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LOW BACK PAIN: EPIDEMIOLOGY, MECHANISMS, AND TREATMENT

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ABSTRACT

Low back pain (LBP) represents a spectrum of different types of pain (nociceptive, neuropathic, nociplastic, non-specific) that frequently overlap. The elements comprising the lumbar spine (soft tissue, vertebrae, zygapophyseal and sacroiliac joints, intervertebral discs, and neurovascular structures) are prone to different stressors, and each of these, alone or in combination, may contribute to LBP. Due to numerous factors related to LBP and the low specificity of imaging and diagnostic injections, diagnostic modalities for this condition continue to be a subject of controversy. The biopsychosocial model posits LBP to be a dynamic interaction between social, psychological and biological factors that can both predispose to and result from injury, and should be considered when devising interdisciplinary treatment plans. Prevention of LBP is recognized as a pivotal challenge in high-risk populations to help tackle high healthcare costs related to therapy and rehabilitation. To a large extent, therapy depends on pain classification, and usually starts with self-care and pharmacotherapy in combination with non-pharmacological modalities such as physical therapies and psychological treatments in appropriate patients. For refractory LBP, a wide range of non-surgical (e.g. epidural steroid injections and spinal cord stimulation for neuropathic pain, and radiofrequency ablation and intra-articular steroid injections for mechanical pain) and surgical (e.g. decompression for neuropathic pain, disc replacement and fusion for mechanical etiologies) treatment options are available in carefully selected patients. Majority of the current treatment options address only single, solitary etiology and given the complex nature of LBP; a multimodal interdisciplinary approach is necessary. Although globally recognized as an important health and socioeconomic challenge with an expected increase of the prevalence, LBP continues to carry tremendous potential for improvement in both diagnostic and therapeutic aspects. Future research on LBP should focus on improving the accuracy and objectivity of diagnostic assessments as well as devising treatment algorithms that consider unique biological, psychological and social factors. High-quality, comparative randomized controlled trials with longer follow-up periods that aim to determine the efficacy and cost-effectiveness of LBP management are warranted.

INTRODUCTION

Low back pain (LBP) represents a spectrum of different types of pain, including nociceptive pain, neuropathic (radicular) pain that travels down the leg(s) and in some cases, nociplastic pain (caused by amplification of pain in the central nervous system, often falling under the umbrella of non-specific LBP). Frequently, these pain subtypes overlap (e.g. a patient with a herniated disc who has back pain, radicular pain, and diffuse symptoms outside patho-anatomical referral patterns.

The low back is anatomically defined as extending from the 12th rib to the iliac crest, and while LBP often coexists and is conflated with buttock pain, the buttock region is anatomically distinct and comprises a region from the iliac crest to the gluteal folds. Most people experience at least one episode of acute LBP in their lifetime. This condition is usually self-limiting, but often becomes chronic.[1] Studies have found that over 60% of individuals with mechanical LBP will continue to experience pain or frequent recurrences 1-year after onset.[2] For new-onset lumbar radiculopathy, between 15% and 40% will experience chronic pain or frequent relapse.[3] Chronic low back pain (CLBP) is a consequence of complex interactions encompassing biological, psychological and social factors.[4]

It is important to understand that pain is distinct from nociception, and includes not just A-delta and C fiber activation, but also context-dependent emotional, cognitive and behavioral elements.[5] This partially explains the poor correlation with pathology and symptoms,[6] and why interventions that have no effect on degenerative processes (e.g. psychological therapies, acupuncture) can have profound effects on pain and quality of life, whereas those that address pathology often fail to provide benefit. This paradigm was eloquently described by Melzack and Casey in their landmark classification of pain into sensory-discriminative, affective-motivational and cognitive-evaluative components.[7] It forms the basis for a multimodal, precision medicine approach to LBP, and is a cornerstone for the biopsychosocial model.[8]

In this Seminar, we provide a brief overview on epidemiology, and the etiological pathways and risk factors that contribute to the pathogenesis of LBP. We also describe the clinical presentation and diagnostic evaluation of LBP, as well as different therapeutic options.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched the MEDLINE, Cochrane Library, and Google Scholar using the key words 'back pain', 'spine OR spinal pain', with the qualifiers 'low OR lumbar', 'radicular', 'neuropathic', 'neurogenic', 'mechanical', 'axial', 'buttock', and 'non-specific' in combination with the terms "epidemiology", "pathogenesis", "clinical presentation", "diagnosis", "imaging", "therapy", "trials", and "prevention" until July 2020 with no date or language restrictions. We prioritized systematic reviews and meta-analyses, and clinical trials that multiple authors judged relevant, but did not exclude any data sources including non-peer-reviewed literature in the public domain. We also included review articles to provide readers with more details and more references than this Seminar permits.

EPIDEMIOLOGY

A study performed in 195 countries assessing the incidence, prevalence and years lived with disability (YLD) for 354 causes found LBP to be the leading cause of worldwide productivity loss as measured in years, and the top cause of YLD in 126 countries.[9] One systematic review of 165 studies from 54 countries estimated the point and 1-month prevalence of LBP to be 11.9±2% and 23.2 ± 2.9%, respectively, and to be most common in middle-aged to elderly females.[10] The authors also found the incidence of LBP to be lower in low- and middle-income vs. high-income economies.[10] A more recent systematic review of 13 studies from North America, Northern Europe and Israel reported the prevalence to range between 1.4% and 20.0%, and the annual incidence ranging between 0.024-7%, being highest in the U.S.[11] A systematic review and meta-analysis of LBP prevalence in low-, low middle-, and upper middle-income countries in Africa showed a pooled lifetime prevalence of 47%.[12] The prevalence of LBP increases with age, with rates of 1-6% in children 7-10 years old, 18% in adolescents,[13] and a peak prevalence ranging from 28% to 42% in persons between 40-69 years of age.[10]

LBP may be classified as mechanical, radicular (neuropathic) or primarily nociplastic in nature, with those distinctions affecting treatment decisions. In studies that sought to determine the breakdown of lumbar pain, the prevalence of neuropathic pain has ranged between 16% and 55% CLBP patients, with one review reporting an aggregate prevalence of 36.6%.[14] Radicular pain

is most commonly associated with herniated nucleus pulposus (HNP) and spinal stenosis (further stratified by location as central, foraminal, or involving the lateral recesses); infrequently, other conditions (e.g. herpes zoster, metastatic cancer) can cause radicular pain. The prevalence of radicular pain due to herniated disc varies between 2-4%, being more common in men and in individuals between 30-50 years.[15] Interestingly, the presence of an HNP does not always result in pain, with one systematic review reporting prevalence rates in asymptomatic individuals ranging from 29% in 20-year-olds, to 43% in 80-year-olds.[16] Most herniated discs will regress within 2 years. In one review, the authors found that spontaneous regression occurred in over 90% of sequestered discs, 70% of herniated discs and over 40% of protruded discs.[17] In another study, 87% of patients reported a decrease in acute pain due to disc herniation at 3 months.[18]

In contrast, spinal stenosis is an anatomically progressive condition and a direct consequence of age-related degenerative processes. However, not everyone with narrowing of the spinal canal will experience radicular pain. In one review, the range of spinal stenosis in asymptomatic individuals ranged from 0% to 56%, with a median of 11%.[19] The authors of the Framingham Study found prevalence rates of 22.5% for relative (lumbar spinal canal diameter ≤12 mm) and 7.3% for absolute acquired lumbar spinal stenosis (diameter ≤10 mm).[20]

Nociplastic pain is the newest category of pain, with the primary pathology being central sensitization. This pain is often referred to as non-specific LBP, though the latter term is often misapplied to individuals whereby the etiology is unknown or ambiguous. Nociplastic pain may also accompany mechanical and neuropathic pain.[21]

SOCIOECONOMICS

The economic burden of low back pain is estimated around £2.8 billion in the United Kingdom[22] and more than $4.8 billion in Australia[23] per year. In the U.S., the annual expenditures for the management of LBP patients are estimated to exceed $100 billion.[24] A retrospective analysis of nearly 2.5 million U.S. patients with newly diagnosed low back or lower extremity pain between 2008 and 2015[25] revealed that 98.8% of cohorts did not undergo surgery in the year following diagnosis. The non-surgical cohort accounted for 26.3% of the total annual costs ($498 million), compared to $265 million (53%) annually for the surgical cohort.[25] Approximately two-thirds of

the economic costs from LBP stem from indirect costs (e.g. loss of productivity).[26] Mutubuki et al. found that female sex, young age, multiple etiologies, poor quality of life, and high disability were predictive of high societal (healthcare, diminished productivity) costs among CLBP patients.[27] Another study showed that expenditures from presenteeism (being present at work with suboptimal performance) were higher than direct medical costs.[28] The nature of CLBP may also result in less quantifiable costs such as difficulties performing domestic chores, caregiving, engaging in recreational activities, struggles with relationships, depression and anxiety.[29]

PATHOGENESIS

Multifactorial etiological pathways and risk factors contribute to pathogenesis of LBP, and this section provides an overview.

Disc Degeneration

In recent systematic review, Battie et al. found inconsistencies when defining the term "degenerative disc disease" and identifying painful discs, which creates confusion in the literature and divergent treatment algorithms.[30] The structures constituting the lumbar spine include muscles, fascia, ligaments, tendons, facet joints, neurovascular elements, vertebrae and intervertebral discs (IVDs), all of which are susceptible to biochemical, degenerative, and traumatic stressors.[31] The discs, which are 70-80% aqueous, are composed of an outer annulus fibrosus and inner nucleus pulposus (NP). IVDs absorb shock, preserve spinal movements, and distribute axial and torsional forces. During healing, neovascularization occurs and minute sensory nerves may penetrate the disrupted annulus and NP, leading to mechanical and chemical sensitization.[32] Although MRI is highly sensitive for detecting disc pathology, a systematic review found conflicting evidence endplate signal changes were associated with LBP and activity limitations.[33] Another systematic review found only a modest correlation between disc space narrowing and LBP in 26,107 patients.[34] Similar to other sources of mechanical pain, discogenic pain can extend into the upper and occasionally lower legs in a non-dermatomal pattern.

Radicular Pain

LBP that extends into the leg, usually below the knee (radicular pain), may result from mechanical nerve root compression and chemical irritation from various inflammatory mediators that leak out of degenerated discs. Unlike referred pain from joints, muscles and discs, the pain typically radiates in a dermatomal distribution. HNP is the most common cause of radicular pain, though after age 60, spinal stenosis is the leading cause. Spinal stenosis is most common at the L4-L5 level and may result from facet joint and ligamentum flavum hypertrophy, congenitally short pedicles, and spondylolisthesis.[35] Spinal stenosis may cause chronic mechanical compression resulting in axonal injury and/or nerve root ischemia. It is important to note, however, that both HNP and spinal stenosis are radiological diagnoses, and that not all people with stenosis and herniations experience pain.

From a radiological perspective, absolute central lumbar stenosis refers to antero-posterior spinal canal diameter <10 mm, while foraminal stenosis relates to a neuroforaminal diameter of <3 mm.[36] A herniated disc is diagnosed when the NP extends beyond the normal confines of the annulus fibrosis, but involves less than 25% of the circumference. Spinal stenosis often co-exists with other conditions (e.g. hypertrophied facet joints causing foraminal narrowing) including herniated disc, with one study reporting a 23% co-prevalence rate.[37] Because most herniated discs are significantly degenerated and the etiologies of spinal stenosis can also cause axial pain, a large majority, but not all cases of lumbar radicular pain co-occur with back pain.[38]

Facet Arthropathy

Facet joints (i.e. zygapophyseal joints) that connect adjacent vertebrae play a role in limiting spine movements and loadbearing as discs age and degenerate. These joints are also prone to degenerative changes, most commonly osteoarthritis.[39] Referred lumbar facet joint pain has a variable presentation; upper lumbar levels are associated with non-dermatomal pain projecting into the hip, flank, and lateral aspects of upper thigh, which is in contrast to pain experienced in the lateral and/or posterior aspects of the thigh observed with the lower levels. The most commonly affected L4-L5 and L5-S1 zygapophyseal joints can sometimes produce pseudo-radicular symptoms extending into the leg.[40]

Myofascial Pain

Muscles, fascia and ligaments may also be pain generators.[41, 42] Muscles pertinent to the genesis of LBP include deep intrinsic (multifidus, rotatores) and the more superficial longissimus, spinalis and iliocostalis muscles (collectively referred to as erector spinae muscles).[43] Back muscles are integral to normal spine stiffness and function, and chronic LBP may be paradoxically associated with both atrophy and increased myoelectric activity, which is consistent with studies showing both increased and decreased activation depending on context.[43, 44] Muscle pathology represents an under-appreciated source of LBP, often misdiagnosed as 'non-specific', and often arises consequent to other primary pathology. Myofascial pain may result from overuse, acute stretch injuries or tears, and diffuse or localized (e.g. trigger points) muscle spasm.

Sacroiliac (SI) Joint Pain

The SI joint consists of an extensive network of ligaments both dorsally and ventrally, and a joint capsule in the anterior, lower-third of the SI junction. Although SI joint pain most frequently presents in buttock, over two-thirds of individuals will experience lumbar pain; in approximately 50% of cases, the pain radiates to the leg, sometimes below the knee.[45] Both the ligaments and fibrous capsule are imbued with nociceptors and both may be a source of pain. Intra-articular pathology is more common in the elderly, while younger individuals with prominent tenderness and a traumatic etiology are more likely to have extra-articular pathology.[46]

Spondyloarthropathies

Spondyloarthropathy refers to a family of inflammatory rheumatic diseases that includes ankylosing spondylitis and psoriatic arthritis. These systemic conditions typically include multiple joints, with ankylosing spondylitis and axial spondyloarthritis preferentially affecting the low back. In addition to facet and SI joint arthritis, other spinal manifestations include enthesitis and autofusion. The prevalence for spondyloarthropathies varies from 0.2-0.5% for ankylosing spondylitis, to 0.05-0.25% for enteropathic axial arthritis.[47]

Summary of Pathogenesis

- Structures that may cause mechanical LBP include discs, facet and SI joints, and soft tissues
- Radicular pain is most commonly caused by a herniated disc in younger population or spinal stenosis in the elderly, and may result from nerve root compression, ischemia, or chemical irritation

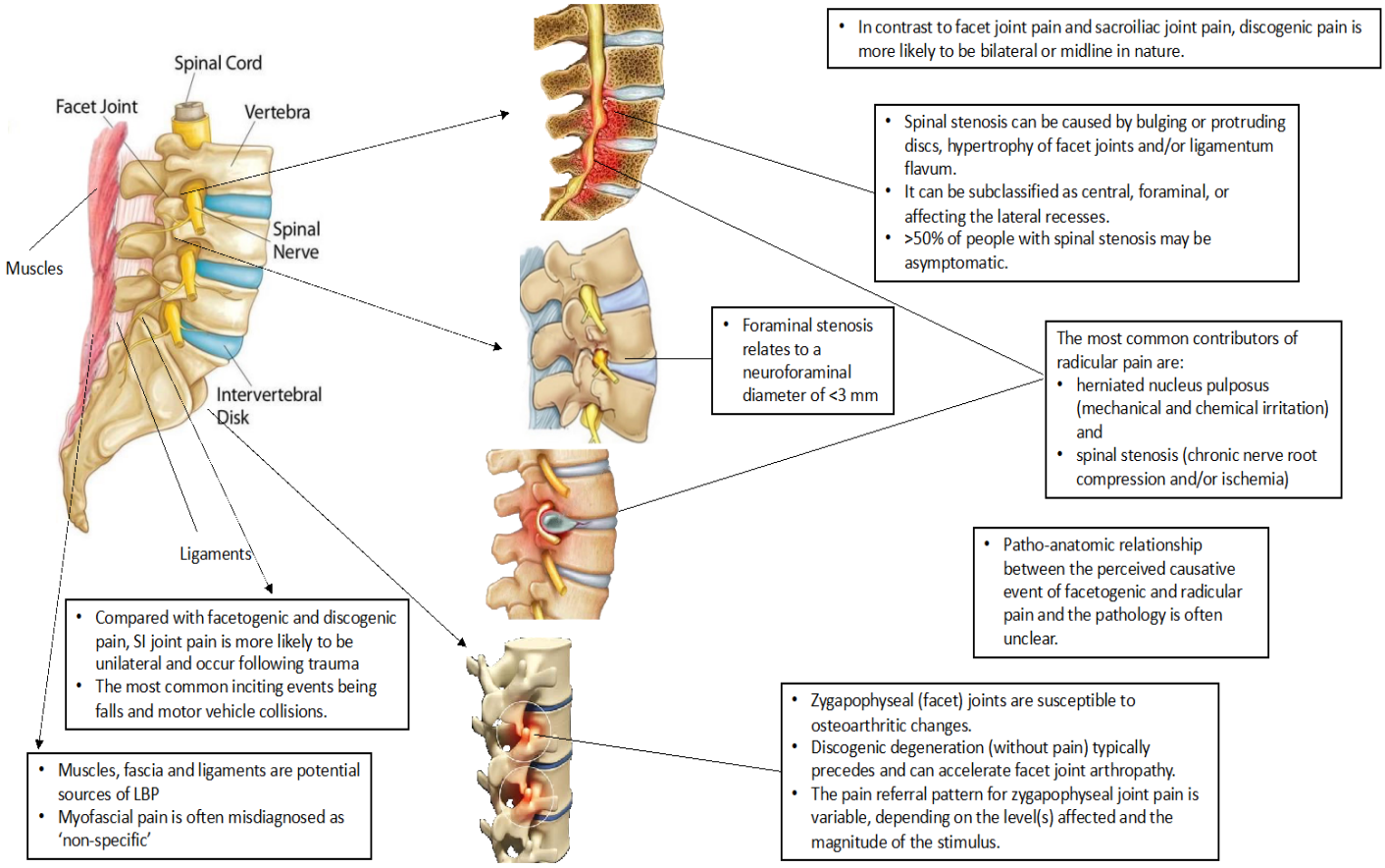

Figure 1. Sagittal view of lumbar spine showing potential pain generators.

Nociplastic Pain

The term nonspecific LBP is ambiguous and evolving. Semantically, it refers to LBP in which a specific pain generator(s) has not been identified – not that one does not exist. Historically, it has been written that approximately 90% of cases of LBP were not associated with a clear-cut etiology, though nearly most studies used for this prevalence rate did not involve the use of advanced diagnostic tools (e.g. diagnostic blocks, electrodiagnostic testing).[48] Many cases were attributed to myofascial pathology, which is present in a high proportion of patients irrespective of whether there is a primary cause.[44] More recently, the term nociplastic pain has

been introduced, in which objective abnormalities may or may not be present, but where the principal mechanism is sensitization of the nervous system.

CHANGES IN THE BRAIN

Structural and functional changes in the brain have generated intense interest in recent years as they might serve as biomarkers linking anatomical changes with pain. Studies have identified common and disease-specific changes in specific white and gray matter brain regions such as dorsolateral prefrontal cortex thalamus, temporal lobes, insula and primary somatosensory cortex in CLBP patients, indicating that chronic pain is associated with structural reorganization.[49] Functional changes, such as alterations in blood flow and metabolism, have also been described. A study performed in CLBP patients have shown that deleterious anatomical and functional changes can be reversed with treatment.[50]

BEHAVIORAL FACTORS

In line with the revised IASP definition of pain, LBP represents not just the sensory awareness of bodily harm, but also an emotional (e.g. fear, sadness, anxiety) experience.[51] Psychologically traumatic events may precipitate or reinforce LBP. In one study evaluating clinician-reported views on LBP triggers (which may underestimate the incidence), 3.1% cited psychological factors as a primary determinant.[52]

Patients' expectations are based on previous experience, cultural attitudes, healthcare beliefs, context, and an understanding of their illness.[53] In clinical studies, negative expectations have been shown to predict poor pain outcomes.[54]

Misinterpretations of pain as a sign of physical harm often lead to fear-avoidance behaviors that further fuel disability, depression and anxiety. Suffering from LBP frequently leads fearful patients to avoid "risky" behaviors, putting them in a vicious cycle of pain–anxiety–avoidance–disability–worsening pain.[55] A large meta-analysis performed in 15,623 patients with chronic musculoskeletal pain, including 6,312 with CLBP, found that higher levels of fear-of-pain, anxiety and fear-avoidance beliefs were significantly associated with greater pain levels and disability.[56]

Traditionally, LBP was considered a result of injury. This model is not only overly simplistic, but does not reflect the power of pain to instigate learning and adaptation. In addition to these non-associative learning mechanisms, individuals with LBP may also learn to predict, control, and prevent pain. Although these forms of learning are natural and adaptive in acute back pain situations, they can become detrimental in the long term when pain persists.

Individuals with LBP can learn to predict pain by detecting non-nociceptive cues or events that precede or coincide with the occurrence of pain. The mechanism of such Pavlovian learning is that after such co-occurrences, the non-nociceptive event elicits an anticipatory fear response in the absence of pain. Such associations not only incite pain-related fear, they also may lead to hyperalgesia.[57] Erroneous beliefs about the relationship between particular movements and pain are prevalent in LBP sufferers,[58] but are also found among health professionals.[59] For example, the use of expressions implying harm (e.g., "Your spine looks like one of a 70-year-old") may inadvertently evoke pain-related fear. Akin to Pavlovian learning is the acquisition of harm expectations, which have shown to be potent predictors of recovery from back pain.[60]

A particular form of learning to control pain is avoidance-learning, where individuals with LBP learn that when they avoid the predictive cues the anticipated "catastrophe" is circumvented. The Fear-Avoidance Model combines the cognitive, emotional, motivational, and behavioral aspects of pain-related behavior into an integrated theoretical framework.[60] Suffering from LBP frequently leads patients into a state of fear to avoid "risky" behaviors, putting them in a vicious cycle of pain–anxiety–avoidance–disability–worsening pain. Whereas avoidance may be adaptive in the short term, its excessive or unnecessary deployment can have detrimental consequences in the long term.[61]

GENETIC FACTORS

The genetic determinants of LBP have received increased attention in recent years, and may someday be part of precision medicine algorithms. Carvalho et al. found that heritability contributed 26% to lifetime prevalence of LBP, 36% for functional limitations, and 25% to pain intensity in 1,598 twins.[62] A systematic review of 27 studies involving twins showed the effects of heritability accounted between 21-67% of back pain burden. One question raised by genetic

studies is how individually identified genes contribute to LBP (i.e. through pain perception, accelerated spondylosis, predisposing psychopathology, lifestyle, response to treatments, etc.), and the role epigenetics plays.

Risk factors related to acute to chronic low back pain progression are listed in **Table 1.**

Table 1: Risk Factors Associated with Progression of Acute to Chronic Low Back Pain

Genetic factors
Female sex
Lifestyle (sedentary lifestyle, obesity, smoking, etc.)
Psychosocial factors (poor social support, anxiety, depression, catastrophizing)
Poor coping mechanisms (e.g. fear-avoidance behavior)
Traumatic injuries
Occupational hazards (e.g. construction work and other types of manual labor, poor job satisfaction, hostile work environment)
Secondary gain
Greater disease burden (higher baseline pain, greater disability, opioid use)

Summary of factors contributing to LBP

- Physical and emotional trauma are often cited as triggers for LBP
- Brain imaging techniques have indicated structural and functional changes as potential biomarkers for CLBP
- Behavioral factors are often overlooked as a cause of pain chronification
- Heritability is a significant contributor to lumbar disc degeneration and herniation, as well as chronic and disabling LBP

CLINICAL PRESENTATION

IVD herniation typically manifests as LBP (i.e. from annular tears and disc disruption) and leg pain (from nerve root irritation or referred pain from degenerated discs). This pain usually resolves over several weeks in patients without neurological deficits but may persist in many people. A prospective cohort study followed 605 patients suffering from LBP with or without sciatica for 2 years, and noted that 54% and 47% had recurrent pain at 6 and 24 months, respectively.[63] The extent of disc herniation does not correlate well with severity of pain.[64] Patients with lumbar spinal stenosis (LSS) may report low back and leg pain, aggravated by walking and alleviated by

bending forward. They often present with a wide-based gait and neurological weakness.[35] These symptoms are referred to as intermittent neurogenic claudication.[65] Neurogenic claudication can be distinguished from vascular claudication in that patients with the latter may have decreased temperature in their feet, diminished distal pulses, and a lower ankle-brachial index. Patients with LSS can often be distinguished from patients with herniated lumbar disc in that they tend to assume a characteristic kyphotic standing posture (flexion of the lumbar spine) to alleviate their symptoms, and physical exam signs such as straight leg raising test are less reliable.[35]

Table 2. Clinical presentation and diagnostic evaluation of low back pain

Source of Pain	Risk Factors	Onset of condition	Clinical presentation*	Physical Findings**	Diagnostic Imaging
Mechanical					
Intervertebral disc[34, 66, 67]	Advanced age, but patients typically younger than those with facetogenic or SI joint pain. Repetitive or acute trauma	Insidious	Low back pain and/or leg pain. Pain worse with sitting.	Midline tenderness Reduced ROM[1], especially bending forward No focal neurological findings	Plain films to evaluate for disc height. MRI to detect annular tears/fissures/high intensity zones (HIZ). Imaging not routinely needed.
Facet joint[68]	Osteoarthritis Spondylolisthesis	Insidious	Axial low back pain Referred pain to hip, flank, upper thigh.	Paraspinal > midline tenderness Reduced back ROM[1] No neurological findings	CT[2] is gold standard for bone pathology, with SPECT[3] scans showing correlation with facet block results. Imaging not routinely needed.
Muscles, fascia and ligaments[67]	Strenuous activity Repetitive or abrupt movements (e.g. coughing, sneezing)	Acute/insidious	Axial low back pain Occasional referred pain to posterior thigh.	Muscle guarding, spasm, edema or atrophy Reduced back ROM No neurological findings	Ultrasound Imaging not routinely needed.
Sacroiliac joint[66, 68]	Bimodal age distribution Trauma, pregnancy, prior surgery, spondyloarthropathy, advanced age, leg length discrepancy.	Often follows trauma in the form of axial loading and abrupt rotation	Buttock pain, low back pain, frequently radiating into the leg or groin. Sitting or rising from sitting may worsen it.	Tenderness near posterior superior iliac spine Pain worse with rising from sitting No focal neurological findings	X-rays and radionuclide bone scans have low sensitivity CT most sensitive for bone involvement MRI[4] may detect active inflammation and soft tissue pathology.
Radicular					

Herniated disc[37, 67, 69]	Peak frequency 30-50 years, higher in males. Heavy lifting Trauma Lifestyle habits (smoking, obesity). Symptoms may be caused by inflammatory cytokine release from discs.	Acute/insidious	Low back pain and/or leg pain	Straight leg raising (SLR) test Crossed SLR test Dermatomal pain location Diminished reflexes depending on nerve root involvement lower extremity muscle weakness depending on nerve root involvement; may be pain-induced or neurological.	MRI for nerve root compromise (sensitivity: 0.25; specificity: 0.92). CT/CT myelography to differentiate soft tissue changes from osteophytes. Imaging recommended for serious or progressive neurological deficits.
Spinal stenosis[70-72]	Advanced age Hypertrophy of facet joints and ligamentum flavum Degenerative spondylolisthesis Disc bulging Congenital (short pedicles)	Insidious	Low back pain Leg pain Wide-based gait Neurological weakness	At least 3/5 findings from patient history and examination (>48 years, leg pain>back pain, bilateral symptoms, pain with walking/standing, pain alleviation with sitting). Improved walking ability with the spine flexed forward; pain relief with bending; and muscle weakness and diminished reflexes depending on nerve root involvement.	MRI for soft tissues and measuring spinal canal diameter CT can assess osseous diameter of spinal canal in axial views, but is less sensitive than MRI. Plain X-rays used to evaluate spinal instability (flexion/extension)

* Considerable overlap within radicular etiologies (spinal stenosis, herniated disc) and within mechanical etiologies (e.g. sacroiliac joint pain, facet joint pain, degenerative discs), with frequent co-occurrence.

** Historical and physical findings tend to be more sensitive than specific, and are not pathognomonic.

1: ROM Range of motion

2: CT: Computed tomography

3: Single photon emission tomography

4: Magnetic resonance imaging

DIAGNOSIS OF LOW BACK PAIN

Recently, an overview of 15 clinical practice guidelines explored diagnostic recommendations for non-specific LBP.[73] Although a large portion of LBP cases are non-specific or resolve without a formal diagnosis, most guidelines recommend history taking and physical examination to identify

specific entities. A majority of guidelines (78%) endorsed neurological examination to identify patients with nerve root compression. Patients with LSS may also require vascular-focused studies in order to differentiate between vascular and neurogenic claudication.[35] More than half the guidelines favored triaging patients into three categories: non-specific LBP, specific mechanical low back pain, or radicular pain; the remainder were against separate classification. The recommendations were uniform against the endorsement of imaging in patients with non-specific LBP; however, more than half of guidelines recommended imaging in patients with 'red flags', with most also endorsing the assessment of 'yellow flags' during evaluation, which may lead to interventions that can prevent persistent disability. A large retrospective review showed that presence of red flags such as fracture, metastases and infection increased the probability of identifying serious spinal pathology, though a negative response to red flag surveillance did not lower the probability of a red flag diagnosis.[74] A comprehensive analysis of 21 guidelines for the management of LBP found inconsistencies as to which red flags to use for the detection of serious spinal pathology.[72] Other flags associated with the development prognosis for LBP include orange (psychiatric symptoms), yellow (beliefs, appraisals, judgments, emotional responses and pain-related behavior), blue (relationship between work and health), and black (system or contextual obstacles) flags.[75]

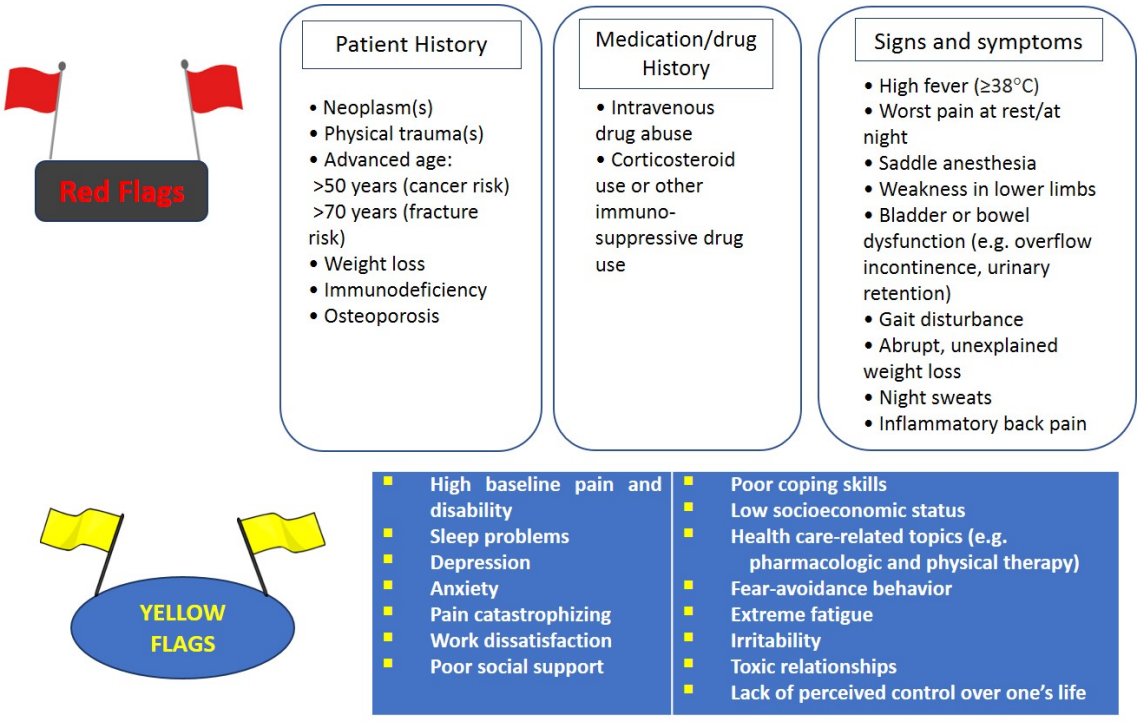

Figure 2. Red and Yellow Flags for Low Back Pain[72, 76]

IMAGING

Numerous guidelines have been published on the use of imaging for LBP, given high rates of use, the high prevalence rates in asymptomatic volunteers (most people have disc degeneration by age 40 years), and the poor correlation between symptoms and pathology.[77] For acute LBP, red flags including severe or progressive neurological deficits, warrant imaging. For chronic LBP, routine imaging is not recommended, though it may be considered on a case-by-case basis, particularly when considering a procedure or findings are likely to affect care.[78, 79] Plain films can be considered when evaluating for spinal instability (flexion-extension), spondylolisthesis or screening for scoliosis. MRI has not been shown to improve outcomes for patients who are candidates for epidural steroid injection (ESI),[80, 81] but may contribute to higher rates of spine surgery and result in higher satisfaction rates.[82] In patients who are candidates for MRI but have contraindications, CT scans have greater than 90% sensitivity for detecting most lumbar pathologie.[83]

SCREENING

Screening tools have been developed to determine which patients with acute LBP are prone to develop chronic pain. Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ), which assesses 24 different parameters, was found to have low-to-moderate positive predictive values.[84] StarT Back Tool (SBT) was developed to identify subgroups of LBP patients requiring early prevention strategies.[85] A large prospective study found SBT acceptable for 1-year disability prediction, but it failed to show discriminative value for future pain.[86]

Several instruments have been developed to distinguish neuropathic from non-neuropathic pain including painDETECT, s-DN4 and s-LANSS.[87] These questionnaires have demonstrated strong correlation, and can be self-administered, though physician designation remains the reference standard. Questionnaires used to identify nociplastic contributions to LBP can include the central sensitization inventory and pain sensitivity questionnaire.[88]

Summary of clinical presentation and diagnostics of LBP

- There is considerable overlap in presentation and co-prevalence between mechanical and radicular pain etiologies.
- Imaging is not routinely recommended unless severe and progressing neurological deficits are noted, or the treatment plan is likely to be impacted.
- Diagnostic blocks are used to link radiological abnormalities with pain complaints, but single blocks are characterized by high false-positive rates and double-blocks are associated with significant false-negatives.
- Screening instruments can help classify pain (e.g. neuropathic vs. nociceptive) and identify those at high risk for chronification, and who might benefit from early interventions.

PREVENTION

Prevention of LBP has received increased attention as societies struggle to find practical solutions to implement. One reason behind the lack of progress may be the underestimation of non-anatomical aspects contributing to LBP such as psychosocial risk factors,[89] and under-utilization of multidimensional interventions.[90] Previous studies on interventions such as exercise, education, and ergonomic modifications have yielded modest results.[91] In adults, a systematic review found moderate-quality evidence that exercise alone or with education was effective for both primary and secondary prevention of LBP, and low-quality evidence that education alone, back braces, shoe inserts and ergonomic corrections were ineffective for the primary prevention of LBP.[92] A more recent systematic review confirmed that exercise alone and in combination with education was effective as a primary prevention strategy for LBP.[93]

TREATMENT

BEHAVIORAL MANAGEMENT OF LOW BACK PAIN

Due to ongoing concerns regarding the risk: benefit ratio of opioids, and suboptimal results in clinical trials evaluating other pharmacological agents, recently published guidelines have proposed non-pharmacological approaches such as exercise and physical therapy as first-line treatments for LBP. The initial encounter with LBP patients should take place in a primary care setting,[31] and begin with familiarizing an individual with their pain condition and self-management techniques. Should reassurance and self-care fail, additional risk-stratified

modalities such as exercises and cognitive behavioral therapy (CBT) can be considered. If LBP persists, pharmacological and procedural options can be trialed.

The management of chronic LBP is notoriously challenging, and the prominent role of negative expectations, pain-related fear, and various avoidance behaviors in sustaining CLBP,[94] warrant a behavioral management approach.[95] Yet, there is also no consensus as to what constitutes an optimal design or duration of treatment.[96] A panoply of psychological treatments for individuals with chronic pain has emerged in the last five decades, and those sharing the aim restoring the pursuit of individual-valued life goals can be roughly classified into clarification-oriented and exposure-based cognitive-behavioral interventions. Clarification-oriented interventions help patients disengage from disabling avoidance behavior by unambiguously providing new information that pain can be self-managed and does not require aggressive protection.[97]

Exposure-based treatments include graded activity, which uses operant learning principles to encourage healthy behaviors,[98] and exposure treatment, which focuses on the reduction of pain-related fears and disabling avoidance behaviors.[99] In a systematic review evaluating CBT for subacute back pain, a majority of included studies reported significant benefit at variable follow-up periods.[100] CBT has also been shown to decrease recovery time and prevent the development of chronic spinal pain.[101] Future research in the area of behavioral treatments should aim to custom interventions. A systematic review on MBSR found only small, short-term differences for improvement in pain and function.[102] A systematic review of ACT on CLBP revealed small to medium effect sizes for measures of functioning, anxiety, and depression, but not for pain or quality of life.[103]

NONPHARMACOLOGICAL TREATMENT OPTIONS

Oliveira et al. summarized recommendations from 15 clinical practice guidelines for the management of non-specific LBP.[73] Eleven of 12 recommended against bed rest for acute LBP, and four were against bed rest for any duration of pain. More than half endorsed maintaining normal activities as part of acute LBP management. Employing a multidisciplinary rehabilitation team was endorsed by 9 of 11 guidelines for CLBP.

The American College of Physicians (ACP) published guidelines with recommendations for noninvasive management of radicular or non-radicular LBP.[104]

The different types of non-pharmacological integrative treatments are shown in **Table 3.**

Table 3. Non-pharmacological integrative treatments for low back pain

Treatment	Description	Effects
Massage[105]	Manual therapy to reduce muscle spasm and increase joint mobility	Immediate benefit for nonspecific LBP vs. no treatment, inactive controls, or sham treatments, though differences in improvements are small; most beneficial as add-on to exercise and/or education
Acupuncture[105]	Manual needle placement on particular points of different anatomical planes to reduce pain.	Global improvement compared with NSAIDs; effect is very small. Inconsistent benefit for pain relief compared with NSAIDs. Acupuncture as add-on to medication is more effective for pain relief and function vs. medication alone; differences are small. Immediate pain relief and function improvement greater than with sham acupuncture, no treatment, NSAIDs, or muscle relaxants; differences are small. Systematic reviews have also found that some forms of sham acupuncture are superior to no-treatment.
Superficial heat and cold[106]	Increases cutaneous blood flow and causes a cooling reaction; can be performed with moist hot packs, fluid therapy, whirlpool, or paraffin; used to relieve muscle spasms, joint contractures and decreased range of motion.	Short-term (4 days) pain and disability reduction for continuous heat wrap vs. oral placebo in acute and subacute LBP (≤3 months); additional benefit as an add-on therapy to exercise. Insufficient evidence for CLBP. Insufficient evidence on the effects of cold therapy.
Psychological therapies (CBT-cognitive behavioral therapy; and operant therapy)[105]	CBT: Managing pain by modifying maladaptive thoughts and behaviors through education and methods to manage symptoms. Operant therapy involves learning through praising or punishing of a particular behavior	Compared to wait-list control, operant therapy and behavioral therapy for short-term post-treatment pain improvement; no therapeutic difference between behavioral therapy and group exercises for pain relief through 6 months.
Yoga[105]	Ancient Indian practice whereby physical, mental and spiritual exercises are used to improve bodily posture and emotional and physical well-being	Yoga is superior to non-yoga exercise for pain and function in CLBP (>12 weeks) patients. Better function in the short- (≤3 months) and long-term (≤1 year).

Tai chi[105]	Ancient Chinese art practiced as a graceful series of slow and focused movements accompanied by deep breathing	Tai chi as stand-alone or add-on therapy can improve pain and function.
Movement control exercise (MVCE)[107]	Physical exercises designed to straighten muscles, alleviate pain and improve spinal posture	Positive effect of MVCE on disability immediately post-treatment and after 12 months.
Spinal manipulative therapy (SMT)[105]	Chiropractic application of controlled manipulation or thrust applied to joints of the spine	SMT is better than sham SMT, inert interventions, or as an adjunct to other interventions for pain and quality of life improvement. Significant short-term (1-3 months) effect on pain/function vs. sham manipulation. Improvement in functional status as adjunct to other interventions.
Technology-Supported Exercise Therapy (TSET)[108]	Simultaneous application of electronic technological systems with exercise therapy	Technological support of physical exercises provides limited benefit for pain, disability, and quality of life. TSET is not more effective than other treatments.
Mini-interventions[109, 110]	Interventions based on features from light mobilization and graded activity programs	Mini-interventions reduce daily subacute LBP symptoms, improve adaptation to pain, and do not increase health care costs.

PHARMACOLOGICAL TREATMENT OPTIONS

Pharmacological treatments may be ideal for patients with multiple areas of pain, multiple LBP contributors, individuals who are procedure-averse or at high risk for complications, and individuals with nociplastic pain. According to ACP guidelines, pharmacological recommendations for acute or subacute LBP should begin with nonsteroidal anti-inflammatory drugs (NSAIDs) or muscle relaxants (moderate-quality evidence).[104] There is no consensus with respect to duration of NSAID use and caution is advised with prolonged use due to concerns for GI and cardiovascular adverse events. A Cochrane review found no significant difference on effectiveness between selective and non-selective NSAIDs for LBP.[111] ACP guidelines recommend tramadol or duloxetine as second-line; and opioids as the last-line therapy for CLBP. NICE guidelines recommend not routinely using opioids for acute LBP, and against them for CLBP.[112] Although opioids are as or more efficacious than other analgesics for both neuropathic and non-neuropathic pain,[113] a meta-analysis showed only modest, short-term pain relief in patients with CLBP.[114] The addictive potential of opioids coupled with plethora side effects have led multiple organizations to recommend them only for LBP refractory to other treatments.[104]

Gabapentinoids are recommended for the treatment of neuropathic pain;[113] however, a systematic review found no strong evidence to support their use for CLBP with or without radicular pain.[115] Tricyclic antidepressants (TCAs) are also used in the management of neuropathic pain, and the serotonin-norepinephrine reuptake inhibitor duloxetine is approved by the U.S. FDA for musculoskeletal pain, including LBP. A systematic review by Chou et al.[116] found evidence supporting duloxetine, but not TCAs and gabapentinoids for CLBP. However, the evidence for duloxetine in lumbosacral radiculopathy was indeterminate.

Summary of prevention and non-interventional therapies of LBP

- Both primary and secondary prevention of LBP focus on education, physical activity, and resumption of daily activities
- Many guidelines suggest conservative non-pharmacological treatment options prior to recommending other treatment modalities
- First-choice pharmacological treatment for mechanical LBP consists of a short course of NSAIDs if not contraindicated, and muscle relaxants when soft tissue pathology is suspected. Duloxetine may be considered for chronic LBP
- CBT and MBSR are two of the most common psychological therapies shown to benefit patients with CLBP, particularly those with high anxiety levels, avoidance behaviors, and dysfunctional beliefs about pain

NON-SURGICAL PROCEDURES

There is wide geographic and practitioner variability in the utilization of procedures to treat LBP, and studies have demonstrated positive correlations between imaging, injections and surgery rates.[117] Given the risks and limited duration of benefit for interventions, procedures should generally be performed on patients who have failed conservative measures, though exceptions may be reasonable in some cases.

LUMBAR EPIDURAL STEROID INJECTIONS & ADHESIOLOYSIS

Despite over 9,000,000 ESI being performed each year in the U.S., utility of lumbar epidural steroid injections (LESI) remains controversial, with studies and reviews performed by interventionalists more likely to yield positive findings than those performed by non-interventionalists.[118] For example, while Spinal Intervention Society (SIS) guidelines tout strong evidence to support LESI for radicular pain, a Cochrane review found only small, short-term

benefits compared to placebo for pain relief and function.[119] For axial LBP, there is a lack of strong evidence supporting benefit, and most guidelines recommend them only for radicular pain.

There are several approaches for the administration of epidural steroids including transforaminal, interlaminar, and caudal routes. Recent comprehensive review of published data found strong evidence for transforaminal ESI in HNP for up to 6 months, but only low-quality evidence for a small effect for spinal stenosis.[120]

Regarding the type of steroid, all placebo-controlled trials have been performed using long-acting particulate steroids, but reviews are mixed regarding whether they provide better or longer relief than non-particulate steroids (e.g. dexamethasone).[120, 121] However, the transforaminal delivery of long-acting particulate steroids has been associated with rare, catastrophic events such as death and paralysis, which has prompted some[121] but not all[122] task forces to recommend that the initial lumbar TFESI be performed with non-particulate steroids. Stratified by pathology, the effectiveness of ESI tends to be better in patients with HNP than spinal stenosis, and weakest in individuals with axial pain and radicular pain from degenerative disc disease without nerve compression.[118] Most of the early (< 2 weeks) effect of ESI derives from the injectate itself (i.e. local anesthetic and saline) rather than the steroids, which prompts questions regarding what constitutes a placebo for ESI.[123, 124] Although multiple studies have found evidence for long-term benefit with serial LESI,[125, 126] the downside is that a single injection typically provides only short-term relief (< 3 months). Regarding the prevention of surgery, a meta-analysis found mixed evidence for a small effect in the short-term for a single LESI, but not in long-term (> 1 year).[127]

SACROILIAC JOINT INJECTIONS

Small controlled studies with short-term (≤ 2 months) follow-up found evidence for intra- and extra-articular steroids in patients with and without spondyloarthropathy.[128] There is some evidence that combination of intra- and extra-articular SI joint steroid injections may have better therapeutic effect.[129] Fluoroscopic guidance has been recommended for performing SI injections; however, there is no agreement regarding the type and dose of steroids used.[129]

FACET JOINT BLOCKS AND RADIOFREQUENCY ABLATION

Facet joints receive innervation from medial branches of the dorsal ramus at 2 levels, which are the target for diagnostic/prognostic nerve blocks. International guidelines on lumbar facet interventions found no evidence for long-term therapeutic benefit from medial branch blocks (MBB) or intra-articular injections with steroids, and concluded that MBB should be the preferred prognostic test before RFA.[130] However, another evidence-based guidelines provided moderate strength of recommendation for both lumbar facet joint nerve blocks as well as lumbar RFA.[131]

A large RCT[132] raised questions regarding the efficacy of radiofrequency treatment of the medial branches of the dorsal ramus; however, the study was widely criticized for their non-rigorous selection criteria and performance.[133, 134] According to NICE guidelines, radiofrequency lumbar medial branch (facet) denervation may be considered after conventional management has failed in individuals with injection-confirmed facetogenic pain.[112]

SACROILIAC JOINT RADIOFREQUENCY

The SI joint is innervated by the lateral branches stemming from the L5-S3, and sometimes S4 dorsal rami. At each level, from 1-4 lateral branches supply nociceptive feedback, primarily from the ligaments; hence, SI joint denervation is ideally suited for younger individuals with suspected extra-articular pain. Although there are numerous uncontrolled trials that have reported benefit, randomized placebo-controlled trials evaluating SI joint denervation are divided regarding efficacy, with the positive studies both being industry funded and utilized internally-cooled electrodes.[135]

SPINAL CORD STIMULATION

A systematic review that compared spinal cord (SCS) stimulation to conventional therapies in over 300,000 patients with CLBP and leg pain found that 8 of the 11 included studies reported SCS to be associated with better outcomes and cost-effectiveness.[136] Major limitations of randomized SCS trials include the effect of industry sponsorship, including programming by company representatives, and the lack of adequate blinding.

SCS has traditionally been utilized for neuropathic pain, particularly in individuals with previous spine surgery and leg greater than back pain. However, a more recent study showed that high-

frequency SCS provided better analgesia and functional improvement than conventional SCS in patients with low back and leg pain, with or without prior surgery.[137] A recent meta-analysis showed that neuromodulation was associated with opioid reduction.[138] Other major advances in neuromodulation include burst DR stimulation, MRI-compatible systems, dorsal root ganglion (DRG) stimulation, and a diverse combination of electrode arrays.

Summary of non-surgical procedures

- LESI may be useful in the treatment of lumbosacral radicular pain, though serial injections provide long-term benefit
- Both intra- and extra-articular SI joint injections can provide short-term pain relief and functional improvement, and are considered the reference standard for identifying a painful joint
- RFA of the lateral branches innervating the SI joint should be considered in patients with SI joint pain who fail to derive long-term benefit from blocks, and may be more effective when aggressive lesioning strategies are utilized.
- RFA of the lumbar medial branches may provide relief to well-selected candidates who respond to diagnostic facet blocks
- SCS is primarily indicated for the treatment of LBP with a neuropathic component that persists after spine surgery, though newer technologies may also alleviate axial LBP.

SURGERY

There has been enormous interest in the past 2 decades regarding the indications and utility of surgery for CLBP. Studies have shown that surgical rates, and the proportion of complex surgeries (e.g. instrumentation) are higher in the U.S. than nearly all other countries, but do not affect LBP disability rates.[139]

For HNP, a systematic review found that surgery results in faster pain relief and functional improvement than conservative management, but no differences were observed after 1 to 2 years.[140] More recently, an RCT found greater improvement in the surgical group compared to conservative care in patients with sciatica secondary to HPN that persisted at 12 months.[141]

In patients with LSS, a systematic review found that decompression surgery resulted in significant improvement compared to conservative management at 3 to 6 months; at 2 to 4 year follow-up, pain and disability outcomes continued to favor the surgical group, but had declined.[142] A later systematic review found no benefit for decompression and fusion compared to decompression alone for stenosis.[143] The 2016 NICE guidelines recommend spinal decompression for people with

radicular pain when non-surgical treatment has not improved pain or function and radiological findings are consistent with radicular symptoms.[112]

Lumbar fusion is often performed for refractory spondylosis. However, a meta-analysis that included studies with long-term follow-up found little benefit for fusion compared to non-operative management.[144] A cohort study evaluating prognostic factors following fusion found that elderly patients undergoing single-level lumbar disc fusion with low baseline disability experienced the best outcomes.[145] According to the NICE guidelines, spinal fusion should not be offered as a treatment for LBP outside of a clinical trial.[112]

Patients with low back pain who undergo spinal surgery may experience recurrent low back pain with or without a radicular component, termed Failed Back Surgery Syndrome (FBSS). It is generally accepted that the incidence ranges between 10% and 40 % after lumbar laminectomy, with or without fusion.[146] Causes may include adhesions, arachnoiditis, complications of the surgery (battered nerve roots), inappropriate patient selection, technical failure, and adjacent segment disease.

Disc replacement is generally limited to individuals with predominantly discogenic pain limited to 1 or 2 segments, and may be associated with better preserved range of motion than arthrodesis. A systematic review that compared lumbar fusion to disc replacement reported short-term benefits favoring disc replacement that may not have been clinically meaningful.[147] An earlier Cochrane review reported disc replacement to have small, clinically questionable benefits compared to fusion surgery and comprehensive rehabilitation in patients with degenerative disc disease.[148] An inherent flaw in surgical studies that use intention-to-treat analysis is that more patients crossover to surgery than vice versa, which can minimize differences.[141]

Summary of surgical procedures

- Surgery may provide short-term benefit compared to non-surgical treatment in refractory cases, but is more beneficial for radicular symptoms
- 10-40% percent of patients end up with FBSS after lumbar surgery
- Strong indications for surgery include cauda equina syndrome, serious or progressive neurological deficits, spinal instability, and possibly refractory pain resulting in significant disability.

LIMITATIONS

Conclusions from narrative reviews rely heavily on article selection, and while we prioritized systematic reviews and meta-analyses, the conclusions in these reviews vary with specialty, which introduces bias. Unlike conditions such as diabetic neuropathy, LBP is a symptom so studies evaluating interventional treatments tailored towards a specific etiology (e.g. injections, surgeries) depend on accurate diagnosis, which is subjective to false-positive and false-negative results. Non-pharmacological treatments (integrative and procedural) are challenging to study using placebos, and uncontrolled studies may overestimate treatment effect. There are also numerous therapies we were not able to evaluate in this review, and the decision about which ones to include were based on what we considered important.

Major Challenges	Future Directions
• The multifactorial nature of most cases of CLBP (e.g. superimposed facetogenic pain, discogenic pain and muscle tension), and the inherent difficulties in identifying pain generators (e.g. lack of MRI specificity, the high false-positive and false-negative rate of diagnostic blocks with no reliable reference standards); • The high placebo response rate for surgery, non-surgical interventions, and integrative therapies that require multiple visits and 'hands-on' care; • Deciding what constitutes a true control (e.g. placebo) treatment, and the cost and ethics involved in performing controlled studies; • Poor translation from clinical trials to clinical practice • The association between disc pathology and low-grade infection in patients with LBP, and the use of antibiotics to treat them.	• Shift from focusing on subjective outcome measures (e.g. pain scores at a cross-section in time) to more objective outcome measures (e.g. step count, functional imaging); • Increase the duration of follow-up in controlled studies; avoid unnecessary provider contact; take steps to maximize blinding effectiveness • Adaptive study designs that consider personalized care models • The inclusion of patients with psychopathology, on opioid therapy, and with a nociplastic component to enhance generalizability; • Meticulous harvest technique; well-designed clinical trials

CONCLUSIONS

The prevalence of CLBP is expected to increase with the aging of populations and as technological advances lead to more sedentary lifestyles. Although this article focuses on specific conditions

and their treatments, there is considerable overlap between LBP etiologies in terms of presentation. There is widespread acceptance of the biopsychosocial model that emphasizes multidimensional components as contributors to LBP and disability, and the diverse consequences of chronic pain that can adversely affect all aspects of life. This model emphasizes behavioral and lifestyle modification and the burgeoning fields of genetics and phenotyping (i.e. precision medicine), a detailed discussion of which is beyond the scope of this article. Whereas the majority of currently available pain management options typically address only single etiologies, given the complex nature of LBP, a multimodal, interdisciplinary approach is warranted.

CONTRIBUTORS

NNK and SCP conceived the design; NNK, JWSV and SCP did the search of published work. All authors wrote the Seminar and approved the submitted version.

DECLARATION OF INTEREST

NNK, KDC, JVZ, JWSV have nothing to disclose.

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