

## Randomized Trial

## Treatment of Functional Chest Pain with Antidepressants: A Meta-Analysis

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**Background:** Recurrent Functional Chest pain (FCP) with normal coronary anatomy and no detectable gastroenterological and respiratory causes is a common problem that sometimes leads to excess use of medical care.

**Objective:** The purpose of this meta-analysis is to investigate the efficacy of antidepressant treatments for FCP.

**Settings:** MEDLINE, PsycINFO, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to July 2011. Randomized controlled trials (RCTs) that tested any type of antidepressants for FCP with normal coronary anatomy were analyzed. Diagnoses included non-specific chest pain, noncardiac chest pain, atypical chest pain, syndrome X, or chest pain with normal coronary anatomy.

**Methods:** Two authors independently extracted data. Effects were summarized using standardized mean differences (SMDs), weighed mean differences (WMD), or odds ratio (OR) by suitable effects model.

**Results:** Seven RCTs (median duration, 5 weeks; range, 3 - 16 weeks) involving 319 participants were included. There was strong evidence for an association of antidepressants with reduction in pain (SMD -1.26; 95% confidence interval [CI], -2.34 to -0.19) and psychological symptoms (SMD -0.87; 95% CI, -1.67 to -0.08) as well as increased side effects (OR 0.34; 95% CI, 0.15 to 0.78). Current analysis did not support the association of antidepressants with improved health related quality of life (WMD 2.00; 95% CI, - 2.54 to - 6.65).

**Limitations:** Demographics, co-morbidities of study participants and the amount of co-medication were not reported, these possible sources of heterogeneity could not be examined.

**Conclusions:** Antidepressant medications are associated with improvements in pain and psychological symptoms. The effects of factors including psychiatric co-morbidity, gender, age, ethnic group, and treating period on the outcomes should be checked further.

**Key words:** Functional chest pain, antidepressants, meta-analysis

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**A** number of terms have been used to describe functional chest pain (FCP) that presented as recurrent angina-like retrosternal chest pain with normal coronary anatomy and no detectable gastroenterological and respiratory causes after an adequate evaluation (1,2). These terms include non-

specific chest pain (NSCP), noncardiac chest pain (NCCP), atypical chest pain, syndrome X, or chest pain with normal coronary anatomy. FCP accounts for more than 50% of chest pain patients admitted to the emergency department (3,4), 2 - 5% of all admissions to the emergency department (2,4), and about 50% of new

chest pain referrals to outpatient cardiac clinics (5). The community prevalence of FCP was reported from 23% to 33% (1,2). Patients with FCP are more likely to suffer from coexisting mood disorder, anxiety, and neuroticism compared to healthy controls or individuals with organic pathology, and to report a low quality of life (6-8). FCP has a benign long-term outcome, however, based on its high prevalence and psychiatric co-morbidity, as well as the significant health care and socioeconomic costs such as repeated visits to consultants, hospitalizations, and work absenteeism (9-11). Effective treatments for FCP are therefore necessary for medical and economic reasons.

Antidepressants can potentially modulate pain perception. They are often used in chronic pain therapy and have been shown to be effective in this setting (12). For these reasons, it would be reasonable to assume a beneficial effect of antidepressant drugs, such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), or psychological therapies, such as cognitive behavioral therapy (CBT), on the symptoms of FCP. The efficacy of psychological intervention has been summarized in a recent meta-analysis (13), but there is no such meta-analysis for antidepressants ever since the first randomized controlled trial (RCT) on this issue in 1994 (14).

It is not clear whether antidepressant treatment is effective on FCP-related symptoms. The methodological quality (internal validity) and generalizability (external validity) of RCTs on antidepressants for FCP are not clear as well. We therefore performed the current meta-analysis with the hope of resolving these issues.

## METHODS

Based on the QUORUM guidelines (Quality of Reporting of Meta-analyses) (15) and the recommendations of the Cochrane Collaboration, we performed the current meta-analysis (16).

### Data Sources and Searches

The electronic databases screened were MEDLINE (1966 through July 2011), PsycINFO (1966 through July 2011), Scopus (1980 through July 2011), and the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3 of 4, July 2011). Searches were limited to human and performed for all languages. The keywords non-specific chest pain, non cardiac chest pain, atypical chest pain, syndrome X, or chest pain with normal coronary anatomy were used in combination with antidepressant, antidepressive agents, tricyclic antidepressant (TCA), selective serotonin reuptake inhibitors (SSRIs), serotonin-

norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, desipramine, imipramine, trimipramine, doxepin, dothiepin, nortriptyline, amitriptyline, paroxetine, sertraline, fluoxetine, citalopram, venlafaxine, duloxetine, milnacipran or desvenlafaxine and randomized controlled trial or controlled clinical trial or review. Limiting the number of reports with a filter did not seem reasonable considering the potential number of studies, thus we did not use a filter such as the highly sensitive search strategy (17). Three of us (W.W., Y-H. S, and Y-T. W) manually and independently screened reference sections of relevant original articles, reviews, and meta-analyses (13) The supplementary material showed the search strategy in CENTRAL as an example.

### Study Selection

Studies were included according to the following criteria: FCP defined based on the symptom and medical negative examination; RCT design with a control group receiving pharmacological placebo; and another group receiving antidepressants. The effect of combinations of antidepressants was not found in all studies. Corresponding authors of RCTs with incomplete data presentation (e.g., missing means, standard deviations of pretest and posttest data, or standard deviations of change scores) were contacted when necessary. One study was excluded since we were not able to obtain missing data (18).

### Data Extraction

Two of us (S-X. W., Y-Q. L.) independently screened the titles and abstracts of potentially eligible studies. The full text articles were examined independently by 2 of us (W.W., W.W.) to determine whether they met the inclusion criteria. Two of us (Y-H. S., Y-Y. W.) independently extracted data (study characteristics and results) using data extraction forms. Point estimates for selected variables were extracted and checked by the other 2 reviewers. All discrepancies were rechecked and consensus was achieved by discussion.  $\kappa$  test was used to assess agreement between reviewers.

We selected pain and psychological symptoms as outcome measures for FCP. Health-related quality of life (HRQOL) was an additional outcome. When researchers reported more than one measure for an outcome, we used the following priority for inclusion in the meta-analysis:

1. Pain: pain intensity measured by categorical scales or visual analogue scales (VAS), pain diaries (mean difference in pain scores or recorded frequency of exacerbation of pain).

2. Psychological symptoms: Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA), Hospital Anxiety and Depression Scale (HADS), Clinical Global Impression Improvement (CGI-I) or severity (CGI-S) scales, and general health questionnaire.
3. HRQOL: The MOS 36-Item Short-Form Health Survey (SF-36).

The Jadad test (5 items) (19) was applied for assessing methodological quality as high (score 5), moderate (score 4), or low (scores 1 - 3).

### Data Synthesis and Analysis

Intention-to-treat data were analyzed whenever available. Nonparametric tests (Mann-Whitney test, Kruskal-Wallis test) were used for comparing continuous variables. A 2-sided P value of .05 or lower was considered significant. Meta-analyses were conducted using Rev-Man analyses software (RevMan 5.0.25) according to Cochrane Handbook for Systematic Reviews of Interventions (20).

For all included studies, the main outcome of FCP was scored according to the patients pain diary or VAS, some also reported the chest pain frequency (14) (Table 1). Be-

Table 1. Main Study Characteristics.

Source (country)	Female Sex/ White race, %	Age, Mean (range) y	Exclusion Criteria	Study Population		Treatment Group		Placebo group Completed, No./total (%)	Method Quality, Jadad Score	Outcome Measures Used for Meta-analysis
				Random-ized/ Screen, N (%)	Completed, No./ total (%)	Duration Treatment, design	Completed, No./ total (%)			
<b>Tricyclic antidepressants: Imipramine</b>										
Cannon et al, 1994 (USA)	66.7/NR	50*(29 - 72)	SSD, CVD, HBP	NR	40/40 (100)	3 wks, imipramine 25 to 50 mg/d, parallel	20/20 (100)	20/20 (100)	4	PAIN diary, Pain VAS
Cox et al, 1998 (UK)	100/NR	53* (35 - 72)	CVD, CCM	18/27 (66.7)	18/18 (100)	5 wks, imipramine, 50 mg/d, crossover	15/18 (83.3)	18/18 (100)	4	Pain diary, Nottingham Health Profile questionnaire
<b>Selective Serotonin Reuptake Inhibitors: Paroxetine</b>										
Doraiswamy et al, 2006 (USA)	42/80	53.3 (18 - 85)	CCM, PD, MD,SA, SR	50/66 (75.8)	43/50 (86)	8 wks, Paroxetine 10-50 mg (median 30, range 5-50 mg) /daily, parallel	22/27 (81.5)	21/23 (91.3)	5	Pain VAS, CGI
Spinhoven et al, 2010 (Dutch)	47.8/NR	55.9(NR)	CVD, Not fluent in Dutch, CCM, mental disorders	95/474 (20.0)	35/46 (76.1)	16 wks, paroxetine 10-40 mg/daily, parallel	16/23 (69.6)	19/23 (82.6)	5	Pain VAS, HADS
<b>Selective Serotonin Reuptake Inhibitors: Sertraline</b>										
Varia et al, 2000 (USA)	NR/NR	NR (18-85)	PA, MD, SA, SSD, sensitivity to sertraline	30/34 (88.2)	25/30 (83.3)	8 wks, sertraline 50 to 200 mg daily, parallel	14/15 (93.3)	11/15 (73.3)	5	Pain VAS, BDI, SF-36
<b>Selective Serotonin Reuptake Inhibitors: Fluoxetine</b>										
Zheng et al, 2006 (China)	51.9/0	60 (NR) Hospital based	CVD, SSD,S Sensitivity to fluoxetine, PMF, schizophrenia	123/NR	81/81 (100)	4 wks, fluoxetine 20 mg daily, parallel	41/41 (100)	40/40 (100)	5	PainVAS, HAMA, HAMD
<b>Serotonin and Noradrenaline Reuptake Inhibitors: Venlafaxine</b>										
Lee et al, 2010 (South Korea)	12/NR	23.5 (20-29) Checked sample size	SSD, mental disorders, APN	50/110 (45.5)	43/50 (86)	4 wks, 75 mg venlafaxine ER 75 mg daily, crossover	22/25 (88)	21/25 (84)	5	Pain VAS, BDI, SF-36
Abbreviations: APN, Autonomic or Peripheral Neuropathy; BDI, Beck Depression Inventory; CCM, Concomitant medications; CGI, Clinical Global Impression; CVD, Cardiovascular Disease; HADS, Hospital Anxiety and Depression Scale; HAMA, and Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; HBP, High Blood Pressure; MD, Major Depression; PD, Panic Disorder; PMF, Pregnancy or Milk Feeding, SA, Substance Abuse; SF-36, The MOS 36-Item Short-Form Health Survey; SR, suicide Risk; SSD: severe somatic disease; NR, not rated; VAS, Visual Analogue Scales; * indicates median value.										

cause most outcomes were presented as continuous data (mean value or mean changes), we used either the weighted mean differences (WMDs) or the standardized mean difference (SMDs) as effect measures. WMDs were calculated for HRQOL outcome because they were measured in different trials on the same scale, SF-36. SMDs were calculated for pain and psychological symptoms outcomes because they were determined in different trials using different scales. Odds ratio (OR) was used in evaluating the antidepressants related side effects. To calculate WMDs or SMDs, we used means and change scores and their standard deviations. When these values were showed in a graph manner without any description of absolute value, we first tried to contact with the authors. Measurements from the graph were used if we could not get data from the authors. When only the standard error was reported, it was converted into standard deviation (20).

$I^2$  statistics were used to measure heterogeneity of the RCTs. If the  $I^2$  value was less than 50%, a fixed-effects meta-analysis was applied. If the  $I^2$  value was 50% or more, the random-effects meta-analysis was used (20). We used Cohen categories (21) to evaluate the magnitude of the effect size, calculated by WMD, SMD, or OR, and designated a D greater than 0.2 through 0.5 as a small effect size, a D greater than 0.5 up to 0.8 as a medium effect size, and a D greater than 0.8 as a large effect size. We used the following descriptors to classify meta-analysis results (22): "strong" indicated consistent findings in multiple (at least 2) high- or moderate-quality RCTs; "moderate" indicated consistent findings in multiple low-quality RCTs or one high- or moderate-quality RCT; "limited" indicated one low-quality RCT; and "conflicting" indicated inconsistent findings among multiple RCTs.

A sensitivity analysis was conducted to determine whether different classes of antidepressants (TCA, SSRIs, and SNRIs) influenced the results by calculating the effect sizes of the outcomes assessed for each class of antidepressants.

Visual assessment of the funnel plot calculated by RevMan Analyses software was used to investigate the potential publication bias (i.e., the association of publication probability with the statistical significance of study results). Publication bias may lead to asymmetrical funnel plots (23). Furthermore, we tested the sensitivity of our results to potential unpublished studies using a file-drawer test for meta-analysis. This test determines how many negative studies with an effect size of  $D = 0.01$  would be needed to negate our findings (fail-safe number) according to a revised version

of Rosenthal method (24) by Orwin (25). If the fail-safe number exceeds the file-drawer number, the results of the meta-analysis can be regarded as robust against potential reporting bias (24,25). The file-drawer number is calculated as  $5k + 10$ ; where  $k$  is the number of study groups in the meta-analysis (24).

## RESULTS

### Study Selection

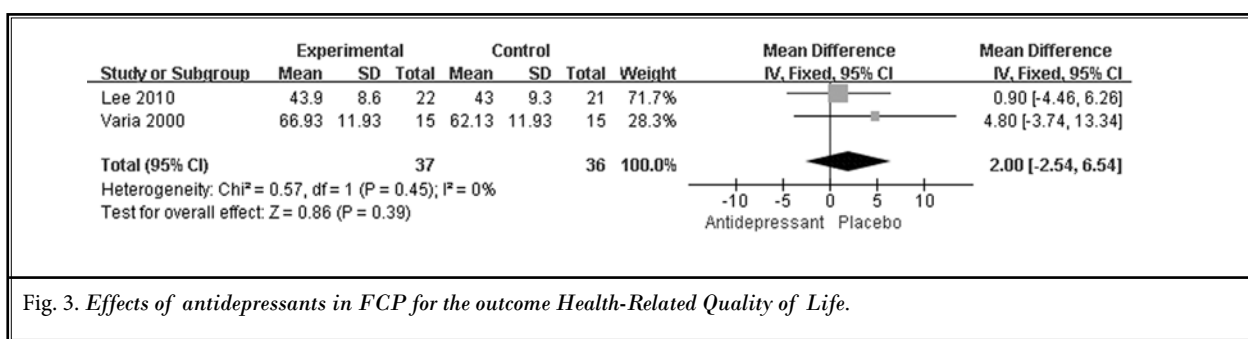
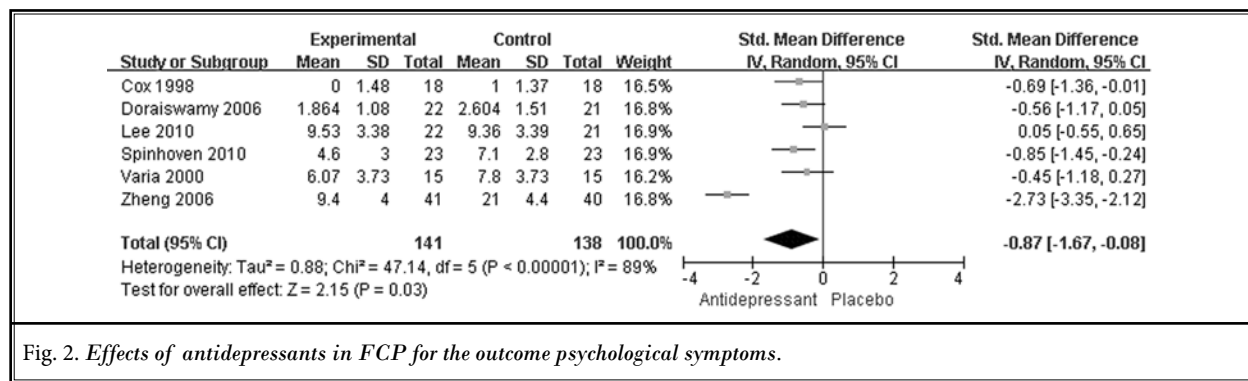
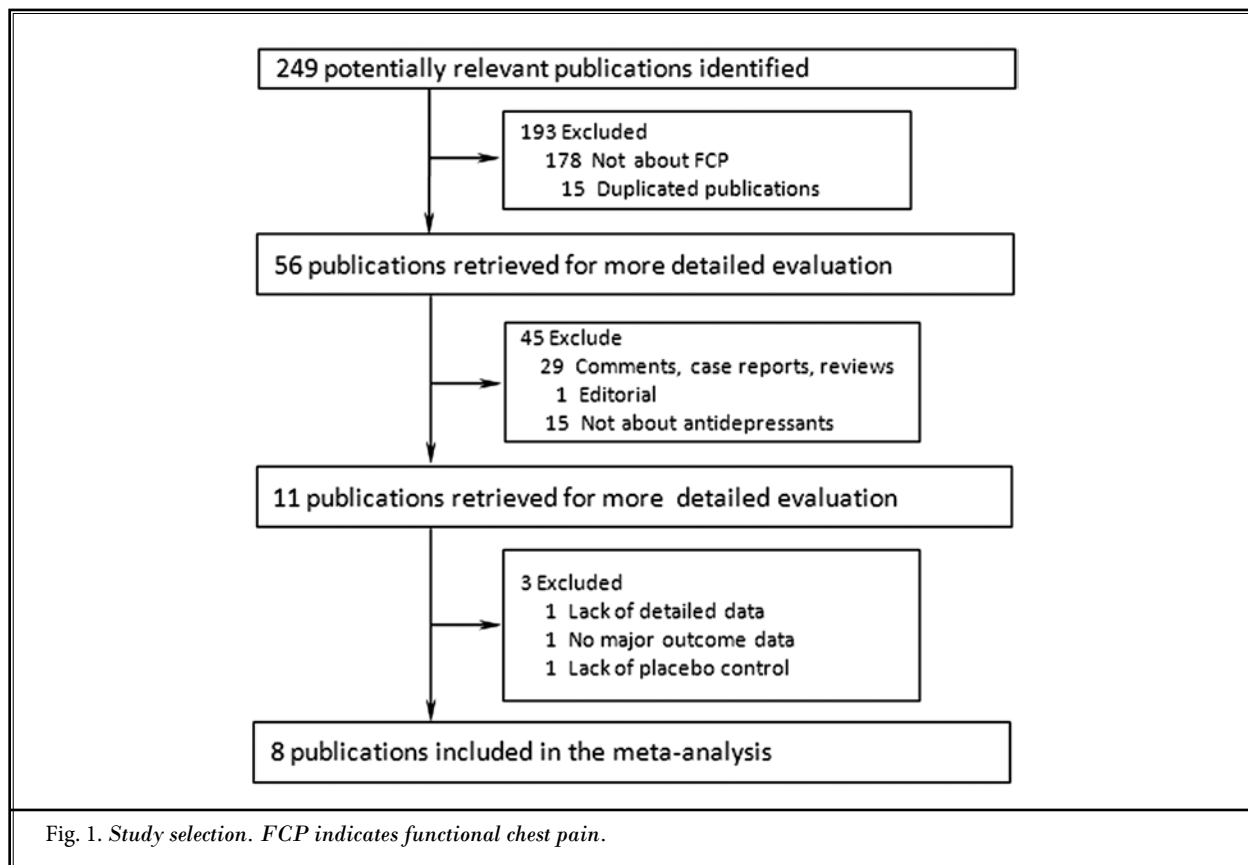
The literature search yielded 249 citations. Initially, 56 publications met our inclusion criteria. The excluded 193 publications contained duplicate publications that reported no more new data, and publications not about FCP. Duplicate publications were excluded after we confirmed that no new data had been added. On more detailed review, an additional 45 papers were excluded for the following reasons: comments, case reports, reviews, editorials and papers without antidepressant treatment groups. Three more publications were further excluded because of lacking of placebo control (26), reporting no major outcome data for this meta-analysis (27), and one without detailed data from the communication with authors (18). The remaining 7 studies from 8 publications met our selection criteria and were included in the meta-analysis (14,28-34) (Fig 1). The inter-rater reliability for this assessment was  $\kappa = 0.96$ .

### Meta-analyses

The effect sizes for all antidepressants are shown in Figs 2, 3, and 4. Based on Cohen categories for evaluating the magnitude of effect sizes, there was strong evidence for a reduction of pain (Fig. 5, SMD,  $-1.26$ ; 95% CI,  $-2.43$  to  $-0.13$ ;  $P = 0.02$ ), psychological symptoms (Fig. 2, SMD,  $-0.87$ ; 95% CI,  $-1.67$  to  $-0.08$ ;  $P = 0.03$ ). But improvements in HRQOL was not supported (Fig. 3, WMD,  $2.00$ ; 95% CI,  $-2.54$  to  $6.54$ ;  $P = 0.39$ ).

Table 2 gives a comparison of the effect sizes of each antidepressant class. There was strong evidence for the efficacy of the TCA imipramine in reducing pain (SMD,  $-0.81$ ; 95% CI,  $-1.28$  to  $-0.34$ ;  $P = 0.0007$ ), but not for psychological symptoms (SMD,  $-0.69$ ; 95% CI,  $-1.36$  to  $-0.01$ ;  $P = 0.05$ ). The data for the effect of TCA imipramine on HRQOL was not available in the selected studies.

There was strong evidence for the efficacy of the SSRIs in improving psychological symptoms (SMD,  $-1.15$ ; 95% CI,  $-2.22$  to  $0.09$ ;  $P = 0.03$ ), but not in reducing pain (SMD,  $-1.27$ ; 95% CI,  $-3.16$  to  $0.63$ ;  $P = 0.19$ ) and



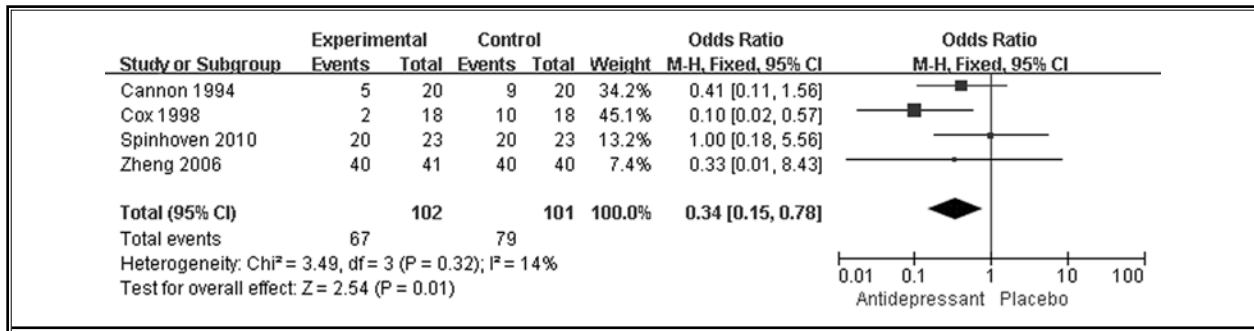


Fig. 4. Effects of antidepressants in FCP for the outcome side effects.

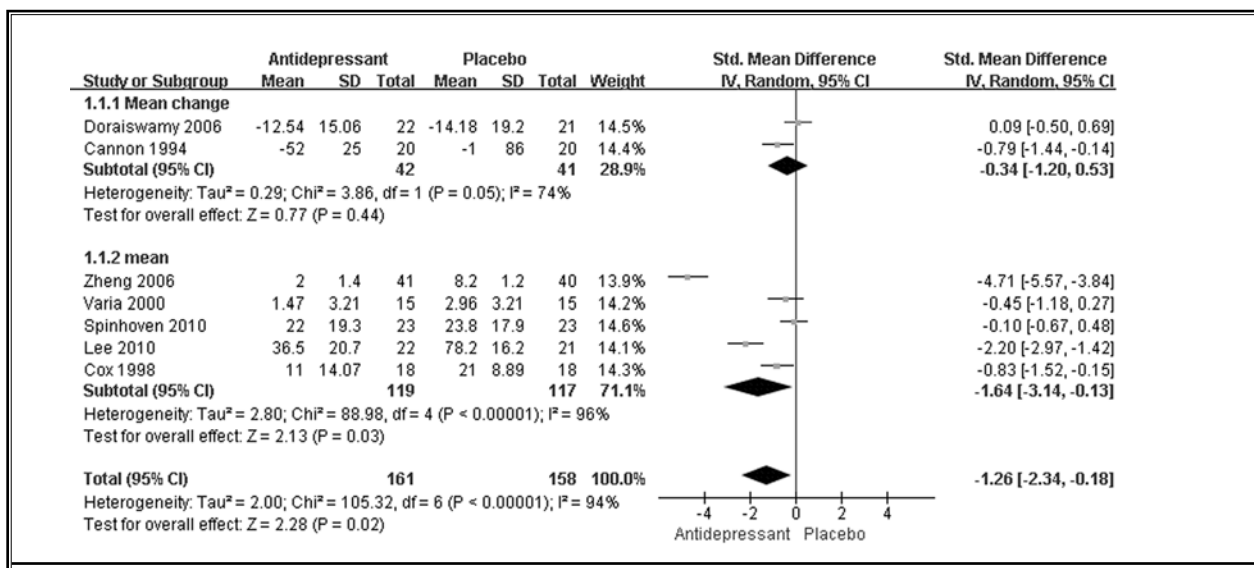


Fig. 5. Effects of antidepressants in FCP for the outcome pain as measured with pain diary or VAS scoring system.

improving HRQOL (WMD, 4.80; 95% CI, -3.74 to 13.34; P = 0.27).

There was strong evidence for the efficacy of the SNRIs venlafaxine in reducing pain (SMD, -2.20; 95% CI, -2.97 to -1.42; P < 0.00001) and improving HRQOL (WMD, 0.74; 95% CI, -4.46 to 6.26; P = 0.03) but not improving psychological symptoms (WMD, 0.05; 95% CI, -0.55 to 0.65; P = 0.87).

We noticed that the study from China showed a very big effect favoring the treatment for both pain and psychological outcomes (28). It is possible that if that study is ruled out, the significant difference between treatment and placebo will disappear. To check this possibility, we performed meta-analysis without including this study. A strong (4 out of 6 studies gave

the similar tendency, P = 0.02) association of antidepressants with reduction in pain (SMD, -0.69; 95% CI, -1.30 to -0.09) was observed (Fig. 6). A strong (4 out of 5 studies gave the similar tendency, P = 0.001) association of antidepressants with reduction in psychological symptoms (SMD, -0.46; 95% CI, -0.75 to -0.18) (Fig. 7) was observed.

#### Adverse events with antidepressant therapy

Six studies reported adverse events data (14,28,30-32,34), but only 4 provided the total number of side effects with antidepressants compared to placebo in a total of 203 patients (14,28,31,34). Thirty-five of 102 (34.3%) patients assigned to antidepressants reported adverse events compared to 22 of 101 (21.8%) allocat-

## Functional Chest Pain and Antidepressants: A Meta-Analysis

Table 2. Sensitivity analysis: Effect sizes of the different classes of antidepressants on the outcome Variables

Outcome	No. of studies	Patients taking antidepressants No.	Statistical Method	Effect size (95% CI)	Test of over effect P value
<b>Tricyclic antidepressants</b>					
Pain	2	38	SMD (Random)	-0.81 (-1.28 - -0.34)	0.0007
Psychological symptoms	1	18	WMD (Fixed)	-0.69 (-1.36 - -0.01)	0.05
HRQOL	0	NA	NA	NA	NA
Side effects	2	38	OR (Fixed)	0.23 (0.08 - 0.65)	0.005
<b>Selective Serotonin Reuptake Inhibitors</b>					
Pain	4	101	SMD (Random)	-1.27 (-3.16 - 0.63)	0.19
Psychological symptoms	4	101	SMD (Random)	-1.15 (-2.22 - 0.09)	0.03
HRQOL	1	15	WMD (Fixed)	4.80 (-3.74 - 13.34)	0.27
Side effects	2	64	OR (Fixed)	0.76 (0.17 - 3.33)	0.72
<b>Serotonin and Noradrenaline Reuptake Inhibitors</b>					
Pain	1	22	WMD (Fixed)	-2.20 (-2.97 - 1.42)	< 0.00001
Psychological symptoms	1	22	WMD (Fixed)	0.05 (-0.55 - 0.65)	0.87
HRQOL	1	22	WMD (Fixed)	0.74 (-4.46 - 6.26)	0.03
Side effects	0	NA	NA	NA	NA

Abbreviations: CI, confidence interval; HRQOL, health-related quality of life; NA, not assessed; SMD, standardized mean difference; WMD, weighted mean difference.

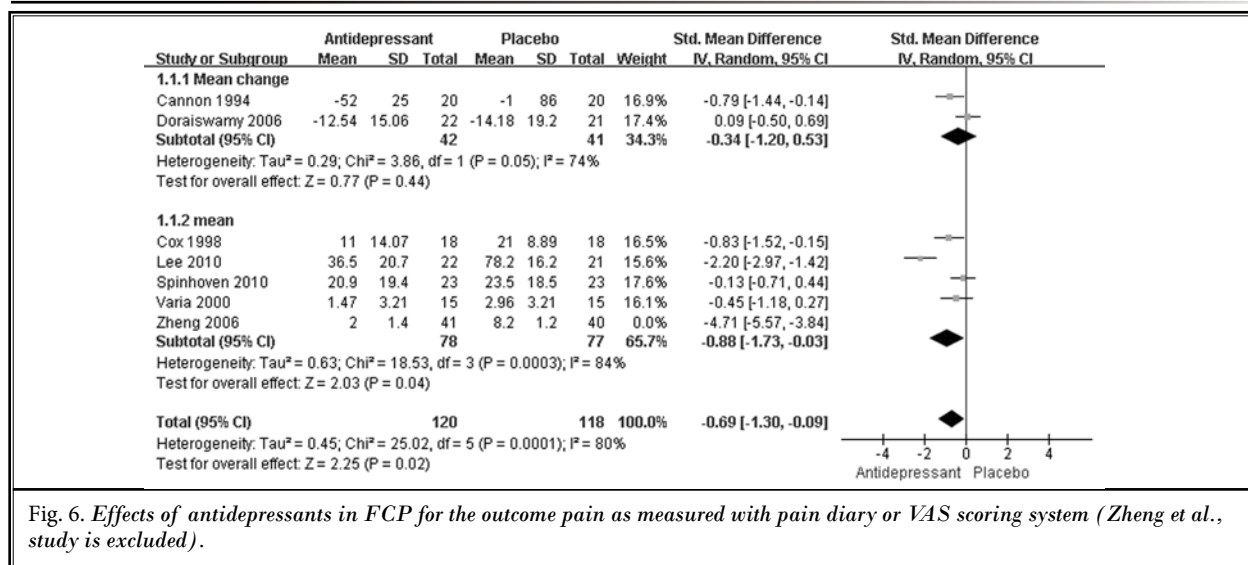


Fig. 6. Effects of antidepressants in FCP for the outcome pain as measured with pain diary or VAS scoring system (Zheng et al., study is excluded).

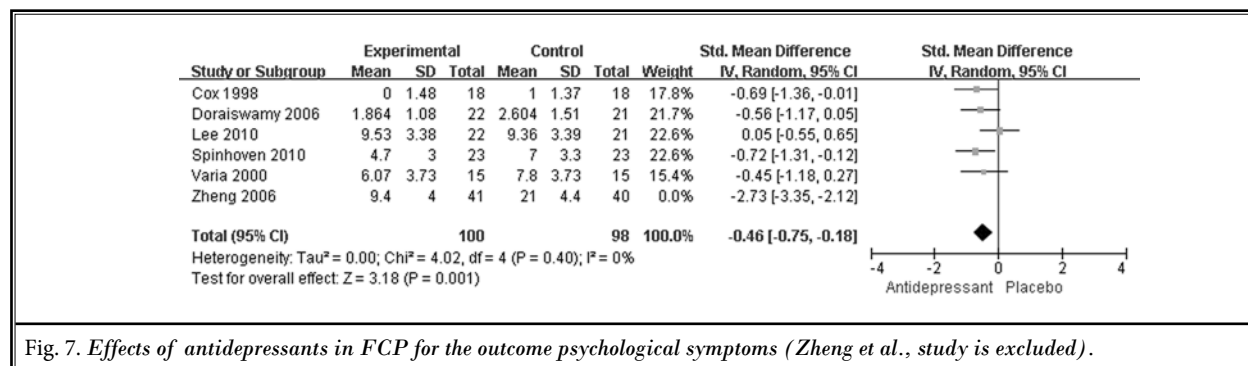


Fig. 7. Effects of antidepressants in FCP for the outcome psychological symptoms (Zheng et al., study is excluded).

ed to placebo. Strong evidence was obtained for the antidepressants with increased side effects (OR, 0.34; 95% CI, 0.15 to 0.78,  $P = 0.01$ ) with no heterogeneity detected between studies ( $I^2 = 14\%$ ,  $P = 0.32$ ) (Fig. 4). There were no serious adverse events, the most common reported by patients allocated to antidepressant therapy were drowsiness and fatigue.

Sensitivity analysis revealed strong evidence for the association of TCAs with increased side effects (OR, 0.23; 95% CI, 0.08 to 0.65,  $P = 0.005$ ). But no significant association between SSRIs and increased side effects can be identified (OR, 0.76; 95% CI, 0.17 to 3.33,  $P = 0.72$ ).

We noticed that one study from UK showed a very big effect favoring the placebo for side effects (34). It is possible that if that study is ruled out, the significant difference between treatment and placebo will disappear. There is no obvious association ( $P = 0.22$ ) of antidepressants with side effects if this was excluded (OR, 0.54; 95% CI, 0.20 to 1.45) (Fig. 8).

**Validity Analysis**

Characteristics of included studies are presented in supplementary Table 2. Inter-rater reliability for characteristics shown in Table 2 was  $\kappa = 0.91$ .

Only one study had a multicenter design. The other 6 had a single-center design. Five studies used a parallel design and 2 used a crossover design. TCAs (imipramine) were investigated in 2 studies. SSRIs were investigated in 4 studies (paroxetine in 2, sertraline in one and fluoxetine in one) and SNRIs (venlafaxine) were studied in one RCT. All the RCTs had only one intervention group and one placebo group.

The median duration of the RCTs was 5 weeks (range, 3 - 16 weeks). Outcomes were assessed at the end of the treatment. No study measured outcomes at an additional follow-up visit after treatment cessation. Serum antidepressant levels were not measured

in any RCTs to assess patients' adherence. One RCT allowed additional therapy with estrogen replacement, thyroid hormone replacement or insulin (14) and another allowed additional therapy with regular anti-anginal medication (34). Additional therapies were not reported in the other 5 RCTs (28-32). No study provided detailed information about nonpharmacological therapies or controlled for nonpharmacological therapies.

Only one study performed a power analysis to ensure an adequate sample size (31). Five studies had a Jadad score of 5, 2 had a Jadad score of 4. Inter-rater reliability for this assessment was  $\kappa = 0.91$ .

Significant heterogeneity was found among the analyzed RCTs in outcome measures for pain and psychological symptoms. The large ranges of the 95% CI in outcome measure of pain and psychological symptoms are also indicative of marked variations among the studies.

Three studies were performed in the United States, 2 were performed in Europe (UK and Netherlands), one was performed in China and one was performed in South Korea. Six studies were outpatient based and one was performed in hospital patients. Patients were recruited from cardiology departments in 3 studies and from research centers in one study. Three publications did not report the recruitment setting.

All studies excluded patients with severe somatic diseases. Four excluded patients with severe mental disorders, one included FCP patients with major depression diagnosis, and 2 did not describe the comorbidity with mental disorders, one included only a specific age category (20 - 29 years). A total of 300 individuals completed treatment, of them, 150 were receiving antidepressants. The median percentages of patients completing the trials were 88.0% for participants randomized to antidepressants and 91.3% for participants randomized to placebo ( $P = 0.582$ ). One study did not report the average age of patients. The median age of

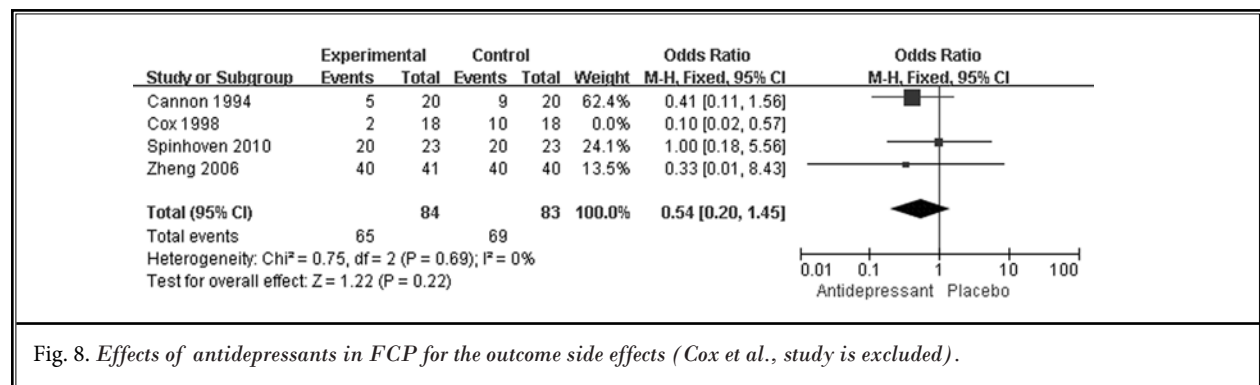


Fig. 8. Effects of antidepressants in FCP for the outcome side effects (Cox et al., study is excluded).



participants (calculated based on individual study) from the other 6 studies was 53.2 years. One study included only women, 6 included both men and women, and 5 specified the percentage of women. The median percentage of women in all studies was 49.9%. One study reported the participants' race of 80% for white. FCP was defined in 6 studies according to symptom and medical negative examination. One study defined FCP according to Rome III criteria for FCP (a normal upper endoscopy, pH testing, and esophageal manometry). No study provided data on nonpsychiatric comorbidities. One study included FCP patients with comorbidity of major depression and another did not provide data on the prevalence of major depressive disorders.

### Publication Bias

Visual assessing of forest plots for subgroup analysis revealed an asymmetric distribution suggesting publication bias. To look into more details on the possible effect of this publication bias on our result, we performed file-drawer test. The fail-safe number with a  $D = 0.01$  as the selected criterion value to "nullify" the average effect on pain was  $n = 868$ ; on psychological symptoms,  $n = 510$ , and on side effects,  $n = 1,164$ . Thus the fail-safe numbers were larger than the Rosenthal rule of thumb (24) of  $n = 45$  for pain,  $n = 40$  for psychological symptoms, and  $n = 30$  for side effects. These results indicate that a publication bias is unlikely to change the overall results of this meta-analysis.

### Discussion

The primary aim of this meta-analysis was to determine the efficacy of antidepressants for treatment of FCP. We found strong evidence for the efficacy of antidepressants in reducing pain and psychological symptoms but against a favorable effect of antidepressants on health related quality of life. The association between antidepressant treatments and side effects is not clear.

We found large effect sizes of TCAs for reducing pain and large effect sizes of SSRIs for reducing psychological symptoms. Conclusions regarding the efficacy of SNRI on outcomes were limited because of only one study with a small sample size. Small sample sizes also limited conclusions regarding the efficacy of individual antidepressants on outcomes.

Doses of TCAs used in the studies, between 25 and 50 mg per day, were typical for pain treatment but far below the doses of TCAs necessary for an antidepressant benefit. This likely explains the positive association

of TCAs for reducing pain in the absence of a benefit for depressive symptoms. Doses of SSRIs and SNRIs were equal to those used for treating affective disorders thus may explain the positive association of SSRIs and SNRIs on improving psychological symptoms.

The internal validity of the RCTs analyzed was limited for the following reasons. First, serum antidepressant levels were not measured in any RCTs to assess patients' adherence. Second, no study controlled for consumption, dose, or adverse effects of concomitant analgesic medications. The influence of this co-medication on study outcomes is unclear. Third, 4 out of 7 studies used a single-blind, placebo lead-in phase ranging from one to 5 weeks. Medication adverse effects indicating the presence of an active drug may have biased those trials without a leading-in phase than those with. Finally, some studies did not report the results of all outcomes that have been assessed.

The external validity of the RCTs analyzed was limited by the following facts. First, the short duration of most studies and the lack of follow-up after treatment cessation leave the questions unanswered whether antidepressants have long-term beneficial effects on FCP symptoms and the optimal treatment duration. One excluded study demonstrated an advantage of low dose TCAs regarding FCP symptoms over an average of 2.6 years (26). Second, despite evidence of a higher prevalence of mental disorders in FCP (6-8), only 4 studies performed a standardized psychiatric interview. No study performed subgroup analyses among participants with vs without major depressive disorder. Third, no definitive statements are possible on the efficacy of antidepressants in men, nonwhite individuals, patients older than 75 years, and children because these subgroups were not analyzed, with the exception of one study with imipramine: no significant difference in outcome measure of pain was observed in men and women (14). Finally, since most studies excluded patients with severe somatic diseases, it is unknown whether antidepressants are effective in these patients with FCP.

This review has limitations. First, since demographics and comorbidities of study participants and the amount of comedication were not reported, these possible sources of heterogeneity could not be examined. Second, we sought to identify unpublished studies but could not retrieve original insignificant data of one unpublished study (18). Third, there are limitations of some methods used in this article, such as using I<sup>2</sup> for assessing the amount of heterogeneity in random-effects meta-analysis (35) and fail-safe numbers (36) for excluding a publication bias.

## CONCLUSION

Short-term usage of imipramine (for all the ages) and venlafaxine (for young adults of 20 to 29 years old) can be considered for the treatment of pain in FCP. This recommendation is based on the number of patients studied (imipramine) and on the effect sizes (venlafaxine). But this analysis also suggested that TCAs may have a higher risk of increased side effects than SSRIs. Before initiating treatment, concomitant diseases related to potential adverse effects of the drugs and patients' preferences should be considered. Goals of pharmacological therapy should be defined (no cure, but possible symptom reduction). Since evidence for a long-term effect of antidepressants in FCP is still lacking, their effects should be reevaluated at regular intervals to determine whether the benefits outweigh adverse effects.

Since the merits of all studied RCTs in the current analysis were weakened by the unreported demographics and comorbidities of study participants and the amount of co-medication, more high quality and more strictly controlled clinical trials are required. Studies of longer duration than those currently available are needed to investigate the long-term efficacy of antidepressant therapy for FCP. It is currently unknown whether the benefits of antidepressants for treatment of FCP persist after cessation of therapy. It is also unknown whether antidepressants reduce FCP-related costs. The identification of patient characteristics associated with positive and negative therapeutic outcomes are needed to better target antidepressant therapy for FCP. Future studies of the effects of antidepressants on FCP should include patients with somatic and mental comorbidities and fully report all patient characteristics and outcomes assessed.

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### Author Contributions

Wen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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### Competing interest statement

All authors have completed the Unified Competing Interest form and declare: no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, no other relationships or activities that could appear to have influenced the submitted work.

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