Antidepressant Therapy for Unexplained Symptoms and Symptom Syndromes

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OBJECTIVE. To determine the efficacy of antidepressant therapy for unexplained symptoms or symptom syndromes.

SEARCH STRATEGIES. We identified original studies through searching MEDLINE, EMBASE, PsycLIT, the Federal Research in Progress database, and *The Cochrane Library*. We also searched the bibliographies of primary and review articles for additional studies.

SELECTION CRITERIA. We excluded trials of patients with neuropathic, oncologic, or degenerative joint pain. Independent duplicate review of 392 articles identified 94 relevant reports of randomized trials involving 6595 patients across 6 symptom syndromes. Independent duplicate assessment was made for inclusion and data abstraction. Meta-analysis was performed on extractable placebo-controlled data.

MAIN RESULTS. Of 94 included trials, most studied either tricyclic antidepressants, antiserotonin antidepressants, selective serotonin reuptake inhibitors (SSRIs), or multiple agents for the treatment of the following syndromes: headache (50), fibromyalgia (18), functional gastrointestinal syndromes (13), idiopathic pain (11), tinnitus (2), and chronic fatigue (2). The quality of the studies was fair (mean score = 4.8 on a scale of 0 to 8). A majority of the studies (69%) demonstrated benefit for at least one outcome measure. Symptom improvement typically did not correlate with depression response in the few studies where it was assessed. 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 standardized 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. Meta-regression indicated no differential effect across the classes of antidepressants; however, onbivariate tally tricyclic studies were associated with a greater likelihood of efficacy than SSRI studies (P = .02).

CONCLUSIONS. 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.

KEY WORDS. Antidepressive agents; depression; symptoms and general pathology (non-MeSH). *(J Fam Pract 1999; 48:980-990)*

CLINICAL QUESTION Are antidepressants efficacious in the treatment of unexplained symptoms and symptom syndromes?

Chronic physical symptoms that defy etiologic understanding but cause significant morbidity are common in outpatient practice, and diagnostic testing frequently fails to reveal a discrete disease that has a specific therapy. Examples include irritable bowel syndrome, migraine or tension headaches, chronic fatigue syndrome, nonulcerative dyspepsia, fibromyalgia, unexplained dyspnea, tinnitus, and idiopathic pain syndromes. For many of these types of syndromes there is increased psychiatric comorbidity, especially depressive and anxiety disorders.[1-3] The vast majority of patients with depression in primary care present with physical, not emotional, complaints.[4-6] Although antidepressant therapy has been demonstrated to be efficacious in pain syndromes for which there is a well-established understanding of the pathophysiology,[7-9] the evidence for its efficacy for other types of physical symptom syndromes has not been critically reviewed.

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METHODS

Data Sources

We searched MEDLINE (1966 to December 1998), PsycLIT (1974 to December 1998), and EMBASE (1974 to December 1998) using the following text words and key words (all languages, limited to "human"): 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, femoxetine, venlafaxine, buproprion, 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. The symptom syndromes we included in the search were derived from a panel of general internists. We used *The Cochrane Library*, searching *The Cochrane Controlled Trials Register* for randomized trials and *The Cochrane Database of Systematic Reviews* for systematic reviews.[10] We also searched the Federal Research in Progress database to identify unpublished literature. All of the citations identified from the search were pulled and their references reviewed for additional articles missed during the database search. All primary articles and review articles and their references were reviewed independently, in duplicate.

Study Selection

Studies were screened for inclusion using the following criteria: adult study population; the symptom syndrome being evaluated was either idiopathic or the pathophysiology was poorly understood; at least one study group received an antidepressant; there was a placebo or non-antidepressant control arm; the allocation of the intervention was randomized (this included crossover trials); and measurable outcomes were reported. Articles were excluded if any of these criteria were not met. Each article was reviewed independently in duplicate for inclusion assessment. Agreement was substantial among raters (κ ranged from .55 - .85 among pairs of raters). Disagreements were arbitrated by discussion and consensus.

Quality Scores

The methodologic quality of each included study was

TABLE 1

Characteristics of Studies of Antidepressants for Idiopathic Symptoms or Symptom Syndromes

Characteristic	Syndrome (No. of Studies)						
	Headache (50)	Fibromyalgia (18)	Functional GI (13)	Idiopathic Pain (11)	Tinnitus (2)	Chronic Fatigue (2)	All (94)
No. of patients (median, range)	48, 16 - 698	41, 21-208	47, 7-428	60, 25-129	26, 117	20, 107	50 7-698
Women, %	77	92	51	65	42	76	76
Setting, %							
primary care	15	6	27	18	0	0	12
referral clinic	85	94	64	82	100	100	87
not stated	0	0	9	0	0	0	1
Year published, %							
before 1980	33	0	18	10	0	0	18
1980-89	38	38	64	45	1988	0	44
1990 or later	29	62	18	45	1993	1996	38
Median duration of symptoms, %							
< 1year	2	0	10	18	0	0	4
1-3 years	21	0	60	27	50	0	22
> 3 years	77	100	30	55	50	100	74
Median duration of trial, weeks	10	8	6	6	6	7	9
Study design, %							
parallel	64	62	83	73	50	100	66
crossover	36	38	17	27	50	0	34
Dropout > 20%, %	40	31	18	55	50	50	40
Country of study, % United States	23	25	45	18	100	50	28
Industry sponsored, %	42	50	50	33	0	100	45

TABLE 2

Summary of Trials Evaluating Efficacy of Antidepressants for Idiopathic Symptoms or Symptom Syndromes

Symptom or Symptom Syndrome	Number of Trials*					Mean Quality†	% of Studies Beneficial	Response Correlates with Depression‡	OR (95%CI)§
	Total	TCA	SSRI	Anti-Serotonin	Other				
Chronic headache	50	21	8	23	—	4.6	62	2/12	3.4 (2.7-4.4)
Fibromyalgia	18	12	4	—	3	5.8	80	1/5	5.1 (3.1-8.5)
Functional GI	13	11	—	2	1	4.1	75	0/1	4.4 (2.5-7.7)
Idiopathic pain	11	8	2	2	—	4.2	66	1/4	2.0 (1.4-2.8)
Tinnitus	2	2	—	—	—	4.0	50	—	—
Chronic fatigue	2	—	2	—	—	4.0	50	—	—
All	**94**	**56**	**17**	**28**	**3**	**4.8**	**67**	**4/22**	**3.4 (2.6-4.3)**

TCA denotes tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; OR, odds ratio; CI, confidence interval; and GI, gastrointestinal.
*Numbers may exceed total because several studies had more than one antidepressant arm.
†Quality scores could range from 0 (poor) to 8 (excellent).
‡Numerator = number of studies in which symptom response to antidepressant correlated with depression response; denominator = total number of studies in which this correlation was assessed.
§Effect magnitude represents the summary odds ratio (using a random effects model) for benefit (dichotomous outcome of "improvement") derived from antidepressant treatment compared with placebo.

assessed using a quality assessment instrument developed and validated by Jadad and colleagues.[11] This instrument uses the following criteria: appropriate randomization and blinding, description of withdrawals, dropouts, statistical analysis, inclusion criteria, exclusion criteria, and the method used to assess adverse effects. The score ranges from 0 (poor) to 8 (excellent). Scores were assessed independently in duplicate by 4 of the investigators (P.G.O., G.T., E.B., J.J). Agreement was substantial (intraclass correlation coefficient >0.70 for all pairs of raters). Disagreements were arbitrated by consensus, and when consensus could not be achieved discordant scores were averaged and rounded to the higher whole number.

Data Abstracted

We abstracted information about the type of syndrome, setting, treatment (including dosage and duration of treatment, active or placebo control, and follow-up), demographics and number of participants enrolled, assessment of comorbid psychiatric disease (and if so, the instrument used), adverse effects, outcomes, and statistical analysis of results reported.

Meta-Analysis

We performed a meta-analysis on only the placebo-controlled studies from which data was extractable. We used the random effects model for combining data proposed by DerSimonian and Laird,[12] and the tests used by Begg and Mazumdar[13] and Egger and coworkers[14] for the assessment of publication bias in placebo-controlled studies. To assess the number of studies necessary to render the effect size insignificant, we used the "file drawer" method of Rosenthal.[15]

RESULTS

There were 392 articles identified by our search strategy of which 94 were included for review. Reasons for exclusion were as follows: review articles (115), observational studies (61), lack of placebo or nonantidepressant controls (50), neuropathic pain (diabetes, postherpetic or traumatic neuralgia, cancer or degenerative joint pain; 24 studies), pediatric patient population (21), duplicate reporting of data (20), and letters (7).

The 6 symptom syndromes in the included studies were: headache (migraine, tension, mixed); fibromyalgia; functional gastrointestinal (GI) disorders (irritable bowel syndrome, functional dyspepsia, idiopathic esophageal contraction abnormalities); idiopathic pain (psychogenic, facial, chest, musculoskeletal, pelvic); tinnitus; and chronic fatigue. The number of trials for each individual syndrome and the general characteristics of these studies are presented in Table 1. The only symptom in our search for which studies of antidepressants could not be found was dyspnea.

Characteristics of Included Studies

We included 94 studies that involved a total of 6595 patients.[1,16-109] In describing all trials as a whole, the median number of patients in each included trial was 50 (range 7 to 698), and the majority of the patients in the trials were women (76% pooled from all the trials, ranging from 42% in the tinnitus trials to 92% in the fibromyalgia trials). Most of the trials were undertaken in referral clinics (87%) rather than a primary care setting (12%). Eighty-two percent of the trials were done after 1980, and most were done in Europe (only 28% were done in the United States). Almost half of the trials were industry sponsored (45%).

The duration of the trials was short (median = 9 weeks) relative to the chronicity of the symptoms (74% of the trial populations had a median duration of symptoms greater than 3 years), and the dropout rate was high — 40% of the trials had dropout rates greater than 20% (ranging from 18% in functional GI trials to 67% in idiopathic pain trials).

Quality of Studies

Overall, the quality of the studies was fair. The principal characteristics responsible for the deficits in quality were appropriateness of randomization (16% of the trials), appropriateness of blinding (35%), and description of the assessment of adverse effects (37%). The descriptions of withdrawals and dropouts (71%), statistical analysis (79%), and inclusion criteria (78%) were considerably better. Intention-to-treat analysis, an item that was not included in the quality assessment tool, was either explicitly stated (or implicitly done when there were no withdrawals) in only 13 of the 55 (24%) parallel-design placebo-controlled studies.

The overall mean quality score was 4.8, ranging from 4.0 in chronic fatigue and tinnitus studies (only 2 studies each), to 5.8 in fibromyalgia studies (Table 2).

Specific Symptom Syndromes

The details of the individual syndromes by antidepressants used, proportion of studies showing benefit, quality scores, correlation with effect on depression, and effect size are presented in Table 2. The dosing and titration of antidepressants in these trials were variable and dependent on the agent used. Generally, doses were titrated, and therapeutic doses were lower than those used in treating depression, except in SSRI trials where the antidepressant doses were typically used without titration.

Chronic Headache. The differences in relative efficacy and general study characteristics were negligible between trials of migraine headache compared with trials of tension headache. We grouped all of these trials under the general term of chronic headache.

There were 50 headache trials of which 22 studied antiserotonin antidepressants (pizotifen, mianserin, and ritanserin);[16-36,65] 19 studied a tricyclic antidepressant (TCA);[37-44,50-60] 7 studied an SSRI;[45-49] one studied both a TCA and an antiserotonin antidepressant,[61] and one studied both a TCA and an SSRI.[62]

Antiserotonin agents are not available in the United States and have been used predominantly in Europe for migraine prophylaxis and depression. They have been demonstrated to have antidepressive effects in placebo-controlled studies.[110,111] Although all of the 7 antiserotonin studies (all pizotifen)[26-28,31-34] that used active nonantidepressive controls (calcium channel blockers, metoprolol, and naproxen) did not find pizotifen to be more efficacious than other treatments, all 16 of the antiserotonin placebo-controlled trials (12 pizotifen, 3 mianserin, 1 ritanserin)[16-25,29,30,35,36,61,65] demonstrated superior efficacy to placebo.

Fifteen of the 21 randomized trials evaluating tricyclic therapy in headache prophylaxis demonstrated improvement in headache symptoms. Thirteen of 16 placebo-controlled trials[37,38,41,44,51,52,54,55,57,59-62] demonstrated some improvement in one of the following outcomes: decreased headache frequency, duration or severity of headache,[37,38,41,44,54,59,60-62] global improvement,[51,55,57] or decreased analgesic use.[54] In the 2 studies comparing tricyclics with nonantidepressant controls, one study[39] showed a tricyclic antidepressant to be superior to propranolol, biofeedback, or abortive therapy given as required. The other[40] showed no benefit of amitriptyline compared with dihydroergotamine. A major limitation of this group of tricyclic studies, however, is that in 10 out of the 21 more than 20% of the randomized patients withdrew from the study.[37,39-44,52,58,59]

Of the 8 placebo-controlled trials of SSRIs for headache, 5 reported efficacy.[45,48,49,62,63] The single study that demonstrated efficacy and controlled for depression showed an independent effect of fluoxetine on a headache index score.[48] However, in this study as with the other SSRI studies on migraine, there was a significant withdrawal rate, 14 out of 32 randomized participants.

Fibromyalgia. For fibromyalgia, there were 18 trials (16 were placebo-controlled) of which 11 studied TCAs,[66-76] 3 studied SSRIs,[78-80] 2 studied a methylator (S-adenosylmethionine [SAMe]),[81,82] one studied an antiserotonin agent,[83] and one examined a TCA, an SSRI, and a combination of both, against placebo.[77]

Of the 12 TCA trials (9 using amitriptyline),[66-73,77] all but one[67] showed benefit for one or more of the following outcomes: pain,[66,68,70-77] morning stiffness,[66,70] global improvement,[66,68,69,76,77] sleep,[66,68,70,76,77] fatigue,[68,70,75,76,77] tender point score (a score based on the number and severity of tender points),[70,73-75] and functional symptoms.[71,76,77] One study compared 2 TCAs, clomipramine and maprotiline, in a placebo-controlled crossover design and showed benefit for both but also showed a patient preference for maprotiline.[74]

There were 4 studies of SSRIs,[77-80] of which one was against a nonantidepressant control.[79] Two of the studies (both fluoxetine)[77,79] demonstrated benefit for pain, functional status,[77] global well-being,[77] sleep,[77] morning stiffness,[79] and tender points.[79] The one study that compared fluoxetine with amitriptyline or the combination of the 2 drugs, showed that both agents were effective and that the combination was most effective.[77]

SAMe is a naturally occurring molecule that is involved in methylation reactions within catecholinergic and serotoninergic neurons and has been demonstrated to be efficacious for the treatment of depression.[112] Both studies of SAMe in fibromyalgia demonstrated improvement in pain,[81,82] and one also demonstrated improvement in trigger points[82] while the other also demonstrated improvement in morning stiffness and fatigue.[81]

The single study of the antiserotonin agent ritanserin demonstrated improvement in headache and feeling refreshed in the morning but no improvement in body pain, fatigue, sleep, morning stiffness, anxiety, and tender points.[83]

Functional Gastrointestinal Disorders. For functional GI disorders there were 13 trials (12 placebo-controlled) of which 10 studied a TCA (8 in irritable bowel syndrome and 2 in functional dyspepsia);[84-93] one trial studied the antiserotonin antidepressant mianserin (in both functional dyspepsia and irritable bowel syndrome);[95] one trial studied both mianserin and a TCA for functional dyspepsia;[94] and one trial studied trazodone in idiopathic esophageal contraction abnormalities.[96]

Of the 11 placebo-controlled studies of irritable bowel syndrome or functional dyspepsia, 10 studied TCAs (trimipramine,[87-89] desipramine,[85,86] amitriptyline,[84,90,91] doxepin,[92] and clomipramine[94]) and 2 studied mianserin.[94,95] All showed benefit for at least one of the following outcomes: functional status,[86,95] stool frequency,[85] symptom scores,[84,87,88] pain[85,90,94,95] and rectosigmoid contractions.[85] Thus, every study except one[93] of an antidepressant for irritable bowel syndrome or functional dyspepsia showed some improvement associated with the antidepressant. The single study of patients with symptomatic but unexplained esophageal contraction abnormalities showed a benefit of trazodone over placebo in improving global well-being.[96]

Idiopathic Pain. For the category of idiopathic pain, we empirically grouped studies that evaluated symptoms or symptom syndromes that did not have accepted diagnostic criteria, were described as idiopathic or psychogenic, or described unexplained symptoms arising from a general anatomical area as opposed to an organ system. This included low back pain, facial pain, pelvic pain, chest pain, temporomandibular joint pain, and idiopathic pain.

Eleven studies were included in this group.[1,94,97-105] Seven examined TCAs, most of which were for nonspecific musculoskeletal symptoms;[1,97-102] 1 studied the antiserotonin antagonist mianserin for musculoskeletal symptoms;[103] one studied both a TCA and an antiserotonin agent for multiple idiopathic syndromes;[94] and 2 studied SSRIs (zimelidine for musculoskeletal symptoms and sertraline for pelvic pain).[104,105]

Of the 8 TCA trials, all were placebo controlled, and 6 showed improvement in pain,[1,97,98,100] analgesic use,[98] global well-being,[99] or functional status.[101] One of the studies compared a TCA with an antiserotonin agent (mianserin) and showed no benefit for either.[94]

Both studies of mianserin showed no benefit for idiopathic pain.[94,103] Of the 2 placebo-controlled SSRI studies, efficacy was shown for zimelidine in idiopathic musculoskeletal pain[104] but not for sertraline for chronic pelvic pain.[105]

Tinnitus. There were 2 randomized placebo-controlled trials of a TCA for chronic tinnitus.[106,107] The better quality study[107] showed improvement in disability and tinnitus loudness with nortriptyline, while a study of trimipramine showed no benefit.[106]

Chronic Fatigue. There are 2 randomized placebo-controlled trials of antidepressants for chronic fatigue syndrome.[108,109] One trial with fluoxetine showed no benefit,[109] while the other trial[109] using phenelzine showed improvement in multiple symptoms, illness severity, and mood.

Antidepressant Efficacy and Depression Response

Depression was assessed in 49 (52%) of the studies, of which 90% used validated tools such as the Beck Depression Inventory, Hamilton Anxiety and Depression index, Montgomery depression scale, Zung, syptom checklist 90, Minnesota Multiphasic Personality Inventory, and the Center for Epidemiologic Study depression inventory. However, an analysis of association between depression and response to treatment was performed in only 24 studies (49% of studies that assessed for depression, 25% of all studies).[1,35-38,41,42,48,49,54,58,60,67,77,78,81,82,84,94,96,98,100,107,108] Of the 24 studies that assessed for an association, only 8 (33%) demonstrated a correlation between physical symptom response and depressive response;[37,38,49,54,60,82,84,94] and only 3 reported any correlation statistics.[38,82,94] Thus, though there appears to be little correlation of effect with depression response in the few studies where it was assessed, it is difficult to draw any conclusions on this relationship given the quality of the analyses and the small numbers of participants in the trials (Table 2).

Antidepressant Efficacy and Study Characteristics

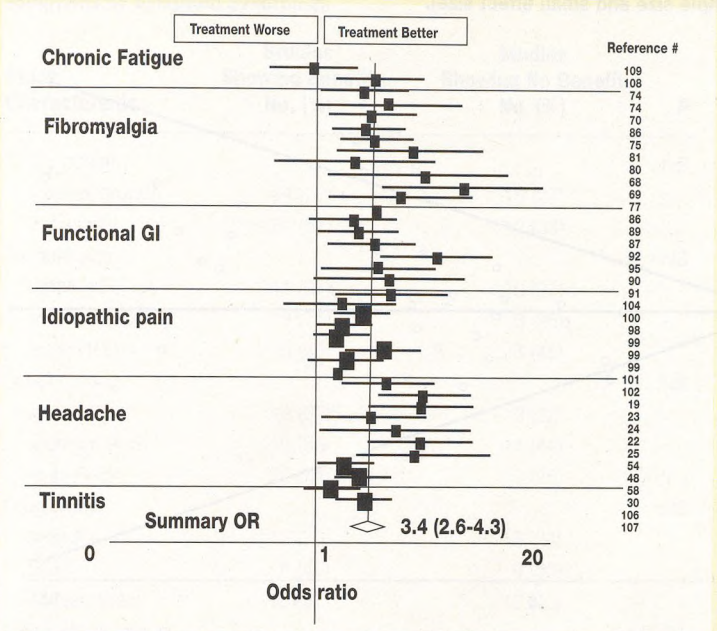
A comparison of trials that showed a benefit with those that did not is displayed in Table 3. The following study characteristics were not associated with a greater likelihood of showing benefit: parallel design, sample size, quality rating, industry sponsorship, or country of study. However, drug class and comparison treatment (placebo or active nonantidepressant control) were associated with trial outcome. Studies with a placebo control were more likely than active nonantidepressant controls to show benefit, though this does indirectly support the benefit associated with antidepressants, since the active controls were usually medications known to be therapeutic. Studies of tricyclic antidepressants were more likely than studies of SSRIs or antiserotonin agents to have a beneficial outcome ($P = .02$).

Meta-Analysis

We synthesized the quantitative data from each placebo-controlled study in which data were extractable (48 studies, 49%). Data were extractable in one or both of 2 forms: a dichotomous outcome of improvement and continuous outcomes from which a standardized effect size could be calculated (standardized mean difference between placebo and active treatment). For the dichotomous outcome of

FIGURE 1

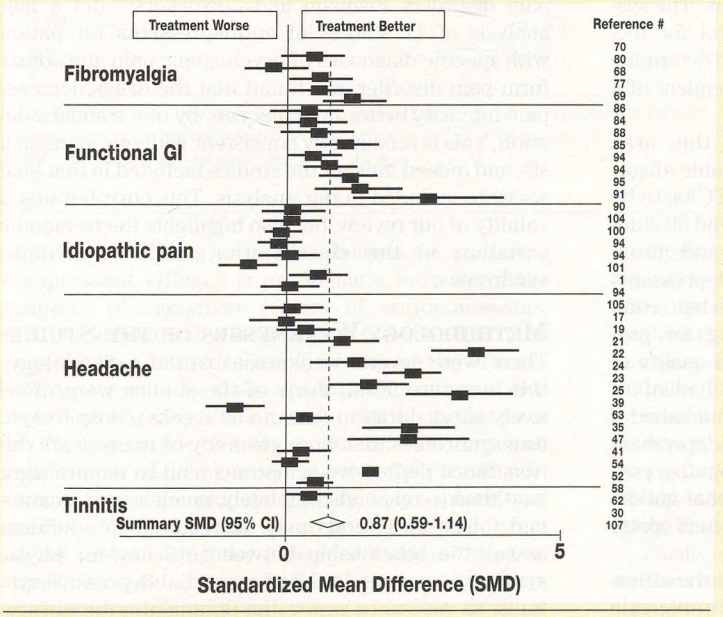
A forest plot with summary odds ratio on dichotomous outcomes in placebo-controlled trials.



OR denotes odds ratio; GI, gastrointestinal disorders.

FIGURE 2

A forest plot with summary standardized mean difference on continuous outcomes in placebo-controlled trials.



GI denotes gastrointestinal disorders.

improvement we used improvement in any of the following outcomes: global assessment (patient or physician), summary symptom index scores (headache index or fibromyalgia symptom score, for example), or pain severity scale scores.

The pooled odds ratio (OR) for the dichotomous outcome of improvement was 3.43 (95% confidence interval [CI], 2.60-4.52; $P = .04$; Figure 1), while the pooled standardized mean difference was 0.87 (95% CI, 0.59-1.14; $P < .001$; Figure 2). The effect size was not homogeneous across all studies, and the treatment of unexplained symptoms with antidepressants was associated with a greater than 3-fold higher likelihood of improvement. For continuous outcomes, antidepressant therapy was associated with almost a full standard deviation improvement. This is considered a large effect size.[112] The absolute percentage difference in improvement between the antidepressant and placebo arms was 32% (95% CI, 15%-48%), yielding a number needed to treat of 3.1 (95% CI, 2.1-6.6) before improving one patient's symptoms.

Publication Bias

An assessment for publication bias against small studies with no or a small effect was determined by pooling all the effect sizes and standard errors from the placebo-controlled studies that had extractable data. There was evidence for significant publication bias ($P < .001$; Figure 3).

Sensitivity Analysis

Using meta-regression, we controlled for the following variables: drug class, withdrawal rates (>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.

Using the assumptions of no effect (OR = 1.0), sample size equal to 50 (the median for all 96 trials), and a variance of 0.57 (the mean variance of the effect size among all the trials), it would take 628 trials in a random effects model to make the summary effect size statistically insignificant.

DISCUSSION

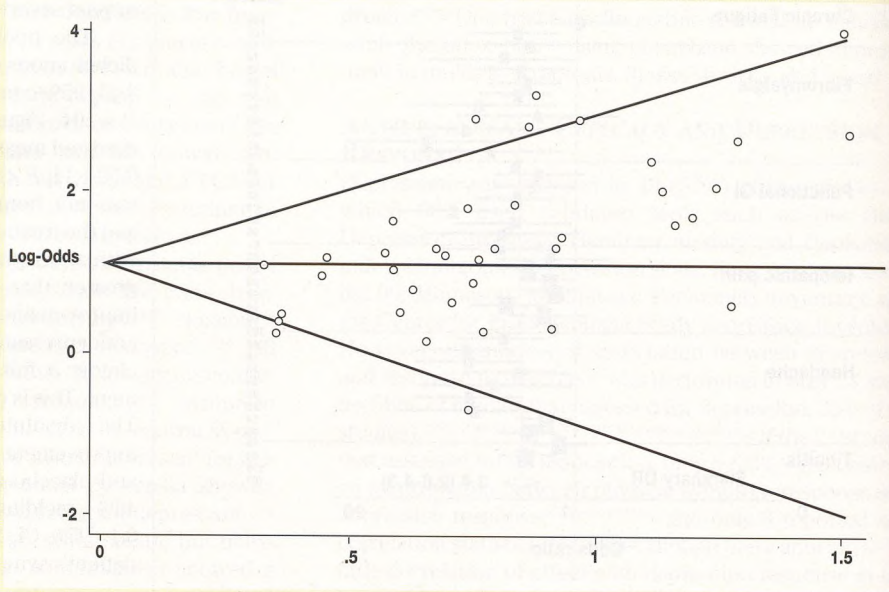
Antidepressants proved efficacious in more

than two thirds of the studies we reviewed. Patients receiving antidepressants were more than 3 times as likely to experience symptomatic improvement than patients receiving placebo. This benefit was consistent across 6 different symptom syndromes. Although there was considerable variability in the methodologic quality of the studies, the beneficial effect demonstrated was similar in low-, medium-, and high-quality studies.

When quantitative synthesis was possible, the consistency of benefit across symptom syndromes suggests some real effect of antidepressants. However, it is not clear from this data whether such therapy is treating underlying subclinical psychiatric disorders, acting merely as a symptom or pain-threshold modifier, or treating a disorder that has a common neurotransmitter pathology. Studies that assessed for comorbid psychiatric disease were in the minority, and of the few that did, there was little correlation between efficacy and depressive symptoms. The systematic assessment of depression and control for this effect was inadequately done in these studies to determine whether the efficacy demonstrated was independent of a depression response.

FIGURE 3

Funnel plot of effect size by standard error of effect size of placebo-controlled trials, demonstrating publication bias by the paucity of trials in the right lower quadrant of the graph (ie, trials with low sample size and small effect size).



Earlier reviews and meta-analyses in this area focused predominantly on well-defined organic disorders and found antidepressants, particularly TCAs, to be efficacious.[7-9] Onghena and colleagues[7] reviewed 39 studies on the analgesic effect of antidepressants and chronic nonmalignant pain. They found that antidepressants have significant efficacy in reducing pain when compared with placebo, even when controlling for psychogenic etiology (though the frequency and quality of controlling for psychiatric disorders in the individual trials was limited). McQuay and coworkers[8] published a systematic review of the literature on antidepressant therapy for neuropathic pain (diabetic neuropathy, postherpetic neuralgia, central pain) and found that antidepressants are effective in alleviating chronic neuropathic pain.

Jung and colleagues[9] looked specifically at the efficacy of SSRIs in the management of selected chronic pain syndromes (diabetic neuropathy, headaches, fibromyalgia, mixed psychogenic, or organic chronic pain) and showed there was benefit for mixed chronic pain but unclear benefit for headaches, diabetic neuropathy, or fibromyalgia.

In the only review of antidepressants and nonorganic pain disorders Fishbain and coworkers[114] did a meta-analysis of 11 studies of antidepressants for patients with specific diagnoses of psychogenic pain and somatoform pain disorder and found that the drugs decreased pain intensity better than placebo, by one standard deviation. This is remarkably consistent with our meta-analysis, and indeed most of the studies included in that analysis were included in our analysis. This corroborates the validity of our review, but also highlights the tremendous variation in the classification of these symptom syndromes.

Methodology Weaknesses of the Studies

There were several weaknesses to the methodology of this literature. First, many of the studies were of relatively short duration (mean = 9 weeks), despite symptom syndromes that were generally of many years duration. Since depressive symptoms tend to require significant time to respond completely, much longer treatment and follow-up periods may be required to confidently assess the relationship between efficacy for physical symptoms and resolution of comorbid depressive symptoms, as well as to assess the optimal duration of treatment. Second, a crossover design was used in one third

TABLE 3

Comparison of Characteristics and Benefit of 94 Randomized Trials Evaluating the Efficacy of Antidepressants in Patients with Idiopathic Symptoms or Symptom Syndromes

Study Characteristic	Studies Showing Benefit No. (%)	Studies Showing No Benefit No. (%)	*P*
Study design			NS
Parallel groups	44 (73)	16 (27)	
Crossover	24 (67)	12 (33)	
Sample size			NS
small (<50)	41 (67)	20 (33)	
medium (50-99)	18 (75)	6 (25)	
large (100+)	6 (55)	5 (45)	
Quality rating			NS
low (0-3)	19 (68)	9 (32)	
medium (4-5)	19 (56)	14 (44)	
high (6-8)	26 (74)	9 (26)	
Drug class			.02
tricyclic	42 (76)	13 (24)	
SSRI	8 (47)	9 (53)	
antiserotonin	16 (57)	12 (43)	
Comparison group			<.0001
placebo	67 (76)	21 (24)	
alternative drug	9 (32)	19 (68)	
Industry-sponsored			NS
yes	29 (69)	13 (31)	
no	34 (64)	19 (36)	
Country of study			NS
United States	19 (70)	8 (30)	
other	47 (59)	23 (41)	

Note: Number of trials exceeds 94 because several studies either used multiple arms with different agents, or involved more than one symptom or symptom syndrome.
SSRI denotes selective serotonin reuptake inhibitor.

of the studies. Using crossover designs for assessing antidepressant efficacy is problematic because of the possibility of carryover effects of antidepressants. Third, withdrawal rates were high in these studies, indicating possible limited generalizability of the efficacy of antidepressants for these syndromes because of side effects. Fourth, double-blind trials with drugs that have side effects may not be truly double blinded, and such potential bias might overestimate an effect for antidepressants relative to placebo. Finally, only a minority of placebo-controlled trials used an intention-to-treat analysis, undermining the power of randomization to minimize bias; thus, it is possible there is a significant overestimation of the effect size in a majority of these studies.

LIMITATIONS

There are several limitations to our systematic review. First, other sources of unpublished studies (eg, pharmaceutical companies) and non-English language literature not included in this review might alter the cumulative evidence we found. However, after repeating our search method including non-English literature there were only 20 additional references, of which a significant proportion were unlikely to meet our inclusion criteria. There was evidence of publication bias, meaning that it is likely there were unpublished studies that showed no efficacy. This is not surprising given the negative stigma associated with unexplained symptom syndromes in the medical community, making it difficult to publish any data in this area, especially data demonstrating no effect. Thus, our meta-analysis of effect size may be an overestimate of the true effect. However, our sensitivity analysis indicates there would have to be more than 600 negative studies to counteract the summary effect found in this review, so any of the limitations involving possible missing literature would likely have only a small impact on the summary effect size in this meta-analysis.

Second, we did not perform blinded review of quality assessment. Blinded review has been demonstrated to produce lower and more consistent scores than open review.[11] Thus, our assessment of study quality may have overestimated the true quality of the evidence. The quality of the studies was not associated with effect size, making this issue less important as a potential bias in our estimate of the effect size.

Third, qualitative tallying can be misleading when describing the evidence, because the magnitude of the effect is not taken into account.[115] Although such a method can be provocative, interpretation needs to be considered with caution, since the assessment of benefit was based on any outcome benefit. We felt that "vote counting" was still a useful way of describing the evidence, especially when describing this data in the context of the factors which might bias the results (study size, design, quality, country of study, and so forth; Table 3).

Finally, on the dichotomous outcome of improvement, we used any of 3 outcomes as a measure. Using multiple outcomes can increase the chances of a positive finding, and our summary odds ratio may overestimate the effect

size. This was a systematic problem with this literature that did not regularly define primary outcome variables.

CONCLUSIONS

Though pooled quantitative data indicate substantial beneficial effect from antidepressants in multiple unexplained symptoms, 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.

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 standardized measures and track depressive as well as physical symptom effects; be of longer duration; test newer antidepressant classes, especially SSRIs (ie, determine whether all classes are equally effective); adhere to methodologic criteria of high-quality studies; and be located in community-based settings.

RECOMMENDATIONS FOR CLINICAL PRACTICE

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.

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