Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society

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Recommendation 1: Clinicians should conduct a focused history and physical examination to help place patients with low back pain into 1 of 3 broad categories: nonspecific low back pain, back pain potentially associated with radiculopathy or spinal stenosis, or back pain potentially associated with another specific spinal cause. The history should include assessment of psychosocial risk factors, which predict risk for chronic disabling back pain (strong recommendation, moderate-quality evidence).

Recommendation 2: Clinicians should not routinely obtain imaging or other diagnostic tests in patients with nonspecific low back pain (strong recommendation, moderate-quality evidence).

Recommendation 3: Clinicians should perform diagnostic imaging and testing for patients with low back pain when severe or progressive neurologic deficits are present or when serious underlying conditions are suspected on the basis of history and physical examination (strong recommendation, moderate-quality evidence).

Recommendation 4: Clinicians should evaluate patients with persistent low back pain and signs or symptoms of radiculopathy or spinal stenosis with magnetic resonance imaging (preferred) or computed tomography only if they are potential candidates for surgery or epidural steroid injection (for suspected radiculopathy) (strong recommendation, moderate-quality evidence).

Recommendation 5: Clinicians should provide patients with evidence-based information on low back pain with regard to their expected course, advise patients to remain active, and provide information about effective self-care options (strong recommendation, moderate-quality evidence).

Recommendation 6: For patients with low back pain, clinicians should consider the use of medications with proven benefits in conjunction with back care information and self-care. Clinicians should assess severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy (strong recommendation, moderate-quality evidence). For most patients, first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs.

Recommendation 7: For patients who do not improve with self-care options, clinicians should consider the addition of nonpharmacologic therapy with proven benefits—for acute low back pain, spinal manipulation; for chronic or subacute low back pain, intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive-behavioral therapy, or progressive relaxation (weak recommendation, moderate-quality evidence).

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Low back pain is the fifth most common reason for all physician visits in the United States (1, 2). Approximately one quarter of U.S. adults reported having low back pain lasting at least 1 whole day in the past 3 months (2), and 7.6% reported at least 1 episode of severe acute low back pain (see Glossary) within a 1-year period (3). Low back pain is also very costly: Total incremental direct health care costs attributable to low back pain in the U.S. were estimated at $26.3 billion in 1998 (4). In addition, indirect costs related to days lost from work are substantial, with approximately 2% of the U.S. work force compensated for back injuries each year (5).

Many patients have self-limited episodes of acute low back pain and do not seek medical care (3). Among those who do seek medical care, pain, disability, and return to work typically improve rapidly in the first month (6). However, up to one third of patients report persistent back pain of at least moderate intensity 1 year after an acute episode, and 1 in 5 report substantial limitations in activity

See also:

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* This paper, written by Roger Chou, MD; Amir Qaseem, MD, PhD, MHA; Vincenza Snow, MD; Donald Casey, MD, MPH, MBA; J. Thomas Cross Jr., MD, MPH; Paul Shekelle, MD, PhD; and Douglas K. Owens, MD, MS, was developed for the American College of Physicians' Clinical Efficacy Assessment Subcommittee and the American College of Physicians/American Pain Society Low Back Pain Guidelines Panel. For members of these groups, see end of text. Approved by the American College of Physicians Board of Regents on 14 July 2007. Approved by the American Pain Society Board Executive Committee on 18 July 2007.

(7). Approximately 5% of the people with back pain disability account for 75% of the costs associated with low back pain (8).

Many options are available for evaluation and management of low back pain. However, there has been little consensus, either within or between specialties, on appropriate clinical evaluation (9) and management (10) of low back pain. Numerous studies show unexplained, large variations in use of diagnostic tests and treatments (11, 12). Despite wide variations in practice, patients seem to experience broadly similar outcomes, although costs of care can differ substantially among and within specialties (13, 14).

The purpose of this guideline is to present the available evidence for evaluation and management of acute and chronic low back pain (see Glossary) in primary care settings. The target audience for this guideline is all clinicians caring for patients with low (lumbar) back pain of any duration, either with or without leg pain. The target patient populations are adults with acute and chronic low back pain not associated with major trauma, children or adolescents with low back pain, and pregnant women; patients with low back pain from sources outside the back (nonspinal low back pain), fibromyalgia or other myofascial pain syndromes, and thoracic or cervical back pain are also included. These recommendations are based on a systematic evidence review summarized in 2 background papers by Chou and colleagues in this issue (15, 16) from an evidence report by the American Pain Society (17). The evidence report (17) discusses the evidence for the evaluation, and the 2 background papers (15, 16) summarize the evidence for management.

Methods

The literature search for this guideline included studies from MEDLINE (1966 through November 2006), the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and EMBASE. The literature search included all English-language articles reporting on randomized, controlled trials of nonpregnant adults (age >18 years) with low back pain (alone or with leg pain) of any duration that evaluated a target medication and reported at least 1 of the following outcomes: back-specific function, generic health status, pain, work disability, or patient satisfaction. The American College of Physicians (ACP) and the American Pain Society (APS) convened a multidisciplinary panel of experts to develop the key questions and scope used to guide the evidence report, review its results, and formulate recommendations. The background papers by Chou and colleagues (15, 16) provide details about the methods used for the systematic evidence review.

This guideline grades its recommendations by using the ACP's clinical practice guidelines grading system, adapted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) work group (**Appendix Table 1**, available at www.annals.org) (18). The evidence in this guideline was first evaluated by the ACP/APS panel by using a system adopted from the U.S. Preventive Services Task Force for grading strength of evidence, estimating magnitude of benefits, and assigning summary ratings (**Appendix Tables 2**, **3**, and **4**, all available at www.annals.org) (19). The evidence was independently reviewed by the ACP's Clinical Efficacy Assessment Subcommittee. The ratings for individual low back pain interventions discussed in this guideline are summarized in **Appendix Table 5** (available at www.annals.org) for acute low back pain (<4 weeks' duration) and in **Appendix Table 6** (available at www.annals.org) for chronic/subacute low back pain (>4 weeks' duration). This guideline considered interventions to have "proven" benefits only when they were supported by at least fair-quality evidence and were associated with at least moderate benefits (or small benefits but no significant harms, costs, or burdens). **Figures 1** and **2** present an accompanying algorithm.

Recommendations: Evaluation of Low Back Pain

Recommendation 1: Clinicians should conduct a focused history and physical examination to help place patients with low back pain into 1 of 3 broad categories: nonspecific low back pain, back pain potentially associated with radiculopathy or spinal stenosis, or back pain potentially associated with another specific spinal cause. The history should include assessment of psychosocial risk factors, which predict risk for chronic disabling back pain (strong recommendation, moderate-quality evidence).

More than 85% of patients who present to primary care have low back pain that cannot reliably be attributed to a specific disease or spinal abnormality (nonspecific low back pain [see Glossary]) (20). Attempts to identify specific anatomical sources of low back pain in such patients have not been validated in rigorous studies, and classification schemes frequently conflict with one another (21). Moreover, no evidence suggests that labeling most patients with low back pain by using specific anatomical diagnoses improves outcomes. In a minority of patients presenting for initial evaluation in a primary care setting, low back pain is caused by a specific disorder, such as cancer (approximately 0.7% of cases), compression fracture (4%), or spinal infection (0.01%) (22). Estimates for prevalence of ankylosing spondylitis in primary care patients range from 0.3% (22) to 5% (23). Spinal stenosis (see Glossary) and symptomatic herniated disc (see Glossary) are present in about 3% and 4% of patients, respectively. The cauda equina syndrome (see Glossary) is most commonly associated with massive midline disc herniation but is rare, with an estimated prevalence of 0.04% among patients with low back pain (24).

A practical approach to assessment is to do a focused history and physical examination to determine the likelihood of specific underlying conditions and measure the

presence and level of neurologic involvement (24, 25). Such an approach facilitates classification of patients into 1 of 3 broad categories: nonspecific low back pain, back pain potentially associated with radiculopathy (see Glossary) or spinal stenosis (suggested by the presence of sciatica [see Glossary] or pseudoclaudication), and back pain potentially associated with another specific spinal cause. The latter category includes the small proportion of patients with serious or progressive neurologic deficits or underlying conditions requiring prompt evaluation (such as tumor, infection, or the cauda equina syndrome), as well as patients with other conditions that may respond to specific treatments (such as ankylosing spondylitis or vertebral compression fracture).

Diagnostic triage into 1 of these 3 categories helps guide subsequent decision making. Clinicians should inquire about the location of pain, frequency of symptoms, and duration of pain, as well as any history of previous symptoms, treatment, and response to treatment. The possibility of low back pain due to problems outside the back, such as pancreatitis, nephrolithiasis, or aortic aneurysm, or systemic illnesses, such as endocarditis or viral syndromes, should be considered. All patients should be evaluated for the presence of rapidly progressive or severe neurologic deficits, including motor deficits at more than 1 level, fecal incontinence, and bladder dysfunction. The most frequent finding in the cauda equina syndrome is urinary retention (90% sensitivity) (24). In patients without urinary retention, the probability of the cauda equina syndrome is approximately 1 in 10 000.

Clinicians should also ask about risk factors for cancer and infection. In a large, prospective study from a primary care setting, a history of cancer (positive likelihood ratio, 14.7), unexplained weight loss (positive likelihood ratio, 2.7), failure to improve after 1 month (positive likelihood ratio, 3.0), and age older than 50 years (positive likelihood ratio, 2.7) were each associated with a higher likelihood for cancer (26). The posttest probability of cancer in patients presenting with back pain increases from approximately 0.7% to 9% in patients with a history of cancer (not including nonmelanoma skin cancer). In patients with any 1 of the other 3 risk factors, the likelihood of cancer only increases to approximately 1.2% (26). Features predicting the presence of vertebral infection have not been well studied but may include fever, intravenous drug use, or recent infection (22). Clinicians should also consider risk factors for vertebral compression fracture, such as older age, history of osteoporosis, and steroid use, and ankylosing spondylitis, such as younger age, morning stiffness, improvement with exercise (see Glossary), alternating buttock pain, and awakening due to back pain during the second part of the night only (27), as specific treatments are available for these conditions. Clinicians should be aware that criteria for diagnosing early ankylosing spondylitis (before the development of radiographic abnormalities) are evolving (28).

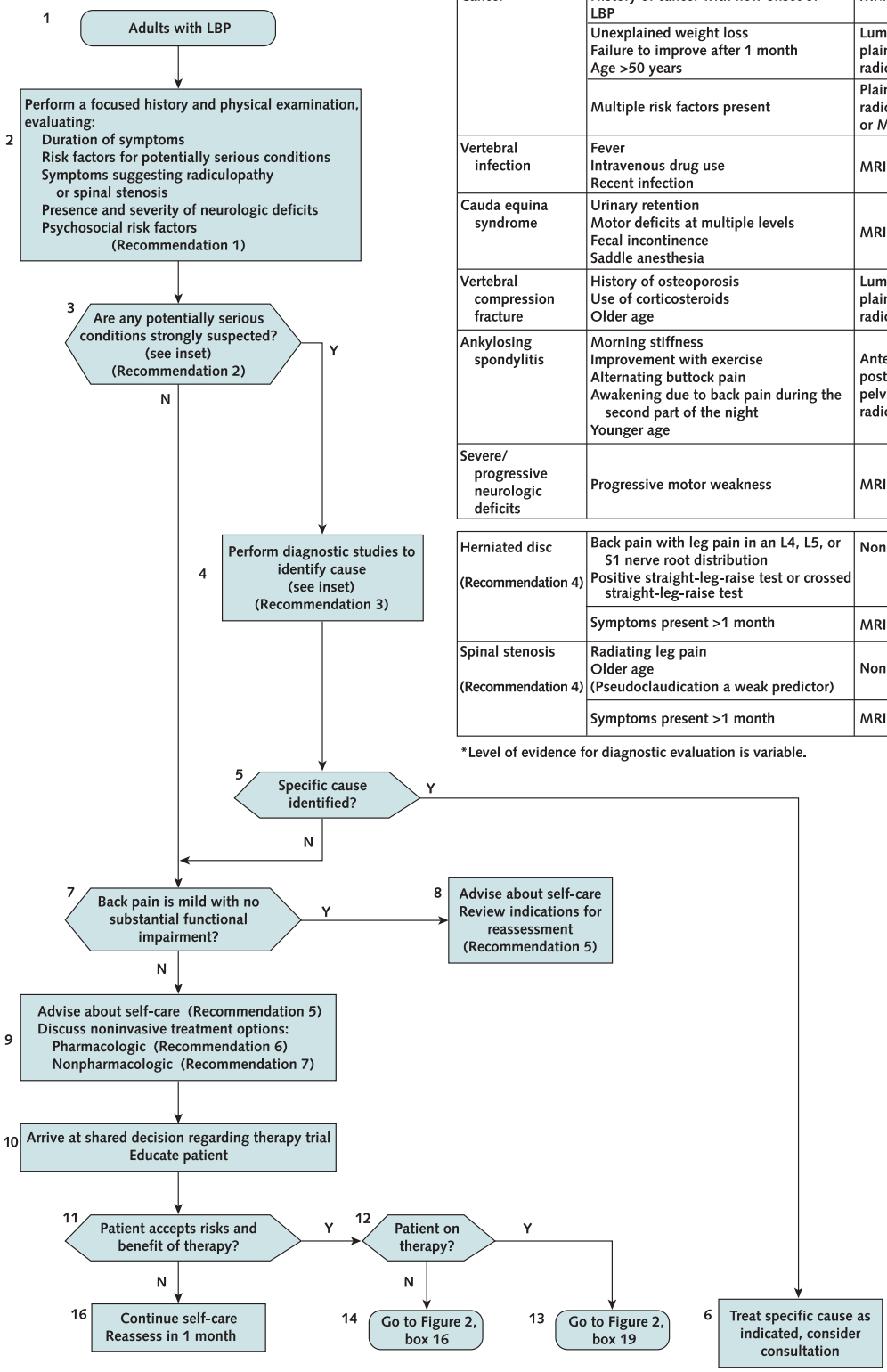
In patients with back and leg pain, a typical history for sciatica (back and leg pain in a typical lumbar nerve root distribution) has a fairly high sensitivity but uncertain specificity for herniated disc (29, 30). More than 90% of symptomatic lumbar disc herniations (back and leg pain due to a prolapsed lumbar disc compressing a nerve root) occur at the L4/L5 and L5/S1 levels. A focused examination that includes straight-leg-raise testing (see Glossary) and a neurologic examination that includes evaluation of knee strength and reflexes (L4 nerve root), great toe and foot dorsiflexion strength (L5 nerve root), foot plantarflexion and ankle reflexes (S1 nerve root), and distribution of sensory symptoms should be done to assess the presence and severity of nerve root dysfunction. A positive result on the straight-leg-raise test (defined as reproduction of the patient's sciatica between 30 and 70 degrees of leg elevation) (24) has a relatively high sensitivity (91% [95% CI, 82% to 94%]) but modest specificity (26% [CI, 16% to 38%]) for diagnosing herniated disc (31). By contrast, the crossed straight-leg-raise test is more specific (88% [CI, 86% to 90%]) but less sensitive (29% [CI, 24% to 34%]).

Evidence on the utility of history and examination for identifying lumbar spinal stenosis is sparse (32). High-quality studies showed a trade-off between sensitivities and specificities, resulting in modest or poor positive likelihood ratios (1.2 for pseudoclaudication and 2.2 for radiating leg pain) (32). Changing symptoms on downhill treadmill testing are associated with the highest positive likelihood ratio (3.1). The usefulness of pain relieved by sitting for predicting presence of spinal stenosis ranges from poor to high (32). Age older than 65 years was associated with a positive likelihood ratio of 2.5 and a negative likelihood ratio of 0.33 in 1 lower-quality study (33). Other findings have only been evaluated in lower-quality studies or are poorly predictive for lumbar spinal stenosis.

Psychosocial factors and emotional distress should be assessed because they are stronger predictors of low back pain outcomes than either physical examination findings or severity and duration of pain (6, 34, 35). Assessment of psychosocial factors identifies patients who may have delayed recovery and could help target interventions, as 1 trial in a referral setting found intensive multidisciplinary rehabilitation more effective than usual care in patients with acute or subacute low back pain identified as having risk factors for chronic back pain disability (36). Direct evidence on effective primary care interventions for identifying and treating such factors in patients with acute low back pain is lacking (37, 38), although this is an area of active research. Evidence is currently insufficient to recommend optimal methods for assessing psychosocial factors and emotional distress. However, psychosocial factors that may predict poorer low back pain outcomes include presence of depression, passive coping strategies, job dissatisfaction, higher disability levels, disputed compensation claims, or somatization (34, 35, 39).

Evidence is also insufficient to guide appropriate inter-

Figure 1. **Initial evaluation of low back pain (*LBP*).**



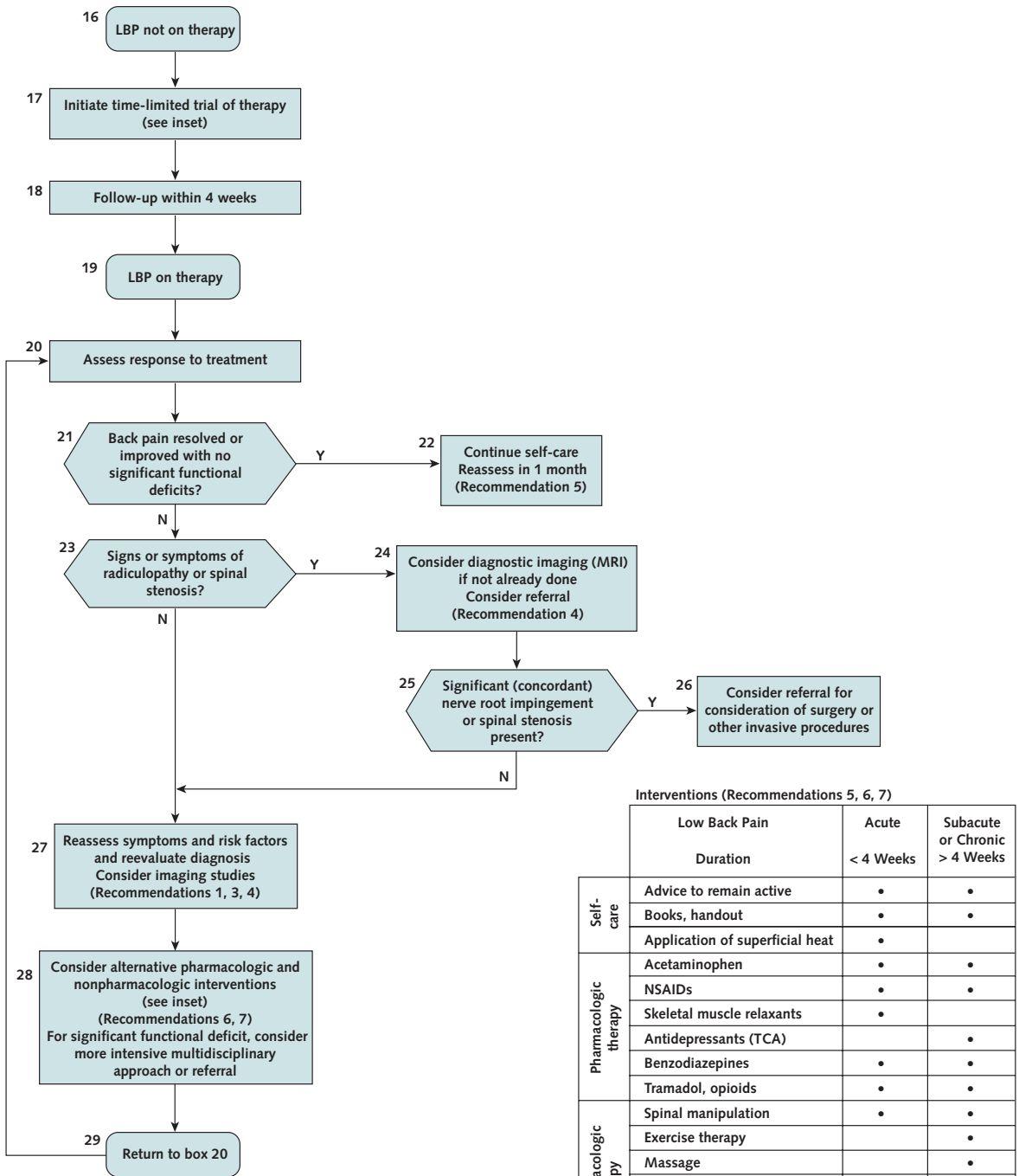
Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging*	Additional studies*
Cancer	History of cancer with new onset of LBP	MRI	ESR
	Unexplained weight loss Failure to improve after 1 month Age >50 years	Lumbosacral plain radiography	
	Multiple risk factors present	Plain radiography or MRI	
Vertebral infection	Fever Intravenous drug use Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	Urinary retention Motor deficits at multiple levels Fecal incontinence Saddle anesthesia	MRI	None
Vertebral compression fracture	History of osteoporosis Use of corticosteroids Older age	Lumbosacral plain radiography	None
Ankylosing spondylitis	Morning stiffness Improvement with exercise Alternating buttock pain Awakening due to back pain during the second part of the night Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Severe/progressive neurologic deficits	Progressive motor weakness	MRI	Consider EMG/NCV
Herniated disc (Recommendation 4)	Back pain with leg pain in an L4, L5, or S1 nerve root distribution Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	Symptoms present >1 month	MRI	Consider EMG/NCV
Spinal stenosis (Recommendation 4)	Radiating leg pain Older age (Pseudoclaudication a weak predictor)	None	None
	Symptoms present >1 month	MRI	Consider EMG/NCV

*Level of evidence for diagnostic evaluation is variable.

Do not use this algorithm for back pain associated with major trauma, nonspinal back pain, or back pain due to systemic illness. CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Figure 2. **Management of low back pain (*LBP*).**



Interventions (Recommendations 5, 6, 7)

	Low Back Pain Duration	Acute < 4 Weeks	Subacute or Chronic > 4 Weeks
Self-care	Advice to remain active	•	•
	Books, handout	•	•
	Application of superficial heat	•	
Pharmacologic therapy	Acetaminophen	•	•
	NSAIDs	•	•
	Skeletal muscle relaxants	•	
	Antidepressants (TCA)		•
	Benzodiazepines	•	•
	Tramadol, opioids	•	•
Nonpharmacologic therapy	Spinal manipulation	•	•
	Exercise therapy		•
	Massage		•
	Acupuncture		•
	Yoga		•
	Cognitive-behavioral therapy		•
	Progressive relaxation		•
	Intensive interdisciplinary rehabilitation		•

• Interventions supported by grade B evidence (at least fair-quality evidence of moderate benefit, or small benefit but no significant harms, costs, or burdens). No intervention was supported by grade A evidence (good-quality evidence of substantial benefit).

MRI = magnetic resonance imaging; NSAIDs = nonsteroidal anti-inflammatory drugs; TCA = tricyclic antidepressants.

vals or methods (such as office visit vs. telephone follow-up) for reassessment of history, physical examination, or psychosocial factors. However, patients with acute low back pain generally experience substantial improvement in the first month after initial presentation (6, 40), suggesting that a reasonable approach is to reevaluate patients with persistent, unimproved symptoms after 1 month. In patients with severe pain or functional deficits, older patients, or patients with signs of radiculopathy or spinal stenosis (see recommendation 4), earlier or more frequent reevaluation may also be appropriate.

Recommendation 2: Clinicians should not routinely obtain imaging or other diagnostic tests in patients with nonspecific low back pain (strong recommendation, moderate-quality evidence).

There is no evidence that routine plain radiography in patients with nonspecific low back pain is associated with a greater improvement in patient outcomes than selective imaging (41–43). In addition, exposure to unnecessary ionizing radiation should be avoided. This issue is of particular concern in young women because the amount of gonadal radiation from obtaining a single plain radiograph (2 views) of the lumbar spine is equivalent to being exposed to a daily chest radiograph for more than 1 year (44). Routine advanced imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) is also not associated with improved patient outcomes (45) and identifies many radiographic abnormalities that are poorly correlated with symptoms (22) but could lead to additional, possibly unnecessary interventions (46, 47).

Plain radiography is recommended for initial evaluation of possible vertebral compression fracture in selected higher-risk patients, such as those with a history of osteoporosis or steroid use (22). Evidence to guide optimal imaging strategies is not available for low back pain that persists for more than 1 to 2 months despite standard therapies if there are no symptoms suggesting radiculopathy or spinal stenosis, although plain radiography may be a reasonable initial option (see recommendation 4 for imaging recommendations in patients with symptoms suggesting radiculopathy or spinal stenosis). Thermography and electrophysiologic testing are not recommended for evaluation of nonspecific low back pain.

Recommendation 3: Clinicians should perform diagnostic imaging and testing for patients with low back pain when severe or progressive neurologic deficits are present or when serious underlying conditions are suspected on the basis of history and physical examination (strong recommendation, moderate-quality evidence).

Prompt work-up with MRI or CT is recommended in patients who have severe or progressive neurologic deficits or are suspected of having a serious underlying condition (such as vertebral infection, the cauda equina syndrome, or cancer with impending spinal cord compression) because delayed diagnosis and treatment are associated with poorer outcomes (48–50). Magnetic resonance imaging is generally preferred over CT if available because it does not use ionizing radiation and provides better visualization of soft tissue, vertebral marrow, and the spinal canal (22). There is insufficient evidence to guide precise recommendations on diagnostic strategies in patients who have risk factors for cancer but no signs of spinal cord compression. Several strategies have been proposed for such patients (22, 51), but none have been prospectively evaluated. Proposed strategies generally recommend plain radiography or measurement of erythrocyte sedimentation rate (a rate $\geq$20 mm/h is associated with 78% sensitivity and 67% specificity for cancer [29]), with MRI reserved for patients with abnormalities on initial testing (22, 51). An alternative strategy is to directly perform MRI in patients with a history of cancer, the strongest predictor of vertebral cancer (51). For patients older than 50 years of age without other risk factors for cancer, delaying imaging while offering standard treatments and reevaluating within 1 month may also be a reasonable option (52).

Recommendation 4: Clinicians should evaluate patients with persistent low back pain and signs or symptoms of radiculopathy or spinal stenosis with MRI (preferred) or CT only if they are potential candidates for surgery or epidural steroid injection (for suspected radiculopathy) (strong recommendation, moderate-quality evidence).

The natural history of lumbar disc herniation with radiculopathy in most patients is for improvement within the first 4 weeks with noninvasive management (53, 54). There is no compelling evidence that routine imaging affects treatment decisions or improves outcomes (55). For prolapsed lumbar disc with persistent radicular symptoms despite noninvasive therapy, discectomy or epidural steroids are potential treatment options (56–60). Surgery is also a treatment option for persistent symptoms associated with spinal stenosis (61–64).

Magnetic resonance imaging (preferred if available) or CT is recommended for evaluating patients with persistent back and leg pain who are potential candidates for invasive interventions—plain radiography cannot visualize discs or accurately evaluate the degree of spinal stenosis (22). However, clinicians should be aware that findings on MRI or CT (such as bulging disc without nerve root impingement) are often nonspecific. Recommendations for specific invasive interventions, interpretation of radiographic findings, and additional work-up (such as electrophysiologic testing) are beyond the scope of this guideline, but decisions should be based on the clinical correlation between symptoms and radiographic findings, severity of symptoms, patient preferences, surgical risks (including the patient's comorbid conditions), and costs and will generally require specialist input.

RECOMMENDATIONS: TREATMENT OF LOW BACK PAIN

Recommendation 5: Clinicians should provide patients with evidence-based information on low back pain with regard to their expected course, advise patients to remain active,

and provide information about effective self-care options (strong recommendation, moderate-quality evidence).

Clinicians should inform all patients of the generally favorable prognosis of acute low back pain with or without sciatica, including a high likelihood for substantial improvement in the first month (6, 40). Clinicians should explain that early, routine imaging and other tests usually cannot identify a precise cause, do not improve patient outcomes, and incur additional expenses. Clinicians should also review indications for reassessment and diagnostic testing (see recommendations 1 and 4). General advice on self-management for nonspecific low back pain should include recommendations to remain active, which is more effective than resting in bed for patients with acute or subacute low back pain (65, 66). If patients require periods of bed rest to relieve severe symptoms, they should be encouraged to return to normal activities as soon as possible. Self-care education books (see Glossary) based on evidence-based guidelines, such as *The Back Book* (67), are recommended because they are an inexpensive and efficient method for supplementing clinician-provided back information and advice and are similar or only slightly inferior in effectiveness to such costlier interventions as supervised exercise therapy, acupuncture (see Glossary), massage (see Glossary), and spinal manipulation (see Glossary) (65, 66, 68–70). Other methods for providing self-care education, such as e-mail discussion groups, layperson-led groups, videos, and group classes, are not as well studied.

Factors to consider when giving advice about activity limitations to workers with low back pain are the patient's age and general health and the physical demands of required job tasks. However, evidence is insufficient to guide specific recommendations about the utility of modified work for facilitating return to work (71). For worker's compensation claims, clinicians should refer to specific regulations for their area of practice, as rules vary substantially from state to state. Brief individualized educational interventions (defined as a detailed clinical examination and advice, typically lasting several hours over 1 to 2 sessions) (see Glossary) can reduce sick leave in workers with subacute low back pain (72–74).

Application of heat by heating pads or heated blankets is a self-care option (see Glossary) for short-term relief of acute low back pain (75). In patients with chronic low back pain, firm mattresses are less likely than a medium-firm mattress to lead to improvement (76). There is insufficient evidence to recommend lumbar supports (77) or the application of cold packs (75) as self-care options.

Although evidence is insufficient to guide specific self-management recommendations for patients with acute radiculopathy or spinal stenosis, some trials enrolled mixed populations of patients with and without sciatica, suggesting that applying principles similar to those used for nonspecific low back pain is a reasonable approach (see also recommendation 4).

Recommendation 6: For patients with low back pain, clinicians should consider the use of medications with proven benefits in conjunction with back care information and self-care. Clinicians should assess severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy (strong recommendation, moderate-quality evidence). For most patients, first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs).

Medications in several classes have been shown to have moderate, primarily short-term benefits for patients with low back pain. Each class of medication is associated with unique trade-offs involving benefits, risks, and costs. For example, acetaminophen is a slightly weaker analgesic than NSAIDs (<10 points on a 100-point visual analogue pain scale) (78–82) but is a reasonable first-line option for treatment of acute or chronic low back pain because of a more favorable safety profile and low cost (79, 82–84). However, acetaminophen is associated with asymptomatic elevations of aminotransferase levels at dosages of 4 g/d (the upper limit of U.S. Food and Drug Administration–[FDA] approved dosing) even in healthy adults, although the clinical significance of these findings are uncertain (85). Nonselective NSAIDs are more effective for pain relief than is acetaminophen (80), but they are associated with well-known gastrointestinal and renovascular risks (83). In addition, there is an association between exposure to cyclooxygenase-2–selective or most nonselective NSAIDs and increased risk for myocardial infarction (86). Clinicians should therefore assess cardiovascular and gastrointestinal risk factors before prescribing NSAIDs and recommend the lowest effective doses for the shortest periods necessary. Clinicians should also remain alert for new evidence about which NSAIDs are safest and consider strategies for minimizing adverse events in higher-risk patients who are prescribed NSAIDs (such as co-administration with a proton-pump inhibitor) (87). There is insufficient evidence to recommend for or against analgesic doses of aspirin in patients with low back pain (88).

Opioid analgesics or tramadol are an option when used judiciously in patients with acute or chronic low back pain who have severe, disabling pain that is not controlled (or is unlikely to be controlled) with acetaminophen and NSAIDs. Because of substantial risks, including aberrant drug-related behaviors with long-term use in patients vulnerable or potentially vulnerable to abuse or addiction, potential benefits and harms of opioid analgesics should be carefully weighed before starting therapy (89–91). Failure to respond to a time-limited course of opioids should lead to reassessment and consideration of alternative therapies or referral for further evaluation (92–94). Evidence is insufficient to recommend one opioid over another (95).

The term *skeletal muscle relaxants* refers to a diverse group of medications, some with unclear mechanisms of action, grouped together because they carry FDA-approved indications for treatment of musculoskeletal conditions or spasticity. Although the antispasticity drug tizanidine has

Glossary

General

Acute low back pain	Low back pain present for fewer than 4 weeks, sometimes grouped with subacute low back pain as symptoms present for fewer than 3 months.
Cauda equina syndrome	Compression on nerve roots from the lower cord segments, usually due to a massive, centrally herniated disc, which can result in urinary retention or incontinence from loss of sphincter function, bilateral motor weakness of the lower extremities, and saddle anesthesia.
Chronic low back pain	Low back pain present for more than 3 months.
Herniated disc	Herniation of the nucleus pulposus of an intervertebral disc through its fibrous outer covering, which can result in compression of adjacent nerve roots or other structures.
Neurogenic claudication	Symptoms of leg pain (and occasionally weakness) on walking or standing, relieved by sitting or spinal flexion, associated with spinal stenosis.
Nonspecific low back pain	Pain occurring primarily in the back with no signs of a serious underlying condition (such as cancer, infection, or cauda equina syndrome), spinal stenosis or radiculopathy, or another specific spinal cause (such as vertebral compression fracture or ankylosing spondylitis). Degenerative changes on lumbar imaging are usually considered nonspecific, as they correlate poorly with symptoms.
Radiculopathy	Dysfunction of a nerve root associated with pain, sensory impairment, weakness, or diminished deep tendon reflexes in a nerve root distribution.
Sciatica	Pain radiating down the leg below the knee in the distribution of the sciatic nerve, suggesting nerve root compromise due to mechanical pressure or inflammation. Sciatica is the most common symptom of lumbar radiculopathy.
Spinal stenosis	Narrowing of the spinal canal that may result in bony constriction of the cauda equina and the emerging nerve roots.
Straight-leg-raise test	A procedure in which the hip is flexed with the knee extended in order to passively stretch the sciatic nerve and elicit symptoms suggesting nerve root tension. A positive test is usually considered reproduction of the patient's sciatica when the leg is raised between 30 and 70 degrees. Reproduction of the patient's sciatica when the unaffected leg is lifted is referred to as a positive "crossed" straight-leg-raise test.

Interventions

Acupressure	An intervention consisting of manipulation with the fingers instead of needles at specific acupuncture points.
Acupuncture	An intervention consisting of the insertion of needles at specific acupuncture points.
Back school	An intervention consisting of education and a skills program, including exercise therapy, in which all lessons are given to groups of patients and supervised by a paramedical therapist or medical specialist.
Brief individualized educational interventions	Individualized assessment and education about low back pain problems without supervised exercise therapy or other specific interventions. As we defined them, brief educational interventions differ from back schools because they do not involve group education or supervised exercise.
Exercise	A supervised exercise program or formal home exercise regimen, ranging from programs aimed at general physical fitness or aerobic exercise to programs aimed at muscle strengthening, flexibility, stretching, or different combinations of these elements.
Functional restoration (also called *physical conditioning, work hardening,* or *work conditioning*)	An intervention that involves simulated or actual work tests in a supervised environment in order to enhance job performance skills and improve strength, endurance, flexibility, and cardiovascular fitness in injured workers.
Interdisciplinary rehabilitation (also called *multidisciplinary therapy*)	An intervention that combines and coordinates physical, vocational, and behavioral components and is provided by multiple health care professionals with different clinical backgrounds. The intensity and content of interdisciplinary therapy varies widely.
Interferential therapy	The superficial application of a medium-frequency alternating current modulated to produce low frequencies up to 150 Hz. It is thought to increase blood flow to tissues and provide pain relief and is considered more comfortable for patients than transcutaneous electrical nerve stimulation.
Low-level laser therapy	The superficial application of lasers at wavelengths between 632 and 904 nm to the skin in order to apply electromagnetic energy to soft tissue. Optimal treatment parameters (wavelength, dosage, dose-intensity, and type of laser) are uncertain.
Massage	Soft tissue manipulation using the hands or a mechanical device through a variety of specific methods. The pressure and intensity used in different massage techniques vary widely.
Neuroreflexotherapy	A technique from Spain characterized by the temporary implantation of staples superficially into the skin over trigger points in the back and referred tender points in the ear. Neuroreflexotherapy is believed to stimulate different zones of the skin than acupuncture.
Percutaneous electrical nerve stimulation (PENS)	An intervention that involves inserting acupuncture-like needles and applying low-level electrical stimulation. It differs from electroacupuncture in that the insertion points target dermatomal levels for local pathology, rather than acupuncture points. However, there is some uncertainty over whether PENS should be considered a novel therapy or a form of electroacupuncture.
Progressive relaxation	A technique which involves the deliberate tensing and relaxation of muscles, in order to facilitate the recognition and release of muscle tension.
Self-care options	Interventions that can be readily implemented by patients without seeing a clinician or that can be implemented on the basis of advice provided at a routine clinic visit.
Self-care education book	Reading material (books, booklets, or leaflets) that provide education and self-care advice for patients with low back pain. Although the specific content varies, self-care books are generally based on principles from published clinical practice guidelines and encourage a return to normal activity, adoption of a fitness program, and appropriate lifestyle modification, and they provide advice on coping strategies and managing flares.
Shortwave diathermy	Therapeutic elevation of the temperature of deep tissues by application of short-wave electromagnetic radiation with a frequency range from 10–100 MHz.

Continued on following page

Glossary—**Continued**

Spa therapy	An intervention involving several interventions, including mineral water bathing, usually with heated water, typically while staying at a spa resort.
Spinal manipulation	Manual therapy in which loads are applied to the spine by using short- or long-lever methods and high-velocity thrusts are applied to a spinal joint beyond its restricted range of movement. Spinal mobilization, or low-velocity, passive movements within or at the limit of joint range, is often used in conjunction with spinal manipulation.
Traction	An intervention involving drawing or pulling in order to stretch the lumbar spine. Various methods are used, usually involving a harness around the lower rib cage and the iliac crest, with the pulling action done by using free weights and a pulley, motorized equipment, inversion techniques, or an overhead harness.
Transcutaneous electrical nerve stimulation (TENS)	Use of a small, battery-operated device to provide continuous electrical impulses via surface electrodes, with the goal of providing symptomatic relief by modifying pain perception.
Yoga	An intervention distinguished from traditional exercise therapy by the use of specific body positions, breathing techniques, and an emphasis on mental focus. Many styles of yoga are practiced, each emphasizing different postures and techniques.

been well studied for low back pain, there is little evidence for the efficacy of baclofen or dantrolene, the other FDA-approved drugs for the treatment of spasticity (96). Other medications in the skeletal muscle relaxant class are an option for short-term relief of acute low back pain, but all are associated with central nervous system adverse effects (primarily sedation). There is no compelling evidence that skeletal muscle relaxants differ in efficacy or safety (96, 97). Because skeletal muscle relaxants are not pharmacologically related, however, risk–benefit profiles could in theory vary substantially. For example, carisoprodol is metabolized to meprobamate (a medication associated with risks for abuse and overdose), dantrolene carries a black box warning for potentially fatal hepatotoxicity, and both tizanidine and chlorzoxazone are associated with hepatotoxicity that is generally reversible and usually not serious.

Tricyclic antidepressants are an option for pain relief in patients with chronic low back pain and no contraindications to this class of medications (98, 99). Antidepressants in the selective serotonin reuptake inhibitor class and trazodone have not been shown to be effective for low back pain, and serotonin–norepineprhine reuptake inhibitors (duloxetine and venlafaxine) have not yet been evaluated for low back pain. Clinicians should bear in mind, however, that depression is common in patients with chronic low back pain and should be assessed and treated appropriately (100).

Gabapentin is associated with small, short-term benefits in patients with radiculopathy (101, 102) and has not been directly compared with other medications or treatments. There is insufficient evidence to recommend for or against other antiepileptic drugs for back pain with or without radiculopathy. For acute or chronic low back pain, benzodiazepines seem similarly effective to skeletal muscle relaxants for short-term pain relief (96) but are also associated with risks for abuse, addiction, and tolerance. Neither benzodiazepines nor gabapentin are FDA-approved for treatment of low back pain (with or without radiculopathy). If a benzodiazepine is used, a time-limited course of therapy is recommended.

Herbal therapies, such as devil's claw, willow bark, and capsicum, seem to be safe options for acute exacerbations of chronic low back pain, but benefits range from small to moderate. In addition, many of the published trials were led by the same investigator, which could limit applicability of findings to other settings (103).

Systemic corticosteroids are not recommended for treatment of low back pain with or without sciatica, because they have not been shown to be more effective than placebo (104–107).

Most medication trials evaluated patients with nonspecific low back pain or mixed populations with and without sciatica. There is little evidence to guide specific recommendations for medications (other than gabapentin) for patients with sciatica or spinal stenosis. Evidence is also limited on the benefits and risks associated with long-term use of medications for low back pain. Therefore, extended courses of medications should generally be reserved for patients clearly showing continued benefits from therapy without major adverse events.

Recommendation 7: For patients who do not improve with self-care options, clinicians should consider the addition of nonpharmacologic therapy with proven benefits—for acute low back pain, spinal manipulation; for chronic or subacute low back pain, intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive-behavioral therapy, or progressive relaxation (weak recommendation, moderate-quality evidence).

For acute low back pain (duration <4 weeks), spinal manipulation administered by providers with appropriate training is associated with small to moderate short-term benefits (108). Supervised exercise therapy and home exercise regimens are not effective for acute low back pain (109), and the optimal time to start exercise therapy after the onset of symptoms is unclear. Other guidelines suggest starting exercise after 2 to 6 weeks, but these recommendations seem to be based on poor-quality evidence (25, 110). Other nonpharmacologic treatments have not been proven to be effective for acute low back pain.

For subacute (duration >4 to 8 weeks) low back pain, intensive interdisciplinary rehabilitation (defined as an intervention that includes a physician consultation coordi-

nated with a psychological, physical therapy, social, or vocational intervention) (see Glossary) is moderately effective (111), and functional restoration (see Glossary) with a cognitive-behavioral component reduces work absenteeism due to low back pain in occupational settings (112). There is little evidence on effectiveness of other treatments specifically for subacute low back pain (113). However, many trials enrolled mixed populations of patients with chronic and subacute symptoms, suggesting that results may reasonably be applied to both situations.

For chronic low back pain, moderately effective nonpharmacologic therapies include acupuncture (114, 115), exercise therapy (109), massage therapy (116), Viniyoga-style yoga (see Glossary) (70), cognitive-behavioral therapy or progressive relaxation (see Glossary) (117, 118), spinal manipulation (108), and intensive interdisciplinary rehabilitation (119), although the level of supporting evidence for different therapies varies from fair to good (**Appendix Table 6**, available at www.annals.org). In meta-regression analyses, exercise programs that incorporate individual tailoring, supervision, stretching, and strengthening are associated with the best outcomes (109). The evidence is insufficient to conclude that benefits of manipulation vary according to the profession of the manipulator (chiropractor vs. other clinician trained in manipulation) or according to presence or absence of radiating pain (108). With the exception of continuous or intermittent traction (see Glossary), which has not been shown to be effective in patients with sciatica (120–122), few trials have evaluated the effectiveness of treatments specifically in patients with radicular pain (122) or symptoms of spinal stenosis. In addition, there is insufficient evidence to recommend any specific treatment as first-line therapy. Patient expectations of benefit from a treatment should be considered in choosing interventions because they seem to influence outcomes (123). Some interventions (such as intensive interdisciplinary rehabilitation) may not be available in all settings, and costs for similarly effective interventions can vary substantially. There is insufficient evidence to recommend the use of decision tools or other methods for tailoring therapy in primary care, although initial data are promising (124–126).

Transcutaneous electrical nerve stimulation (see Glossary) and intermittent or continuous traction (in patients with or without sciatica) have not been proven effective for chronic low back pain (**Appendix Table 6**, available at www.annals.org). Acupressure (see Glossary), neuroreflexotherapy (see Glossary), and spa therapy (see Glossary) have not been studied in the United States, and percutaneous electrical nerve stimulation (see Glossary) is not widely available. There is insufficient evidence to recommend interferential therapy (see Glossary), low-level laser therapy (see Glossary), shortwave diathermy (see Glossary), or ultrasonography. Evidence is inconsistent on back schools (see Glossary), which have primarily been evaluated in occupational settings, with some trials showing small, short-term benefits (127).

It may be appropriate to consider consultation with a back specialist when patients with nonspecific low back pain do not respond to standard noninvasive therapies. However, there is insufficient evidence to guide specific recommendations on the timing of or indications for referral, and expertise in management of low back pain varies substantially among clinicians from different disciplines (including primary care providers). In general, decisions about consultation should be individualized and based on assessments of patient symptoms and response to interventions, the experience and training of the primary care clinician, and the availability of specialists with relevant expertise. In considering referral for possible surgery or other invasive interventions, other published guidelines suggest referring patients with nonspecific low back pain after a minimum of 3 months (25) to 2 years (128) of failed nonsurgical interventions. Although specific suggestions about timing of referral are somewhat arbitrary, one factor to consider is that trials of surgery for nonspecific low back pain included only patients with at least 1 year of symptoms (129–131). Other recommendations for invasive interventions are addressed in a separate guideline from the APS (17).

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Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to

override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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Appendix Table 1. **The American College of Physicians Clinical Practice Guidelines Grading System***

Quality of Evidence	Strength of Recommendation	
	Benefits Do or Do Not Clearly Outweigh Risks	Benefits and Risks and Burdens are Finely Balanced
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or harms	I recommendation	

* Adapted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) work group.

Appendix Table 2. **Methods for Grading the Strength of the Overall Evidence for an Intervention***

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least 2 consistent, higher-quality trials).
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (at least 1 higher-quality trial of sufficient sample size; 2 or more higher-quality trials with some inconsistency; at least 2 consistent, lower-quality trials, or multiple consistent observational studies with no significant methodologic flaws).
Poor	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

* Adapted from methods developed by the U.S. Preventive Services Task Force (19).

Appendix Table 3. Definitions for Estimating Magnitude of Effects*

Size of Effect	Definition
Small/slight	Pain scales: Mean 5- to 10-point improvement on a 100-point VAS or equivalent Back-specific functional status: Mean 5- to 10-point improvement on the ODI, 1–2 points on the RDQ, or equivalent All outcomes: SMD, 0.2–0.5
Moderate	Pain scales: Mean 10- to 20-point improvement on a 100-point VAS or equivalent Back-specific functional status: Mean 10- to 20-point improvement on the ODI, 2–5 points on the RDQ, or equivalent All outcomes: SMD, 0.5–0.8
Large/substantial	Pain scales: Mean >20-point improvement on a 100-point VAS or equivalent Back-specific functional status: Mean >20-point improvement on the ODI, >5 points on the RDQ, or equivalent All outcomes: SMD >0.8

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

Appendix Table 4. Recommendations and Summary Ratings*

Grade	Recommendation
A	The panel strongly recommends that clinicians consider offering the intervention to eligible patients. *The panel found good evidence that the intervention improves health outcomes and concludes that benefits substantially outweigh harms.*
B	The panel recommends that clinicians consider offering the intervention to eligible patients. *The panel found at least fair evidence that the intervention improves health outcomes and concludes that benefits moderately outweigh harms, or that benefits are small but there are no significant harms, costs, or burdens associated with the intervention.*
C	The panel makes no recommendation for or against the intervention. *The panel found at least fair evidence that the intervention can improve health outcomes, but concludes that benefits only slightly outweigh harms, or the balance of benefits and harms is too close to justify a general recommendation.*
D	The panel recommends against offering the intervention. *The panel found at least fair evidence that the intervention is ineffective or that harms outweigh benefits.*
I	The panel found insufficient evidence to recommend for or against the intervention. *Evidence that the intervention is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

* Adapted from methods developed by the U.S. Preventive Services Task Force (19).

Appendix Table 5. Level of Evidence and Summary Grades for Noninvasive Interventions in Patients with Acute Low Back Pain*

Intervention	Level of Evidence	Net Benefit	Grade
Acetaminophen	Good	Moderate	B
Nonsteroidal anti-inflammatory drugs	Good	Moderate	B
Skeletal muscle relaxants	Good	Moderate	B
Superficial heat	Good	Moderate	B
Advice to remain active	Good	Small (no significant harms)	B
Benzodiazepines	Fair	Moderate	B
Opioids and tramadol	Fair	Moderate	B
Self-care education books	Fair	Small (no significant harms)	B
Herbal therapies	Fair (devil's claw and white willow bark) to poor (cayenne)	Moderate (devil's claw and white willow bark), unable to estimate (cayenne)	B (devil's claw and white willow bark)
Spinal manipulation	Fair	Small to moderate	B/C
Advice to rest in bed	Good	No benefit	D
Exercise therapy	Good	No benefit	D
Systemic corticosteroids	Fair	No benefit	D
Aspirin	Poor	Unable to estimate	I
Acupuncture	Poor	Unable to estimate	I
Back schools	Poor	Unable to estimate	I
Interferential therapy	Poor	Unable to estimate	I
Low-level laser	Poor	Unable to estimate	I
Lumbar supports	Poor	Unable to estimate	I
Massage	Poor	Unable to estimate	I
Modified work	Poor	Unable to estimate	I
Shortwave diathermy	Poor	Unable to estimate	I
Transcutaneous electrical nerve stimulation	Poor	Unable to estimate	I
Superficial cold	Poor	Unable to estimate	I

* See **Appendix Tables 1**, **2**, and **3** for explanation of grades. Low back pain is considered acute if its duration is <4 weeks.

Appendix Table 6. **Level of Evidence and Summary Grades for Noninvasive Interventions in Patients with Chronic or Subacute Low Back Pain***

Intervention	Level of Evidence	Net Benefit	Grade
Acetaminophen	Good	Moderate	B
Acupuncture	Fair (some inconsistency vs. sham acupuncture)	Moderate	B
Psychological therapy (cognitive-behavioral therapy or progressive relaxation)	Good for cognitive-behavioral, fair for progressive relaxation	Moderate (cognitive-behavioral) to substantial (progressive relaxation)	B
Exercise therapy	Good	Moderate	B
Interdisciplinary rehabilitation	Good	Moderate	B
Nonsteroidal anti-inflammatory drugs	Good	Moderate	B
Spinal manipulation	Good	Moderate	B
Opioids and tramadol	Fair (primarily indirect evidence from trials of patients with other pain conditions)	Moderate	B
Brief individualized educational interventions	Fair	Moderate	B
Benzodiazepines	Fair	Moderate	B
Massage	Fair	Moderate	B
Yoga	Fair (for Viniyoga) to poor (for Hatha yoga)	Moderate (Viniyoga), unable to estimate (Hatha yoga)	B (Viniyoga)
Tricyclic antidepressants	Good	Small to moderate	B/C
Antiepileptic drugs	Fair (for gabapentin) to poor (for topiramate)	Small (gabapentin in patients with radiculopathy), unable to estimate (topiramate)	C (gabapentin), I (topiramate)
Back schools	Fair (some inconsistency)	Small	C
Firm mattresses	Fair	No benefit or harm	D
Traction	Fair	No benefit (continuous or intermittent traction), small to moderate (autotraction for sciatica)	D (continuous or intermittent traction), C (autotraction for sciatica)
Aspirin	Poor	Unable to estimate	I
Biofeedback†	Poor	Unable to estimate	I
Interferential therapy	Poor	Unable to estimate	I
Low-level laser	Poor	Unable to estimate	I
Lumbar supports	Poor	Unable to estimate	I
Shortwave diathermy	Poor	Unable to estimate	I
Skeletal muscle relaxants	Poor	Unable to estimate	I
Transcutaneous electrical nerve stimulation	Poor	Unable to estimate	I
Ultrasonography	Poor	Unable to estimate	I

* See **Appendix Tables 1, 2,** and **3** for explanation of grades. Low back pain is considered subacute at 1–3 months' duration and chronic at >3 months' duration.
† The use of auditory or visual signals reflecting muscle tension or activity to learn how to inhibit or reduce the muscle activity.

Annals of Internal Medicine | Clinical Guidelines

Medications for Acute and Chronic Low Back Pain: A Review of the Evidence for an American Pain Society/American College of Physicians Clinical Practice Guideline

Roger Chou, MD, and Laurie Hoyt Huffman, MS

Background: Medications are the most frequently prescribed therapy for low back pain. A challenge in choosing pharmacologic therapy is that each class of medication is associated with a unique balance of risks and benefits.

Purpose: To assess benefits and harms of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, benzodiazepines, antiepileptic drugs, skeletal muscle relaxants, opioid analgesics, tramadol, and systemic corticosteroids for acute or chronic low back pain (with or without leg pain).

Data Sources: English-language studies were identified through searches of MEDLINE (through November 2006) and the Cochrane Database of Systematic Reviews (2006, Issue 4). These electronic searches were supplemented by hand searching reference lists and additional citations suggested by experts.

Study Selection: Systematic reviews and randomized trials of dual therapy or monotherapy with 1 or more of the preceding medications for acute or chronic low back pain that reported pain outcomes, back-specific function, general health status, work disability, or patient satisfaction.

Data Extraction: We abstracted information about study design, population characteristics, interventions, outcomes, and adverse events. To grade methodological quality, we used the Oxman criteria for systematic reviews and the Cochrane Back Review Group criteria for individual trials.

Data Synthesis: We found good evidence that NSAIDs, acetaminophen, skeletal muscle relaxants (for acute low back pain), and tricyclic antidepressants (for chronic low back pain) are effective for pain relief. The magnitude of benefit was moderate (effect size of 0.5 to 0.8, improvement of 10 to 20 points on a 100-point visual analogue pain scale, or relative risk of 1.25 to 2.00 for the proportion of patients experiencing clinically significant pain relief), except in the case of tricyclic antidepressants (for which the benefit was small to moderate). We also found fair evidence that opioids, tramadol, benzodiazepines, and gabapentin (for radiculopathy) are effective for pain relief. We found good evidence that systemic corticosteroids are ineffective. Adverse events, such as sedation, varied by medication, although reliable data on serious and long-term harms are sparse. Most trials were short term (≤4 weeks). Few data address efficacy of dual-medication therapy compared with monotherapy, or beneficial effects on functional outcomes.

Limitations: Our primary source of data was systematic reviews. We included non–English-language trials only if they were included in English-language systematic reviews.

Conclusions: Medications with good evidence of short-term effectiveness for low back pain are NSAIDs, acetaminophen, skeletal muscle relaxants (for acute low back pain), and tricyclic antidepressants (for chronic low back pain). Evidence is insufficient to identify one medication as offering a clear overall net advantage because of complex tradeoffs between benefits and harms. Individual patients are likely to differ in how they weigh potential benefits, harms, and costs of various medications.

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In the United States, low back pain is the fifth most common reason for all physician office visits and the second most common symptomatic reason (1, 2). Medications are the most frequently recommended intervention for low back pain (1, 3). In 1 study, 80% of primary care patients with low back pain were prescribed at least 1 medication at their initial office visit, and more than one third were prescribed 2 or more drugs (4).

The most commonly prescribed medications for low back pain are nonsteroidal anti-inflammatory drugs (NSAIDs), skeletal muscle relaxants, and opioid analgesics (4–7). Benzodiazepines, systemic corticosteroids, antidepressant medications, and antiepileptic drugs are also prescribed (8). Frequently used over-the-counter medications include acetaminophen, aspirin, and certain NSAIDs.

A challenge in choosing pharmacologic therapy for low back pain is that each class of medication is associated with a unique balance of benefits and harms. In addition, benefits and harms may vary for individual drugs within a medication class. Previous reviews found only limited evidence to support use of most medications for low back pain. For example, a systematic review published in 1996 found insufficient evidence to support use of any medication for low back pain other than NSAIDs (good evidence) and skeletal muscle relaxants (fair evidence) (9).

This article reviews current evidence on benefits and harms of medications for acute and chronic low back pain.

See also:

Print
Related articles 478, 492
Summary for Patients I-45

Web-Only
Appendix Tables
CME quiz
Conversion of graphics into slides
Audio summary

It is part of a larger evidence review commissioned by the American Pain Society and the American College of Physicians to guide recommendations for management of low back pain (10).

Methods

Data Sources and Searches

An expert panel convened by the American Pain Society and the American College of Physicians determined which medications would be included in this review. The panel chose acetaminophen, NSAIDs (nonselective, cyclooxygenase-2 selective, and aspirin), antidepressants, benzodiazepines, antiepileptic drugs, skeletal muscle relaxants, opioid analgesics, tramadol, and systemic corticosteroids.

We searched MEDLINE (1966 through November 2006) and the Cochrane Database of Systematic Reviews (2006, Issue 4) for relevant systematic reviews, combining terms for low back pain with a search strategy for identifying systematic reviews. When higher-quality systematic reviews were not available for a particular medication, we conducted additional searches for primary studies (combining terms for low back pain with the medication of interest) on MEDLINE and the Cochrane Central Register of Controlled Trials. Full details of the search strategies are available in the complete evidence report (10). Electronic searches were supplemented by hand searching of reference lists and additional citations suggested by experts. We did not include trials published only as conference abstracts.

Evidence Selection

We included all randomized, controlled trials that met all of the following criteria: 1) reported in the English language, or in a non-English language but included in an English-language systematic review; 2) evaluated nonpregnant adults (>18 years of age) with low back pain (alone or with leg pain) of any duration; 3) evaluated a target medication, either alone or in addition to another target medication ("dual therapy"); and 4) reported at least 1 of the following outcomes: back-specific function, generic health status, pain, work disability, or patient satisfaction (11, 12).

We excluded trials that compared dual-medication therapy with therapy using a different medication, medication combination, or placebo. We also excluded trials of low back pain associated with acute major trauma, cancer, infection, the cauda equina syndrome, fibromyalgia, and osteoporosis or vertebral compression fracture.

Because of the large number of trials evaluating medications for low back pain, our primary source for trials was systematic reviews. When multiple systematic reviews were available for a target medication, we excluded outdated systematic reviews, which we defined as systematic reviews with a published update, or systematic reviews published before 2000. When a higher-quality systematic review was not available for a particular intervention, we included all relevant randomized, controlled trials.

Data Extraction and Quality Assessment

For each included systematic review, we abstracted information on search methods; inclusion criteria; methods for rating study quality; characteristics of included studies; methods for synthesizing data; and results, including the number and quality of trials for each comparison and outcome in patients with acute (<4 weeks' duration) low back pain, chronic/subacute (>4 weeks' duration) low back pain, and back pain with sciatica. If specific data on duration of trials were not provided, we relied on the categorization (acute or chronic/subacute) assigned by the systematic review. For each trial not included in a systematic review, we abstracted information on study design, participant characteristics, interventions, and results.

We considered mean improvements of 5 to 10 points on a 100-point visual analogue pain scale (or equivalent) to be small or slight; 10 to 20 points, moderate; and more than 20 points, large or substantial. For back-specific functional status, we classified mean improvements of 2 to 5 points on the Roland–Morris Disability Questionnaire (scale, 0 to 24) and 10 to 20 points on the Oswestry Disability Index (scale, 0 to 100) as moderate (13). We also considered standardized mean differences of 0.2 to 0.5 to be small or slight; 0.5 to 0.8, moderate; and greater than 0.8, large (14). Some evidence suggests that our classification of mean improvements and standardized mean differences for pain and functional status are roughly concordant in patients with low back pain (15–20). Because few trials reported the proportion of patients meeting specific thresholds (such as >30% reduction in pain score) for target outcomes, it was usually not possible to report numbers needed to treat for benefit. When those were reported, we considered a relative risk (RR) of 1.25 to 2.00 for the proportion of patients reporting greater than 30% pain relief (or a similar outcome) to indicate a moderate benefit.

Two reviewers independently rated the quality of each included trial. Discrepancies were resolved through joint review and a consensus process. We assessed internal validity (quality) of systematic reviews by using the Oxman criteria (**Appendix Table 1**, available at www.annals.org) (21, 22). According to this system, systematic reviews receiving a score of 4 or less (on a scale of 1 to 7) have potential major flaws and are more likely to produce positive conclusions about effectiveness of interventions (22, 23). We classified such systematic reviews as "lower quality"; those receiving scores of 5 or more were graded as "higher quality."

We did not abstract results of individual trials if they were included in a higher-quality systematic review. Instead, we relied on results and quality ratings for the trials as reported by the systematic reviews. We considered trials receiving more than half of the maximum possible quality score to be "higher quality" for any quality rating system used (24, 25).

We assessed internal validity of randomized clinical trials not included in a higher-quality systematic review by

using the criteria of the Cochrane Back Review Group (**Appendix Table 2**, available at www.annals.org) (26). We considered trials receiving more than half of the total possible score (≥6 of a maximum 11) "higher quality" and those receiving less than half "lower quality" (24, 25).

Data Synthesis

We assessed overall strength of evidence for a body of evidence by using methods adapted from the U.S. Preventive Services Task Force (27). To assign an overall strength of evidence (good, fair, or poor), we considered the number, quality, and size of studies; consistency of results among studies; and directness of evidence. Minimum criteria for fair- and good-quality ratings are shown in **Appendix Table 3** (available at www.annals.org).

Consistent results from many higher-quality studies across a broad range of populations support a high degree of certainty that the results of the studies are true (the entire body of evidence would be considered good quality). For a fair-quality body of evidence, results could be due to true effects or to biases operating across some or all of the studies. For a poor-quality body of evidence, any conclusion is uncertain.

To evaluate consistency, we classified conclusions of trials and systematic reviews as positive (the medication is beneficial), negative (the medication is harmful or not beneficial), or uncertain (the estimates are imprecise, the evidence unclear, or the results inconsistent) (22). We defined "inconsistency" as greater than 25% of trials reaching discordant conclusions (positive vs. negative), 2 or more higher-quality systematic reviews reaching discordant conclusions, or unexplained heterogeneity (for pooled data).

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Results

Literature Reviewed

We reviewed 1292 abstracts identified by searches for systematic reviews. Of these, 21 appeared potentially relevant and were retrieved. We excluded 7 outdated reviews of NSAIDs (28), antidepressants (29–31), and multiple drugs (9, 32, 33) (**Appendix Table 4**, available at www.annals.org). We also excluded 3 reviews that did not clearly use systematic methods (34–36) and 4 systematic reviews that evaluated target medications but did not report results specifically for patients with low back pain (37–39). We included 7 systematic reviews (**Appendix Table 5**, available at www.annals.org) of NSAIDs (40, 41), antidepressants (42, 43), skeletal muscle relaxants, and benzodiazepines (44–46), or multiple medications (47, 48) (quality ratings shown in **Appendix Table 6**, available at www.annals.org).

We conducted 8 additional searches (1586 citations) for randomized trials of acetaminophen, celecoxib, aspirin, the serotonin–norepinephrine reuptake inhibitors duloxetine and venlafaxine, antiepileptic drugs, opioids, tramadol, and systemic corticosteroids.

Acetaminophen

Six unique trials of acetaminophen were included in a Cochrane review of NSAIDs (40, 41) and a systematic review of multiple medications for low back pain (47). From 134 potentially relevant citations, we identified 3 other trials of acetaminophen that met inclusion criteria (49–51). The longest trial of acetaminophen for acute or chronic low back pain lasted 4 weeks. We excluded 2 trials that did not evaluate efficacy of acetaminophen specifically for low back pain and 11 trials that compared dual therapy with acetaminophen plus another medication to a different medication, medication combination, or placebo.

For acute low back pain, 1 lower-quality trial included in the Cochrane review found no difference between acetaminophen (3 g/d) and no treatment (52). Four trials (3 of acute low back pain and 1 of mixed-duration back pain) found no clear differences in pain relief between acetaminophen at dosages up to 4 g/d and NSAIDs (40, 41).

For chronic low back pain, 1 higher-quality trial found acetaminophen inferior to diflunisal for patients reporting good or excellent efficacy after 4 weeks (53). Several other higher-quality systematic reviews of patients with osteoarthritis (not limited to the back) consistently found acetaminophen slightly inferior to NSAIDs for pain relief (standardized mean difference, about 0.3) (54–57).

There is insufficient evidence from 5 trials (1 higher-quality [51]) comparing acetaminophen with interventions other than NSAIDs (other medications, physical therapy, superficial heat, a corset, or spinal manipulation) to accurately judge relative efficacy (49–51, 58, 59).

Adverse events associated with acetaminophen for low back pain were poorly reported in the trials. Data on potentially serious harms, such as gastrointestinal bleeding, myocardial infarction, and hepatic adverse events, are particularly sparse.

NSAIDs

A total of 57 unique trials of NSAIDs were included in 3 systematic reviews (40, 41, 47, 48). From 74 potentially relevant citations for aspirin and 85 potentially relevant citations for celecoxib (the only cyclooxygenase-selective NSAID available in the United States), we identified 1 trial of aspirin that met inclusion criteria (60). We excluded 1 trial that did not evaluate aspirin specifically for low back pain (61), 10 trials that evaluated selective NSAIDs not available in the United States, and 3 trials that evaluated celecoxib in postoperative settings.

For acute low back pain, a higher-quality Cochrane review (51 trials) found nonselective NSAIDs superior to placebo for global improvement (6 trials; RR, 1.24 [95%, CI, 1.10 to 1.41]) and for not requiring additional analgesics (3 trials; RR, 1.29 [CI, 1.05 to 1.57]) after 1 week of

therapy (40, 41). For chronic low back pain, an NSAID (ibuprofen) was also superior to placebo in 1 higher-quality trial (62). A second, higher-quality systematic review that included fewer ($n = 21$) trials reached conclusions consistent with the Cochrane review (47). For back pain with sciatica, 1 higher-quality systematic review found no difference between NSAIDs and placebo on a combined outcome of effectiveness (3 trials; odds ratio, 0.99 [CI, 0.6 to 1.7]) (48).

The Cochrane review found no evidence from 24 trials that any nonselective NSAID is superior to others for pain relief (40, 41). It also found no clear differences in efficacy between NSAIDs and opioid analgesics or muscle relaxants, although trials were limited by small sample sizes (6 trials, 1 higher-quality; 16 to 44 patients) (40, 41). Use of NSAIDs also was no more effective than nonpharmacologic interventions (spinal manipulation, physical therapy, bed rest).

The Cochrane review found that nonselective NSAIDs were associated with a similar risk for any adverse event compared with placebo (RR, 0.83 [CI, 0.64 to 1.08]) (40, 41). However, the trials were not designed to evaluate risks for less common but serious gastrointestinal and cardiovascular adverse events (63–65). Data on long-term benefits and harms associated with use of NSAIDs for low back pain are particularly sparse. Only 6 of 51 trials included in the Cochrane review were longer than 2 weeks in duration (the longest evaluated 6 weeks of therapy) (40, 41).

We found insufficient evidence from 1 lower-quality trial to accurately judge benefits or harms of aspirin (acetylsalicylic acid) for low back pain (60). Evidence regarding gastrointestinal safety of aspirin is primarily limited to trials of aspirin for prophylaxis of thrombotic events (66, 67).

Antidepressants

Ten unique trials were included in 3 systematic reviews of antidepressants (42, 43, 47). In all of the trials, the duration of therapy ranged from 4 to 8 weeks. From searches for the serotonin–norepinephrine reuptake inhibitors duloxetine or venlafaxine, we identified no relevant trials from 14 citations.

For chronic low back pain, 2 higher-quality systematic reviews (1 qualitative [43] and 1 quantitative [42]) consistently found antidepressants to be more effective than placebo for pain relief. Effects on functional outcomes were inconsistently reported and did not indicate clear benefits. Pooling data for all antidepressants, the quantitative systematic review (9 trials) estimated a standardized mean difference of 0.41 (CI, 0.22 to 0.61) for pain relief. However, effects on pain were not consistent across antidepressants. Tricyclic antidepressants were slightly to moderately more effective than placebo for pain relief in 4 (43) and 6 (42) trials (2 higher-quality) included in the systematic reviews, but paroxetine and trazodone (antidepressants without inhibitory effects on norepinephrine uptake) were no more effective than placebo in 3 trials. Maprotiline, the only tetracyclic antidepressant evaluated in trials included in the systematic reviews, is not available in the United States. There was insufficient evidence from 1 lower-quality trial (which found no differences) (68) to directly judge relative effectiveness of tricyclic antidepressants versus selective serotonin reuptake inhibitors.

One systematic review found that antidepressants were associated with significantly higher risk for any adverse event compared with placebo (22% vs. 14%), although harms were generally not well reported (42). Drowsiness (7%), dry mouth (9%), dizziness (7%), and constipation (4%) were the most common adverse events. The trials were not designed to assess risks for serious adverse events, such as overdose, increased suicidality, or arrhythmias.

Benzodiazepines

Eight trials of benzodiazepines were included in a higher-quality Cochrane review of skeletal muscle relaxants (45, 46). The trials ranged from 5 to 14 days in duration.

For acute low back pain, 1 higher-quality trial found no differences between diazepam and placebo (69), but another, lower-quality trial found diazepam superior for short-term pain relief and overall improvement (70). For chronic low back pain, pooled results from 2 higher-quality trials found tetrazepam to be associated with a greater likelihood of pain relief (RR, 1.41 [CI, 1.08 to 1.85]) and global improvement (RR, 1.59 [CI, 1.03 to 2.38]) compared with placebo after 10 to 14 days (71, 72). A third, lower-quality, placebo-controlled trial of diazepam for chronic low back pain found no benefit (73).

In head-to-head trials included in the Cochrane review, efficacy did not differ between diazepam and tizanidine (1 higher-quality trial of acute low back pain [74]) or cyclobenzaprine (1 lower-quality trial of chronic low back pain [73]). For acute low back pain, a third, higher-quality trial found diazepam inferior to carisoprodol for muscle spasm, functional status, and global efficacy (global rating of "excellent" or "very good," 70% vs. 45% of patients) (75). One study that pooled data from 20 trials ($n = 1553$) found no difference between diazepam and cyclobenzaprine for short-term (14 days) global improvement (both were superior to placebo) but was excluded from the Cochrane review because it included patients with back or neck pain (mixed duration) (76).

Central nervous system events, such as somnolence, fatigue, and lightheadedness, were reported more frequently with benzodiazepines than with placebo (45, 46).

Antiepileptic Drugs

We identified no systematic reviews of antiepileptic drugs for low back pain. From 94 citations, we identified 2 trials of gabapentin (77, 78) and 2 trials of topiramate (79, 80) that met inclusion criteria (**Appendix Table 7**, available at www.annals.org). The trials ranged from 6 to 10 weeks in duration. We identified no other trials of antiepileptic drugs for low back pain.

For low back pain with radiculopathy, 3 small (41 to

80 patients) trials found gabapentin (2 trials [78], 1 higher-quality [77]) and topiramate (1 higher-quality trial [79]) to be associated with small improvements in pain scores compared with placebo (or diphenhydramine as active placebo [79]). One trial reporting functional outcomes found no differences (79). For chronic low back pain with or without radiculopathy, 1 higher-quality trial found topiramate moderately superior to placebo for pain, but only slightly superior for functional status (80).

There was no clear difference between gabapentin and placebo in rates of withdrawal due to adverse events. However, drowsiness (6%), loss of energy (6%), and dizziness (6%) were reported with gabapentin (77). Compared with diphenhydramine (active placebo), topiramate was associated with higher rates of withdrawal due to adverse events (33% vs. 15%), sedation (34% vs. 3%), and diarrhea (30% vs. 10%) in 1 trial (79).

Skeletal Muscle Relaxants

Thirty-six unique trials of skeletal muscle relaxants (drugs approved by the U.S. Food and Drug Administration for treatment of spasticity from upper motor neuron syndromes or spasms from musculoskeletal conditions) were included in 4 systematic reviews (44–48). The duration of therapy in all trials was 2 weeks or less, with the exception of a single 3-week trial.

For acute low back pain, a higher-quality Cochrane review found skeletal muscle relaxants moderately superior to placebo for short-term (2 to 4 days' duration) pain relief (at least a 2-point or 30% improvement on an 11-point pain rating scale) (45, 46). The RRs for pain relief were 1.25 (CI, 1.12 to 1.41) after 2 to 4 days and 1.72 (CI, 1.32 to 2.22) after 5 to 7 days, based on 1 lower-quality and 3 higher-quality trials that could be pooled. There was insufficient evidence to conclude that any specific muscle relaxant is superior to others for benefits or harms (45, 46). However, there is only sparse evidence (2 trials) on efficacy of the antispasticity drugs dantrolene and baclofen for low back pain. Tizanidine, the other skeletal muscle relaxant approved by the Food and Drug Administration for spasticity, was efficacious for acute low back pain in 8 trials. Only 1 trial of patients with chronic low back pain—a lower-quality trial of cyclobenzaprine that did not report pain intensity or global efficacy—evaluated a skeletal muscle relaxant available in the United States (73).

Two other systematic reviews had a smaller scope than the Cochrane review but reached consistent conclusions (44, 47). One of the systematic reviews included 2 additional lower-quality trials of cyclobenzaprine for chronic or subacute low back or neck pain that reported mixed results compared with placebo (44). Another systematic review (48), which focused on interventions for sciatica, found no difference between tizanidine and placebo in 1 higher-quality trial (81).

Skeletal muscle relaxants were associated with a higher total number of adverse events (RR, 1.50 [CI, 1.14 to 1.98]) and central nervous system adverse events (RR, 2.04 [CI, 1.23 to 3.37]) compared with placebo, although most events were self-limited and serious complications were rare (45, 46).

Opioid Analgesics

We identified no systematic reviews of opioids for low back pain. From 600 potentially relevant citations, we identified 9 trials of opioid analgesics that met inclusion criteria (**Appendix Table 8**, available at www.annals.org) (59, 82–89). Twelve trials were excluded because they evaluated dual therapy with an opioid plus another medication compared with another medication or medication combination, 1 trial because it evaluated single-dose therapy, 2 trials because they did not report efficacy of opioids specifically for low back pain, and 2 trials because they did not evaluate any included outcome.

For chronic low back pain, a single higher-quality trial found that sustained-release oxymorphone or sustained-release oxycodone was superior to placebo by an average of 18 points on a 100-point pain scale (87). However, opioids were titrated to stable doses before randomization, so poorer outcomes with placebo could have been due in part to cessation of opioid therapy and to withdrawal. Two lower-quality trials reported no significant differences between propoxyphene and placebo for back pain of mixed duration (83) or codeine and acetaminophen for acute back pain (59).

Two systematic reviews of placebo-controlled trials of opioids for various noncancer pain conditions (most commonly osteoarthritis and neuropathic pain) found opioids to be moderately effective, with a mean decrease in pain intensity with opioids in most trials of at least 30% (38), or a standardized mean difference for pain relief of −0.60 (CI, −0.69 to −0.50) (39). In 1 of the reviews, opioids were also slightly superior for functional outcomes (standardized mean difference, −0.31 [CI, −0.41 to −0.22]) (39). Estimates of benefit were similar for neuropathic and nonneuropathic pain.

There was no evidence from 5 lower-quality trials that sustained-release opioid formulations are superior to immediate-release formulations for low back pain on various outcomes (84–86, 88, 89). In addition, different long-acting opioids did not differ in 2 head-to-head trials (82, 87).

In 1 higher-quality trial, 85% of patients with low back pain randomly assigned to receive opioids reported adverse events, with constipation and sedation as the most frequent symptoms (87). Trials of opioids were not designed to assess risk for abuse or addiction and generally excluded higher-risk patients. In addition with the exception of 2 longer-term (16 weeks and 13 months) studies (82, 88), all trials lasted fewer than 3 weeks.

Tramadol

Three trials of tramadol (90–92) were included in a systematic review of various medications for low back pain (47). From 147 potentially relevant citations, we identified

2 other trials of tramadol that met inclusion criteria (93, 94). We excluded 3 trials that evaluated dual therapy with tramadol plus another drug versus another drug or drug combination (95–97), 1 trial published only as an abstract (98), and 1 small (40 patients) trial cited in an electronic database that we could not locate (99).

For chronic low back pain, tramadol was moderately more effective than placebo for short-term pain and functional status after 4 weeks in 1 higher-quality trial (92). Evidence from 2 trials (1 higher-quality) (90, 91) was insufficient to judge efficacy of tramadol versus the combination of acetaminophen plus codeine or dextropropfen–trometamol (an NSAID not available in the United States). Two other lower-quality trials found no differences in benefits or harms between sustained-release and immediate-release tramadol for chronic low back pain (93, 94). No trial compared tramadol with acetaminophen or opioid monotherapy, or with other NSAIDs. Tramadol was associated with similar rates of withdrawal due to adverse events compared with placebo (92) or the combination of acetaminophen plus codeine (91).

Systemic Corticosteroids

We identified no systematic reviews of systemic corticosteroids for low back pain. From 418 potentially relevant citations, we identified 4 trials that met inclusion criteria (**Appendix Table 9**, available at www.annals.org) (100–103). We excluded 3 trials that evaluated systemic corticosteroids in operative or postoperative settings and 1 German-language trial.

For acute sciatica or sciatica of unspecified duration, 3 small (33 to 65 patients), higher-quality trials consistently found systemic corticosteroids associated with no clinically significant benefit compared with placebo when given parenterally (single injection) or as a short oral taper (100, 102, 103). For patients with acute low back pain and a negative result on a straight-leg-raise test, a fourth trial found no difference in pain relief through 1 month between a single intramuscular injection of methylprednisolone (160 mg) and placebo (101).

A large (500-mg) intravenous methylprednisolone bolus was associated with 2 cases of transient hyperglycemia and 1 case of facial flushing in 1 trial (100). Another trial found a smaller (160-mg) intramuscular methylprednisolone injection associated with no cases of hyperglycemia requiring medical attention, infection, or gastrointestinal bleeding (101). Adverse events were poorly reported in the other trials.

Dual-Medication Therapy

Five trials comparing dual therapy with a skeletal muscle relaxant plus an analgesic (acetaminophen or an NSAID) versus the analgesic alone were included in a systematic review of skeletal muscle relaxants (45, 46). One other trial evaluated an opioid plus an NSAID versus an NSAID alone (88). We identified no other trials evaluating dual-medication therapy versus monotherapy from any of the other systematic reviews or searches.

A higher-quality Cochrane review of skeletal muscle relaxants (45, 46) found tizanidine combined with acetaminophen or an NSAID to be consistently associated with greater short-term pain relief than acetaminophen or NSAID monotherapy in 3 higher-quality trials. However, 2 lower-quality trials found no benefits from adding orphenadrine to acetaminophen or cyclobenzaprine to an NSAID. Compared with acetaminophen or an NSAID alone, adding a muscle relaxant was associated with a higher risk for adverse events of the central nervous system (4 trials; RR, 2.44 [CI, 1.05 to 5.63]) but a trend toward lower risk for gastrointestinal adverse events (4 trials; RR, 0.54 [CI, 0.26 to 1.14]). Overall risk for adverse events did not significantly differ (4 trials; RR, 1.34 [CI, 0.67 to 2.67]).

For chronic low back pain, 1 small (36 patients) trial found an opioid with naproxen slightly superior to naproxen alone for pain (5 to 10 points on a 100-point scale), anxiety, and depression after 16 weeks, but results are difficult to interpret because doses of naproxen were not clearly specified (88).

Discussion

This review synthesizes evidence from systematic reviews and randomized, controlled trials of medications for treatment of low back pain. Main results are summarized in **Appendix Tables 10** (acute low back pain), **11** (chronic or subacute low back pain), and **12** (low back pain with sciatica) (available at www.annals.org).

We found good evidence that acetaminophen, NSAIDs, skeletal muscle relaxants (for acute low back pain), and tricyclic antidepressants (for chronic low back pain) are effective for short-term pain relief. Effects were moderate, except in the case of tricyclic antidepressants (small to moderate effects). We also found fair evidence that tramadol, benzodiazepines, and gabapentin (for radiculopathy) are effective for pain relief. Interpreting evidence on efficacy of opioids for low back pain is challenging. Although evidence on opioids versus placebo or nonopioid analgesics specifically for low back pain is sparse and inconclusive, recent systematic reviews of opioids for various chronic pain conditions found consistent evidence of moderate benefits (38, 39). For all medications included in this review, evidence of beneficial effects on functional outcomes is limited. We found good evidence that systemic corticosteroids are ineffective for low back pain with or without sciatica. We could not draw definite conclusions about efficacy of other medications for sciatica or radiculopathy because few trials have specifically evaluated patients with this condition. One systematic review identified only 7 trials evaluating medications for sciatica (48).

Assessing comparative benefits between drug classes was difficult because of a paucity of well-designed, head-

to-head trials. Gabapentin, for example, has been evaluated in only 2 small, short-term, placebo-controlled trials, and no trials directly compared potent opioids with other analgesics. One exception is acetaminophen, which was slightly but consistently inferior for pain relief compared with NSAIDs—although this conclusion assumes that estimates of pain relief from trials of osteoarthritis can be applied to patients with low back pain (54–57).

We also found little evidence of differences in efficacy within medication classes. However, head-to-head trials between drugs in the same class were mostly limited to NSAIDs and skeletal muscle relaxants. Among skeletal muscle relaxants, we found sparse evidence on efficacy of the antispasticity medications baclofen and dantrolene. Among antidepressants, tricyclics are the only class shown to be effective for low back pain, although other drugs with effects on norepinephrine uptake (such as duloxetine and venlafaxine) have not yet been evaluated.

In contrast to limited evidence of clear differences in benefits, we found clinically relevant differences between drug classes in short-term adverse events. For example, skeletal muscle relaxants, benzodiazepines, and tricyclic antidepressants are all associated with more central nervous system events (such as sedation) compared with placebo. Opioids seem to be associated with particularly high rates of short-term adverse events, particularly constipation and sedation. Data on serious (life-threatening or requiring hospitalization) adverse events associated with use of medications for low back pain are sparse. For NSAIDs, this is a critical deficiency because much of the uncertainty regarding their use centers on relative gastrointestinal and cardiovascular safety (63). For opioids and benzodiazepines, reliable evidence on such risks as abuse, addiction, and overdose is not available. Among skeletal muscle relaxants, clinical trials have shown no clear differences in rates of adverse events, but carisoprodol is known to be metabolized to meprobamate (a scheduled drug), dantrolene carries a black box warning for potentially fatal hepatotoxicity, and observational studies have found both tizanidine and chlorzoxazone to be associated with usually reversible and mild hepatotoxicity (104).

Our evidence synthesis has several potential limitations. First, because of the large number of published trials, our primary source of data was systematic reviews. The reliability of systematic reviews depends on how well they are conducted. We therefore focused on results from higher-quality systematic reviews, which are less likely than lower-quality reviews to report positive findings (22, 23). In addition, overall conclusions were generally consistent between multiple higher-quality systematic reviews of a medication. Second, we only included randomized, controlled trials. Although well-conducted randomized, controlled trials are less susceptible to bias than other study designs, nearly all are "efficacy" trials conducted in ideal settings and selected populations, usually with short-term follow-up. "Effectiveness" trials or well-designed observational studies could provide important insight into benefits and harms of medications for low back pain in real-world practice. Third, high-quality data on harms are sparse. Better assessment and reporting of harms in clinical trials would help provide more balanced assessments of net benefits (105). Fourth, reporting of outcomes was poorly standardized across trials. In particular, the proportion of patients meeting predefined criteria for clinically important differences was rarely reported, making it difficult to assess clinical significance of results. Fifth, language bias could affect our results because we included non–English-language trials only if they were included in English-language systematic reviews. However, only 2 systematic reviews restricted inclusion solely to English-language trials (42, 44). Finally, the systematic reviews included in our evidence synthesis did not assess for potential publication bias. Formal assessments of publication bias would be difficult to interpret because of small numbers of studies and clinical diversity among trials (106).

We also identified several research gaps that limited our ability to reach more definitive conclusions about relative benefits and harms of medications for low back pain. First, no trials formally evaluated different strategies for choosing initial medications. In addition, evidence is sparse on effectiveness of dual-medication therapy relative to monotherapy or sequential treatment, even though patients are frequently prescribed more than 1 medication (4). There is also little evidence on long-term (>4 weeks) use of any medication included in this review, particularly with regard to long-term harms.

In summary, several medications evaluated in this report are effective for short-term relief of acute or chronic low back pain, although each is associated with a unique set of risks and benefits. Individuals are likely to differ in how they prioritize the importance of these various benefits and harms. For mild or moderate pain, a trial of acetaminophen might be a reasonable first option because it may offer a more favorable safety profile than NSAIDs. However, acetaminophen also seems less effective for pain relief. For more severe pain, a small increase in cardiovascular or gastrointestinal risk with NSAIDs in exchange for greater pain relief could be an acceptable tradeoff for some patients, but others may consider even a small increase in these risks unacceptable. For very severe, disabling pain, a trial of opioids in appropriately selected patients (107–109) may be a reasonable option to achieve adequate pain relief and improve function, despite the potential risks for abuse, addiction, and other adverse events. Factors that should be considered when weighing medications for low back pain include the presence of risk factors for complications, concomitant medication use, baseline severity of pain, duration of low back symptoms, and costs. As in other medical decisions, choosing the optimal medication for an individual with low back pain should always involve careful consideration and thorough discussion of potential benefits and risks.

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Appendix Table 1. Quality Rating System for Systematic Reviews

Criteria for Assessing Scientific Quality of Research Reviews*	Operationalization of Criteria
	The purpose of this index is to evaluate the scientific quality (i.e., adherence to scientific principles) of research overviews (review articles) published in the medical literature. It is not intended to measure literary quality, importance, relevance, originality, or other attributes of overviews.
	The index is for assessing overviews of primary ("original") research on pragmatic questions regarding causation, diagnosis, prognosis, therapy, or prevention. A research overview is a survey of research. The same principles that apply to epidemiologic surveys apply to overviews: A question must be clearly specified; a target population identified and accessed; appropriate information obtained from that population in an unbiased fashion; and conclusions derived, sometimes with the help of formal statistical analysis, as is done in meta-analyses. The fundamental difference between overviews and epidemiologic studies is the unit of analysis, not the scientific issues that the questions in this index address.
1. Were the search methods reported? *Were the search methods used to find evidence (original research) on the primary questions stated?* "Yes" if the review states the databases used, date of most recent searches, and some mention of search terms.	Because most published overviews do not include a methods section, it is difficult to answer some of the questions in the index. Base your answers, as much as possible, on information provided in the overview. If the methods that were used are reported incompletely relative to a specific question, score it as "can't tell," unless there is information in the overview to suggest that the criterion was or was not met.
2. Was the search comprehensive? *Was the search for evidence reasonably comprehensive?* "Yes" if the review searches at least 2 databases and looks at other sources (e.g., reference lists, hand searches, queries of experts).	
3. Were the inclusion criteria reported? *Were the criteria used for deciding which studies to include in the overview reported?*	
4. Was selection bias avoided? *Was bias in the selection of studies avoided?* "Yes" if the review reports how many studies were identified by searches, numbers excluded, and appropriate reasons for excluding them (usually because of predefined inclusion/exclusion criteria).	
5. Were the validity criteria reported? *Were the criteria used for assessing the validity of the included studies reported?*	
6. Was validity assessed appropriately? *Was the validity of all the studies referred to in the text assessed by using appropriate criteria (either in selecting studies for inclusion or in analyzing the studies that are cited)?* "Yes" if the review reports validity assessment and did some type of analysis with it (e.g., sensitivity analysis of results according to quality ratings, excluded low-quality studies).	
7. Were the methods used to combine studies reported? *Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?* "Yes" for studies that did qualitative analysis if report mentions that quantitative analysis was not possible and reasons that it could not be done, or if "best evidence" or some other grading of evidence scheme used.	
8. Were the findings combined appropriately? *Were the findings of the relevant studies combined appropriately relative to the primary question the overview addresses?* "Yes" if the review performs a test for heterogeneity before pooling, does appropriate subgroup testing, appropriate sensitivity analysis, or other such analysis.	For question 8, if no attempt has been made to combine findings, and no statement is made regarding the inappropriateness of combining findings, check "No." If a summary (general) estimate is given anywhere in the abstract, the discussion, or the summary section of the paper, and it is not reported how that estimate was derived, mark "No" even if there is a statement regarding the limitations of combining the findings of the studies reviewed. If in doubt, mark "Can't tell."
9. Were the conclusions supported by the reported data? *Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?*	For an overview to be scored as "Yes" in question 9, data (not just citations) must be reported that support the main conclusions regarding the primary question(s) that the overview addresses.
10. What was the overall scientific quality of the overview? *How would you rate the scientific quality of this overview?*	The score for question 10, the overall scientific quality, should be based on your answers to the first 9 questions. The following guidelines can be used to assist with deriving a summary score: If the "Can't tell" option is used 1 or more times on the preceding questions, a review is likely to have minor flaws at best and it is difficult to rule out major flaws (i.e., a score ≤4). If the "No" option is used on question 2, 4, 6, or 8, the review is likely to have major flaws (i.e., a score ≤3, depending on the number and degree of the flaws).

Scoring: Each Question Is Scored as Yes, Partially/Can't Tell, or No

Extensive Flaws		Major Flaws		Minor Flaws		Minimal Flaws
1	2	3	4	5	6	7

* Operationalization of the Oxman criteria (21), adapted from reference 22.

Appendix Table 2. Quality Rating System for Randomized, Controlled Trials*

Criteria List for Assessment of Methodologic Quality†	Operationalization of Criteria	Score
A. Was the method of randomization adequate?	A random (unpredictable) assignment sequence. An example of adequate methods is a computer-generated random-number table and use of sealed opaque envelopes. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.	Yes/No/Don't Know
B. Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/Don't Know
C. Were the groups similar at baseline regarding the most important prognostic factors? *"Yes," if similar:* *Age and sex* *Description of type of pain* *Intensity, duration, or severity of pain*	To receive a "yes," groups have to be similar at baseline regarding demographic factors, duration or severity of symptoms, percentage of patients with neurologic symptoms, and value of main outcome measure(s).	Yes/No/Don't Know
D. Was the patient blinded to the intervention?	The reviewer determines whether enough information about the blinding is given in order to score a "yes."	Yes/No/Don't Know
E. Was the care provider blinded to the intervention?	Use the author's statement on blinding, unless there is a differing statement/reason not to (no need for explicit information on blinding).	Yes/No/Don't Know
F. Was the outcome assessor blinded to the intervention?		Yes/No/Don't Know
G. Were co-interventions avoided or similar?	Co-interventions should be avoided in the trial design or similar between the index and control groups.	Yes/No/Don't Know
H. Was adherence acceptable in all groups?	The reviewer determines whether adherence to the interventions is acceptable, based on the reported intensity, duration, number, and frequency of sessions for both the index intervention and control intervention(s).	Yes/No/Don't Know
I. Was the dropout rate described and acceptable? *≤15% dropout rate is acceptable.*	The number of participants who are included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and dropouts does not exceed 15% and does not lead to substantial bias, a "yes" is scored.	Yes/No/Don't Know
J. Was the timing of the outcome assessment in all groups similar?	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.	Yes/No/Don't Know
K. Did the analysis include an intention-to-treat analysis? *"Yes," if <5% of randomly assigned patients were excluded.*	All randomly assigned patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of nonadherence and co-interventions.	Yes/No/Don't Know

* This list includes only the 11 internal validity criteria that refer to characteristics of the study that might be related to selection bias (criteria A and B), performance bias (criteria D, E, G, and H), attrition bias (criteria I and K), and detection bias (criteria F and J). The internal validity criteria should be used to define methodological quality in the meta-analysis.
† Adapted from methods developed by the Cochrane Back Review Group (26).

Appendix Table 3. Methods for Grading the Overall Strength of the Evidence for an Intervention*

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least 2 consistent, higher-quality trials).
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (at least 1 higher-quality trial of sufficient sample size; 2 or more higher-quality trials with some inconsistency; or at least 2 consistent, lower-quality trials, or multiple consistent observational studies with no significant methodological flaws).
Poor	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

* Adapted from methods developed by the U.S. Preventive Services Task Force (27). The overall evidence for an intervention was graded on a 3-point scale (good, fair, poor).

Appendix Table 4. **Excluded Systematic Reviews***

Drug	Study, Year (Reference)	Reason for Exclusion
Antidepressants	Fishbain, 2000 (37)	Not specific for LBP
	Goodkin and Gullion, 1989 (29)	Outdated Not specific for LBP
	Onghena and Van Houdenhove, 1992 (30)	Outdated Not specific for LBP
	Turner and Denny, 1993 (31)	Outdated
Multiple drugs	Deyo, 1996 (9)	Outdated
	van der Weide et al., 1997 (33)	Outdated
	van Tulder et al., 1997 (32)	Outdated
NSAIDs	Koes et al., 1997 (28)	Outdated
Opioids	Bartleson, 2002 (34)	Systematic methods not clearly described
	Brown et al., 1996 (35)	Systematic methods not clearly described
	Furlan et al., 2006 (39)	Not specific for LBP
	Kalso et al., 2004 (38)	Not specific for LBP
Systemic corticosteroids	Rozenberg et al., 1998 (36)	Systematic methods not clearly described

* LBP = low back pain; NSAIDs = nonsteroidal anti-inflammatory drugs.

Appendix Table 5. Systematic Reviews of Medications for Low Back Pain*

Drug	Study, Year (Reference)	Type of Systematic Review	Included Trials (Higher-Quality Trials), *n/n*†	Trials Not Included in Any Other Relevant Systematic Review, *n*	Duration of Treatment in Included Trials	Sample Sizes of Included Trials, *n*	Interventions Evaluated (Number of Trials)	Main Conclusions	Overall Quality per Oxman Scale (1–7)
Acetaminophen (6 unique trials in 2 systematic reviews)	Schnitzer et al., 2004 (47)	Qualitative (efficacy of multiple medications)	3 (1)	1	7 d–5 wk (median, 4 wk)	30–60 (median, 39)	Acetaminophen, 4 g/d (2), 2 g/d (1)	Does not draw specific conclusions about acetaminophen	4
	van Tulder et al., 2000 (40, 41)	Qualitative	5 (1)	3	7 d–4 wk (median, 2 wk)	30–70 (median, 50)	Acetaminophen, 4 g/d (3), 2 g/d (1), dose not specified (1)	Acetaminophen vs. NSAIDs for acute LBP (3 lower-quality RCTs): no differences in 2 trials; in 3rd trial, 2 of 4 evaluated NSAIDs were superior to acetaminophen Acetaminophen vs. diflunisal for chronic LBP (1 RCT): diflunisal superior for patients reporting no or mild LBP after 2–4 wk and for global assessment of efficacy	7
Antidepressants (10 unique trials in 3 systematic reviews)	Salerno et al., 2002 (42)	Quantitative	9 (5)	2	4–8 wk (median, 6 wk)	16–103 (median, 50)	Nortriptyline (1), imipramine (2), amitriptyline (1), desipramine (1), doxepine (2), maprotiline (1), paroxetine (2), trazodone (1)	Antidepressant vs. placebo for chronic LBP (9 RCTs): SMD, 0.41 (95% CI, −0.61 to 0.22) for pain (9 RCTs); SMD, 0.24 (95% CI, −0.69 to −0.21) for activities of daily living (5 RCTs)	
	Schnitzer et al., 2004 (47)	Qualitative (efficacy of multiple medications)	7 (4)	1	4–8 wk (median, 8 wk)	16–103 (median, 50)	Nortriptyline (1), imipramine (1), amitriptyline (2), maprotiline (1), paroxetine (2), fluoxetine (1) trazodone (1)	Antidepressants vs. placebo for chronic LBP (7 RCTs): antidepressants superior to placebo in 5 of 7 trials	5
	Staiger et al., 2003 (43)	Qualitative	7 (6)	0	4–8 wk (median, 8 wk)	16–103 (median, 50)	Nortriptyline (1), imipramine (2), amitriptyline (1), maprotiline (1), paroxetine (2), trazodone (1)	Tricyclic and tetracyclic antidepressant vs. placebo for chronic LBP (5 RCTs): 3 of 5 trials, including the 2 highest-quality trials, found mild to moderate, significant benefits for pain; insufficient evidence on functional status Paroxetine or trazodone vs. placebo for chronic LBP (3 RCTs): no consistent benefits on pain (SMD range, −0.13 to 0.32 in 3 RCTs)	6

Appendix Table 5—**Continued**

Drug	Study, Year (Reference)	Type of Systematic Review	Included Trials (Higher-Quality Trials), *n/n*†	Trials Not Included in Any Other Relevant Systematic Review, *n*	Duration of Treatment in Included Trials	Sample Sizes in Included Trials, *n*	Interventions Evaluated (Number of Trials)	Main Conclusions	Overall Quality per Oxman Scale (1–7)
Benzodiazepines (8 unique trials in 1 systematic review)	van Tulder et al., 2003 (45, 46)	Qualitative and quantitative	8 (5)	8	6–14 d (median, 8 d)	50–152 (median, 73)	Diazepam (6), tetrazepam (2)	Diazepam vs. placebo for acute LBP (1 RCT): diazepam superior for short-term pain and overall improvement Tetrazepam vs. placebo for chronic LBP (3 RCTs): RR, 1.41 (CI, 1.08–1.85, 2 RCTs) for pain relief >20% or score >16 on a 100-point visual analogue scale after 8–14 d and RR, 1.59 (CI, 1.03–2.38) for global improvement after 8–14 d (2 RCTs) Benzodiazepine vs. skeletal muscle relaxants (3 RCTs): no differences in higher-quality trials	7
NSAIDs (57 unique trials in 3 systematic reviews)	Schnitzer et al., 2004 (47)	Qualitative (efficacy of multiple medications)	21 (10)	5	7 d–8 wk (median, 14 d)	30–282 (median, 73)	Naproxen (4), ibuprofen (1), indomethacin (4), diclofenac (3), piroxicam (6), diflunisal (6), others (9)	NSAIDs for acute LBP (14 RCTs): NSAIDs superior to placebo in 2 of 3 RCTs; 9 of 11 RCTs of NSAIDs vs. active control found significant improvements from baseline in NSAID group NSAIDs for chronic LBP (4 RCTs): NSAIDs superior to placebo in 1 RCT; 3 of 3 RCTs of NSAIDs vs. active control found significant improvements from baseline in NSAID group	5
	van Tulder et al., 2000 (40, 41)	Qualitative and quantitative	51 (15)	34	1−2 d to 6 wk (median, 12 d)	20–459 (median, 72)	Naproxen (4), ibuprofen (6), indomethacin (10), diclofenac (15), piroxicam (7), diflunisal (8), others (18)	NSAID vs. placebo for acute LBP (9 RCTs): RR, 1.24 (CI, 1.10–1.41) for global improvement after 1 wk (6 RCTs) and RR, 1.29 (CI, 1.05–1.57) for not requiring additional analgesics after 1 wk (3 RCTs)	7
	Vroomen et al., 2000 (48)	Quantitative efficacy of medications for sciatica)	4 (2)	1	2−4 d to 17 d (median, 10 d)	40–214 (median, 54)	Indomethacin (1), piroxicam (1), others (2)	NSAID vs. placebo for sciatica (3 RCTs): OR, 0.99 (CI, 0.6−1.7)	5

Continued on following page

Appendix Table 5. Systematic Reviews of Medications for Low Back Pain*

Drug	Study, Year (Reference)	Type of Systematic Review	Included Trials (Higher-Quality Trials), *n/n*†	Trials Not Included in Any Other Relevant Systematic Review, *n*	Duration of Treatment in Included Trials	Sample Sizes in Included Trials, *n*	Interventions Evaluated (Number of Trials)	Main Conclusions	Overall Quality per Oxman Scale (1–7)
Skeletal muscle relaxants (38 unique trials in 4 systematic reviews)	Browning et al., 2001 (44)	Quantitative (efficacy of cyclobenzaprine for back or neck pain)	14 (5)	11	5–21 d (median, 14 d)	48–1153 (median, 100)	Cyclobenzaprine (14)	Cyclobenzaprine vs. placebo for acute or chronic LBP or neck pain: OR, 4.7 (CI, 2.7–8.1) for global improvement (10 RCTs); SMD, 0.41 (CI, 0.29–0.53) for local pain at 1–4 d (7 RCTs); SMD, 0.54 (CI, 0.34–0.74) for function at 1–4 d (6 RCTs), results for function similar at >9 d	7
	Schnitzer, 2004 (47)	Qualitative (efficacy of multiple medications)	5 (4)	1	5–10 d (median, 7 d)	49–361 (median, 112)	Tizanidine (3), baclofen (1), other (1)	SMR vs. placebo for acute LBP (5 RCTs): SMR superior in 4 of 5 RCTs (no benefit in 1 of 3 RCTs of tizanidine); benefit mostly short-term and early (<7 d)	5
	van Tulder et al., 2003 (45, 46)	Qualitative and quantitative	26 (20)	19	Single dose—21 d (median, 7 d)	20–361 (median, 80)	Cyclobenzaprine (5), carisoprodol (3), chlorzoxazone (1), orphenadrine (4) methocarbamol, tizanidine (8), dantrolene (1), baclofen (1), others (5)	SMR vs. placebo for acute LBP (8 RCTs): RR, 1.25 (CI, 1.12–1.41) for pain relief of >20% or score >16 on a 100-point visual analogue scale after 2–4 d (3 RCTs), RR, 1.72 (CI, 1.32–2.22) for pain relief after 5–7 d (2 RCTs), RR, 2.05 (CI, 1.05–4.00) for global improvement after 2–4 d (4 RCTs), and RR, 1.47 (CI, 0.88–2.44) for global improvement after 5–7 d (4 RCTs)	7
	Vroomen et al., 2000 (48)	Qualitative (efficacy of medications for sciatica)	1 (1)	0	7 d	112	Tizanidine (1)	Tizanidine vs. placebo for sciatica (1 higher-quality RCT): no difference	5

* LBP = low back pain; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk; SMD = standardized mean difference; SMR = skeletal muscle relaxant.
† Higher-quality trials were defined as those receiving >50% of maximum possible quality rating score used by each systematic review.

Appendix Table 6. Quality Ratings of Systematic Reviews of Medications for Low Back Pain*

Drug	Study, Year (Reference)	Search Methods?	Comprehensive?	Inclusion Criteria?	Bias Avoided?	Validity Criteria?	Validity Assessed?	Methods for Combining Studies?	Appropriately Combined?	Conclusions Supported?	Overall Quality per Oxman Scale (1–7)
Antidepressants	Salerno et al., 2002 (42)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	6
	Staiger et al., 2003 (43)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Multiple drugs	Schnitzer et al., 2004 (47)	Yes	Partial	Yes	Yes	Yes	Yes	No	Yes	Partial	5 (4 for acetaminophen)
	Vroomen et al., 2000 (48)	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	5
NSAIDs	van Tulder et al., 2000 (40, 41)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Skeletal muscle relaxants and benzodiazepines	Browning et al., 2001 (44)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
	van Tulder et al., 2003 (45, 46)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7

* NSAIDs = nonsteroidal anti-inflammatory drugs.

Appendix Table 7. **Randomized, Controlled Trials of Antiepileptic Drugs for Low Back Pain***

Study, Year (Reference)	Patients, *n*	Duration of Follow-up, *wk*	Main Results	Quality Score†
Yildirim et al., 2003 (78)	50 (radiculopathy)	8	Gabapentin, titrated to 3600 mg/d, vs. placebo Back pain at rest (mean change from baseline on 0–3 scale): −1.04 vs. −0.32 ($P < 0.01$)	3/11
McCleane et al., 2001 (77)	80 (radiculopathy)	6	Gabapentin, titrated to 1200 mg/d, vs. placebo Back pain at rest (mean change from baseline on 0–10 VAS): −0.51 ($P > 0.05$) vs. 0.1 ($P > 0.05$) Back pain with movement (mean change from baseline on 0–10 VAS): −0.47 ($P < 0.05$) vs. 0.01 ($P > 0.05$) Leg pain (mean change from baseline on 0–10 VAS): −0.45 ($P < 0.05$) vs. −0.24 ($P > 0.05$)	8/11
Khoromi et al., 2005 (79)	41 (radiculopathy)	6, followed by crossover	Topiramate, titrated to 400 mg/d (average dosage, 208 mg/d), vs. diphenhydramine, titrated to 50 mg/d (average dosage, 40 mg/d) Average pain (mean change from baseline on 0–10 scale): Leg pain, −0.98 vs. −0.24 ($P = 0.06$) Back pain, −1.36 vs. −0.49 ($P = 0.017$) Overall pain, −0.33 vs. 0.49 ($P = 0.02$) Global pain relief moderate or better: 15/29 (54%) vs. 7/29 (24%) ($P = 0.005$) Global pain relief "a lot" or "complete": 9/29 (31%) vs. 1/29 (3.4%) ODI score: −5 vs. −3 ($P > 0.05$) Beck Depression Inventory score: no difference SF-36 score: no differences for any subscale after correction for multiple comparisons	7/11
Muehlbacher et al., 2006 (80)	96 (chronic low back pain with or without radiculopathy)	10	Topiramate, titrated to 300 mg/d, vs. placebo Pain Rating Index (mean change from baseline on 0–100 scale): −12.9 vs. −1.5 ($P < 0.001$) SF-36 physical functioning subscale score (mean change from baseline on 0–100 scale): 8.7 vs. −0.4 ($P < 0.01$, favors topiramate) SF-36, bodily pain subscale score (0–100): 4.1 vs. 0.9 ($P < 0.01$, favors topiramate) SF-36, other subscale scores: differences in change compared with baseline ranged from 0.6 (role–emotional) to 8.3 (role–physical) points, favoring topiramate for all comparisons at $P < 0.05$	7/11

* ODI = Oswestry Disability Index; SF-36 = Short Form-36; VAS = visual analogue scale.
† Using Cochrane Back Review Group methods; maximum score, 11.

Appendix Table 8. **Randomized, Controlled Trials of Opioids for Low Back Pain***

Type of Trial	Study, Year (Reference)	Patients, *n*	Duration of Follow-up	Main Results	Quality Score†
Opioids vs. placebo or acetaminophen	Barratta et al., 1976 (83)	61	14 d	Propoxyphene vs. placebo Pain on active improvement (mean improvement from baseline): 0.8 vs. 0.4 ($P > 0.05$) Global improvement at least "satisfactory": 22% vs. 14% ($P > 0.05$)	4/11
	Hale et al., 2005 (87)	235	18 d	Long-acting morphine vs. long-acting oxycodone vs. placebo Pain intensity (100-point VAS), mean differences vs. placebo: −18.21 (morphine) vs. −18.55 (oxycodone) ($P = 0.0001$ for each comparison) Global assessment at least "good": 59% vs. 63% vs. 27%	7/11
	Wiesel et al., 1980 (59)	50	14 d	Codeine vs. acetaminophen Mean time before return to work: 10.7 d vs. 13.0 d ($P > 0.05$)	1/11
Sustained-release vs. immediate-release opioid formulations	Gostick et al., 1989 (84)	61	2 wk, followed by crossover	Sustained-release vs. immediate-release dihydrocodeine No differences for pain intensity, rescue drug use, global efficacy, patient preference	5/11
	Hale et al., 1997 (85)	104	5 d	Sustained-release codeine plus acetaminophen vs. immediate-release codeine plus acetaminophen Long-acting codeine superior for pain intensity, but nonequivalent codeine use (200 mg vs. 71 mg)	5/11
	Hale et al., 1999 (86)	57	4–7 d followed by crossover	Sustained-release vs. immediate-release oxycodone No differences for overall pain intensity, mean pain intensity, or rescue drug use	4/11
	Jamison et al., 1998 (88)	36	16 wk	Sustained-release morphine + immediate-release oxycodone (titrated dose) + naproxen vs. immediate-release oxycodone (set dose) + naproxen vs. naproxen alone (mean scores over 16 wk; outcomes for first 4 items expressed on 0–100 scales) Average pain: 54.9 vs. 59.8 vs. 65.5 Anxiety: 11.2 vs. 15.0 vs. 31.6 Depression: 10.8 vs. 16.4 vs. 26.9 Level of activity: 49.3 vs. 49.3 vs. 51.5 Duration of sleep (means): 5.9 h vs. 5.9 h vs. 6.1 h	3/11
	Salzman et al., 1999 (89)	57	10 d	Sustained-release vs. immediate-release oxycodone No differences for pain intensity, time to stable pain control, mean number of dose adjustments	3/11
Long-acting opioid vs. long-acting opioid	Allan et al., 2005 (82)	683	13 mo	Transdermal fentanyl vs. sustained-release oral morphine No differences for pain scores, rescue medication use, quality of life, loss of working days	4/11
	Hale et al., 2005 (87)	235	18 d	Sustained-release morphine vs. sustained-release oxycodone No differences for pain intensity, pain relief, pain interference with activities, global assessment	7/11

* VAS = visual analogue scale.
† Using Cochrane Back Review Group methods; maximum score, 11.

Appendix Table 9. **Randomized, Controlled Trials of Systemic Corticosteroids for Low Back Pain with or without Sciatica***

Study, Year (Reference)	Patients, *n* (Population)	Duration of Follow-up	Main Results	Quality Score†
Finckh et al., 2006 (100)	65 (acute sciatica)	30 d	Methylprednisolone, 500-mg bolus, vs. placebo Leg pain, difference between interventions in VAS pain scores (0–100 scale): 5.7 (favors methylprednisolone) at day 3, ($P = 0.04$), not significant after 3 d ($P = 0.22$) Proportion with >20-mm improvement in VAS pain score after 1 d: 48% vs. 28% ($P = 0.097$)	10/11
Friedman et al., 2006 (101)	88 (no sciatica)	1 mo	Methylprednisolone, 160 mg IM bolus, vs. placebo Pain, mean change from baseline (0–10 scale): −4.1 vs. −4.8 ($P > 0.05$) after 1 wk, −5.1 vs. −5.8 ($P > 0.05$) after 1 mo RDQ-18, mean score (0–18): 2.6 vs. 3.4 after 1 wk, 2.6 vs. 3.1 after 1 mo	11/11
Haimovic and Beresford, 1986 (102)	33 (sciatica, duration of symptoms unclear)	1–4 y	Dexamethasone, 1-wk oral taper, vs. placebo Early improvement: 33% (7/21) vs. 33% (4/12) Sustained improvement (1–4 y): 50% (8/16) vs. 64% (7/11)	6/11
Porsman and Friis, 1979 (103)	52 (sciatica, duration of symptoms unclear)	≥9 d	Dexamethasone, 1-wk IM taper vs. placebo "Positive effect": 52% (13/25) vs. 58% (14/24) Subsequent surgery: 32% (8/25) vs. 25% (6/24)	6/11

* IM = intramuscular; RDQ = Roland–Morris Disability Questionnaire; VAS = visual analogue scale.
† Using Cochrane Back Review Group methods; maximum score, 11.

Appendix Table 10. Summary of Evidence on Medications for Acute Low Back Pain*

Drug	Trials (Trials Rated Higher-Quality by ≥1 Systematic Review), *n (n)*†	Net Benefit‡	Effective vs. Placebo?	Inconsistency?§	Directness of Evidence?	Overall Quality of Evidence	Comments
Acetaminophen	3 (0)	Moderate	Unclear (1 lower-quality trial showing no difference)	Some inconsistency (vs. NSAIDs)	Direct	Good	Few data on serious adverse events
Antidepressants	0	No evidence	No evidence	No evidence	No evidence	No evidence	
Antiepileptic drugs	0	No evidence	No evidence	No evidence	No evidence	No evidence	Evaluated only in patients with radicular LBP
Benzodiazepines	5 (3)	Moderate	Unable to determine (2 trials with inconsistent results)	Some inconsistency (vs. placebo and vs. skeletal muscle relaxants)	Direct, with supporting indirect evidence from mixed populations with back and neck pain	Fair	No reliable data on risks of abuse or addiction No differences between diazepam and cyclobenzaprine for short-term global efficacy (both superior to placebo) in 1 large, short-term trial of patients with back or neck pain (mixed duration)
NSAIDs	31 (10)	Moderate	Yes (7 trials)	No	Direct	Good	May cause serious gastrointestinal and cardiovascular adverse events; insufficient evidence to judge benefits and harms of aspirin or celecoxib for LBP
Opioids	1 (1)	Moderate	No evidence	Not applicable	Data available from trials of opioids for other acute pain conditions	Fair	No reliable data on risks of abuse or addiction
Skeletal muscle relaxants	31 (21)	Moderate	Yes (19 trials)	No	Direct	Good	Little evidence on efficacy of antispasticity skeletal muscle relaxants baclofen and dantrolene for LBP
Systemic corticosteroids	1 (1)	Not effective	No (1 trial)	No	Direct	Fair	Mostly evaluated in patients with radicular LBP
Tramadol	1 (1)	Unable to estimate	No evidence	Not applicable	Direct	Poor	The only trial compared tramadol with an NSAID not available in United States

* LBP = low back pain; NSAIDs = nonsteroidal anti-inflammatory drugs.
† Higher-quality trials were defined as those receiving >50% of maximum possible quality rating score used by each systematic review.
‡ Based on evidence showing that medication is more effective than placebo, and/or evidence showing that medication is at least as effective as other medications or interventions thought to be effective, for 1 or more of the following outcomes: pain, functional status, or work status. Compared with placebo, small benefit was defined as 5–10 points on a 100-point visual analogue scale (VAS) for pain (or equivalent), 1–2 points on the Roland–Morris Disability Questionnaire (RDQ), 10–20 points on the Oswestry Disability Index (ODI), or a standardized mean difference (SMD) of 0.2–0.5. Moderate benefit was defined as 10–20 points on a 100-point VAS for pain, 2–5 points on the RDQ, 10–20 points on the ODI, or an SMD of 0.5–0.8. Large benefit was defined as >20 points on a 100-point VAS for pain, >5 points on the RDQ, >20 points on the ODI, or an SMD >0.8.
§ Inconsistency was defined as >25% of trials reaching discordant conclusions on efficacy (no effect vs. positive effect was considered discordant).

Appendix Table 11. Summary of Evidence on Medications for Chronic or Subacute Low Back Pain*

Drug	Trials (Trials Rated Higher-Quality by ≥1 Systematic Review), *n (n)*†	Net Benefit‡	Effective vs. Placebo?	Inconsistency?§	Directness of Evidence?	Overall Quality of Evidence	Comments
Acetaminophen	2 (1)	Moderate	No trials in patients with LBP	No	Data available from trials of acetaminophen for osteoarthritis	Good	Asymptomatic elevations of liver function test results at therapeutic doses
Antidepressants	10 (5)	Small to moderate	Yes (9 trials)	No	Direct	Good	Only tricyclic antidepressants have been shown effective for LBP No evidence on duloxetine or venlafaxine
Antiepileptic drugs	1 (1)	Small to moderate	Yes (1 trial of topiramate)	Not applicable	Direct	Poor	1 small trial evaluated topiramate for back pain with or without radiculopathy
Benzodiazepines	3 (2)	Moderate	Mixed results (3 trials)	Some inconsistency (vs. placebo)	Direct	Fair	No reliable data on risks for abuse or addiction
NSAIDs	6 (3)	Moderate	Yes (1 trial)	No	Direct	Good	May cause serious gastrointestinal and cardiovascular adverse events Insufficient evidence to judge benefits and harms of aspirin or celecoxib for LBP
Opioids	7 (1)	Moderate	Yes (1 trial)	No	Most trials compare different opioids or opioid formulations	Fair	No reliable data on risks of abuse or addiction
Skeletal muscle relaxants	6 (2)	Unable to estimate	Unclear (5 trials)	Not applicable	Most trials evaluated skeletal muscle relaxants not available in United States or mixed populations of patients with back and neck pain	Poor	The 2 higher-quality trials evaluated skeletal muscle relaxants not available in United States
Systemic corticosteroids	0	No evidence	No evidence	No evidence	No evidence	No evidence	Mostly evaluated in patients with radicular LBP
Tramadol	4 (1)	Moderate	Yes (1 trial)	No	Direct	Fair	

* LBP = low back pain; NSAIDs = nonsteroidal anti-inflammatory drugs.
† Higher-quality trials were defined as those receiving >50% of maximum possible quality rating score used by each systematic review.
‡ Based on evidence showing that medication is more effective than placebo, and/or evidence showing that medication is at least as effective as other medications or interventions thought to be effective, for 1 or more of the following outcomes: pain, functional status, or work status. Compared with placebo, small benefit was defined as 5–10 points on a 100-point visual analogue scale (VAS) for pain (or equivalent), 1–2 points on the Roland–Morris Disability Questionnaire (RDQ), 10–20 points on the Oswestry Disability Index (ODI), or a standardized mean difference (SMD) of 0.2–0.5. Moderate benefit was defined as 10–20 points on a 100-point VAS for pain, 2–5 points on the RDQ, 10–20 points on the ODI, or an SMD of 0.5–0.8. Large benefit was defined as >20 points on a 100-point VAS for pain, >5 points on the RDQ, >20 points on the ODI, or an SMD >0.8.
§ Inconsistency was defined as >25% of trials reaching discordant conclusions on efficacy (no effect vs. positive effect was considered discordant).

Appendix Table 12. Summary of Evidence on Medications for Sciatica or Radicular Low Back Pain*

Drug	Trials (Trials Rated Higher-Quality by ≥1 Systematic Review), *n (n)*†	Net Benefit‡	Effective vs. Placebo?	Inconsistency?§	Directness of Evidence?	Overall Quality of Evidence	Comments
Antiepileptic drugs	3 (2)	Small	Yes (2 trials of gabapentin and 1 trial of topiramate)	No	Direct	Fair	No trials of antiepileptic drugs other than gabapentin or topiramate
Nonselective NSAIDs	4 (2)	Not effective	No (3 trials)	No	Direct	Fair	NSAIDs more effective than placebo in mixed populations of patients with low back pain with or without sciatica
Systemic corticosteroids	3 (3)	Not effective	No (3 trials)	No	Direct	Good	

* NSAIDs = nonsteroidal anti-inflammatory drugs.
† Higher-quality trials were defined as those receiving >50% of maximum possible quality rating score used by each systematic review.
‡ Based on evidence showing that medication is more effective than placebo, and/or evidence showing that medication is at least as effective as other medications or interventions thought to be effective, for 1 or more of the following outcomes: pain, functional status, or work status. Compared with placebo, small benefit was defined as 5–10 points on a 100-point visual analogue scale (VAS) for pain (or equivalent), 1–2 points on the Roland–Morris Disability Questionnaire (RDQ), 10–20 points on the Oswestry Disability Index (ODI), or a standardized mean difference (SMD) of 0.2–0.5. Moderate benefit was defined as 10–20 points on a 100-point VAS for pain, 2–5 points on the RDQ, 10–20 points on the ODI, or an SMD of 0.5–0.8. Large benefit was defined as >20 points on a 100-point VAS for pain, >5 points on the RDQ, >20 points on the ODI, or an SMD >0.8.
§ Inconsistency was defined as >25% of trials reaching discordant conclusions on efficacy (no effect vs. positive effect was considered discordant).