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Efficacy of citalopram or amitriptyline versus no treatment in patients with functional chest pain

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Abstract

Background Functional chest pain (FCP) is characterized by the presence of chest pain of presumed esophageal origin, but with a negative workup on routine investigations, including ruling out gastroesophageal reflux disease (GERD). Antidepressants are frequently prescribed to treat FCP and are presumed to act as neuromodulators of visceral hypersensitivity. However, there is little evidence of their efficacy in patients with FCP. We retrospectively assessed the efficacy of citalopram or amitriptyline vs. no treatment in patients with FCP.

Methods Esophageal diseases, including GERD, eosinophilic esophagitis and major esophageal motility disorders, were excluded. Thus, patients with established FCP according to Rome IV criteria were included in the study. Then, patients treated for at least 3 months with citalopram 20 mg, amitriptyline 50 mg, or observation were selected. The primary endpoint was complete disappearance or significant amelioration of symptoms at the end of treatment.

Results Over a 5-year period, 102 patients (74 female; mean age 49±10 years) were diagnosed with FCP and were recognized to have received once daily citalopram (n=32), amitriptyline (n=34), or no treatment (n=36). After a 3-month follow up, improvement in chest pain was reported by 16 (47.1%) patients treated with citalopram, 18 (56.3%) patients treated with amitriptyline, and 4 (11.1%) patients without treatment (P=0.02 and 0.01 for no treatment vs. citalopram and amitriptyline therapy, respectively).

Conclusion Both citalopram and amitriptyline are effective pharmacological options in the symptomatic relief of almost 50% patients with well characterized FCP.

Keywords Functional chest pain, citalopram, amitriptyline, antidepressants, esophagus

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Introduction

Functional chest pain (FCP) comprises a distinct clinical entity that belongs in the spectrum of diseases classified broadly as non-cardiac chest pain (NCCP) [1]. NCCP is a heterogeneous disorder defined as "angina-like" chest pain not due to ischemic heart disease or other cardiac pathology. The prevalence of NCCP is calculated to be 19-33%. Among patients with NCCP the vast majority have been found to have gastroesophageal reflux disease (GERD), a minority have esophageal dysmotility and 1 of 3 patients are thought to have FCP [2]. According to Rome IV criteria, FCP is defined as recurring, unexplained, retrosternal chest pain of presumed esophageal origin, not explained on the basis of reflux disease, other mucosal or motor processes, and representing pain different from heartburn. There is no sex predominance among patients with FCP. FCP is often diagnosed in patients <45 years old [3].

The first step in the clinical evaluation of a patient who presents with chest pain is exclusion of cardiac disease. Further diagnostic workup includes upper gastrointestinal (GI) endoscopy, esophageal manometry, ambulatory 24-h esophageal pH monitoring, and an empirical trial with a high-dose proton pump inhibitor (PPI). It has been suggested that upper GI endoscopy is of very limited value, but it has a clear

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exclusionary role in ruling out the presence of eosinophilic esophagitis. Ambulatory pH monitoring is particularly helpful in those patients who had a normal endoscopy and failed to respond to a therapeutic trial with PPIs. In cases where GERD has been excluded, high-resolution manometry (HRM) is considered to be an appropriate test to exclude a diagnosis of major esophageal motility disorders.

The pathophysiological background of FCP seems to be an altered sensation of pain at the central level, as well as splanchnic hypersensitivity to various triggering factors [4]. Peripheral hypersensitivity in association with abnormal central processing leads to altered pain perception [5,6]. According to recent data, the deregulation of parasympathetic tone plays a crucial role in splanchnic hypersensitivity [7]. Antidepressants can ameliorate peripheral and central hyperalgesia via 2 mechanisms. First, pain sensation is transmitted to the spinal cord in a top-down fashion through a complex descending projection from brain nuclei. As the aforementioned projections are primarily opioidergic, noradrenergic, and serotonergic, antidepressants are thought to interfere with these modulatory processes. Second, antidepressants may interfere with the function of pain-related brain circuits through their monoaminergic actions, especially as emotional and cognitive circuits targeted by antidepressants are highly intertwined with pain processing regions [8]. Thus, antidepressants could be a promising treatment option, as they function as modifiers of the neuronal pathways implicated in splanchnic hypersensitivity. Antidepressants with different mechanisms of action, such as tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors, have been tested in patients with FCP. Although treatment with antidepressants seems to be efficient in up to a half of those patients, these results came from studies involving patients with NCCP in general and not solely with FCP [9,10]. Therefore, we aimed to evaluate the efficacy of 2 different antidepressants, one TCA and one SSRI in patients diagnosed with FCP.

Patients and methods

Study subjects

Data from patients who attended the outpatient Gastroenterology Clinic of Laiko General Hospital during a 4-year period (2017-2020) and were diagnosed with NCCP were retrospectively collected. Fig. 1 shows the process of patient selection. Before their inclusion in the study, patients had undergone a cardiological assessment by an expert (electrocardiogram, Doppler ultrasonography, and coronary angiogram as needed after cardiologist's assessment). Patients with abnormalities of cardiac function to which the pain could be possibly attributed were excluded from the study. A total of 534 patients were considered as candidates for inclusion in the study, all of whom were diagnosed with NCCP according to Rome IV criteria (at least 3 episodes per week of chest pain in the previous 3 months). Patients diagnosed with depression or

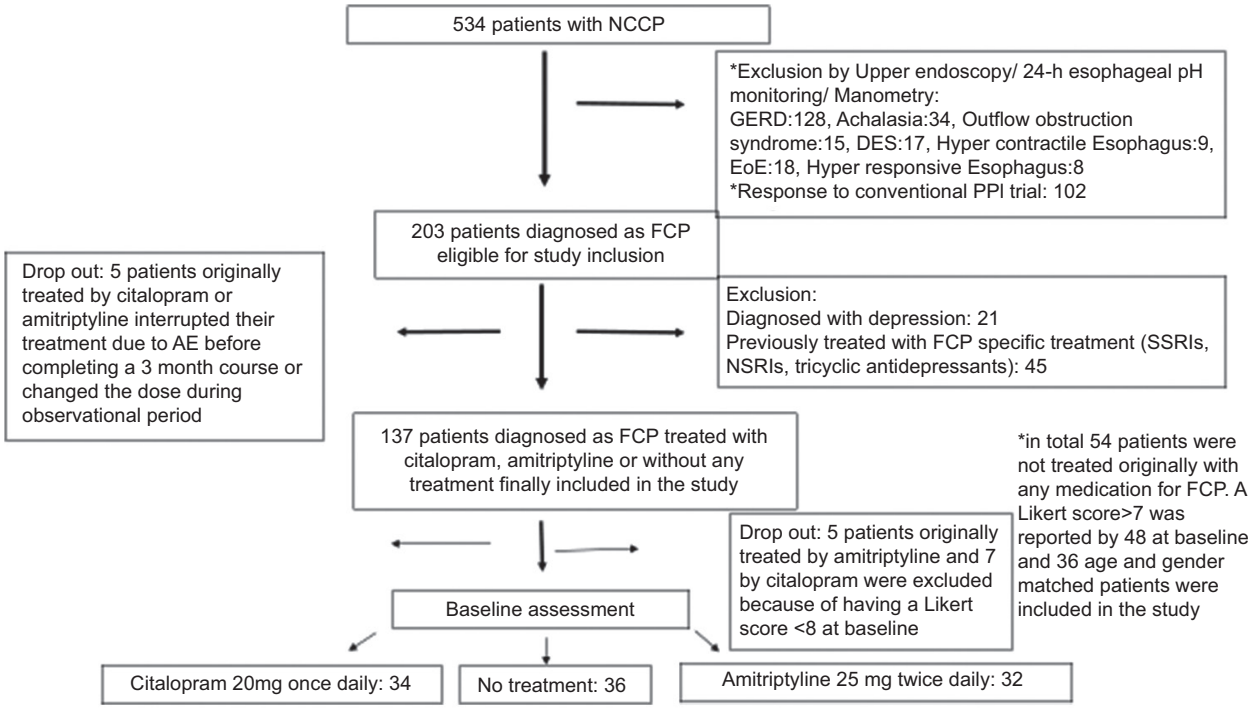

Figure 1 Flowchart of the study group selection
NCCP, non-cardiac chest pain; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; DES, diffuse esophageal spasm; FCP, functional chest pain; AE, adverse event

had previously been treated with antidepressants were excluded from the study. Patients with a normal upper endoscopy, normal 24-h esophageal pH± impedance monitoring (examination of PPIs, total acid exposure <4.2%, <80 episodes of reflux, negative Symptomatic index and/or Symptom Associated Possibility) and no major dysmotility disorders (diagnosed by HRM) were considered to fulfil Rome IV criteria for FCP. All patients included were on stable medication for coronary artery disease and diabetes during the study period, and no interaction between other drugs and an antidepressant was expected.

Only patients treated with amitriptyline or citalopram and no previous specific treatment for FCP were included in our study. In total, 40 patients treated with amitriptyline 50 mg daily (25 mg b.i.d.) and 43 patients treated with citalopram 20 mg (q.d.) were identified. Three patients under amitriptyline treatment and 2 under citalopram interrupted their treatment before the end of the 3-month period because of adverse effects, or changed the dose given during the examined period, and were excluded from the study. All 78 remaining patients, treated with amitriptyline or citalopram, received a steady dose of 50 mg and 20 mg, respectively, for the entire study period.

At each patient visit, a Likert scale of 0-10 for pain assessment (0, no pain; 1-3, mild pain; 4-6, moderate pain; and 7-10, severe pain) was available, as it is included in our outpatient clinic's daily practice for all patients with NCCP. Among the numerical scales for pain assessment, the 10-point Likert scale is a valid, simple scale and has been most widely used in neuropathic pain studies [6]. All patients included had to have reported a Likert pain score >7 at baseline. Five patients treated with amitriptyline and 7 treated with citalopram were excluded because a Likert pain score <8 was documented at their baseline visit. Patients were considered as responders to treatment if a Likert score of 3 or less was documented during their final visit.

Finally, 32 patients treated with amitriptyline and 34 with citalopram were included in the study. In addition, 36 age- and sex-matched patients with a diagnosis of FCP, who had never reported any disease-specific treatment and had a baseline Likert score of >7, were included in our study as a control group.

All epidemiological, anthropometric clinical and laboratory data were retrospectively collected from the patients' records. Epidemiological and clinical data were collected at the baseline visit (initiation of treatment with amitriptyline or citalopram, or on the first visit of untreated patients), and the patients' response to treatment 3 months after the baseline visit was documented. Any side effects were reported.

The study protocol was approved by the Ethics Committee of Laiko General Hospital, Athens, Greece and conformed to all ethical guidelines issued by the 2000 revision (Edinburgh) of the 1975 Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using SPSS V23 (SPSS software; SPSS Inc, Chicago, IL, USA). Data were expressed as frequencies, mean ± standard deviation (SD), or median (interquartile range [IQR]), as appropriate. Quantitative variables were compared between groups using Student's *t*-test or the Mann-Whitney test for normally distributed and non-normally distributed variables, respectively. Qualitative variables were compared using the chi-squared test or Fisher's exact test, as appropriate. As treatment response was expressed as a qualitative variable, comparisons between treatment groups were made separately in pairs, using the chi-squared test as appropriate. The associations between quantitative variables were assessed using Spearman's correlation coefficient. Multivariate logistic regression analysis models were used to identify independent, significant, predictive factors of a poor dichotomous outcome. Only parameters with a significant or a trend for a significant association (P<0.10) with the dependent variable in the univariate analysis were included in the multivariate analysis models. All tests were 2-sided and P-values <0.05 were considered to be significant.

Results

Baseline epidemiological and laboratory characteristics of the patients enrolled according to treatment group are shown in Tables 1-3. The majority of the studied subjects were female (M/F: 28/74) and were equally distributed among the 3 groups. Mean age was 49±10 years old (min 20, max 63; citalopram 49±10, amitriptyline 50±11, controls 53±6) and did not differ between treated vs untreated patients (P=0.112) or between patients receiving amitriptyline vs citalopram (P=0.447). Mean body mass index (BMI) was 25.7±3 kg/cm^2.

Among the total examined population, 36/102 (17.6%) patients were diagnosed with type 2 diabetes, while 20/102 (19.6%) had coronary artery disease under stable treatment. Both diagnoses were equally distributed among the 3 treatment groups (Tables 1-3).

A minority of examined patients also reported symptoms such as regurgitation (8/102, 7.8%) and heartburn (22/102, 21.6%), while 1 patient reported weight loss. None of the patients reported dysphagia (Table 1).

Table 1 Baseline characteristics of study patients

Baseline characteristics	All patients
Age (years)	49±10 (min 20, max 63)
Sex (M/F)	28/74
BMI (kg/cm^2)	25.7±3
Comorbidities	
Diabetes type 2	17/102(16.7%)
Coronary artery disease	20/102 (19.6%)
Other esophageal symptoms	
Regurgitation	8/102 (7.8%)
Heartburn	22/102 (21.6%)

*Values expressed as mean ± SD

BMI, body mass index; M, male; F, female; BMI, body mass index; SD, standard deviation

Table 2 Baseline characteristics of study patients including pH-metry impedance findings and HRM findings and response to treatment by Likert score

Baseline characteristics	Treated patients (n=66)	Untreated patients (n=36)	P-value (treated vs. untreated)
Age (years)	50±9	53±6	0.112
Sex (M/F)	21/45	7/29	0.134
BMI (kg/cm^2)	25.2±2.8	26.4±3.2	0.103
Comorbidities			
Diabetes type 2	13/66(19.7%)	4/36 (11.1%)	0.407
Coronary artery disease	15/66 (22.7%)	5/36 (13.9%)	0.434
Other esophageal symptoms			
Regurgitation	6/66 (9.1%)	2/36 (5.6%)	0.709
Heartburn	14/56 (21.2%)	8/36 (22.2%)	>0.99
Reflux episodes (n)	15±8	17	0.372
AET (%)	1.55±0.87	1.67±0.86	0.486
DCI (mmHg/sec/cm^2)	2430.9±1029.5	2245.5±833.6	0.342
IRP (mmHg)	7.5±2.0	7.4±2.2	0.783
Baseline Likert score	8.94±0.80	9.03±0.81	0.597
Likert score after 3-month treatment	3.60±3.21	6.97±2.73	<0.001

*Values expressed as mean ± SD

BMI, body mass index; HRM, high-resolution manometry; AET, acid exposure time; DCI, distal contractile integral; IRP, integrated relaxation pressure

Table 3 Baseline characteristics and treatment efficacy according to specific therapy

Baseline characteristics	Citalopram-treated patients (n=34)	Amitriptyline-treated patients (n=32)	P-value (citalopram vs. amitriptyline
Age (years)	49±10	51±7	0.447
Sex (M/F)	10/24	11/21	0.793
BMI (kg/cm²)	24.1±2.6	26.6±2.4	0.102
Comorbidities			
Diabetes type 2	8/34 (23.5%)	5/32 (7.9%)	0.540
Coronary artery disease	9/34 (26.5%)	7/32 (15.6%)	0.777
Other esophageal symptoms			
Regurgitation	4/34 (11.8%)	2/32 (6.3%)	0.673
Heartburn	8/34 (23.5%)	6/32 (18.8%)	0.766
Baseline Likert score	8.97±0.85	8.90±0.98	0.747
Likert score after 3-month treatment	3.85±3.08	3.34±3.36	0.523

*Values expressed as mean ± SD

BMI, body mass index; M, male; F, female

After 3 months, disappearance or amelioration (Likert score <4) of chest pain was reported by 38/102 patients (39.2%), comprising 16/34 (47.1%) patients treated with citalopram, 18/32 (56.3%) patients treated with amitriptyline and 4/36 (11.1%) patients without treatment (P=0.02 and 0.01 for citalopram/and amitriptyline therapy vs. no treatment, respectively) (Tables 2,3). In total, approximately 50% of patients treated with antidepressants (either amitriptyline or citalopram) responded to treatment (34/66, 51.5%), in comparison to only 4/36 patients who did not receive either treatment (P=0.002). No difference in treatment response was documented between patients treated with amitriptyline and patients treated with citalopram (P=0.473) (Fig. 2).

Patients who respond to antidepressants

Among patients treated with antidepressants the response to treatment was not affected by either age (with response 52±7 vs. 48±10 without response, P=0.142) or sex (male: 12/21, 57.1% vs. female: 22/45, 48.19%, P=0.603). Patients' BMI was also not correlated with their treatment response (with response 26.4±3.1 kg/cm^2 vs. 25.9±2.7kg/cm^2 without response, P=0.105).

The existence of comorbidities (coronary artery disease or type 2 diabetes) did not affect the response to treatment (14/24, 58.3% vs. 20/42, 47.6% among patients without comorbidities, P=0.451). However, patients who reported other symptoms,

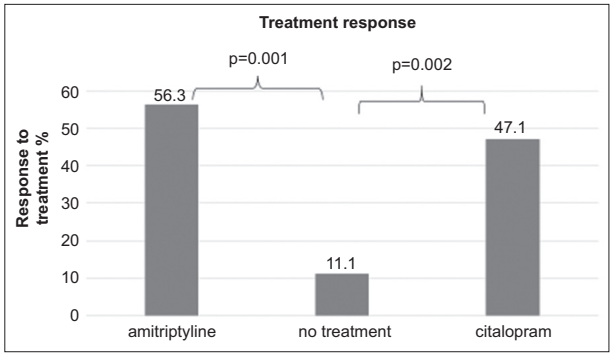

Figure 2 Comparison of treatment efficacy with amitriptyline or citalopram vs. no treatment

such as regurgitation and/or heartburn, were more likely to respond to treatment than patients without other symptoms (16/18, 88.9% vs. 18/48, 37.5%, P<0.001). In the multivariate analysis, reporting of symptoms such as regurgitation and/or heartburn was also the only parameter correlated with the patients' response (P=0.001, exp(B)=56.154).

Discussion

Our study found that treatment with antidepressants (either amitriptyline or citalopram) ameliorates FCP symptoms in approximately half of patients. Moreover, we found that the positive effect of treatment with antidepressants is even greater in patients presenting with additional esophageal symptoms, such as heartburn or regurgitation.

Antidepressant medications are considered the mainstay of treatment in patients with FCP in clinical practice, even though data from various clinical studies, using different drugs, are conflicting [1]. Previous studies, assessing the effect of antidepressants (imipramine or sertraline or venlafaxine) in FCP, documented that treatment with antidepressants had significant beneficial effects on chest pain severity or frequency compared with placebo and can reduce symptoms by more than 50% [11-15]. In contrast, 3 other studies failed to show any benefit for paroxetine and trazodone in the treatment of FCP in comparison to placebo [16-18]. Moreover, a recent meta-analysis that included only studies evaluating the effectiveness of SSRIs in NCCP, concluded that SSRIs were not superior to placebo in improving chest pain or depression symptoms [19]. On the other hand, a recent systematic review came to the conclusion that clinical studies provide modest evidence for both TCAs and SSRIs in ameliorating FCP symptoms [5]. Unfortunately, among the existing studies only the study by Lee *et al*, using venlafaxine, included solely patients with an FCP diagnosis [11]. Lee *et al* assessed the efficacy of an extended-release formulation of venlafaxine vs. placebo, taken for 4 weeks, among a group of 43 young, mainly male patients. The authors concluded that venlafaxine treatment significantly improved symptoms in approximately 50.0% of patients and this effect persisted for the entire treatment period.

Although our study population and the drugs used were different (middle-aged, female patients, SSRIS and TCA) compared to those of Lee *et al*, our results support the use of antidepressants in patients diagnosed with FCP.

No difference between TCA (amitriptyline) or SSRI (citalopram) treatment was observed. We had previously shown citalopram to be effective in a select group of patients with hypersensitive esophagus, suggesting a possible role of the drug in influencing esophageal perception [20]. This observation may explain the greater benefit of antidepressant treatment in patients with complementary esophageal symptoms besides chest pain. What is more, data from a previously published study, among patients with GERD and no complete response to PPIs, have shown that adding amitriptyline to PPIs led to a reduction in both anxiety and typical GERD symptoms, such as heartburn and regurgitation, by 64.96% and 94.20%, respectively. Our results are in agreement with the results of the abovementioned study [21].

The main limitation of our study was its retrospective design. However, we included a well-defined FCP population and we compared the efficacy of antidepressants to an age- and sex-matched control group of patients, thus minimizing any putative bias. Although absence of concurrent heartburn is a requirement for FCP diagnosis, we finally included these patients in the study, as we failed to address the presence of overt GERD overlap (negative diagnostic test, no response to PPIs).

In conclusion, both SSRIs and TCA antidepressants significantly improved symptoms in patients with FCP. This observation may further assist clinicians when it comes to treatment selection among patients who have been thoroughly studied and diagnosed with FCP.

Summary Box

What is already known:

- Functional chest pain (FCP) is characterized by the presence of chest pain of presumed esophageal origin, but a negative workup on routine investigations, including ruling out gastroesophageal reflux disease
- Antidepressants are frequently prescribed to treat FCP
- There is little evidence of antidepressants' efficacy in patients with FCP

What the new finding is:

- Treatment of FCP with either citalopram or amitriptyline showed a symptomatic relief in almost 50% of the patients

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