Antidepressant therapy for unexplained symptoms and symptom syndromes
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Authors' objectives
To determine the efficacy of antidepressant therapy for unexplained symptoms or symptom syndromes.

Searching
MEDLINE from 1966 to December 1998, PsycLIT from 1974 to December 1998, and EMBASE from 1974 to December 1998, were searched using the following textwords and keywords: 'antidepressive agents' "or" 'selective serotonin reuptake inhibitors', 'monoamine oxidase inhibitors', 'tricyclic', 'amitriptyline', 'amoxapine', 'clomipramine', 'trimipramine', 'desipramine', 'doxepin', 'imipramine', 'maprotiline', 'nortriptyline', 'protriptyline', 'trazodone', 'nefazodone', 'fluoxetine', 'fluvoxamine', 'paroxetine', 'sertraline', 'fluvoxamine', 'venlafaxine', 'bupropion', 'citalopram', 'mianserin', 'pizotyline', 'pizotifen', 'antidepressive agents' "and" 'headache', 'colonic diseases-functional', 'abdominal pain', 'dyspepsia', 'chronic fatigue syndrome', 'fibromyalgia', 'myofascial pain syndromes', 'dyspnea', 'tinnitus', 'back pain', 'pelvic pain' and 'chest pain'. Additional published and unpublished studies were located by searching The Cochrane Library, in particular the Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews, and the Federal Research in Progress database, and by examining the references of retrieved articles.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), in which at least one study group received an antidepressant and there was a placebo or non-antidepressant control arm, were included.

Specific interventions included in the review
Antidepressant compared with either a placebo or non-antidepressant control. The dosing and titration of antidepressants in these trials were variable and dependent on the agent used (no specific details are reported in the paper). Generally, doses were titrated, and therapeutic doses were lower than those used in treating depression, except in trials of selective serotonin re-uptake inhibitors (SSRIs) where the antidepressant doses were typically used without titration.

Participants included in the review
Patients were eligible for inclusion if the symptom syndrome being evaluated was either idiopathic or the pathophysiology was poorly understood. The six symptom syndromes identified in the included studies were: headache (migraine, tension, mixed), fibromyalgia, functional gastrointestinal (GI) disorders (irritable bowel syndrome, functional dyspepsia, and idiopathic oesophageal contraction abnormalities), idiopathic pain (psychogenic, facial, chest, musculoskeletal, pelvic), tinnitus and chronic fatigue. Across all trials, the majority of patients were female (76%), most trials were undertaken in referral clinics (87%), and most patients had a median duration of symptoms greater than 3 years (74%).

Outcomes assessed in the review
The improvement in symptoms was assessed.

How were decisions on the relevance of primary studies made?
Each article was reviewed independently and in duplicate for inclusion, and any disagreements were resolved by discussion and consensus.

Assessment of study quality
Methodological assessment was conducted according to the scale of Jadad et al. (see Other Publications of Related Interest no.1). Scores were assessed independently and in duplicate by four reviewers. Disagreements were arbitrated by consensus, and when consensus could not be achieved discordant scores were averaged and rounded to the higher
whole number.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on the following: type of syndrome; setting; treatment including dosage and duration of treatment, active or placebo control, and follow-up; demographics and number of participants enrolled; any assessment of co-morbid psychiatric disease, and the instrument used to do so; adverse effects; outcomes; and statistical analysis of the results reported.

Methods of synthesis
How were the studies combined?
A narrative synthesis of all included studies, by indication, was presented. In addition, a meta-analysis was performed on the placebo-controlled studies from which data were extractable, using the random-effects model proposed by DerSimonian and Laird (see Other Publications of Related Interest no.2). The authors used the tests proposed by Begg and Mazumdar (see Other Publications of Related Interest no.3) and Egger et al. (see Other Publications of Related Interest no.4) for the assessment of publication bias in placebo-controlled studies. To assess the number of studies necessary to render the effect size insignificant, the 'file drawer' method of Rosenthal (see Other Publications of Related Interest no.5) was used.

How were differences between studies investigated?
Trials showing beneficial effects were compared with those that did not for the following study characteristics: design (parallel versus crossover), sample size (less than 50, 50 to 99, and greater than 100), quality rating (low, medium and high), drug class (tricyclic antidepressant, SSRI and antiserotonin agents), comparison group (placebo or alternative drug), industry sponsorship (yes or no), and country of study (USA versus other).

Results of the review
Ninety-four RCTs (n=6,595). The number of trials varied across the different symptoms or symptom syndromes: 50 studied headache, 18 fibromyalgia, 13 functional GI disorders, 11 idiopathic pain, 2 tinnitus and 2 chronic fatigue. The number of participants per indication was not reported, although the median number of participants across all trials was 50 (range: 7 - 698)

The quality of the included studies was fair (mean=4.8, on a scale of 0 to 8). The mean quality scores for each syndrome examined showed a degree of variation and were: 4.6 for headache, 5.8 for fibromyalgia, 4.1 for functional GI disorders, 4.2 for idiopathic pain, 4.0 for tinnitus, and 4.0 for chronic fatigue.

Across all indications, a majority of studies (67%) showed beneficial effects for the use of antidepressants. Among symptoms and symptom syndromes, there was some variation in the percentage of studies with beneficial effects: headache 62% of studies, fibromyalgia 80%, functional GI 75%, idiopathic pain 66%, tinnitus 50%, and chronic fatigue 50%. Symptom improvement typically did not correlate with depression response in the few studies in which it was assessed (4 out of 22).

The following study characteristics were not associated with a greater likelihood of showing benefit: parallel design, sample size, quality rating, industry sponsorship and country of study. However, drug class and comparison treatment (placebo or active non- antidepressant control) were associated with trial outcome. Studies with a placebo control were more likely than active non- antidepressant controls to show benefit (p<0.001). Studies of tricyclic antidepressants were more likely to have a beneficial outcome (P=0.02) than studies of SSRIs or antiserotonin agents.

Meta-analysis of all extractable data showed a substantial benefit from antidepressants: for the dichotomous outcome of improvement, the odds ratio was 3.4 (95% confidence interval, CI: 2.6, 4.5), and for continuous outcomes, the standardised mean difference was 0.87 (95% CI: 0.59, 1.14). The absolute percentage difference in improvement between the antidepressant and placebo arms was 32%, yielding a number-needed-to-treat of 3 to improve one person's symptoms.
There was significant publication bias against trials with low sample sizes and small effect sizes (95% CI: 2.1, 6.6, p<0.001)  

Meta-regression indicated there was no differential effect across the classes of antidepressants, withdrawal rates (greater than 20%), quality of study, type of symptom or syndrome, year of publication (before or after 1980) and sample size. None of these variables significantly affected the summary effect size. Similarly, the effect size for each individual syndrome was not significantly different.

**Authors' conclusions**

Pooled quantitative data indicate a substantial beneficial effect from the use of antidepressants for the treatment of multiple unexplained symptoms. However, there is a lack of high-quality evidence that systematically assesses this effect independent of depressive illness. Also, there were insufficient trials of SSRIs to make confident conclusions about the relative efficacy among different classes of antidepressants. Therefore, although antidepressants can be effective for various physical symptoms and symptom syndromes, the relation of outcome to depression and the efficacy of SSRIs needs further study.

**CRD commentary**

The review question was stated clearly and supported by study inclusion criteria. The literature search was thorough, and the validity assessment was completed with a published checklist. The description of primary studies was limited, though the large number of studies included in the review precluded detailed description. The heterogeneity identified when pooling all the studies in the meta-analysis suggests that quantitative pooling by indication may have been more appropriate.

In general, the review methodology was good and well reported, though details regarding the process of data extraction, e.g. how many reviewers were involved, was lacking. The authors' conclusions do follow from the data presented.

**Implications of the review for practice and research**

Practice: The authors state that physicians caring for patients with unexplained symptoms should focus their efforts on developing a therapeutic relationship, thoroughly exploring and treating any underlying depressive or anxiety disorder, and considering antidepressant therapy even if a depressive disorder is not evident.

Research: The authors state that future studies should include larger samples to allow for control of possible confounders; use parallel design studies to avoid the issue of possible carryover effect; examine for depression using standardised measures, and track depressive as well as physical symptom effects; be of longer duration; test newer antidepressant classes, especially SSRIs, in order to determine whether all classes are equally effective; adhere to methodological criteria of high-quality studies; and be located in community-based settings.

**Funding**

MacArthur Foundation Initiative on Depression in Primary Care.

**Bibliographic details**


**PubMedID**

10628579

**Other publications of related interest**


This additional published commentary may also be of interest. Price J. Review: antidepressants are effective for clinical improvement in unexplained physical symptoms and syndromes. Evid Based Med 2000;5:143.

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Antidepressive Agents /therapeutic use; Antidepressive Agents, Tricyclic /therapeutic use; Chronic Disease; Colonic Diseases, Functional /drug therapy; Depression /drug therapy; Evidence-Based Medicine; Female; Fibromyalgia /drug therapy; Headache /drug therapy; Humans; Male; Pain /drug therapy; Randomized Controlled Trials as Topic /standards; Serotonin Agents /therapeutic use; Syndrome

AccessionNumber
12000001069

Date bibliographic record published
31/01/2002

Date abstract record published
31/01/2002

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.