

Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline

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Background: A 2007 American College of Physicians guideline addressed pharmacologic options for low back pain. New evidence and medications have now become available.

Purpose: To review the current evidence on systemic pharmacologic therapies for acute or chronic nonradicular or radicular low back pain.

Data Sources: Ovid MEDLINE (January 2008 through November 2016), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and reference lists.

Study Selection: Randomized trials that reported pain, function, or harms of systemic medications versus placebo or another intervention.

Data Extraction: One investigator abstracted data, and a second verified accuracy; 2 investigators independently assessed study quality.

Data Synthesis: The number of trials ranged from 9 (benzodiazepines) to 70 (nonsteroidal anti-inflammatory drugs). New evidence found that acetaminophen was ineffective for acute low back pain, nonsteroidal anti-inflammatory drugs had smaller benefits for chronic low back pain than previously observed, duloxetine was effective for chronic low back pain, and benzodiazepines were ineffective for radiculopathy. For opioids, evidence

remains limited to short-term trials showing modest effects for chronic low back pain; trials were not designed to assess serious harms. Skeletal muscle relaxants are effective for short-term pain relief in acute low back pain but caused sedation. Systemic corticosteroids do not seem to be effective. For effective interventions, pain relief was small to moderate and generally short-term; improvements in function were generally smaller. Evidence is insufficient to determine the effects of antiseizure medications.

Limitations: Qualitatively synthesized new trials with prior meta-analyses. Only English-language studies were included, many of which had methodological shortcomings. Medications injected for local effects were not addressed.

Conclusion: Several systemic medications for low back pain are associated with small to moderate, primarily short-term effects on pain. New evidence suggests that acetaminophen is ineffective for acute low back pain, and duloxetine is associated with modest effects for chronic low back pain.

Primary Funding Source: Agency for Healthcare Research and Quality. (PROSPERO: CRD42014014735)

Ann Intern Med. doi:10.7326/M16-2458

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This article was published at Annals.org on 14 February 2017.

Annals.org

Low back pain is one of the most frequently encountered conditions in clinical practice (1, 2). The most commonly prescribed medications for low back pain are nonsteroidal anti-inflammatory drugs (NSAIDs), skeletal muscle relaxants, antidepressants, and opioids (3–5); benzodiazepines, systemic corticosteroids, and antiseizure medications are also prescribed (3). Patients often use over-the-counter acetaminophen and NSAIDs.

A 2007 guideline (6) and associated systematic review (7) from the American College of Physicians (ACP) and American Pain Society (APS) found evidence to support the use of acetaminophen and NSAIDs as first-line pharmacologic options for low back pain; secondary options were skeletal muscle relaxants, benzodiazepines, and antidepressants. New evidence and medications are now available. Here, we review the current evidence on benefits and harms of medications for low back pain. This article has been used by ACP to update a clinical practice guideline, also in this issue.

METHODS

Detailed methods and data for our review, including the analytic framework, additional medications

(topical capsaicin and lidocaine), nonpharmacologic therapies (addressed in a separate article) (8), search strategies, inclusion criteria, data extraction and quality-rating methods, and additional outcomes (for example, quality of life, global improvement, and patient satisfaction), are available in the full report (9). The protocol was developed by using a standardized process (10) with input from experts and the public and is registered in the PROSPERO database (11). This article addresses the key question, what are the comparative benefits and harms of different systemic pharmacologic therapies for acute or chronic nonradicular low back pain, radicular low back pain, or spinal stenosis?

Data Sources and Searches

A research librarian searched Ovid MEDLINE (January 2007 through April 2015), the Cochrane Central

See also:

Related articles 1
Editorial comment 2

Web-Only
Supplement

Table 1. Definitions for Magnitude of Effects, Based on Mean Between-Group Differences

Slight/Small	Moderate	Large/Substantial
Pain		
5-10 points on a 0- to 100-point VAS or the equivalent	>10-20 points on a 0- to 100-point VAS or the equivalent	>20 points on a 0- to 100-point VAS or the equivalent
0.5-1.0 points on a 0- to 10-point numerical rating scale or the equivalent	>1-2 points on a 0- to 10-point numerical rating scale or the equivalent	>2 points on a 0- to 10-point numerical rating scale or the equivalent
Function		
5-10 points on the ODI	>10-20 points on the ODI	>20 points on the ODI
1-2 points on the RDQ	>2-5 points on the RDQ	>5 points on the RDQ
Pain or function		
0.2-0.5 SMD	>0.5-0.8 SMD	>0.8 SMD

ODI = Oswestry Disability Index; RDQ = Roland Morris Disability Questionnaire; SMD = standardized mean difference; VAS = visual analogue scale.

Register of Controlled Trials, and the Cochrane Database of Systematic Reviews (through April 2015). We used the prior ACP/APS review (12) to identify earlier studies. Updated searches were performed through November 2016. We also reviewed reference lists and searched ClinicalTrials.gov.

Study Selection

Two investigators independently reviewed abstracts and full-text articles against prespecified eligibility criteria. The population was adults with nonradicular or radicular low back pain of any duration (categorized as acute [<4 weeks], subacute [4 to 12 weeks], and chronic [≥ 12 weeks]). Excluded conditions were low back pain due to cancer, infection, inflammatory arthropathy, high-velocity trauma, or fracture; low back pain during pregnancy; and presence of severe or progressive neurologic deficits. We evaluated acetaminophen, NSAIDs, opioids, tramadol and tapentadol, antidepressants, skeletal muscle relaxants, benzodiazepines, corticosteroids, and antiseizure medications versus placebo, no treatment, or other therapies. We also evaluated the combination of 2 medications versus 1 medication alone. Outcomes were long-term (≥ 1 year) or short-term (≤ 6 months) pain or function, mood (for antidepressants), risk for surgery (for corticosteroids), and harms.

Given the large number of medications addressed, we included systematic reviews of randomized trials (13, 14). For each medication, we selected the most recent, most relevant, and highest-quality comprehensive systematic review based on a validated assessment tool (14, 15). If more than 1 good-quality systematic review was available, we preferentially selected updates of those used in the ACP/APS review. We supplemented systematic reviews with additional trials. Although we did not include systematic reviews identified in update searches, we checked reference lists for additional studies. We excluded non-English-language articles and abstract-only publications.

Data Extraction and Quality Assessment

One investigator extracted study data, and a second verified accuracy. For systematic reviews, we abstracted details about inclusion criteria, search strategy, databases searched, search dates, number and charac-

teristics of included studies, quality assessment methods and ratings, synthesis methods, and results. For randomized trials, we abstracted details about the setting, sample size, eligibility criteria, population characteristics, treatment characteristics, results, and funding source.

Two investigators independently assessed the quality of each study as good, fair, or poor using criteria developed by the U.S. Preventive Services Task Force (for randomized trials) (16) and AMSTAR (A Measurement Tool to Assess Systematic Reviews) (14).

For primary studies included in systematic reviews, we used both the quality ratings and the overall grade (for example, good, fair, or poor, or high or low) as determined in the reviews.

We classified the magnitude of effects as small/ slight, moderate, or large/substantial based on the definitions in the ACP/APS review (Table 1) (6, 17). We also reported risk estimates based on the proportion of patients achieving successful pain or function outcomes (for example, $>30\%$ or $>50\%$ improvement).

Data Synthesis and Analysis

We synthesized data qualitatively for each medication, stratified according to the duration of symptoms (acute, subacute, or chronic) and presence or absence of radicular symptoms. We reported meta-analysis results from systematic reviews. When statistical heterogeneity was present, we examined the degree of inconsistency and evaluated subgroup and sensitivity analyses. We did not conduct an updated meta-analysis; rather, we qualitatively examined whether results of new studies were consistent with pooled or qualitative findings from prior systematic reviews. Qualitative assessments were based on whether the findings from the new studies were in the same direction as the prior systematic reviews and whether the magnitude of effects was similar; when prior meta-analyses were available, we analyzed whether the estimates and CIs from new studies were encompassed in the CIs from pooled estimates. We assessed the strength of evidence (SOE) for each body of evidence as high, moderate, low, or insufficient based on aggregate study quality, precision, consistency, and directness (18).

Role of the Funding Source

The Agency for Healthcare Research and Quality (AHRQ) of the U.S. Department of Health and Human Services funded this review. AHRQ staff assisted in developing the scope and key questions. The AHRQ had no role in study selection, quality assessment, or synthesis.

RESULTS

Literature Search

The search and selection of articles are summarized in the **Figure**. Database searches found 2847 potentially relevant articles. After dual review of abstracts and titles, we selected 746 articles for full-text dual review; 46 publications met inclusion criteria. Quality ratings are summarized in **Supplement Tables 1 and 2** (available at [Annals.org](#)).

Acetaminophen

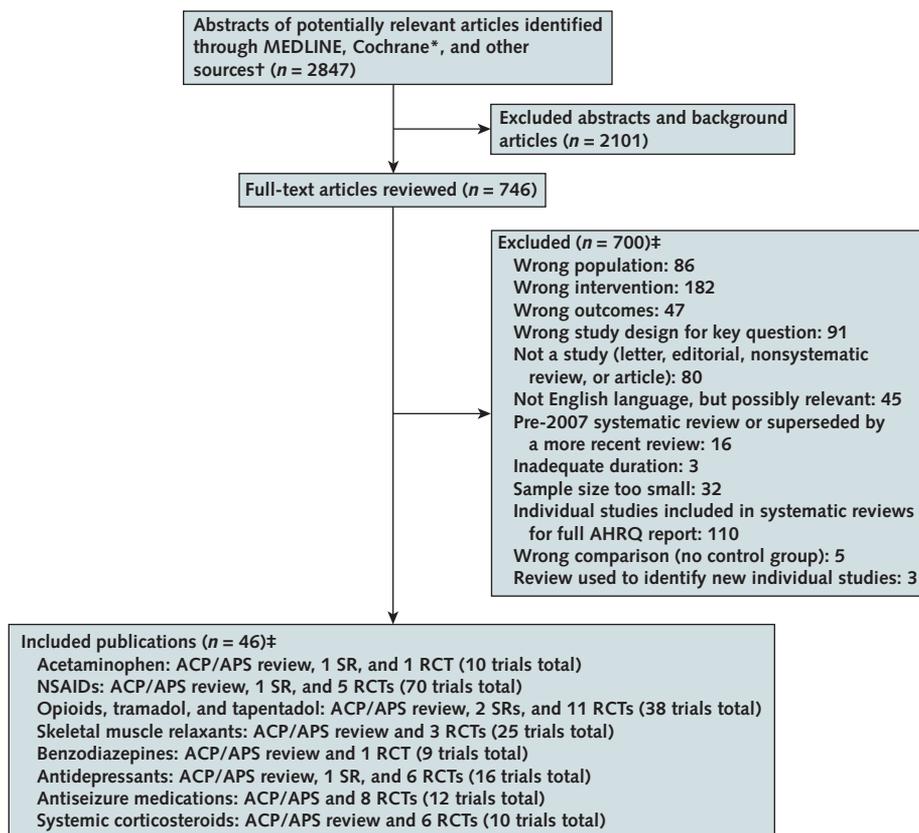
Ten trials evaluated acetaminophen; 9 of these (sample sizes, 39 to 456) were included in the ACP/APS review (19). We identified 1 additional large ($n = 1643$), good-quality, placebo-controlled trial (20). Six trials

compared acetaminophen with NSAIDs and were included in a systematic review of NSAIDs (**Supplement Table 3**, available at [Annals.org](#)) (21, 22). Along with the new trial, 3 others (23–25) were rated good- or high-quality.

For acute low back pain, 1 new trial found no differences between 4 weeks or less of scheduled or as-needed acetaminophen (about 4 g/d) and placebo in pain (differences, ≤ 0.20 point on a 0- to 10-point scale), function (differences, ≤ 0.60 point on the 0- to 24-point Roland-Morris Disability Questionnaire [RDQ]), or risk for serious adverse events (about 1% in each group) after 12 weeks (**Supplement Table 4**, available at [Annals.org](#)) (20). One trial of acetaminophen versus no treatment included in the ACP/APS review (26) also found no differences.

We found no difference between acetaminophen and NSAIDs in pain intensity (standardized mean difference [SMD], 0.21 [95% CI, -0.02 to 0.43]) at 3 weeks or less based on 3 low-quality trials, although estimates favored NSAIDs (22). Acetaminophen had a lower risk for adverse events than NSAIDs (relative risk [RR], 0.57 [CI, 0.36 to 0.89]). Evidence was insufficient to deter-

Figure. Summary of evidence search and selection.



ACP = American College of Physicians; AHRQ = Agency for Healthcare Research and Quality; APS = American Pain Society; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized, controlled trial; SR = systematic review.

* Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

† Other sources include prior reports, reference lists of relevant articles, and systematic reviews.

‡ Publications may be included or excluded for multiple reasons.

mine the effects of acetaminophen versus various non-pharmacologic therapies (24, 27, 28) or amitriptyline (25); each comparison was evaluated in 1 trial with methodological shortcomings. No study evaluated acetaminophen for chronic or radicular low back pain.

NSAIDs

Seventy trials evaluated NSAIDs; 57 were in the ACP/APS review. Sixty-five trials (total $n = 11\,237$; sample sizes, 20 to 690), 28 of which were high-quality, were included in a systematic review (**Supplement Table 3**) (22). We identified 5 additional trials ($n = 54$ to 525) (**Supplement Table 5**, available at Annals.org) (29–33). One trial was rated good-quality (31), and 4 were rated fair-quality (29, 30).

For acute back pain, 1 systematic review (22) found that NSAIDs were associated with greater mean improvements in pain intensity than placebo (4 trials: weighted mean difference, -8.39 points on a 0- to 100-point scale [CI, -12.68 to -4.10 points]; chi-square test, 3.47 points; $P > 0.10$) (34–37). One additional trial ($n = 171$) reported consistent findings (29). Three trials in this review found no differences between an NSAID and placebo in the likelihood of pain relief (38–40). Most trials did not report effects on function, although 1 trial (41) found that NSAIDs were associated with greater improvement on the RDQ than placebo (differences, 2.4 to 2.9 points; $P < 0.001$).

For chronic low back pain, 1 systematic review (22) found that NSAIDs were associated with greater mean pain relief than placebo after 12 weeks (4 trials: weighted mean difference, -12.40 points on a 0- to 100-point scale [CI, -15.53 to -9.26 points]; chi-square test, 1.82 points; $P > 0.50$). However, 2 trials that were not included reported smaller effects on pain (0.41 to 0.59 point after 12 to 16 weeks on a 0- to 10-point scale), although NSAIDs were associated with an increased likelihood of pain relief versus placebo in both studies ($\geq 30\%$ pain relief: 56.8% vs. 31.7% and 37.0% vs. 27.0%; $P < 0.05$ in both studies) (32, 33). Four trials found that NSAIDs were associated with no to small effects on the RDQ versus placebo (mean differences, about 0.02 to 2 points) (32, 33, 42, 43).

For radiculopathy, the ACP/APS review (22) reported small and inconsistent effects on pain from 2 trials (36, 44). Neither study assessed effects on function.

Evidence was insufficient to determine the effects of an NSAID plus another intervention versus this intervention alone or an NSAID versus another intervention (other interventions were a skeletal muscle relaxant, dolotefin, exercise therapy, and massage) (30, 31, 38, 45). Each comparison was evaluated in only 1 trial with methodological shortcomings. There were no clear differences in pain relief between different NSAIDs for acute or chronic low back pain (21 and 6 trials, respectively) (22).

The systematic review (22) found that NSAIDs were associated with more adverse effects than placebo (10 trials: RR, 1.35 [CI, 1.09 to 1.68]), although serious harms were rare. Cyclooxygenase-2-selective NSAIDs

had a lower risk for adverse effects than nonselective NSAIDs (4 trials: RR, 0.83 [CI, 0.70 to 0.99]).

Opioids, Tramadol, and Tapentadol

Twenty-seven trials (sample sizes, 21 to 981) evaluated opioids, tramadol (a dual-action analgesic with weak opioid μ -receptor affinity), or tapentadol (a dual-action analgesic with strong μ -receptor affinity) versus placebo or other treatments; 14 were included in the ACP/APS review and 16 (13 rated low risk of bias) were reported in a systematic review (**Supplement Table 3**) (46). Three trials (1 higher-quality) (47) were included in the ACP/APS review (47–49). We identified 8 additional trials (**Supplement Table 6**, available at Annals.org) (50–57): 2 good-quality (50, 51), 5 fair-quality (53–57), and 1 poor-quality (52). Methodological shortcomings included high attrition (30% to 60% in most trials), use of an enriched enrollment randomized withdrawal design (58) by some trials (47, 52, 56, 57, 59–64), and short follow-up (maximum of 16 weeks) (48). We also identified 11 trials that compared opioids. Eight trials (47, 48, 65–70) were included in a systematic review (71), but 3 others were not (72–74).

For acute low back pain, 1 trial found no difference between oxycodone or acetaminophen plus naproxen ($n = 108$) and placebo plus naproxen ($n = 107$) in pain or function (54).

For chronic low back pain, 1 systematic review (46) found that strong opioids (morphine, oxymorphone, hydromorphone, and tapentadol) were associated with greater short-term relief than placebo for pain (6 trials: SMD, -0.43 [CI, -0.52 to -0.33]; $I^2 = 0.0\%$; mean difference, about 1 point on a 0- to 10-point pain scale) and function (4 trials: SMD, -0.26 [CI, -0.37 to -0.15]; $I^2 = 0.0\%$; mean difference, about 1 point on the RDQ); 4 additional trials (47, 50, 52, 56) reported consistent results. Tramadol also resulted in greater short-term relief than placebo for pain (5 trials: SMD, -0.55 [CI, -0.66 to -0.44]; $I^2 = 86\%$; mean difference, ≤ 1 point on a 0- to 10-point pain scale) and function (5 trials: SMD, -0.18 [CI, -0.29 to -0.07]; $I^2 = 0\%$; mean difference, about 1 point on the RDQ); 2 additional trials (51, 53) reported consistent results. Two trials found that buprenorphine patches were associated with greater short-term pain relief (about 1 point on a 0- to 10-point scale) than placebo patches, with inconsistent effects on function (63, 75–77); 1 additional trial (57) of buccal buprenorphine reported consistent results. Three trials in this review (46) reported inconsistent effects of opioids versus NSAIDs for pain relief (48, 78); 1 of the trials (48) found no difference in function.

The review (46) found that opioids had a higher risk for nausea, dizziness, constipation, vomiting, somnolence, and dry mouth than placebo. Trials were not designed to assess long-term harms or the risk for overdose, abuse, or addiction.

For symptomatic spinal stenosis, a small ($n = 21$) trial found no differences between single-dose immediate-release oxymorphone and placebo in pain, function, or other outcomes (55).

Four trials found no clear differences among various long-acting opioids in pain or function (47, 65, 66, 72, 74). Six trials found no clear differences between long- and short-acting opioids in pain (48, 67-70,73). Although some trials found long-acting opioids associated with greater pain relief, patients randomly assigned to these drugs also received higher doses.

Skeletal Muscle Relaxants

Twenty-five trials (sample sizes, 20 to 562) evaluated skeletal muscle relaxants; 22 (17 high-quality) were included in a systematic review (Supplement Table 3) (79) used in the ACP/APS review. We identified 3 additional fair-quality trials (Supplement Table 7, available at Annals.org) (54, 80, 81).

For acute low back pain, the systematic review (79) found skeletal muscle relaxants superior to placebo for short-term pain relief (≥ 2 -point or 30% improvement on a 0- to 10-point visual analogue scale [VAS]) after 2 to 4 days (4 trials: RR, 1.25 [CI, 1.12 to 1.41]; $I^2 = 0\%$) and 5 to 7 days (3 trials: RR, 1.72 [CI, 1.32 to 2.22]; $I^2 = 0\%$) (79). An additional trial ($n = 562$) reported consistent findings (81). Evidence was insufficient to determine effects on function, which most trials did not report. Compared with placebo, skeletal muscle relaxants were associated with increased risk for any adverse event (8 trials: RR, 1.50 [CI, 1.14 to 1.98]) and central nervous system events (primarily sedation) (8 trials: RR, 2.04 [CI, 1.23 to 3.37]; $I^2 = 50\%$) (79).

Evidence was insufficient from 3 small placebo-controlled trials with inconsistent results and methodological shortcomings to determine the effects of skeletal muscle relaxants on chronic low back pain (82-84). Four trials showed inconsistent effects of a skeletal muscle relaxant plus an NSAID versus an NSAID alone (54, 79, 80). Although estimates from 3 trials favored the combination for effects on pain intensity, the fourth trial found no effects on pain or function (54). Three trials in the review (79) found no differences among various skeletal muscle relaxants on any outcome (85-87).

Benzodiazepines

Nine trials (sample sizes, 30 to 152) evaluated benzodiazepines; 8 of these trials (5 high-quality) were included in a systematic review (79) used in the ACP/APS review (Supplement Table 3). The ninth, a good-quality trial ($n = 60$) (Supplement Table 8, available at Annals.org), evaluated benzodiazepines for radicular pain (88).

For acute nonradicular low back pain, 2 trials reported inconsistent effects of benzodiazepines versus placebo (89, 90); the higher-quality trial ($n = 50$) (89) found no difference between diazepam and placebo in the likelihood of reduced pain and tenderness at 5 days (76% vs. 72%; RR, 1.06 [CI, 0.76 to 1.47]). For chronic nonradicular low back pain, 2 high-quality trials ($n = 50$ and 152) (91, 92) found tetrazepam associated with a lower likelihood of no improvement in pain at 5 to 7 days (RR, 0.82 [CI, 0.72 to 0.94]) and 10 to 14 days (RR, 0.71 [CI, 0.54 to 0.93]) than placebo. Evidence was

inconsistent from 2 trials on the effects of benzodiazepines versus skeletal muscle relaxants (93, 94).

The new trial found no difference in function between diazepam, 5 mg 3 times daily, and placebo for acute radiculopathy (median improvement on the RDQ at 1 week, 3.0 vs. 5.0 points [$P = 0.67$]; median improvement on the RDQ at 1 year, 2 vs. 1 point) (88). Diazepam was less likely to be associated with pain relief of 50% or greater at 1 week (41% vs. 79%; RR, 0.5 [CI, 0.3 to 0.8]).

A systematic review (79) found that compared with placebo, benzodiazepines were associated with greater risk for central nervous system adverse events, such as somnolence, fatigue, and lightheadedness, although harms were not well-reported. No trial was designed to evaluate risk for addiction, abuse, or overdose.

Antidepressants

Sixteen trials ($n = 16$ to 404) evaluated antidepressants; 7 were used in the ACP/APS review, and 10 trials (7 high-quality) were included in a systematic review (Supplement Table 3) (95). We identified 6 additional trials (Supplement Table 9, available at Annals.org): 1 good-quality (96), 3 fair-quality (97-99), and 2 poor-quality (100, 101). Two trials required patients to have depression and low back pain (102, 103). No trial evaluated antidepressants for acute low back pain.

For chronic low back pain, a systematic review (95) found no difference in pain between tricyclic antidepressants (4 trials: SMD, -0.10 [CI, -0.51 to 0.31]; $I^2 = 32\%$) or selective serotonin reuptake inhibitors (3 trials: SMD, 0.11 [CI, -0.17 to 0.39]; $I^2 = 0\%$) and placebo. Antidepressants were not associated with reduced depression (SMD, 0.06 [CI, -0.29 to 0.40]; $I^2 = 0\%$) or improved function (SMD, -0.06 [CI, -0.40 to 0.29]; $I^2 = 0\%$), but each outcome was evaluated in only 2 trials.

Three trials not in that review found that the serotonin norepinephrine reuptake inhibitor duloxetine, 60 mg/d, was associated with lower pain intensity at 12 to 13 weeks, although effects were small (differences, 0.60 to 0.79 point on the 0- to 10-point Brief Pain Inventory severity scale) (96-98). One trial of duloxetine also found an increased likelihood of 50% or greater pain relief after 12 weeks (49% vs. 35%; RR, 1.41 [CI, 1.11 to 1.78]) (97). All 3 trials found that duloxetine was associated with greater improvement in function than placebo on the Brief Pain Inventory interference scale (mean between-group difference, 0.58 to 0.74 point), but 1 trial found no difference on the RDQ (mean change from baseline, -2.69 vs. -2.22 points; $P = 0.26$) (97). There were no differences between duloxetine and placebo in the risk for serious adverse events (96-98), although duloxetine was associated with increased risk for withdrawal due to adverse events (3 trials: odds ratio, 2.72 [CI, 1.74 to 4.24]; $I^2 = 0\%$). Duloxetine was associated with increased risk for nausea ($P < 0.05$).

Evidence to directly compare serotonin norepinephrine reuptake inhibitors with other antidepressants was very limited. One fair-quality trial ($n = 85$) found no

Table 2. Pharmacologic Therapies Versus Placebo for Acute Low Back Pain

Drug	Pain			Function		
	Magnitude of Effect	Evidence	SOE	Magnitude of Effect	Evidence	SOE
Acetaminophen	No effect	1 RCT	Low	No effect	1 RCT	Low
NSAIDs	Small (pain intensity); no effect (pain relief)	1 SR (4 RCTs), 1 RCT	Moderate	Small	2 RCTs	Low
Opioids	No evidence	–	–	No evidence	–	–
Skeletal muscle relaxants	Pain relief: relative risk, 1.72 (95% CI, 1.32–2.22) at 5–7 d	1 SR (4 RCTs), 1 RCT	Moderate	No evidence	–	–
Benzodiazepines	Unable to estimate	2 RCTs	Insufficient	Unable to estimate	2 RCTs	Insufficient
Antiseizure medications	No evidence	–	–	No evidence	–	–
Systemic corticosteroids	No effect	2 RCTs	Low	No effect	2 RCTs	Low

NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized, controlled trial; SOE = strength of evidence; SR = systematic review.

differences between duloxetine and escitalopram (a selective serotonin reuptake inhibitor) in pain or function (96, 99). One small trial ($n = 25$) provided insufficient evidence to determine the effects of duloxetine for radicular pain (101).

Antiseizure Medications

Twelve trials ($n = 29$ to 309) evaluated antiseizure medications; 4 (104–107) were reported in the ACP/APS review (Supplement Table 3). We identified 8 additional trials (Supplement Table 10, available at Annals.org) (108–115). Seven of these (108–113, 115) evaluated pregabalin and 1 (114) evaluated gabapentin. Of the 12 antiseizure medication trials, 6 (106, 108, 109, 111–113) were rated fair-quality and 6 (104, 105, 107, 110, 114, 115) were rated poor-quality.

No trial evaluated antiseizure medications for acute low back pain. For chronic nonradicular back pain, 2 fair-quality trials found that pregabalin was associated with no effects on pain intensity versus placebo (differences, 0.14 to 0.21 point on a 0- to 10-point scale) (108, 111). One trial found no effect on function on the Oswestry Disability Index (ODI) (108), and the other found that pregabalin had slightly worse scores on the RDQ (13 vs. 11 points; $P = 0.01$) (111). Evidence was insufficient to determine adverse effects of topiramate or pregabalin versus placebo because of inconsistent findings.

For chronic radicular back pain, 3 poor-quality trials reported inconsistent findings for gabapentin (dose titrated up to 1200 to 3600 mg/d) versus placebo (105, 107, 114). Effects on pain intensity ranged from 0.3 to 1.9 points on a 0- to 10-point scale. One fair-quality and 1 poor-quality trial reported inconsistent effects of topiramate, with small to moderate effects on some measures of pain (104, 106); no effects on leg pain or the ODI were reported in 1 of the trials (106).

Evidence was insufficient from single trials with methodological shortcomings to determine the effects of pregabalin versus other medications (110, 113, 115) or pregabalin plus another medication versus the other medication alone (109, 112, 113).

Systemic Corticosteroids

Ten trials (sample size, 29 to 269) evaluated systemic corticosteroids; 4 (116–119) were included in the

ACP/APS review (Supplement Table 3). We identified 6 additional trials (Supplement Table 11, available at Annals.org) (120–125). Treatment ranged from a single dose to a 21-day course; corticosteroid doses varied. Eight trials evaluated patients with radiculopathy; of these, 3 (116, 124, 125) required imaging correlation. Four trials (116, 117, 121, 125) were rated good-quality, 5 fair-quality (118–120, 122, 124), and 1 poor-quality (123).

For acute nonradicular low back pain, 2 trials ($n = 86$ and 67) found no differences between a single intramuscular injection or a 5-day course of systemic corticosteroids and placebo in pain or function (117, 120). For spinal stenosis, 1 trial ($n = 61$) found no differences through 12 weeks of follow-up between a 3-week course of prednisone and placebo in pain intensity or the RDQ (124). No trial evaluated systemic corticosteroids for chronic nonradicular pain.

For radicular low back pain of varying duration, 6 trials consistently found no differences between systemic corticosteroids and placebo in pain (116, 118, 119, 121, 123, 125). For function, the largest ($n = 269$) good-quality trial found that systemic corticosteroids were associated with small effects (difference in ODI at 52 weeks, 7.4 [CI, 2.2 to 12.5]) (125), but 2 other trials found no effects (121, 123). Two trials found no effects of systemic corticosteroids on the likelihood of spine surgery (116, 125).

In the largest trial, oral prednisone (initial dose, 60 mg/d) increased risk for any adverse event (49% vs. 24%; $P < 0.001$), insomnia (26% vs. 10%; $P = 0.003$), nervousness (18% vs. 8.0%; $P = 0.03$), and increased appetite (22% vs. 10%; $P = 0.02$) (125). A smaller ($n = 39$) trial found that a tapering course of intramuscular dexamethasone (initial dose, 64 mg/d) was associated with increased risk for any adverse effect (32% vs. 5.0%; RR, 6.32 [CI, 0.84 to 47.7]), but there were no withdrawals due to adverse events (122). Serious harms were not reported in any trial, but harms were not well-reported in some trials.

DISCUSSION

Many systemic pharmacologic therapies have some evidence of effectiveness in acute (Table 2 and

Supplement Table 12, available at Annals.org) or chronic low back pain (Table 3 and Supplement Table 13, available at Annals.org). Benefits were generally observed for short-term (generally <3 months) pain and were small (5 to 10 points on a 100-point VAS) to moderate (10 to 20 points), based on the ACP/APS categories (19). Function was reported less consistently than pain, and effects were typically smaller or not observed. Evidence on other outcomes (for example, quality of life, mood, work, analgesic use, or health care use) was sparse and is described in the full report (9). As in the ACP/APS review, evidence on pharmacologic therapies for radiculopathy was very limited (Table 4). The SOE ratings are summarized in Supplement Table 14 (available at Annals.org).

New evidence affected findings for several medications. The ACP/APS review concluded that acetaminophen was effective for acute low back pain, primarily based on trials showing similar effectiveness of acetaminophen compared with NSAIDs. However, the first large, well-conducted, placebo-controlled trial found that acetaminophen was ineffective for acute low back pain (low SOE) (20). Newer trials reported that NSAIDs had smaller benefits than placebo for chronic low back pain than previously observed (32, 33). For antidepressants, several trials found duloxetine, a serotonin norepinephrine reuptake inhibitor introduced after the prior ACP/APS review, to be more effective than placebo for chronic low back pain, although effects were small (moderate SOE) (96–98). Previous reviews found that tricyclic antidepressants were modestly effective for chronic low back pain; however, a meta-analysis with newer trials found no differences versus placebo (moderate SOE) (95). For antiseizure medications, new placebo-controlled trials on pregabalin for radicular low back pain are available but had methodological shortcomings and reported inconsistent results (insufficient SOE) (108, 111). A recent trial on radiculopathy found that compared with placebo, benzodiazepines

were associated with no difference in function but more pain (low SOE) (88).

Other conclusions were relatively unchanged. Skeletal muscle relaxants relieved short-term acute low back pain but caused sedation (moderate SOE). Systemic corticosteroids do not seem to be effective for radicular or nonradicular low back pain in improving pain (moderate SOE), although a recent trial reported small effects on function (125). Evidence on benzodiazepines for nonradicular back pain remains sparse (insufficient SOE) (23). For opioids, evidence remains limited to short-term trials showing modest effects versus placebo for chronic low back pain (moderate SOE) (46). Trials were not designed to assess the risk for overdose or opioid use disorder because of relatively small samples, short follow-up, and exclusion of higher-risk patients; in addition, many studies used an enriched enrollment randomized withdrawal design, which could underestimate harms (58). Observational studies have found an association between prescribed opioids and serious harms, such as overdose (126), and clinical guidelines recommend risk assessment, careful patient selection, use of lower doses, and close monitoring and follow-up of patients prescribed these drugs (127). For nonopioid medications, serious harms were generally not observed, although the studies were not designed to assess uncommon or longer-term harms.

Relatively few studies compared the effectiveness of different medications for low back pain or a combination of 2 medications versus 1 medication alone. There were no clear differences between opioids and NSAIDs, benzodiazepines and skeletal muscle relaxants, or acetaminophen and NSAIDs.

We categorized the magnitude of effects for pain and function using the thresholds in the ACP/APS review (Table 1). Effects that were classified as small (for example, 5 to 10 points on a 0- to 100-point scale for pain or function) are below some of the proposed thresholds for the minimum clinically important differ-

Table 3. Pharmacologic Therapies Versus Placebo for Chronic Low Back Pain

Drug	Pain			Function		
	Magnitude of Effect	Evidence	SOE	Magnitude of Effect	Evidence	SOE
Acetaminophen	No evidence	–	–	No evidence	–	–
NSAIDs	Small to moderate	1 SR (4 RCTs), 2 RCTs	Moderate	None to small	4 RCTs	Low
Opioids (strong opioids)	Small	1 SR (6 RCTs), 4 RCTs	Moderate	Small	1 SR (4 RCTs), 4 RCTs	Moderate
Opioids (buprenorphine patch or sublingual)	Small	3 RCTs	Low	Unable to estimate	3 RCTs	Insufficient
Tramadol	Moderate	1 SR (5 RCTs), 2 RCTs	Moderate	Small	1 SR (5 RCTs), 2 RCTs	Moderate
Skeletal muscle relaxants	Unable to estimate	3 RCTs	Insufficient	–	–	–
Benzodiazepines: tetrazepam	Failure to improve at 10–14 d: relative risk, 0.71 (95% CI, 0.54–0.93)	1 SR (2 RCTs)	Low	–	–	–
Tricyclic antidepressants	No effect	1 SR (4 RCTs)	Moderate	No effect	1 SR (2 RCTs)	Low
Antidepressants: selective serotonin reuptake inhibitors	No effect	1 SR (3 RCTs)	Moderate	–	–	–
Antidepressants: duloxetine	Small	3 RCTs	Moderate	Small	3 RCTs	Moderate
Gabapentin/pregabalin	Unable to estimate	2 RCTs	Insufficient	Unable to estimate	2 RCTs	Insufficient

NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized, controlled trial; SOE = strength of evidence; SR = systematic review.

Table 4. Pharmacologic Therapies Versus Placebo for Radicular Low Back Pain

Drug	Pain			Function		
	Magnitude of Effect	Evidence	SOE	Magnitude of Effect	Evidence	SOE
NSAIDs	Unable to estimate	1 SR (2 RCTs)	Insufficient	-	-	-
Benzodiazepines: diazepam	Relative risk, 0.5 (95% CI, 0.3-0.8) for pain relief	1 RCT	Low	No effect	1 RCT	Low
Antidepressants: duloxetine	Unable to estimate	1 RCT	Insufficient	Unable to estimate	1 RCT	Insufficient
Systemic corticosteroids	No effect	6 RCTs	Moderate	No to small effect	6 RCTs	Moderate
Gabapentin/pregabalin	Unable to estimate	5 RCTs	Insufficient	Unable to estimate	5 RCTs	Insufficient

NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized, controlled trial; SOE = strength of evidence; SR = systematic review.

ence (for example, 15 points on a 0- to 100-point VAS for pain, 2 points on a 0- to 10-point numerical rating scale for pain or function, 5 points on the RDQ, and 10 points on the ODI) (17). Factors that may support the use of interventions associated with small effects include low risk for harms, low costs, or strong patient preferences; in addition, some patients will have greater-than-average effects. The magnitude of effects might vary depending on baseline severity (128); most trials enrolled patients with at least moderate pain (for example, >5 points on a 0- to 10-point numerical rating scale).

Our findings have implications for clinical practice. Guidelines currently recommend acetaminophen as a first-line option for acute and chronic low back pain (6, 129). The use of opioids for chronic pain has become an area of increasing concern (130). Since the ACP/APS guideline was published, the antidepressant duloxetine has been approved by the U.S. Food and Drug Administration for low back pain and seems to be more effective and safer than tricyclic antidepressants.

Our review has limitations. Reviewing all primary literature was not feasible because of the large number of medications addressed. We included higher-quality, recent systematic reviews that were most relevant to the scope of our review (131), supplemented with additional primary trials. Although we did not update meta-analyses reported in systematic reviews, we evaluated the consistency of results from new trials against prior pooled estimates. We excluded non-English-language articles and did not search for abstract-only publications. Some systematic reviews that we used included such articles but did not affect our conclusions. Our ability to assess for publication bias was limited because of methodological limitations in the trials and study heterogeneity and because few trials were available for many comparisons. Although we did not include new or updated systematic reviews identified in update searches (132-134), we used these searches to identify additional trials. Our findings were generally concordant with new reviews. We did not evaluate the effectiveness of medications injected for local effects; epidural steroid injections were recently reviewed elsewhere (135).

The evidence base has limitations. Effects on pain and function were typically reported as mean differences. Few studies reported the likelihood of clinically significant improvements (136). Data were sparse for

several medications, and many studies had methodological flaws. Some studies did not clearly describe important patient characteristics, such as the duration of symptoms, presence of radiculopathy, or use of co-interventions. Older adults were underrepresented, and most antidepressant trials excluded or included few patients with depression (95). Therefore, evidence to determine how medication effectiveness varies in important subgroups is lacking. Most studies were funded by industry. For example, all placebo-controlled trials of duloxetine for nonradicular low back pain were funded by the manufacturer and nearly all trials of opioids were industry-funded.

More research is needed to determine effective treatments for radicular low back pain. Trials with longer-term follow-up are needed to help understand whether benefits are sustained. Studies are particularly needed on the long-term effectiveness and harms of opioids for chronic low back pain in clinically representative populations. More research is also needed to better understand whether combining medications is associated with incremental benefits and which combinations and sequences of medications are the most effective. Trials should routinely assess important outcomes, such as mood, quality of life, return to work, and health care use, and more consistently and rigorously evaluate and report harms.

In conclusion, several systemic pharmacologic therapies for low back pain are associated with small to moderate, primarily short-term effects on pain. Effects on function were generally smaller than effects on pain. New evidence suggests that acetaminophen is ineffective for acute low back pain and that duloxetine is associated with modest effects for chronic low back pain. More research is needed to understand the optimal selection of medications, the best combinations and sequencing of treatments, and the most effective medications for radicular low back pain.

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Disclaimer: The authors of this manuscript are responsible for its content. A representative from the Agency for Healthcare Research and Quality (AHRQ) served as a Contracting Officer's Technical Representative and provided technical assistance during the conduct of the full evidence report and pro-

vided comments on draft versions of the full evidence report. The AHRQ did not directly participate in the literature search; determination of study eligibility criteria; data analysis or interpretation; or preparation, review, or approval of the manuscript for publication. Statements in the report should not be construed as endorsement by AHRQ or the U.S. Department of Health and Human Services. The AHRQ retains a license to display, reproduce, and distribute the data and the report from which this manuscript was derived under the terms of the Agency's contract with the author.

Grant Support: By contract HHS290201200014I from AHRQ, U.S. Department of Health and Human Services.

Disclosures: Dr. Chou reports grants from AHRQ and funds for manuscript preparation from ACP during the conduct of the study. Dr. Deyo reports grants from AHRQ during the conduct of the study; grants from the National Institutes of Health (NIH), AHRQ, Centers for Disease Control and Prevention, and Patient-Centered Outcomes Research Institute (PCORI) outside the submitted work; personal fees from UpToDate and other support from Kaiser Permanente outside the submitted work; and a financial gift from NuVasive as part of a lifetime achievement award from the International Society for Study of the Lumbar Spine. Dr. Friedly reports grants from AHRQ during the conduct of the study and grants from PCORI and NIH outside the submitted work. Dr. Skelly reports grants from AHRQ during the conduct of the study and other support from the Washington State Health Technology Assessment Program and AOSpine North America outside the submitted work. Dr. Weimer, Ms. Dana, and Ms. Grusing reports grants from AHRQ during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-2458.

Reproducible Research Statement: *Study protocol:* See PROSPERO (www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014014735). *Statistical code:* Not applicable. *Data set:* See the Supplement (available at Annals.org) and full report (available at www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2178).

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