empirical trial of high-dose lansoprazole on symptom response of patients with non-cardiac chest pain – a randomized, double-blind, placebo-controlled, crossover trial. *Aliment. Pharmacol. Ther.* 19, 1123–1130 (2004).

58. Seo TH, Kim JH, Lee JH *et al.* Clinical distinct features of noncardiac chest pain in young patients. *Neurogastroenterol. Motil.* 16, 166–171 (2010).

59. Pandak WM, Arezo S, Everett S *et al.* Short course of omeprazole: a better first diagnostic approach to noncardiac chest pain than endoscopy, manometry or 24-hour esophageal pH monitoring. *J. Clin. Gastrenterol.* 35(4), 307–314 (2002).

60. de Leone A, Tonini M, Dominici P, Grossi E, Pace F. The proton pump inhibitor test of gastroesophageal reflux disease: optimal cut-off value and duration. *Dig. Liver Dis.* 42, 785–790 (2010).

61. Xia HH, Lai KC, Lam SK *et al.* Symptomatic response to lansoprazole predicts abnormal acid reflux in endoscopy-negative patients with non-cardiac chest pain. *Aliment. Pharmacol. Ther.* 17, 369–377 (2003).

62. Fass R, Malagon I, Schmulson M. Chest pain of esophageal origin. *Curr. Opin. Gastroenterol.* 17, 376–380 (2001).

63. Modlin IM, Hunt RH, Malfertheiner P *et al.* Diagnosis and management of non-erosive reflux disease – The Vevey NERD Consensus Group. *Digestion* 80(2), 74–88 (2009).

64. Nagahara A, Asaoka D, Hojo M *et al.* Observational comparative trial of the efficacy of proton pump inhibitors versus histamine-2 receptor antagonists for uninvestigated dyspepsia. *J. Gastroenterol. Hepatol.* 25(Suppl. 1), S122–S128 (2010).

65. DeMeester T, O'Sullivan G, Bermudez G *et al.* Esophageal function in patients with angina-type chest pain and normal coronary angiograms. *Ann. Surg.* 196, 488–498 (1982).

66. Grossi L, Spezzaferro M, Sacco LF, Marzio L. Effect of baclofen on oesophageal motility and transient lower oesophageal sphincter relaxations in GORD patients: a 48-h manometric study. *Neurogastroenterol. Motil.* 20, 760–766 (2008).

67. Boeckxstaens GE, Rydholm H, Lei A, Adler J, Ruth M. Effect of lesogaberan, a novel GABAB-receptor agonist, on transient lower oesophageal sphincter relaxations in male subjects. *Aliment. Pharmacol. Ther.* 31, 1208–1217 (2010).

68. Beaumont H, Smout A, Aanen M *et al.* The GABAB receptor agonist AZD9343 inhibits transient lower oesophageal sphincter relaxations and acid reflux in healthy volunteers: a Phase I study. *Aliment. Pharmacol. Ther.* 30, 937–946 (2009).

69. Gerson LB, Huff FJ, Hila A *et al.* Arbaclofenplacarbil decreases postprandial reflux in patients with gastroesophageal reflux disease. *Am. J. Gastroenterol.* 105, 1266–1275 (2010).

70. Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional Nissen fundoplication. *Ann. Surg.* 250, 698–706 (2009).

71. Patti MG, Molena D, Fisichella PM, Perretta S, Way LW. Gastroesophageal reflux disease (GERD) and chest pain. Results of laparoscopic antireflux surgery. *Surg. Endosc.* 16, 563–566 (2002).

72. Chen RY, Thomas RJ. Results of laparoscopic fundoplication where atypical symptoms coexist with oesophageal reflux. *Aust. NZ J. Surg.* 70, 840–842 (2000).

73. Farrell TM, Richardson WS, Trus TL, Smith CD, Hunter JG. Response of atypical symptoms of gastro-oesophageal reflux to antireflux surgery. *Br. J. Surg.* 88, 1649–1652 (2001).

74. Rakita S, Villadolid D, Thomas A *et al.* Laparoscopic nissen fundoplication offers high patient satisfaction with relief of extraesophageal symptoms of gastroesophageal reflux disease. *Am. Surg.* 72, 207–212 (2006).

75. Schwartz MP, Wellink H, Gooszen HG, Conchillo JM, Samsom M, Smout AJ. Endoscopic gastroplication for the treatment of gastrooesophageal reflux disease: a randomised, sham-controlled trial. *Gut* 56, 20–28 (2007).

76. Liao CC, Lee CL, Lin BR *et al.* Endoluminalgastroplication for the treatment of gastroesophageal reflux disease: a 2-year prospective pilot study from Taiwan. *J. Gastroenterol. Hepatol.* 23, 398–405 (2008).

77. Anand N, Paterson WG. Role of nitric oxide in esophageal peristalsis. *Am. J. Physiol.* 255, G123–G131 (1994).

78. Kikendall JW, Mellow MH. Effect of sublingual nitroglycerin and long-acting nitrate preparations on esophageal motility. *Gastroenterol.* 79, 703–706 (1980).

79. Konturek JW, Gillessen A, Domschke W. Diffuse esophageal spasm: a malfunction that involves nitric oxide? *Scand. J. Gastroenterol.* 30, 1041–1045 (1995).

80. Allen M, Mellow M, Robinson MG, Orr WC. Comparison of calcium channel blocking agents and an anticholinergic agent on oesophageal function. *Aliment. Pharmacol. Ther.* 1, 153–159 (1987).

81. Richter JE, Spurling TJ, Cordova CM, Castell DO. Effects of oral calcium blocker, diltiazem, on esophageal contractions. *Dig. Dis. Sci.* 29(7), 649–656 (1984).

82. Richter JE, Dalton CB, Buice RG, Castell DO. Nifedipine: a potent inhibitor of contractions in the body of the human esophagus. *Gastroenterology* 89, 549–554 (1985).

83. Cattau EL, Castell DO, Johnson DA *et al.* Diltiazem therapy for symptoms associated with nutcracker esophagus. *Am. J. Gastroenterol.* 86(3), 272–275 (1991).

84. Davies HA, Lewis MJ, Rhodes J, Henderson AH. Trial of nifedipine for prevention of oesophageal spasm. *Digestion* 36, 81–83 (1987).

85. Richter JE, Dalton CB, Bradley LA, Castell DO. Oral nifedipine in the treatment of noncardiac chest pain in patients with the nutcracker esophagus. *Gastroenterology* 93, 21–28 (1987).

86. Bortolotti M, Labriola E, Bacchelli S *et al.* 'Oesophageal angina' in patients with angina pectoris: a possible side effect of chronic therapy with nitroderivates and Ca- antagonists. *Ital. J. Gastroenterol.* 24, 405–408 (1992).

87. Hughes J, Lockhart J, Joyce A. Do calcium antagonists contribute to gastro-oesophageal reflux disease and concomitant noncardic chest pain? *Br. J. Clin. Pharmacol.* 64(1), 83–89 (2007).

88. Yoshida K, Furuta K, Adachi K *et al.* Effects of antihypertensive drugs on esophageal body contraction. *World J. Gastroenterol.* 16(8), 987–991 (2010).

89. Bortolotti M, Pandolfo N, Giovannini M, Mari C, Miglioli M. Effect of sildenafil on hypertensive lower oesophageal sphincter. *Eur. J. Clin. Invest.* 32(9), 682–685 (2002).

90. Lee JI, Park H, Kim JH, Lee SI, Conklin JL. The effect of sildenafil on oesophageal motor function in healthy subjects and patients with nutcracker oesophagus. *Neurogastroenterol. Motil.* 15, 617–623 (2003).

91. Rhee PL, Hyun JG, Lee JH *et al.* The effect of sildenafil on lower esophageal sphincter and body motility in normal male adults. *Am. J. Gastroenterol.* 96(12), 3251–3257 (2001).

92. Eherer AJ, Schwetz I, Hammer HF *et al.* Effect of sildenafil on oesophageal motor function in healthy subjects and patients with oesophageal motor disorders. *Gut* 50, 758–764 (2002).

93. Bortolotti M, Mari C, Giovannini M, Pinna S, Miglioli M. Effects of sildenafil on esophageal motility of normal subjects. *Dig. Dis. Sci.* 46(11), 2301–2306 (2001).

94. Kim HS, Conklin JL, Park H. The effect of sildenafil on segmental oesophageal motility and gastro-oesophageal reflux. *Aliment. Pharmacol. Ther.* 24, 1029–1036 (2006).

95. Prakash C, Clouse RE. Long-term outcome from tricyclic antidepressant treatment of function chest pain. *Dig. Dis. Sci.* 44(12), 2373–2379 (1999).

96. Peghini PL, Katz PO, Castell DO. Imipramine decreases oesophageal pain perception in human male volunteers. *Gut* 42, 807–813 (1998).

97. Becker B, Morel N, Vanbellinghen AM, Lebrun P. Blockade of calcium entry in smooth muscle cells by the antidepressant imipramine. *Biochem. Pharmacol.* 68, 833–842 (2004).

98. Bromm B, Meier W, Scharein E. Imipramine reduces experimental pain. *Pain* 25, 245–251 (1986).

99. Cannon RO III, Quyyumi AA, Mincemoyer R *et al.* Imipramine in patients with chest pain despite normal coronary angiograms. *N. Engl. J. Med.* 330(20), 1411–1417 (1994).

100. Gorelick AB, Koshy SS, Hooper FG *et al.* Differential effects of amitriptyline on perception of somatic and visceral stimulation in healthy humans. *Am. J. Physiol.* 275, G460–G466 (1998).

101. Francis JK, Rebecca AS, Somers TJ *et al.* Effects of coping skills training and sertraline in patients with non-cardiac chest pain: a randomized controlled study. *Pain* 152, 730–741 (2011).

102. Doraiswamy PM, Varia I, Hellegers C *et al.* A randomized controlled trial of paroxetine for noncardiac chest pain. *Psychopharmacol. Bull.* 39(1), 15–24 (2006).

103. Lee H, Kim HJ, Min BH *et al.* Efficacy of venlafaxine for symptomatic relief in young adult patients with functional chest pain: a randomized, double-blind, placebo-controlled, crossover trial. *Am. J. Gastroenterol.* 105, 1504–1512 (2010).

104. Wulsin LR, Maddock R, Beitman B, Dawaher R, Wells VE. Clonazepam treatment of panic disorder in patients with recurrent chest pain and normal coronary arteries. *Int. J. Psychiatry Med.* 29(1), 97–105 (1999).

105. Beitman BD, Basha IM, Trombka LH *et al.* Pharmacotherapeutic treatment of panic disorder in patients presenting with chest pain. *J. Fam. Pract.* 28(2), 177–180 (1989).

106. Rao SS, Mudipallu RS, Mujica V *et al.* An open-label trial of theophylline for functional chest pain. *Dig. Dis. Sci.* 47(12), 2763–2768 (2002).

107. Rao SS, Ranjit S, Mudipallu RS, Remes-Troche JM, Utech CL, Zimmerman B. Theophylline improves esophageal chest pain – A randomised, placebo-controlled study. *Am. J. Gastroenterol.* 102, 930–938 (2007).

108. Borjesson M, Pilhall M, Eliasson T, Norssell H, Mannheimer C, Rolny P. Esophageal visceral pain sensitivity: effect of TENS and correlation with manometric findings. *Dig. Dis. Sci.* 43(8), 1621–1628 (1998).

109. Miller L, Pullela S, Parkman H *et al.* Treatment of chest pain in patients with noncardiac, nonreflux, nonachalasia spastic esophageal motor disorders using botulinum toxin injection into the gastroesophageal junction. *Am. J. Gastroenterol.* 97, 1640–1646 (2002).

110. Vanuytsel T, Bisschps R, Holvoet L *et al.* A sham-controlled study of injection of botulinum toxin in non-achalasia esophageal motility disorder. *Gastroenterol*ogy 136(5 Suppl. 1), A-152 (2009).

111. Klimes I, Mayou R, Pearce MJ, Coles L, Fagg JR. Psychological treatment for atypical non-cardiac chest pain: a controlled evaluation. *Psychol. Med.* 20, 605–611 (1990).

112. Bass C, Wade C. Chest pain with normal coronary arteries: a comparative study of psychiatric and social morbidity. *Psychol. Med.* 14, 51–61 (1984).

113. Kisely SR, Campbell LA, Skerritt P, Yelland MJ. Psychological interventions for symptomatic management of non-specific chest pain in patients with normal coronary anatomy. *Cochrane Database Syst. Rev.* 1, CD004101 (2010).

114. Jonsbu E, Dammen T, Morken G, Moum T, Martinsen EW. Short-term cognitive behavioral therapy for non-cardiac chest pain and benign palpitations: a randomized controlled trial. *J. Psychosom. Res.* 70, 117–123 (2011).

115. Jones H, Cooper P, Miller V, Brooks N, Whorwell PJ. Treatment of non-cardiac chest pain: a controlled trial of hypnotherapy. *Gut* 55, 1403–1408 (2006).

116. Gasiorowska A, Navarro-Rodriguez T, Dickman R *et al.* Clinical trial: the effect of Johrei on symptoms of patients with functional chest pain. *Aliment. Pharmacol. Ther.* 29, 126–134 (2008).

117. Kahn S. The challenge of evaluating the patient with chest pain. *Arch. Pathol. Lab. Med.* 124, 1418–1419 (2000).

118. Eslick GD, Coulshed DS, Talley NJ. Review article: the burden of illness of non-cardiac chest pain. *Aliment. Pharmacol. Ther.* 16, 1217–1223 (2002).

119. Prina LD, Decker WW, Weaver AL *et al.* Outcome of patients with a final diagnosis of chest pain of undetermined origin admitted under the suspicion of acute coronary syndrome: a report from the Rochester Epidemiology Project. *Ann. Intern. Med.* 43, 59–67 (2004).

120. Schey R, Villarrea AL, Fass R. Noncardiac chest pain: current treatment. *Gastroenterol. Hepatol. (New York)* 3(4), 255–262 (2007).

121. Fang J, Bjorkman D. A critical approach to noncardiac chest pain: pathophysiology, diagnosis, and treatment. *Am. J. Gastroenterol.* 96, 958–968 (2001).

Medscape
EDUCATION   Management of noncardiac chest pain in women

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions (with a minimum 70% passing score) and earn continuing medical education (CME) credit, please go to www.medscape.org/journal/wh. Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on Medscape.org. If you are not registered on Medscape.org, please click on the New Users: Free Registration link on the left hand side of the website to register. Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding the content of this activity, contact the accredited provider, CME@medscape.net. For technical assistance, contact CME@webmd.net. American Medical Association's Physician's Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please refer to http://www.ama-assn.org/ama/pub/category/2922.html. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for ***AMA PRA Category 1 Credit(s)™***. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit may be acceptable as evidence of participation in CME activities. If you are not licensed in the US, please complete the questions online, print the AMA PRA CME credit certificate and present it to your national medical association for review.

Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.					
	1	**2**	**3**	**4**	**5**
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Your patient is a 41-year-old woman with a history of hypertension. She complains of central chest pain which is not related to exercise. As you evaluate this patient, what should you consider regarding the epidemiology of noncardiac chest pain (NCCP) in women?

    ☐ **A**   The rates of NCCP are similar among women and men in all age groups

    ☐ **B**   African–Americans are the racial/ethnic group most likely to report NCCP

    ☐ **C**   Patients with NCCP are more likely to smoke and drink alcohol

    ☐ **D**   NCCP usually improves during pregnancy and then returns after delivery

2. What should you consider regarding this patient's risk for coronary artery disease and its outcomes?

    ☐ **A**   The risk for in-hospital mortality following myocardial infarction is similar among women and men

    ☐ **B**   Nearly one third of women with myocardial infarction may have atypical symptoms

    ☐ **C**   Cardiac syndrome X is defined by normal exercise testing

    ☐ **D**   Women with myocardial infarction usually seek healthcare resources earlier than men

www.manaraa.com

3. Upon further questioning, you believe that this patient has gastroesophageal reflux disease (GERD). Which of the following statements regarding GERD and NCCP is most accurate?

☐ **A**   Less than 5% of patients with NCCP have abnormal esophageal acid exposure

☐ **B**   The presence of *Helicobacter pylori* significantly increases the risk for GERD

☐ **C**   Most patients with NCCP due to GERD have erosive esophagitis

☐ **D**   GERD is the most common cause of NCCP

4. Which of the following statements regarding the treatment of GERD in the setting of NCCP is most accurate?

☐ **A**   Lifestyle modification alone usually resolves symptoms

☐ **B**   Proton pump inhibitors are the mainstay of therapy

☐ **C**   Histamine-2 receptor antagonists are as effective as proton pump inhibitors

☐ **D**   Laparoscopic Nissen fundoplication nearly always produces complete resolution of symptoms

www.manaraa.com