Low Back Pain

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- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of patients with back pain.

Accreditations & Approvals

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About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Disclosure Statement

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Course Objective

The purpose of this course is to provide healthcare professionals with a greater understanding of the pathophysiology and differential diagnosis of low back pain conditions so they may effectively treat or manage low back pain, resulting in improved patient health, quality of life, and satisfaction.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the epidemiology of back pain, including economic and societal costs.
2. Identify modifiable and nonmodifiable risk factors for back pain.
3. Review prognostic factors for unsatisfactory treatment response or progression to chronic low back pain.
4. Describe the clinical course of low back pain.
5. Describe the pathophysiology of the different types of back pain.
6. Outline the assessment and diagnosis of low back pain, including "red flags" evident on the initial assessment.
7. Assess approaches to enhancing the assessment of low back pain.
8. Compare available approaches for the management of acute and chronic low back pain.
9. Describe non-drug therapies that may be helpful for low back pain.
10. Discuss the use of complementary and alternative modalities for the treatment of low back pain.
11. Review the available oral pharmacotherapies for the treatment of low back pain.
12. Compare and contrast topical medications for the management of low back pain.
13. Evaluate the efficacy of spinal surgery to manage low back pain.
14. Assess the indications and potential benefits of epidural injections for the management of low back pain.
15. Identify barriers to the effective care of chronic back pain.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

When it occurs, back pain is most often localized to the lower back, and chronic back pain is almost always chronic low back pain (LBP). Although acute-onset LBP is a common problem that usually resolves within four to six weeks, many patients develop a persistent, disabling pain syndrome with a diminishing prognosis for return to normal function. When LBP continues beyond 12 weeks, the prospect for subsequent remission is poor and progression to chronic LBP is likely. Chronic LBP imposes a great burden: for patients, pain and disability; for society and the healthcare system, an enormous expense in direct and indirect costs.

The status of care for patients with LBP is far from adequate and is fraught with a multiplicity of barriers (patient, professional, and system based) to the delivery of more satisfactory, cost-effective care. In primary care settings, low adherence to clinical practice guidelines for LBP is prevalent, most commonly involving neglect in assessing serious pathologic causes of LBP, overuse of diagnostic imaging, inappropriate advice concerning sick leave and activity, underuse of evidence-supported therapy, and overuse of approaches deemed ineffective. Interestingly, physician knowledge, experience, and interest in LBP has not been found to correlate with effective treatment decisions or adherence to practice guidelines [1; 2].

Objective, comprehensive clinical practice guidelines become outdated when important studies are subsequently published, leaving clinicians with deficient and incomplete guidance. Despite research breakthroughs and diverse therapeutic options, only a minority of patients experience substantial treatment benefit. Many remain in pain, and inadequate pain relief is common even with careful, sequential trials of evidence-based pharmacotherapies recommended in practice guidelines [3; 4]. A potential cause may be the over-reliance on randomized controlled trial outcomes to determine the direction of patient care. While these trials control for many factors that confound outcomes in uncontrolled trials,

the restrictive inclusion criteria and inflexible dosing and titration can limit their clinical applicability or underestimate treatment benefit from attrition of patients who would otherwise respond well to a tailored approach. Patients with chronic LBP are typically complex in clinical presentation and more often resemble patients excluded from randomized controlled trials [5].

Patients with refractory chronic LBP can be desperate for treatment that relieves their pain. Numerous therapies for chronic LBP are available, but many lack sufficient safety and efficacy evaluation. This is where clinician-patient dialogue and shared decision-making are important. The clinician reviews the known risks, benefits, and gaps in evidence, and the patient shares his/her expectations and preferences [4]. In short, the tyranny of data should be tempered by clinical judgment [5].

The objective of this course is to provide clinicians with information to more effectively care for patients with back pain. Discussion will include clinical practice guideline recommendations for LBP, evidence that expands or challenges this guidance, assessment and treatment approaches not addressed by practice guidelines, obstacles to more effective care of patients with back pain, and methods to help identify research that is clinically useful. In this course, the term chronic LBP, in the absence of qualifiers, refers to pain of nonspecific etiology.

EPIDEMIOLOGY

LBP is a highly prevalent condition associated with substantial economic expenditures and losses. It can incur serious and prolonged patient suffering, diminished quality of life, and disability. LBP is the chronic pain syndrome responsible for the greatest clinical, social, economic, and public health burden [6; 7].

INCIDENCE AND PREVALENCE

A 2009 population survey of U.S. adults measured the prevalence of pain for a prior three-month time interval. Respondents who reported recent pain were asked to rate their functional impairment from the pain. Of common causes of pain, LBP showed highest prevalence and life impairment in its sufferers (***Table 1***) [8].

In 2018, 29% of adults reported LBP in the past three months. The prevalence was slightly greater for women (30.7%) than men (27.4%) and among those with lower educational attainment (33.9%), defined as non-high school graduates, compared with those with a Bachelor's degree or higher (25.5%) [9]. Persons older than 75 years of age were more likely to report past-three-month LBP (37.3%) compared with 36.5% of adults 65 to 74 years of age and 33.0% of adults 45 to 64 years of age. This is followed by adults 18 to 44 years of age, of whom 24.4% reported LBP. Lower family income (35.1% in ≤$35,000, 23.8% in ≥$100,000) and poverty status (35.6% in poor, 27.3% in non-poor) also appear to be factors, likely related (at least in part) to the type of work typical of the group [9]. White women are more likely to report LBP (32.2%) compared with African American women (31.2%) and Hispanic women (28.5%). Among men, the highest prevalence of LBP occurs among White men (29.2%) compared with Hispanic men (25.7%) and African American men (22.2%) [9].

Genetic or ethnic factors may influence the prevalence of some known causes of LBP. For example, the prevalence rate of lumbar spondylolisthesis is 25% in Inuit Eskimo, 6% in White, and 2% to 3% in Black populations. Reasons for the high prevalence in Inuits are not known but may be genetically mediated [10].

Data on changes in LBP prevalence over time are somewhat conflicting, and causality is difficult to establish. Data from the Department of Veterans Affairs health system showed an annualized increase in LBP prevalence of roughly 5% per year, larger than the increases in depression, diabetes, and

EXTENT OF PAIN-RELATED DISABILITY AMONG ADULTS WITH PAIN IN THE LAST THREE MONTHS, UNITED STATES			
Type of Pain	**Experienced in the Past Three Months**	**Difficulty with Basic Actions[a]**	**Complex Activity Limitation[b]**
Low back pain	28.1%	51.6%	55.0%
Severe headache or migraine	16.1%	31.0%	33.5%
Neck pain	15.1%	30.2%	34.4%
Knee pain	19.5%	37.3%	38.6%
Shoulder pain	9.0%	17.7%	21.4%
Finger pain	7.6%	14.3%	16.3%
Hip pain	7.1%	15.0%	18.4%
[a]Basic actions are defined as movement, emotion, seeing, hearing, or cognition. [b]Complex activities are defined as self-care, social activities, or school/work.			
Source: [8]			*Table 1*

hypertension [11; 12]. National claims data indicate that the proportion of physician office visits for LBP decreased from 18.1% in 2013 to 5.3% in 2018. It is likely the claims figures under-report population incidence because many people do not seek medical care for LBP, but the data are a valid indicator of population-level change [13; 14].

PERSONAL IMPACT

Worldwide, LBP is the single greatest cause of disability and years lived with disability, and in the United States, roughly 1% to 2% of the adult population is disabled by chronic LBP. LBP is the most common reason cited for curtailment of activity by young adults and for sick leave from work in all age groups [13; 15].

ECONOMIC AND SOCIETAL COSTS

Accurate cost estimates incurred by LBP are difficult to calculate because expenditures for pain and other conditions are intertwined. What is known is the economic impact of LBP in the United States is substantial and likely to increase in the future. The full 2010 cost impact of chronic pain ranged from $560 to $635 billion, with pain care accounting for $261 to $300 billion and lost productivity from pain ranging from $299 to $335 billion [8]. The annual cost of disability from all causes was an estimated $300 billion, with back pain and arthritis the two leading causes of disability [16]. In 2013, low back and neck pain accounted for the third highest amount of healthcare spending, costing an estimated $67.5 to $94.1 billion. Healthcare spending for low back and neck pain has increased by $57.2 billion since 1993 [17].

An estimated 12% to 15% of annual healthcare provider visits in the United States are related to LBP [18]. The estimated 8% of patients whose LBP is chronic and debilitating account for 50% of direct medical expenditures for back pain, estimated at $85 billion [13; 19]. Together with costs from decreased wages and lost productivity, the total is $100 to $200 billion [20].

While the healthcare costs for LBP are substantial, they may account for as little as 15% of total costs, with up to 85% coming from indirect costs. Sizeable contribution to indirect costs comes from lost productivity, which includes absenteeism from work, impaired productivity at work (presenteeism), and employer cost of hiring a replacement. Other costs include workers' compensation, disability benefits, lost earnings, litigation, and early retirement [21].

Between 1999 and 2010, there was a 106% increase in primary care physician referrals of patients with LBP to specialist physicians. This is important because such referrals contribute to increases in costly and often ineffective interventional and surgical treatment [22].

Between 2000 and 2009, interventional pain medicine procedures for back pain in the Medicare population increased more than 200% from 1,469,495 to 4,645,679 annually [7; 23]. However, follow-up has shown that between 2009 and 2016 there was a more modest increase of 18.6%, with 5,509,306 procedures in 2016 [7]. From 1997 to 2005, medical costs for spinal pain treatment increased 65%, and the dominant contributor to cost increases was interventional pain medicine procedures [24].

RISK AND PROGNOSTIC FACTORS

RISK FACTORS FOR DEVELOPING BACK PAIN

Risk factors for developing LBP can be generally categorized as nonmodifiable, such as old age, female sex, poverty, and lower education level, and modifiable, including higher body mass index (BMI), smoking, lower perceived general health status, physical activity (e.g., bending, lifting, twisting), repetitive tasks, job dissatisfaction, and depression. The greatest contributors to LBP episodes are single-event or repetitive exposures to mechanical stress and age-related degenerative spinal changes. With chronic LBP, mechanical and biophysiologic factors play a minimal secondary role to the primary contribution from psychosocial factors [25].

Smoking

Smoking has been linked to a greater risk for chronic pain by multiple studies, and studies of LBP have found higher rates of intervertebral disk degeneration among smokers. A study of 5,333 patients with chronic back pain assessed pain levels before treatment (86.5% treated for spine degenerative disease) and at mean eight-month follow-up. Baseline pain levels were more severe in current smokers compared with never-smokers and former smokers, and this pattern continued through follow-up. At the last follow-up, a 30% or greater reduction in worst pain level was noted in 31.2% of never-smokers, 29.1% of former smokers, 16.6% of current smokers, and 32.0% of smokers who quit during the study. Never-smokers experienced the greatest reductions in disability compared with current smokers [26].

Obesity

Obesity contributes to factors that promote the development of some pain states, including LBP. Persons with LBP exhibit abnormal movement patterns that include gait and postural dysfunction, increased thoracolumbar stiffness, decreased proprioception, and alteration in abdominal and extensor muscle activation. Pain can result from joint or structural damage due to aberrant or increased biomechanical forces over time. These processes are accelerated by obesity, and regardless of age, obesity contributes to chronic LBP, mobility impairment, and ultimately physical disability. The relationship between obesity-related LBP and functional decline is mediated by skeletal muscle strength deterioration, systemic inflammation, and psychosocial characteristics, such as pain catastrophizing, kinesiophobia, and depression. Morbid obesity greatly alters biomechanical forces on lower back tissues to accelerate the development of chronic back pain syndromes [27].

Overweight and obesity are risk factors for both lumbar radicular pain and sciatica, and a direct relationship exists between BMI and low back pathology and pain in men and women. A meta-analysis of 28 studies found overweight and obesity were associated with lumbar radicular pain, increased the risk of hospitalization for sciatica, and increased the risk of lumbar disk herniation surgery. These associations were similar for men and women [28]. Clarification of whether or not LBP precedes obesity was addressed by an 11-year longitudinal study of 25,450 individuals. Among those without LBP at baseline, a significant positive association was found between BMI ≥30 and risk of LBP in men and women, and risk of chronic LBP recurrence in women, but not men. In contrast, LBP at baseline had little effect on later changes in BMI [29].

Adipose tissue releases inflammatory mediators that contribute to the development of chronic, low-grade inflammation in obesity, which may accelerate the development of sciatica or cause sciatica symptoms to persist. Obesity may delay disk injury healing and lead to slower and less overall improvement in back-related disability, regardless of treatment modality. Obesity also increases the risk of recurrent disk herniation following lumbar surgical repair. Intervertebral disk nutrition may be disrupted by obesity, impairing the healing process. Long-term data have found BMI to be the strongest predictor of lumbar artery occlusion in patients with sciatica, suggesting impairment of nutrition as a pathway for the relationship between obesity and sciatica [30; 31; 32].

EVIDENCE-BASED PRACTICE RECOMMENDATION

Although overweight/obesity and smoking are associated with the increased prevalence of low back pain, the Institute of Health Economics reports there is insufficient evidence to recommend modifying these risk factors for the prevention of low back pain.

(https://www.cfpc.ca/CFPC/media/Resources/Pain-Management/Low_Back_Pain_Guidelines_Oct19.pdf. Last accessed July 25, 2022.)

Strength of Recommendation: Systematic review

Age

Among those older than 60 years of age, more than 90% of the population demonstrate various degenerative spine changes on x-ray and magnetic resonance imaging (MRI), including disk herniation, spinal stenosis, and foraminal stenosis. In most persons, these changes are asymptomatic. Current thinking is that pain associated with lumbar disk herniation and radiating symptoms primarily results from inflammatory mediators rather than mechanical compression. It has only recently become clear that imaging-detected degenerative changes, disk abnormalities, and other spinal anomalies lack correlation with or prediction of pain [33].

Vitamin D Deficiency

Interest in the role of vitamin D deficiency in pain was spurred by findings of highly prevalent vitamin D deficiency among primary care patients with persistent, nonspecific musculoskeletal pain refractory to pharmacotherapy [34]. Pain patients with vitamin D deficiency also require twice the opioid dosing for substantially greater duration versus non-deficient patients [35].

Vitamin D is essential for normal muscle function and bone formation, maintenance, and remodeling, and it possesses anti-inflammatory properties through regulation of interleukin (IL), tumor necrosis factor (TNF), and macrophage activity. Vitamin D deficiency (hypovitaminosis D) is highly prevalent in patients with back pain, and symptoms often resolve three to seven months after vitamin D treatment. Hypovitaminosis D symptoms can appear before the onset of pathologic changes associated with persistent musculoskeletal pain conditions and persist following resolution of obvious pathology. These findings are relevant in the surgical treatment of LBP (e.g., lumbar fusion). Despite a technically successful surgery, many patients lack meaningful pain reduction, and in patients obtaining pain relief, many fail to show functional improvement. Hypovitaminosis D is thought to be a major contributing factor to the lack of analgesic or functional improvements in these patients [36; 37].

Evaluation of 350 patients who had undergone lumbar spinal stenosis found vitamin D deficiency in 74.3%, with substantially higher prevalence in subgroups with medical comorbidity, urban residence, lower sunlight exposure, and severe leg and/or back pain. The association between pain and deficiency remained significant after adjusting for sunlight exposure [38].

RISK FACTORS FOR PROGRESSION OF ACUTE LBP TO CHRONIC LBP

Psychosocial factors, but not specific physical or imaging findings, have shown consistent utility in predicting the development of chronic LBP in patients with recent-onset LBP. This predictive ability has led to universal recommendation for psychosocial assessment of new patients with LBP. This is termed "yellow flag" assessment [39; 40; 41; 42].

Perception of pain as a threat produces fear and anxiety and physiologic (e.g., increased heart rate, dilated pupils), cognitive (e.g., catastrophizing thoughts or decision making), and behavioral (e.g., fight-or-flight) responses. Pain-related fear can impose greater limitations in patient function than debility from pain itself, and the associated negative thoughts of treatment, the future, and oneself can disrupt rehabilitation and recovery [43; 44; 45]. This pessimism over one's ability to recover is a negative outcome predictor. In a study of patients with LBP evaluated in primary care and followed over several years, the greatest association with pain at five years was found with acute pain severity and conviction of one's pain persisting unchanged for an extended period. This negative pain belief predicted clinically significant LBP independent of numerous prognostic factors, including pain intensity. This predictive validity was found at short- and long-term follow-up [46]. Another trial followed patients with LBP from inpatient release through long-term follow-up and found affective health and coping during acute pain significantly predicted pain reduction and improved function [47].

Psychosocial factors for developing chronicity include [39; 40; 41; 42]:

- Negative belief that pain is harmful or potentially severely disabling
- High levels of "fear avoidance" behaviors
- Poor or maladaptive coping strategies
- Expectation that passive, rather than active, treatment is beneficial
- Excessive focus on pain
- High emotional distress levels
- Depressed mood, low morale, and social withdrawal
- Resistance to change
- Low self-efficacy

- Family reinforcement of illness behavior
- Concurrent social or financial problems
- Troubled childhood (e.g., abuse, parental death, addiction)

Kinesiophobia describes the excessive, irrational, and disabling fear of movement and activity from its anticipated result of injury or re-injury. Pain-related fear is closely associated with catastrophic interpretations of pain and can promote behaviors such as avoidance, escape, and hyper-vigilance. While pain-related behaviors can lead to disuse syndromes from activity avoidance, greater consequences result from its role in complicating and perpetuating the underlying psychophysiologic contribution to chronic LBP [48; 49].

Several work and workplace factors strongly predict work disability and development of chronic LBP. In workers with difficulty returning to normal job duties 4 to 12 weeks from acute LBP onset, the longer additional time is taken away from work for LBP, the lower the chances of ever returning to work. Fewer than 50% of patients disabled longer than six months return to work, and for those absent two years, the return to work rate is close to zero. Low workplace support is strongly predictive of chronicity in patients with acute back pain [25; 42].

Specific work-related factors that may predict chronicity include:

- Job dissatisfaction
- Conflict with supervisors or coworkers
- High physical demands
- Inability to modify work
- High levels of job stress
- Disputed or unresolved workers' compensation claim

IATROGENIC RISK FACTORS

In the course of clinical evaluation and care, patient expectations and provider decision and communication style may inadvertently lead to an exacerbation of LBP or promote chronicity of the condition. The early use of MRI or other imaging modalities should be avoided in most cases of LBP, in part because it is unlikely to influence early management decisions. Moreover, nonspecific imaging abnormalities are often seen and reported, which, for the patient, may promote anatomic fixation, undermine patient perception of and confidence in their health, trigger pain-related fear-avoidance and catastrophizing behaviors, and increase the risk of iatrogenic precipitation of chronic LBP. A qualitative study involving Aboriginal Australians was conducted to determine the effect of their beliefs about the cause of their chronic low back pain. Most of the 32 participants attributed the pain to structural/anatomic vulnerability of the spine, a belief that was derived from healthcare practitioners and the results of spinal radiologic imaging. Negative causal beliefs and a pessimistic future outlook were more common among those who were more disabled [50].

The lay public has repeatedly held fast to the belief that any given case of LBP must have a demonstrable structural cause, leading to doctor shopping and excessive demands for diagnostic testing. Pain care providers are also partially responsible, by reinforcing erroneous, disabling, and costly pain beliefs and behavior. Interventional pain medicine has a recognized but limited role in a few specific LBP indications. Interventional pain medicine physicians have been the focal point of criticism for perpetuating the reductionistic and disproven biomedical paradigm of nonspecific LBP origin and treatment, but practitioners of non-invasive back pain therapies, such as chiropractic, physiotherapy, and osteopathy, have also contributed to widespread counter-therapeutic patient beliefs [51].

PROGNOSTIC FACTORS OF UNSATISFACTORY TREATMENT RESPONSE

Several biopsychosocial factors can interfere with treatment response. The following factors should be assessed if pain and functional status do not improve or worsen without obvious cause [52]:

- Medical comorbidities
- Psychiatric and psychologic comorbidity
- Another pain condition
- Substance abuse
- Previous surgeries
- Tobacco use
- Head trauma history
- BMI
- Sleep disorders
- Employment status
- Concurrent pharmacotherapies
- Social support
- Physical conditioning
- Current pain intensity

Psychosocial factors of poor outcomes in lumbar surgery include mood disorders, unresolved litigation or claims, history of child abuse, and maladaptive pain coping or beliefs [53]. The predictive power of these variables on surgical outcomes surpasses radiographic findings, neurologic signs, and other medical indices. Psychologic screening of implantable neuromodulation device candidates increased successful outcomes from 33% to 70% and is now standard protocol. In outcome studies of spinal cord stimulation in patients with failed back surgery syndrome, inadequate psychologic screening was associated with 50% short-term and 35% long-term benefit, while adequate psychologic screening led to 85% short-term and 60% long-term success rates [53].

In patients with failed back surgery syndrome, risk factors of poor outcomes with spinal cord stimulation include [54; 55]:

Pre-Operative

- Anxiety
- Depression
- Misidentification of pain origin
- Obesity
- Cigarette smoking
- Unresolved litigation or claims

Surgical

- Revision surgery
- Poor candidate for surgical technique
- Incorrect spinal level of intervention

Post-Operative

- Central sensitization
- Progressive spinal disease
- Epidural fibrosis
- Nerve injury
- Infection
- Hematoma
- Myofascial pain

CLINICAL COURSE

The most commonly cited short-term prognosis data state that most patients with acute LBP recover in a matter of weeks with limited or no therapy; specifically, 60% to 70% of patients recover by 6 weeks and 80% to 90% by 12 weeks [25; 56]. These early prognosis projections are at variance with data derived from a study of patients presenting to primary care providers with nonspecific acute LBP [57]. This study found that 33% of patients experienced spontaneous resolution by 3 months, 57% still had problematic pain at 6 months, and 65% reported some degree of pain at 12 months after onset. Of patients with persistent pain at 3 months, only 1% to 7% experienced recovery 3 to 12 months from onset [57].

This study confirmed the impression of experienced clinicians that the clinical course of most patients with acute LBP in a primary care practice does not conform to the conventional notion that nonspecific acute LBP has a favorable natural history and resolves within several weeks [58]. The reason for this discrepancy may be that most patients who develop acute LBP with favorable prognosis do not seek medical care [59]. In those seeking care, pain and disability can be ongoing and recurrent pain episodes may be common. Up to 70% of patients who initially improve following medical care experience recurring pain episodes [58].

PATHOPHYSIOLOGY

The traditional biomedical paradigm considers back pain a symptom of a primary condition, resolved by treating the peripheral pain generator. While effective for specific LBP conditions with identifiable pain causality, this biomedical paradigm is not useful when applied to chronic back pain because it fails to consider the impact of peripheral and central nervous system (CNS) alterations that amplify and perpetuate pain and the substantial contribution from psychosocial factors [60; 61]. A corollary of the biomedical paradigm is mind-body dualism, whereby pain causation is viewed as distinctly the result of either biologic or psychologic factors. Patients with severe chronic LBP who lack corresponding positive imaging findings may be informed their pain lacks organic basis and is therefore "all in their head" [62].

Chronic LBP reflects the uncoupling of pain from its original peripheral origin; it is a distinct disease process rather than a symptom [61]. Likewise, the extent of peripheral tissue damage is no longer viewed as the sole determinant of pain presence, severity, and duration. Chronic LBP is now understood as a multifactorial entity determined by inputs from numerous and complex electrochemical, biocellular, cognitive, and emotional factors. The broad range of individual pain responses to stimuli reflects the highly individualistic phenomenon of pain [63; 64].

Pain is broadly categorized as nociceptive, inflammatory, neuropathic, or centralized. Nociceptive and inflammatory pain overlap and result from peripheral tissue injury, damage, or disease. Both are protective and adaptive for survival when acute but are considered pathologic when pain continues after peripheral tissue healing. Neuropathic pain results from injury, damage, or disease to peripheral nervous structures or sensory pathways in the spinal cord or brain, and regardless of duration, it is pathologic. Centralized pain reflects aberrant function in various CNS pathways and is now thought to account for fibromyalgia, irritable bowel syndrome, and other chronic conditions [65; 66]. Centralized pain is not associated with any common back pain condition or peripheral tissue injury and therefore is not discussed further in this course. These pain subcategories are not distinct and do not account for individual variations. Many cases of chronic LBP represent a mixture of pain subcategories [65].

Neuroscience findings have refuted previous assumptions of back pain pathophysiology. Healthcare providers should understand these changes in how pain is conceptualized, because the management of LBP can hinge on proper matching of pain pathophysiology and treatment mechanism. Effective chronic LBP management requires replacement of several entrenched paradigms with the following [67]:

- Pain is not an accurate measure of tissue state.
- Pain is modulated by multiple factors across somatic, psychologic, and social domains.
- The relationship between pain and tissue state further weakens as pain persists.
- Pain represents a conscious correlate of the implicit perception that tissue is in danger, not the actual tissue state and not the actual threat to tissue.

This section describes the underlying pathways and mechanisms of pain processing and experience in the normal state and in chronic back pain. In addition, neuroscience discoveries in chronic LBP, and pathoanatomic processes in specific LBP conditions will be discussed.

PAIN PHYSIOLOGY

Pain begins when peripheral tissue injury, infection, or peripheral nerve injury triggers a complex local response that converts the injurious stimuli into an impulse. While local processes differ, the resultant nociceptive, inflammatory, or neuropathic pain impulse is transmitted to the brain through interconnected pathways involving similar mechanistic processes spanning the peripheral nervous system, spinal cord, and various brain regions. The structure and function of these mechanisms and pathways undergo alteration in chronic LBP and represent therapeutic targets.

Nociception is the mechanism that encodes and processes noxious (potentially injurious to tissue) stimuli. Nociceptors are sensory neurons that respond to noxious stimuli. Several events are required for nociceptor relay of noxious stimuli to the brain for pain perception: peripheral nociception, spinal cord transmission, brain projection of pain pathways, and relay down descending pain pathways.

Peripheral Nociception

Nociceptors are specialized high-threshold afferent (sensory) neurons. Activation by noxious stimuli (e.g., extreme heat/cold, cutting, inflammation) transduces energy into an action potential, transmitted to the spinal cord along an axon contained in a C (non-myelinated) or A-delta (myelinated) nerve fiber [66; 68; 69]. Several receptors also signal noxious stimuli, including transient receptor potential and acid-sensing ion channels and potassium channels [70; 71].

Inflammatory Pain

Tissue injury or infection prompts the release of chemical mediators that trigger inflammatory response, including cyclooxygenase-2 (COX-2), mast cells, and other enzymes. Chemical mediators activate and sensitize nociceptors via ligand-gated ion channels or metabotropic receptors. Other modulators of nociception function are recruited as signaling molecules in pain pathways [71; 72; 73].

Nociceptor activation induces a cascade that sensitizes nociceptors and alters voltage-gated sodium and transient receptor potential channel kinetics and threshold. Substance P, calcitonin gene-related peptide (CGRP), and other neuropeptides are released from peripheral terminals to recruit serum factors and inflammatory cells at the injury site to produce neurogenic edema. Tissue sensitivity around the injury is termed peripheral sensitization and represents primary hyperalgesia. Inflammation alters protein synthesis in the dorsal root ganglion cell body, leading to ion channel expression of transient receptor potential vanilloid 1 (TRPV1) and transport of peripheral opioid receptors. This upregulation of opioid receptors in peripheral inflammation sites helps account for opioid efficacy in inflammatory pain [71; 74]. In contrast, peripheral nerve injury can decrease mu-opioid receptor expression in dorsal root ganglion neurons, diminishing the analgesic efficacy of opioids [75].

In all peripheral pain types, sodium channels facilitate neuron excitability and signaling of action potentials to the spinal cord. Changes in sodium channel kinetics following peripheral tissue damage contribute to hyperexcitability, and different pain states are characterized by upregulation or downregulation in sodium channel expression [76].

Spinal Cord Transmission

The peripheral nociceptive signal is transmitted to the dorsal root ganglion, where the peripheral neuron synapses with a central neuron. The neuron terminals release excitatory neurotransmitters according to stimuli intensity. These include glutamate, aspartate, substance P, CGRP, and brain-derived neurotrophic factor (BDNF). Depolarized primary afferent terminals release glutamate, which activates postsynaptic AMPA receptors to rapidly signal the location and intensity of noxious stimuli. A high-intensity stimulus normally elicits brief localized pain, and the relationship between afferent input and dorsal horn neuron output is proportionate and predictable [77; 78].

Before relay to the brain by ascending spinal pathways, the signal can be modulated by peripheral or descending spinal pathway neurons. Inhibitory mechanisms in the dorsal horn are activated to reduce excitatory response to persistent peripheral input, involving endorphins, enkephalins, serotonin, and norepinephrine [68].

Brain Projections of Pain Pathways

The pain signal is relayed through spinal pathways into the midbrain, forebrain, and cortex. Distinct qualities of the pain experience are mediated by activation of the specific brain regions receiving the ascending projections, including pain location and type by the thalamus and somatosensory cortex; integration of nociceptive information with arousal, homeostatic, and autonomic responses by the medulla and brainstem; emotional, affective, and motivational components of pain in the ventromedial hypothalamus, central nucleus of the amygdala, anterior cingulate cortex, insular, and prefrontal cortex; fight-or-flight response and stress-induced analgesia in the periaqueductal grey and rostral ventromedial medulla; and projections to the reticular formation that mediates regulation of descending pathways to the spinal cord [79; 80]. Signal processing in the brainstem, thalamus, and cerebral cortex results in pain perception [68].

Descending Modulatory Pain Pathways

Descending pathways from the cortex, thalamus, or brainstem extend down the spine to the dorsal horns. With tissue insult, the nociceptive signal is relayed into and through the brain. The signal, now experienced as pain, is routed down descending pathways to the dorsal horn receiving peripheral inputs to dampen pain perception by modulating signal transmission through presynaptic and postsynaptic action and actions on intrinsic interneurons. This is termed the top-down pain modulatory system. The relative balance between descending inhibition and facilitation varies by type and intensity of stimulus and by time from injury. Serotonergic and noradrenergic pathways contribute to modulatory effect [79; 81; 82].

CHRONIC LOW BACK PAIN

The standard definition of chronic pain as pain lasting longer than three months provides a temporal index, but it is not very helpful as a biologic or mechanistic index [83]. Chronic LBP not only involves the dissociation of ongoing pain from the extent of tissue harm; it also impacts numerous brain circuits by inducing massive reorganization of cortical anatomy and physiology. The extent of this reorganization is largely driven by the saliency of unrelenting pain that recruits emotion-mediating brain regions, including limbic structures, which reorganize the cortex to reflect suffering and coping strategies. This in turn alters spinal cord processes through descending modulatory pathways [84].

Development of Chronic LBP

Progression from acute to chronic LBP coincides with the development of widespread alteration in pain pathways and brain regions that modulate specific aspects of pain processing. Psychosocial factors contribute to the development and perpetuation of chronic LBP. When chronic LBP is alleviated, some brain regions and mediated functions become normalized. Other brain regions may remain impaired, in which case, clinical improvement and restoration of the patient's functional status remains difficult.

Peripheral Sensitization

Peripheral sensitization develops at the site of peripheral nerve injury, tissue injury, or inflammation. With peripheral sensitization, nociceptors' nerve endings develop lowered threshold and heightened response to tissue stimuli that trigger activation.

Central Sensitization

Central sensitization refers to the amplification of neural signaling within the CNS that elicits pain hypersensitivity. When this process is established, little peripheral input may be required to maintain a painful state [85; 86].

The process of central sensitization begins when post-synaptic terminals of ascending neurons in the dorsal horn become altered by nociceptive barrage. The surge of excitatory signaling transmitters and modulators (e.g., glutamate, substance P, CGRP, BDNF) bind to receptors on spinal cord neurons and activate intracellular signaling pathways, which phosphorylate membrane channels of the glutamate receptors *N*-methyl-D-aspartate receptor (NMDA) and AMPA. This lowers the threshold and opening characteristics of the channels and results is increased CNS neuron excitation, substantial increase in pain transmission, and the development of central sensitization. The greatest contribution to initiation of central sensitization comes from post-synaptic NMDA receptor activation in the spinal cord and, subsequently, in the thalamus, limbic system, and cerebral cortex [87; 88; 89; 90].

Post-synaptic NMDA receptor activation alters signaling pathways, which amplifies nociceptive responses and can induce functional antagonism to opioid analgesic effects [91; 92; 93]. Acting in concert with other activated ligand-gated sodium and potassium channels, NMDA receptor activation allows entry of calcium ions, which alters intracellular signal processing in chronic pain. NMDA receptor ion channels possess binding sites for NMDA antagonists used in pain medicine, such as ketamine, dextromethorphan, amantadine, and memantine [91; 94].

The onset of central sensitization promotes the transition from acute to chronic LBP. The core process that underlies the development of central sensitization is neuroplasticity, the cellular process of neuronal cytoarchitecture alteration through physical remodeling. The process of neuronal cytoarchitecture alteration begins with peripheral upregulation of COX-2 and IL-1b-sensitizing neurons, which sensitize second-order spinal neurons by activating NMDA receptor acid channels and signaling microglia [95]. Brain regions become activated, including areas that mediate sensory nociceptive and pain processing, emotional processing of pain, pain modulation, pre-motor activity, and pain cognition. The cascading changes in brain circuitry enhance pain pathway sensitivity; alter sensory, emotional, and modulatory pathways; and generate new behaviors, such as increased pain sensitivity/responses, depression, and altered cognition [90; 96; 97].

Central sensitization is difficult to control and is best treated by combining modalities with different mechanisms to target the peripheral nociception origin and top-down (brain-orchestrated) and bottom-up (peripheral input) mechanisms. Top-down interventions include opioids and combined mu-opioid receptor agonist and noradrenaline reuptake inhibitor drugs. Bottom-up approaches include topically applied analgesics. Interventions that target metabolic (e.g., ketogenic diets) and neurotrophic factors (e.g., decrease BDNF) are novel and promising methods to diminish CNS hyperexcitability in central sensitization. Conservative therapy with pain neuroscience education, cognitive-behavioral therapy (CBT), and exercise therapy should be included to help modulate CNS excitation [67; 98; 99; 100; 101].

Neuropathic Involvement in Chronic LBP

Neuropathic contribution to non-radicular, nonspecific chronic LBP occurs in as many as 37% of patients and should be considered in the assessment and treatment of patients with nonspecific chronic LBP. Some mechanisms and targeting in neuropathic contribution to chronic LBP include ectopic impulses, central sensitization and plasticity, low threshold A-beta fiber-mediated pain, and loss of descending modulation [102].

Ectopic impulse activity causes sudden, brief pain with lancinating or sharpening features, resulting from increased density of dysfunctional sodium channels along the nerve length. Analgesia can be achieved by the sodium channel blockers lidocaine, mexiletine, carbamazepine, and lamotrigine. The role of NMDA receptor activation in synaptic plasticity and central sensitization can be targeted with the NMDA antagonist drugs ketamine and dextromethorphan and the opioid levorphanol.

Peripheral nerves can regenerate, but sprouting errors can occur when A-beta fibers become cross-linked to C fibers, inducing severe, sharp pain in areas where pain was previously absent. Mechanisms involve sodium channel excitability and spinal cord hyperexcitability; gamma-aminobutyric acid (GABA) inhibitory drugs and calcium-channel blockers are mainly used to address this type of pain.

Loss of descending modulation results from transmitter dysregulation. Serotonin and norepinephrine modulate pain in the descending control system. Drugs that inhibit reuptake of both transmitters are more effective for pain control than sole transmitter targeting and are more likely to improve mood symptoms. This explains why serotonin and norepinephrine reuptake inhibitors (SNRIs) are more effective than selective serotonin reuptake inhibitors (SSRIs).

Psychologic Factors

The contribution of psychologic factors to chronic LBP is essential to consider, as discussed. Depressive symptoms, pain catastrophizing, and fear avoidance in LBP are thought to enhance pain facilitatory pathways in the CNS, resulting in sensitization of dorsal horn spinal cord neurons and the development of exaggerated pain perception [86]. Pain catastrophizing refers to exaggerated negative thoughts and emotions surrounding pain, and this pain coping style significantly contributes to variability in pain perception. Catastrophizing adversely impacts pain by inducing an aroused, negative emotional state that worsens pain and fosters helplessness that decreases adaptive pain responding. This promotes the alteration of neural processes related to pain attention and response. People with trauma histories are more likely to catastrophize, suggesting that catastrophizing may mediate the effects of earlier psychologic stress on pain [62].

Emotional distress, including significant anxiety and depression symptoms, increases the neurotransmission of the inflammatory mediators substance P, IL-1, and IL-6, which triggers release of corticotropin-releasing factor and elevation of systemic corticosteroid levels. This further heightens pain sensitization and contributes to pain behaviors [103]. Individual differences in acute stress response may contribute to broad pain response variations by influencing neurophysiologic mechanisms that underlie pain perception [104]. Chronic pain does not disrupt acute stress response or the sensory dimensions of pain but induces long-term alteration in neural systems that underlie affective-motivational functions [105; 106; 107].

In one study, patients with subacute LBP were followed over one year, and brain images of those with resolved or persistent LBP were compared. As LBP persisted, the location of brain activity in pain perception shifted from regions involved in nociception to regions that engaged emotion-related circuitry (i.e., the medial prefrontal cortex and amygdala).

LBP persistence was also associated with declining activity in acute pain regions. These findings were replicated in a comparison of patients with LBP for two months or more than 10 years. The very high correlation between LBP for 1 year and more than 10 years indicates that as chronic LBP develops during the first 12 months from onset, the brain carves a chronic pain state, making this first year a critical period for LBP chronification. Despite reorganization of pain processing and response to brain emotion circuits, baseline depression and anxiety scores in patients who progressed to chronic LBP did not differ from patients who recovered from chronic LBP scores at 12 months. Instead, the qualitative subjective properties of the pain were sufficient to shift its representation from acute pain to emotion circuitry. This was the first study to identify a brain signature for the transition to chronic LBP [108].

Neuroscience Findings

Neuroimaging evidence shows that patients with chronic LBP develop alterations in brain structure, function, and chemistry. An effort has been made to identify the neural correlates of chronic LBP in order to better understand causation, consequence, and potential interventions in at-risk patients. Functional MRI has shown reversal in some of these changes [83].

It is well established that chronic pain is linked to impairment of memory, attention span, and mental flexibility, but less well studied is whether overall cognitive function predicts risk for chronic pain. A cohort of 189 patients assessed at pre-surgery (non-spinal) and at 6- and 12-months post-surgery found a significant (and predictable) correlation between persistent pain at 12 months and poor baseline performance in cognitive flexibility, visuospatial processing, and visual memory independent of anxiety or depression. Impaired cognitive performance also predicted pain intensity and neuropathic symptoms in patients with pain, unassociated with type of surgery or pre-surgical pain. These findings suggest that patients with deficits in executive functioning or memory have a greater risk of pain chronicity after a painful event [109]. A cross-sectional study of 2,022 community-dwelling older adults found that cognitive impairment was associated with bodily pain, particularly among participants with LBP, waist pain, or sciatica [110]. In patients with chronic LBP, the strength of functional connectivity between the medial prefrontal cortex and nucleus accumbens predicted the transition to chronic back pain one year later with greater than 80% accuracy. These elements of emotional learning circuitry predicting transition to chronic pain may help identify strategies to prevent pain chronification [111].

Other research into neural factors that contribute to chronic LBP has found that subacute pain is associated with robust changes in hippocampal functional connectivity, the nature of which influences recovery. The reorganization of processing in the hippocampus, and between the hippocampus and the cortex, appears to contribute to the transition from subacute to chronic LBP and may explain learning difficulties and emotional abnormalities associated with chronic pain [112].

Functional and structural MRI studies in patients with chronic pain have identified brain and peripheral nerve abnormalities, with some pre-existing and others resulting from prolonged pain and related neuroinflammation over time. The data suggest that some chronic LBP arises from a combination of pre-existing vulnerabilities and sustained abnormal pain input [113].

Chronic LBP is associated with abnormalities in brain structure and function, including reduced cortical gray matter in the bilateral dorsolateral prefrontal cortex (DLPFC), thalamus, brainstem, primary somatosensory cortex (S1), and posterior parietal cortex. These abnormalities are not unique to chronic LBP and are found in many chronic pain conditions. Other studies have linked the DLPFC to pain modulation, placebo analgesia, perceived control of pain, and pain catastrophizing [114]. Some of these chronic pain-associated neuroanatomical and functional changes may be reversible with effective pain control. Patients with untreated chronic LBP have shown a thinner left DLPFC with abnormal activation during cognitive-related tasks.

After six months of pain alleviation, the left DLPFC became thicker, and the extent of neuroanatomic recovery was dependent on the extent of clinical improvement. Successful pain reduction also normalized cognitive task-related brain activity in the left DLPFC [115].

Heritable Factors

Data show that pain sensitivity is heritable to some degree, with genetic contribution accounting for an estimated 50% of pain variance [85]. Statistically significant genetic-mediated responses have been found to most painful stimuli, varying by pain type, with provocation of different mechanistic pathways [116]. By employing a classic twin-design, the authors of one study found genetic influences on nociceptive processing in the midcingulate cortex and bilateral posterior insula and genetic contributions to large-scale functional connectivity during nociceptive processing [117]. The catechol-O-methyltransferase (COMT) enzyme metabolizes catecholamines and modulates adrenergic, noradrenergic, and dopaminergic signaling. A functional polymorphism in the gene that encodes COMT reduces its activity and has been linked to pain sensitivity. In patients with discogenic subacute LBP and sciatica, this genotype did not influence pain or disability at new-onset, but significantly increased pain and disability after six months. Thus, COMT polymorphism may contribute to protracted LBP, sciatica, and disability following lumbar disk herniation [118].

A variation in the gene encoding serotonin receptor 3B (5-HTR3B) has been correlated with high scores on pain catastrophizing, pain-related magnification, and helplessness. The 3B receptor is associated with descending pain modulation pathways, and a relationship between pain catastrophizing and a serotonin receptor polymorphism is likely [119]. High expression of polymorphism in the promoter region of the serotonin transporter gene has been linked to increased pain intensity during unpleasant affective states and decreased pain intensity during positive (but not neutral) emotional states. This polymorphism may importantly contribute to the capacity for emotional modulation of pain [120].

PATHOANATOMIC BASIS OF COMMON LBP CONDITIONS

Definitions

LBP can originate from many underlying causes. The following are the most common LBP conditions.

Lumbar (intervertebral) disk disorders: Also simply referred to as disk disorders, this includes degenerative disk disease and disk herniation.

Degenerative lumbar disk disease: Degenerative changes in the three-joint complex, comprised of the facet joints and anterior lumbar disk. Annular fissures and tears develop from repetitive microtrauma. The disk becomes vulnerable to herniation, and resultant loss of water retention ability and disk height leads to disk resorption, internal disruption and additional disk tears, and loss of mechanical integrity at the three-joint complex. Further degeneration involves additional narrowing of disk space, fibrosis, and osteophyte formation [121; 122; 123].

Lumbar disk herniation: Displacement of disk material (e.g., nucleus pulposus) outside the annulus fibrosus due to progressive loss of disk hydration and height and inappropriate load transfer to annulus and endplates [123].

Lumbar radiculopathy: With L4–L5 involvement, pain that radiates down the leg below the knee in the distribution of the sciatic nerve [124]. Formerly thought to result from mechanical compression by disk material, now known to be caused by nerve root inflammation from leakage of inflammatory mediators from the nucleus pulposus into the epidural space. These include cytokines, leukotrienes, nitric oxide, immunoglobulins, ILs, PGE-2, and metalloproteinases [125; 126]. Disk herniation can be asymptomatic and may not produce radicular symptoms [123].

Lumbar spinal stenosis: Narrowing of the central or lateral recesses of the spinal canal and/or the neural foramina [127].

Neurogenic claudication: Pain enveloping the buttocks, posterior thigh, calf, and groin, often, but not always, associated with lumbar spinal stenosis [127].

Lumbar spondylolisthesis: Subluxation or slippage of one vertebral body relative to another, which may cause pain and neurologic deficit [128].

Lumbar spondylosis: Degenerative osteoarthritic changes affecting the spinal unit [129].

Myofascial pain syndrome: A regional muscle pain syndrome caused by myofascial trigger points, which are hyperirritable zones in a palpable taut band of skeletal muscle. Symptoms include local and referred pain, muscle stiffness and weakness, and sensory changes [130].

Facet joint pain: Pain resulting from disruption in normal architecture, biomechanics, or function of facet joints, caused by degenerative changes, injury, or mechanical strain [131].

Failed back surgery syndrome: Failed back surgery syndrome is not a single entity, but a complex syndrome with multiple potential causalities, including structural pathogenesis, improper surgical technique, altered biomechanics, and/or central sensitization [55; 124].

Anatomic Pathogenesis of LBP

In the typical healthy back, the basic unit of the spine (the "functional spinal unit") includes two adjacent vertebral bodies with two posterior facet joints, an intervertebral disk, and surrounding ligaments. The disk absorbs energy and distributes weight evenly from one spinal segment to the next while allowing movement of protective bony elements [25].

The lumbar spine (L1–L5) is inferior to the twelfth thoracic spinous process and superior to the first sacral spinous process. The sacral spine is inferior to the first sacral spinous process and superior to the sacrococcygeal joint. LBP may be more specifically termed lumbosacral spinal pain, because it encompasses lumbar and sacral spinal pain. Lumbosacral spinal pain can occur in either or both regions and represents "low back pain" [25].

Radicular pain results from spinal nerve provocation by inflammatory molecules, mechanical impingement, or both, and describes pain referred to the lower extremity along the corresponding dermatome. Also called sciatica, the term "radicular pain" may be preferred because pain originates from nerve roots or the dorsal root ganglion of a spinal nerve [25].

Repetitive mechanical stress or aging can lead to progressive degenerative changes in the functional spinal unit, usually at L4–L5 with LBP present. Early degenerative changes include loss of hydration of the nucleus pulposus along with mild loss of disk height. Internal disk disruption begins with radial and/or concentric fissures from the nucleus pulposus periphery to the annulus fibrosus [25]. Lumbosacral pain can develop when the fissures or material from the nucleus pulposus extend to the peripheral annulus fibrosis, activating the sinuvertebral nerve. Radicular pain can develop when material from the nucleus pulposus extends outside the annulus fibrosis (e.g., herniated nucleus pulposus) to produce an intense inflammatory reaction by surrounding the spinal nerve.

Advanced degenerative changes are associated with dehydration of the nucleus pulposus and marked loss of disk height, osteophyte formation, and ligament thickening [25]. Central canal lumbar stenosis results from the combined effects of facet hypertrophy (enlargement) and thickening of the ligamentum flavum and posterior longitudinal ligaments. These and other degenerative changes may produce neurogenic claudication. Progressive disk or facet joint degeneration may lead to chronic lumbosacral pain, while stenosis of the spinal canal lateral recess and the intervertebral foramen produced by facet hypertrophy causes nerve root compression and radicular pain.

Myofascial Pain Syndrome

Trigger points in myofascial pain syndrome develop from direct or indirect muscle trauma and overload. Primary causative factors are usually structural or mechanical (e.g., intense exercise, sustained abnormal postures, anatomic abnormalities, joint dysfunction, chronic repetitive overuse, poor work-related ergonomics). Nonstructural factors (e.g., anxiety, sleep deprivation, fatigue, chronic infection, iron, vitamin, mineral, and endocrine deficiency states) may also be at play, often working in combination with mechanical factors. An estimated 9 million people in the United States experience myofascial pain, and myofascial pain syndrome affects up to 95% of patients with chronic pain. One study at a large pain center found myofascial pain syndrome to be the primary cause of pain in 85% of patients [132; 133].

Acute myofascial pain triggered by identifiable local muscle strain has a favorable prognosis. When myofascial pain syndrome expands from local to regional pain and becomes chronic, pain is often difficult to control. Myofascial pain syndrome can resemble or co-occur with other pain conditions and present as painful, restricted range of motion, stiffness, referred pain, or autonomic dysfunction. The pain pattern reflects the involved muscle(s) [130; 132; 134].

Failed Back Surgery Syndrome

Failed back surgery syndrome, also termed post-laminectomy pain, refers to post-spinal surgery chronic pain with or without lower extremity radiculopathy. More than 300,000 spine surgeries are performed annually in the United States for pain relief, and up to 100,000 patients develop failed back surgery syndrome [135; 136]. Recurrent disk herniation, epidural abscess, scar tissue formation around nerve roots, facet joint syndrome, or muscle spasm may contribute to the clinical features of failed back surgery syndrome [33]. In patients with previous fusion surgery and worsening axial back pain, additional wear and tear on the facet joints and disks directly above and below the fused segment(s) can generate significant pain. Patients with persistent radicular pain often have chronic nerve injury requiring treatment for neuropathic pain. Clinical assessment should attempt to clarify the original LBP condition, the surgical approach, and whether the chronic LBP is recurrent or new-onset pain requiring further evaluation [137].

ASSESSMENT AND DIAGNOSIS

Roughly 85% of LBP lacks apparent etiology and is termed nonspecific. Clinical practice guidelines for LBP recommend assessment of new patients by triage, with LBP grouped as nonspecific, potentially serious, associated with radiculopathy or spinal stenosis. Several LBP syndromes and conditions have been studied with radiographic imaging (usually MRI) in an effort to establish causality. These include lumbago, myofascial syndrome, muscle spasm, mechanical LBP, lumbar strain, facet joint dysfunction, and bulging lumbar disk. No specific, defining radiographic abnormality has been identified. These conditions, often presenting as acute LBP, are considered vague and nonspecific, and imaging studies are of limited value in establishing the cause, directing therapy, or predicting the clinical course. As an example, many persons with lumbar spine degenerative change or disk protrusion evident on MRI are not experiencing LBP. Thus, some abnormalities detected by MRI are nonspecific and of uncertain relevance to the patient's complaint. A diagnostic imaging workup does not improve clinical outcomes in most patients with acute LBP [60].

RED FLAG ASSESSMENT IN PATIENTS WITH LOW BACK PAIN	
Possible Etiology	**Red Flags**
Malignancy	History of or current cancer diagnosis Systemically unwell Unexplained weight loss in the past six months Constant, progressive, nonmechanical pain Altered sensation from trunk down
Vertebral fracture	Age older than 70 years Significant age-relative trauma Long-term corticosteroid use Altered sensation from trunk down Pain worse with flexion, pulling up from supine to sitting position, and from sitting to standing
Cauda equina syndrome	Acute-onset urinary retention Loss of anal sphincter tone or fecal incontinence Saddle anesthesia Widespread (more than one nerve root) or progressive motor weakness in legs Gait disturbances
Vertebral infection	Systemically unwell Constant, progressive, nonmechanical pain Recent bacterial infection or spinal region wound Intravenous drug abuse Immunosuppression from steroids, transplant drugs, or HIV Altered sensation from trunk down
Source: [40; 139; 140; 141]	*Table 2*

While most LBP cases lack serious pathology, each case is deserving of a careful clinical assessment for symptoms and signs (termed "red flags") associated with serious pathology. Patients with red flags are redirected to urgent diagnostic workup and intervention. Patients without red flags should be assessed for the possibility of radiculopathy and lumbar spinal stenosis, which, with diagnostic confirmation, may require early specialist referral. LBP may be classified as nonspecific when there are no red-flag indicators, radiculopathy, or suspicion of lumbar spinal stenosis. Once red flag indicators are excluded, all patients should be evaluated for risk factors of poor prognosis and chronicity ("yellow flags"). Patients with yellow flags should receive psychosocial intervention to minimize chronification and disability. Patients with painful recurrence following LBP remission require assessment of new-onset LBP [41; 124; 138].

HISTORY AND PHYSICAL EXAM

Red Flag Assessment

Red flag assessment during history and physical exam identifies the subset of patients who may have serious pathologic conditions that require urgent diagnosis and therapeutic intervention. Such conditions include vertebral osteomyelitis, epidural space infection, tumor, osteoporosis, fracture, structural deformity, inflammatory disorder, or cauda equina syndrome. Because some red-flag conditions have low prevalence or less risk from delayed or missed diagnosis, some signs are more important to assess than others. A more focused red flag assessment is recommended, narrowed to identify malignancy, fracture, cauda equina syndrome, and vertebral infection (***Table 2***) [40; 139; 140; 141].

History

When evaluating back pain, it is important to ask patients about current pain characteristics, including pain severity; the time and event of onset; postures or activities that worsen or lessen pain; and occupational, social, and activity limitations from pain. The patient's prior history of systemic disease (e.g., osteoporosis, cancer, arthritis, infection), history of trauma, immunosuppression, constitutional symptoms, substance use, and previous back pain, including symptoms, diagnosis, testing or imaging results, treatment, and response, should be noted [39; 40]. Possible origin outside of the spine should be considered, including pancreatitis, nephrolithiasis, aortic aneurysm, or systemic disease, such as endocarditis or viral syndromes. Sensory and motor changes may also provide insight into the underlying cause of back pain, and the pattern and nature of any lower extremity symptoms, gait abnormalities, and/or presence of significant neurologic deficits or bowel or bladder dysfunction should be explored.

As discussed, yellow flags are risk factors for poor treatment response and progression to chronic LBP and should be assessed in all patients. High-risk patients require psychosocial therapy because most interventions are ineffective in facilitating return to work following extended disability leave for LBP [39; 40; 41; 42; 142].

Physical Examination

All patients presenting with LBP should be observed for posture, seating position, spinal contour, and skin discoloration. The spine should also be palpated for tenderness. A thorough neurologic exam can help to identify spinal level and nerve root involvement. The exam should include [40; 143; 144]:

- Gait:
  - Heel walking (L4–L5)
  - Toe walking (S1)
- In standing position:
  - Movement testing, flexion and extension
  - Trendelenburg test (L5)
  - Repeat toe raise (S1)
- In sitting position:
  - Patellar reflex (L3–L4)
  - Quadriceps power (L3–L4)
  - Ankle dorsiflexion strength (L4–L5)
  - Great toe extension (L5)
  - Flexion strength (S1)
  - Plantar response
  - Upper motor test
- Kneeling position:
  - Ankle reflex (S1)
- Supine lying position:
  - Passive straight leg raise
- Prone lying position:
  - Femoral nerve stretch (L3–L4)
  - Gluteus maximus power (S1)
  - Saddle sensation testing (S2–S4)
  - Passive back extension (using arms to elevate upper body)
- Dermatomes

In addition, there is a group of physical signs that may indicate an underlying non-organic or psychologic basis for LBP. This group of signs, termed Waddell signs, includes [41]:

- Non-anatomic superficial tenderness
- Positive simulation tests (i.e., pain from axial loading and en bloc rotation)
- Non-positive tests with distraction (e.g., no pain with full knee extension while seated, but supine straight leg raise is markedly positive)
- Non-anatomic motor or sensory loss
- Verbal over-reaction or exaggerated body language

PREVALENCE OF MRI-DETECTED SPINAL ABNORMALITIES IN PERSONS WITHOUT A HISTORY OF LOW BACK PAIN	
MRI Finding	**Frequency of Finding**
Disk bulge	24% to 53%
Disk protrusion	20% to 63%
Disk extrusion	1% to 18%
Any disk pathology[a]	57% to 64%
Nerve root deviation or compression	4%
[a]Any bulge, protrusion, extrusion, or sequestration	
Source: [146; 147; 148; 149; 150; 151]	*Table 3*

If three or more of these signs are positive, this suggests psychogenic contribution to LBP; at least two positive signs suggests poor surgical but not rehabilitation outcome, subjective pain reporting unreliable for evaluation of therapy response, and risk of disability. It is important not to label positive findings as malingering [41].

DIAGNOSTIC IMAGING AND TESTING

As noted, MRI is highly sensitive but often nonspecific in identifying back pain causation [145]. As such, MRI and x-ray are widely discouraged from use in the assessment of nonspecific acute LBP [40; 140; 144]. In the past, spinal MRI of asymptomatic persons was considered valuable for early detection and intervention of back problems invariably leading to pain. However, this has been dispelled by findings of highly prevalent MRI-detected spinal abnormalities in persons without LBP history (***Table 3***) [146; 147; 148; 149; 150; 151]. In one study, asymptomatic persons with MRI-detected disk herniation were followed, and imaging abnormality lacked prediction of pain development [152]. In another study, patients with symptomatic lumbar disk herniation were treated conservatively and followed. Nearly all showed further disk degeneration, but baseline MRI findings were unrelated to pain continuation [153].

In the first visit, the use of imaging studies should be limited to suspected red-flag conditions. To minimize diagnostic and interpretation errors, imaging should only be ordered by clinicians with the skills to organize and interpret radiographic and MRI images [154].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Radiology asserts that routine imaging patients with acute LBP of less than six weeks' duration and no red-flag symptoms provides no clinical benefit. This type of LBP is considered a self-limiting condition that is responsive to medical management and physical therapy in most patients.

(https://acsearch.acr.org/docs/69483/Narrative. Last accessed July 25, 2022.)

Strength of Recommendation: 2 (Usually not appropriate)

MRI and computed tomography should be reserved for persistent pain and evidence of radiculopathy or lumbar spinal stenosis when surgery or epidural steroid injections are considered. Nerve root, facet joint, medial branch, or sacroiliac joint blocks lack sufficient evidence as LBP diagnostic procedures. However, medial branch nerve block has been recommended for diagnosing facet joint pain prior to radiofrequency denervation [154].

LABORATORY TESTS

Laboratory tests can help confirm suspicion of spinal infection or tumor. With spine infection, laboratory testing is low in specificity, and diagnostic confirmation requires MRI and, frequently, biopsy [140].

ENHANCING ASSESSMENT AND DIAGNOSIS

Efforts to improve outcomes in patients with LBP have included a focus on assessment and diagnosis, and specifically on identifying more accurate prognostic factors and subgrouping of patients categorized as having nonspecific LBP.

Subgrouping Patients with Nonspecific LBP

Many believe the current "one-size-fits-all" approach for nonspecific LBP contributes to poor patient outcomes because nonspecific LBP is not a homogeneous condition. This has prompted efforts to identify meaningful, clinically relevant typologies for patient subgrouping. Several approaches have been validated and published, with the goal of improving treatment outcomes through better disease-treatment matching.

Most guidelines for chronic LBP recommend a diagnostic triage to group patients by nonspecific, specific, and radicular LBP. This differentiation is not straightforward; patients with disk herniation are either grouped as specific with radicular pain or nonspecific with degenerative disk disease without radicular pain. Also, the definition of radicular pain is inconsistent.

To address these and other limitations with the triage approach, an alternative classification system for chronic LBP was developed to differentiate patients with pain of nociceptive, peripheral neuropathic, or central sensitization origin using a mechanism-based classification of LBP signs and symptoms [155]. The system was developed and validated using data from 464 patients with a range of back and leg symptoms; the majority had pain duration longer than three months (chronic). Factors with the greatest predictive ability for each of the three back pain mechanisms include [155; 156; 157]:

Nociceptive Pain

- Clear and proportionate mechanical/anatomical nature to aggravating and easing factors
- Usually intermittent and sharp with movement or mechanical provocation
- At rest, tends to be a constant dull ache or throbbing pain
- The absence of dysesthesia, disturbed sleep, antalgic postures, and pain of a burning, shooting, or electric shock-like quality

Peripheral Neuropathic Pain

- Pain referred in a dermatomal or cutaneous distribution
- History of nerve injury, pathology, or mechanical compromise
- Pain or symptom provocation with mechanical or movement tests that move, load, or compress neural tissue

Central Sensitization

- Disproportionate, nonmechanical, unpredictable pattern of pain provocation by multiple nonspecific aggravating or easing factors
- Pain disproportionate to the extent of injury or pathology
- Strongly associated with maladaptive psychosocial factors, such as negative emotions, poor self-efficacy, and maladaptive pain beliefs and behaviors
- Diffuse non-anatomic areas of pain tenderness on palpation

Building on this classification system, Vining et al. developed an evidence-based clinical tool for application in the assessment and diagnosis of patients with LBP (***Table 4***) [155; 156; 157; 158; 159]. This tool was created to help fulfill the unmet need for an easily applied diagnostic classification system based on the underlying pain mechanism, especially with nonspecific LBP [158].

LOW BACK PAIN DIAGNOSTIC CATEGORIES AND KEY INFORMATION			
Category	**Definition**	**Key Findings**	**Diagnostic Standard Used**
Screening	Findings indicating recent injury, special testing, referral, or need for emergent evaluation	Evidence of possible fracture, progressive neurologic deficit, infection, tumor, or other etiology	N/A
Functional instability	Disruption of neuromuscular control of a spinal joint neutral zone during normal physiologic demand	Positive prone passive lumbar extension Hypermobile lumbar segment(s) Absence of hypomobile lumbar segment	Radiographic measurements of intervertebral motion
Nociceptive (pain from noxious stimulation of peripheral tissues)			
Discogenic	Pain from the posterior annulus and near the endplate	Centralization with repeated end-range loading Any two: Centralization with repeated motion, vulnerable/apprehensive when stooped, lumbar extension loss	Lumbar discography
Sacroiliac joint	Pain from the sacroiliac joint and/or supporting ligaments	Sacroiliac joint area pain with three or more positive findings on: Gaenslen left and right, thigh thrust, sacral thrust, iliac comp, distraction tests	Fluoroscopically guided, controlled anesthetic block
Zygapophyseal joint	Pain from zygapophyseal joint structures, including the joint capsule and subchondral bone	Three or more: Age older than 50 years, relief by walking, relief by sitting, paraspinal onset, positive extension-rotation test	Fluoroscopically guided, controlled anesthetic block
Myofascial	Pain from muscles, tendons, and/or fascial tissue in the low back	Pain with use of involved muscle and trigger points	None
Neuropathic (pain from peripheral or central nervous system tissues)			
Compressive radiculopathy	Pain from compression and inflammation of a nerve root	Absent ankle/knee reflex Pain worse in lower extremity than in back Dermatome distribution (cough, sneeze, straining) Paresis (extremity motor strength loss) Finger to floor distance >25 cm	Clinical findings in individuals with nerve root compression confirmed by MRI
		LANSS score >12	Expert opinion
Non-compressive radiculopathy	Pain from compression, stretch and/or inflammation of peripheral nerve structures	LANSS score >12	Expert opinion
		Compressive radiculopathy criteria are not met	N/A

Table 4 continues on next page.

LOW BACK PAIN DIAGNOSTIC CATEGORIES AND KEY INFORMATION *(Continued)*			
Category	**Definition**	**Key Findings**	**Diagnostic Standard Used**
Neurogenic claudication	Pain from ischemia/compression of individual nerve roots, the cauda equina, or the spinal cord	Age older than 60 years Activity induced lower extremity pain with relief upon forward bending or rest Symptoms worsened by standing or extension Urinary incontinence	Expert opinion
		Negative ABI	Doppler ultrasound
Central	Pain from a lesion or dysfunction within the central nervous system	Disproportionate pain Unpredictable symptom aggravation and relief Maladaptive psychosocial factors Non-anatomic distribution	Expert opinion
Other			
Other diagnoses	Diagnoses not categorized above	Dependent on suspected condition	N/A
ABI = ankle-brachial index, LANSS = Leeds assessment of neuropathic symptoms and signs pain scale, MRI = magnetic resonance imaging.			
Source: Reprinted from Vining R, Potocki E, Seidman M, Morgenthal AP. An evidence-based diagnostic classification system for LBP. J Can Chiropr Assoc. 2013;57(3):189-204, with permission from the Journal of the Canadian Chiropractic Association. *Table 4*			

Non-radicular chronic LBP was long assumed to be the prototype of the chronic nociceptive pain state. However, neuropathic pain can also result from injured afferent nerves, and back pain, including axial back pain, is now known to involve neuropathic pain components, making it a mixed pain syndrome with overall pain perception from both nociceptive and neuropathic mechanisms [160]. This mechanistic heterogeneity indicates a more complex framework than previously assumed and may explain the often-disappointing results with pharmacotherapy. Better approximation of the mechanistic contribution may be gained from a symptom constellation approach to assessment. Such an approach was evaluated in 7,772 patients with LBP (37% of which showed neuropathic pain as the dominant pain component) and 1,083 patients with axial LBP (of whom 12.1% showed sensory symptoms consistent with neuropathic pain). Five LBP subgroups were identified with distinct mechanistic and sensory profiles [161].

The largest subgroup (26%) displayed a lack of distinct sensory abnormalities and few sensory symptoms. Another subgroup (21%) reported a predominance of lumbar region "pain attacks," whereby lumbar spine movement induces severe lumbar pain lasting several seconds. Pain is evoked by ectopic discharges originating from sensitized nerves, such as those innervating facet joints and outer intervertebral disk layers. Pressure to the vicinity of afflicted nerves stimulates release of pro-inflammatory cytokines and neurotrophins, producing synergistic mechanical and chemical irritation to annulus fibrosus cells.

In a third group (21%), pain was primarily experienced as a dull and aching quality localized in the back. This nociceptive back pain is evoked by noxious stimulation of deep somatic structures in the lumbar spine, induced by the ingrowth of small nociceptive nerve fibers into degenerated intervertebral disks. Lumbar muscles are explicitly tender to pressure stimuli due to the musculoskeletal basis of the pain.

The last two groups experienced LBP characterized by burning and prickling sensations, reflecting an isochronic occurrence of neuropathic and nociceptive pain components. With intervertebral disk damage, the disk is invaded by blood vessels and small nociceptive nerve fibers. Macrophages secrete pro-inflammatory cytokines, TNF-α, and other neurotrophins that act as growth factors. Nociceptive fibers sprout from the outer part into the inner areas of the disk, including the nucleus pulposus. Axonal sprouts within diseased disks become damaged from compressing forces and irritated by contact with inflammatory agents, and these damaged afferent fibers in the disk develop neuropathic pain mechanisms reflected by neuropathic symptoms.

Data on these "nonspecific" subtypes suggest that sensory profiles based on descriptor severity may be more accurate than pain intensity alone, especially with different underlying mechanisms operating in tandem. These phenotypic differences in sensory profiles and comorbidities may explain inconsistent treatment response and assist in tailored individualized therapy for patients.

Prognostic Factors

Yellow flag assessment is widely used and necessary, but some have argued insufficient, to identify patients at high risk of progression to chronic pain and disability. This has prompted research to identify additional risk factors of chronic pain and disability.

To improve outcomes in the primary care of patients with LBP, a newer approach places patients into three subgroups based on core modifiable predictors of chronicity. This allows delivery of targeted treatment to intervene and alter the clinical course. A central feature for risk identification and subgroup placement is the Keele STarT Back tool, a validated instrument that includes nine items related to physical and psychologic predictors of chronicity. The scores place patients into low-, medium-, or high-risk categories. A six-item version was also developed for primary care use and identifies patients as either low risk or not low risk of chronicity. During the initial primary care contact, patients with low risk of chronicity should receive reassurance, education, and advice and be told to return if pain persists. Those scoring as not low risk are referred to a physiotherapist and are scored using the longer instrument. Medium-risk patients receive physiotherapy to address pain and disability, and high-risk patients receive additional cognitive-behavioral approaches that address psychosocial obstacles to recovery [162]. The authors of one study found that the tool may be useful in physiotherapy practice, both as a screening tool for yellow flags and as a tool to guide and assist the level of treatment for patients with LBP [163].

TREATMENT OPTIONS

Standard clinical practice guidelines for LBP are organized around the assumption of favorable prognosis, spontaneous resolution of most acute LBP cases, and conservative care dictated by the benign clinical course [57]. This assumption of benign prognosis is disputed by more recent data, which also stress the importance of earlier, more aggressive intervention to minimize the development of chronic LBP.

It is increasingly clear that nonspecific LBP is not a homogeneous condition, and "one-size-fits-all" treatment for nonspecific LBP may contribute to unsatisfactory outcomes for many patients. As discussed, several approaches to nonspecific LBP subgrouping have been validated and published, with the goal of improving treatment outcomes through better patient-therapy matching.

TREATMENT OF ACUTE AND SUB-ACUTE LBP

Clinical practice guidelines usually structure recommendations for LBP management by time from onset, with acute pain duration less than 4 to 6 weeks, sub-acute pain 6 to 12 weeks, and chronic pain longer than 12 weeks. During initial and all follow-up visits, pain level should be measured using a 0–10 point numerical rating scale to help monitor pain progression, remission, and treatment response [164]. The Oswestry Low Back Pain Disability Questionnaire may be considered to assess perceived level of disability related to functional limitation [164]. Patients should be asked if pain interferes with daily activities or impacts/changes social functioning, sleep, sexual activity, or weight [164].

Most patients with back pain report receiving limited information on self-management. Patients should receive sufficient information and resources, such as links to online audio and literature resources, paper-based information, and healthcare organizations specializing in pain or spinal disease that may be contacted for assistance by phone. With the burden imposed by LBP, direct support, reinforcement, and frequent primary care contact are often most important [154].

In the absence of red flags or radiculopathy, acute LBP is a condition and not a diagnosis. It is treated nonspecifically with pharmacotherapy, physical therapy, and advice on self-management. If LBP is severe or persistent, the underlying cause should be diagnosed to facilitate its management [164].

Acute LBP

Nonspecific Acute LBP

When a patient presents with LBP of less than four to six weeks, the mainstays of management are patient education, reassurance, and advice on self-management. Patients should be assured that prognosis is generally good, often resolving with little intervention. Self-care recommendations include [1; 40; 41; 138; 140]:

- Stay active, avoid bed rest, and return to normal activities as tolerated.
- Avoid twisting and bending.
- Use heat or ice packs, whichever provides the most comfort.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Institute for Clinical Systems Improvement, clinicians should advise patients with acute and subacute low back pain to stay active and continue activities of daily living within the limits permitted by their symptoms.

(https://www.icsi.org/guideline/low-back-pain. Last accessed July 25, 2022.)

Strength of Recommendation/Level of Evidence: Strong Recommendation/Moderate Quality Evidence

Analgesic medications may be used, and the selection is determined by pain severity. Except for minor pain, medications should be prescribed on a time contingent (every four to six hours) and not a pain contingent (as needed) basis. Most patients should start with a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen; a muscle relaxant may be added, based on pain severity. With severe pain, a short course of opioid therapy may be warranted [1; 40; 41; 138; 140].

Spinal manipulation may be helpful for some patients. If it is not the first episode of LBP, physical therapy (e.g., McKenzie method, spine stabilization) should be considered.

In patients at risk for chronic LBP (i.e., who have yellow flags), discuss and address barriers to treatment success. These patients should avoid time off of work, if possible, and minimize activity restrictions. Short-term accommodations in the workplace may be discussed with employers [1; 40; 41; 138; 140].

If pain is not significantly improved after two to four weeks, the patient may switch to a different NSAID. If not done after the first visit, consider physical therapy or spinal manipulation. Adding a muscle relaxant or short-term (two weeks or less) benzodiazepine therapy may be considered. If pain persists in patients at risk for chronic disability, refer to a back pain specialist after two weeks or a multidisciplinary pain program after six weeks.

Acute/Sub-Acute Lumbar Disk Herniation with Radiculopathy

Pain from radiculopathy requires a unique care pathway, because patients can be in severe pain that often poorly responds to basic analgesics and neuropathic pain medications [41; 154; 165]. Earlier treatment may result in greater improvement, while delayed medical, physical, interventional, or surgical treatment may increase the risks of delayed recovery, chronic pain, and disability [126]. In those with severe pain and impairment, earlier referral (within two weeks of presentation) is probably most helpful [154].

At the first office visit, patients with less severe radicular pain may benefit from standard management. Patients should be advised that lumbar radiculopathy takes time to resolve, but 50% of cases improve by six weeks and 90% recover without surgery [41; 154; 165]. Bed rest for five or fewer days may be needed, but longer rests delay recovery. Remaining tolerably active and gradually returning to normal activities as one's condition improves speeds recovery.

The best positions/activities for patients with acute lumbar radiculopathy are those where they remain comfortable. Spinal manipulation may be helpful as well. Muscle relaxants can be useful, but patients with severe pain may require short-term opioid therapy [41; 154; 165].

If no improvement is noted after one to two weeks, the neurologic exam screening should be repeated to assess for new or worsening weakness. If the pain is not severe, physical therapy (McKenzie exercises) and/or specialist referral should be considered. Patients should be advised to view physical therapy as a learning opportunity, with the eventual goal of self-management at home. If no relief is noted after four to six physical therapy sessions, the treatment plan should be changed or physical therapy should be discontinued [41; 154; 165].

If pain continues for three or more weeks without improvement, an MRI should be ordered; if not diagnostic, an electromyogram (EMG) should be ordered. If pathology is proven by MRI/EMG, the patient should be referred for evaluation by a surgeon. If pathology is not proven by MRI/EMG, the patient should be referred to a back pain specialist. If strict criteria are met, epidural steroid injection may be considered [166]. These criteria will be discussed in detail later in this course.

Sub-Acute LBP

Nonspecific Sub-Acute LBP

In terms of physical and exercise therapy for nonspecific sub-acute LBP, the emphasis is on progression to normal functioning through aerobic conditioning, postural correction, and flexibility exercises. Physical therapy is recommended to optimize core strengthening and muscular stability by improving strength and endurance; neuromuscular control; proper load balance between trunk, pelvis, and legs; and soft tissue flexibility [40; 41; 124; 167; 168].

A multidisciplinary pain program or functional restoration with CBT is recommended to reduce work absenteeism from LBP. Patients with high disability and/or psychologic distress who lack response to one or more less intensive therapy should be referred to a specialist [40; 41; 124; 167; 168].

Over-the-counter analgesics are the first-line therapy for pain control. Alternative options include manual therapy and/or spinal manipulation, acupuncture, and participation in a multidisciplinary pain program. If over-the-counter analgesics are ineffective, a COX-2 inhibitor and/or weak opioid may be used. A tricyclic antidepressant (TCA) (e.g., amitriptyline, imipramine, nortriptyline, desipramine) or a short-term benzodiazepine trial may be added for continued pain despite other therapies. Strong opioids may be warranted for short-term use in severe pain, with specialist referral for patients requiring prolonged strong opioids [40; 41; 124; 167; 168]. CBT is effective in reducing duration of disability.

Any persistent, severe nonspecific LBP despite optimal care should initiate specialist referral to assess for suitability for invasive interventions. Appropriate care is required for any significant psychologic symptoms before surgery. Within the first three months of pain, surgery only benefits patients with severe spinal disease or debilitating symptoms and physiologic evidence with imaging confirmation of specific nerve root compromise.

TREATMENT OF CHRONIC LBP

In most patients presenting with chronic LBP, pain generation has expanded beyond the original peripheral spinal origin to involve a network of peripheral and CNS pathways and structures. In many cases, pain continues unabated despite resolution of the original peripheral tissue insult. For a minority of carefully selected patients, injection-based therapies can bring short-term pain relief, but multidisciplinary care is required for long-term improvement in pain and function.

All patients with chronic LBP should be provided with evidence-based information and advice to remain active and to use self-care options [40; 167]. Patients with chronic back pain should receive multi-modality therapy, with medications used in conjunction with back care information and self-management. Many patients benefit from acetaminophen or NSAIDs, the first-line suggestions. With all analgesics, potential benefits should be weighed against risks and patient comorbidity. Interventional therapies are recommended only for symptomatic pain relief, with full discussion of the potential benefits, risks, and evidence with each suggested approach.

Nonspecific Chronic LBP

All patients with non-radicular LBP who lack response to standard therapies should be considered for intensive multidisciplinary pain programs with a CBT emphasis [124; 169]. However, less intensive multidisciplinary pain programs (<100 hours) lack benefit beyond usual care or unimodality rehabilitation.

Functional restoration is more effective than standard physical therapies, exercise programs, spinal manipulation, and exercise therapy plus behavioral therapy for reducing time lost from work. It is important for functional restoration to include a CBT component. Exercise therapy that includes individual tailoring, supervision, stretching, and strengthening may be prescribed [124]. Massage may also be helpful.

Pharmacotherapies with proven efficacy include [124]:

- NSAIDs
- Norepinephrine reuptake inhibitors
- Oral mu agonist opioids
- Tramadol
- Short-term benzodiazepine trial
- Duloxetine
- Topical lidocaine patch
- Muscle relaxants (e.g., tizanidine)
- TCAs

In addition, the following alternative/complementary therapies have been suggested as beneficial [124; 169]:

- Harpagoside (a molecule derived from the *Harpagophytum procumbens* root)
- *Salix alba* (white willow bark)
- Neuroreflexotherapy
- Acupuncture
- Yoga
- Transcutaneous electrical nerve stimulation (TENS) (as part of a multimodal approach)

Specific Spine Conditions

Lumbar Spinal Stenosis

Depending on the intensity of the pain associated with lumbar spinal stenosis, NSAIDs, short-acting or extended-release/long-acting opioids, muscle relaxants, antiepileptics, SNRIs, and/or TCAs may be prescribed [127; 169; 170; 171]. Patients should be advised to avoid spinal extension and nerve root tension from exercise. When the pain is subacute, patients may undergo lumbar stabilization focusing on flexion-based exercises, pelvic posture correction, and core strengthening to prevent excessive lumbar extension and promote hamstring relaxation. Lumbar corsets to provide support and maintain a slightly flexed posture should only be used intermittently [127; 169; 170; 171]. Alternative approaches, such as acupuncture, manual therapy, and TENS, should be considered. For persistent disabling leg pain, a decompression surgery consult may be necessary.

If neurogenic claudication is also present, lumbar epidural steroid injections may be used for short-term pain relief [166]. When walking limitations are present, gabapentin may be effective.

Myofascial Back Pain

The goal of treating myofascial back pain is symptom relief, trigger point inactivation, and resolution of perpetuating factors [130; 172; 173]. Potentially effective noninvasive modalities include manual therapy, stretching, heat/ice, ultrasound, electric stimulation, microcurrent therapy, and laser therapy. Stretching, strengthening exercises, massage, and iontophoresis may also be helpful.

The pharmacotherapy with the strongest evidence for myofascial pain is benzodiazepines combined with ibuprofen or amitriptyline (not as monotherapy) [130; 172; 173]. Second-line options include topical methyl salicylate, menthol, and diclofenac patch. Although antiepileptics, antidepressants, muscle relaxants, NSAIDs, and tramadol are widely used, they are largely lacking evaluation.

Trigger point injection with local anesthetic may also be used [169]. Efficacy depends on accurate identification of trigger points and needle placement and is enhanced by physiotherapy. There is less injection pain with lidocaine 0.25% than 1%, with comparable efficacy. Botulinum toxin may also be effective in treatment-resistant trigger points. The addition of a steroid to the local anesthetic is common but lacks supportive evidence and should be avoided due to risks of muscle necrosis, skin depigmentation, and other adverse events. Long-term pain relief requires resolution of underlying pathology, such as abnormal posture/muscle imbalance, depression, anxiety, sleep disturbance, metabolic abnormalities, psychosocial stressors, and fear avoidance behavior [130; 172; 173].

Failed Back Surgery Syndrome

As noted, failed back surgery syndrome is not a single entity, but a complex syndrome of multiple potential etiologies, including poor surgical technique, mechanical factors, central sensitization, or a combination. Successful identification of the pain mechanism and pain control outcome is best achieved by assessing the time frame of symptom development [124]. Spinal cord stimulation is recommended [124].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Society of Interventional Pain Physicians, spinal cord stimulation is indicated in chronic low back pain with lower extremity pain secondary to failed back surgery syndrome, after exhausting multiple conservative and interventional modalities.

(https://www.painphysicianjournal.com/2013/april/2013;16;S49-S283.pdf. Last accessed July 25, 2022.)

Level of Evidence: 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)

Other Conditions

Implantable intrathecal opioid infusion and spinal cord stimulation are recommended for severe, intractable LBP [4]. For patients with facet joint pain, radiofrequency denervation is recommended when previous diagnostic or therapeutic injection of facet joint or medial branch nerve have provided temporary relief 154; 169]. Facet joint injection is not recommended [174].

Neuropathic Chronic LBP

The Canadian Pain Society recommends a fourth group of medications for patients with neuropathic LBP lacking benefit or tolerability to TCAs or gabapentinoids (first-line), SNRIs or topical lidocaine (second-line), or tramadol/traditional opioids (third-line) [175]. This group includes cannabinoids, methadone, mexiletine, clonidine, the SSRIs citalopram or paroxetine, and the anticonvulsants lamotrigine, topiramate, or valproic acid.

Intravenous lidocaine is recommended in patients unresponsive to oral analgesic therapy [4]. A trial of 5–7.5 mg/kg may provide pain relief from several hours to four weeks. Alternatively, intravenous ketamine is recommended for short-term pain relief. If used, it should be infused in a hospital setting under specialist care.

Considerations for Analgesia in Elderly Patients

Acetaminophen is recommended for initial and ongoing treatment of persistent musculoskeletal back pain in older patients [176]. There is a strong recommendation against the use of NSAIDs, amitriptyline, and imipramine due to the possible adverse effects. Systemic corticosteroids should only be used in pain from systemic inflammatory disease or metastatic bone pain.

Opioids are recommended for most elderly patients with moderate-to-severe pain, pain-related functional impairment, or diminished quality of life due to pain [176]. If opioids are warranted, around-the-clock dosing should be used to achieve steady-state in frequent or constant pain. If extended-release/long-acting opioids are used, it is vital to anticipate, assess, and prevent breakthrough pain or add short-acting or immediate-release opioid formulations. Do not exceed safe acetaminophen or NSAIDs limits with fixed-dose opioid combination agents [176].

Nonpharmacologic therapies and adjuvant analgesic drugs should be considered for all elderly patients with neuropathic back pain or refractory chronic LBP to enhance analgesia. In cases of localized neuropathic or non-neuropathic chronic LBP, consider topical NSAIDs or lidocaine. For regional back pain syndromes, capsaicin, menthol, or other topical agents may be beneficial. Clinicians are advised to cautiously consider glucosamine, chondroitin, cannabinoids, botulinum toxin, alpha-2 adrenergic agonists, calcitonin, vitamin D, bisphosphonates, and/or ketamine for specific pain syndromes.

NON-DRUG THERAPIES

Mattress Type

For chronic LBP, a randomized controlled trial found that a medium-firm mattress was superior for pain while lying in bed and was associated with greater improvement in pain-related disability after 90 days compared to a firmer mattress [177].

Patient Education

Educating patients with LBP about their condition and treatment options is essential in order to reduce misconceptions of therapy and, ultimately, to reduce disability. Education facilitates communication and allows the clinician to understand patient needs, goals, and beliefs or attitudes that can impose barriers to recovery. Addressing patient needs and goals can include discussion of pain concerns, rehabilitation options, pharmacotherapy, and smoking cessation. Education is also important for helping patients attain optimal pain outcomes. Without slow titration and education on prescribed drugs, patients are likely to abandon even the most established, high-evidence drugs when adverse effects begin [102; 178].

Therapeutic Pain Neuroscience Education

With central sensitization present in chronic LBP, the brain produces pain, fatigue, and other "warning signs" of tissue harm without actual tissue damage or nociception. Explaining the mechanism of central sensitization with evidence from neuroscience to patients with chronic LBP is a therapeutic strategy known as therapeutic pain neuroscience education or TPNE [98; 99].

TPNE helps patients with chronic pain understand their pain and make sense of the lack of objective biomarkers or imaging findings. A main goal is changing pain beliefs through the reconceptualization pain. This involves patient knowledge that pain persists without tissue damage, is disproportionate to tissue damage and/or that tissue damage (and nociception) does not by itself result in pain. The distinction between "hurting versus harming" is addressed [98; 99].

Exercises and physical activity are introduced under time-contingent (e.g., perform for five minutes regardless of pain) instead of symptom-contingent (e.g., stop when painful) conditions. Research shows that symptom-contingent approaches can facilitate brain production of nonspecific warning signs, while time-contingent approaches can deactivate brain-orchestrated top-down pain facilitatory pathways. Reduced CNS hyperexcitability and increased prefrontal cortical volume have also been found in response to time-contingent therapy [179; 180].

To reconceptualize pain and convince patients that CNS hypersensitivity, rather than tissue damage, is the likely cause of pain symptoms, TPNE is delivered in two to three sessions over two to three weeks. Potential patient misunderstanding of being told the pain is "all in their head" can be prevented by front-end coverage of pain neurophysiology and chronic pain, before discussing potential sustaining factors such as emotions, stress, illness perceptions, pain cognitions, and pain behavior [181].

Cognition-Targeted Neuromuscular Training

TPNE is optimally used in tandem with a time-contingent, cognition-targeted approach to daily activity and exercise therapy to address pain beliefs and cognitions before, during, and after exercise therapy. Neuroscience-informed exercise for chronic LBP involves a cognition-targeted neuromuscular training approach incorporating several modifications to conventional physical therapy that have been shown to improve patient outcomes. As noted, all exercises should be performed in a time-contingent instead of symptom-contingent manner. Progression to the next exercise level can be preceded by motor imagery for retraining brain circuitry responsible for successful execution of the targeted movement. The physical therapist should address patient pain cognitions to help patients attain positive perceptions about their pain, treatment, and exercise outcome. Discussion of patient perceptions about each exercise should include anticipated consequences (e.g., pain increase, further low back damage) and should challenge patient cognitions concerning the exercises. Pre-exercise communication reinforces the principles of TPNE and their application [98; 99; 182].

Patient Self-Management

Improving patient self-management is considered an important goal to decrease patient burden and service utilization. Patient self-management involves strategies to manage and monitor spinal health, assume a primary role in LBP management, and learn skills for daily use in managing back pain. Self-management of LBP is nearly universal in clinical practice guidelines for back pain, but patients often do not appreciate the improvements in their condition resulting from this approach [183].

In a meta-analysis of 13 randomized controlled trials of self-management in LBP, average improvement was calculated using a 0–100 scale. Evidence shows that patients with chronic LBP require a 20% to 30% pain and disability reduction to view an intervention as worthwhile, and the average improvement with self-management was 6% [184]. Therefore, patients are unlikely to consider the benefits from self-management efforts as meaningful. The small benefit in pain and disability challenges treatment guideline endorsement of self-management for LBP [183].

Exercise and Activity-Based Therapy

Exercise therapy produces moderate pain reduction in patients with chronic LBP independent of increases in musculoskeletal strength and significantly reduces work disability, regardless of exercise type [185; 186]. Pain reduction can occur with physical therapy, but functional improvement is the primary goal. In patients with chronic LBP, studies have demonstrated positive outcomes with aggressive exercise. Exercise has been favorably compared with surgical intervention and has eliminated the need for spinal surgery in some patients. Patient care should include appropriately aggressive exercise as a core element in chronic LBP management [187].

The goal of returning patients to previous activity level is best achieved by increasing strength, flexibility, endurance, and balance. Resistance (strength) training is the only approach that improves all four factors at the same time and reduces kinesiophobia, depression, vertebral fractures, and recidivism [187].

Outcomes of core stabilization exercises are equivocal, but lumbar extensor strengthening has shown benefit by reducing pain and healthcare utilization and increasing quality of life. Motivational issues can detract from gains in function, and patients should receive time and distance guidelines and specific, measurable goals to help prevent engaging in progressively less intense home exercise [187]. Exercise frequency has been found more important than the type, duration, or intensity of the exercise [188]. A review of randomized controlled trials found that, compared with usual care, exercise therapy improved post-treatment pain intensity and disability and long-term function in chronic LBP [189].

It is important to consider that exercise worsens pain and symptoms in some patients. Poor exercise response is thought to reflect dysfunctional endogenous analgesia, with exercise failing to help restore homeostatic balance. This deficit of endogenous analgesia in some patients with chronic pain should be considered in order to help these patients avoid the detrimental effects of exercise-induced pain and distress [190].

Manual- and Physiotherapy-Based Therapies

Spinal Manipulation Therapy

Spinal manipulation therapy is performed by mobilization, whereby spinal joints are passively moved by a therapist, and by manipulation, whereby a manual impulse or thrust is applied to a joint at the end of a passive range of motion, often accompanied by a cracking sound [191]. For acute LBP, spinal manipulation therapy was found no more effective than inert interventions, sham spinal manipulation therapy, or use as adjunct therapy. Spinal manipulation therapy also seems no better than other recommended therapies [192].

For chronic LBP, spinal manipulation therapy has been found to produce a small but significant short-term effect on pain relief and functional status in comparison with other interventions. Spinal manipulation therapy has a significant short-term effect on pain relief and functional status when added to another intervention. No serious complications have been observed [193]. Spinal manipulation therapy is cost-effective as treatment of chronic back pain, either alone or in combination with general primary care, exercise, and physiotherapy [194; 195].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Physical Therapy Association asserts that thrust or nonthrust joint mobilization may be used to reduce pain and disability in patients with acute LBP.

(https://www.jospt.org/doi/10.2519/jospt.2021.0304. Last accessed July 25, 2022.)

Strength of Recommendation: A (Strong evidence)

Therapeutic Massage

A Cochrane review concluded therapeutic massage had no serious side effects and resulted in more beneficial pain relief than joint mobilization, relaxation, physical therapy, self-care education, or acupuncture for LBP [196]. Acupressure or pressure point massage provided more relief than Swedish massage. In an update to the review, massage was not found to be an effective treatment for LBP [197]. For acute LBP, massage was found to be better than inactive controls for pain in the short term, but not for function. For subacute and chronic LBP, massage was better than inactive controls for pain and function in the short term, but not in the long term [197]. In another study, Chinese massage combined with herbal ointments was found more effective than massage plus placebo ointment among athletes with nonspecific LBP [198].

Psychologic Therapies

Encouraging patients with chronic LBP to participate in psychologic pain treatments can be difficult, because patients often insist on somatic interventions and regard psychologic interventions as inferior. Information on neurophysiologic changes associated with psychologic interventions can be presented to patients as a strategy to motivate acceptance and dispel preconception [199]. Information related to pain-related neurophysiologic alteration and treatment effects of psychologic therapies on brain and peripheral measures of pain is especially useful to enhance treatment motivation and facilitate treatment [199; 200]. This is similar to pain neuroscience education.

CBT and behavioral therapies are the most widely used psychologic treatments for chronic pain. Operant-behavioral treatments, such as exposure treatment and acceptance- and commitment-based approaches, are also used. While relatively few studies have examined the neurophysiologic correlates of these therapies in patients with chronic LBP, CBT has been found effective in sub-acute or chronic LBP across a range of dimensions [195; 199].

Cognitive-Behavioral Therapy

Interventions that use CBT include creative visualization, imagery, progressive muscle relaxation techniques, and problem-solving techniques. The goal of CBT is to promote patient understanding, acceptance, and self-management of chronic LBP through the development of adaptive coping behaviors and strategies, which eventually empowers the patient. CBT is effective for subacute and chronic LBP, and there is moderate-to-strong evidence for CBT use early in recovery in patients with specific biopsychosocial issues. Strong evidence indicates that CBT should be used in most patients with nonspecific LBP lasting longer than 12 weeks. Comparable outcomes have been found between fear-avoidance training and spinal fusion in chronic LBP. CBT is cost effective, adds 20% efficacy to usual rehabilitation, and reduces the duration of recurrence [60; 201; 202].

Studies have identified core brain regions that mediate effective cognitive interventions. These include increased rostral anterior cingulate cortex activation and decreased dorsal anterior cingulate cortex activation with cognitive distraction; involvement of the ventral lateral prefrontal cortex, mid-cingulate cortex, thalamus, amygdala, and post-central gyrus with cognitive reappraisal; and correlation of right anterolateral prefrontal cortex and the dorsal anterior cingulate cortex activation with increased self-control over pain [203; 204; 205].

Cognitive and learning factors contribute to placebo analgesia, considered a type of psychologic modulation of pain that is mediated by descending spinal pathways involving the anterior cingulate cortex and periaqueductal gray that alters transmission of nociceptive input at the spinal cord level [206; 207]. CBT specifically alters prefrontal cortex activity in response to pain in patients with fibromyalgia [208]. Operant-behavioral therapies have been advocated for patients with low activity levels, with prominent pain behaviors that are reinforced by significant others [209; 210]. Patients with fibromyalgia who received operant-based pain extinction training displayed a shift from greater anterior insula to posterior insula activation post-treatment. Changes in pain-related interference were closely related to changes in blood oxygen level-dependent activation of the posterior insula, primary somatosensory cortex, thalamus, and striatum [211]. These findings suggest that different behavioral treatments may impact different brain circuits [199].

Stepped Care in the Primary Care Setting

Measurement-based stepped care is a management approach for patients with chronic LBP in primary care that blends the stepped care approach used for many chronic diseases with the system of pain assessment and care used by pain specialists. Stepped care is well established in managing complex chronic illness, increasing treatment intensity levels for patients with no response to lower-level treatment intensity. This approach moves beyond the biomedical paradigm by systematically evaluating complex biopsychosocial factors associated with chronic pain. Systematic measurement enhances identification of specific problem areas at baseline and throughout treatment, assisting clinicians in deciding to intensify treatment or make specialist referral [212]. Relevant biopsychosocial domains are measured at baseline and during treatment with specific instruments [212]. Input from the results of these instruments helps guide the primary care provider to make referrals specific to the problem domain (***Table 5***) [212; 213].

Multidisciplinary and Functional Restoration Programs

Multidisciplinary pain programs are used for chronic LBP with the goal of restoring and improving physical and emotional functioning and quality of life. In contrast to other pain programs, multidisciplinary pain programs provide interdisciplinary care, with collaboration by providers from different program components to develop and implement patient care. Core components of multidisciplinary pain programs are medical and behavioral therapy, physical reconditioning, and education; adjunctive modalities can be added. Multidisciplinary pain programs are often viewed as the last resort for intractable pain, and many enrolled patients have exhausted most other non-invasive options. However, they may be considered earlier in the disease course. Multidisciplinary pain programs may improve chronic LBP outcomes by simultaneously addressing multiple contributing factors to chronic pain [214]. These programs cause few if any adverse effects, in contrast to surgery or long-term opioid therapy [215]. The biopsychosocial model of chronic pain (the theoretical basis of multidisciplinary pain programs) describes psychosocial factors as part of a complex system with dynamic and reciprocal inter-relationships between biologic, psychologic, and sociocultural factors that shape patient pain experience and therapeutic response [216].

BIOPSYCHOSOCIAL ASSESSMENT AND REFERRAL OF PATIENTS WITH CHRONIC LOW BACK PAIN			
Domain	**Instrument**	**Measurement-Based Score**	**Step Care Referral**
Pain intensity	Intensity numerical rating scale (1–10)	Score ≥7 without diagnosis/ plan	Pain specialist
Pain interference	Interference numerical rating scale (1–10)	Score >4	Physiatry, occupational therapy, and/or physical therapy or vocational rehabilitation
Mood	PHQ-4, PHQ-9, or PC-PTSD	PHQ-4 score ≥6 or PC-PTSD score ≥3[a]	Behavioral health specialist
Sleep quality	STOP-BANG	STOP-BANG score ≥3, high morphine equivalent dose, or the use of opioids and sedatives	Sleep specialist
Risk of opioid misuse	ORT	ORT score ≥8, more than four minor urinary drug test aberrancies, or any serious aberrancies	Addiction specialist

ORT = Opioid Risk Tool, PC-PTSD = Primary Care-PTSD Screen, PHQ = Patient Health Questionnaire, STOP-BANG = sleep apnea questionnaire.
[a]Based on DSM-IV diagnostic criteria for PTSD. If using DSM-5 criteria, >3 is considered optimally sensitive and >4 is considered optimally efficient.

Source: [212] *Table 5*

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Colorado Division of Workers' Compensation asserts that interdisciplinary rehabilitation programs are the gold standard of treatment for individuals with chronic low back pain who have not responded to less intensive modes of treatment or individuals who require concurrent treatment for chemical dependency.

(https://codwc.app.box.com/v/rule-17-exhibit-1. Last accessed July 25, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

A review of 41 randomized controlled trials examining chronic LBP found that multidisciplinary pain programs resulted in significantly less pain and disability than usual care or physical modalities; these benefits persisted at long-term follow-up. A positive benefit was also found on work status versus physical modalities [217]. Multidisciplinary pain programs were found cost-effective as therapy for sub-acute or chronic LBP [195].

Multidisciplinary pain programs have been expanding in other countries, but have been declining in the United States. The most pressing problems are declining access and lack of reimbursement from third-party payers. The decline in multidisciplinary pain programs and their lack of recognition as the standard of care for chronic pain has been attributed to three dichotomies whereby the multidisciplinary pain program model inherently contradicts prevailing healthcare financing and provision [215; 218; 219]:

- Interdisciplinary collaboration in multidisciplinary pain programs versus the discipline-segmented organization of major medical centers: Multidisciplinary pain programs require integrated care across several disciplines; in contrast, major medical centers are aligned in silos by field and are increasingly competitive with each other for resources, including patients, space, and research dollars.

- Collaborative care in multidisciplinary pain programs versus the fee-for-service model of healthcare payments: Multidisciplinary pain programs face obstacles in adequate reimbursement for essential but time-intensive assessments and collaborative meetings. The pervasive fee-for-service model preferentially rewards spinal procedures and surgery over assessments and behavioral therapy.
- Rehabilitative therapy with focus on individualized patient assessment and behavioral change in multidisciplinary pain programs versus the curative medical model of treatment: This aspect of multidisciplinary pain programs is not only resisted by healthcare payers and providers wanting higher compensation, but also by patients with chronic pain, who may prefer to obtain "cure" from interventional, surgical, or drug therapy approaches than the intensive cognitive and behavioral changes required by multidisciplinary pain programs.

An intensive, multidisciplinary functional restoration program was prospectively evaluated in 87 patients with up to two-year follow-up. Results found a 60% reduction in the number of sick days [220]. Patient outcomes with the same functional restoration program were compared to less intensive ambulatory-based individual physiotherapy in a randomized controlled trial of 132 patients with chronic LBP. The more intensive functional restoration program was superior in reduction of sick days and physical capacity, but improvements in pain intensity and quality of life were comparable [221; 222].

Predictive factors of positive functional outcome were studied in 524 patients with chronic LBP admitted to a two-week intensive multidisciplinary pain program with CBT, physical therapy, and educational components. Patients had a mean 13-year LBP duration. At one-year follow-up, employed patients with mild-to-moderate disability showed greatest benefit. Baseline psychologic factors were unrelated to outcome, indicating that highly distressed patients equally benefited. However, patients with formal psychiatric disorder were excluded from enrollment [223].

Lumbar spinal stenosis is considered most effectively treated by surgery. Although surgery may provide the best outcomes among therapeutic options in restoring function and reducing pain, surgery is often less than effective and a sizeable proportion of patients do not regain good function. Active rehabilitation has been found the most effective post-surgical rehabilitation approach for improving short- and long-term (back-related) functional status and secondary outcomes such as short-term improvement in LBP and long-term improvement in LBP and leg pain [224].

Functional Restoration

Functional restoration is a variant of multidisciplinary pain programs, with an emphasis on preventing disability and returning to work and previous functioning. Functional restoration programs incorporate the following approaches [225]:

- Repeated quantification of physical deficits to guide, individualize, and monitor physical rehabilitation progress
- Psychosocial and socioeconomic assessment to guide, individualize, and monitor pain, disability, behavior, and outcomes
- Multimodal disability management programs using CBT approaches
- Psychopharmacologic interventions, as needed, for detoxification and psychosocial management
- Ongoing outcome assessment using standardized outcome criteria and objective data collection through structured interviews
- An interdisciplinary, medically directed team approach with frequent conferences and collaboration

Systematic reviews and randomized controlled trials have found strong evidence of pain reduction and improved function with functional restoration compared with less intensive programs or usual care in patients with LBP [226; 227]. Randomized controlled trials have shown prevention of progression to chronic LBP in patients with acute pain, and in patients with chronic LBP, substantially lower rates of chronic pain disability, healthcare utilization, medication use, self-reported pain variables, and back pain treatment costs relative to usual care. These positive outcomes have been consistent in studies conducted in states and countries with markedly different economic and social conditions and workers' compensation systems and in studies enrolling patients with unresolved workers' compensation claims [225]. Less intensive programs have no advantage over non-multidisciplinary outpatient therapy or usual care [228].

The primary deterrent to broader use of this approach is the reluctance of third-party payers to authorize its use because of its perceived high cost. These perceptions are misguided in terms of the potential long-term cost savings of such a program. Similarly, cost-saving efforts by third-party payers to reimburse for only a portion of functional restoration programs diminish effectiveness [225].

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Complementary and alternative medicine (CAM) is widely used in the United States. In 2012, more than 59 million Americans made out-of-pocket CAM expenditures totaling $30.2 billion [229]. Of this, 60% was for manipulative and body-based therapies (e.g., chiropractic or osteopathic manipulation, massage therapy), 24% for mind-body therapies, 10% for alternative medical systems, and 6.4% each for biologically based and energy healing therapies [230]. Integrative medicine combines appropriate healthcare strategies and disciplines for patient benefit, typically by blending traditional medicine and CAM [231]. Many CAM modalities address LBP mechanisms, stress response, or both, and use as monotherapy or combined with other modalities may diminish chronic stress response and interfere with the pain-stress cycle [231; 232].

Acupuncture

Acupuncture is a Chinese medicine technique whereby needles are slightly inserted in particular points on the body to stimulate energy fields and meridians. There is now greater understanding of the mechanisms that mediate successful acupuncture therapy, specifically stimulation of the fascia, a web of connective tissue that envelops muscle fiber and surrounds, separates, and connects organs and allows them to slide past one another when necessary [233]. Thoracolumbar fascia mediates force transfer, and disruption of its self-regulatory features may contribute to LBP. Stimulation by acupuncture needles inserted into muscle fascia induces the realignment of fibroblasts [234; 235; 236].

According to the Colorado Division of Workers' Compensation, true and sham acupuncture improves function in patients with chronic low back pain as compared to usual care. Acupuncture reduces pain in patients with acute and chronic low back pain, as compared to sham acupuncture. Individuals with positive expectations of acupuncture likely experience enhanced treatment benefit.

(https://codwc.app.box.com/v/rule-17-exhibit-1. Last accessed July 25, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

A review of acupuncture randomized controlled trials in chronic LBP found significant reductions in pain and disability with acupuncture or sham acupuncture versus conventional therapy or no therapy; a significant difference in acupuncture versus no treatment or routine care at 8- and 12-week follow-up; and a significant improvement in pain, function, and quality of life with acupuncture versus routine care at three months. The results suggest benefit from acupuncture beyond improvement from usual care in chronic LBP [237]. Acupuncture was also

evaluated in a low-income, urban healthcare setting in 226 patients with chronic pain (60% with chronic back pain). Treatment once weekly up to 18 weeks led to statistically significant but clinically modest improvements in pain and physical well-being [238]. Acupuncture has been found to be a cost-effective therapy for sub-acute or chronic LBP [195].

Reviews and clinical practice guidelines have broadly concluded acupuncture in acute LBP lacks evidence. However, a randomized controlled trial of 58 patients with severely disabling acute LBP compared diclofenac injection to motion-style acupuncture treatment, an approach whereby part of the body moves passively or actively while retaining acupuncture needles. Following a single session of both treatments, motion-style acupuncture treatment led to a 3.12 greater mean pain reduction (on a 0–10 scale) and a 33% greater reduction in disability than diclofenac. These differences remained significant two and four weeks post-treatment. Motion-style acupuncture treatment showed immediate pain relief and functional recovery in disabling acute LBP [58]. A Mayo Clinic review stated that acupuncture efficacy is difficult to evaluate under controlled conditions because of the individualized and tailored approach of acupuncture to specific patient needs [239]. Bias has also been identified in Cochrane reviews of acupuncture [240]. Positive response to acupuncture and other CAM therapies has long been attributed to placebo response from high patient expectations, but this has been generally disproven [241]. Due to ongoing interest in acupuncture as a therapy for LBP, a proposal was announced in July 2019 in which Medicare will cover acupuncture as an alternative to opioids for LBP research. If the proposal is accepted, participants must be enrolled in an approved study and agree to have outcomes data collected [242]. In 2020, the Centers for Medicare and Medicaid Services (CMS) issued a decision memo indicating that CMS will cover acupuncture for chronic low back pain under section 1862(a)(1)(A) of the Social Security Act [243].

Yoga

Yoga is an ancient discipline, originating in the Indian subcontinent, designed to restore balance and health to the physical, mental, emotional, and spiritual dimensions of the practitioner. Yoga has gained popularity in the United States, and proponents claim benefits from yoga that include reduced inflammation and decreased heart rate and blood pressure [244]. Yoga has also become increasingly used in patients with chronic musculoskeletal pain, including back pain, and has been investigated in several trials [245]. A review of randomized controlled trials in chronic LBP found that yoga showed a medium-to-large effect size in reducing disability and pain. The same benefits remained at follow-up, with somewhat smaller effect sizes. Despite differences in yoga style and duration in the reviewed trials, treatment outcomes were consistent [246]. Little is known of the mechanisms in yoga benefit [247]. Generalizability to diverse populations was assessed in 95 low-income urban minorities with moderate-to-severe chronic LBP. Following 12 weeks of once- or twice-weekly yoga classes, both groups showed significant reductions in pain (30% and 36%, respectively) and disability (36% for both) [248].

Yoga is not free of potential injury. A survey of 1,336 yoga instructors found the most frequent and severe injuries involved the neck, lower back, shoulder, wrists, and knees. Risk factors for yoga injury include poor technique or alignment, previous injury, excessive effort, and improper instruction. Specific yoga forms were associated with specific injuries, including neck injuries from headstand and shoulder stand, and low back injuries from forward bends, twists, and backbends. Recommendations to reduce yoga injuries include population-specific instructor training, appropriate placement of new students, improved understanding of appropriate effort levels, improved teacher detection of overzealous students and improper alignment, and the use of assistants to watch for overzealous and poorly aligned students in large classes [249].

Mindfulness-Based Stress Reduction

Mindfulness is an approach derived from Buddhist spiritual tradition that has been secularized and integrated into behavioral treatment approaches. Mindfulness is described as a specific state of consciousness that is non-elaborative with non-judgmental moment-to-moment awareness. It helps achieve acceptance and trust in one's own experience. The most widely used of these interventions is mindfulness-based stress reduction, developed as a component of behavioral medicine for patients with chronic pain and stress-related complaints. Components of mindful-based stress reduction include sitting meditation, walking meditation, hatha yoga, and body scan, a mindfulness practice in which attention is sequentially focused on different parts of the body. Mindful-based stress reduction also instructs on applying mindfulness to everyday life [250].

A review of three mindful-based stress reduction trials involving 117 patients with chronic LBP found statistically and clinically significant short-term improvements in pain and disability compared with usual care in patients with failed back surgery syndrome, and no improvements in pain or disability but greater short-term improvements of pain acceptance in two trials of elderly patients with specific or nonspecific chronic LBP. In aggregate, these outcomes were inconclusive in pain reduction but suggest greater pain acceptance with mindful-based stress reduction in patients with chronic LBP [250].

Tai Chi

Tai chi is a traditional mind-body exercise that enhances balance, strength, flexibility, and self-efficacy. It has been found to reduce pain, depression, and anxiety in diverse groups of patients with chronic pain conditions. The physical component provides exercise consistent with guideline recommendations, while the mental component addresses the cognitive and emotional well-being of the patient. Tai chi is a safe and economical option that helps reduce disability without introducing an intrinsic risk and addresses the cognitive, emotional, and social needs associated with chronic pain and disability [251; 252].

Therapeutic Ultrasound

Ultrasound involves the application of high-frequency sound waves up to 3 MHz to the low back surface (above the pain source). A randomized controlled trial found ultrasound effective in chronic LBP compared with placebo ultrasound [253]. A case series of patients with acute pain from lumbar disk herniation and radiculopathy found that 41% of subjects were free of pain following ultrasound, compared with 12% following sham ultrasound and 6.8% with analgesics [254]. However, a 2014 Cochrane review did not find any convincing evidence of the efficacy of ultrasound for LBP, and there was no high-quality evidence of improvement of pain or quality of life [255]. A 2020 update to this review reiterated these findings [256].

Low-Level Laser Therapy

Low-level laser therapy involves application of laser at wavelengths of 632–904 nm to the skin in order to direct electromagnetic energy to soft tissues. While the mechanism and optimal treatment parameters are unclear, low-level laser therapy may alter fibroblast function to reduce inflammation and accelerate tissue repair. A review of seven small studies in patients with nonspecific LBP found low-level laser therapy more effective in reducing pain versus sham laser [124; 191; 257].

Neuroreflexotherapy

Neuroreflexotherapy involves temporary superficial implantation of small staples into the skin over trigger points in the back and referred tender points in the ear. Similar to acupuncture, neuroreflexotherapy uses devices for skin puncture but is believed to stimulate different zones. In patients with chronic LBP, several randomized trials found neuroreflexotherapy substantially superior to sham therapy or usual care for short-term pain relief [124].

Interferential Therapy

Interferential therapy applies medium-frequency alternating current modulated to produce low frequencies of 150 Hz or less and is suggested to provide analgesia by increasing blood flow to tissues. Randomized controlled trials have found no difference in LBP outcomes with interferential therapy versus spinal manipulation, traction, or TENS [124; 258].

Transcutaneous Electrical Nerve Stimulation

TENS uses a small, battery-operated device to provide continuous electrical impulses to the site of the most severe pain via surface electrodes. TENS is thought to reduce pain by modifying pain perception and possibly by raising spinal fluid endorphins. Despite widespread use, there is little published evidence from randomized controlled trials of efficacy in chronic LBP [124; 259]. One meta-analysis of TENS for chronic LBP included 267 patients with a mean treatment period of six weeks and a mean follow-up of seven weeks. This study showed significant pain reduction when using TENS [260]. A later meta-analysis found that TENS for chronic LBP offered only short-term improvement of functional disability [261]. However, more studies are required to determine the efficacy of TENS on chronic LBP.

Percutaneous Electrical Nerve Stimulation

With percutaneous electrical nerve stimulation, low-level electrical stimulation is applied though acupuncture-like needles inserted into points that target dermatomal levels for local pathology. In chronic LBP with or without radiculopathy, research has shown superior pain reduction versus TENS and minimal exercise intervention, with benefit duration of two months or less [124].

Cranial Electrical Stimulation

Cranial electrical stimulation uses microcurrent therapy, with a mechanism that differs from TENS. A review found cranial electrical stimulation effective in the treatment of chronic pain, including headaches, and intractable pain conditions. It is promising as a treatment for chronic LBP, but little evidence has been published [259; 262].

Biofeedback

Biofeedback has been widely used for managing chronic pain, especially tension and migraine headaches. EMG electrodes are placed on the involved muscle, and the patient learns to reduce muscle contractions through a feedback procedure. Biofeedback has shown benefit in pain with a muscle component, including some forms of back pain, and has been used as a component in stress reduction. Biofeedback can train patients to reduce bracing of posture and improve self-regulation of body physiology that impacts pain. However, biofeedback requires multiple sessions and trained personnel [259]. Electroencephalography (EEG) biofeedback is a newer approach and is little studied in chronic LBP.

Hypnosis

An analgesic effect from hypnosis has been confirmed, believed to result from selective reduction of pain-related affect, reductions in sensory pain, and inhibition of pain signaling at the spinal level of processing. However, little research is available in patients with LBP [259].

Ozone Therapy

Ozone (O_3) is an allotropic form of oxygen primarily used in Europe as an alternative treatment option for patients with LBP from disk herniation. Ozone is administered percutaneously as an oxygen-ozone gas mixture at nontoxic concentrations of 1–40 mcg ozone per mL of oxygen. Proposed mechanisms of analgesia include anti-inflammatory and antioxidant action on the nucleus pulposus. The safety and efficacy of percutaneous ozone injection in LBP secondary to disk herniation was reviewed using four randomized controlled trials and eight observational studies. Based on pain reduction at six-month follow-up, the authors strongly recommended intradiscal and paravertebral ozone therapy [263].

Another systematic review of 439 references selected seven studies reviewing ozone therapy for LBP from disk herniation [264]. Of these seven studies, researchers found that there was an improvement in pain and functional scores in all, but only three studies evaluated side effects, leading researchers to conclude that complications, both minor and serious, are under-reported. Due to inconsistent methodologies and findings, researchers in this study recommend additional studies to determine safety and efficacy of ozone therapy [264].

Essential Oxygenated Oil

Essential oxygenated oil is a topical analgesic new to the U.S. market, but used in Europe for decades. Essential oxygenated oil is obtained by subjecting corn or nut oil to an accelerated peroxidation process, producing triglycerol-oxyester oil. Its mechanism is not fully known but likely involves the microcirculatory system and inhibition of lipid peroxidation, inhibition of the arachidonic acid pathway, or both [265; 266]. Several randomized controlled trials have evaluated essential oxygenated oil as an alternative to NSAIDs or opioids in patients with moderate-to-severe acute, chronic, or degenerative pain from sciatica, post-traumatic pain, tendonitis, back pain, or sprain. Treatment for 7 to 28 days showed positive analgesic effects in acute and chronic pain, improved oxygen content in the skin, few side effects, and no allergic reactions [265].

Comfrey Root

The root of comfrey (*Symphytum officinale*) has been used for centuries as a medicinal treatment of muscle and joint pain. It is thought that the root constituents of allantoin and rosmarinic acid contribute to the anti-inflammatory effects in back pain treatment. A safety concern involves pyrrolizidine alkaloids present in the raw plant material, which possess genotoxic properties. In Europe, all medicinal comfrey root products are required to be pyrrolizidine alkaloid-depleted or pyrrolizidine alkaloid-free [267].

In one study, patients with acute upper or lower back pain received comfrey root extract or placebo cream, applied three times per day for five days. Pain intensity on active challenge decreased a median 95.2% with comfrey and 37.8% with placebo. A rapid-onset effect (within one hour of application) was reported. Mild adverse events occurred in 5% of participants [268].

In another study, patients with acute back pain received comfrey extract plus methyl nicotinate, methyl nicotinate only, or placebo cream applied three times per day for five days. Average pain scores and pain at rest were significantly lower with combination therapy than methyl nicotinate alone, with both significantly lower than with placebo. Investigator assessment of "good" or "excellent" global efficacy was 93.3% with combination therapy, 51.2% with methyl nicotinate, and 7.6% with placebo. Application site reactions occurred in 5% of subjects, mostly with methyl nicotinate [269].

Patient Expectation and CAM Outcomes

Positive patient outcomes in CAM therapies have long been attributed to nonspecific placebo response, reflecting an expectation of benefit. In 64 patients with chronic LBP evaluated before CAM therapy, baseline treatment outcome expectations clustered into pain relief, improved function, improved physical fitness, and enhanced well-being. Patients were modest in expectation level of positive therapy outcomes and reluctant to articulate optimistic expectations, and many drew the distinction between expectation and hope. Improvements from therapy in pain level, function, physical fitness, and well-being were strongly inter-related, with improvement in one domain benefiting other domains. These findings contradict the belief that positive CAM benefit is solely explained by high pre-treatment expectations [241].

Likewise, in acupuncture-naïve patients with chronic LBP, higher pre-treatment expectations for success did not predict pain or functional improvement. An association did develop with ongoing treatments, but positive pre-treatment attitude toward acupuncture was not associated with superior outcomes [270].

PHARMACOTHERAPIES

There are few current, comprehensive practice guidelines for back pain therapy with analgesics. Therefore, this section will emphasize research identifying promising analgesic approaches, challenging current assumptions of the safety or efficacy (or the lack of) in established analgesic therapies, or modifying use or delivery of established therapies to improve safety or efficacy.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs represent the foundation of back pain pharmacotherapy. Anti-inflammatory activity accounts for a proportion of analgesia from NSAIDs. Cell injury generates enzymes that release arachidonic acid from cell membranes, and arachidonic acid is converted into prostaglandins, thromboxanes, leukotrienes, and other eicosanoids. The prostaglandins PGE2 and PGF2a contribute to inflammation and sensitize nociceptors innervated by A-delta and C nerve fibers. Other prostaglandins are needed for homeostasis. NSAIDs inhibit the enzyme cyclooxygenase (COX) required for synthesis of arachidonic acid into prostaglandins and other eicosanoids. COX-1 is noncontributory to inflammation but is involved in homeostatic functions and mediates gastrointestinal protection by the gastric mucosa. COX-2 is induced during inflammation and amplifies inflammatory response, but it also contributes to kidney and cardiovascular homeostasis and helps maintain vascular integrity. Thus, COX inhibitors reduce inflammation and pain but can interfere with homeostatic functions, such as proper renal blood flow and gastric mucosa protection. NSAID analgesia also results from central activity, possibly through substance P and NMDA inhibition [68; 271; 272].

NSAIDs are subgrouped by dominant COX isoenzyme activity. NSAIDs that inhibit COX-1 and 2 are termed non-selective NSAIDs. NSAIDs with greater COX-2 inhibition are termed coxibs, COX-2 selective NSAIDs, or COX-2 inhibitors. COX-2 inhibition is not an absolute NSAID characteristic, as COX-2 selective agents also possess varying degrees of COX-1 inhibition [272; 273].

Gastrointestinal Toxicity

Nonspecific NSAIDs were the first to enter commercial use. However, evidence began accumulating that associated non-selective NSAIDs use with gastrointestinal bleeding and toxicity, and in 1997, nonspecific NSAIDs were linked to 107,000 hospitalizations and 16,500 fatalities from upper gastrointestinal morbidity [68; 274]. All-cause mortality rates fell from 11.6% pre-1997 to 7.4% post-1997, while NSAID-induced mortality rates from upper gastrointestinal bleed or perforation increased from 14.7% before 1997 to 20.9% after 1997. Thus, mortality per event has fallen when unrelated to NSAIDs, while NSAID-associated mortality has increased [275].

Up to 40% of NSAIDs users develop upper gastrointestinal symptoms, most frequently gastroesophageal reflux and/or dyspeptic symptoms. Serious and potentially fatal upper gastrointestinal toxicities, including symptomatic and/or complicated peptic ulcer, bleeding, perforation, or obstruction, occur in 1% to 2% of NSAID users and are influenced by dose and exposure [276]. COX-2 inhibitors are associated with significantly lower risks of upper gastrointestinal perforation, obstruction, and bleeding compared with non-selective NSAIDs plus proton pump inhibitors [277]. The highest risk of serious gastrointestinal morbidity is found with piroxicam, azapropazone, and ketorolac; the lowest risk is with aceclofenac, ibuprofen, and celecoxib [276; 278].

Piroxicam's half-life of greater than 30 hours may explain its propensity for gastrointestinal toxicity, and oral ketorolac dosing is limited to five days due to well-recognized gastrointestinal and renal toxicity profile. Ketorolac is a highly potent analgesic. While it is unsuitable to manage acute or chronic LBP, a role in hyperacute LBP is worth consideration, especially when opioid analgesia is not the best option [273].

The incidence of lower gastrointestinal toxicity with NSAID use has been increasing, likely due to enhanced detection by new diagnostic modalities (e.g., capsule endoscopy, device-assisted enteroscope). Evidence suggests comparable risks of lower gastrointestinal and upper gastrointestinal bleeding and perforation from NSAIDs. The most frequent lower gastrointestinal morbidities include increased gut permeability, gut inflammation, blood loss and anemia, malabsorption, and mucosal ulceration. Lower gastrointestinal complications from NSAIDs can be fatal [276].

Cardiovascular Toxicity

The COX-2 inhibitor celecoxib was introduced in 1999, quickly followed by rofecoxib and valdecoxib, to retain the benefits of non-selective NSAIDs without the associated upper gastrointestinal toxicity. However, rofecoxib and valdecoxib were withdrawn from the market in 2004 and 2005 due to adverse cardiovascular events [272; 273]. Nonspecific NSAIDs have been assumed to carry the greatest risk of upper gastrointestinal morbidity with little risk of cardiovascular morbidity, with the reverse true for coxibs [279]. However, this was challenged by a meta-analysis that found comparable cardiovascular risks between coxibs, high-dose diclofenac, and possibly ibuprofen. The incidence of major cardiovascular events was increased 33% with diclofenac, primary from non-fatal myocardial infarction or coronary death. Ibuprofen increased the risk of major coronary event, while naproxen did not elevate the risk. Use of any NSAID roughly doubled the risk of heart failure [279; 280].

Another meta-analysis found naproxen the least harmful NSAID in cardiovascular risk, with coxibs displaying the highest risk of myocardial infarction. Ibuprofen and diclofenac are associated with the highest risk of stroke, and diclofenac is associated with a high risk of cardiovascular fatality. Naproxen may be safer in risk for cardiovascular events but carries a very high risk of gastrointestinal complications. The authors concluded that no NSAID is safe for cardiovascular risk and prescribing any NSAID requires assessment of patient cardiovascular risk factors [281; 282].

A large meta-analysis of hundreds of randomised trials comparing NSAIDs with placebo or one NSAID with another NSAID found a statistically significant increase in the risk of serious cardiovascular adverse effects (i.e., MIs and vascular deaths) with COX-2 inhibitors and with diclofenac [283]. High-dose ibuprofen (2,400 mg daily) increased cardiovascular risk to the same degree as diclofenac or COX-2 inhibitors. No increased risk was found with ibuprofen 1,200 mg daily. Two meta-analyses showed that all NSAIDs roughly doubled the risk of heart failure. One meta-analysis showed a small, statistically significant increase in the risk of atrial fibrillation. From a cardiovascular perspective, the NSAIDs of choice are ibuprofen (not more than 1,200 mg per day) and naproxen; COX-2 inhibitors, diclofenac, and high-dose ibuprofen (2400 mg per day) are best avoided [283].

Efficacy

NSAIDs are effective in reducing acute LBP and pain associated with several chronic LBP conditions, though no benefit has been found in LBP with radiating symptoms [284]. The data on acute LBP are less convincing than with non-radicular chronic LBP, but, given the toxicity potential with acetaminophen, NSAIDs seem preferable in acute LBP [273]. NSAIDs have a ceiling effect, where further dose escalation increases side effects but not analgesia [285]. Analgesic efficacy between coxibs and non-selective NSAIDs is comparable, and consistent differences in pain reduction for specific NSAIDs have not been found [284]. For unknown

reasons, up to 70% to 80% of patients preferentially respond to a specific NSAID. Response cannot be predicted, but some patients lacking response to one NSAID will achieve full benefit from another [286].

NSAIDs remain among the most commonly prescribed drugs for neuropathic LBP despite repeated demonstration of ineffectiveness, reflecting prescribers' unfamiliarity with the mechanistic basis of LBP [102]. Short-term use of NSAIDs for acute LBP is appropriate in most cases, but NSAIDs in chronic back pain should only be used in carefully selected patients for occasional use to manage pain flares, and never for long-term therapy [273].

Acetaminophen

Acetaminophen is a nonsalicylate antipyretic analgesic that may be used alone or combined with other agents (usually opioids). Unlike aspirin, it lacks antiplatelet effects and gastric mucosa compromise. Acetaminophen does not have peripheral anti-inflammatory effects and produces analgesia that is additive to NSAIDs. Despite decades of use, the exact mechanism of action for acetaminophen remains unclarified [68; 285].

Acetaminophen is widely recommended as first-line analgesia for acute and chronic LBP because of enduring assumptions of efficacy and safety. However, research has challenged these assumptions. In one study, 1,649 patients with acute LBP were randomized to regular dosing (three times per day, ≤4,000 mg/day), as-needed dosing (take as needed for pain relief, ≤4,000 mg/day), or placebo. All groups were instructed to continue as needed, up to 28 days. Average time to recovery was 17 days in the regular and as-needed groups, and 16 days in the placebo group. The average number of tablets consumed per day was about four in all groups. Side effects in each group were also similar [287].

With increasing evidence of liver toxicity, the U.S. Food and Drug Administration (FDA) recommends a maximum 3,250 mg/day dose ceiling for acetaminophen, and McNeil Consumer Healthcare voluntarily lowered the maximum dose of its 500-mg tablets of acetaminophen to 3,000 mg. Acetaminophen is usually well tolerated, but overdose can result in fatal hepatic necrosis, and patients with alcoholism or liver impairment risk hepatotoxicity at standard doses. Acetaminophen has a lower risk of gastrointestinal toxicity than NSAIDs and is rarely associated with renal toxicity [285; 288].

TCAs

TCAs are subgrouped into amines and their demethylated amine derivatives. Common TCAs include amitriptyline, imipramine, trimipramine, clomipramine, doxepin, nortriptyline, desipramine, and protriptyline [289]. The mechanism of analgesic action includes norepinephrine and serotonin re-uptake inhibition in descending inhibitory pathways, and sodium channel blockade with amitriptyline and doxepin. Analgesic action is independent of antidepressant action, occurs at lower doses, and is much more rapid in onset. TCAs can enhance opioid analgesia and are more commonly used with neuropathic LBP [289]. TCAs are not FDA-approved for pain treatment due to possible side effects, which are more likely and consequential in frail patients [102]. Amitriptyline is approved solely for depression, but its off-label use is among the highest of all medications, primarily from use in pain therapy [290].

In chronic LBP, nortriptyline and desipramine are preferred over amitriptyline and imipramine as they show fewer side effects with comparable efficacy. TCA advantages include once-daily dosing and low cost [289]. However, TCAs exhibit a wide range of adverse effects, which differ among the various agents. Common adverse effects include anticholinergic effects, antihistaminergic effects, and orthostatic hypotension (α-1 adrenergic receptor blockade). Anticholinergic side effects include urinary retention, dry mouth, and constipation. Cardiac complications are described as a possible TCA side effect in patients with a history of coronary artery disease, more likely with doses greater than 100 mg/day. Potential side effects and overdose risks should be considered when prescribing antidepressants for chronic LBP; in TCAs, risks include weight gain, driving impairment, falls, and greater overdose lethality potential than other analgesic antidepressants [285; 291].

Selective SNRIs

SNRIs are thought to alleviate pain through norepinephrine and serotonin re-uptake inhibition in descending inhibitory spinal pathways [292]. Duloxetine is efficacious in chronic LBP treatment, with significant pain reduction and improved function compared with placebo at 60 and 120 mg/day, with 120 mg more effective [293; 294]. Responders in a randomized controlled trial showed further improvements in pain, physical function, and quality of life during open-label extension through one-year follow-up [295]. A database review found that patients with chronic LBP initiating duloxetine versus standard of care for pain management were less likely to use opioids, had fewer days on opioids, and initiated opioids later than the standard care cohort, suggesting an opioid-sparing effect of duloxetine in chronic LBP [292].

Venlafaxine has efficacy in several neuropathic pain conditions, but it is not as well researched in chronic LBP. At doses less than 150 mg/day, venlafaxine has greater serotonergic activity and behaves more like an SSRI; at doses greater than 150 mg, SNRI activity becomes dominant, suggesting a 150-mg dose "basement" as pain treatment. Venlafaxine requires tapering instead of abrupt cessation due to the potential for a withdrawal syndrome. Anticholinergic effects are virtually nonexistent from SNRIs, making them favorable in elderly or comorbid patients [296].

Anticonvulsants

Anticonvulsants produce analgesia through diverse mechanisms, including voltage-gated calcium or sodium channel modulation, glutamate antagonism, enhancement of GABA inhibitory systems, or a combination of these actions [285]. Gabapentin is the most widely prescribed anticonvulsant for chronic pain in the United States. Neuropathic pain efficacy with gabapentin was first demonstrated in 1998, along with analgesic synergism when combined with morphine. Gabapentin and its analog pregabalin lack hepatic enzyme induction and adverse drug-drug interactions. Common side effects include somnolence, dizziness, fatigue, and weight gain. Gabapentin is considered benign in overdose. The older anticonvulsants phenobarbital, phenytoin, valproic acid, and carbamazepine may be beneficial but are seldom used due to the risks for side effects, drug interactions, and toxicity [285; 297]. Combining gabapentin or pregabalin with other analgesics has been recommended to target multiple pain pathways and increase analgesia over monotherapy [298].

Benzodiazepines

Benzodiazepines have intrinsic analgesic properties due to $GABA_A$ receptor binding that facilitates GABA activity in the CNS. These drugs are effective as muscle relaxants and may facilitate recovery from acute back pain. Patients with chronic LBP and comorbid anxiety, mood, or sleep disorders may benefit from short-term benzodiazepines, but long-term use is constrained by drowsiness, ataxia, and tolerance. Co-use with opioids may increase analgesia but potentiate respiratory depression, potentially leading to life-threatening consequences. Patient selection should consider history of substance abuse or addiction, as benzodiazepines possess abuse liability [285; 299].

Skeletal Muscle Relaxants

Skeletal muscle relaxants are widely prescribed for relief of painful and disabling muscle spasms that can occur with LBP or myofascial pain syndrome [300]. Baclofen, dantrolene, and tizanidine are FDA-approved for spasticity and act through different mechanisms. Baclofen blocks pre- and post-synaptic GABAB receptors; tizanidine is a CNS α2 receptor agonist; and dantrolene inhibits calcium release from muscle sarcoplasmic reticulum. Diazepam, clonidine, gabapentin, and botulinum toxin are also used off-label for muscle spasticity [300].

Carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine are approved for musculoskeletal disorders. Their broad diversity can guide clinical use. Cyclobenzaprine, closely related to TCAs, should be avoided in patients at risk for arrhythmia or with lowered seizure threshold. Therapeutic actions of most are vague, but sedative effects may contribute [285; 299; 300].

Most skeletal muscle relaxants have similar efficacy and show superiority to placebo in acute and chronic LBP. With cyclobenzaprine or diazepam, significantly more patients attained moderate-to-marked improvement in muscle spasm compared with placebo. Patient preference was found greater for baclofen or dantrolene vs. diazepam. Side effects include drowsiness, dry mouth, and dizziness. Comparative studies of opioids and skeletal muscle relaxants have not been published [285; 299; 300].

Opioid Therapy

A variety of issues are encountered when prescribing opioids for back pain. This section will discuss the long-term use of opioids to manage chronic severe pain, use in specific LBP populations, and other information relevant to primary care practice.

The use of opioids to manage acute and cancer pain is established and relatively straightforward, but their appropriateness for chronic pain is sometimes disputed [215]. The most common side effects are dry mouth, constipation, and nausea. A substantial minority of subjects in randomized controlled trials of opioids for chronic noncancer pain drop out due to side effects (20% to 30% with opioids vs. 5% to 15% with placebo) [215].

Some patients on long-term opioid therapy receive increasing opioid doses over time. Potential causes include pain increase from progression of underlying disease, development of opioid tolerance, or development of opioid-induced hyperalgesia (i.e., increased pain sensitivity). In some cases, dose escalation may reflect addiction or drug diversion, though studies suggest fewer than one in five patients receiving opioids for chronic noncancer pain develop problems with abuse or addiction [215]. Still, opioids possess abuse liability, and use without medical supervision can be hazardous, despite the misperception of greater safety as a pharmaceutical versus a street drug. The abuse liability also requires patients to ensure safe storage of their opioid medication. Due to their abuse potential, opioids are strictly regulated at the federal and state level, imposing barriers for patients to receive appropriate opioid treatment. When prescribing opioids, extensive documentation should be maintained. A systematic review of abuse-deterrent and non-abuse-deterrent opioid formulations concluded that both produced significantly greater pain reduction than placebo and showed comparable efficacy and safety profiles [301].

One meta-analysis of 88 randomized controlled trials compared the efficacy of different pharmacologic therapies for LBP [302]. The trials compared placebos, NSAIDs, opioids, skeletal muscular relaxants, pregabalin (or gabapentin), and some drug combinations. Only skeletal muscle relaxants were found to significantly decrease the pain intensity of acute (including subacute) LBP. Several kinds of drugs significantly decreased the pain of chronic LBP, but only opioids and COX-2-selective NSAIDs effectively reduced pain and improved function. Pregabalin (or gabapentin) appeared to be an effective, but the authors recommended caution with its use for LBP [302].

Opioid Efficacy in Nonspecific Chronic LBP

A 2013 meta-analysis reviewed randomized controlled trials of analgesics for nonspecific chronic LBP, with emphasis on opioids. Opioid trials using opioid control groups were excluded. Tramadol, oxycodone, and oxymorphone studies had 12-week follow-up, while buprenorphine trials had 8- to 24-week follow-ups [303]. The magnitude of pain reduction was marginally greater with tramadol, comparable with oxycodone, dramatically greater with oxymorphone, and significantly greater with buprenorphine compared with placebo. Global improvement in patient functioning was substantially greater with tramadol, oxycodone, and oxymorphone, and comparable with buprenorphine. The side effect risk (vs. placebo) was significantly greater with tramadol and buprenorphine, marginally greater with oxymorphone, and comparable with oxycodone [303]. In this study, oxymorphone showed the greatest magnitude of improvement from baseline on measures of pain intensity and overall patient functioning, with side effects nominally higher than placebo [303]. Patients receiving placebo were as likely to also use acetaminophen or NSAIDs as those assigned opioids.

Another meta-analysis reviewed 15 placebo-controlled randomized trials of opioids in chronic LBP. The researchers found that tramadol was superior to placebo in improving pain and functioning in five studies, and comparable to celecoxib in one trial [304]. Transdermal buprenorphine was somewhat superior to placebo in pain control but not meaningfully different in improved function in two trials. The magnitude of pain reduction with strong opioids (i.e., morphine, hydromorphone, oxycodone, oxymorphone, and tapentadol) was large for ≥30% (moderate) reduction and for ≥50% pain reduction. One trial each showed comparable improvement in pain and function with morphine compared with TCAs in chronic radicular LBP and tramadol compared with TCAs in chronic LBP. In this meta-analysis, adverse events were not reported. Tramadol, buprenorphine, and strong opioids all showed efficacy in controlling chronic LBP for up to 15 weeks [304].

Long-Term Opioid Therapy

Although there is moderate evidence that opioids provide short-term relief for patients with chronic LBP, evidence of long-term effectiveness is poor, based on small-scale, uncontrolled studies [305]. One long-term (median: 8.5 years) study assessed opioid therapy in 84 patients with intractable, severe chronic pain [306]. Twenty-four patients with chronic LBP and radiculopathy were maintained on a median 510 mg/day morphine equivalent dose. The most commonly used opioids were oxycodone, morphine, transdermal fentanyl, and hydromorphone. The median duration of current opioid dose was 3.5 years. At baseline, all patients had severe or very severe pain. At last follow-up, 46% rated their pain as mild, 49% as moderate, and 5% as severe but reduced from baseline. After reaching stable analgesia, 81% rated pain reduction as ≥50%, and 42% rated their pain reduction as ≥70% [306]. In total, 26% reported significant side effects of constipation, fatigue/drowsiness, dry mouth, or weight gain. One event each of constipation, dry mouth, weight gain, urinary retention, memory impairment, vomiting, and reduced libido were described as intolerable.

In 78 patients with disability comparisons, the greatest changes occurred in 65 patients who were bedridden, chair bound, or incapable of any activity of daily living at baseline who became capable of doing some or all activities of daily living or returning to work at follow-up [306]. Quality of life ratings were slightly below normative age-matched population values and not indicative of significant impairment in health-related quality of life. Composite overall physical and mental health scores were slightly below normal.

No increase in infections was found relative to population norms. Sexual function was at least moderately impaired in 85%, but opioid attribution was obscured by age, concomitant medications, and serious medical comorbidity. Problematic opioid use developed in four patients (about 5%) with histories of alcohol use disorder or bipolar disorder early in treatment [306]. All regained opioid stability with good long-term pain control after comorbid psychiatric conditions were addressed.

In 95% of patients, pain levels were reduced from severe/very severe to mild or moderate [306]. Most did not report significant adverse effects; of those who did, few were intolerable. Unexpectedly, 70% reported mild or absent constipation, and hyperalgesia or immune impairment was not detected. Most patients were older than 65 years of age and/or had significant comorbidity, such as diabetes or vascular disease. Although uncontrolled, this long-term study provides information unobtainable by randomized controlled trials in a patient population with severe intractable chronic pain closely monitored over time. This small study shows that immune impairment, tolerance, or hyperalgesia may not develop from long-term opioid therapy in some patients. A caveat is that patients required opioid therapy before enrollment; those lacking opioid response or tolerability were unlikely to enroll [306].

A two-year, multi-center, prospective cohort study evaluated the effectiveness of long-term opioid therapy in 529 patients with chronic noncancer pain [307]. A pain inventory and treatment outcome survey were used to measure pain outcomes

and quality of life. Propensity score matching was used to adjust for differences between opioid users and nonusers. At baseline, the rate of prescription opioid use was 59.7%, which increased to 70.3% over two years. Opioid users reported no improvement in pain symptoms or physical or emotional function but did report higher satisfaction with care and outcomes at one year of follow-up. At two years, opioid users reported no improvement in pain relief, functional outcomes, or quality of life. These findings emphasize the need for proper patient selection and outcome assessment [307].

Levorphanol

Termed the "forgotten opioid," levorphanol is not often prescribed but may be effective in hospice and palliative care or for neuropathic pain syndromes requiring opioids [308; 309]. Although levorphanol has been available in the United States since 1953, it is largely unknown to most pain clinicians, in part because levorphanol is not marketed or promoted [310; 311]. The unique, non-opioid properties of levorphanol suggest a potentially important role in pain therapy.

Advances in pain research during the 1990s began identifying the mechanistic basis of neuropathic and treatment-resistant chronic pain, and the centrality of NMDA receptor activation in both. Further research found that levorphanol and methadone possessed potent NMDA receptor activity [312]. Levorphanol and methadone are both potent mu opioid receptor agonists with unique non-opioid mechanisms. Both are NMDA receptor antagonists and serotonin and norepinephrine reuptake inhibitors [310]. Levorphanol differs from methadone by its more powerful NMDA antagonism (comparable in potency to ketamine), greater NMDA and mu opioid receptor affinity, lower serotonin and norepinephrine receptor affinity, and full kappa-opioid receptor agonism [313; 314]. These properties suggest levorphanol efficacy in chronic neuropathic LBP and severe treatment-refractory nociceptive or mixed nociceptive-neuropathic back pain conditions.

Importantly, levorphanol has many safety advantages over methadone. Methadone's complex pharmacology imposes a hazard when prescribed without sufficient knowledge and experience to mitigate the risks that arise from the extended half-life (15 to 60 hours) exceeding analgesia (4 to 8 hours); numerous drug interactions, which may delay clearance with resultant accumulation to fatal levels; risk of prolonged QTc interval; and activity as a P-glycoprotein substrate. Between 2000 and 2007, methadone prescribing for pain increased dramatically, often by providers lacking sufficient training. By 2009, methadone accounted for 2% of written opioid prescriptions but more than 30% of prescribed opioid-related deaths [315; 316]. In contrast, levorphanol lacks metabolic competition with most drugs, lacks known cardiac toxicity, and is not a P-glycoprotein substrate [309]. However, levorphanol does possess a half-life (11 to 16 hours) exceeding analgesia (6 to 15 hours), and safe prescribing requires dose titration spaced four days apart to avoid drug accumulation [317].

Few studies of levorphanol have been published; its generic status eliminates market incentive for drug company-funded research [311]. An eight-week trial randomized 81 patients with severe, chronic, treatment-refractory neuropathic pain to high-dose (0.75 mg) or low-dose (0.15 mg) levorphanol capsules, titrated to a maximum 21 mg per day. Pain reduction was 36% with high-dose (mean: 8.9 mg/day) and 21% with low-dose (mean: 2.7 mg/day) therapy. Both dose groups showed comparable improvement in sleep and affective distress. Pain levels returned to baseline after levorphanol taper. No addictive behavior was observed [318]. In a separate case series, 31 patients with severe, chronic neuropathic pain received levorphanol following treatment failure with other opioids, including methadone. Pain relief was rated excellent by 52% and fair by 22%, for a response rate of 74%. Some levorphanol responders were methadone nonresponders [311].

Methadone

As noted, methadone was increasingly prescribed for the treatment of chronic pain beginning in 2000. Deaths related to methadone peaked in 2007 and have been gradually declining since, mostly due to increased education and stricter prescribing guidelines [316]. This focus on safety was prompted by data showing large increases in methadone-associated overdose deaths paralleling its increasing use for chronic pain. Clinical practice guidelines were developed to promote safer methadone prescribing for chronic pain. Among the recommendations are [320]:

- Educate patients on methadone safety.
- Use electrocardiogram to identify patients at greater risk for methadone-related arrhythmia.
- Use alternative opioids in patients at high risk of QTc interval prolongation.
- Use careful dose initiation and titration.
- Be diligent in monitoring and patient follow-up.

Cannabinoids

Cannabinoids, which include the plant *Cannabis* and several pharmaceutical products that mimic the analgesic molecular constituents of *Cannabis*, have shown increasing promise in alleviating severe LBP and neuropathic LBP in particular. However, evidence of efficacy is preliminary. If used, it should be considered an adjunctive option for patients for whom first-line options have failed [321; 322].

Combination Pharmacotherapy

When managing chronic LBP, the use of multiple analgesics with complementary pharmacologic mechanisms—termed rational polypharmacy—may offer advantages of additive pain control, fewer adverse events, and reduced opioid dosing (when opioids are included) [309]. Despite a robust theoretical basis, few well-designed, randomized controlled trials using a combined mechanism approach in chronic LBP have been published, and chronic LBP guidelines have not addressed it. Scarcity in the literature is likely the result of difficulty and complexity in performing clinical trials of multiple active treatments, the inherent inflexibility of clinical trial protocols in allowing individualized dosing and titration, and the absence of an economic incentive [323]. However, the findings of published studies suggest an added benefit with combined pharmacotherapies [323].

Celecoxib Plus Pregabalin

Patients with chronic neuropathic or nociceptive LBP from disk prolapse, lumbar spondylosis, and/or spinal stenosis treated with celecoxib and/or pregabalin for 12 weeks showed significantly greater pain reduction with combined therapy than with monotherapy. Pregabalin dose requirements were significantly lower when combined with celecoxib. Monotherapy and combination treatment showed similar incidence of adverse events [324].

Buprenorphine Plus Pregabalin

In one study, patients with chronic neuropathic or nociceptive LBP received buprenorphine transdermal system for four weeks and were then randomized to additional pregabalin 150 mg or placebo for four weeks. After one month, transdermal buprenorphine produced significant pain reduction. After two months, further reductions in pain scores were only significant in patients receiving transdermal buprenorphine plus pregabalin [325].

Morphine Plus Nortriptyline

A trial randomized 61 patients with chronic lumbar radiculopathic pain to morphine (15–90 mg), nortriptyline (25–100 mg), morphine plus nortriptyline, or active placebo (benztropine) therapy for nine weeks. More patients attained moderate or better pain reduction with combination treatment (67%) than placebo (37%), morphine alone (42%), or nortriptyline alone (40%). The additive benefits

from morphine plus nortriptyline may reflect successful targeting of multiple pain pathways in this difficult-to-treat pain condition [326]. In a randomized, double-blind trial, patients with neuropathic pain were randomized to receive oral nortriptyline, morphine, or a combination of the two [327]. During each of three 6-week periods, doses were titrated toward maximal tolerated dose (MTD). The primary outcome was average daily pain at MTD. Secondary outcomes included other pain, mood and quality of life measures, and adverse effects. Sixty-two patients were screened, 52 enrolled, and 39 completed at least two treatment periods. Average daily pain (0–10) at baseline was 5.3. At MTD, it was 2.6 for nortriptyline plus morphine, 3.1 for nortriptyline alone, and 3.4 for morphine alone. Brief Pain Inventory scores for average and present pain were also significantly lower for the combination than for each drug alone. Moderate-to-severe constipation was reported in 43% of patients treated with combination therapy, in 46% treated with morphine alone, and in 5% of patients treated with nortriptyline alone. Moderate-to-severe dry mouth was reported in 58% of patients treated with combination therapy, in 49% treated with nortriptyline alone, and in 13% of patients treated with morphine alone [327].

Topical Analgesics

Some analgesics are now formulated to bypass the systemic distribution produced by oral administration through transdermal delivery. Topical analgesics are used for the delivery of locally effective drug concentrations to the peripheral application site, with low systemic exposure and, presumably, lower risk of systemic adverse effects [328]. Potential benefits of topical analgesic delivery include reduced side effects, painless drug delivery, improved patient adherence and acceptance, ease of discontinuation, avoidance of first-pass metabolism, and direct access to the peripheral tissue target [329].

Although most topical analgesics produce clinically effective drug concentrations at the peripheral site without clinically relevant systemic concentrations, the therapeutic effects may not be strictly limited to the peripheral target. For example, topical morphine and fentanyl produce analgesia through central and peripheral mechanisms of action despite low systemic concentrations. Factors that influence penetration and absorption of topical analgesics include the biochemical properties of adjuvants in the topical formulation and inter-individual variability in skin absorption [330; 331]. Compounding pharmacies often include dimethyl sulfoxide in topical formulations of drugs that lack the properties for optimal cutaneous absorption [328].

In general, topical opioids, NSAIDs, and salicylates have not shown the systemic side effects that limit the use of their oral counterparts [332]. However, topical analgesics are not without side effects, most commonly skin irritation or dryness. Penetration enhancers (e.g., dimethyl sulfoxide) are associated with significant skin dryness resulting from lipids dissolving on the skin surface [333].

NSAIDs

Effort has been made to improve NSAID tolerability for elderly and medically comorbid patients by shifting from oral to topical NSAIDs. As of 2009, topical NSAIDs were recommended in seven of nine clinical guidelines for pain [334].

NSAIDs are the most widely studied topical analgesics [332]. Topically applied NSAIDs are suitable for the treatment of many back pain conditions as they penetrate the muscle and joint tissues proximal to and below the site of application. A comparison study of topical NSAIDs, topical salicylate, and capsaicin in chronic musculoskeletal pain found highest rates of significant pain control with topical NSAIDs [335; 336; 337].

Of all topical NSAIDs, diclofenac has the most evidence supporting its use and is the sole NSAID with FDA approval for topical use. Approved formulations include diclofenac sodium 1% and 3% gel, diclofenac sodium 1.5% topical solution in 45.5% dimethyl sulfoxide, diclofenac epolamine topical patch 1.3%, and diclofenac sodium topical solution 2% [328; 338]. Topical diclofenac has shown efficacy in pain reduction superior to placebo; comparable to topical NSAIDs indomethacin, ketoprofen, and piroxicam; and comparable to oral NSAIDs diclofenac, ibuprofen, and naproxen. The effectiveness, safety, and tolerability of topical diclofenac support its use for a variety of inflammatory chronic back pain conditions [335; 339]. Randomized controlled trials of diclofenac applied three times daily showed that benefits began at 1 week, were fully apparent by 4 weeks, and were maintained to 12 weeks [340].

The most common adverse effects with diclofenac are mild site reactions, such as erythema or pruritus. No severe or systemic gastrointestinal effects have been observed with topical diclofenac or other topical NSAIDs, and skin irritation is significantly less common with patch versus gel [332]. Systemic exposure from diclofenac epolamine topical patch is 1% that of an oral 75-mg dose. The steady-state plasma concentrations are also significantly lower and unlikely to result in COX-1-mediated effects [341]. From 1993 to 2008, 46 million patients worldwide received diclofenac epolamine topical patch, and adverse events were reported in 108 patients. Most were skin reactions or lack of efficacy; six were serious gastrointestinal events, but none were believed causally related to the diclofenac epolamine topical patch [342]. The FDA requires that manufacturers incorporate standard NSAID warnings of serious liver disease risks into the labeling of topical diclofenac; however, to reach systemic levels from one 150-mg oral dose of diclofenac, 100 patches would need to be worn simultaneously [273; 309; 343]. Diclofenac topical (3% gel) also contains a boxed warning related to serious cardiovascular thrombotic events and serious gastrointestinal bleeding, ulceration, and perforation [344].

NSAIDs are recommended for analgesia in many LBP conditions, and topical formulations should be considered for use in patients with acute or chronic back pain conditions for which oral NSAIDs are indicated [332; 345]. It is important to note that, unlike oral NSAIDs, topical NSAIDs cannot target central and peripheral pain mechanisms, are ineffective for neuropathic pain and widespread musculoskeletal pain, and lack sufficient penetration for use in chronic LBP caused by arthritis [309].

Anesthetic Analgesics

Aberrant ion channel (particularly sodium channel) activity contributes to chronic pain conditions involving neuropathy. Topical anesthetic analgesics produce analgesia by disrupting pain signal transmission between afferent nerve fibers and the CNS, primarily from binding affinity to voltage-gated sodium and/or potassium ion channels. Lidocaine is nonselective for sodium and potassium ion channels, while tetracaine is more selective for sodium ion channel binding. Binding to these receptor sites reversibly inhibits neuronal action potential to prevent transmission and conduction of nerve impulses, producing analgesia through inhibition of ectopic discharge in sensitized and hyperactive subcutaneous nociceptors. Lidocaine also shows widespread nerve fiber activity suppression, while tocainide is more selective to C-afferent conductivity suppression [328; 346; 347].

Topical analgesic agents that interact with sodium and potassium channels include lidocaine 5% patch; a self-heating patch containing 70 mg each of tetracaine and lidocaine; a eutectic mixture of 2.5% each of lidocaine and prilocaine; and a cream with 7% concentrations of lidocaine and tetracaine [328]. Lidocaine-containing creams show a maximum skin penetration depth of 3–5 mm, and circulating lidocaine levels following topical application vary broadly across patients. Systemic absorption of topical anesthetics does occur but has not been associated with side effects or toxicity. The primary side effects are application-site reactions, such as skin discoloration, erythema, and irritation [328; 348].

Lidocaine 5% patch or plaster has efficacy superior to placebo and comparable or superior to oral pregabalin in pain reduction with postherpetic neuralgia or diabetic neuropathy. It has also shown greater improvements in quality of life and fewer side effects than oral pregabalin [332]. In patients with post-traumatic peripheral neuropathy, lidocaine 8% pump spray significantly reduced pain and tactile allodynia for a median five hours after application [349].

In some patients with chronic back pain with neuropathic contribution, lidocaine 5% patch may be effective in reducing pathologic pain from abnormally increased sodium channel expression, although patient response is variable [346]. A placebo-controlled trial of 5% lidocaine patch in chronic LBP found no difference between active and placebo patch; however, 50% of subjects in both groups experienced substantial pain reduction, and the high placebo-response rate to the inert patch created difficulty in appraising true lidocaine efficacy [346]. A Cochrane review assessed the analgesic efficacy of topical lidocaine for chronic neuropathic pain in adults [350]. The review included 12 studies and 508 participants. Six studies enrolled participants with moderate or severe postherpetic neuralgia, and the remaining studies enrolled different, or mixed, neuropathic pain conditions, including trigeminal neuralgia and postsurgical or post-traumatic neuralgia. Four different formulations of topical lidocaine were used: 5% medicated patch, 5% cream, 5% gel, and 8% spray. Seven studies used multiple doses, with one- to four-week treatment periods, and five used single applications. Only one multiple-dose study reported the review's primary outcome of participants with ≥50% or ≥30% pain intensity reduction. In all but one study, very low-quality evidence indicated that lidocaine was better than placebo for some measure of pain relief [350].

Capsaicin

Capsaicin is a constituent of hot peppers and a topical analgesic with efficacy in several musculoskeletal and neuropathic pain conditions. The mechanism of analgesia is mediated by action on TRPV1 receptors, temperature sensors that regulate pain signaling on peripheral sensory neurons. TRPV1 receptors are initially activated and then desensitized by capsaicin, leading to reversible loss of C fiber function [340]. Capsaicin also inhibits the activity of bradykinin, a neuropeptide involved in the inflammatory process [328].

Capsaicin is available as 0.75% or 0.5% cream, 8% patch, or 0.25% lotion. The 8% patch is associated with significant local reactions, including pain, pruritus, and swelling. Instructions for its use state that application should only be performed under physician supervision, and pre-treatment of the application site with a local anesthetic is recommended [328]. A single 60-minute application of the 8% capsaicin patch has shown significantly greater pain relief compared to a low-concentration 0.04% capsaicin patch, a difference that was sustained as long as 12 weeks [351].

Opioids

Peripheral tissue inflammation upregulates opioid receptors and stimulates local endogenous opioid peptide production in immune cells. These cells provide the targets for opioid binding and activation by opioid drugs and the rationale for topical opioid analgesia. Topical application also bypasses systemic distribution and side effects [352].

Topical opioids are not commercially available and require compounding pharmacist preparation [353]. Most studies have evaluated morphine and have found side effects of application site itching and burning with morphine and placebo vehicle-gel [353; 354]. Case series trials found rapid reduction of pain from tumor skin infiltration, malignant and non-malignant skin ulcers, severe oral mucositis, knee arthritis, and tenesmoid pain. Randomized controlled trials in painful skin ulcers found significantly lower pain scores with topical opioids compared with placebo [354].

In a small study, patients with chronic, intractable pain (due to disk degeneration in 61% of cases) received topical morphine, oxycodone, or hydromorphone for six months to apply as needed. Treatment was used at least once per day by 100% of participants and for breakthrough pain by 67%. Effective pain relief up to three hours per application was reported by 85%, and reductions in oral opioids, pain flare-ups, and stiffness were reported by at least 30% of participants [355]. In a separate study, patients with severe back pain received morphine cream, applied one to three times per day. Following application, 88% reported pain reduction of 40% to 50% lasting four or more hours; 19% reported relief lasting longer than one day. Responders were then randomized (double-blind) to active or placebo cream. Twenty-four hours post-treatment, pain-free movement was experienced by 44% with morphine vs. 0% with placebo [356].

TCAs

Although recommended as a treatment option for chronic LBP, TCAs are inappropriate for many patients, and others may find the side effects intolerable. Topical TCA formulations have been developed to offset these potential risks, and other topical formulations combine TCAs with another analgesic acting through complementary pain pathways. A 2% amitriptyline/1% ketamine formulation has shown efficacy in various neuropathic pain conditions in the absence of meaningful systemic concentrations. Topical 3.3% doxepin/0.025% capsaicin has also been found effective in other types of neuropathic pain [333; 357; 358].

Injection, Intravenous, and Infusion Therapies

Lidocaine

Lidocaine has been used systemically as an analgesic in diverse chronic back pain conditions, typically as single IV infusion at sub-anesthetic doses ranging from 1 mg/kg to 6 mg/kg over 30 to 120 minutes [359]. Lidocaine relieves pain by blocking spinal dorsal horn sodium ion gate channels and by inhibiting neuronal ectopic discharge and aberrant electrical discharge in peripheral neuromata and dorsal root ganglia. The analgesic effect of IV lidocaine is unrelated to its anesthetic mechanism, as lidocaine half-life is 120 minutes and analgesia substantially longer [359; 360; 361; 362].

A review of IV lidocaine found that lidocaine 5 mg/kg showed clear benefit in reducing chronic pain immediately post-infusion, but pain relief did not persist longer than one week. The most common side effects were somnolence, light-headedness, headache, nausea, dry mouth, and perioral numbness [359]. A randomized controlled trial found no significant long-term analgesic or quality of life benefit from IV lidocaine for chronic neuropathic pain [363].

Ketamine

Ketamine infusion has demonstrated efficacy in chronic pain, including chronic neuropathic LBP, but side effects have limited its use. The most common of these are hallucinations or depersonalization/derealization. Other less troublesome side effects include somnolence, feelings of insobriety, nausea or vomiting, and drowsiness. Benzodiazepine co-administration may eliminate or dramatically reduce the development of hallucinations, depersonalization/derealization, and insobriety [364]. In addition to pain alleviation, trials of ketamine infusion in severe chronic LBP have demonstrated opioid-sparing effects, reductions in opioid tolerance, and suppression of opioid-induced hyperalgesia [365].

Botulinum Toxin A

Botulinum toxin A was evaluated in 31 patients with chronic LBP randomized to injections of botulinum or saline at five lumbar paravertebral sites on the side with pain. After three weeks, pain reduction of 50% or greater was attained by 73.3% of patients treated with botulinum and 25% of those treated with saline. At eight weeks, ≥50% pain reduction was reported in 60% of patients who received botulinum toxin A, compared with 12.5% of those who received saline. Improved functioning at eight weeks was found in 66.7% with botulinum toxin A and 18.8% with saline. No patients reported side effects [366].

A single-blind, randomized clinical trial study of 50 patients with refractory chronic LBP similarly assigned patients to receive either botulinum toxin or saline injections in the paraspinal muscles where the pain localized [367]. After four weeks, 76% of the participants receiving botulinum reported improvements in pain, compared with 20% of patients receiving saline. After eight weeks, the botulinum treatment group was significantly more likely to report improvements in functionality (68% vs. 12%) [367]. The American Academy of Neurology has concluded botulinum toxin A is possibly effective for chronic, predominantly unilateral LBP, but its role in chronic LBP treatment should be clarified by larger randomized controlled trials in homogenous populations [368; 369].

Bisphosphonates

A randomized, placebo-controlled study evaluated the analgesic effect of IV pamidronate in 44 patients with chronic LBP and evidence of degenerative spine disease. Pamidronate administered as two 90-mg infusions decreased pain intensity for six months, with significantly different improvements from placebo in daily average pain score, proportion of responders, changes in worst pain, and pain interference of daily function. No serious pamidronate-related adverse events or other significant safety findings were observed [370].

Zoledronic acid was evaluated in a study of 40 patients with chronic LBP of moderate-severe intensity, with MRI-detected modic changes (i.e., pathologic vertebral endplate and bone marrow changes). After one month, single-infusion zoledronic acid 5 mg led to significantly greater reduction in pain and disability compared with placebo, but no differences were observed at one year. NSAIDs were used by 20% of patients randomized to zoledronic acid and by 60% of those receiving placebo. Acute fever, flu-like symptoms, or arthralgia occurred in 95% with zoledronic acid and 35% with placebo [371].

One study compared changes in the size and type of modic changes, detected using MRI, after a single intravenous infusion of 5 mg zoledronic acid or placebo among chronic LBP patients. The authors sought to determine whether the changes correlated with pain symptoms [372]. Nineteen patients in the zoledronic acid group and 20 in the placebo group had an MRI at baseline and again at one year. The level, type, and volume of all modic changes were evaluated and classified as type I or type II. In the zoledronic acid group, 84.2% of patients had primarily type I dominant modic changes, compared with 50% in the placebo group. Researchers observed that the volume of the type I primary modic change decreased in the zoledronic acid group but increased in the placebo group. Zoledronic acid additionally tended to speed up conversion of type I dominant changes into type II dominant changes [372].

Anti-Nerve Growth Factor

Nerve growth factor (NGF) is a neurotrophic factor associated with pain signaling, active in several mechanistic pathways to initiate and maintain hypersensitivity and persistent pain. Clinical trials have shown pain reduction using NGF antagonists in osteoarthritis and interstitial cystitis, and agents with anti-NGF activity may be efficacious in chronic back pain [373]. In a review of four randomized controlled trials of anti-NGF agents in back pain treatment, two studies of tanezumab in chronic non-radicular LBP showed significant pain and disability reduction at 12 weeks compared with naproxen or placebo controls. Reduction was greater in pain than disability. Trials of fulranumab or REGN475 did not show benefit. Possible anti-NGF side effects include headache, hyperesthesia, abnormal peripheral sensation, and dizziness. Serious side effects were not observed in any trial [373; 374].

Tumor Necrosis Factor Antagonists

In a review of randomized controlled trials of anti-TNF in discogenic lumbar radiculopathy, a significant reduction in LBP and/or leg pain was found in 60% of epidural etanercept participants compared with placebo. A three-arm study found adalimumab superior to etanercept in LBP, and a dose-response study found significant pain reduction only with the lowest (0.5 mg) etanercept dose. Subcutaneous adalimumab led to significantly decreased back pain scores from six weeks through six months and less need for surgery than patients receiving placebo. No differences from placebo were found in oral REN-1654, subcutaneous etanercept, intravenous infliximab, or intradiscal etanercept. Adverse events with epidural etanercept were similar to placebo. In aggregate, the data are promising, but further research is needed to clarify optimal dose, route of administration, and anti-TNF agent [375].

Endocrine-Targeted Therapy in Chronic Refractory Pain

A subgroup of patients with chronic pain is refractory to standard drug and non-drug therapies. Uncontrolled pain profoundly impacts endocrine function, and normalization of key hormones may reduce pain. Hormone abnormalities were assessed in 61 patients with treatment-resistant chronic pain. Most (80.3%) had at least one abnormality, most commonly related to adrenocorticotropic hormone (27.3%), cortisol (32.8%), pregnenolone (20.8%), progesterone (20.8%), dehydroepiandrosterone (37.2%), and testosterone (37.2%); 11.5% showed significant hypothalamic-pituitary-adrenal suppression. Therapy was targeted at normalizing hormone elevations or deficiencies. Within 60 days, hormone abnormalities were normalized, and pain alleviated to the extent that all patients resumed normal function. This suggests that patients with chronic pain who lack pharmacotherapy response may have profound hormone abnormalities that, once corrected, can facilitate effective pain control from standard approaches. While not specific to chronic LBP, these results may be relevant due to shared physiologic effect of severe uncontrolled pain and common mechanisms of chronic pain [376].

Pharmacotherapy for Neuropathic LBP

Confirmation of neuropathic involvement in chronic LBP has challenged conventional assumptions and management [160]. Evaluation of 7,772 patients with chronic LBP found predominant pain contribution from neuropathic causes in 37%, with higher pain intensity experienced by this subgroup [377].

Patients with radiculopathy pain are five times more likely than patients with non-radicular LBP to receive pharmacotherapy, but most lack sufficient evidence to explain their widespread use [40; 378; 379]. Radiculopathy and other neuropathic LBP types are often undertreated or ineffectively treated. Treatment paradigms have come under increasing scrutiny as a result of the greater understanding of neuropathic mechanisms, including those of radiculopathy. Mediocre pain outcomes in radiculopathy may be largely due to failure in using mechanism-based treatment approaches [380]. Medications effective in other neuropathic conditions (e.g., nortriptyline, morphine, pregabalin, topiramate) are largely ineffective for lumbosacral radiculopathy, and departure from suggested first- and second-line medications may be required [381].

INTERVENTIONAL PAIN MEDICINE THERAPIES

Use of interventional pain medicine in back pain increased 11.8% per year between 2000 and 2009, but began declining at a rate of 0.8% per year between 2009 and 2018 [382]. During this period, utilization of interventional techniques declined 6.7%, with an annual decline of 0.8% per 100,000 in the Medicare population, despite an increase of 0.7% per year growth in this population and a 3% annual increase in Medicare participation [382]. From 2009 to 2018, the rate of utilization of epidural and adhesiolysis procedures decreased at a rate of 2.6% annually. Disc procedures and other types of nerve blocks decreased 1% annually, while facet joint interventions and sacroiliac joint blocks increased 0.9% annually [382]. Utilization patterns among patients who have Medicare Advantage Plans, which constitutes nearly 30% of the Medicare population, were not included in this analysis [382].

There is a vast array of interventional approaches to the diagnosis and treatment of LBP. Few have been rigorously evaluated, and fewer still have shown consistent benefit. However, several non-interventional pain medicine organizations have included interventional approaches in their clinical practice guidelines for severe intractable pain.

Spinal Surgery

Roughly 80% of patients evaluated by neurosurgeons are referred for spinal pain, but surgery is indicated in fewer than 10% [383]. In many cases, primary care providers lack an understanding of back pain amenable to surgery. Patients in pain may wait for extended periods for initial consult, only to be sent back to primary care; improved knowledge can limit inappropriate patient referral. Spinal surgery in acute LBP is limited to patients with severe or progressive motor weakness or cauda equina syndrome. Surgical options and appropriate chronic LBP indications include spinal compression surgery, fusion surgery, and disk arthroplasty [383; 384].

Spinal decompression surgery involves complete or partial removal of lumbar spine structures causing neural impingement, such as large disk herniations and spinal stenosis. This includes open discectomy, microdiscectomy, and laminectomy. Fusion surgery joins adjacent vertebrae in an unstable vertebral motion segment to alleviate pain in advanced spinal degeneration. Disk arthroplasty treats degenerative changes confined to one vertebral motion segment by disk removal with artificial disk replacement.

Evidence supports laminectomy for disabling leg pain due to spinal stenosis and open discectomy or microdiscectomy for radiculopathic pain associated with lumbar disk herniation. Post-surgery symptom relief seldom persists longer than two years. Better outcomes with radiculopathy and lumbar disk herniation are associated with patient age younger than 40 years of age and symptom duration less than three months [165; 383]. Fusion surgery has a weak recommendation for non-radicular chronic LBP associated with degenerative disk disease, with greatest benefit in patients with moderately severe pain or disability, one or more years of conservative management without improvement, and absence of psychiatric or medical comorbidities [124; 383].

Epidural Steroid Injection

Epidural steroid injection involves corticosteroid plus local anesthetic injection into the space between the dura and the spine. Arachidonic acid release from tissues is induced by phospholipase A2. Metabolism of arachidonic acid by the COX and lipoxygenase pathways generates prostaglandins, prostacyclins, thromboxanes, and leukotrienes. Prostaglandins and other arachidonic acid byproducts initiate or exacerbate pain by inducing inflammation and sensitizing peripheral nociceptors. Corticosteroids inhibit phospholipase A2, accounting for their anti-inflammatory properties. Steroids may also inhibit pain by suppressing ectopic discharge from injured nerve fibers and blocking conduction of normal unmyelinated C fiber [385].

Some potential mechanisms of epidural steroid injection benefit do not actually involve steroids. Local anesthetic injection can increase blood flow to ischemic nerve roots and, similar to steroids, suppress ectopic discharges from injured neurons to inhibit or block nociceptive transmission. In addition, epidural administration of any injectate, including saline, can promote analgesia through washout of inflammatory molecules. A significant correlation has been found between epidural volume and pain relief, regardless of steroid dose, at 6- and 12-week follow-up [385; 386].

Epidural Steroid Injections for Lumbar Radiculopathy

Corticosteroid injection into the epidural space for LBP treatment was first reported in 1953, and despite numerous publications and exponential increases in use, its efficacy and safety remain controversial [385]. Interventional pain medicine specialists strongly believe in the efficacy of this intervention for lumbar radicular pain, reinforced by more than five decades of use and centrality in numerous pain programs [387]. The benefit of epidural steroid injection varies, with efficacy best demonstrated in short-term pain relief of persistent radiculopathy with lumbar disk herniation [50]. Evidence for epidural steroid injection in spinal stenosis is less robust than for herniated disk, but greater than with failed back surgery syndrome and axial back pain without radiating symptoms [385].

The conceptual appeal of epidural steroid injection is that subsequent pain relief allows the body time to heal while avoiding the long-term consequences of central sensitization. However, more than 70% of radiculopathies recover within six months, and a similar proportion of disk herniation undergoes resorption within one year [385].

Epidural steroid injection is also advocated as an effective means to reduce lumbar surgery. This is contradicted by epidemiologic data showing increased lumbar surgery in those receiving epidural steroid injections, especially with more than three epidural steroid injections over a two-year period [13]. Some advocate for epidural steroid injection as a non-addictive LBP treatment that eliminates or seriously reduces need for opioids, but this is not yet supported by evidence [13].

Clinical practice guidelines generally support the use of epidural steroid injections for patients with disk herniation and persistent lumbar radiculopathy who are experiencing pain severe enough to cause functional impairment with failure of noninvasive care after four weeks [50; 166]. Contrast-enhanced fluoroscopy is suggested for accurate delivery [165]. There is no evidence that any specific injection approach (e.g., interlaminar, transforaminal, caudal) influences the risks or effectiveness [165]. This approach is suggested only for short-term (two to four weeks) pain relief in lumbar radiculopathy; epidural steroid injection has no impact on functional impairment, need for surgery, or pain relief beyond three months [4; 165; 166; 388].

Epidural Steroid Injections for Spinal Stenosis

Roughly 25% of the estimated 2.2 million lumbar epidural steroid injections performed annually in Medicare patients are for lumbar spinal stenosis [389]. Epidural steroid injection is presumed to relieve pain by reducing nerve root inflammation and ischemia, and it is widely used for lumbar spinal stenosis despite the lack of rigorous evidence and the despite the fact that clinical practice guidelines have found insufficient evidence to evaluate the benefits and harms of this use [4; 390; 391].

In a multisite, randomized controlled trial, 400 patients (mean age: 68 years) with lumbar spinal stenosis and moderate-to-severe leg pain and disability (duration of three months or longer in 80% to 88%, respectively) were randomized to receive an epidural injection of corticosteroid plus lidocaine or lidocaine alone. At six weeks, patients in both groups had improved, with no between-group differences with respect to improvement in functional status or leg pain intensity scores; no differences were noted with different sites of injection (interlaminar vs. transforaminal) either. A greater number of participants in the epidural steroid injection group reported treatment satisfaction (67% vs. 54%) and depression symptom improvement. Those who received epidural steroid injection showed higher cortisol suppression levels at three and six weeks, possibly from systemic steroid absorption [390]. Despite modest benefit at three weeks, the anticipated longer-term benefits never materialized, raising serious questions regarding the benefits of this approach in lumbar spinal stenosis [390; 391]. A later multicenter, randomized controlled trial of epidural corticosteroid injections, including repeat injections, on outcomes through 12 months also reported no long-term benefit [382].

In another study, researchers reviewed data from 13,741 patients in the six-month period before and after epidural steroid injection for LBP. Roughly 64% of patients used opioids before epidural steroid injection and 67% used opioids after. About 38% were prescribed opioids after but not before epidural steroid injection, while 16% were prescribed opioids before but not after. Those receiving more than three epidural steroid injections were significantly more likely to begin opioids and undergo lumbar surgery than those who received three or fewer injections [13; 392].

Ketamine-Augmented Epidural Steroid Injection

To evaluate ketamine-augmented epidural steroid injection, 200 patients with lumbar disk herniation and radiculopathic pain were randomized to epidural steroid injection (triamcinolone/bupivacaine) plus ketamine (30 mg) or placebo. Mean pain scores were significantly lower with ketamine-augmented therapy compared with placebo at every follow-up point from 1 month to 12 months. Likewise, at every follow-up, disability scores were significantly lower in the ketamine group. Ketamine side effects included post-injection delusions lasting a mean 45 minutes; none required intervention [393]. To compare the analgesic efficacy of two different doses of epidural ketamine in chronic LBP, 60 patients received either 25 mg or 50 mg ketamine as an adjunct to 40 mg triamcinolone (total 6 mL volume given epidurally) [394]. Efficacy was evaluated in terms of pain scores, duration of pain-free period, patient satisfaction score, and number of repeat injections with either dose. Data were collected at baseline and again at 2, 4, 8, and 12 weeks postprocedure. Pain within the groups over time showed significant improvement from baseline. Pain between the groups showed comparable scores at 12 weeks. Patient satisfaction scores, pain-free duration, and number of repeat injections were statistically comparable. Quality of life improved and longer pain-free intervals were observed in the 50 mg ketamine group, but more side effects were reported [394]. It is important to note that racemic ketamine should be avoided for epidural use because the preservatives have shown neurotoxicity [393].

Adverse Events

In 2014, the FDA issued a warning regarding rare but serious adverse events associated with epidural steroid injection use [395]. Serious adverse events included death, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, stroke, seizures, nerve injury, and brain edema. Many cases were temporally associated with the epidural steroid, occurring within minutes to 48 hours post-injection. Many patients did not recover. Healthcare professionals should include this information when discussing benefits and risks of epidural steroid injections with patients [395].

Neuromodulation Interventions

Implantable devices are available for patients with severe refractory chronic LBP. Positive response to a temporary trial is required before permanent implantation.

Spinal Cord Stimulation

Spinal cord stimulation is primarily used to reduce severe and persistent neuropathic pain from lumbosacral radiculopathy or failed back surgery syndrome. It acts by modulating spinal cord and CNS afferent input. A comparison of spinal cord stimulation with conventional medical management in failed back surgery syndrome with radicular pain found greater than 50% pain reduction at one- and two-year follow-up in 48% and 47% of patients with spinal cord stimulation vs. 9% and 7% of patients managed conventionally. During the trial, 31% of patients undergoing spinal cord stimulation required device-related surgical revision [396; 397]. As such, spinal cord stimulation should be considered in patients with failed back surgery syndrome who are not candidates for corrective surgery and have failed conservative evidence-based treatment [4].

The most challenging aspect of spinal cord stimulation therapy is patient selection. In order for patients to be considered for spinal cord stimulation, other options should have been ineffective or be contraindicated. Spinal cord stimulation is indicated for severe neuropathic pain persisting at least six months [4]. Psychologic assessment is required to identify motivational, social, psychologic, and social support factors that predispose to poor treatment outcome. Failure of spinal cord stimulation treatment is associated with active substance abuse, secondary gain, unrealistic expectations, personality disorders, litigation, and depression. These factors may account for previous treatment failures to a greater extent than sole inability to control the biologic cause of the pain [398].

Implantable Intrathecal Drug Delivery

Implantable intrathecal drug delivery systems are routinely used for cancer pain when oral or transdermal analgesics are ineffective or intolerable. In LBP, implantable intrathecal drug delivery is reserved for severe, chronic, refractory axial or neuropathic radicular pain, most frequently in failed back surgery syndrome, spinal stenosis, and intractable LBP with or without radicular pain. Similar to spinal cord stimulation, implantable intrathecal drug delivery is reserved for patients who have exhausted other options, with psychologic screening for negative prognostic factors [399]. Evidence in chronic LBP is limited, but several trials have found significant pain relief lasting longer than one year [400]. Pain control usually requires multiple analgesics, typically an opioid, local anesthetic, and alpha-2 agonist. Baclofen is often added for refractory spasms and additional analgesia. Patients are seen at least monthly for pump reservoir refill. Symptoms consistent with spinal cord or nerve root compression, known adverse events with implantable intrathecal drug delivery, require prompt, aggressive investigation [399].

BARRIERS TO EFFECTIVE CARE OF CHRONIC LBP

Over the past two decades, healthcare expenditures for LBP have increased dramatically. While a large volume of pre-clinical and clinical research, review papers, and practice guidelines on chronic LBP have been published, patient outcomes remain unimproved. Chronic LBP remains a frustrating condition for clinicians and for patients, who often obtain little improvement in pain and functioning with standard therapies. Data indicate that more effective patient care is hampered by several factors, including:

- Flaws and limitations in pain therapy research
- Biased or deficient clinical practice guidelines
- Declining availability of multidisciplinary pain programs
- Increasing dominance of interventional pain medicine and replacement of the biopsychosocial approach by the biomedical treatment model
- Conflicting interests that supersede delivery of patient-centered care
- Fundamental structural flaws in health care, reimbursement, and compensation systems

The International Association for the Study of Pain has identified areas of crisis in pain care in the United States: poor evidence base in most treatment approaches; inadequate primary care provider pain education; the unknown value of opioid therapy for chronic pain; pain provider reimbursement; and declining access to multidisciplinary pain programs [5].

LIMITATIONS IN PAIN THERAPY RESEARCH

A frequent criticism of opioid therapy for chronic pain is the publication of few long-term (i.e., longer than one year) randomized controlled trials, cited as proof that long-term opioid safety and efficacy lacks evidence. However, this is not unique to opioids, as no analgesic used in chronic pain has evidence of long-term efficacy [401]. Pharmaceutical randomized controlled trials usually do not extend past 8 to 12 weeks, and long-term randomized controlled trials are difficult to perform for many reasons. The complexity and expense of evaluating combined drug therapies create obstacles for investigators and are unattractive to industry funding [323; 402]. Ethical constraints interfere with initiating long-term placebo-controlled analgesic trials, such as the necessary encouragement of patients in moderate-to-severe pain to remain adherent to possibly inert placebo therapy for study duration [318].

Randomized controlled trials are considered the "gold standard" in evidence-based medicine, but possess important limitations. Trial outcomes may have limited clinical use because typical patients with chronic LBP often bear little resemblance to tightly screened participants. With complex comorbidity, older age, and requirement of multiple medications the norm, patients with chronic LBP seen in practice more closely resemble patients excluded from enrollment. Randomized controlled trials also typically use strict, inflexible dosing parameters. This can lead to dropout by patients lacking benefit or tolerance who would otherwise show good therapeutic response using a tailored approach. Opioid randomized controlled trials often have high dropout rates, which can drive down efficacy to result in underestimation of true patient benefit [402].

Long-term observational studies provide clinically important information unobtainable by randomized controlled trials [5]. Although non-blinded trials have the potential for confounding by subject and observer bias, multiple-year trial durations make dissipation of earlier placebo response from investigator enthusiasm or subject expectation highly probable [306]. Spontaneous remission in the natural history of pain is also unlikely in a cohort with intractable chronic pain [402]. Placebo-controlled randomized trials have long been the preferred study design, but comparative effectiveness research is becoming emphasized to address numerous concerns over the process of new technology entrance into clinical practice.

DECLINING AVAILABILITY OF MULTIDISCIPLINARY PAIN PROGRAMS

The inadequate care of chronic LBP is in part the result of the demise of multidisciplinary pain programs and the dominance of interventional pain medicine, a reflection of a movement away from biopsychosocial-based care and toward the biomedical model. With sole emphasis on the neurophysiologic aspects of pain and the pain experience, the biomedical model is reductionistic in its approach to chronic pain [403]. The old biomedical model viewed LBP causation as tissue pathology involving structural, anatomic, and biomechanical factors. Largely ineffective for chronic LBP, the biomedical approach led to unacceptable failure rates, adverse iatrogenic effects, and escalating costs [21; 135]. Recognition of a need for an alternative model of care coincided with breakthrough insights in back pain mechanisms, evolution of the biopsychosocial pain model, and development of biopsychosocial-based multidisciplinary chronic pain management programs, also termed multidisciplinary pain programs [404].

Earlier multidisciplinary pain programs were generally located in academic medical centers and staffed by scientist-practitioners, attracted by the resources and opportunities to improve chronic pain patient care. With increasing popularity and demand, some programs began delivering diverse, uncoordinated, and ineffective care while remaining highly profitable. The efficacy and cost-effectiveness shown in the published research increasingly did not apply to many programs calling themselves "multidisciplinary," because the positive outcomes in the literature reflected multidisciplinary pain programs in academic medical centers, where quality of care (not profit) was the objective. Erosion in quality and patient outcomes in many multidisciplinary pain programs led to declining reimbursement, the closing of effective academic multidisciplinary pain programs, and conversion of others to interventional pain medicine centers. Fueling this trend were changes in reimbursement and health insurance practices and financial incentives in anesthesiology residency programs, which also began using interventional pain medicine procedures as a primary measure for pain medicine competence [53; 405].

THE RISE OF INTERVENTIONAL PAIN MEDICINE

Against the backdrop of preferential reimbursement for procedure-based patient care in the current healthcare system, a small but influential subgroup has been remaking the care of patients with spinal pain. The American Society of Interventional Pain Physicians (ASIPP) is the largest and most influential interventional pain medicine professional organization. Aggressive interventional pain medicine advocacy by the ASIPP has fueled guideline conflict with the American Pain Society (APS), which some see as a battle by proxy between interventional and medical pain practitioners. Following publication of guidelines by the APS that concluded interventional pain medicine therapies were not recommended for nonspecific chronic LBP, the ASIPP has refuted the APS's conclusions and underlying evidence, essentially challenging the tenets of evidence-based medicine, comparative effectiveness research, and guideline development [124; 406; 407; 408; 409]. All back pain clinical practice guidelines lacking key contribution by interventional pain medicine physicians have been declared invalid by the ASIPP [410]. (Note: The APS voted to file for Chapter 7 bankruptcy dissolution in 2019, partially due to the national public attention of opioid overprescribing and lawsuits against pharmaceutical companies, leading to withdrawal of financial support to such societies [411].)

The growth of interventional pain medicine has fundamentally altered the nature of medical care for patients with chronic LBP by shifting the orientation from a patient-centered to a modality-centered model. The premise of interventional pain medicine is that targeted peripheral tissue intervention alleviates LBP and broadly improves patient mood, physical function, and quality of life. Maladaptive pain behaviors and psychosocial dysfunction associated with chronic pain are largely unaddressed. Patients may be referred to an allied pain therapist, but benefits from combining therapies may be undermined by lack of coordinated and integrated pain care. Peripheral target identification relies on imaging findings, despite the lack of correlation between imaging results and pain and the discouragement of imaging in most patients with LBP [53; 412; 413].

As discussed, research indicates that psychosocial factors largely influence patient outcomes across the spectrum of LBP interventions. The highly variable outcomes of interventional pain medicine and the inability of imaging and physical findings to predict nerve blockade outcomes for chronic LBP suggest benefit from using psychologic predictors of interventional pain medicine outcome [53].

Maladaptive pain beliefs may be encouraged by the interventional pain medicine approach. For patients with unrelenting LBP, interventional pain medicine may seem to be the only means for achieving cure, leading patients to believe that return to more normal function requires dramatic pain reduction and relieving them of responsibility for their own pain management. Desperation for pain relief, and unrealistic expectations of interventional pain medicine, can trigger dysfunctional pain behaviors and a cycle of unneeded diagnostic testing, repeated ineffective interventional pain medicine, doctor shopping, delay or avoidance of pain therapy emphasizing functional improvement, risk for iatrogenic complications, and eventual disability and hopelessness.

Any modality that views chronic LBP in strictly physiologic terms deviates from modern understanding of pain pathophysiology and the principles of effective pain management [53; 414; 415]. An effective pain management plan acknowledges that perceived belief of one's ability to control pain is associated with less severe pain and higher levels of functional activity. Self-efficacy is the conviction that one can perform a specific task or induce a desired outcome and is strongly associated with reduced pain, disability, and depression. Self-efficacy and confidence in one's ability to control pain can be attained with psychologic interventions in a multidisciplinary context [53].

It is important to remember that some patients with chronic LBP clearly obtain meaningful and prolonged pain relief from interventional pain medicine, and some techniques seem uniquely effective in specific severe, chronic conditions. This indicates the best interests of pain medicine are served by interventional pain medicine as a partner in the family of pain therapies [53].

FINANCIAL AND MONETARY INFLUENCES

The quality of pain treatment is adversely impacted when patient-centered care is superseded by conflicting financial interests or lack of reimbursement for needed care. Numerous technologies have been developed for minimally invasive intervention in LBP, only to be later found as inferior to existing therapies [13; 416].

Full discussion of funding and reimbursement for LBP care is beyond the scope of this course. However, inadequate pain care is facilitated by a reimbursement system structured to favor procedures over assessment, problem-solving, and patient support related to psychosocial issues. This reimbursement system has contributed to interventional pain medicine proliferation over the past 20 years [5]. Along with rewarding procedure-based care, there is a corresponding disincentive, through lack of reimbursement, for taking the time to listen and understand the social and cognitive concerns of patients [417].

HEALTHCARE PROVIDER EDUCATION

The high prevalence of patients with LBP dictates that primary care clinicians provide the majority of care. According to the Institute of Medicine, provider education deficits remain the primary contributor to inadequate pain treatment in the United States [8]. The hours for teaching cannot be increased, and replacement of any existing curricular content with pain education is unlikely [5]. Similar gaps in knowledge regarding chronic pain have been noted in nurses, occupational therapists, and physical therapists [418; 419; 420]. Improvements in knowledge and practices regarding chronic pain management would directly impact patient outcomes and appropriate prescribing practices.

PATIENT SATISFACTION RATINGS

Patient satisfaction is an essential aspect of clinical care, and patient satisfaction surveys are increasingly used as a benchmark of quality of care; however, their use can have unintended consequences, such as the promotion of opioid prescribing. Clinical practice guidelines suggest taking necessary time to inquire about psychosocial concerns and to discuss the range of more appropriate alternative approaches when patients request opioids [421]. Such encounters can be challenging and time-consuming. Patients may lack interest in non-opioid alternatives and may be dissatisfied if their requests are not met. Fulfilling patient expectations usually results in a more satisfied patient, while nonfulfillment correlates with dissatisfaction [422].

Compensation may partially depend on the quality of services provided, which is increasingly measured by achieving patient satisfaction targets. Patients may become frustrated or angry when they do not receive the treatment they want and confuse getting what they want with good medical care [422; 423]. While patient satisfaction is important, it should not be sought at the expense of quality of care.

COMMUNICATION WITH NON-ENGLISH-PROFICIENT PATIENTS

Pain is a subjective experience, and strong patient-clinician communication is a cornerstone of effective pain management. Communicating effectively is more challenging when the patient's primary language differs from that of the practitioner. According to the U.S. Census Bureau, more than 66 million Americans speak a language other than English in the home, with approximately 25.3 million of them (8.2% of the population) speaking English less than "very well" [424]. It has been suggested that when patients are first evaluated, they should be asked

what language is spoken at home and if they speak English "very well" [425]. In addition, patients should also be asked what language they prefer for their medical care information, as some patients prefer their native language even though they have said they can understand and discuss symptoms in English [425]. Many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care and that the use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care [426; 427].

"Ad hoc" interpreters (untrained staff members, family members, friends) are often used instead of professional interpreters for a variety of reasons, including convenience and cost. However, the reliability and specificity of information obtained through ad hoc interpreters is less than with professional interpreters [319]. In addition, individuals with limited English language skills have indicated a preference for professional interpreters rather than family members. A systematic review of the literature has shown that the use of professional interpreters facilitates a broader understanding and leads to better clinical care than the use of ad hoc interpreters [427].

CONCLUSION

Back pain in general, and LBP in particular, is highly prevalent and is associated with substantial economic expenditures (mainly health care) and losses (e.g., absenteeism, lost productivity). It can incur serious and prolonged patient suffering, diminished quality of life, and disability. LBP is the chronic pain syndrome responsible for the greatest clinical, social, economic, and public health burden in the United States [6; 7]. By completing this course, healthcare professionals should have a greater understanding of the pathophysiology and differential diagnosis of LBP conditions, the distinction between acute and chronic back pain and its management implications, and knowledge of appropriate treatment options that are guided by advances in pain neuroscience.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

Works Cited

1. Scott NA, Moga C, Harstall C. Managing low back pain in the primary care setting: the know-do gap. *Pain Res Manag*. 2010;15(6):392-400.
2. Buchbinder R, Staples M, Jolley D. Doctors with a special interest in back pain have poorer knowledge about how to treat back pain. *Spine (Phila Pa 1976)*. 2009;34(11):1218-26.
3. Martinsons J. Guidelines target interventional therapies and surgery. *Am Pain Soc Bull*. 2008;18:3-6.
4. Mailis A, Taenzer P. Evidence-based guideline for neuropathic pain interventional treatments: spinal cord stimulation, intravenous infusions, epidural injections and nerve blocks. *Pain Res Manage*. 2012;17(3):150-158.
5. Loeser JD. Five crises in pain management. *Pain Clin Updates*. 2012;20(1):1-4.
6. Manchikanti L, Singh V, Pampati V, Smith HS, Hirsch JA. Analysis of growth of interventional techniques in managing chronic pain in the Medicare population: a 10-year evaluation from 1997 to 2006. *Pain Physician*. 2009;12(1):9-34.
7. Manchikanti L, Soin A, Mann D, et al. Reversal of growth of utilization of interventional techniques in managing chronic pain in Medicare population post-Affordable Care Act. *Pain Physician*. 2017;20(7):551-567.
8. Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: The National Academies Press; 2011.
9. National Center for Health Statistics. Summary Health Statistics: National Health Interview Survey, 2018: Table A-5a. Available at https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_A-5.pdf. Last accessed June 14, 2022.
10. Ibrahimi DM, Beaty NB, Crandall KM, et al. A review of lumbar spondylolisthesis. *Eur Musculoskelet Rev*. 2011;6:110-113.
11. Sinnott P. Administrative delays and chronic disability in patients with acute occupational low back injury. *J Occup Environ Med*. 2009;51(6):690-699.
12. U.S. Department of Veterans Affairs, U.S. Department of Defense. 2017 VA/DoD Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain. Available at https://www.healthquality.va.gov/guidelines/Pain/lbp/VADoDLBPCPG092917.pdf. Last accessed June 14, 2022.
13. Friedly J, Standaert C, Chan L. Epidemiology of spine care: the back pain dilemma. *Phys Med Rehabil Clin N Am*. 2010;21(4):659-677.
14. Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey: 2018 National Summary Tables. Available at https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2018-namcs-web-tables-508.pdf. Last accessed June 14, 2022.
15. Hoy D, March L, Brooks P, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014;73(6):968-974.
16. Centers for Disease Control and Prevention. Prevalence and most common causes of disability among adults—United States, 2005. *MMWR*. 2009;58(16):421-426.
17. Dieleman JL, Baral R, Birger M, et al. US spending on personal health care and public health, 1996–2013. *JAMA*. 2016;316(24):2627-2646.
18. Iannuccilli JD, Prince EA, Soares GM. Interventional spine procedures for management of chronic low back pain: a primer. *Semin Intervent Radiol*. 2013;30(3):307-317.
19. Linton SJ, Maher CG, Van Zundert J. Low back pain: basic mechanisms, treatment, and management. In: Tracey I (ed). *Pain 2012: Refresher Courses, 14th World Congress on Pain*. Seattle, WA: IASP Press; 2012.
20. Freburger JK, Holmes GM, Agans RP, et al. The rising prevalence of chronic low back pain. *Arch Intern Med*. 2009;169(3):251-258.
21. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J*. 2008;8(1):8-20.
22. Mafi JN, McCarthy EP, Davis RB, Landon BE. Worsening trends in the management and treatment of back pain. *JAMA Intern Med*. 2013;173(17):1573-1581.
23. Manchikanti L, Benyamin RM, Hansen H, Swicegood JR, Hirsch JA. Reversal of epidural cuts in 2015 physician payment schedule: two steps forward one step back. *Pain Physician*. 2014;17(5):E565-E573.
24. Manchikanti L, Abdi S, Atluri S, et al. An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. *Pain Physician*. 2013;16(2 Suppl):S49-S283.
25. Rathmell JP. A 50-year-old man with chronic low back pain. *JAMA*. 2008;299(17):2066-2077.
26. Behrend C, Prasarn M, Coyne E, Horodyski M, Wright J, Rechtine GR. Smoking cessation related to improved patient-reported pain scores following spinal care. *J Bone Joint Surg Am*. 2012;94(23):2161-2166.
27. Vincent HK, Adams MC, Vincent KR, Hurley RW. Musculoskeletal pain, fear avoidance behaviors, and functional decline in obesity: potential interventions to manage pain and maintain function. *Reg Anesth Pain Med*. 2013;38(6):481-491.

28. Shiri R, Lallukka T, Karppinen J, Viikari-Juntura E. Obesity as a risk factor for sciatica: a meta-analysis. *Am J Epidemiol*. 2014;179(8):929-937.
29. Heuch I, Heuch I, Hagen K, Zwart JA. Body mass index as a risk factor for developing chronic low back pain: a follow-up in the Nord-Trøndelag Health Study. *Spine (Phila Pa 1976)*. 2013;38(2):133-139.
30. Rihn JA, Kurd M, Hilibrand AS, et al. The influence of obesity on the outcome of treatment of lumbar disc herniation: analysis of the Spine Patient Outcomes Research Trial (SPORT). *J Bone Joint Surg Am*. 2013;95(1):1-8.
31. Karppinen J, Kurunlahti M, Taimela S, Haapea M, Vanharanta H, Tervonen O. Determinants of lumbar artery occlusion among patients with sciatica: a three-year follow-up with magnetic resonance angiography. *Eur Spine J*. 2005;14(7):664-670.
32. Meredith DS, Huang RC, Nguyen J, Lyman S. Obesity increases the risk of recurrent herniated nucleus pulposus after lumbar microdiscectomy. *Spine J*. 2010;10(7):575-580.
33. Zhou Y. Principles of pain management. In: Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC (eds). *Bradley's Neurology in Clinical Practice*. 6th ed. Philadelphia, PA: Saunders; 2012: 783-801.
34. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc*. 2003;78(12):1463-1470.
35. Turner MK, Hooten WM, Schmidt JE, Kerkvliet JL, Townsend CO, Bruce BK. Prevalence and clinical correlates of vitamin D inadequacy among patients with chronic pain. *Pain Med*. 2008;9(8):979-984.
36. Rodriguez WJ, Gromelski J. Vitamin D status and spine surgery outcomes. *ISRN Orthopedics*. 2013;471695:1-12.
37. Knutsen KV, Brekke M, Gjelstad S, Lagerlov P. Vitamin D status in patients with musculoskeletal pain, fatigue and headache: a cross-sectional descriptive study in a multi-ethnic general practice in Norway. *Scand J Prim Health Care*. 2010;28(3):166-171.
38. Kim TH, Lee BH, Lee HM, et al. Prevalence of vitamin D deficiency in patients with lumbar spinal stenosis and its relationship with pain. *Pain Physician*. 2013;16(2):165-176.
39. Stevans JM, Saper RB. Chronic low back pain. In: Rakel D (ed). *Integrative Medicine*. 3rd ed. Madison, WI: Elsevier Inc.; 2012: 260-269.
40. Chou R, Huffman LH. 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. *Ann Intern Med*. 2007;147(7):505-514.
41. University of Michigan Health System. Guidelines for Clinical Care: Acute Low Back Pain. Available at http://www.med.umich.edu/1info/FHP/practiceguides/back/back.pdf. Last accessed June 14, 2022.
42. Airaksinen O, Brox JI, Cedraschi C, et al. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J*. 2006;15(Suppl 1):S192-S300.
43. Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med*. 2007;30(1):77-94.
44. Salzman CD, Fusi S. Emotion, cognition, and mental state representation in amygdala and prefrontal cortex. *Annu Rev Neurosci*. 2010;33:173-202.
45. Martin AL, Halket E, Asmundson GJ, Flora DB, Katz J. Posttraumatic stress symptoms and the diathesis-stress model of chronic pain and disability in patients undergoing major surgery. *Clin J Pain*. 2010;26(6):518-527.
46. Campbell P, Foster NE, Thomas E, Dunn KM. Prognostic indicators of low back pain in primary care: five-year prospective study. *J Pain*. 2013;14(8):873-883.
47. Fuss I, Angst F, Lehmann S, Michel BA, Aeschlimann A. Prognostic factors for pain relief and functional improvement in chronic pain after inpatient rehabilitation. *Clin J Pain*. 2014;30(4):279-285.
48. Verbunt JA, Seelen HA, Vlaeyen JW, et al. Disuse and deconditioning in chronic low back pain: concepts and hypotheses on contributing mechanisms. *Eur J Pain*. 2003;7(1):9-21.
49. Bränström H, Fahlström M. Kinesiophobia in patients with chronic musculoskeletal pain: differences between men and women. *J Rehabil Med*. 2008;40(5):375-380.
50. Lin IV, O'Sullivan PB, Coffin JA, Mak DB, Toussaint S, Straker LM. Disabling chronic low back pain as an iatrogenic disorder: a qualitative study in Aboriginal Australians. *BMJ Open*. 2013;3(4):e002654.
51. Zusman M. Belief reinforcement: one reason why costs for low back pain have not decreased. *J Multidiscip Healthc*. 2013;6:197-204.
52. Peppin JF. The use of opioids in chronic pain: complexity and practice. *Pain Medicine News*. 2012;(Suppl):61-67.
53. Roth RS, Geisser ME, Williams DA. Interventional pain medicine: retreat from the biopsychosocial model of pain. *Transl Behav Med*. 2012;2(1):106-116.
54. Bagnall D. Failed back surgery syndrome. In: Micheo W (ed). *Musculoskeletal, Sports, and Occupational Medicine*. New York, NY: Demos Pub; 2011: 25-27.

55. Micheo WF, Sepúlveda FL, Amill R. Post-Laminectomy Pain. Available at https://now.aapmr.org/post-laminectomy-pain. Last accessed June 14, 2022.
56. Andersson GB. Epidemiological features of chronic low-back pain. *Lancet*. 1999;354(9178):581-585.
57. Itz CJ, Geurts JW, van Kleef M, Nelemans P. Clinical course of non-specific low back pain: a systematic review of prospective cohort studies set in primary care. *Eur J Pain*. 2013;17(1):5-15.
58. Shin J-S, Ha I-H, Lee J, et al. Effects of motion style acupuncture treatment in acute low back pain patients with severe disability: a multicenter, randomized, controlled, comparative effectiveness trial. *Pain*. 2013;154(7):1030-1037.
59. Walker BF, Muller R, Grant WD. Low back pain in Australian adults: health provider utilization and care seeking. *J Manipulative Physiol Ther.* 2004;27(5):327-335.
60. Weiner SS, Nordin M. Prevention and management of chronic back pain. *Best Pract Res Clin Rheumatol*. 2010;24(2):267-279.
61. Buckenmaier CC, Gallagher RM, et al. War on pain: new strategies in pain management for military personnel and veterans. *Fed Pract*. 2011;28(Suppl 2):1-16.
62. Lumley MA, Cohen JL, Borszcz GS, et al. Pain and emotion: a biopsychosocial review of recent research. *J Clin Psychol.* 2011;67(9):942-968.
63. Ebrahimi-Nejad G, Ebrahimi-Nejad A, Bahrampour A, Kohan S. Comparisons of emotion status and pain perception in neurosurgical patients before and after surgery. *J Med Sci Res*. 2007;1(1):51-57.
64. Melzack R. Evolution of the neuromatrix theory of pain. The Prithvi Raj lecture: presented at the Third World Congress of World Institute of Barcelona, 2004. *Pain Pract.* 2005;5(2):85-94.
65. Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. *Lancet Neurol.* 2013;12(11):1084-1095.
66. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu Rev Neurosci*. 2009;32:1-32.
67. Moseley GL. Reconceptualising pain according to modern pain science. *Phys Ther Rev*. 2007;12(3):169-178.
68. Slater D, Kunnathil S, McBride J, Koppala R. Pharmacology of nonsteroidal antiinflammatory drugs and opioids. *Semin Intervent Radiol*. 2010;27(4):400-411.
69. Basbaum AI, Bautista DM, Scherrer G. Julius D. Cellular and molecular mechanisms of pain. *Cell.* 2009;139(2):267-284.
70. Patapoutian A, Tate S, Woolf CJ. Transient receptor potential channels: targeting pain at the source. *Nat Rev Drug Discov*. 2009;8(1):55-68.
71. Woolf CJ, Ma Q. Nociceptors: noxious stimulus detectors. *Neuron*. 2007;55(3):353-64.
72. Schafers M, Sorkin L. Effect of cytokines on neuronal excitability. *Neurosci Lett*. 2008;437(3):188-193.
73. White FA, Wilson NM. Chemokines as pain mediators and modulators. *Curr Opin Anaesthesiol.* 2008;21(5):580-585.
74. Stein C, Clark JD, Oh U, et al. Peripheral mechanisms of pain and analgesia. *Brain Res Rev*. 2009;60(1):90-113.
75. Tsao H, Galea MP, Hodges PW. Driving plasticity in the motor cortex in recurrent low back pain. *Eur J Pain*. 2010;14(8):832-839.
76. Cummins TR, Sheets PL, Waxman SG. The roles of sodium channels in nociception: implications for mechanisms of pain. *Pain*. 2007;131(3):243-257.
77. Sandkuhler J. Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev*. 2009;89(2):707-758.
78. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science*. 2000;288(5472):1765-1769.
79. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron*. 2007;55(3):377-391.
80. Tracey I. Imaging pain. *Br J Anaesth*. 2008;101(1):32-39.
81. Suzuki R, Rygh LJ, Dickenson AH. Bad news from the brain: descending 5-HT pathways that control spinal pain processing. *Trends Pharmacol Sci.* 2004;25(12):613-617.
82. Millan MJ. Descending control of pain. *Prog Neurobiol.* 2002;66(6):355-474.
83. Borsook D, Becerra L, Hargreaves R. Biomarkers for chronic pain and analgesia. Part 1: the need, reality, challenges, and solutions. *Discov Med*. 2011;11(58):197-207.
84. Apkarian AV. The brain in chronic pain: clinical implications. *Pain Manag*. 2011;1(6):577-586.
85. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3 Suppl):S2-S15.
86. Roussel NA, Nijs J, Meeus M, et al. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clin J Pain*. 2013;29(7):625-638.
87. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med*. 2004;140(6):441-451.

88. Henry DE, Chiodo AE, Yang W. Central nervous system reorganization in a variety of chronic pain states: a review. *PMR*. 2011;3(12):1116-1125.
89. Lee YC, Nassikas NJ, Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arthritis Res Ther*. 2011;13(2):211.
90. Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert Rev Neurother*. 2012;12(5):577-585.
91. Kosharskyy B, Almonte W, Shaparin N, Pappagallo M, Smith H. Intravenous infusions in chronic pain management. *Pain Physician*. 2013;16(3):231-249.
92. Bleakman D, Alt A, Nisenbaum ES. Glutamate receptors and pain. *Semin Cell Dev Biol*. 2006;17(5):592-604.
93. Childers WE Jr, Baudy RB. *N*-methyl-D-aspartate antagonists and neuropathic pain: the search for relief. *J Med Chem*. 2007;50(11):2557-2562.
94. Chizh BA, Headley PM. NMDA antagonists and neuropathic pain: multiple drug targets and multiple uses. *Curr Pharm Des*. 2005;11(23):2977-2994.
95. Voscopoulos C, Lema M. When does acute pain become chronic? *Br J Anaesth*. 2010;105(S1):i69-i85.
96. Seifert F, Maihofner C. Functional and structural imaging of pain-induced neuroplasticity. *Curr Opin Anaesthesiol*. 2011;24(5):515-523.
97. Flor H, Nikolajsen L, Jensen TS. Phantom limb pain: a case of maladaptive CNS plasticity? *Nat Rev Neurosci*. 2006;7(11):873-881.
98. Nijs J, Malfliet A, Ickmans K, Baert I, Meeus M. Treatment of central sensitization in patients with "unexplained" chronic pain: an update. *Expert Opin Pharmacother.* 2014;15(12):1-13.
99. Nijs J, Meeus M, Cagnie B, et al. A modern neuroscience approach to chronic spinal pain: combining pain neuroscience education with cognition-targeted motor control training. *Phys Ther*. 2014;94(5):730-738.
100. Gorji SM, Samakosh HMN, Watt P, Marchetti PH, Oliveira R. Pain neuroscience education and motor control exercises versus core stability exercises on pain, disability, and balance in women with chronic low back pain. *Int J Environ Res Public Health*. 2022;19(5):2694.
101. Malfliet A, Kregel J, Coppieters I, et al. Effect of pain neuroscience education combined with cognition-targeted motor control training on chronic spinal pain: a randomized clinical trial. *JAMA Neurol*. 2018;75(7):808-817.
102. Yang CM, Chen TS, Wu ST, et al. Mechanistic-based treatment for common neuropathic pain and the treatment dilemma of the elderly. *J Neurol Epidemiol*. 2013;1:3-14.
103. Omoigui S. The biochemical origin of pain—proposing a new law of pain: the origin of all pain is inflammation and the inflammatory response. Part 1 of 3: a unifying law of pain. *Med Hypotheses*. 2007;69(1):70-82.
104. Vachon-Presseau E, Martel M-O, Mathieu R, et al. Acute stress contributes to individual differences in pain and pain-related brain activity in healthy and chronic pain patients. *J Neurosci*. 2013;33(16):6826-6833.
105. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. *Prog Neurobiol*. 2009;87(2):81-97.
106. Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. *Neuron*. 2010;66(1):149-160.
107. Baliki MN, Petre B, Torbey S, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci*. 2012;15(8):1117-1119.
108. Hashmi JA, Baliki MN, Huang L, et al. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain*. 2013;136(Pt 9):2751-2768.
109. Attal N, Masselin-Dubois A, Martinez V, et al. Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort. *Brain*. 2014;137(Pt 3):904-917.
110. Huang CC, Lee LH, Lin WS, Hsiao TH, Chen IC, Lin CH. The association between bodily pain and cognitive impairment in community-dwelling older adults. *J Pers Med*. 2022;12(3):350.
111. Apkarian AV, Baliki MN, Farmer MA. Predicting transition to chronic pain. *Curr Opin Neurol*. 2013;26(4):360-367.
112. Mutso AA, Petre B, Huang L, et al. Reorganization of hippocampal functional connectivity with transition to chronic back pain. *J Neurophysiol*. 2014;111(5):1065-1076.
113. Davis KD, Moayedi M. Central mechanisms of pain revealed through functional and structural MRI. *J Neuroimmune Pharmacol*. 2013;8(3):518-534.
114. Seminowicz DA, Davis KD. Pain enhances functional connectivity of a brain network evoked by performance of a cognitive task. *J Neurophysiol*. 2007;97(5):3651-3659.
115. Seminowicz DA, Wideman TH, Naso L, et al. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *J Neurosci*. 2011;31(20):7540-7550.

116. Norbury TA, MacGregor AJ, Urwin J, Spector TD, McMahon SB. Heritability of responses to painful stimuli in women: a classical twin study. *Brain*. 2007;130(Pt 11):3041-3049.

117. Kastrati G, Rosén J, Thompson WH, et al. Genetic influence on nociceptive processing in the human brain – a twin study. *Cereb Cortex*. 2022;32(2):266-274.

118. Jacobsen LM, Schistad EI, Storesund A, et al. The COMT rs4680 Met allele contributes to long-lasting low back pain, sciatica and disability after lumbar disc herniation. *Eur J Pain*. 2012;16(7):1064-1069.

119. Horjales-Araujo E, Demontis D, Lund EK, et al. Polymorphism in serotonin receptor 3B is associated with pain catastrophizing. *PLoS ONE*. 2013;8(11):e78889.

120. Horjales-Araujo E, Demontis D, Lund EK, et al. Emotional modulation of muscle pain is associated with polymorphisms in the serotonin transporter gene. *Pain*. 2013;154(8):1469-1476.

121. Laplante B, DePalma MJ. Spine osteoarthritis. *PMR*. 2011;4(5 Suppl):S28-S36.

122. Kalichman L, Hunter DJ. The genetics of intervertebral disc degeneration: associated genes. *Joint Bone Spine*. 2008;75(4):388-396.

123. Annaswamy TM, Taylor C. Lumbar Disc Disorders. Available at https://now.aapmr.org/lumbar-disc-disorders. Last accessed June 14, 2022.

124. Chou R, Atlas S, Stanos S, Rosenquist R. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. *Spine (Phila Pa 1976)*. 2009;34(10):1078-1093.

125. Rhee J, Schaufele M, Abdu W. Radiculopathy and the herniated lumbar disk: controversies regarding pathophysiology and management. *Instr Course Lect*. 2007;56:287-299.

126. Shelerud R. Lumbar Radiculopathy. Available at https://now.aapmr.org/lumbar-radiculopathy. Last accessed June 14, 2022.

127. Nance PW Lumbar Stenosis. Available at https://now.aapmr.org/lumbar-stenosis. Last accessed June 14, 2022.

128. Furman MB, Liu J, Patel SI. Lumbar Spondylolisthesis. Available at https://now.aapmr.org/lumbar-spondylolisthesis. Last accessed June 14, 2022.

129. Nagpal A, Swearingen A. Lumbar Spondylosis without Myelopathy. Available at https://now.aapmr.org/lumbar-spondylosis-without-myelopathy. Last accessed June 14, 2022.

130. Giamberardino MA, Affaitati G, Fabrizio A, Costantini R. Myofascial pain syndrome and their evaluation. *Best Pract Res Clin Rheumatol*. 2011;25(2):185-198.

131. Nance PW, Adcock EM. Facet Mediated Pain. Available at https://now.aapmr.org/facet-mediated-pain. Last accessed June 14, 2022.

132. Malenga GA, Cruz EJ. Myofascial low back pain: a review. *Phys Med Rehabil Clin N Am*. 2010;21(4):711-724.

133. Tough EA, White AR, Richards S, Campbell J. Variability of criteria used to diagnose myofascial trigger point pain syndrome: evidence from a review of the literature. *Clin J Pain*. 2007;23(3):278-286.

134. Yap EC. Myofascial pain: an overview. *Ann Acad Med Singapore*. 2007;36(1):43-48.

135. Chan CW, Peng P. Failed back pain surgery syndrome. *Pain Med*. 2011;12(4):577-606.

136. Waguespack A, Schofferman J, Slosar P, Reynolds J. Etiology of long-term failures of lumbar spine surgery. *Pain Med*. 2002;(1):18-22.

137. Orhurhu VJ, Chu R, Gill J. *Failed Back Surgery Syndrome*. Treasure Island (FL): StatPearls Publishing; 2022.

138. Goertz M, Thorson D, Bonsell J, et al. Adult Acute and Subacute Low Back Pain. Available at https://www.icsi.org/guideline/low-back-pain. Last accessed June 14, 2022.

139. Downie A, Williams CM, Henschke N, et al. Red flags to screen for malignancy and fracture in patients with low back pain: systematic review. *BMJ*. 2013;347:f7095.

140. Casazza BA. Diagnosis and treatment of acute low back pain. *Am Fam Physician*. 2012;85(4):343-350.

141. Henschke N, Maher CG, Refshauge KM, et al. Prevalence of and screening for serious spinal pathology in patients presenting to primary care settings with acute low back pain. *Arthritis Rheum*. 2009;60(10):3072-3080.

142. Kouka N, Stein JD. Low Back Pain: Controversies and Efficacy of Clinical Practice Guidelines. Available at https://prezi.com/2vykeq_ohcci/low-back-pain-controversies-and-efficacy-of-clinical-practice-guidelines. Last accessed June 14, 2022.

143. Hall H, Alleyne J, Rampersaud YR. Making sense of low back pain. *J Curr Clin Care*. 2013;11:12-23.

144. O'Connor FG. Back Pain. Paper presented at: AAFP Scientific Assembly. September 14–17, 2011; Orlando, FL.

145. Webster BS, Choi Y, Bauer AZ, Cifuentes M, Pransky G. The cascade of medical services and associated longitudinal costs due to nonadherent magnetic resonance imaging for low back pain. *Spine (Phila Pa 1976)*. 2014;39(17):1433-1440.

146. Greenberg JO, Schnell RG. Magnetic resonance imaging of the lumbar spine in asymptomatic adults. *J Neuroimaging*. 1991;1(1): 2-7.

147. Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects: a prospective investigation. *J Bone Joint Surg Am.* 1990;72(3):403-408.

148. Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. *N Engl J Med.* 1994;331:69-73.

149. Boos N, Rieder R, Schade V, Spratt KF. Semmer N, Aebi M. The diagnostic accuracy of magnetic resonance imaging, work perception, and psychosocial factors in identifying symptomatic disk herniations. *Spine (Phila Pa 1976).* 1995;20(24):2613-2625.

150. Weishaupt D, Zanetti M, Hodler J, Boos N. MR imaging of the lumbar spine: prevalence of intervertebral disk extrusion and sequestration, nerve root compression, end plate abnormalities, and osteoarthritis of the facet joints in asymptomatic volunteers. *Radiology.* 1998;209(3):661-666.

151. Wood KB, Garvey TA, Gundry C, Heithoff KB. Magnetic resonance imaging of the thoracic spine: evaluation of asymptomatic individuals. *J Bone Joint Surg Am.* 1995;77(11):1631-1638.

152. Borenstein DG, O'Mara JW Jr, Boden SD, et al. The value of magnetic resonance imaging of the lumbar spine to predict low-back pain in asymptomatic subjects: a seven-year follow-up study. *J Bone Joint Surg Am.* 2001;83A(9):1306-1311.

153. Masui T, Yukawa Y, Nakamura S, et al. Natural history of patients with lumbar disc herniation observed by magnetic resonance imaging for minimum 7 years. *J Spinal Disord Tech.* 2005;18(2):121-126.

154. Lee J, Gupta S, Price C, Baranowski AP. Low back and radicular pain: a pathway for care developed by the British Pain Society. *Br J Anaesth.* 2013;111(1):112-120.

155. Smart KM, Blake C, Staines A, Thacker M, Doody C. Mechanisms-based classifications of musculoskeletal pain: part 1 of 3: symptoms and signs of central sensitisation in patients with low back (+/- leg) pain. *Man Ther.* 2012;17(4):336-344.

156. Smart KM, Blake C, Staines A, Doody C. Mechanisms-based classifications of musculoskeletal pain: part 2 of 3: symptoms and signs of peripheral neuropathic pain in patients with low back (+/- leg) pain. *Man Ther.* 2012;17(4):345-351.

157. Smart KM, Blake C, Staines A, Doody C. Mechanisms-based classifications of musculoskeletal pain: part 3 of 3: symptoms and signs of nociceptive pain in patients with low back (+/- leg) pain. *Man Ther.* 2012;17(4):352-357.

158. Vining R, Potocki E, Seidman M, Morgenthal AP. An evidence-based diagnostic classification system for low back pain. *J Can Chiropr Assoc.* 2013;57(3):189-204.

159. Petersen T, Laslett M, Juhl C. Clinical classification in low back pain: best-evidence diagnostic rules based on systematic reviews. *BMC Musculoskelet Disord.* 2017;18(1):188.

160. Freynhagen R, Baron R. The evaluation of neuropathic components in low back pain. *Curr Pain Headache Rep.* 2009;13(3):185-190.

161. Forster M, Mahn F, Gockel U, et al. Axial low back pain: one painful area, many perceptions and mechanisms. *PLoS ONE.* 2013;8(7):e68273.

162. Sowdena G, Hill JC, Konstantinou K, et al. Targeted treatment in primary care for low back pain: the treatment system and clinical training programmes used in the IMPaCT Back study (ISRCTN 55174281). *Fam Pract.* 2012;29(1):50-62.

163. Robinson HS, Dagfinrud H. Reliability and screening ability of the StarT Back screening tool in patients with low back pain in physiotherapy practice, a cohort study. *BMC Musculoskelet Disord.* 2017;18:232.

164. International Spine and Pain Institute. Oswestry Low Back Disability Questionnaire. Available at https://aaos.org/globalassets/quality-and-practice-resources/patient-reported-outcome-measures/spine/oswestry-2.pdf. Last accessed June 14, 2022.

165. Kreiner DS, Hwang SW, Easa JE, et al. An evidence-based clinical guideline for the diagnosis and treatment of lumbar disc herniation with radiculopathy. *Spine J.* 2014;14(1):180-191.

166. North American Spine Society. *Lumbar Epidural Injections: Defining Appropriate Coverage Positions.* Burr Ridge, IL: North American Spine Society; 2014.

167. National Institute for Health and Care Excellence. Low Back Pain and Sciatica in Over 16s: Assessment and Management. Available at https://www.nice.org.uk/guidance/NG59. Last accessed June 14, 2022.

168. Nguyen TH, Randolph DC. Nonspecific low back pain and return to work. *Am Fam Physician.* 2007;76(10):1497-1502.

169. American Society of Anesthesiologists Task Force on Chronic Pain Management, American Society of Regional Anesthesia and Pain Medicine. Practice guidelines for chronic pain management: an update report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia. *Anesthesiology.* 2010;112(4):810-833.

170. Genevay S, Atlas SJ. Lumbar spinal stenosis. *Best Pract Res Clin Rheumatol.* 2010;24(2):253-265.

171. Kim HJ, Chen HJ, Han CD, et al. The risk assessment of a fall in patients with lumbar spinal stenosis. *Spine (Phila Pa 1976).* 2011;36(9):E588-E592.

172. O'Neill BJ, Tahaei A. Myofascial Pain. Available at https://now.aapmr.org/myofascial-pain. Last accessed June 14, 2022.

173. Annaswamy TM, De Luigi A, O'Neill B, Keole N, Berbrayer D. Emerging concepts in the treatment of myofascial pain: a review of medications, modalities, and needle-based interventions. *PMR*. 2011;3(10):940-961.

174. Canadian Agency for Drugs and Technologies. Facet Joint Injection as Diagnostic and Therapeutic Tools for Pain of the Cervical and Lumbar Spine: A Review of Clinical and Cost-Effectiveness. Available at https://www.cadth.ca/media/pdf/I3003_tr_Facet_Joint_Injections_e.pdf. Last accessed June 14, 2022.

175. Iskedjian M, Einarson TR, Walker JH, Jovey R, Moulin D. *Anticonvulsants, Serotonin-Norepinephrine Reuptake Inhibitors, and Tricyclic Antidepressants in Management of Neuropathic Pain: A Meta-Analysis and Economic Evaluation*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

176. American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57(8):1331-1346.

177. Kovacs FM, Abraira V, Pena A, et al. Effect of firmness of mattress on chronic non-specific low-back pain: randomised, double-blind, controlled, multicentre trial. *Lancet*. 2003;362(9396):1599-1604.

178. Benedetti F, Amanzio M. The placebo response: how words and rituals change the patient's brain. *Patient Educ Couns*. 2011;84(3):413-419.

179. Ang DC, Chakr R, Mazzuca S, France CR, Steiner J, Stump T. Cognitive-behavioral therapy attenuates nociceptive responding in patients with fibromyalgia: a pilot study. *Arthritis Care Res*. 2010;62(5):618-623.

180. de Lange FP, Koers A, Kalkman JS, et al. Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. *Brain*. 2008;131(Pt 8):2172-2180.

181. Nijs J, Paul van Wilgen C, Van Oosterwijck J, van Ittersum M, Meeus M. How to explain central sensitization to patients with "unexplained" chronic musculoskeletal pain: practice guidelines. *Man Ther*. 2011;16(5):413-418.

182. Moseley GL. Joining forces-combining cognition-targeted motor control training with group or individual pain physiology education: a successful treatment for chronic low back pain. *J Man Manip Ther*. 2003;11(2):88-94.

183. Oliveira VC, Ferreira PH, Maher CG, Pinto RZ, Refshauge KM, Ferreira ML. Effectiveness of self-management of low back pain: systematic review with meta-analysis. *Arthritis Care Res*. 2012;64(11):1739-1748.

184. Ferreira ML, Ferreira PH, Latimer J, et al. Consumers' perceptions of the smallest worthwhile effect of interventions for non-specific low back pain. *J Clin Epidemiol*. 2012;65(3):253-261.

185. Steiger F, Wirth B, de Bruin ED, Mannion AF. Is a positive clinical outcome after exercise therapy for chronic non-specific low back pain contingent upon a corresponding improvement in the targeted aspect(s) of performance? A systematic review. *Eur Spine J*. 2012;21(4):575-598.

186. Oesch P, Kool J, Hagen KB, Bachmann S. Effectiveness of exercise on work disability in patients with non-acute non-specific low back pain: systematic review and meta-analysis of randomised controlled trials. *J Rehabil Med*. 2010;42(3):193-205.

187. Dreisinger TE. Exercise in the management of chronic back pain. *Ochsner J*. 2014;14(1):101-107.

188. Aleksiev AR. Ten-year follow-up of strengthening versus flexibility exercises with or without abdominal bracing in recurrent low back pain. *Spine (Phila Pa 1976)*. 2014;39(13):997-1003.

189. van Middelkoop M, Rubinstein SM, Kuijpers T, et al. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. *Eur Spine J*. 2011;20(1):19-39.

190. Daenen L, Varkey E, Kellmann M, Nijs J. Exercise, not to exercise, or how to exercise in patients with chronic pain? Applying science to practice. *Clin J Pain*. 2015;31(2):108-114.

191. Salzberg LD, Manusov EG. Management options for patients with chronic back pain without an etiology. *Health Serv Insights*. 2013;6:33-38.

192. Rubinstein SM, Terwee CB, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for acute low back pain: an update of the Cochrane review. *Spine (Phila Pa 1976)*. 2013;38(3):E158-E177.

193. Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain. *Cochrane Database Syst Rev*. 2011;(2):CD008112.

194. Michaleff ZA, Lin CW, Maher CG, van Tulder MW. Spinal manipulation epidemiology: systematic review of cost effectiveness studies. *J Electromyogr Kinesiol*. 2012;22(5):655-662.

195. Lin CW, Haas M, Maher CG, Machado LA, van Tulder MW. Cost-effectiveness of guideline-endorsed treatments for low back pain: a systematic review. *Eur Spine J*. 2011;20(7):1024-1038.

196. Furlan AD, Imamura M, Dryden T, Irvin E. Massage for low-back pain. *Cochrane Database Syst Rev*. 2008;(4):CD001929.

197. Furlan AD, Giraldo M, Baskwill A, Irvin E, Imamura M. Massage for low-back pain. *Cochrane Database Syst Rev*. 2015;(9):CD001929.

198. Kong LJ, Fang M, Zhan HS, et al. Chinese massage combined with herbal ointment for athletes with nonspecific low back pain: a randomized controlled trial. *Evid Based Complement Alternat Med*. 2012;2012:695726.

199. Flor H. Psychological pain interventions and neurophysiology. *Am Psychol*. 2014;69(2):188-196.
200. Newman MG. Technology in psychotherapy: an introduction. *J Clin Psychol*. 2004;60(2):141-145.
201. Brox JI, Storheim K, Grotle M, Tveito TH, Indahl A, Eriksen HR. Systematic review of back schools, brief education, and fear-avoidance training for chronic low back pain. *Spine J*. 2008;8(6):948-958.
202. van Tulder MW, Koes B, Malmivaara A. Outcome of non-invasive treatment modalities on back pain: an evidence-based review. *Eur Spine J*. 2006;15(Suppl 1):S64-S81.
203. Bantick SJ, Wise RG, Ploghaus A, Ckare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional *MRI*. *Brain*. 2002;125(Pt 2):310-319.
204. Lawrence JM, Hoeft F, Sheau KE, Mackey SC. Strategy-dependent dissociation of the neural correlates involved in pain modulation. *Anesthesiology*. 2011;115(4):844-851.
205. Wiech K, Kalisch R, Weiskopf N, Pleger B, Stephan KE, Dolan RJ. Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. *J Neurosci*. 2006;26(44):11501-11509.
206. Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: psychological and neurobiological mechanisms. *Pain*. 2013;154(4):511-514.
207. Eippert F, Bingel U, Schoell ED, et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron*. 2009;63(4):533-543.
208. Jensen KB, Kosek E, Wicksell R, et al. Cognitive behavioral therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgia. *Pain*. 2012;153(7):1495-1503.
209. Thieme K, Flor H, Turk, DC. Psychological pain treatment in fibromyalgia syndrome: efficacy of operant behavioural and cognitive behavioural treatments. *Arthritis Res Ther*. 2006;8(4):R121.
210. Thieme K, Turk DC, Flor H. Responder criteria for operant and cognitive-behavioral treatment of fibromyalgia syndrome. *Arthritis Rheum*. 2007;57(5):830-836.
211. Diers M, Yilmaz P, Rance M, et al. Treatment-related changes in brain activation in patients with fibromyalgia syndrome. *Exp Brain Res*. 2012;218(4):619-628.
212. Tauben D. Chronic pain management: measurement-based step care solutions. *IASP*. 2012;20(8):1-8.
213. Reference: Prins A, Bovin MJ, Kimerling R, et al. Primary Care PTSD Screen for DSM-5 (PC-PTSD-5). Available at https://www.ptsd.va.gov/professional/assessment/documents/pc-ptsd5-screen.pdf. Last accessed June 14, 2022.
214. Stanos S, Houle TT. Multidisciplinary and interdisciplinary management of chronic pain. *Phys Med Rehabil Clin N Am*. 2006;17(2):435-450.
215. Jeffery MM, Butler M, Stark A, Kane RL. *Multidisciplinary Pain Programs for Chronic Noncancer Pain*. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
216. Dworkin SF, Von Korff M, LeResch L. Epidemiologic studies of chronic pain: a dynamic-ecologic perspective. *Ann Behav Med*. 1992;14(1):3-11.
217. Kamper SJ, Apeldoorn AT, Chiarotto A, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. *Cochrane Database Syst Rev*. 2014;(9):CD000963.
218. Schatman ME. Interdisciplinary chronic pain management: perspectives on history, current status, and future viability. In: Fishman SM, Ballantyne J, Rathmell J (eds). *Bonica's Management of Pain*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2010: 1523-1532.
219. Meldrum ML. Brief history of multidisciplinary management of chronic pain, 1900–In: Schatman ME, Campbell A (eds). *Chronic Pain Management: Guidelines for Multidisciplinary Program Development*. New York, NY: Informa Healthcare USA; 2007: 1-13.
220. Bontoux L, Dubus V, Roquelaure Y, et al. Return to work of 87 severely impaired low back pain patients two years after a program of intensive functional rehabilitation. *Ann Phys Rehabil Med*. 2009;52(1):17-29.
221. Petit A, Roche-Leboucher G, Bontoux L, et al. Effectiveness of three treatment strategies on occupational limitations and quality of life for patients with non-specific chronic low back pain: is a multidisciplinary approach the key feature to success: study protocol for a randomized controlled trial. *BMC Musculoskelet Disord*. 2014;15:131.
222. Roche G, Ponthieux A, Parot-Shinkel E, et al. Comparison of a functional restoration program with active individual physical therapy for patients with chronic low back pain: a randomized controlled trial. *Arch Phys Med Rehabil*. 2007;88(10):1229-1235.
223. van Hooff ML, Spruit M, O'Dowd JK, et al. Predictive factors for successful clinical outcome 1 year after an intensive combined physical and psychological programme for chronic low back pain. *Eur Spine J*. 2014;23(1):102-112.
224. McGregor AH, Probyn K, Cro S, et al. Rehabilitation following surgery for lumbar spinal stenosis. *Cochrane Database Syst Rev*. 2013;12:CD009644.
225. Gatchel RJ, Mayer TG. Evidence informed management of chronic low back pain with functional restoration. *Spine J*. 2008;8(1):65-69.

226. Carragee EJ. Persistent low back pain. *N Engl J Med*. 2005;352(18):1891-1898.
227. van Tulder M, Koes B, Bombardier C. Low back pain. *Best Pract Res Clin Rheumatol*. 2002;16(5):761-775.
228. Guzman J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary rehabilitation for chronic low back pain: systematic review. *BMJ*. 2001;322(7301):1511-1516.
229. Nahin RL, Barnes PM, Stussman BJ. Expenditures on complementary health approaches: United States, 2012. *Natl Health Stat Report*. 2016;95:1-11.
230. Davis MA, Weeks WB. The concentration of out-of-pocket expenditures on complementary and alternative medicine in the United States. *Altern Ther Health Med*. 2012;18(5):36-42.
231. Tick H. Integrative pain medicine: a holistic model of care. *IASP*. 2014;22(2):1-6.
232. Thayer JF, Sternberg E. Beyond heart rate variability: vagal regulation of allostatic systems. *Ann N Y Acad Sci*. 2006;1088:361-372.
233. Langevin HM. Connective tissue: a body-wide signaling network? *Med Hypotheses*. 2006;66(6):1074-1077.
234. Langevin HM, Churchill DL, Fox JR, et al. Biomechanical response to acupuncture needling in humans. *J Appl Physiol*. 2001;91(6):2471-2478.
235. Langevin HM, Churchill DL, Wu J, et al. Evidence of connective tissue involvement in acupuncture. *FASEB J*. 2002;16(8):872-874.
236. Langevin HM, Fox JR, Koptiuch C, et al. Reduced thoracolumbar fascia shear strain in human chronic low back pain. *BMC Musculoskelet Disord*. 2011;12:203.
237. Hutchinson AJP, Ball S, Andrews JCH, Jones GG. The effectiveness of acupuncture in treating chronic non-specific low back pain: a systematic review of the literature. *J Orthop Surg Res*. 2012;7:36-42.
238. McKee MD, Kligler B, Fletcher J, et al. Outcomes of acupuncture for chronic pain in urban primary care. *J Am Board Fam Med*. 2013;26(6):692-700.
239. Chon TY, Lee MC. Acupuncture. *Mayo Clin Proc*. 2013;88(10):1141-1146.
240. Sood A, Sood R, Bauer BA, Ebbert JO. Cochrane systematic reviews in acupuncture: methodological diversity in database searching. *J Altern Complement Med*. 2005;11(4):719-722.
241. Hsu C, Sherman KJ, Eaves ER, et al. New perspectives on patient expectations of treatment outcomes: results from qualitative interviews with patients seeking complementary and alternative medicine treatments for chronic low back pain. *BMC Complement Altern Med*. 2014;14:276.
242. Centers for Medicare and Medicaid Services. CMS Proposes to Cover Acupuncture for Chronic Low Back Pain for Medicare Beneficiaries Enrolled in Approved Studies. Available at https://www.cms.gov/newsroom/press-releases/cms-proposes-cover-acupuncture-chronic-low-back-pain-medicare-beneficiaries-enrolled-approved. Last accessed June 14, 2022.
243. Centers for Medicare and Medicaid Services. Acupuncture for Chronic Low Back Pain. Available at https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=295. Last accessed June 14, 2022.
244. Ross A, Thomas S. The health benefits of yoga and exercise: a review of comparison studies. *J Altern Complement Med*. 2010;16(1):3-12.
245. Sherman KJ, Cherkin DC, Wellman RD, et al. A randomized trial comparing yoga, stretching, and a self-care book for chronic low back pain. *Arch Intern Med*. 2011;171(22):2019-2026.
246. Holtzman S, Beggs RT. Yoga for chronic low back pain: a meta-analysis of randomized controlled trials. *Pain Res Manag*. 2013;18(5):267-272.
247. Sherman KJ, Wellman RD, Cook AJ, et al. Mediators of yoga and stretching for chronic low back pain. *J Evid Based Complement Altern Med*. 2013;(2013):130818.
248. Saper RB, Boah AR, Keosaian J, Cerrada C, Weinberg J, Sherman KJ. Comparing once- versus twice-weekly yoga classes for chronic low back pain in predominantly low income minorities: a randomized dosing trial. *Evid Based Complement Alternat Med*. 2013;2013:658030.
249. Fishman LM, Saltonstall E, Genis S. Understanding and preventing yoga injuries. *Int J Yoga Ther*. 2009;19:47.
250. Cramer H, Haller H, Lauche R, Dobos G. Mindfulness-based stress reduction for low back pain: a systematic review. *BMC Complement Altern Med*. 2012;12:162.
251. Hawker GA, Milan S, Bednis K, Stanitis I. Osteoarthritis year 2010 in review: non-pharmacologic therapy. *Osteoarthritis Cartilage*. 2011;19(4):366-374.
252. Song R, Roberts BL, Leo EO, Lam P, Bae SC. A randomized study of the effects of t'ai chi on muscle strength, bone mineral density, and fear of falling in women with osteoarthritis. *J Altern Complement Med*. 2010;16(3):227-233.
253. Ebadi S, Ansari NN, Naghdi S, et al. The effect of continuous ultrasound on chronic non-specific low back pain: a single blind placebo-controlled randomized trial. *BMC Musculoskelet Disord*. 2012;13:192.

254. Nwuga VC. Ultrasound in treatment of back pain resulting from prolapsed intervertebral disc. *Arch Phys Med Rehabil*. 1983;64(2):88-89.

255. Ebadi S, Henschke N, Nakhostin Ansari N, et al. Therapeutic ultrasound for chronic low-back pain. *Cochrane Database Syst Rev*. 2014;(3):CD009169.

256. Ebadi S, Henschke N, Forogh B, et al. Therapeutic ultrasound for chronic low back pain. *Cochrane Database Syst Rev*. 2020;(7):CD009169.

257. Yousefi-Nooraie R, Schonstein E, Heidari K, et al. Low level laser therapy for nonspecific low-back pain. *Cochrane Database Syst Rev*. 2008;(2):CD005107.

258. Facci LM, Nowotny JP, Tormem F, Trevisani VF. Effects of transcutaneous electrical nerve stimulation (TENS) and interferential currents (IFC) in patients with nonspecific chronic low back pain: randomized clinical trial. *Sao Paulo Med J*. 2011;129(4):206-216.

259. Shanti BF, Tan G, Shanti IF. Adjuvant Analgesia for Management of Chronic Pain. Available at https://www.practicalpainmanagement.com/treatments/pharmacological/adjuvant-analgesia-management-chronic-pain. Last accessed June 14, 2022.

260. Jauregui JJ, Cjerian JJ, Gwam CU, et al. A meta-analysis of transcutaneous electrical nerve stimulation for chronic low back pain. *Surg Technol Int*. 2016;28:296-302.

261. Wu LC, Weng PW, Chen CH, H YY, Tsuang YH, Chiang CJ. Literature review and meta-analysis of transcutaneous electrical nerve stimulation in treating chronic back pain. *Reg Anesth Pain Med*. 2018;43(4):425-433.

262. Kulkarni AD, Smith RB. The use of microcurrent electrical therapy and cranial electrotherapy stimulation in pain control. *Clin Prac Alt Med*. 2001;2(2):99-102.

263. De Oliveira FN, Dotta L, Sasse A, Teixera MJ, Fonoff ET. Ozone therapy as a treatment for low back pain secondary to herniated disc: a systematic review and meta-analysis of randomized controlled trials. *Pain Physician*. 2012;15(2):E115-E129.

264. Costa T, Linhares D, Ribeiro da Silva M, Neves N. Ozone therapy for low back pain: a systematic review. *Acta Reumatol Port*. 2018;43(3):172-181.

265. Pappagallo M, Leslie JB, Raffa RB, et al. Evaluation of a novel topical essential oxygen oil for the treatment of pain in acute tendinopathy and sprains. *Muscles Ligaments Tendons J*. 2011;1(1):25-30.

266. Pergolizzi JV, Pappagallo M, Raffa B, et al. Preliminary observations of a novel topical oil with analgesic properties for treatment of acute and chronic pain syndromes. *Pain Pract*. 2010;10(3):201-213.

267. Staiger C. Comfrey root: from tradition to modern clinical trials. *Wien Med Wochenschr*. 2013;163(3-4):58-64.

268. Giannetti BM, Staiger C, Bulitta M, Predel HG. Efficacy and safety of a comfrey root extract ointment in the treatment of acute upper or lower back pain: results of a double-blind, randomised, placebo controlled, multicentre trial. *Br J Sports Med*. 2010;44(9):637-641.

269. Pabst H, Schaefer A, Staiger C, Junker-Samek M, Predel HG. Combination of comfrey root extract plus methyl nicotinate in patients with conditions of acute upper or low back pain: a multicentre randomised controlled trial. *Phytother Res*. 2013;27(6):811-817.

270. Sherman KJ, Cherkin DC, Ichikawa L, et al. Treatment expectations and preferences as predictors of outcome of acupuncture for chronic back pain. *Spine (Phila Pa 1976)*. 2010;35(15):1471-1477.

271. Behnen EMT. Ask the expert: which NSAIDs are most selective for COX-1 and COX-2? *Pract Pain Manag*. 2013;13(7):2-5.

272. Canadian Agency for Drugs and Technologies in Health. Non-Steroidal Anti-Inflammatory Drugs for Pain: A Review of Safety. Available at https://www.cadth.ca/sites/default/files/pdf/htis/aug-2013/RC0471%20NSAID%20safety%20final.pdf. Last accessed June 14, 2022.

273. Kuritzky L, Samraj GP. Nonsteroidal anti-inflammatory drugs in the treatment of low back pain. *J Pain Res*. 2012;5:579-590.

274. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med*. 1998;105(1B):31S-38S.

275. Straube S, Tramèr MR, Moore RA, Derry S, McQuay HJ. Mortality with upper gastrointestinal bleeding and perforation: effects of time and NSAID use. *BMC Gastroenterol*. 2009;9:41.

276. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. *Arthritis Res Ther*. 2013;15(Suppl 3):S3.

277. Jarupongprapa S, Ussavasodhi P, Katchamart W. Comparison of gastrointestinal adverse effects between cyclooxygenase-2 inhibitors and non-selective, non-steroidal anti-inflammatory drugs plus proton pump inhibitors: a systematic review and meta-analysis. *J Gastroenterol*. 2013;48(7):830-838.

278. Castellsague J, Riera-Guardia N, Calingaert B, et al. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (The SOS Project). *Drug Saf*. 2012;35(12):1127-1146.

279. Speed C, Wolfarth B. Challenges of pain masking in the management of soft tissue disorders: optimizing patient outcomes with a multi-targeted approach. *Curr Med Res Opin*. 2014;30(5):953-959.

280. Coxib and Traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769-779.

281. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network analysis. *BMJ*. 2011;342:c7086.

282. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med*. 2011;8(9):e1001098.

283. NSAIDs and serious cardiovascular disorders: especially COX-2 inhibitors and diclofenac. *Prescrire Int*. 2016;25(167):14-16.

284. Roelofs PD, Deyo RA, Koes BW, et al. Non-steroidal anti-inflammatory drugs for low back pain. *Spine (Phila Pa 1976)*. 2008;33(16):1766-1774.

285. Laguerre PJ. Alternatives and adjuncts to opioids for the treatment of chronic pain. *N C Med J*. 2013;74(3):209-214.

286. Abramson SB, Weaver AL. Current state of therapy for pain and inflammation. *Arthritis Res Ther*. 2005;7(Suppl 4):S1-S6.

287. Williams CM, Maher CG, Latimer J, et al. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. *Lancet*. 2014;384(9954):1586-1596.

288. Schilling A, Corey R, Leonard M, Eghtesad B. Acetaminophen: old drug, new warnings. *Cleve Clin J Med*. 2010;77(1):19-27.

289. Smith HS, Kara SD, Argoff CE. Management of neuropathic pain: current insights and future perspectives. *US Neurology*. 2012;8(1):57-61.

290. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med*. 2006;166(9):1021-1026.

291. Henry JA, Alexander CA, Sener EK. Relative mortality from overdose of antidepressants. *BMJ*. 1995;310(6974):221-224.

292. Andrews JS, Wu N, Chen SY, Yu X, Peng X, Novick D. Real-world treatment patterns and opioid use in chronic low back pain patients initiating duloxetine versus standard of care. *J Pain Res*. 2013;6:825-835.

293. Skljarevski V, Ossanna M, Liu-Seifert H, et al. A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain. *Eur J Neurol*. 2009;16(9):1041-1048.

294. Skljarevski V, Zhang S, Desaiah D, et al. Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. *J Pain*. 2010;11(12):1282-1290.

295. Skljarevski V, Zhang S, Chappell AS, Walker DJ, Murray I, Backonia M. Maintenance of effect of duloxetine in patients with chronic low back pain: a 41-week uncontrolled, dose-blinded study. *Pain Med*. 2010;11(5):648-657.

296. Kalso E, Aldington DJ, Moore RA. Drugs for neuropathic pain. *BMJ*. 2013;347:f7339.

297. Stillman M. Clinical approach to patients with neuropathic pain. *Cleve Clin J Med*. 2006;73(8):726-736.

298. Toth C. Pregabalin: latest safety evidence and clinical implications for the management of neuropathic pain. *Ther Adv Drug Saf*. 2014;5(1):38-56.

299. Jackson KC II, Argoff CE. Skeletal muscle relaxants. In: Benzon HT, Rathmell JP, Wu CL, Turk DC, Argoff CE (eds). *Raj's Practical Management of Pain*. 4th ed. Philadelphia, PA: Mosby Elsevier; 2008: 693-698.

300. Chou R, Huffman LH. Guideline for the Evaluation and Management of Low Back Pain. Available at https://mipropiolio.files.wordpress.com/2015/10/american-pain-society-clinical-guideline-for-the-evaluation-and-management-of-low-back-pain.pdf. Last accessed June 14, 2022.

301. Michna E, Cheng WY, Korves C, et al. Systematic literature review and meta-analysis of the efficacy and safety of prescription opioids, including abuse-deterrent formulations, in non-cancer pain management. *Pain Med*. 2014;15(1):79-92.

302. Jiang J, Pan H, Chen H, et al. Comparative efficacy of pharmacological therapies for low back pain: a Bayesian network analysis. *Front Pharmacol*. 2022;13:811962.

303. Chung JWY, Zeng Y, Wong TKS. Drug therapy for the treatment of chronic nonspecific low back pain: systematic review and meta-analysis. *Pain Physician*. 2013;16(6):E685-E704.

304. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low back pain: an update of the Cochrane review. *Spine (Phila Pa 1976)*. 2014;39(7):556-563.

305. Shaheed CA, Maher CG, Williams KA, Day R, McLachlan AJ. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis. *JAMA Intern Med*. 2016;176(7):958-968.

306. Watson CPN, Watt-Watson J, Chipman M. The long-term safety and efficacy of opioids: a survey of 84 selected patients with intractable chronic noncancer pain. *Pain Res Manage*. 2010;15(4):213-217.

307. Veiga DR, Monteiro-Soares M. Mendonça L, Sampaio R, Castro-Lopes JM, Azevedo LF. Effectiveness of opioids for chronic noncancer pain; a two-year multicenter, prospective cohort study with propensity score matching. *J Pain*. 2019;20(6):706-715.

308. Prommer E. Levorphanol: the forgotten opioid. *Support Care Cancer*. 2007;15(3):259-264

309. Atkinson TJ, Fudin J, Pandula A, Mirza M. Medication pain management in the elderly: unique and underutilized analgesic treatment options. *Clin Ther*. 2013;35(11):1669-1689.

310. Zorn KE, Fudin J. Treatment of neuropathic pain: the role of unique opioid agents. *Practical Pain Manage*. 2011;5:26-33, 119.

311. McNulty JP. Can levorphanol be used like methadone for intractable refractory pain? *J Palliat Med*. 2007;10(2):293-296.
312. Stringer M, Makin M, Miles J, Morley JS. D-morphine, but not L-morphine, has low micromolar affinity for the non-competitive *N*-methyl-D-aspartate site in rat forebrain: possible clinical implications for the management of neuropathic pain. *Neurosci Lett*. 2000;295(1-2):21-24.
313. Codd EE, Shank RP, Schupsky JJ, Raffa RB. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: structural determinants and role in antinociception. *J Pharmacol Exp Ther*. 1995;274(3):1263-1270.
314. Blake A, Bot G, Li S, Freeman JC, Reisine T. Differential agonist regulation of the human K-opioid receptor. *J Neurochem*. 1997;68(5):1846-1852.
315. Centers for Disease Control and Prevention. [Archive]. Methadone Linked to 30 Percent of Prescription Painkiller Overdose Deaths. Available at https://www.cdc.gov/media/releases/2012/p0703_methadone.html. Last accessed June 14, 2022.
316. Jones CM, Baldwin GT, Manocchio T, White JO, Mack KA. Trends in methadone distribution for pain treatment, methadone diversion, and overdose deaths—United States, 2002–2014. *MMWR*. 2016;65:667-671.
317. Dixon R, Crews T, Inturrisi C, Foley K. Levorphanol: pharmacokinetics and steady-state plasma concentrations in patients with pain. *Res Commun Chem Pathol Pharmacol*. 1983;41(1):3-17.
318. Rowbotham M, Twilling L, Davies P, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med*. 2003;348(13):1223-1232.
319. Flores G. Language barriers to health care in the United States. *N Engl J Med*. 2006;355(3):229-231.
320. Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *J Pain*. 2014;15(4):321-337.
321. Kalant H. Marihuana: medicine, addictive substance, or both? A common-sense approach to the place of cannabis in medicine. *CMAJ*. 2013;4(3):4-9.
322. Fitzcharles MA, Baerwald C, Ablin J, et al. Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis). *Schmerz*. 2016;30:47.
323. Romanò CL, Romanò D, Lacerenza M. Antineuropathic and antinociceptive drugs combination in patients with chronic low back pain: a systematic review. *Pain Res Treat*. 2012;2012:154781.
324. Romanò CL, Romanò D, Bonora C, Mineo G. Pregabalin, celecoxib, and their combination for treatment of chronic low-back pain. *J Orthop Traumatol*. 2009;10(4):185-191.
325. Pota V, Maisto M, Pace MC, Aurilio C. Association of buprenorphine TDS and pregabalin in the treatment of low back pain. *Eur J Pain*. 2007;11(1):83.
326. Khoromi S, Cui L, Nackers L, Max MB. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. *Pain*. 2007;130(1-2):66-75.
327. Gilron I, Tu D, Holden RR, Jackson AC, DuMerton-Shore D. Combination of morphine with nortriptyline for neuropathic pain. *Pain*. 2015;156(8):1440-1448.
328. Barkin RL. The pharmacology of topical analgesics. *Postgrad Med*. 2013;125(4 Suppl 1):7-18.
329. Zempsky W. Use of topical analgesics in treating neuropathic and musculoskeletal pain. *Pain Medicine News*. 2013;9:1-4.
330. Haroutiunian S, Drennan DA, Lipman AG. Topical NSAID therapy for musculoskeletal pain. *Pain Med*. 2010;11(4):535-549.
331. Jorge LL, Feres CC, Teles VE. Topical preparations for pain relief: efficacy and patient adherence. *J Pain Res*. 2010;4:11-24.
332. Argoff CE. Topical analgesics in the management of acute and chronic pain. *Mayo Clin Proc*. 2013;88(2):195-205.
333. Arnstein PM. The future of topical analgesics. *Postgrad Med*. 2013;125(4):34-41.
334. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage*. 2010;18(4):476-499.
335. Stanos SP, Galluzzi KE. Options in topical therapies in the management of patients with acute pain. *Postgrad Med*. 2013;125(4): 19-24.
336. Heyneman CA, Lawless-Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases: a comparison. *Drugs*. 2000;60(3):555-574.
337. Mason L, Moore RA, Edwards JE, McQuay HJ, Derry S, Wiffen PJ. Systematic review of efficacy of topical rubefacients containing salicylates for the treatment of acute and chronic pain. *BMJ*. 2004;328(7446):995.
338. Brooks M. Topical Diclofenac 2% (Pennsaid) for Knee OA Pain Clears FDA. Available at https://www.medscape.com/viewarticle/819436. Last accessed June 14, 2022.
339. Zacher J, Altman R, Bellamy N, et al. Topical diclofenac and its role in pain and inflammation: an evidence-based review. *Curr Med Res Opin*. 2008;24(4):925-950.
340. Sawynok J, Fitzcharles MA. Topical analgesics for pain. *Can J CME*. 2013;3:61-63.

341. Petersen B, Rovati S. Diclofenac epolamine (Flector) patch: evidence for topical activity. *Clin Drug Investiq*. 2009;29(1):1-9.

342. McCarberg B, Argoff C. Topical diclofenac epolamine patch 1.3% for the treatment of acute pain caused by soft tissue injury. *Int J Clin Pract*. 2010;64(11):1546-1553.

343. U.S. Food and Drug Administration. Flector Patch: Medical Review Part 1. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021234s000_MedR_P1.pdf. Last accessed June 14, 2022.

344. LexiComp Online. Available at https://online.lexi.com. Last accessed June 14, 2022.

345. Argoff CE. Introduction. *Postgrad Med*. 2013;125(Suppl 1):3-6.

346. Hashmi JA, Baliki MN, Huang L, et al. Lidocaine patch (5%) is no more potent than placebo in treating chronic back pain when tested in a randomised double blind placebo controlled brain imaging study. *Mol Pain*. 2012;8:29.

347. Brau ME, Vogel W, Hempelmann G. Fundamental properties of local anesthetics: half-maximal blocking concentrations for tonic block of NA+ and K+ channels in peripheral nerve. *Anesth Analg*. 1998;87(4):885-889.

348. Gammaitoni AR, Davis MW. Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. *Ann Pharmacother*. 2002;36(2):236-240.

349. Kanai A, Segawa Y, Okamoto T, Koto M, Okamoto H. The analgesic effect of a metered-dose 8% lidocaine pump spray in posttraumatic peripheral neuropathy: a pilot study. *Anesth Analg*. 2009;108(3):987-991.

350. Derry S, Wiffen PJ, Moore RA, Quinlan J. Topical lidocaine for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2014;(7):CD010958.

351. Irving GA, Backonja MM, Dunteman E, et al. A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. *Pain Med*. 2011;12(1):99-109.

352. Stein C. Targeting pain and inflammation by peripherally acting opioids. *Front Pharmacol*. 2013;4:123.

353. Tennant F. Topical Use of Morphine. Available at https://www.practicalpainmanagement.com/treatments/pharmacological/non-opioids/topical-use-morphine. Last accessed June 14, 2022.

354. Jacobsen J. Topical opioids for pain. *J Palliat Med*. 2009;12(4):380-381.

355. Tennant F. Use and Benefits of Topical Opioids by Intractable Pain Patients. Poster presented at: 21st Annual Clinical Meeting of the American Academy of Pain Management; September 21–24, 2010; Las Vegas, Nevada.

356. Tennant F, Moll D, DePaulo V. Topical morphine for peripheral pain. *Lancet*. 1993;342(8878):1047-1048.

357. Lynch ME, Clark AJ, Sawynok J, Sullivan M. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. *Anesthesiology*. 2005;103(1):140-146.

358. McCleane G. Topical application of doxepin hydrochloride, capsaicin and a combination of both produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. *Br J Clin Pharmacol*. 2000;49(6):574-579.

359. Quon JA, Fedder PG. *Intravenous Lidocaine for Chronic Pain: A Systematic Review*. Richmond: WorkSafeBC; 2010.

360. Tremont-Lukats IW, Hutson PR, Backonja M-M. A randomized, double-masked, placebo-controlled pilot trial of extended IV lidocaine infusion for relief of ongoing neuropathic pain. *Clin J Pain*. 2006;22(3):266-271.

361. Woolf CJ, Wiesenfeldhallin Z. The systemic administration of local-anesthetics produces a selective depression of C-afferent fiber evoked activity in the spinal cord. *Pain*. 1985;23(4):361-374.

362. Boas RA, Covino BG, Shahnarian A. Analgesic responses to IV lignocaine. *Br J Anaesth*. 1982;54(5):501-505.

363. Moulin DE, Morley-Forster PK, Pirani Z, Rohfritsch C, Stitt L. Intravenous lidocaine in the management of chronic peripheral neuropathic pain: a randomized-controlled trial. *Can J Anaesth*. 2019;66(7):820-827.

364. Bredlau AL, Thakur R, Korones DN, Dworkin RH. Ketamine for pain in adults and children with cancer: a systematic review and synthesis of the literature. *Pain Med*. 2013;14(10):1505-1517.

365. Kapural L, Kapural M, Bensitel T, Sessler DI. Opioid-sparing effect of intravenous outpatient ketamine infusions appears short-lived in chronic-pain patients with high opioid requirements. *Pain Physician*. 2010;13(4):389-394.

366. Foster L, Clapp L, Erickson M, Jabbari B. Botulinum toxin A and chronic low back pain: a randomized, double-blind study. *Neurology*. 2001;56(10):1290-1293.

367. Jazayeri SM, Ashraf A, Fini HM, Karimian H, Nasab MV. Efficacy of botulinum toxin type A for treating chronic low back pain. *Anesth Pain Med*. 2011;1(2):77-80.

368. Naumann M, So Y, Argoff CE, et al. Assessment: botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2008;70(19):1707-1714.

369. Machado D, Kumar A, Jabbari B. Abobotulinum toxin A in the treatment of chronic low back pain. *Toxins*. 2016;8(12):374.

370. Pappagallo M, Breuer B, Lin HM, et al. A pilot trial of intravenous pamidronate for chronic low back pain. *Pain*. 2014;155(1):108-117.

371. Koivisto K, Kyllönen E, Haapea M, et al. Efficacy of zoledronic acid for chronic low back pain associated with Modic changes in magnetic resonance imaging. *BMC Musculoskelet Disord*. 2014;15:64.

372. Koivisto K, Jarvinen J, Karppinen J, et al. The effect of zoledronic acid on type and volume of Modic changes among patients with low back pain. *BMC Musculoskelet Disord*. 2017;18(1):274.

373. Leite VF, Buehler AM, El Abd O, et al. Anti-nerve growth factor in the treatment of low back pain and radiculopathy: a systematic review and a meta-analysis. *Pain Physician*. 2014;17(1):E45-E60.

374. Katz N, Borenstein DG, Birbara C, et al. Efficacy and safety of tanezumab in the treatment of chronic low back pain. *Pain*. 2011;152(10):2248-2258.

375. Pimentel DC, Abd OE, Benyamin RM, et al. Anti-tumor necrosis factor antagonists in the treatment of low back pain and radiculopathy: a systematic review and meta-analysis. *Pain Physician*. 2014;17(1):E27-E44.

376. Tennant F. Hormone Abnormalities in Uncontrolled Chronic Pain Patients. Paper presented at: The American Academy of Pain Management Annual Clinical Meeting; September 18–21, 2014; Phoenix, AZ.

377. Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22(10):1911-1920.

378. Koes BW, van Tulder M, Lin CW, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. *Eur Spine J*. 2010;19(12):2075-2094.

379. Pinto RZ, Maher CG, Ferreira ML, et al. Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis. *BMJ*. 2012;344:e497.

380. Hurley RW, Adams MC, Benzon HT. Neuropathic pain: treatment guidelines and updates. *Curr Opin Anaesthesiol*. 2013;26(5):580-587.

381. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;85(3 Suppl):S3-S14.

382. Friedly JL, Comstock BA, Turner JA, et al. Long-term effects of repeated injections of local anesthetic with or without corticosteroid for lumbar spinal stenosis: a randomized trial. *Arch Phys Med Rehabil*. 2017;98(8):1499-1507.

383. Australian Safety and Efficacy Register of New Interventional Procedures, Surgical. Spinal Surgery for Chronic Low Back Pain: Review of Clinical Evidence and Guidelines. Available at https://database.inahta.org/article/16507. Last accessed June 14, 2022.

384. Morlion B. Chronic low back pain: pharmacological, interventional and surgical strategies. *Nat Rev Neurology*. 2013;9(8):462-473.

385. Cohen SP, Bicket MC, Jamison D, Wilkinson I, Rathmell JP. Epidural steroids: a comprehensive, evidence-based review. *Reg Anesth Pain Med*. 2013;38(3):175-200.

386. Rabinovitch D, Peliowski A, Furlan A. Influence of lumbar epidural injection volume on pain relief for radicular leg pain and/or low back pain. *Spine J*. 2009;9(6):509-517.

387. Benoist M, Boulu P, Hayem G. Epidural steroid injections in the management of low-back pain with radiculopathy: an update of their efficacy and safety. *Eur Spine J*. 2012;21(2):204-213.

388. American Academy of Neurology. Use of Epidural Steroid Injections to Treat Radicular Lumbosacral Pain. Available at https://www.aan.com/Guidelines/home/GetGuidelineContent/251. Last accessed June 14, 2022.

389. Manchikanti L, Pampati V, Falco FJ, Hirsch JA. Assessment of the growth of epidural injections in the Medicare population from 2000 to 2011. *Pain Physician*. 2013;16(4):E349-E364

390. Friedly JL, Comstock BA, Turner JA, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med*. 2014;371:11-21.

391. Andersson GBJ. Epidural glucocorticoid injections in patients with lumbar spinal stenosis. *N Engl J Med*. 2014;371(1):75-76.

392. Friedly J, Nishio I, Bishop MJ, Maynard C. The relationship between repeated epidural steroid injections and subsequent opioid use and lumbar surgery. *Arch Phys Med Rehabil*. 2008;89(6):1011-1015.

393. Amr YM. Effect of addition of epidural ketamine to steroid in lumbar radiculitis: one-year follow-up. *Pain Physician*. 2011;14(5):475-481.

394. Gupta R, Kaur H, Kaur S, Mahajan L, Kaur T. To compare the analgesic efficacy of two different doses of epidural ketamine in chronic low back pain patients: a randomised double-blind study. *Indian J Anaesth*. 2020;64(9):768-773.

395. U.S. Food and Drug Administration. FDA Requires Label Changes to Warn of Rare but Serious Neurologic Problems after Epidural Corticosteroid Injections for Pain. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-requires-label-changes-warn-rare-serious-neurologic-problems-after. Last accessed June 14, 2022.

396. Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain*. 2007;132(1-2):179-188.

397. Kumar K, Taylor RS, Jacques L, et al. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery*. 2008;63(4):762-770.

398. Patel SK, Gozal YM, Saleh MS, Gibson JL, Karsy M, Mandybur GT. Spinal cord stimulation failure: evaluation of factors underlying hardware explantation. *J Neurosurg*. 2019;32(1):133-138.
399. Shah N, Padalia D. *Intrathecal Delivery System*. Treasure Island (FL): StatPearls Publishing; 2022.
400. Patel VB, Manchikanti L, Singh V, Schultz DM, Hayek SM, Smith HS. Systematic review of intrathecal infusion systems for long-term management of chronic non-cancer pain. *Pain Physician*. 2009;12(2):345-60.
401. Häuser W, Tölle TR. Meta-analysis of pain studies: what have we learned? *Best Pract Res Clin Rheumatol*. 2015;29:131-146.
402. Watson CPN. Opioids in chronic noncancer pain: more faces from the crowd. *Pain Res Manage*. 2012;17(4):263-275.
403. Bendelow G. Chronic pain patients and the biomedical model of pain. *Virtual Mentor*. 2013;15(5):455-459.
404. Turk DC, Swanson KS, Tunks ER. Psychological approaches in the treatment of chronic pain patients: when pills, scalpels, and needles are not enough. *Can J Psychiatry*. 2008;53(4):213-223.
405. Giordano J, Schatman ME, Höver G. Ethical insights to rapprochement in pain care: bringing stakeholders together in the best interest(s) of the patient. *Pain Physician*. 2009;12(4):E265-E275.
406. Chou R, Loeser JD, Owens DK, et al. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: an evidenced-based clinical practice guideline from the American Pain Society. *Spine (Phila Pa 1976)*. 2009;34(10):1066-1077.
407. Manchikanti L, Datta S, Derby R, Wolfer LR, Benyamin RM, Hirsch JA. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: Part 1: diagnostic interventions. *Pain Physician*. 2010;13(3):E141-E174.
408. Manchikanti L, Datta S, Gupta S, et al. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: Part 2: therapeutic interventions. *Pain Physician*. 2010;13(4):E215-E264.
409. Manchikanti L, Benyamin RM, Falco FJ, Caraway DL, Datta S, Hirsch JA. Guidelines warfare over interventional techniques: is there a lack of discourse or straw man? *Pain Physician*. 2012;15(1):E1-E26.
410. Manchikanti L, Falco FJ, Boswell MV, Hirsch JA. Facts, fallacies, and politics of comparative effectiveness research: part 2: implications for interventional pain management. *Pain Physician*. 2010;13(1):E55-E79.
411. American Pain Society. Update on the Society. Available at https://painmed.org/american-pain-society/. Last accessed June 14, 2022.
412. Taylor ML. The impact of the "business" of pain medicine on patient care. *Pain Med*. 2011;12(5):763-772.
413. Richeimer SH. Are we lemmings going off a cliff? The case against the "interventional" pain medicine label. *Pain Med*. 2010;11(1):3-5.
414. Hartrick CT. Quality assessment in clinical trials: considerations for outcomes research in interventional pain medicine. *Pain Pract*. 2008;8(8):433-438.
415. Sinnott P, Wagner TH. Low back pain in VA users. *Arch Intern Med*. 2009;169(14):1338-1339.
416. Carragee EJ, Deyo RA, Kovacs FM, et al. Clinical research: is the spine field a mine field? *Spine (Phila Pa 1976)*. 2009;34(5):423-430.
417. Aronoff GM. The evolution of pain treatment: is it all about money? *Pain Practice*. 2011;12(4):326-330.
418. Scudds R, Scudds R, Simmonds M. Pain in the physical therapy (PT) curriculum: a faculty survey. *Physiother Theory Pract*. 2001;17(4):239-256.
419. Strong J, Tooth L, Unruh A. Knowledge about pain among newly graduated occupational therapists: relevance for curriculum development. *Can J Occup Ther*. 1999;66(5):221-228.
420. Duke G, Haas BK, Yarbrough S, Northam S. Pain management knowledge and attitudes of baccalaureate nursing students and faculty. *Pain Manag Nurs*. 2013;14(1):11-19.
421. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-130.
422. Matthias MS, Parpart AL, Nyland KA, et al. The patient-provider relationship in chronic pain care: providers' perspectives. *Pain Med*. 2010;11(11):1688-1697.
423. Zgierska A, Miller M, Rabago D. Patient satisfaction, prescription drug abuse, and potential unintended consequences. *JAMA*. 2012;307(13):1377-1378.
424. U.S. Census Bureau. Selected Social Characteristics in the United States: 2020 American Community Survey 5-Year Estimates. Available at https://data.census.gov/cedsci/table?q=DP02#. Last accessed June 14, 2022.
425. Karliner LS, Napoles-Springer AM, Schillinger D, Bibbins-Domingo K, Pérez-Stable EJ. Identification of limited English proficient patients in clinical care. *J Gen Intern Med*. 2008;23(10):1555-1560.
426. Flores G. The impact of medical interpreter services on the quality of health care: a systematic review. *Med Care Res Rev*. 2005;62(3):255-299.
427. Karliner LS, Jacobs EA, Chen AH, Mutha S. Do professional interpreters improve clinical care for patients with limited English proficiency? A systematic review of the literature. *Health Serv Res*. 2007;42(2):727-754.

Evidence-Based Practice Recommendations Citations

Toward Optimized Practice. *Guideline for the Evidence-Informed Primary Care Management of Low Back Pain*. 2nd ed. Edmonton: Toward Optimized Practice; 2019. Available at https://www.cfpc.ca/CFPC/media/Resources/Pain-Management/Low_Back_Pain_Guidelines_Oct19.pdf. Last accessed July 25, 2022.

Patel ND, Broderick DF, Burns J, et al. *ACR Appropriateness Criteria: Low Back Pain*. Reston, VA: American College of Radiology; 2021. Available at https://acsearch.acr.org/docs/69483/Narrative. Last accessed July 25, 2022.

Thorson D, Campbell R, Massey M, et al. *Adult Acute and Subacute Low Back Pain*. Bloomington, MN: Institute for Clinical Systems Improvement; 2018. Available at https://www.icsi.org/guideline/low-back-pain. Last accessed July 25, 2022.

Manchikanti L, Abdi S, Atluri S, et al. An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. *Pain Physician*. 2013;16(2 Suppl):S49-S283. Available at https://www.painphysicianjournal.com/2013/april/2013;16;S49-S283.pdf. Last accessed July 25, 2022.

George SZ, Fritz JM, Silfies SP, et al. Interventions for the management of acute and chronic low back pain: revision 2021. *J Orthop Sports Phys Ther*. 2021;51(11):CPG1-CPG60. Available at https://www.jospt.org/doi/10.2519/jospt.2021.0304. Last accessed July 25, 2022.

Colorado Division of Workers' Compensation. *Low Back Pain Medical Treatment Guidelines*. Denver, CO: Colorado Division of Workers' Compensation; 2022. Available at https://codwc.app.box.com/v/rule-17-exhibit-1. Last accessed July 25, 2022.