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Pharmacologic Management of Chronic Low Back Pain

Synthesis of the Evidence

Andrew P. White, MD,* Paul M. Arnold, MD,† Daniel C. Norvell, PhD,‡ Erika Ecker, BS,‡ and Michael G. Fehlings, MD, PhD, FRCSC§

Study Design. Systematic review of the literature with subgroup analysis for heterogeneous treatment effects.

Objective. The objectives of this systematic review were to summarize prior Cochrane reports regarding the safety and effectiveness of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and antidepressants for treatment of chronic low back pain (LBP) and to evaluate whether certain subpopulations respond more favorably to pharmacological management.

Summary of Background Data. While medications are a mainstay of LBP management, there is uncertainty as to the optimal use of commonly prescribed medications such as opioids, antidepressants, and NSAIDS.

Methods. To summarize the overall treatment effect and safety for each of the three pharmacological drug classes (opioids, NSAIDs, or antidepressants), we summarized existing Cochrane reviews. To evaluate whether the effects of treatment varied by specific subgroups of patients, we sought randomized controlled trials (RCTs) evaluating one of the three pharmacological drug classes *versus* an alternative management for chronic LBP.

Results. Based on the Cochrane reviews, opioids are more effective than placebo with respect to pain and disability, with a much greater effect size for pain than disability. When compared with NSAIDs, opioids did not confer a greater benefit with regard to pain and disability. The rate of side effects from opioids is significantly greater than placebo with differences ranging between 2% and 9%. The systematic review of RCTs showed that antidepressants are not more effective than placebo with respect to pain, functional status, or depression. Certain subgroup treatment effects were identified, supporting our hypothesis that chronic LBP should be considered a heterogeneous set of disorders. As such, chronic LBP subgroups should be considered both when making clinical treatment decisions and when designing future research trials.

Conclusion. Opioids and NSAIDs are effective for chronic LBP, while antidepressants have no meaningful clinical benefit. Based on the significant rate of side effects with opioids and the lack of convincing superiority over NSAIDs, opioids are not recommended as a treatment for chronic LBP. Attention to subgroups of patients will likely help guide treatment, and will likely help increase the clinical impact of future research.

Clinical Recommendations. Recommendation 1: NSAIDs should be considered as a treatment of chronic LBP (Strength: Strong). There is evidence demonstrating favorable effectiveness, but also significant side effects that may have meaningful clinical consequences.

Recommendation 2: Opioids may be considered in the treatment of chronic LBP but should be avoided if possible (Strength: Weak). There is evidence demonstrating favorable effectiveness compared to placebo, similar effectiveness compared to NSAIDs, and with significant side effects including decreasing effectiveness related to habituation when used long-term.

Recommendation 3: Antidepressants should not be routinely used for the treatment of chronic LBP (Strength: Strong). There is evidence that they are not more effective than placebo with respect to pain, functional status, or depression.

Based on the hypothesis that chronic LBP is a symptom reflective of a heterogeneous group of disorders, categorization of certain patient specific subgroups may be helpful in guiding future treatment decision making. It is likely that inclusion of subgroup factors in future RCTs will provide information needed to improve the strength and specificity of future clinical recommendations.

Key words: antidepressants, drugs, heterogeneity of treatment effect, low back pain, nonsteroidal anti-inflammatories, opiates, randomized trials, systematic review. **Spine 2011;36:S131–S143**

Chronic low back pain (LBP) is a common disorder. It afflicts 70% to 85% of the people in North America at some point in their lives. In the United States, back pain is the most common reason for persons under 45 years of

From the *Harvard Medical School, Department of Orthopaedic Surgery, Beth Israel Deaconess Medical Center, Boston, MA; †Department of Neurosurgery, University of Kansas Medical Center, Kansas City, KS; ‡Spectrum Research, Inc., Tacoma, WA; and §Division of Neurosurgery, University of Toronto, Toronto, Ontario, Canada.

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Address correspondence and reprint requests to Andrew P. White, MD, Department of Orthopaedic Surgery, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Stoneman 10, Boston, MA 02215; E-mail: apwhite@bidmc.harvard.edu

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age to limit activities, including work-related activities.[1] For this reason, in part, LBP has become a major socioeconomic problem. Direct and indirect economic losses have been estimated to be nearly $90 billion annually.[2]

Medication is the most frequently used intervention for chronic LBP. The popularity of pharmacologic management may be related to many factors, including high patient volume and turnover in busy primary care practices, pervasive availability and marketing of pain management clinics, and raised expectations for physicians to continuously suppress pain. There is an increasing recognition that many patients are made to feel entitled to a "pain free" life. One study reported that primary care physicians prescribed one or more medications for 80% of their patients with chronic LBP and two or more medications for 35% of their patients with chronic LBP.[3]

The most commonly prescribed medications include nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and antidepressants. NSAIDs are the most frequently prescribed medications worldwide and are frequently recommended as an option in chronic LBP treatment. Many other types of medications are used, however, including Tylenol, skeletal muscle relaxants, benzodiazepines, systemic corticosteroids, and antiepileptics.

While chronic LBP is common, expensive, and most frequently treated with medications, the literature is relatively devoid of high quality medical evidence upon which strong treatment recommendations can be made. This is not related to a lack of data, however; there is an abundance of information available on this common treatment method for patients with this common disorder. There are many randomized controlled trials (RCTs) available. Furthermore, several reviews regarding the most frequently prescribed medications (NSAIDs, opioids, antidepressants) have been published in recent years. These reports have not been encouraging.

Roelofs *et al*[4] published a Cochrane review comparing NSAIDs with placebo or other medications for the treatment of acute and chronic LBP. They reviewed 65 trials representing 11,237 patients. They classified 28 of these studies as high quality. These authors concluded that NSAIDs were slightly effective for short-term relief of acute and chronic LBP and that NSAIDs were not more effective than other drugs including acetaminophen, narcotics, and muscle relaxants. A Cochrane review by Deshpande *et al*[5] considered the efficacy of opioid medications for treatment of chronic LBP. This review included four trials. Three of the trials compared Tramadol to placebo, representing 908 patients. The fourth trial compared morphine (or morphine derivative) to NSAIDs, representing 36 patients. These Cochrane review authors reported that those receiving Tramadol had more pain relief and less difficulty with daily activities as compared with placebo, and that those receiving morphine (or derivative) had little or no difference in pain relief as compared with NSAID. They also reported that weak opioids reduce pain but had minimal effect on function.[5] The third recent Cochrane review considered antidepressants. In this review, Urquhart evaluated 10 RCTs to evaluate if antidepressants are more effective than placebo for treatment of acute and chronic LBP. The pooled analysis showed no difference in pain relief between antidepressant and placebo. The qualitative analysis found conflicting evidence on the effect of antidepressants on pain intensity and no clear evidence that antidepressants reduce depression in patients with chronic LBP.[6]

In general, the results of treatment for chronic LBP in RCTs are less than encouraging.[7] Poor treatment results, however, may be related to incorrectly classifying chronic LBP as a homogeneous entity when in fact it is heterogeneous.[8–10] Chronic LBP may be best characterized as a symptom reflective of many heterogeneous disorders, each with a different cause. As such, each patient with chronic LBP may respond more favorably or less favorably to a given treatment, since any given treatment may or may not be particularly appropriate for the root cause of each individual's pain.

The heterogeneity of patients with chronic LBP has an important effect on the results of RCTs evaluating this group. Results from RCTs represent average effects (population means) and, while estimates of the average treatment effect are useful, some individuals will respond more positively or more negatively than the reported average. Such variation in results is termed heterogeneity of treatment effects (HTE).[11] When the same treatment results in different outcomes in different patients, HTE is present. One way to identify HTE is to analyze the effect of treatment in subgroups of patients with certain baseline characteristics.

Subgroup analyses may be prone to spurious results, however. This is due to the problem of multiple testing.[12] Many caution against subgroup analyses, especially *post hoc* comparisons.[13] Nevertheless, identification of subgroup effects in clinical trials can generate important hypotheses about potential factors that modify treatment effects. Recommended reporting of subgroups analysis includes statistical tests of interaction or heterogeneity and a description of whether the subgroup analysis was prespecified or *post hoc*.[13–15] When attempting to evaluate possible HTE for a systematic review, care must be taken in selecting the appropriate study designs and in ensuring the results are presented in such a way that the possibility of HTE can be assessed. Ideally, one identifies randomized trials that compare the two treatments of interest (*e.g.*, opioids *vs.* placebo), and report treatment effects by subgroup (*e.g.*, smokers and nonsmokers) in addition to the overall treatment effect. It is not uncommon to find that there is little to no treatment effect in all patients; however, with enough study power and careful planning, subgroup differences may exist. Given that only one treatment is evaluated in a case series, this design does not address the question of whether treatment differences vary according to differing subgroup characteristics.[15–18]

The goal of this investigation was to help determine the safety and effectiveness of medications commonly prescribed in the treatment of chronic LBP and to determine if specific subgroups respond more favorably than the mean population to these medications. As such, we developed the following clinical questions:

1. What is the relative effectiveness and safety of opioids in the treatment of chronic LBP and does it differ by subpopulation?
2. What is the relative effectiveness and safety of NSAIDs for the treatment of chronic LBP and does it differ by subpopulation?
3. What is the relative effectiveness and safety of antidepressants for the treatment of chronic LBP and does it differ by subpopulation?

MATERIALS AND METHODS

Electronic Literature Database

A systematic search was conducted in MEDLINE and the Cochrane Collaboration Library for literature published from January 1978 through December 2010. We limited our results to Cochrane reviews, RCTs, studies with human subjects, and to articles published in the English language. All previously published systematic reviews were also checked to ensure inclusion of previously summarized RCTs regarding (1) opioids, (2) NSAIDs, and (3) antidepressants for the treatment of chronic LBP.[6,19,20] While we are aware that there are many other medications commonly prescribed, including Tylenol, these three drug classes were ultimately selected for analysis, since there is not significant published data on other medications to accommodate systemic analysis. In addition, we recognize that it is important to differentiate between the short-term and long-term risks and benefits of these medications. In this inquiry regarding chronic LBP, the long-term safety and efficacy of the treatment is of particular interest. As such, we focused our analysis not only on patients with chronic LBP, but also on medication treatments ongoing for more that 12 weeks.

To summarize the overall treatment effect and safety for each of the three drug classes (opioids, NSAIDs, antidepressants), we reviewed previously published Cochrane reviews. To evaluate whether the effects of treatment varied by specific subgroups, we sought RCTs evaluating one of the three drug classes *versus* an alternative management for chronic LBP. More specifically, we approached the literature to identify the following: (1) RCTs designed specifically for evaluating this comparison stratifying the random assignment on one or more subgroups, (2) RCTs designed specifically for this comparison that included a subgroup analysis stratifying on one or more subgroups, (3) RCTs that made the comparison among patients within a specific subgroup (*e.g.*, neurological deficit only or no depression) to compare with other RCTs that were conducted among patients without characteristics of this subgroup. We excluded studies that did not report medication effectiveness and/or safety (*i.e.*, one medication *vs.* another medication) separately for the subgroups being compared unless they performed a statistical test for determining if the subgroup modified the effectiveness and/or safety (*i.e.*, test for interaction). For example, if the authors reported a multivariate regression that included a subgroup variable (*e.g.*, age or sex) and the treatment variable (*e.g.*, drug therapy *vs.* alternative care), without an interaction term, the study was excluded. Articles were also excluded if they included the following patient groups: pediatric patients (<18 years of age), patients with radiculopathy, prior surgical intervention, primary diagnoses of cancer, deformity, instability, infection, and/or trauma contributing to the LBP condition. Other exclusions included non-Cochrane reviews, editorials, case reports, and non–English-written studies, and studies without subgroup analyses (Figure 1).

Data Extraction

For the Cochrane reviews, we extracted data only relevant to chronic LBP as other conditions including acute LBP were often summarized in these reviews. For the subgroup analyses, each retrieved citation was reviewed by two independently working reviewers (D.C.N., E.E.). Some articles were excluded on the basis of information provided by the title or abstract if they clearly were not a randomized trial or were evaluating a patient population that did not meet our inclusion criteria. Otherwise, all full text reports were reviewed by the two reviewers regardless of whether the abstract reported a subgroup analysis. Any disagreement between them was resolved by consensus. From the included articles, the following data were extracted for both treatment groups if the data were available: outcome, risk factor or subpopulation, rates of outcome (where appropriate), pre- and posttreatment and

	Inclusion	Exclusion
Patients	• Adults • Chronic LBP • Centralized or radiating pain	• <18 years old • Radiculopathy • Prior surgical intervention • Cancer, deformity, instability, infection, trauma

Intervention	• Oral (systemic) pharmacotherapy
	  • Nonsteroidal anti-inflammatory drugs
	  • Opioids
	  • Antidepressants
		• Injection pharmacotherapy
		• Herbal pharmacotherapy
		• Topical pharmacotherapy
		• Acupuncture
		• Active or passive nonsurgical therapy

Comparator	• Other oral (systemic) pharmacotherapy • No pharmacotherapy intervention	• Injection pharmacotherapy • Herbal pharmacotherapy • Topical pharmacotherapy • Acupuncture
Outcomes	• Pain • Physical function • Quality of life • Adverse outcomes to pharmacotherapy	• Costs
Study design	• Cochrane reviews for overall safety and efficacy • RCTs subanalyses of risk factors	For overall safety and efficacy • Non-Cochrane reviews (others included in discussion) For subgroup analyses • No separate treatment effect for each subgroup of interest • Included risk factor regression analysis but did not do a test for interaction • Case reports • Nonclinical studies • Case series • Non-English literature

Figure 1. Inclusion and exclusion criteria.

change scores (where appropriate), effect estimates (*e.g.*, odds ratio, relative risk, treatment effect), and associated *P* values. Tests for interaction of treatment effects were included when reported by the author.

Study Quality

For assessing the level of evidence for the overall treatment effect of pharmacologic interventions, we rated each Cochrane review using both a quantitative and qualitative analysis. For assessing the level of evidence for subgroup effects, level of evidence ratings were assigned to each article independently by two reviewers using criteria set by *The Journal of Bone and Joint Surgery, American Volume* (*J Bone Joint Surg Am*)[21] for therapeutic studies and modified to delineate criteria associated with methodological quality and described elsewhere.[22]

Analysis

We summarized the findings from the three Cochrane reviews. We included the study level summary findings from the meta-analyses provided by the authors including standardized mean differences (SMDs) for continuous outcome measures and risk differences (RDs) for binary outcomes. We constructed forest plots using these effect sizes and confidence intervals to provide a visual demonstration of treatment effects. For the subgroup analyses, data between studies were not pooled because of heterogeneity of subject populations, outcome measures, lack of raw data (in some instances), and differing effect estimates. In rare cases, we were able to report or calculate effect sizes from subgroup analyses.

Overall Strength of Body of Literature

To determine the overall strength of the evidence we used a modification of the GRADE criteria. Initial strength was established on the basis of study design and was subsequently upgraded or downgraded on the basis of the results. Level of evidence ratings were assigned to each article independently by two reviewers using criteria set by *The Journal of Bone and Joint Surgery, American Volume* (*J Bone Joint Surg Am*)[21] for therapeutic studies and modified to delineate criteria associated with risk of bias and methodological quality described elsewhere.[22] The initial strength of the overall body of evidence was considered high if the majority of the studies were level I or II and low if the majority of the studies were level III or IV. We downgraded the body of evidence one or two levels based on the following criteria: (1) inconsistency of results, (2) indirectness of evidence, (3) imprecision of the effect estimates (*e.g.*, wide confidence intervals) (4) if the authors did not state *a priori* their plan to perform subgroup analyses and if there was no test for interaction. We upgraded the body of evidence one or two levels based on the following criteria: (1) large magnitude of effect or (2) dose-response gradient. The overall strength of the body of literature was expressed in terms of the impact that further research may have on the results. An overall strength of high means we have high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.

No. of studies	Treatment comparison	Population CLBP (n)	CLBP data reported separately (Y/N)
NSAIDS (Roelofs)			
16	Placebo	4	Y
7	Paracetamol	2	N
9	Other drugs	1	N
4	Non-drug treatment	0	n/a
33	Other NSAIDs	1	N
3	NSAID + muscle relaxants	0	n/a
3	NSAID + B-vitamins	1	N
OPIODS (Deshpande)			
3	Placebo	3	Y
1	Other analgesics	1	Y
ANTIDEPRESSANTS (Urquhurt)			
10	Placebo	9 (1 unspecified)	Y

n/a = not applicable; NSAID = non-steroidal antiinflammatory drug.

Figure 2. Number of studies in the Cochrane reviews reporting on chronic low back pain (CLBP) patients.

An overall strength of moderate is interpreted as moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. A grade of low means we have low confidence that the evidence reflects the true effect. In this case, further research would be likely to change the confidence in the estimate of effect and likely to change the estimate. A grade of insufficient suggests that evidence is unavailable or does not permit a conclusion.

RESULTS

Study Selection

Three Cochrane reviews were identified that addressed the efficacy and safety of opioids, NSAIDs, and antidepressants for the treatment of LBP. Two of the reviews (regarding opioids and antidepressants)[5,6] included studies with populations comprising chronic LBP patients only (one of the 14 study populations was unspecified). In the third review (regarding NSAIDs),[4] the majority of studies were conducted in patients with acute LBP; only four studies comparing NSAIDs to placebo were in chronic low back patients with results reported separately and were included in the final analysis (Figure 2).

For the subpopulations, our search strategy identified 97 total citations. Of these, 34 were excluded by abstract and 63 full text articles (all RCTs) were retrieved to determine if they met the criteria. Of these 63, all were RCTs, but only 12 reported treatment effects separately by subgroup (Figure 3). This highlights the deficiencies in the literature that describes comparative pharmacology effects by different risk factors in patients with chronic LBP. It also serves to provide hypotheses regarding the possibility of HTE by subpopulations. Data across studies could not be pooled due to the differences in subgroups, treatment comparisons, and outcomes recorded. Therefore, individual study findings are presented.

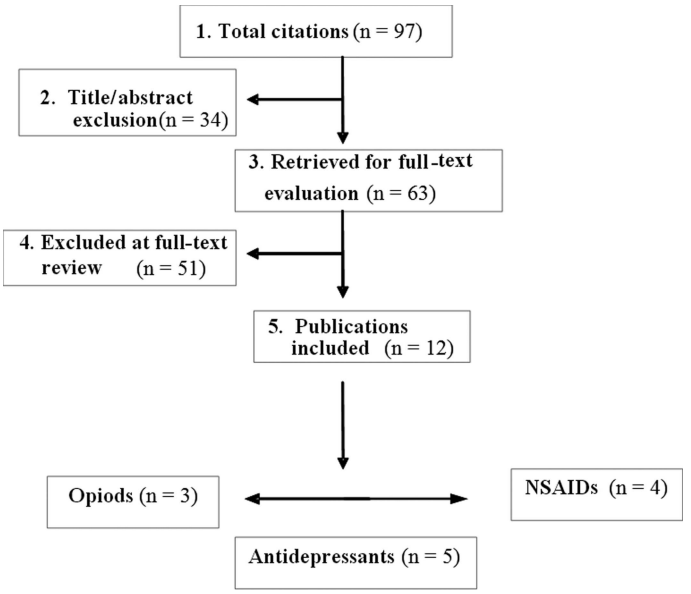


Figure 3. Results of subgroup literature search.

What is the relative effectiveness and safety of opioids in the treatment of chronic LBP and are there differences by subpopulation?

Efficacy

A meta-analysis of three trials investigated the efficacy of opioids (tramadol) *versus* placebo in a total of 908 patients with chronic LBP with and without radiating pain[5] (Table 1). Studies were excluded if patients' LBP was due to nondegenerative pathologies such as infection, neoplasm, and compression fractures. In the pooled analysis, compared with those on placebo, patients who received tramadol reported better pain relief with a mean 10.8-point difference in the 100-mm visual analog scale (VAS). They also reported improved function, with a mean 1-point difference as measured by the Roland Disability Questionnaire. SMDs for opioids *versus* placebo were –0.71 (95% CI: –0.84 to –0.57) for pain and –0.17 (95% CI: –0.30 to –0.04) for disability (Table 2). This difference favoring opioids was statistically significant (Figure 4A). Only one study compared opioids with other analgesics and the authors reported better pain relief in both morphine groups (set-dose and titrated-dose) compared with the naproxen group and a greater effect in the titrated-dose *versus* the set-dose morphine group (Table 2). The Cochrane review's calculations, however, failed to show a statistically significant difference in pain relief between the titrated-dose group and the control group (SMD, –0.58; 95% CI, –1.42 to 0.26), probably due to the small sample size (Figure 4B). No significant difference in disability was found when the morphine groups were compared with the naproxen group (SMD, –0.06; 95% CI, –0.88 to 0.76) (Figure 4B).

Safety

Headache and nausea were the only side effects reported among all three studies comparing opioids with placebo and were more prevalent in the opioid group (risk difference [RD] = 9%; 95% CI, 6%–12% and RD = 3%; 95% CI, 0%–6%, respectively). In two studies (654 patients), somnolence, constipation, dry mouth, and dizziness were more common after treatment with opioids with RDs ranging from 7% to 9% (95% CI, 4%–13%) (Table 2). Finally, one study (336 patients) reported a significantly greater incidence of pruritus, vomiting, anorexia, and increased sweating in the opioid *versus* placebo group with RDs ranging from 4% to 6% (95% CI, 1%–10%). For the comparison between opioids and other analgesics, the most frequent side effects were dry mouth, drowsiness, headaches, constipation, and nausea. No intergroup differences were reported.

Subpopulations

Three studies were identified that examined the efficacy of opioids for the treatment of chronic LBP in various subpopulations. Of these, only one trial reported significant treatment effects by subgroup. This trial is summarized below. The remaining two studies[23,24] that reported no significant treatment effects by subgroup are briefly outlined in Table 1 (see Table 1, Supplemental Digital Content 1, http://links.lww.com/BRS/A542). Details of these study populations and results can be found in the Web appendices (see Supplemental Digital Content 1, http://links.lww.com/BRS/A542).

In the one trial that reported a significant treatment effect (TE) by a subgroup, the change in Bowel Function Index score and the number of complete spontaneous bowel movements was examined. A subset of 59 patients with high Bowel Function Index scores (≥50) at baseline was treated with oxycodone PR (n = 30) or oxycodone PR/naloxone PR (n = 29).[25] Compared with the group receiving oxycodone PR, those on oxycodone PR/naloxone PR had a significantly greater improvement in bowel function (TE based on Bowel Function Index score: –11.8; mean difference in number of complete spontaneous bowel movements: 2.0), Table 2 in the Web appendices (see Table 2, Supplemental Digital Content 1, http://links.lww.com/BRS/A542).

What is the relative effectiveness and safety of NSAIDS for the treatment of chronic LBP and are there differences by subpopulation?

Efficacy

A meta-analysis of four trials compared the efficacy of NSAIDs[4] with the efficacy of placebo in 1020 patients with chronic LBP with or without radiating pain (Table 1). Studies were excluded if patients' LBP was due to specific pathologies such as infection, neoplasm, metastasis, rheumatoid arthritis, or fractures. Pooled results of all four studies indicated a statistically significant decrease in pain intensity (100 mm VAS) after treatment with NSAIDs compared with placebo (weighted mean difference –12.4; 95% CI –15.5 to –9.3) (Table 3 and Figure 5).

Safety

Side effects were reported in the same four studies in 1034 patients. In the pooled results, significantly more side effects

TABLE 1. Inclusion and Exclusion Criteria for Studies Included in the Cochrane Reviews

Study	Inclusion Criteria	Exclusion Criteria
Opioids (Deshpande *et al*[5])	RCT and quasi-RCTs Male and female Age ≥ 18 years Persistent LBP that has lasted for ≥ 12 weeks With or without radiating symptoms to the legs With or without prior low back surgery	LBP due to specific pathologies (*i.e.*, cancer, infections, inflammatory arthritic conditions to include osteoarthritis, and compression fracture) Studies with < 50% of the participants with chronic LBP or failing to report results separately for this specific cohort Pain in areas other than the low back History of substance abuse Spinal stenosis, spondylolisthesis, symptomatic disk herniation (two studies)
NSAIDs (Roelofs *et al*[4])	RCTs and double-blind controlled trials Age ≥ 18 years Males and females Nonspecific LBP with or without sciatica Acute (≤ 12 weeks) and chronic (> 12 weeks) LBP One or more type of NSAID; additional interventions allowed if there was a contrast for NSAIDs	LBP due to specific pathologies (*i.e.*, infection, neoplasm, metastasis, osteoporosis, rheumatoid arthritis, or fractures)
Antidepressants (Urquhart *et al*[6])	RCTs with a placebo control group Adults Males and females Nonspecific LBP with or without radiation and with or without leg pain Somatic or radicular pain or both	LBP due to specific pathologies (*i.e.*, infection, neoplasm, metastasis, osteoporosis, rheumatoid arthritis, or fractures) Investigated effect of antidepressant medication on depression Study specifically in patients with major depressive order
	Any type of antidepressant (*i.e.*, tricyclic, heterocyclic, SSRI, MAOI, and "atypical")	

LBP indicates low back pain; MAOI, monoamine oxidase inhibitor; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor.

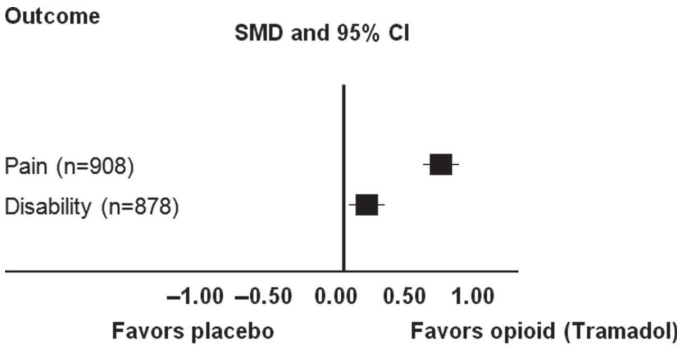
were reported in the NSAID group compared with the placebo group (risk ratio 1.24; 95% CI, 1.07–1.43) (Table 3). Specific side effects were not listed.

Subpopulations

Four studies were identified that reported the efficacy of NSAID treatment for chronic LBP in subpopulations. Of these, only two trials reported significant treatment effects by subgroup and are summarized below; the remaining two studies[26,27] that reported no significant treatment effects by subgroup are briefly outlined in Table 1 in the Web appendices (see Table 1, Supplemental Digital Content 1, http://links.lww.com/BRS/A542). Details of these study populations and results can also be found in the Web appendices (see Supplemental Digital Content 1, http://links.lww.com/BRS/A542).

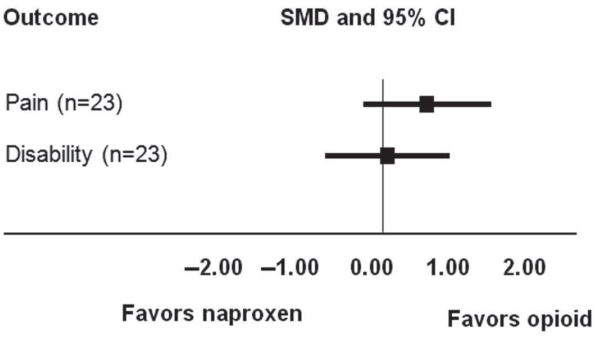
Among the studies reporting significant treatment effect (TE) by subgroups, one study[24] reported that anxiety was a significant factor effecting pain improvement. Anxiety was measured with the Hospital Anxiety and Depression Scale and effectiveness of treatment was measured by change in Low Back Intensity Scale scores. As compared with placebo, patients receiving 25 mg rofecoxib had decreased effectiveness of treatment with increasing anxiety (see Table 3, Supplemental Digital Content 1, http://links.lww.com/BRS/A542). In patients with no anxiety, the TE between 25 mg rofecoxib and placebo was –19.5, compared to those with mild anxiety, –9.9, and those with moderate/severe anxiety, 1.8; $P = 0.013$. A similar trend was not evident in differences between the 50-mg rofecoxib and placebo treatment groups or in the subgroup analysis based on the Hospital Anxiety and Depression Scale depression interpretation, as well as other variables investigated.

The second study looked at the effect of pain characteristics on pain scores in patients prescribed various types of NSAID treatments (aspirin, dextropropoxyphene and paracetamol, indomethacin, mefenamic acid, paracetamol, and phenylbutazone).[28] Only two factors showed significant interactions with treatment. These were (1) whether pain was brought on by sneezing and (2) whether pain radiated from the primary focus (see Table 4, Supplemental Digital Content 1, http://links.lww.com/BRS/A542). In patients who had pain brought on by sneezing, treatment with aspirin, phenylbutazone, or dextropropoxyphone plus paracetamol, resulted in significantly better pain relief than mefenamic acid (1.06, 1.65, and 1.79 *vs.* 2.47, respectively, $P < 0.05$). The same was true when aspirin was compared with indomethacin (1.06 *vs.* 2.28,



*Treatment effect favors opiods for both pain and disability.

(A)



*Treatment effect favors neither Opioids or NSAIDs for pain or disability. Note very small sample size.

(B)

Figure 4. A, Forest plot representing the standardized mean differences (SMD) and 95% confidence interval (CI) comparing opioids (Tramadol) to placebo from Cochrane review by Desphande. Treatment effect favors opioids for both pain and disability. **B**, Forest plot representing the SMD and 95% CI comparing opioids (oxycodone) to naproxen. Treatment effect favors opioids or nonsteroidal anti-inflammatory drugs for pain or disability. Note very small sample size.

$P < 0.05$). When comparing patients with radiating (with or without sneezing) *versus* nonradiating pain, mefenamic acid was significantly more effective in reducing pain than phenylbutazone and indomethacin in patients with nonradiating pain (0.98 *vs.* 2.47 and 2.75, respectively, $P < 0.05$).

What is the relative effectiveness and safety of antidepressants for the treatment of chronic LBP and are there differences by subpopulation?

Efficacy

A meta-analysis of pain outcomes was possible in 6 of the 10 trials comparing antidepressants with placebo.[6] A total of 376 patients with nonspecific chronic LBP with and without radiating pain were analyzed (Table 1). Studies were excluded if patients' LBP was due to specific pathologies such as infection, neoplasm, metastasis, osteoporosis, rheumatoid arthritis, or fractures. No significant difference was seen in pain relief (VAS) between the two study groups (SMD = –0.04; 95% CI, –0.25 to 0.17) (Table 4 and Figure 6). Functional outcome (Oswestry Disability Index, Sickness Impact Profile) and depression (Montgomery Asberg Depression Rating Scale, Beck Depression Inventory) were reported by only two small studies (132 patients) and the pooled analysis showed no significant difference in improvement of either outcome between those on antidepressants and those taking placebo (SMD = –0.06; 95% CI, –0.40 to 0.29 and MD = 0.06; 95% CI, –0.029 to 0.40, respectively) (Table 4 and Figure 6). A separate analysis was performed to evaluate the effect of different types of antidepressants on pain intensity. The pooled analysis revealed no significant difference in pain relief between either tricyclic antidepressants compared with placebo (three trials, 148 patients) or selective serotonin-reuptake inhibitors (SSRI) compared with placebo (three trials, 199 patients) (SMD = –0.10; 95% CI, –0.51 to 0.31 and SMD = 0.11; 95% CI, –0.17 to 0.39, respectively) (Table 4).

Safety

No data on safety were reported in these trials. The adverse effects of antidepressants have been well established in other studies, however, and are reviewed below in the discussion.

Subpopulations

Five studies were identified that reported the efficacy of antidepressants for the treatment of chronic LBP in subpopulations. No significant treatment effects by subgroup were reported by any of the trials (see Table 1, Supplemental Digital Content 1, http://links.lww.com/BRS/A542). One of the studies, which compared Tofranil with placebo in groups with and without previous history of LBP, did report appreciable, though not statistically significant numerical difference between the subgroups.[29] In particular, antidepressants were favored over placebo for decreasing stiffness in patients with no history of LBP, and for decreasing psychosocial symptoms of anxiety, depression, and other traits (Middlesex Hospital Questionnaire), in patients with a history of LBP (see Table 10, Supplemental Digital Content 1, http://links.lww.com/BRS/A542).

Evidence Summary

The overall strength of the evidence evaluating the efficacy of NSAIDs, opioids, and antidepressants is "high," that is, we have high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect (Table 5). There is little research published evaluating subgroup effects among these three drug classes. Therefore, the evidence is "insufficient" for whether specific patients respond more favorably than others to specific pharmacology management strategies. That is, evidence either is unavailable or does not permit a conclusion; however, some hypotheses can be generated and considered for future research planning.

DISCUSSION

The purpose of this systematic review was to determine the relative effectiveness and safety of opioids, NSAIDs, and antidepressants in the treatment of chronic LBP and to determine if the treatment effects differed by subpopulation. We

TABLE 2. Efficacy and Safety Results for Opioids Compared With Placebo and Other Analgesics for the Treatment of CLBP as Reported by the Cochrane Review

Outcome (Follow-up)	No. of Studies	No. of Patients	Opioid Treatment	Effect Size*
Versus placebo				
Efficacy (4–12 weeks)				
Pain†	3	908	Tramadol 37.5 mg + acetaminophen 325 mg (two studies); tramadol 50 mg (max 400 mg daily)	–0.71 (–0.84 to –0.57)
Disability‡	3	878	Tramadol 37.5 mg + acetaminophen 325 mg (two studies); tramadol 50 mg (max 400 mg daily)	–0.17 (–0.30 to –0.04)
Safety/side effects (4–12 weeks)				
Headaches	3	908	Tramadol 37.5 mg + acetaminophen 325 mg (two studies); tramadol 50 mg (max 400 mg daily)	0.09 (0.06–0.12)
Nausea	3	908	Tramadol 37.5 mg + acetaminophen 325 mg (two studies); tramadol 50 mg (max 400 mg daily)	0.03 (0.00–0.06)
Somnolence	2	654	Tramadol 37.5 mg + acetaminophen 325 mg	0.09 (0.05–0.13)
Constipation	2	654	Tramadol 37.5 mg + acetaminophen 325 mg	0.08 (0.04–0.12)
Dry mouth	2	654	Tramadol 37.5 mg + acetaminophen 325 mg	0.07 (0.04–0.10)
Dizziness	2	654	Tramadol 37.5 mg + acetaminophen 325 mg	0.08 (0.04–0.12)
Pruritis	1	318	Not reported	0.06 (0.01–0.10)
Fatigue	1	318	Not reported	0.04 (–0.00 to 0.09)
URTI	1	318	Not reported	–0.02 (–0.08 to 0.03)
Sinusitis	1	318	Not reported	0.02 (–0.03 to 0.06)
Vomiting	1	336	Not reported	0.06 (0.02–0.10)
Anorexia	1	330	Not reported	0.04 (0.01–0.07)
Increased sweating	1	336	Not reported	0.04 (0.01–0.07)
Hot flushes	1	336	Not reported	0.02 (–0.00 to 0.05)
Versus other analgesics (naproxen)				
Efficacy (32 weeks)				
Pain†	1	23	Oxycodone 5 mg (max 20 mg daily); oxycodone + sustained-release morphine sulphate (max 200 mg morphine equivalent daily)	–0.58 (–1.42 to 0.26)
Disability‡	1	23	Oxycodone 5 mg (max 20 mg daily); oxycodone + sustained-release morphine sulphate (max 200 mg morphine equivalent daily)	–0.06 (–0.88 to 0.76)

**For efficacy, the statistical method used was the standard mean difference (IV, fixed, 95% CI); for safety, risk difference (M-H, random, 95% CI).*

†VAS (100 mm) was used to measure pain in two studies; the primary efficacy outcome in the third was the time to discontinuation of therapy due to inadequate pain relief. Higher score means worse pain levels.

‡The Roland Morris Disability Questionnaire was used to measure functional outcome in all three studies; scores range from 0 to 24, 0 = no disability.

CLBP indicates chronic low back pain; max, maximum; URTI, upper respiratory tract infection.

evaluated the relative effectiveness by summarizing recently published Cochrane reviews on each of these drug classes. To examine the effects in subpopulations, we used a systematic approach that would allow us to evaluate study outcomes based on the heterogeneity of treatment effects. We reviewed the full texts of 63 RCTs and identified 12 studies that reported subgroup effects by treatment spread across the three drug classes. This demonstrates a significant deficiency in the literature. Since chronic LBP is likely to be a heterogeneous disorder, related to a heterogeneous set of causes, it

TABLE 3. Efficacy and Safety Results for NSAIDs Compared to Placebo for the Treatment of CLBP as Reported by the Cochrane Review

Outcome	No. of Studies	No. of Patients	NSAID Treatment	Effect Size*
Efficacy				
Change in pain intensity on VAS (100 mm)†	4	1020	Naproxen 275 mg (2 cap 2× daily); diflunisal 250 mg (2 cap 2× daily); valdecoxib 40 mg daily; rofecoxib 25 mg daily, rofecoxib 50 mg daily; indomethacin 25 mg (3× daily)	–12.40 (–15.53 to –9.26)
Safety/side effects				
Proportion of patients experiencing side effects†	4	1034	Naproxen 275 mg (2 cap 2× daily), diflunisal 250 mg (2 cap 2× daily); valdecoxib 40 mg daily; rofecoxib 25 mg daily, rofecoxib 50 mg daily; indomethacin 25 mg (3× daily)	1.24 (1.07–1.43)

**For efficacy, the statistical method used was the mean difference (IV, fixed, 95% CI); for safety, risk ratio (M-H, random, 95% CI).*

†Follow-up ≤ 12 weeks.

NSAIDs indicates nonsteroidal anti-inflammatory drugs; VAS, visual analog scale.

is likely that certain subgroups will respond differently than others to a particular treatment. Since there is a significant deficit in the published literature, with little to no information available on subgroups within the chronic LBP population, it is unfortunately difficult to determine if certain patient groups respond better to pharmacological treatment than others. Such knowledge, if it existed, would likely assist the provider in treatment decision making.

We recognize that prescription of multiple medications or multiple therapies may occur simultaneously. Concomitant therapies are likely to be the norm. For example, a patient with chronic LBP may receive two or more medication therapies, as well as exercise therapies at the same time. There may be an additive effect to such a strategy. This additive effect is discussed in the introduction article in this focus issue. In our analysis of these medications, we were not able to determine the additive effect of multiple or combination pharmacologic therapies.

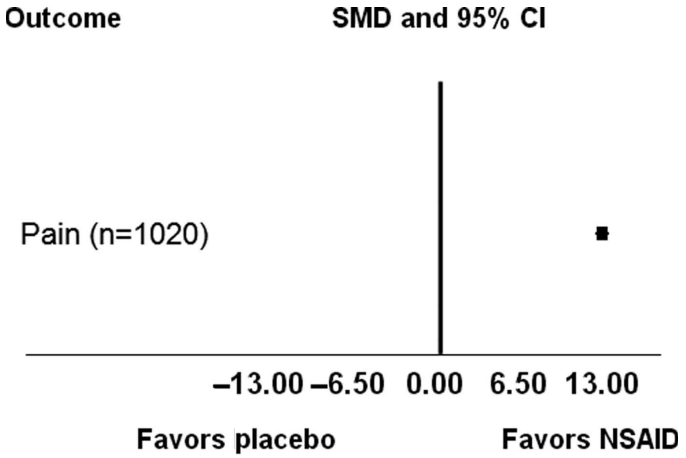


Figure 5. Forest plot representing the standardized mean difference (SMD) and 95% confidence interval (CI) comparing nonsteroidal anti-inflammatory drugs (NSAIDs) to placebo. Treatment effect favors nonsteroidal anti-inflammatory drugs for pain reduction.

We considered three classes of medications in this analysis. We recognize, however, that many other types of medications commonly prescribed. Tylenol is used quite frequently, for example, as are muscle relaxants, anticonvulsants, and others. The three drug classes analyzed (NSAIDs, opioids, and antidepressants) were selected for analysis since the bulk of the available published data is focused on these medications.

In this analysis, we strived to recognize the critical importance of differentiating between the short-term and long-term risks and benefits of these medications. In this inquiry regarding chronic LBP, the long-term safety and efficacy of the pharmacologic treatment is of particular interest. As such, we focused our analysis not only on patients with chronic LBP, but also on medication treatments ongoing for more that 12 weeks. Our conclusions and recommendations also are a reflection of this recognition; the long-term efficacy and the long-term risk profile of habituating medications are considerably different than the short-term efficacy and risks. These well recognized long-term risks include death, and are and well reported.[30]

From our analysis of the Cochrane reviews, we did observe that opioids are more effective than placebo with respect to pain and disability improvement. The effect size was much greater for pain than disability. When compared with NSAIDs, however, in a small trial, there was no significant difference between the two with respect to pain and disability. The rate of side effects related to opioids is significantly greater than placebo, however, ranging from differences of 2% to 9%. The side effects are well known, and can be associated with severe adverse events.[31]

TABLE 4. Efficacy Results for Antidepressants Compared to Placebo for the Treatment of CLBP as Reported by the Cochrane Review

Outcome (Follow-up)	No. of Studies	No. of Patients	Antidepressant Treatment	Effect Size*
Any antidepressants				
Efficacy (4–12 weeks)				
Pain†	6	376	Maprotiline 50 mg/100 mg for 3 days each then 150 mg thereafter, paroxetine 10 mg/20 mg for 3 days each then 30 mg thereafter; despiramine 50, 110 150 ng/mL, fluoxetine 100, 200, 400 ng/mL; paroxetine 20 mg; trazodone 50 mg (up to max 600 mg daily); imipramine 25 mg 3× daily; bupropion SB 150 mg/300 mg	–0.04 (–0.25 to 0.17)
Specific functional status‡	2	132	Paroxetine 20 mg daily; trazodone 50 mg (up to max 600 mg daily)	–0.06 (–0.40 to 0.29)
Depression§	2	132	Paroxetine 20 mg daily; trazodone 50 mg (up to max 600 mg daily)	0.06 (–0.29 to 0.40)
SSRIs				
Efficacy (8–12 weeks)				
Pain¶	3	199	Paroxetine 10 mg/20 mg for 3 days each then 30 mg thereafter; paroxetine 20 mg daily; fluoxetine 100, 200, and 400 ng/mL	0.11 (–0.17 to 0.39)
TCAs				
Efficacy (4–12 weeks)				
Pain‖	4	148	Maprotiline 50 mg/100 mg for 3 days each then 150 mg thereafter; despiramine 50, 110, 150 ng/mL (two arms of the same trial); imipramine 25 mg 3× daily	–0.10 (–0.51 to 0.31)

**Statistical method used was the standard mean difference (IV, fixed, 95% CI).*

†Pain was measured using a pain intensity score (0–20 scale) in three studies, VAS (100 mm) scores in one, VAS (10 mm) scores in one, and an unspecified measure in one.

‡Function was measured using the Oswestry Disability Index and the Sickness Impact Profile physical in one study each.

§Depression was measured using the Montgomery Asberg Depression Rating Scale and the Beck Depression Inventory in one study each.

¶Pain was measured using a pain intensity score (0–20 scale) in two studies and VAS (100 mm) scores in one.

‖Pain was measured using a pain intensity score (0–20 scale) in three studies and the method was not specified in one.

CLBP indicates chronic low back pain; NR, not reported; max, maximum; SSRI, selective serotonin reuptake inhibitors; SR, sustained release; TCA, tricyclic antidepressant.

As for differing effects by subpopulations, only one RCT reported subgroup differences for opioids. Among patients with a history of bowel dysfunction, a combination of oxycodone and naloxone led to significantly better improvement in bowel function compared with oxycodone only. Two other studies did not find treatment effect differences by age, sex, or race.

From the Cochrane review analysis, NSAIDs were found to be significantly more effective than placebo with respect to pain improvement. When compared with opioids in a small trial, however, there was no significant difference between the two with respect to pain and disability. With this comparison indicating similar effectiveness between NSAIDs and opioids, prescribing decision making may then be made on comparisons of other factors. These other factors, such as safety profile, cost, and long-term effectiveness (*i.e.*, risk of habituation) all favor NSAIDs over opioids. NSAIDs are of course not without risk; patients were at a 24% greater risk of side effects when taking NSAIDs instead of placebo. The side effects were not summarized, but the gastrointestinal risks are well established.[32]

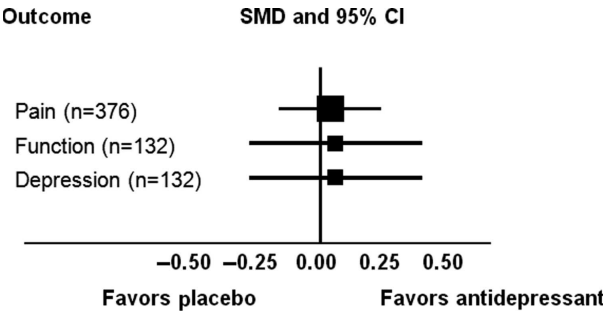


Figure 6. Forest plot representing the standardized mean differences and 95% confidence interval comparing antidepressants to placebo. Treatment effect favors neither antidepressants nor placebo.

TABLE 5. Rating of Overall Strength of Evidence for Each Key Question

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table.

Baseline strength: Risk of bias (including control of confounding) is accounted for in the individual article evaluations. High = majority of articles level I/II. Low = majority of articles Level III/IV. Downgrade: Inconsistency† of results (1 or 2); indirectness of evidence (1 or 2); imprecision of effect estimates (1 or 2); subgroup analyses not stated *a priori* and no test for interaction (2). Upgrade: Large magnitude of effect (1 or 2); dose-response gradient (1).

Question 1: What is the relative effectiveness and safety of opioids in the treatment of chronic LBP in patient subpopulations?

Outcome	Strength of Evidence	Conclusions/Comments	Baseline	Downgrade	Upgrade
Overall Pain Disability Side effects	High	Opioids are more effective than placebo with respect to pain and disability improvement from a meta-analysis including nearly 1000 subjects from three RCTs. The effect size was much greater for pain than disability. However, when compared with NSAIDs in a very small trial, there was no significant difference between the two with respect to pain and disability. The rate of side effects from opioids is significantly greater than placebo ranging from differences of 2% to 9%. The most common side effects are headaches, nausea, somnolence, constipation, dry mouth, dizziness, and pruritis.	High level I/II studies	No	No
Subgroups Bowel dysfunction	Insufficient	Among patients with chronic LBP and history of bowel dysfunction, a combination of oxycodone and naloxone led to significantly better improvement in bowel function compared to oxycodone only.	High level I/II studies	Yes (3) Subgroup analyses not stated *a priori* and inconsistent	No

Question 2: What is the relative effectiveness and safety of NSAIDs for the treatment of chronic LBP in patient subpopulations?

Outcome	Strength of Evidence	Conclusions/Comments	Baseline	Downgrade	Upgrade
Overall Pain Disability Side effects	High	NSAIDs are significantly more effective than placebo with respect to pain improvement from a meta-analysis including over 1000 subjects from four RCTs. The effect size exceeded 12. However, when compared with opioids in a very small trial, there was no significant difference between the two with respect to pain and disability. The relative risk of a side effect taking an NSAID *versus* placebo is significant at 1.24.	High level I/II studies	No	No
Subgroups Anxiety Radiating pain	Insufficient	Patients with no or mild anxiety had a greater reduction in LBP intensity scores with NSAIDs (rofecoxib) compared with placebo. On the contrary, patients with moderate to severe anxiety had a greater reduction with placebo than NSAIDs. In patients who had pain brought on by sneezing, treatment with aspirin and other specific NSAIDs resulted in significantly better pain relief than mefenamic acid. Aspirin was also more effective than indomethacin in this subgroup. When comparing patients with radiating (with or without sneezing) *versus* nonradiating pain, mefenamic acid was significantly more effective in reducing pain than phenylbutazone and indomethacin in patients with nonradiating pain.	High level I/II studies	Yes (3) Subgroup analyses not stated *a priori* and inconsistent	No

Question 3: What is the relative effectiveness and safety of antidepressants for the treatment of chronic LBP in patient subpopulations?

Outcome	Strength of Evidence	Conclusions/Comments	Baseline	Downgrade	Upgrade
Overall Pain Disability Depression Side effects	High	Antidepressants are not more effective than placebo with respect to pain in a meta-analysis of 376 patients from six studies. They were also not more effective with respect to functional status or depression among 132 patients from two studies. There were no differences between differing types of antidepressants. An evaluation of side effects was not reported.	High level I/II studies	No	No

(*Continued*)

TABLE 5. (*Continued*)

Outcome	Strength of Evidence	Conclusions/Comments	Baseline	Downgrade	Upgrade
Subgroups Previous history of LBP	Insufficient	Patients with a previous history of LBP have improved psychosocial outcomes (including anxiety and depression) with antidepressants compared to placebo but less improvement in stiffness.	High level I/II studies	Yes (3) Subgroup analyses not stated *a priori* inconsistent, and imprecise estimates	No

**Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation. Additional domains: dose-response, strength of association, publication bias.*

†Single study = consistency unknown.

AHRQ indicates Agency for Healthcare Research and Quality; LBP, low back pain; NSAIDs, nonsteroidal anti-inflammatory drugs; RCT, randomized controlled trial.

As for differing effects by subpopulations, patients with no or mild anxiety had a greater reduction in LBP intensity scores with NSAIDs (rofecoxib) compared with placebo. On the contrary, patients with moderate to severe anxiety had a greater reduction with placebo than NSAIDs. This is concordant with our hypothesis that in this heterogeneous population, certain subgroups will respond more favorably than others to a particular treatment. Specifically in this case, patients that experience chronic LBP as a manifestation of anxiety, or have LBP exacerbated by anxiety, would not be expected to find relief with an anti-inflammatory medication.

In patients who had pain brought on by sneezing, treatment with aspirin and other specific NSAIDs resulted in significantly better pain relief. Aspirin was also more effective than indomethacin in this subgroup. When comparing patients with radiating (with or without sneezing) *versus* nonradiating pain, mefenamic acid was significantly more effective in reducing pain than phenylbutazone and indomethacin in patients with nonradiating pain.

From the Cochrane review analysis, antidepressants were not found to be more effective than placebo with respect to pain, functional status, or depression. There were no differences found between differing types of antidepressants. While an evaluation of side effects was not reported, significant side effects are well known and are reported elsewhere.[33] From the subgroup analyses, patients with a previous history of LBP had improved psychosocial outcomes (including anxiety and depression) with antidepressants compared with placebo but less improvement in stiffness.

Based on our review, both opioids and NSAIDs appear to have similar efficacy with regard to pain and disability in patients with chronic LBP. Based on the serious side effect profile of opioids, it is recommended that NSAIDs be considered the first line pharmacological treatment for chronic LBP. We recommend that opioids be avoided if possible, particularly in the long-term treatment of this chronic condition, but may be considered as a second line treatment. Antidepressants are no more effective than placebo, however, and as such, we do not recommend that they be used for the treatment of chronic LBP.

➢ Key Points

- ❑ For chronic LBP, opioids are more effective than placebo with respect to effects on pain and disability with a much greater effect on pain than disability.
- ❑ When compared to NSAIDs, opioids did not confer a significantly greater benefit with regard to effects on pain and disability.
- ❑ Antidepressants are not an effective treatment for chronic LBP.
- ❑ Based on the significant rate of side effects with opioids and the lack of convincing superiority over NSAIDs, opioids are not recommended as first line treatment for chronic LBP.

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