Do Antidepressant Medications Relieve Chronic Low Back Pain?

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Background. Antidepressant medications are commonly prescribed for patients with chronic low back pain. A literature synthesis was performed to determine whether antidepressants are more effective than placebos in decreasing pain, disability, depression, and analgesic medication use in such patients.

Methods. English-language journal articles were identified from MEDLINE and PsycLIT databases, bibliographies, and inquiries to researchers and drug companies. Articles were included if they reported data from placebo-controlled or drug comparison trials of antidepressants for patients with low back pain. Six articles met these criteria.

Results. Three studies compared the effects of antidepressants and placebos on pain; two found no difference and one found a trend toward superiority of imipramine for patient-rated symptoms but no difference in investigator ratings. Effects on functional disability were examined in three antidepressant–placebo comparisons; only one found the antidepressant to be more effective. Antidepressant effects of an antidepressant vs placebo were compared in three studies; none found a significant difference. Effects on analgesic medication use were compared in three studies; one found amitriptyline to be superior and the others found no difference. Serious methodologic flaws characterized all six studies, and insufficient reporting of data precluded meta-analysis.

Conclusions. The literature has not demonstrated that antidepressants are superior to placebos in improving low back pain or related problems. However, further randomized controlled trials are needed to determine whether antidepressants are useful for low back pain.

Key words. Antidepressive agents; backache; drug therapy; placebo study; literature review. (*J Fam Pract 1993; 37:545-553*)

Back pain is the second leading symptom prompting visits to physicians in the United States.[1] For women 35 to 64 years of age and men 25 to 64 years of age, back discomfort is the leading symptomatic reason for visiting office-based physicians.[2] Data from the National Ambulatory Medical Care Surveys (NAMCS) of 1977 and 1978 revealed that 61% of patients with back symptoms were treated by primary care physicians, and back symptoms ranked second among presenting complaints in the caseloads of internists and general and family practitioners.[1] Data from the 1985 NAMCS also indicate that the physicians who see the most patients with back pain are those in primary care specialties.[3] Similarly, population-based data from the second US National Health and Nutrition Examination Survey (NHANES–II), conducted between 1976 and 1980, indicated that by far the most common provider of care for low back pain was the general practitioner (59% of people with low back pain had sought care from a general practitioner).[4]

Patients with back pain are frequently treated with a variety of medications. Drugs were prescribed in 61.5% of physician office visits for back symptoms from 1977 to 1978.[1] Although data from that survey have not been published concerning the prevalence of prescription of antidepressant medications for patients with low back pain in primary care, it is known that tricyclic antidepressants were prescribed by primary care physicians in 2% of

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all office visits made by patients with low back pain in 1985.[3] Even though antidepressant medications have not been approved by the US Food and Drug Administration for the treatment of pain,[3] physicians prescribe antidepressant medications to patients with low back pain for a number of reasons. These include the belief that the antidepressant medication may have analgesic effects, belief that the patient may be depressed (a common concomitant of chronic pain), and belief that help with sleep is needed.[5–7] It is commonly thought that antidepressants relieve pain in doses smaller than are needed to relieve depression,[8–12] and that analgesic effects appear earlier than antidepressant effects.[9,13]

Multiple recent articles have suggested that antidepressant medications are helpful for many chronic pain syndromes.[3,5,9,10,14–20] Some authors believe that antidepressant medication helps chronic pain indirectly because of its beneficial impact on depression[21] or sleep or both[20]; others believe it has an analgesic effect independent of its antidepressant action.[22] This analgesic effect has been postulated to relate to similarities between neurotransmitter systems involved in depression and in pain. It has been further hypothesized that serotonergic antidepressants (eg, clomipramine, fluoxetine) have greater analgesic properties than do more noradrenergic antidepressants because serotonergic systems have been shown to be involved in pain in animals.[23,24] In fact, the second-generation antidepressant trazodone was developed in a process that involved testing potential drugs by assessing animal responses to noxious stimuli.[25] However, serotonergic antidepressants have not been found to have greater analgesic effects than noradrenergic antidepressants,[18] and noradrenergic systems may also be involved in pain.[26,27] Thus, the mechanisms by which antidepressants may relieve depression and pain are not understood.[14,15]

A number of reviews of the literature pertaining to the effectiveness of antidepressants for various pain problems have been published, sometimes with conflicting conclusions.[8,14–16,18,28] For example, in the family practice literature, in the same year (1989), one article stated that "many antidepressant drugs . . . are known to be effective in treating . . . back pain,"[10] (p213) while another stated that "the role of antidepressants in back pain . . . is less clear."[29] (p234) A more recent article in the family practice literature states that "a large and consistent body of literature suggests that [tricyclic antidepressants] may have specific beneficial effects in . . . chronic low back pain."[3] (p24)

The reason for undertaking this literature synthesis was to update previous reviews with an extensive literature search and application of systematic, objective methods of data abstraction to articles identified as pertinent. The focus was on examining the literature to address basic questions of practical importance to primary care physicians making decisions concerning optimal treatments for patients suffering low back pain. There is a great need for scientific information concerning outcomes of various treatments for low back problems in primary care settings, given the frequency of such problems and the fact that back pain is a more chronic recurrent condition than previously thought.[30] Specifically, we wanted to determine the following for patients with chronic low back pain:

1. Whether antidepressant medications, as a group, are more effective than placebo in decreasing pain, disability, depression, and analgesic medication use
2. Whether the analgesic effects of antidepressant medications are independent of their antidepressant effects.

Methods

Article Selection

The MEDLINE (from 1966) and PsycLIT (from 1967) bibliographic databases through December 1992 were searched to identify relevant English-language journal articles. The search strategies used included the following terms: *antidepressive agents, antidepressants*, the names of specific antidepressant medications, and *chronic pain, low back pain*, and *backache*. Articles were also identified from bibliographies of articles and book chapters, and from inquiries to pharmaceutical companies and to several expert researchers in the field. By these methods 423 articles were identified, and their titles and abstracts (when available) were reviewed. Any articles that appeared to be possibly relevant to this literature synthesis were then retrieved and read. Studies were included if they reported data from placebo-controlled or drug comparison trials evaluating antidepressant medication in samples consisting exclusively of people with low back pain. Six articles met these criteria.[31–36]

Data Extraction

A standardized coding form was developed, and each article was read independently by two clinical psychologist clinician-researchers, who used the form to extract data on study methods, subject characteristics, antidepressants studied and their dosages, lengths of trials, measures, and results. Disagreements were discussed until a consensus was reached.

Results

We found only six controlled or comparison studies that evaluated the efficacy of antidepressant medication for low back pain. The studies and their sample sizes, medications and dosages, length of trial, and results reported are listed in the Table. Three studies[31–33] were randomized, placebo-controlled trials. One study[34] used a crossover design with randomly assigned treatment-placebo sequences. Two uncontrolled studies by Ward and colleagues[35,36] compared two antidepressants, but it was not stated whether subjects were randomly assigned to treatments. Ward's 1986 study[35] was an extension of the 1984 study by Ward et al,[36] and included data from subjects in the 1984 study. The six identified studies varied greatly in terms of subject characteristics (eg, depressive symptoms, level of pain intensity and disability, duration of pain), antidepressant medication(s) studied, dosage, study design, and measures.

Is antidepressant medication superior to placebo in decreasing pain? Only three studies attempted to determine whether antidepressant medication was superior to placebo in decreasing pain. Of the three, two found no difference. Jenkins et al[33] reported similar improvements in patient ratings of pain on a visual analogue scale and in clinician ratings of patients' pain level in imipramine and placebo groups. However, no statistical analyses were reported. Goodkin et al[32] found no difference between trazodone and a placebo on visual analogue scale ratings of pain intensity. The third study, by Alcoff et al,[31] reported a borderline ($P = .058$) statistically significant difference between imipramine and placebo on patient ratings of back pain severity.

Research by Ward and colleagues[36] also addressed the efficacy of antidepressants for pain relief after "eliminating placebo responders" following a 2-week placebo washout period. This study compared doxepin and desipramine to examine whether a more sedating antidepressant (doxepin) might prove more useful for chronic low back pain. Patients in both antidepressant groups reported significantly reduced levels of pain severity (mean for all patients decreased from 5.8 to 3.0 on a scale of 1 to 10, $P < .005$) and frequency (from pain experienced 90% of the time to pain experienced 52% of the time, $P < .01$). Pain severity, but not frequency, decreased significantly more in the doxepin than in the desipramine group (data and statistics were not reported for this finding). The lack of a placebo group makes it impossible to assess how much of the change in reported pain is attributable to specific effects of the antidepressants and how much represents improvement associated with the natural course of the pain or the nonspecific effects of being in a pain treatment trial.

If antidepressants do exert more than a placebo influence on pain, there should be some kind of a relation between blood levels of medication and pain symptoms. (Of course, this may not be a linear relation; medication may only need to be above a certain threshold level to affect pain, or there may be a therapeutic window.) Only two studies reported data bearing on this relation; one found no linear relation between imipramine blood levels and patient symptoms,[31] and the other found that increased trazodone blood level was correlated with *increased* pain as measured by a visual analogue scale.[32]

Is there a significant difference between antidepressant medication and placebo in decreasing functional disability? Three studies examined this issue; only one found the antidepressant medication to be superior on any measure. Alcoff et al[31] found imipramine to be superior to placebo in increasing the frequency of certain recent daily activities, according to patients' self-report by questionnaire, but there were no significant differences between the antidepressant and the placebo in patient symptoms and physical findings as evaluated by the clinical investigators. Alcoff et al[31] speculate that both the patients and physicians may have correctly guessed whether the patient was receiving the active medication or the inert placebo because both groups were knowledgeable about side effects commonly associated with the medication. Goodkin et al[32] found the placebo to be superior to trazodone in decreasing disability as assessed by the Sickness Impact Profile[37] (an interviewer-administered form). Pheasant et al[34] found no difference between amitriptyline and an active placebo (atropine) in decreasing functional disability as rated by a physician or as measured by patient responses to an activity-restriction questionnaire.

Similarly, Jenkins et al[33] reported no clear benefit for imipramine over placebo in improving physical measures such as straight leg raise, and forward, backward, and lateral flexion obtained by a physician or physical therapist. However, no statistical analyses were presented. No assessment of change in overall daily functioning was included in this study.

Is there a significant difference between antidepressant medication and placebo in decreasing depression? Three studies[31–33] of patients with varying levels of depressive symptoms found no differences between placebos and antidepressants in effects on depression. However, each of these studies included some patients who were not depressed, and patients not depressed initially would not have much room to improve on depression measures. All

Table. Controlled and Comparison Trials of Antidepressants for Low Back Pain

Study/Patients	Drug	Dose (per day) Initial (mg)	Dose (per day) Maximum (mg)	Dose (per day) Average (mg)	Started Trial (n)	Finished Trial (n)	Length of Trial (wk)	Results Reported	Comments
Jenkins et al (1976)[33] Rehabilitation unit inpatients	Imipramine Placebo (inert)	75 —	75 —	75 —	30 29	23 21	4 —	Pain improved in both groups (exact means and standard deviations pre- and post-treatment were not reported), with no apparent differences between groups; in the 15 most depressed subjects (BDI scores >14), BDI scores decreased in 6 of the 8 imipramine vs 3 of the 7 placebo patients ($P = .10$)	All subjects concurrently treated in inpatient rehabilitation program; statistical analyses for effects on pain not reported; study was carried out "with close and valued assistance from Geigy Pharmaceuticals"(p 29)
Alcoff et al (1982)[31] Family practice outpatients with LBP ≥6 wk or ≥2 prior episodes ≥2 wk duration and current episode ≥2 wk	Imipramine Placebo (inert)	75 —	150 —	NR —	28 22	21 20	8 —	Imipramine superior to placebo in decreasing self-reported functional limitations; trend toward superiority of imipramine in decreasing pain severity; no difference between groups in clinician-rated symptoms and physical findings, or in changes in depression	Higher dropout rate in imipramine group; statistical analyses appeared to be comparisons of all subjects who completed at least 2 weeks of the trial, apparently excluding two placebo subjects who dropped out in the first 2 weeks, and did not adjust for baseline status or for length of time on drug or placebo; means and standard deviations were not reported for any measure
Pheasant et al (1983)[34] Hospital LBP clinic outpatients with ≥1 y disabling LBP and insufficient improvement with conservative care for ≥3 mo	Amitriptyline Placebo (atropine)	50 0.2	150 0.6	NR NR	16 16	9 9	6 —	No differences between treatments in decreasing disability; greater decrease in analgesic use with amitriptyline	Study employed crossover design with randomly assigned treatment sequences and a washout period following each sequence; treatments were compared only for the 9 patients who completed the study (ie, data from amitriptyline period were compared with data from placebo period for 9 patients); high attrition rate and very small sample
Goodkin et al (1990)[32] University Pain Clinic and VAMC outpatients, community volunteers with ≥1 y continuous LBP or two prior episodes of LBP ≥2 wk duration and ≥2 wk current episode	Trazodone Placebo (inert)	50 —	600 —	201 —	22 20	21 19	6 —	No significant difference between treatments in reducing narcotic use, depression, or pain; increased blood levels of trazodone correlated with *increased* pain; placebo superior to trazodone in decreasing physical and psychosocial disability	Subjects generally had a long history of pain, were quite disabled, and were diverse in terms of source; only 13 trazodone and 16 placebo subjects were compliant with medication prescriptions throughout trial, but data were analyzed for all subjects enrolled, to the extent possible; clinical evaluator's guesses as to treatment of each subject were no better than chance
Ward et al (1984)[36] Community volunteers with HDRS scores ≥18, diagnosis of major affective disorder, unipolar depression, or dysthymic disorder, and back pain ≥6 mo with average severity of ≥4 on a 0–10 scale	Desipramine Doxepin	50 50	3* 3*	173 188	36 —	26 –	4 —	Doxepin significantly better than desipramine in decreasing pain; no difference in decreasing depression; changes in depression did not correlate significantly with changes in pain	N values reported only for entire study, not for each treatment; all subjects were first given placebo for 2 weeks, responders were dropped from the study; no data or information concerning statistical analysis presented to support statements that doxepin was superior in decreasing pain but not depression
Ward (1986)[35] Community volunteers with characteristics described above under Ward et al (1984)[36]	Desipramine Doxepin	50 50	3* 3*	173 188	NR —	35 —	4 —	No difference between drugs in decreasing pain severity	This study appears to include the 26 patients who completed the study described by Ward et al.[36] The paper states that there were no significant differences between doxepin and desipramine in decreasing pain severity, pain frequency, or depression, but presents no supporting data. Patients with shorter current pain episodes showed better "response" (unclear definition)

NOTE: In the studies of Jenkins, Alcoff, Pheasant, and Goodkin and their colleagues, the subjects were diverse in terms of depressive symptoms. In the two studies by Ward and co-workers, all the subjects were depressed.
**mg per kg of body weight. BDI denotes Beck Depression Inventory; NR, no report; LBP, low-back pain; VAMC, Veterans Administration Medical Center; HDRS, Hamilton Depression Rating Scale.*

three studies relied on the Beck Depression Inventory (BDI)[38] to measure change in depressive symptoms over the treatment trial. In the study by Alcoff et al,[31] only four patients were reported to be mildly depressed and three severely depressed initially, based on BDI scores. In the study by Goodkin et al,[32] initial mean BDI scores for the placebo and the drug treatment groups were moderate and comparable, and both groups had wide initial variability in depression levels. Jenkins et al[33] reported low and comparable baseline median scores for the drug and placebo groups and wide variability overall. In this study, a subsample of the 15 most depressed patients (8 given imipramine, 7 given placebo) appeared to experience greater abatement of their depressive symptoms from imipramine than from the placebo, but this difference was not statistically significant. In the study by Ward et al[36] of patients who were all clinically depressed initially, doxepin and desipramine were associated with significant improvement in depression. The mean Hamilton Depression Rating Scale score for all patients decreased from 26.4 to 9.7 ($P < .001$). A 40% or greater reduction in depressive symptoms was found in 73% of patients completing the study.

Is there a significant difference between antidepressant medication and a placebo in decreasing analgesic medication use? Three studies examined this question. Pheasant et al[34] found amitriptyline to be superior to atropine placebo; Alcoff et al[31] and Goodkin et al[32] found no difference between antidepressant medication and inert placebo. In the Pheasant et al study,[34] analgesic use was assessed by having a pharmacist count the unused prescribed analgesic pills every 2 weeks for 6 weeks. Prescribed analgesics were acetaminophen or aspirin, with or without codeine, according to patients' preferences. In the study by Alcoff et al,[31] analgesic use was measured by patient self-report of the average number of pain pills or tablets consumed per day in the past week. Goodkin et al[32] monitored drug intake by urine toxicology screening tests at each visit. Unlike the other two studies, Goodkin et al[32] reported only on reductions in narcotics intake and not on other analgesic medication use. Their article did not state what statistical analyses were performed to compare reductions in narcotics intake or how narcotics use was operationally defined. None of these studies reported any subject exclusion criteria for the presence of substance abuse or dependence at the start of the treatment trials.

Are analgesic effects of antidepressants independent of antidepressant effects? Only the two studies by Ward and colleagues[35,36] in which all subjects were clinically depressed, examined whether changes in depression correlated significantly with changes in pain. The first study,[36] involving 26 subjects who completed a trial of doxepin or desipramine, reported a trend toward a significant relation between changes in pain and depression ($r = .28$, $P = .099$). However, the paper did not state which pain and depression measures were used in this analysis. The 1986 article by Ward,[35] which included these subjects plus nine additional subjects, did report a significant association. Decreases on the Hamilton Depression Rating Scale[39] (from a mean of 26.2 to 9.1) correlated .61 ($P < .001$) with decreases in pain severity (from 5.7 to 3.1 on a scale of 0 to 10) and .47 ($P < .003$) with decreases in pain frequency (from 76.5% to 54.6% of the time). No study examined whether antidepressants were differentially effective in relieving pain in depressed as compared with nondepressed patients.

Quality of Studies

Details of how patients were randomized to treatment groups were generally not reported. Although all studies were "double-blind," no study presented data on the number of patients who were able to correctly guess whether they were prescribed active medication or placebo. Only Goodkin et al[32] reported information concerning whether clinical evaluators were able to correctly guess medications. In no study was outcome clearly assessed independently of the treating clinician. This is a major problem because clinician ratings may be biased by guesses as to what treatment the patient is receiving based on knowledge of the side effects reported. Even when outcome is assessed by patient questionnaires, if these are completed in the presence of the treating clinician, subject responses may be biased by demand characteristics of that situation. No antidepressant–placebo comparison study presented information concerning the number of subjects diagnosed as clinically depressed by standardized criteria such as the DSM-III-R,[40] although earlier studies, of course, were performed before these were available. No study reported the results of power calculations, and all studies had fairly small samples; thus, the studies may have lacked sufficient power to detect true differences between antidepressant and placebo treatments. Attrition rates were high in all studies except the one by Goodkin et al.[32] Furthermore, only Goodkin et al[32] attempted to obtain and analyze outcome data for all patients who began the study regardless of compliance.

Discussion

The literature does not demonstrate the superiority of antidepressant medication over placebo in decreasing low

back pain or associated disability and depression. Of the three studies that examined the effects on pain, two[32,33] found no pain-relieving properties of antidepressant medication, and one study[31] found a borderline statistically significant pain-relieving effect for antidepressant medication. Of the three studies that assessed functional disability or activity level, only one study[31] found an effect for antidepressant medication. This effect was found only for patient self-ratings of frequency of certain daily activities; no effects were found on ratings made by clinical investigators. In one study[32] a placebo was found to be superior to trazodone in decreasing disability, and in the third study,[34] no placebo–antidepressant differences in effects on disability were found. In three studies[31–33] that included both depressed and nondepressed patients, antidepressant medication and placebo were found to be equivalent in improving depression measure scores. One study[34] found antidepressant medication to be superior to placebo in decreasing analgesic medication use; two studies[31,32] found no such difference. No study reported consistent superiority of antidepressant medication over placebo across outcome measures. These published studies may be a biased sample of the studies conducted; there may well exist other studies that were never published because they failed to find a significant difference between the medication and the placebo. Such publication bias (studies that show a treatment effect are more likely to be published) has been demonstrated in other clinical research areas.[41–43]

Although we must conclude that there is at this date no convincing scientific evidence supporting the use of antidepressant medication for low back pain relief, we must also emphasize that the literature does not conclusively demonstrate that antidepressants have no specific effects on low back pain, disability, and associated problems. The studies generally had small sample sizes and may have lacked statistical power to detect possible differences between antidepressant and placebo groups. Pooling data across studies using meta-analytic techniques could potentially reveal differences that individual studies were not sufficiently powerful to detect. Thus, it is particularly unfortunate that differences among the studies (especially in terms of medications, doses, and outcome measures), insufficient reporting of data, and the small number (three) of randomized, placebo-controlled trials (the study by Pheasant et al[34] used a crossover design) precluded the use of meta-analytic statistical techniques for this literature synthesis. These factors greatly limit the conclusions that can be drawn concerning the study questions. Variations in patient populations sampled and in whether patients were allowed to use other analgesics, as well as poor specification of study inclusion and exclusion criteria, further contributed to the inability to pool data across studies and draw generalizable conclusions.

Subjects in the six studies were drawn from different populations. These included rehabilitation unit inpatients, family practice outpatients, outpatients in a low back pain clinic and in a pain clinic, Veterans Administration Medical Center outpatients, and community volunteers. It cannot be determined from the literature whether patients with low back problems seen in different settings (eg, primary practice vs pain clinic) may respond differently to antidepressants. Only one study enrolled subjects from family practice settings, although several studies recruited community volunteers, who might be similar to patients drawn from primary care populations.

An additional study,[44] which did not meet criteria for inclusion in this synthesis because the sample was of patients with diverse chronic pain problems, deserves mention. Patients with chronic pain were randomly assigned to 6 weeks of treatment with the tricyclic antidepressant clomipramine, the antidepressant mianserin (a noradrenaline re-uptake blocker), or placebo. Only 10 patients with low back pain completed the study, and this small sample size precluded meaningful statistical analysis; but it is interesting that the most improvement in pain was reported by the patients receiving the placebo. Overall, in this study of 253 patients with different idiopathic pain syndromes, the two antidepressants were not superior to placebo in reducing pain.

The literature is not adequate to answer the question of whether antidepressants have analgesic effects independent of antidepressant effects for patients with chronic low back pain. Ward et al[36] found a trend toward a statistically significant relation between changes in depression and changes in pain; and, with a larger sample, Ward[35] found moderate and statistically significant correlations between changes in pain severity and frequency and changes in clinician-rated depressive symptoms. No other studies examined this issue. Furthermore, the failure of most studies to adequately assess depression before and after treatment in the subjects studied makes it impossible to determine whether antidepressants are differentially effective in relieving pain in depressed patients as compared with nondepressed patients.

The studies also did not yield information bearing on two widely held beliefs. First, there are no data concerning whether antidepressant medications are effective in relieving low back pain in smaller doses than those used for treating depression. Second, there is no evidence to support the proposition that serotonergic antidepressants are more likely to have analgesic effects on low back pain than are more noradrenergic drugs. In one study[32] of the serotonergic drug trazodone, the placebo was

found to be superior to trazodone in decreasing physical and psychosocial disability in patients.

The duration of the medication trials was fairly short, ranging from 4 to 8 weeks across studies. It is not known whether analgesic effects might have become more apparent with longer trials. The effects of an antidepressant drug on a depressed patient may not be fully realized until 6 weeks after initiating therapy.[45]

Major problems in the study methods and reporting characterized this literature. Most worthy of comment are issues related to dropouts, statistical power, placebos, and information reported. Dropout rates ranged from 5% to 44%. Information concerning reasons for attrition in placebo and treatment groups (eg, adverse side effects, failure to improve) was typically not reported. All but one study analyzed results comparing placebos with active treatments using only treatment completers; results from these studies should therefore be interpreted with caution. Most clinical trial methodologists agree that statistical analyses should compare all patients enrolled in a study according to random assignment, whether or not they complied with or completed the assigned treatment (intention-to-treat analysis).[46] Analysis based on treatment actually received is problematic for several reasons. There may no longer be balance across treatment groups in patient characteristics that may influence outcome; the sample size and power are reduced; and bias is introduced by using compliance (a factor often related to outcome, regardless of whether the subject received active treatment or placebo) to determine the comparison groups.[46]

In interpreting the results of these studies, it is also important to consider the type of placebo used. The expectations of patients and clinicians greatly influence pain relief reported after the use of medication.[47] The use of lactose or inert placebos without the well-known side effects of antidepressants may have the effect of both subject and clinician correctly guessing from the side effects whether the patient is receiving a placebo or a medication.[48] Studies are less likely to demonstrate the superiority of an antidepressant medication over placebo for improving depression when the placebo is atropine than when it is inert.[49] Other studies have shown that greater blindness of study participants as to who received the placebo and who received the active drug is associated with smaller advantages for the antidepressant over the placebo in decreasing depression.[50,51] In this literature synthesis, only the study by Pheasant et al[34] used a non-inert placebo. No study reported data on whether patients guessed the identity of the drug they took; thus, it is not clear whether any of these studies were truly double-blind in effect.

Given all of these considerations, it is imperative that future studies of the efficacy of antidepressant medication for pain problems include a credible placebo-control condition. Patients are likely to seek treatment and enroll in studies when pain is relatively bad and to improve over time with or without treatment.[52] Further contributing to improvement are nonspecific effects such as those associated with being in a study and receiving attention from study doctors and staff. Improvement associated with natural history and nonspecific factors may be responsible for much or all of any improvement clinicians may observe in low back pain patients treated with antidepressants.

Conclusions

Because a methodologically sound body of literature is lacking in this area, the questions we addressed in this review cannot be firmly resolved. Further randomized, placebo-controlled, double-blind studies are clearly needed to assess the efficacy and effectiveness of different antidepressant medications, at different dosages, compared with one another and with placebo (if possible, an active placebo with side effects similar to those of the active drug). Improvements in study methods to avoid problems such as those discussed here are of course essential. Effects of medication vs placebo on pain, depressive symptoms, and functional disability, as rated by subjects and observers blind to treatment group assignment and side effects experienced, should be compared not only in terms of statistically significant differences, but also in terms of clinically significant differences.

Meanwhile, given the lack of scientific support for the pain-relieving properties of antidepressants, physicians may want to exercise caution in prescribing these medications in hopes of pain relief for patients with low back pain who are not clinically depressed. Symptoms of depression in these patients (such as persistent dysphoria or anhedonia; changes in sleep, appetite, or weight; decreased energy level; feelings of worthlessness; suicidal ideation) consistent with a diagnosis of major depression according to the American Psychiatric Association's DSM-III-R criteria[40] should be assessed and treated. Antidepressant medications can be expensive (especially the newest ones) and can produce side effects ranging from bothersome to dangerous, such as dry mouth, drowsiness, constipation, urinary retention, orthostatic hypotension, and mania.[19,53,54] Furthermore, some antidepressant medications can be used alone, or in combination with other substances, to commit suicide.[19] On the other hand, antidepressant medications may be a useful tool for alleviating clinical depression in this patient population, and have the advantage of not leading

to physiological dependence or abuse. Furthermore, they may be helpful in improving sleep, a frequent problem reported by patients with low back pain.

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