

The Effect of Antidepressant Treatment on Chronic Back Pain

A Meta-analysis

Stephen M. Salerno, MD, MPH; Robert Browning, MD; Jeffrey L. Jackson, MD, MPH

Background: Back pain is one of the most common problems in primary care. Antidepressant medication is often prescribed, especially for chronic back discomfort, to alleviate pain and restore the patient's ability to conduct activities of daily living.

Objective: To assess the efficacy of antidepressants in treating back pain in adults.

Methods: We searched the MEDLINE (1966-2000), PsycLit, Cinhal, EMBASE, AIDSLINE, HealthSTAR, CANCERLIT, the Cochrane Library (clinical trials registry and the Database of Systematic Reviews), Micromedex, and Federal Research in Progress databases and references of reviewed articles. Included articles were written in English and dealt with randomized placebo-controlled trials of antidepressant medication use among adults with chronic back pain. Two reviewers abstracted data independently. Two continuous outcomes, change in back pain severity and ability to perform activities of daily living, were measured. Study quality was assessed

with the methods used by Jadad and colleagues, and data were synthesized using a random-effects model.

Results: Nine randomized controlled trials with 10 treatment arms and 504 patients were included. Seven treatment arms included patients with major depression. Patients had chronic back pain, averaging 10.4 years. Patients treated with antidepressants were more likely to improve in pain severity than those taking placebo (standardized mean difference, 0.41; 95% confidence interval, 0.22-0.61) but not in activities of daily living (standardized mean difference, 0.24; 95% confidence interval, -0.21-0.69). Patients treated with antidepressants experienced more adverse effects (22% vs 14%, $P=.01$) than those receiving placebo.

Conclusion: Antidepressants are more effective than placebo in reducing pain severity but not functional status in chronic back pain.

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From the Departments of Medicine, Uniformed Services University of the Health Sciences (Drs Salerno and Jackson), Walter Reed Army Medical Center (Drs Salerno and Jackson), and National Naval Medical Center (Dr Browning), Bethesda, Md. Dr Salerno is now with the Tripler Army Medical Center, Department of Medicine, Tripler Army Medical Center, Hawaii.

BACK AND NECK pain are common, accounting for 200 000 office visits (1.8%) in the United States per year.¹ It is estimated that up to 50% of working adults experience back pain every year,² and 70% of all adults experience it at some time in their lives.³ Most episodes are self-limited, with 90% of patients improving within 3 months.⁴

Although most patients with back pain return to full activity following their acute injury, patients with persistent back discomfort may incur serious disability and consume substantial health care resources. Data from the National Council on Compensation Insurance show that 20% of claimants who had back pain for more than 4 months account for 60% of the back pain health care costs.⁵ Despite the profound impact chronic back pain has on patients and the health care sys-

tem, relatively little research has been performed on its treatment. Suggested beneficial therapies for prolonged back pain have included long-term use of narcotics,⁶ transcutaneous electrical nerve stimulation,⁷ acupuncture,⁸ nonsteroidal anti-inflammatory drugs,⁹ and facet joint injection.¹⁰

Antidepressant medications have also been suggested as a potentially beneficial therapy in treating back pain.¹¹⁻¹⁵ Some authors believe that antidepressant medications, particularly serotonergic antidepressants, have analgesic effects independent of their antidepressant properties^{16,17} and are especially effective in neuropathic pain.¹⁸ However, other authors,¹⁸⁻²² including the Agency for Health Care Quality and Research in their 1994 practice guideline on back pain, do not believe the current evidence supports using antidepressants in back pain treatment. Despite

conflicting literature, there is evidence that physicians do prescribe antidepressants for patients with back pain. Primary care physicians prescribe antidepressants in the setting of back discomfort at 2% to 23% of visits.^{23,24} Because the use of antidepressants in back pain therapy remains controversial, we conducted a meta-analysis of the English-language literature.

METHODS

For this review, we searched MEDLINE (1966-August 2000), PsycLit (1987-August 2000), Cinhal (1982-2000), EMBASE (1974-August 2000), AIDSLINE, HealthSTAR, CancerLIT, and Micromedex using *antidepressants* as the text word and keyword (all languages). An additional search was performed using the medical subject heading term *antidepressive agents* combined with the text words *back pain*, *low back pain*, *pain*, *spasm*, and *clinical trial*. We used the Cochrane Library, searching the clinical trials registry for randomized trials, and the Cochrane Database of Systematic Reviews for systematic reviews. A search of the Federal Research in Progress database was conducted to identify unpublished literature. We also searched the references of reviewed articles for additional articles missed by the computerized database search. Studies were screened for inclusion through review of the abstract or the published article if the abstract was unclear. We included articles that had the following characteristics: patients having low back discomfort for 2 or more months, randomization, placebo control, at least one group receiving an antidepressant medication, and measurable outcomes reported.

Included study quality was assessed using a 6-item instrument developed and validated by Jadad et al.²⁵ The 6 items in this scale include (1) description of randomization, (2) adequacy of blinding, (3) description of withdrawals and dropouts, (4) appropriateness of statistical analysis, (5) description of inclusion and exclusion criteria, (6) and method for assessing adverse treatment effects. Two reviewers

(S.M.S. and J.L.J.) assessed study quality independently with substantial interrater agreement ($\kappa=0.89$). Disagreements were arbitrated by consensus.

Abstracted data included setting, country of origin, treatment characteristics (dose, duration, follow-up), demographics, number of patients enrolled, follow-up losses, adverse effects, and outcomes. Outcomes were extracted as either dichotomous or continuous variables (or both), depending on how they were reported in the studies.

All analyses were performed using Stata statistical software (version 7.0; Stata Corp, College Station, Tex). Assessment for publication bias was performed using the methods of Egger et al,²⁶ and heterogeneity was assessed visually with Galbraith plots²⁷ and Q (χ^2) statistics using the methods of Mantel-Haenszel. The random-effects model of DerSimonian and Laird²⁸ was used to calculate summary standardized mean differences. Analysis of outcomes involved comparing standardized differences in means between control and treatment groups. Mean outcome scores for the 2 major outcomes of pain severity and activities of daily living for the placebo and treatment groups were standardized by dividing the scores by their SD. The difference between these standardized outcome scores was calculated for each study and analyzed. This approach is especially appropriate when studies measure the same concept but use a variety of continuous scales. By standardization, the study results were transformed to a common scale (SD units) that facilitates pooling. This method of evaluating outcomes is also known as *effect size*. An effect size of 0.2 is considered small, 0.5 is moderate, and greater than 0.8 is large.²⁹

Several measures of the sensitivity of the meta-analysis results to various assumptions were conducted. We tested the relative influence of each individual study on our results by sequentially dropping individual treatment arms and calculating summary measures. We also explored several sources of heterogeneity, including year and country of publication, study quality scores, and antidepressant type using meta-regression.

RESULTS

Our literature search produced 315 articles, 23 of which seemed to be potential candidates for inclusion in the analysis. Of these 23, a total of 13 were excluded. Four were excluded because they were written in languages other than English,³⁰⁻³³ 3 were review articles,^{15,21,22} and 3 were case reports.³⁴⁻³⁶ One article did not separate patients with back pain from patients with other chronic pain syndromes,³⁷ and another article did not report the level of baseline patient pain or the number of subjects in the treatment and placebo arms.³⁸ A final article was excluded because it dealt exclusively with patients with acute back pain and used an active acetaminophen arm rather than a control.³⁹ Of the 10 articles that met inclusion criteria, 2 duplicated results from a single trial,^{40,41} producing a final number of 9 studies (**Table 1**). One study included 2 active treatment arms, which were considered separately during the analysis.⁴²

The 9 randomized controlled trials were of moderate quality, with a mean \pm SD quality score of 5.1 ± 2.2 (median, 6; range, 2-8). Although all studies were randomized and placebo controlled, there were a number of specific quality problems, including inadequate description of the method of randomization method in 5,^{41,45,47-49} incomplete description of blinding techniques in 2,^{47,49} excessive (>10%) withdrawal of participants in 5,^{40,45-48} no intention-to-treat analysis in 5,^{40,46-49} and no sample size calculations in most.^{40,45-49} None of the studies directly tested patients for the effectiveness of blinding, but 7 of the studies had more adverse effects in the treatment than placebo groups, suggesting failure to maintain blinding (**Table 2**). Three studies had negligible descriptions of adverse events.^{40,43,49}

Multiple types and doses of antidepressants were used in the reviewed studies. Only 2 studies used newer selective serotonin reuptake inhibitors.^{42,43} The remainder used older heterocyclic or tricyclic compounds. Some studies used antidepressants with serotonergic properties such as trazodone,⁴⁸ whereas other articles used compounds with

Table 1. Characteristics of Included Studies

Source, y (Country)	Syndrome and Comments	Drug Dosage	Trial Length, wk	Quality Score (0-8)	Quality Problems*
Dickens et al, ⁴³ 2000 (England)	Low back pain >6 months, coexisting clinical depression, patient- and physician-rated outcomes	Paroxetine, 20 mg/d (n = 44), vs placebo (n = 48)	8	7	Inadequate discussion of adverse events
Atkinson et al, ⁴² 1999 (United States)	Chronic daily low back pain >6 months, no current mood disorder, patient- and physician-rated outcomes	Maprotiline, 150 mg every night (n = 33), vs paroxetine, 30 mg every night (n = 34), vs active placebo vs diphenhydramine, 37.5 mg every night (n = 36)	8	8	...
Atkinson et al, ⁴⁴ 1998 (United States)	Chronic daily low back pain >6 months, no current mood disorder, patient- and physician-rated outcomes	Nortriptyline, 100 mg every night (n = 38), vs placebo (n = 40)	8	8	...
Goodkin et al, ⁴⁸ 1990 (United States)	Chronic low back pain >12 months, patients with and without depression, patient- and physician-rated outcomes	Trazodone, 100 mg 4 times daily (n = 22), vs placebo (n = 20)	6	6	Inadequate description of randomization, no sample size calculations, >10% withdrawals, no intention-to-treat analysis
Hameroff et al, ⁴⁹ 1984 (United States)	Chronic cervical and/or lumbar spine pain >2 months, coexisting clinical depression, patient-rated outcomes	Doxepin, 300 mg every night (n = 30), vs placebo (n = 30)	6	3	Inadequate description of randomization, no sample size calculations, blinding procedure not fully described, inadequate discussion of adverse events, no intention-to-treat analysis
Ward et al, ⁴¹ 1984 (United States)	Chronic low back pain >6 months, patients with depression, physician- and patient-rated outcomes	Desipramine, 3 mg/kg, vs doxepin, 3 mg/kg, vs placebo (n = 26); pre-post study with desipramine and doxepin patients compared with placebo run-in	4	2	Inadequate description of randomization, no sample size calculations, unknown number of patients in desipramine and doxepin arms, inadequate description of withdrawals and side effects, no intention-to-treat analysis
Alcoff et al, ⁴⁶ 1982 (United States)	Chronic low back pain >6 weeks, patients with and without depression, physician- and patient-rated findings	Oral imipramine, 150 mg every night (n = 28), vs placebo (n = 22)	8	6	No sample size calculations, >10% withdrawals, no intention-to-treat analysis, P values given without complete outcomes measures
Pheasant et al, ⁴⁵ 1983 (United States)	Chronic low back pain >1 year, patients with depression, physician- and patient-rated outcomes	Oral amitriptyline, 150 mg every night, vs atropine, 0.2 mg (n = 9, randomized, blind crossover study)	6	4	Inadequate description of randomization, no sample size calculations, >10% withdrawals, no intention-to-treat analysis
Jenkins et al, ⁴⁷ 1976 (England)	Acute and chronic low back pain, patients with and without depression, physician- and patient-rated outcomes	Oral imipramine, 25 mg 3 times daily (n = 23), vs placebo (n = 21)	4	3	Inadequate description of randomization, no sample size calculations, blinding procedure not fully described, >10% withdrawals, no intention-to-treat analysis

*Ellipses indicate not applicable.

mostly noradrenergic properties such as nortriptyline⁴⁴ or maprotiline.⁴² Some trials used antidepressants with mixed properties such as doxepin,^{40,49} amitriptyline,⁴⁵ and imipramine.^{46,47} The doses of antidepressants varied, but all studies used therapeutic doses typically effective in treating depression. All studies used antidepressants as ad-

juvant therapy and allowed patients to continue using other analgesics. Study duration ranged from 4 to 8 weeks, with an average length of 6.8 weeks.

All studies included patients with chronic low back pain, although one study⁴⁹ included patients with cervical back pain, and another study⁴⁷ included some patients

with acute back pain. The definition of chronic pain varied widely, with most studies^{40,42-45,48} defining chronic as pain lasting longer than 6 months. Two used more lenient inclusion criteria of roughly 2 or 3 months,^{46,49} 2 required pain lasting for more than a year,^{45,48} and 1 did not specify a definition of chronic pain.⁴⁷ The average duration of chronic pain for pa-

Table 2. Comparison of Adverse Effects Between Antidepressants (n = 287) and Placebo (n = 252)

Adverse Effect	Antidepressants, No. (%)	Placebo, No. (%)	P Value
Drowsiness	21 (7.3)	15 (6.0)	.61
Dry mouth	27 (9.4)	20 (7.9)	.55
Dizziness	19 (6.6)	15 (6.0)	.84
Constipation	13 (4.5)	7 (2.8)	.28
Sexual dysfunction	4 (1.4)	1 (0.4)	.23
Any	63 (22.0)	34 (13.5)	.01

Table 3. Standardized Mean Differences Between Treatment With Placebo and Antidepressants

Outcome	Standardized Mean Difference (95% Confidence Interval)	No. of Studies	Heterogeneity*	P Value	Publication Bias P Value†
Decrease in pain severity	0.41 (0.22-0.61)	10	10.47	.32	.35
Activities of daily living	0.24 (-0.21-0.69)	5	12.76	.01	.90

* χ^2 Test for heterogeneity; $P < .10$ indicates heterogeneity of effect size between studies.
†Egger test; $P < .10$ indicates bias against small, negative studies.

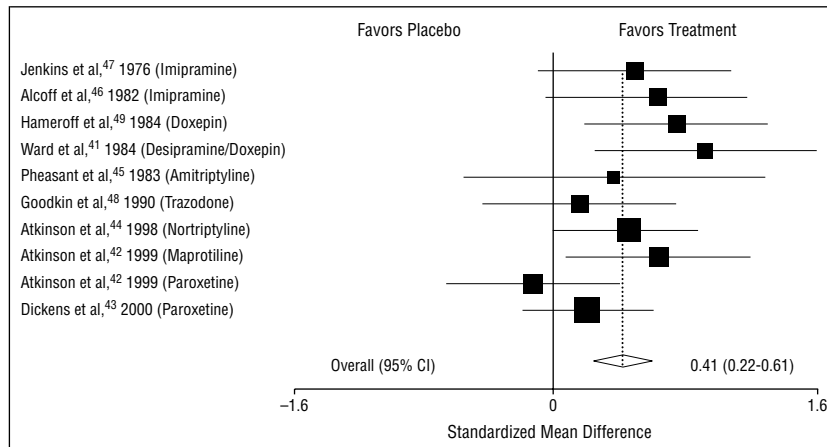


Figure 1. Standardized mean difference in pain improvement for patients undergoing antidepressant therapy. CI indicates confidence interval.

tients enrolled in the studies was 10.4 years. The studies varied regarding including patients with psychiatric diagnoses. Seven studies^{40,43,45-49} included patients with depression, whereas 2 studies^{42,44} specifically excluded them.

Exclusion criteria for the studies varied widely. The most common reason for exclusion was cardiac disease, which was mentioned in 5 studies.^{42,44-46,48} Other reasons cited for exclusion were urinary retention or renal disease,^{44,45,48} glaucoma,⁴⁵ pregnancy,^{45,48} chronic obstructive pulmonary disease,^{42,44} and a history of substance abuse.^{42,44} One study mentioned no specific exclusion criteria.⁴⁹

All of our studies had extractable continuous data, but we were unable to extract any consistent dichotomous outcomes. All of the outcomes were patient rated. Data were abstracted for 2 continuous variables: pain severity and effect on activities of daily living (**Table 3**). Pain severity was assessed in all studies. For pain assessment, 4 studies used simple visual analog scales, with scores varying from 10 to 100 points,^{43,47-49} 2 studies used the Descriptor Differential Scale,^{42,44} and 3 studies devised a numerical pain assessment scale not previously described.^{40,45,46} Activities of daily living were assessed in 5 studies. One study used the Oswestry Disability

Index,⁴³ 2 trials used the Sickness Impact Profile,^{44,48} 1 study used the Clinical Global Assessment Scale,⁴⁹ and 1 study used assessment scales not previously described in the literature.⁴⁵

When the 9 trials with 10 active treatment arms were synthesized using a random-effects model to assess changes in pain severity, patients treated with antidepressants experienced a small but significant improvement of 0.41 (95% confidence interval [CI], 0.22-0.61) in the standardized mean difference for pain severity (**Figure 1**). There was no statistical evidence of significant effect size heterogeneity ($\chi^2_9 = 10.47$, $P = .32$). Despite the lack of statistical heterogeneity, we still used a random-effects model because of the clinical diversity of antidepressants used and variation of inclusion criteria among the studies. There was no evidence of publication bias (Egger test, $P = .35$).

The 5 trials that measured global functional status showed a nonsignificant improvement of 0.24 (95% CI, -0.21-0.69) in the standardized mean difference (**Figure 2**). There was evidence of effect size heterogeneity ($\chi^2_4 = 12.76$, $P < .01$), but no evidence of publication bias (Egger test, $P = .90$).

Sensitivity analysis was performed to assess the effect of study quality, year of publication, country of publication, duration of treatment, and type of antidepressant. We also explored the effect of dropping individual studies from our meta-analysis. None of the parameters included in our sensitivity analysis significantly changed our results.

COMMENT

Our meta-analysis suggests that antidepressant therapy has a small but significant effect when compared with placebo in reducing chronic back pain. A similar small but nonsignificant trend in improving function in activities of daily living was noted.

There are several theoretical reasons why antidepressants might benefit patients with back discomfort. Antidepressants may ameliorate the patient's perception of pain by treating the underlying depres-

sion and improving sleep.⁵⁰ In 6 of 7 studies^{40,43,46,47-49} that included depressed patients and measured pre-trial and post-trial indexes of depression, improvement in depression was noted, reaching statistical significance in 4 studies.^{40,47-49}

Some authors hypothesize that there are similarities between neurotransmitter systems involved in depression and pain and that there are beneficial effects on pain separate from antidepressant effects.¹⁶ There is evidence that antidepressant therapy has significant benefits in other chronic pain syndromes such as fibromyalgia,⁵¹ irritable bowel disease,⁵² and migraine headaches.^{53,54} In fact, the 1997 guideline by the American Society of Anesthesiologists for the treatment of chronic pain recommends antidepressants as adjunct therapy for chronic pain syndromes.⁵⁵

The benefits of the small improvement in back pain severity must be weighed against the considerable amount of adverse effects observed. More than a fifth of patients undergoing antidepressant therapy experienced adverse reactions, compared with 14% of controls. Because adverse reactions were poorly reported in several studies, this likely underestimates the degree to which they occurred. The high doses of antidepressants used may explain the high incidence of adverse reactions. The most common adverse reactions included drowsiness, dry mouth, dizziness, and constipation.

There are a number of important limitations to our findings. First, nearly all the studies in our meta-analysis were underpowered, and the advantages to antidepressant therapy may be greater than stated. Although our meta-analysis comprised nearly 30 years of research, there were only 287 patients studied in the active treatment groups and 252 in the control groups. Our meta-analysis may not have been sufficiently powered to demonstrate a difference in activities of daily living. With only 5 studies measuring this outcome, our power was only 0.63 to show this degree of difference. Thus, it is possible that at least a modest effect on patient's activities of daily living was missed. Second,

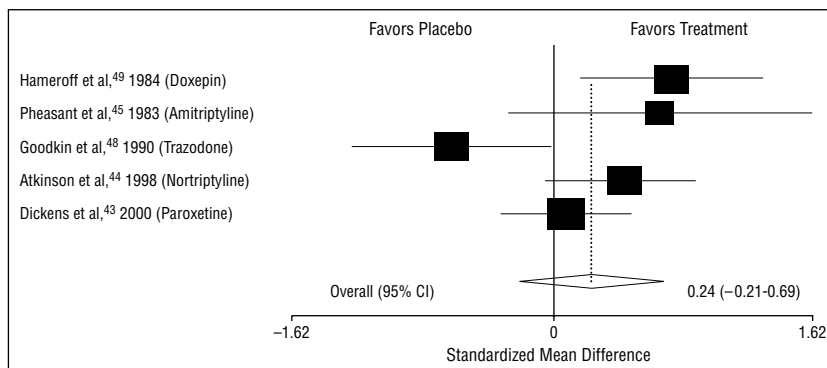


Figure 2. Standardized mean difference in improvement of activities of daily living for patients undergoing antidepressant therapy. CI indicates confidence interval.

our study cannot draw conclusions about antidepressants in the therapy of acute back pain. It is possible that antidepressant therapy may be useful in this setting. One trial testing amitriptyline against acetaminophen found amitriptyline to be the superior therapy.³¹ Cyclobenzaprine, a skeletal muscle relaxant, has also recently been shown to be effective therapy for acute back pain.⁵⁶ The chemical structure of cyclobenzaprine differs from tricyclic antidepressants by only one heterophile bond, which may explain why antidepressants could be effective in the short-term setting. Third, it is difficult to make a firm conclusion on whether antidepressant therapy will be effective in the treatment of low back pain in patients without depression. Only 2 studies^{42,44} specifically excluded patients with depression, making our analysis inappropriate to answer this question with certainty. However, both studies demonstrated a benefit in pain reduction using tricyclic antidepressants, and one showed no benefit with selective serotonin reuptake inhibitors. These results are similar to studies that include patients with depression. Few studies collected information on workers' compensation or litigation. One of the most important predictors of recovery from chronic back pain is lack of involvement in these processes.^{57,58} Given the chronic nature of these patients' symptoms, it is possible that many were involved in either workers' compensation or litigation, which would have confounded our results. Finally, many studies were of relatively low quality, most measured few outcomes,

and some used poorly validated instruments to assess functional status or pain. Better-quality studies using standardized, validated instruments are needed.

In conclusion, adjunct antidepressant therapy at doses therapeutic for depression is associated with a small but significant reduction in the severity of chronic back pain but not improvement in activities of daily living. Antidepressant therapy was associated with significantly more adverse effects than placebo. Larger, better-designed randomized control trials that weigh the benefits and adverse effects of antidepressant therapy are needed before the use of antidepressants can be routinely recommended as therapy for back pain in patients without depression.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting those of the US Department of the Army, the US Department of the Navy, or the US Department of Defense.

Corresponding author and reprints: Stephen M. Salerno, MD, MPH, Department of Medicine (ATTN: MCHK-DM), 1 Jarrett White Rd, Tripler Army Medical Center, HI 96859-5000 (e-mail: smsalerno@mindspring.com).

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