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GUIDELINE TREATMENT RECOMMENDATIONS FOR NONSPEIFIC LOW BACK PAIN WITH OR WITHOUT RADICULOPATHY

NONPHARMACOLOGIC AND PHARMACOLOGIC INTERVENTIONS

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ABBREVIATIONS

ACP	American College of Physicians
ACR	American College of Radiology
ACOG	American College of Obstetricians and Gynecologists
AGEP	acute generalized exanthematous pustulosis
AGS	American Geriatrics Society
AOPT	Academy of Orthopedic Physical Therapy
APTA	American Physical Therapy Association
APS	American Pain Society
CNS	central nervous system
COX	cyclooxygenase
CPG	clinical practice guideline
CBT	cognitive behavioral therapy
CT	computed tomography
CV	cardiovascular
CYP	cytochrome
DDIs	drug-drug interactions
DoD	Department of Defense
FDA	Food and Drug Administration
GI	gastrointestinal
ICSI	Institute for Clinical Systems Improvement
IV	intravenous
LBP	low back pain
LOE	level of evidence
MBR	multidisciplinary biopsychosocial rehabilitation
MBSR	mindfulness-based stress reduction
MDD	major depressive disorder
MME	morphine milligram equivalents
MRI	magnetic resonance imaging
NASS	North American Spine Society
NICE	National Institute for Health and Care Excellence
NSAID	Nonsteroidal anti-inflammatory drug
PT	physical therapy
PUD	peptic ulcer disease
RCT	randomized controlled trial
REMS	Risk Evaluation and Mitigation Strategy
SIADH	syndrome of inappropriate antidiuretic hormone
SJS	Stevens-Johnson Syndrome
SMRs	skeletal muscle relaxants
SNRI	serotonin-norepinephrine reuptake inhibitor
SR	systematic review
SSRI	selective serotonin reuptake inhibitors
TCA	tricyclic antidepressant
TEN	toxic epidermal necrolysis
TENS	transcutaneous electrical nerve stimulation
TOP	Toward Optimized Practice
VA	Veterans Affairs

EXECUTIVE SUMMARY

Background:

Disease Introduction: Low back pain (LBP) is a symptom of many conditions, including degenerative disc disease, sciatica, osteoarthritis, ankylosing spondylitis, spinal stenosis, malignancy, and cauda equina.[1] In the United States (US), LBP is one of the most common adult diagnoses, with up to 84% experiencing it during their lifetime.[2,3]

LBP is categorized by duration of symptoms as acute (≤ 4 weeks), subacute (4–12 weeks), or chronic (>12 weeks), although the defining timeframes may vary slightly between the acute and subacute categories.[4] LBP is also categorized based on the presence or absence of neurologic features (ie, non-radiating LBP vs radiculopathy or radicular LBP).[1,3,5] LBP with lumbosacral radiculopathy, also referred to as sciatica, often presents as sensory loss, motor loss, or paresthesia extending into the leg(s).[6,7] Typically LBP, is self-limiting,[1,2] with resolution of symptoms usually (but not exclusively) expected within 2 to 6 weeks of initial onset.[8]

This report reviews recent (within the past 5 years) US guideline recommendations for diagnosis and noninvasive treatment of nonspecific LBP with or without radiculopathy, including the following 13 interventions:

7 *nonpharmacologic* interventions, including "active" (c-d) and "passive" therapies (e-g)[9]

a. Self-care
b. Heat/cold therapy
c. Exercise
d. Psychological therapies (eg, cognitive behavioral therapy [CBT], mindfulness-based stress reduction [MBSR])
e. Acupuncture
f. Massage
g. Spinal manipulation

6 *pharmacologic* interventions

h. Topical therapies
i. Nonsteroidal anti-inflammatory drugs (NSAIDs)
j. Acetaminophen
k. Duloxetine, primarily, or other antidepressants (eg, tricyclic antidepressant [TCAs], selective serotonin reuptake inhibitors [SSRIs])
l. Skeletal muscle relaxants (SMRs)
m. Opioids

Methods:

Literature searches for clinical practice guidelines (CPGs) addressing pharmacologic therapy for nonspecific LBP were carried out in Ovid Medline and Epistemonikos. We also searched guideline databases (TRIP, Guideline Central, UpToDate, and ECRI Guidelines Trust) and organizational websites (American College of Physicians [ACP], North American Spine Society [NASS], Institute for Clinical Systems Improvement [ICSI], and the Department of Veterans Affairs/Department of Defense [VA/DoD])

for recent US CPGs. The Institute for Clinical and Economic Review (ICER) website was additionally searched for relevant reviews about treatment of LBP.

Recommendations were extracted from the following 4 CPGs:

- 2020 NASS Evidence-Based Clinical Guidelines for Multidisciplinary Spine Care: Diagnosis and Treatment of Low Back Pain[4]
- 2018 ICSI Adult Acute and Subacute Low Back Pain[5]
- 2017 ACP Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline[3]
- 2017 VA/DoD Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain *(published in literature in 2019)*[1,2]

To supplement the guideline recommendations, other guidelines pertaining to subspecialities of medicine (eg, radiology, physical therapy, chiropractic) and from other countries (UK, Canada) were included in this report.

Guideline recommendations:

Diagnosis: Given the vast array of possible causes of LBP symptoms, most guidelines recommend a triage approach to diagnosis, regardless of symptom duration.[10,11] At the initial evaluation, clinicians should perform a detailed history and assessment to identify neurological deficits (eg, radiculopathy, lower extremity dysesthesia and/or paraesthesia) and serious pathological causes of LBP (eg, malignancy, infection, spinal stenosis, spondylolisthesis, disc herniation, and vertebral fracture) that would require additional diagnostic evaluations and/or referral.[1,5] Generally, the use of radiographic imaging to diagnosis LBP with or without radiculopathy, such as magnetic resonance imaging (MRI) or computed tomography (CT) should be reserved for patients presenting with serious pathological causes.[1,2,5]

Nonpharmacologic Interventions:

Therapies for which a recommendation is provided for include the following:

1. **Self-care:** Appropriate education on self-care is recommended for all patients with nonspecific LBP with or without radiculopathy.[1,5]
2. **Heat/cold therapy:** Heat (eg, heating pad, heated blankets) is recommended for transient pain relief in patients with acute or subacute nonspecific LBP.[1-5] The application of cold therapy (eg, ice packs) is generally not recommended due to a lack of evidence;[1,2,4,5] however, due to the minimal risk of harm, cold therapy may be used short-term for symptomatic relief.[5,9]
3. **Exercise therapy:** Continuing regular physical activity, recommended for all patients experiencing nonspecific LBP with or without radiculopathy,[1,5] should be distinguished from exercise therapy, consisting of supervised or home-based programs that improve muscle strength and/or flexibility.[11] Exercise therapy (eg, clinician-directed programs, yoga, tai chi, pilates) is recommend exclusively for the management of chronic nonspecific LBP with or without radiculopathy.[1,3,4] A multidisciplinary biopsychosocial rehabilitation (MBR) method incorporating physical and behavioral/psychological interventions to manage symptoms is recommended for patients with more severe or complicated chronic nonspecific LBP, unresponsive to other "limited approaches".[1,2]

4. **Psychological therapies:** Guidelines support cognitive behavioral therapy (CBT) and mindfulness-based stress reduction (MBSR) exclusively for chronic nonspecific LBP due to the conflicting evidence of CBT and MBSR for the management of acute or subacute nonspecific LBP.[1,3-5] CBT and MBSR may be used alone or in combination with other nonpharmacologic therapies.[4,9,12]
5. **Acupuncture:** Guidelines are conflicting about the therapeutic utility of acupuncture depending on symptom duration, which may be due to the substantial heterogeneity of the evidence.[1] ACP (2017) recommends acupuncture for acute, subacute, and chronic nonspecific LBP;[3] ICSI (2018) recommends acupuncture only for subacute nonspecific LBP;[5] and VA/DoD and NASS (2017, 2020) recommends acupuncture only for chronic nonspecific LBP.[1,4]
6. **Massage:** Guidelines favor massage for pain reduction in patients with subacute or chronic nonspecific LBP, but fail to provide guidance for its use.[1,3,5] US guidelines lack a uniform consensus regarding the short-term benefit of massage for pain relief when used in combination with an exercise program among those with subacute or chronic nonspecific LBP.[3-5]
7. **Spinal manipulation:** Spinal manipulation is recommended for acute, subacute, and chronic nonspecific LBP,[1,3-5] particularly as an early intervention for acute conditions.[5]

Pharmacologic Interventions

*Therapies for which a recommendation is not provided (**for or against)** include* antiepileptics (including **gabapentinoids** gabapentin, pregabalin) and lidocaine patches. For example,

- NASS (2020), a recent guideline, did not discuss potential supportive information for gabapentinoids or topical lidocaine for LBP with neuropathic features; this may be due to the guideline's focus on non-radicular LBP.[4]
- Other guidelines and expert reviews that address neuropathic pain (which may include radiculopathy) do recommend gabapentinoids and topical lidocaine.[13-17]

*Therapies for which a recommendation is provided **for** include the following:*

1. **Topical therapies:** NASS (2020) recommends topical capsaicin for short-term use (≤ 3 months) in LBP.[4] Other guidelines neither address topical therapies nor make recommendations about their use, due to insufficient evidence.[1,3,5]
2. **NSAIDs:** US guidelines recommend oral NSAIDs for short-term pain management in patients with acute, subacute, and chronic nonspecific LBP with or without radiculopathy.[1,3-5] Except NASS, most guidelines favor cyclooxygenase-2s (COX-2s) over conventional NSAIDs; NASS favors non-selective NSAIDs due to inconclusive evidence for the use of selective NSAIDs.[4]
3. **Acetaminophen:** Due to consistent evidence demonstrating a lack of efficacy, concerns of harm predominates recommendations about acetaminophen, which results in conflicting recommendations in acute nonspecific LBP.[1,3,5] ACP (2017) no longer recommends it for acute nonspecific LBP with or without radiculopathy due to a lack of superiority vs placebo.[3] ICSI recommends it for pain in acute and subacute nonspecific LBP with or without radiculopathy.[5]
4. **Antidepressants/ duloxetine:** NASS and NICE recommend against antidepressants for nonspecific LBP.[4,12] VA/DoD and ACP recommend consideration of duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI) for chronic nonspecific LBP with or without radiculopathy.[1-3] According to a 2017 Canadian guideline, SNRIs or TCAs are recommended in

patients with nonspecific LBP with co-emergent musculoskeletal complaints of neuropathic pain.[8] ICSI, a guideline that focuses on acute and subacute treatment, did not address antidepressants for the management of nonspecific LBP.[5]

5. **Skeletal muscle relaxants (SMRs):** Guidelines recommend non-benzodiazepine SMRs (eg, cyclobenzaprine, tizanidine) for short-term (< 1 week) use in nonspecific LBP with or without radiculopathy.[1,3,5] VA/DoD recommends muscle relaxants only for acute exacerbations in chronic nonspecific LBP;[1] this is likely due to an unfavorable side effect profile, which outweighs any benefit with long-term use.[5]
6. **Opioids:** US guidelines only recommend a short-course of opioids as a last-line option in most LBP conditions, especially chronic nonspecific LBP with inadequate relief from other medications (eg, NSAIDs, duloxetine), and only when therapeutic benefits outweigh the risks.[3] However, some guidelines provide a separate recommendation for tramadol, perhaps due to its slightly different mechanism of action (ie, inhibiting serotonin and norepinephrine reuptake).[13] ACP (2017) lists tramadol as a second-line agent for chronic nonspecific LBP.[3] ICSI recommends a trial of short-acting opioids in patients with severe acute pain that has not responded to non-opioids; in such cases, clinicians should use the lowest effective dose (≤ 100 morphine milligram equivalents [MME] total) for ≤ 3 days.[5]

Safety warnings and precautions for select pharmacologic therapies:

NSAIDs, regardless of selectivity, carry a black box warning for increased risks of cerebrovascular events (myocardial infarction [MI] and stroke) and GI events (bleeding, ulceration, and perforation).[18] CV thrombotic event risks may vary across the NSAIDs, but such risks are thought to occur early, and to increase with prolonged use.[18] Older adults and patients with a previous history of peptic ulcer disease (PUD) and/or ulcers have increased risks for serious GI events; these events may occur at any time during NSAID use, with or without warning symptoms.[18]

Acetaminophen has the potential to cause rare but serious, potentially fatal skin reactions, such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN).[19] High doses (ie, > 4 grams/day) can also cause hepatic failure and death.[20,21]

Duloxetine carries a black box warning for increased risk of suicidality, including emergent thoughts and behaviors among pediatrics, adolescents, and young adults.[22]

Warnings and precautions differ between SMRs, with some agents having the potential to cause anticholinergic side effects (eg, cyclobenzaprine, orphenadrine),[23] while the majority tend to increase the risk of CNS depression (eg, sedation), especially with concomitant use of other CNS depressants (eg, alcohol, opioids).[24-27]

Opioids carry a black box warning for addiction, abuse and misuse, mandatory participation by the Food and Drug Administration (FDA) in a Risk Evaluation and Mitigation Strategy (REMS) program, increased risk for fatal respiratory depression and overdose with accidental consumption, the possibility for neonatal opioid withdrawal syndrome, and the potential for drug-drug interactions.[28,29] Significant respiratory depression, which may result in respiratory arrest and death has occurred with opioid use.[28,29] Drug-drug interactions (DDIs), including those due to drug metabolism or concurrent CNS depressants (eg, benzodiazepines, alcohol, SMRs) increase these risks.[28,29]

Summary of the treatment approach for nonspecific LBP with or without radiculopathy:
(Refer to Table 12)

US guidelines tend to recommend education on self-care as the first-line option for patients presenting with nonspecific LBP with or without radiculopathy, regardless of symptom duration or severity.[1,5,9] Nonpharmacologic interventions are preferred over pharmacologic treatments for acute, subacute, and chronic nonspecific LBP management due to the lower inherent risks;[3] however, a combination of both modalities are often used in clinical practice to gain better symptom control.[9] Usually pharmacologic treatment is reserved for patients presenting with more severe symptoms that fail to produce an adequate response to nonpharmacologic interventions.[3,9]

Generally, NSAIDs are considered the first-line pharmacologic option for the treatment of nonspecific LBP with or without radiculopathy.[9] Acetaminophen may be considered as an alternative in patients that are not appropriate candidates for NSAIDs.[9]

Typically, non-benzodiazepine SMRs are reserved as second-line pharmacologic agents for short-term (< 1 week) use in the management of nonspecific LBP when therapy with NSAIDs or acetaminophen has failed;[9] however, ACP (2017) recommends SMRs as first-line agents for acute or subacute nonspecific LBP, with the decision to select an NSAID or SMR based on patient specific factors (eg, benefit/risk, preference).[3]

Although VA/DoD does not explicitly state the place in therapy for duloxetine, ACP lists it as a second-line agent for individuals with chronic nonspecific LBP that previously failed nonpharmacologic interventions and NSAIDs.[1,3] Tramadol is also recommended as a second-line agent for the treatment of chronic nonspecific LBP by ACP, whereas other opioids are reserved as last-line agents.[3] Duloxetine may be preferred over tramadol in individuals with a history of substance use disorders, or concurrent depression or neuropathic pain.[8,9]

Opioids are considered a last-line option (except tramadol), generally for chronic nonspecific LBP after failure of all other alternative therapies (nonpharmacologic and pharmacologic).[3,8] Guidelines tend to discourage the use of opioids for acute or subacute nonspecific LBP;[3,5] however, ICSI (2018) mentions that opioids may be used at the clinician's discretion after failure of non-opioid agents and nonpharmacologic interventions in patients with severe acute pain.[5] Due to the risk of significant adverse events generally outweighing the potential small improvement in pain relief, it is recommended that opioid therapy should be prescribed for the shortest needed duration at the lowest effective dose.[1,4,5]

1.0 INTRODUCTION

Low back pain (LBP) is a common symptom that can manifest as a result of many possible underlying disease states.[1] LBP may be categorized as nonspecific LBP, or back pain due to an associated condition (eg, degenerative disc disease, ankylosing spondylitis, spinal stenosis), with or without radiculopathy.[1] In the United States (US), LBP is one of the most common conditions among adults, with up to 84% of people experiencing it during their lifetime.[2,3]

While LBP can be self-limiting, a third of patients may progress to chronic LBP.[3,5] Chronic LBP is a leading cause of disability worldwide,[30] resulting in a significant economic burden.[5,31] A study of US healthcare spending from 1996 to 2016 showed that costs related to LBP and neck pain was the highest out of 154 other conditions, with costing approximately $134.5 billion in 2016.[32]

A variety of therapies (nonpharmacologic and pharmacologic), including effective self-care strategies are utilized for acute, subacute, and chronic nonspecific LBP. The use of nonpharmacologic interventions are preferred over pharmacologic treatments due to the lower inherent risks;[3] however, a combination of both modalities are often used in clinical practice to gain better symptom control.[9]

The objective of this report is to provide an overview of recent US guideline recommendations pertaining to the diagnosis and noninvasive treatment options for nonspecific LBP with or without radiculopathy.

Table 1 includes the pharmacologic and nonpharmacologic treatment options for nonspecific LBP with or without radiculopathy that are discussed in this report.

Table 1. Nonpharmacologic and Pharmacologic Interventions for Nonspecific Low Back Pain

Nonpharmacologic Interventions		
• Self-care • Psychological therapies (eg, CBT, MBSR)	• Heat/cold therapy • Acupuncture • Spinal manipulation	• Exercise • Massage
Pharmacologic Interventions		
• Topical therapies • Duloxetine	• NSAIDs • SMRs	• Acetaminophen • Opioids

Abbreviations: CBT, cognitive behavioral therapy; MBSR, mindfulness-based stress reduction; NSAIDs, nonsteroidal anti-inflammatory drugs; SMRs, skeletal muscle relaxants

2.0 METHODS

2.1 Systematic Literature Search

Search strategies, consisting of keyword phrases and controlled vocabulary, were developed for Ovid Medline and Epistemonikos (see **Appendix A** for the complete search strategy). The databases were searched from January 2017 to January 2022 for clinical practice guidelines (CPGs) addressing at least pharmacologic management for nonspecific LBP or LBP with neuropathic symptoms (eg, radiculopathy). Reference lists of CPG review articles were additionally screened to identify any additional relevant practice guidelines published within the past 5 years.

The following databases or organizational websites were searched for recent (ie, within the past 5 years) *United States (US)* CPGs pertaining to the nonpharmacologic and pharmacologic management of LBP (nonspecific with or without radiculopathy):

1. TRIP (https://www.tripdatabase.com/), Guideline Central (https://www.guidelinecentral.com/), UpToDate (https://www.uptodate.com), ECRI Guidelines Trust (https://guidelines.ecri.org/)
2. North American Spine Society (NASS), American College of Physicians (ACP), Institute for Clinical Systems Improvement (ICSI), Department of Veterans Affairs/Department of Defense (VA/DoD)

The Institute for Clinical and Economic Review (ICER) website (https://www.icer.org/) was additionally searched for relevant reviews about treatment of LBP.

Excluded guidelines met one or more of the following criteria:

1. Published prior to 2017
2. Only pertain to invasive treatments (ie, epidural and lumbar facet joint injections, surgery)
3. Only address specific LBP conditions (eg, spinal stenosis, spondylolisthesis, lumbar disc herniation, vertebral fracture)
4. Pertain to only a subspeciality of medicine that did not include pharmacologic interventions (eg, radiology, physical therapy, chiropractic)

2.2 Literature Search Results

The following 4 CPGs were included, listed in order of most recent publication year:

- 2020 NASS Evidence-Based Clinical Guidelines for Multidisciplinary Spine Care: Diagnosis and Treatment of Low Back Pain[4]
- 2018 ICSI Adult Acute and Subacute Low Back Pain[5]
- 2017 ACP Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline[3]
- 2017 VA/DoD Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain *(published in a medical journal in 2019)*[1,2]

Appendix B lists additional guidelines that were reviewed for information regarding the management of LBP.

3.0 DISEASE OVERVIEW

The symptom of low back pain (LBP) may be associated with various conditions including degenerative disc disease, sciatica, osteoarthritis, ankylosing spondylitis, spinal stenosis, malignancy, and cauda equina syndrome.[1] According to the North American Spine Society (NASS), LBP is defined as "pain of musculoskeletal origin extending from the lowest rib to the gluteal fold" that may radiate "as somatic referred pain into the thigh (above the knee)".[4] Approximately 90% of LBP cases are diagnosed as nonspecific back pain.[8]

In the United States (US), LBP is one of the most common adult conditions, with up to 84% of adults experiencing it during their lifetime.[2,3] The prevalence and onset of age depends on the etiology of the LBP.[31] LBP is more prevalent in women than in men (29.6% vs. 25.4%, respectively).[1] Even after initial

recovery, LBP symptom recurrence is common, with 24–80% of people experiencing a return of LBP symptoms within a year of recovery.[5]

LBP is categorized based on the duration of symptoms as acute (≤ 4 weeks), subacute (4–12 weeks), or chronic (>12 weeks), although the defining timeframes may vary slightly between the acute and subacute categories.[4] LBP is also categorized based on the presence or absence of neurologic features (ie, non-radiating LBP vs radiculopathy or radicular LBP).[1,3,5] Radiculopathy is used to describe a range of symptoms including pain that results from spinal nerve root impingement (which may be caused by stenosis, bone spurs, disc herniation, among others).[3,6] LBP with radiculopathy presents as sensory loss or paresthesia extending in a dermatomal pattern to the leg(s) and/or motor loss in a myotomal pattern into the leg(s).[6]

Acute LBP episodes may be triggered by physical (eg, inappropriate lifting) and/or psychosocial factors (eg, exhaustion).[33] Typically LBP is self-limiting,[1,2] with resolution of symptoms within 2 to 6 weeks of initial onset, but symptoms may persist longer.[8] Due to the self-limited nature, many patients do not seek medical treatment which may impact the persistence of symptoms.[3,5] Other factors, also known as "yellow flags" that impact chronicity include psychosocial (ie, depression) and employment factors (job satisfaction, employment status).[4,5,8]

3.1 Diagnosis

Given the vast array of possible causes of LBP symptoms, guidelines recommend a triage approach to diagnosing LBP, regardless of symptom duration.[10,11] At the initial evaluation, clinicians should perform a detailed history and assessment to identify neurological deficits (eg, radiculopathy, lower extremity dysesthesia and/or paresthesia) and serious pathological causes of LBP (eg, malignancy, infection, spinal stenosis, spondylolisthesis, disc herniation, vertebral fracture) that would require additional diagnostic evaluations and/or referral.[1,5] Signs and symptoms that may be indicative of a serious pathological condition are referred to as "red flags" (see **Table 2** for examples).[1,5,34] Diagnosis and treatment for all the possible back disorders that can manifest LBP is beyond the scope of this report.

Generally, the use of radiographic imaging to diagnosis LBP with or without radiculopathy, such as magnetic resonance imaging (MRI) or computed tomography (CT) should be reserved for patients presenting with red flags.[1,2,5] In the absence of red flags, the harms outweigh the benefits in most patients with non-specific LBP.[1,2,5] In this patient population, imaging may discover asymptomatic anatomic abnormalities,[34] resulting in additional costs, unnecessary exposure to radiation, and undue patient anxiety.[5,8] According to the American College of Radiology (ACR) Appropriateness Criteria (2021),[35] imaging is usually appropriate for the following populations, in addition to the presentation of red flags:

- Older individuals and patients with low-velocity trauma, osteoporosis, or prolonged steroid use
- Patients with subacute or chronic LBP with or without radiculopathy deemed "surgical or intervention candidates" that experience constant or progressive symptoms throughout or after "6 weeks of optimal medical management"[35]
- Patients that previously underwent lumbar surgery with new or worsening symptoms

Additionally, imaging may be warranted in patients with serious or worsening pain or neurological deficits, or when symptoms persist for > 12 weeks.[1,7]

Table 2 provides several examples of serious underlying conditions that can cause LBP with the associated red flags that may warrant additional investigation. It also includes the recommended diagnostic imaging based on guidelines (VA/DoD 2017, ICSI 2018, and NASS 2020) and guidance from the American College of Radiology for LBP (2021).

Table 2. Examples of Red Flags or Risk Factors for Low Back Pain Caused by a Serious Underlying Condition[1,4,5,8,35]

Conditions or Feasible Cause	Red Flags or Risk Factors	Recommended Diagnostic Imaging
Infection	• **Fever** • **IV drug use** • **Immunosuppression** • Recent prior infection	MRI with contrast[a] ESR
Fracture	• Previous diagnosis of osteoporosis • Long-term use of corticosteroids • Advanced age (≥ 75 years of age) • History of recent trauma • Risk for stress fracture in younger patients with overuse	Lumbosacral plain radiography MRI[b], CT, or SPECT as appropriate for uncertain results
Ankylosing spondylitis	• Stiffness in the morning • Improves with exercise • Pain in the right then left buttock or vice versa • Awakening due to LBP during the early morning • Younger age of onset	Anterior-posterior pelvis plain radiography
Herniated disc	• Radicular LBP (eg, sciatica) • Lower extremity dysesthesia (eg, pain) and/or paresthesia (eg, "pins and needles") • Positive straight-leg-raise (Lasègue test) or crossed straight-leg-test	None
	• **Worsening or severe lower extremity neurologic deficits (eg, weakness)** • **Symptoms persisting beyond one month**	MRI[b]
Spinal stenosis	• Radicular LBP (eg, sciatica) • Lower extremity dysesthesia (eg, pain) and/or paresthesia (eg, "pins and needles") • Neurogenic claudication • Advanced age (> 50 years of age)	None
	• **Worsening or severe lower extremity neurologic deficits (eg, weakness)** • **Symptoms persisting beyond one month**	MRI[b]
Cauda equina or conus medullaris syndrome[c]	• **Urinary retention** • **Incontinence (urinary and/or fecal)** • **Saddle anesthesia** • **Worsening or severe lower extremity neurologic deficits (eg, weakness)** • **Changes in anal sphincter tone**	Emergent MRI[b]

Table 2. Examples of Red Flags or Risk Factors for Low Back Pain Caused by a Serious Underlying Condition[1,4,5,8,35]

Conditions or Feasible Cause	Red Flags or Risk Factors	Recommended Diagnostic Imaging

Abbreviations: CT, computed tomography; ESR, electron spin resonance; IV, intravenous; LBP, low back pain; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography

[a] *Avoid contrast in contraindicated patients (eg, renal insufficiency), use MRI without contrast instead*

[b] *Avoid in patients with contraindications (eg, patients with pacemakers), use CT or CT myelogram instead*

[c] *Immediate medical emergency; delay in treatment may result in lifelong disability*

Bold text *signifies "red flags" according to the NASS 2020 and 2018 ICSI guidelines. Note that red flag conditions may vary based on the guideline reviewed.*

Physical examination of patients with LBP with or without radiculopathy should include neurologic evaluation (eg, straight-leg-raise, reflexes, strength), assessment of spinal posture and range of motion, and other examinations as indicated.[5,34] If radiculopathy is suspected, nerve conduction tests may be used to distinguish a neuropathic or muscular issue.[6]

According to the VA/DoD and ICSI guidelines, patient histories should be assessed for serious underlying pathological conditions (eg, cauda equina syndrome, malignancy, infection), previous LBP experiences, prior treatments for the management of LBP, including response, characteristics of the pain (eg, location, intensity, duration, exacerbating/ alleviating factors), evaluation of radiculopathy or neurologic deficits (eg, sensory and strength changes), and psychosocial factors, known as "yellow flags" (eg, depression).[1,2,5] The objective assessment of yellow flags may be conducted by using validated risk stratification tools such as STarT Back (Subgroups for Targeted Treatment) to identify patients at high-risk of developing chronic back pain.[5,9,12]

Table 3 includes some yellow flags that are associated with an increased chance of developing chronic LBP.

Table 3. Yellow Flags Associated with an Increased Chance of Developing Chronic Low Back Pain

Yellow Flag[5,8,34]
• Dependent on passive treatments (eg, massage, acupuncture) instead of participating in active therapies (eg, exercise) • Perception that pain and activity are detrimental (eg, fear avoidant behaviors) • History of back pain, work absence • Depression, negative mindset, distress, anti-social behaviors • Issues with contested claim reimbursement • Work-related dissatisfaction

While a careful history and physical examination are useful to identify lumbosacral radiculopathy, also referred to as sciatica,[6,7] there is not a definitive test to make the diagnosis.[7] A patient-based questionnaire (painDETECT) may be used as a screening tool to identify patients with a neuropathic pain component.[36] The questionnaire consists of seven sensory pain symptom questions ranging on a scale from 0, "never", to 5, "very strongly"; one question on the pattern of pain (ie, pain attacks with or without pain in between, or persistent pain) graded from –1 to +1; and one "yes or no" question on radiating pain graded 0, "no radiation" or +2, "radiating".[36] Patient scores are calculated based on the

addition of the individual questions with a maximum score of 38.[36] A score of ≥ 19 indicates a high chance (>90%) of a neuropathic pain element being present, whereas scores ≤ 12 indicate that a neuropathic pain element is doubtful (<15%).[36] Results are inconclusive for the presence of neuropathic pain for scores ranging from 13–18.[36]

Table 4 provides some signs and symptoms that are associated with lumbosacral radicular pain, also referred to as sciatica that may aid in the differential diagnosis from nonspecific LBP.

Table 4. Distinguishing Characteristics of Lumbosacral Radicular Pain (Sciatica)

Signs and Symptoms of Sciatica[7]
• One-sided leg pain that is more intense than the low back pain • Leg pain that radiates posteriorly and extends below the knee • Lack of feeling and/or paresthesia in the affected leg • Positive neural examination test (eg, straight leg raise) with worsening pain • Presence of a neurological deficit (eg, motor weakness, lack of tendon reflexes, sensory impairment)

US guideline recommendations pertaining to diagnosis and imaging of LBP are provided in **Table 5,** with the corresponding strength and level of evidence (LOE). An interpretation of the recommendation strength and LOE is provided in **Appendix C.**

Table 5. Select Diagnosis and Imaging Guideline Recommendations for Low Back Pain

Professional Organization (Year) and Guideline Recommendations	
North American Spine Society [NASS] (2020)[4]	**Recommendation Strength (LOE)[a]**
Diagnosis	
• A potential predictor of recurrence of LBP is a history of the condition	Suggested ***(B)***
○ Previous episodes of LBP are considered a prognostic indicator for chronicity	Suggested ***(B)***
• When assessing the risk of conversion from acute to chronic LBP, psychosocial and workplace factors should be evaluated, in addition to pain severity and functional impairment	Recommended ***(A)***
○ After an acute episode, psychosocial factors should be used as prognostic indicators for returning to work	Recommended ***(A)***
• In patients with diffuse LBP and soreness, a non-anatomical cause may be considered	May be considered ***(C)***
Imaging	
• Obtaining imaging without the presence of red flags	Insufficient or conflicting evidence ***(I)***
• Imaging results are a contributing factor to guide treatment decision-making	Insufficient or conflicting evidence ***(I)***
Institute for Clinical Systems Improvement [ICSI] (2018)[5]	**Recommendation Strength (LOE)[a]**
Diagnosis	
• A "biopsychosocial assessment" should be conducted in patients presenting with acute or subacute LBP	Consensus ***(N/A)***
Imaging	

Table 5. Select Diagnosis and Imaging Guideline Recommendations for Low Back Pain

Professional Organization (Year) and Guideline Recommendations	
• In patients presenting with no red flags and nonspecific or radicular LBP, imaging (x-ray, CT, MRI) is not recommended	Strong ***(moderate)***
The Department of Veterans Affairs/Department of Defense [VA/DoD] (2017)[1,2]	**Recommendation Strength (LOE)[a, b]**
Diagnosis	
• A history and physical exam, including evaluating neurologic deficits (eg, radiculopathy), red flags, and psychosocial factors should be conducted in patients presenting with LBP	Strong for [Recommend]
○ Perform a mental health screening and use the results to guide treatment	Weak for [Suggest offering]
Imaging	
• Patients presenting with red flags or serious/worsening neurologic deficits should have diagnostic imaging and laboratory testing, as applicable	Strong for [Recommend}
• Routine imaging or invasive diagnostic tests **should not** be obtained in patients with localized, non-radiating acute back pain	Strong against [Recommend against]

Abbreviations: CT, computed tomography; LBP, low back pain; LOE, level of evidence; MRI, magnetic resonance imaging; N/A, not applicable;

[a] See Appendix C for interpretation of level of evidence (LOE) and strength of recommendations

[b] The 2017 VA/DoD guideline does not report the LOE for their recommendations

4.0 GUIDELINES FOR THE TREATMENT OF NONSPEIFIC LOW BACK PAIN

A variety of therapies (nonpharmacologic and pharmacologic), including effective self-care strategies are utilized for acute, subacute, and chronic nonspecific LBP. Radicular pain is treated the same as nonspecific LBP, but a referral to a spine specialist may be warranted in patients with no improvement after 4 to 6 weeks of treatment.[5] Additionally, steroid injections (not reviewed in this report) may be an option in this patient population.[1,5,12]

Table 6 provides an overview of the scope and target population of reviewed guidelines for nonspecific LBP with or without radiculopathy.

Table 6. Scope and Target Population of Reviewed Guidelines for Nonspecific Low Back Pain[a]

Guideline (Professional Organization; Year)	Guideline Scope	Target Population
Low back pain and sciatica in over 16s: assessment and management **(NICE; 2016)**[12] [b]	Provides clinical recommendations for the diagnosis and treatment (nonpharmacologic and pharmacologic, including surgical therapies) of sciatica and LBP	Patients **(≥16 years of age)** with nonspecific LBP or sciatica No exclusions are mentioned
Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline **(ACP; 2017)**[3] [c, d]	Guidance on noninvasive pharmacologic and nonpharmacologic therapies based on efficacy and safety evidence for LBP **Excluded:** topical pharmacologic treatments and epidural injections	**Adults (≥ 18 years of age)** with acute, subacute, and chronic nonspecific LBP with or without radiculopathy, or symptomatic spinal stenosis **Excluded:** patients < 18 years of age, pregnant women, LBP from sites located outside of the spinal area (non-spinal LBP) such as thoracic or cervical back pain, and fibromyalgia or other myofascial pain conditions
Evidence-informed primary care management of low back pain: clinical practice guideline **(TOP; 2017)**[8] [b]	Provide evidence-based recommendations for diagnosis, and pharmacologic and nonpharmacologic therapies	**Adults (≥ 18 years of age)** with acute, subacute, and chronic nonspecific LBP with or without radiculopathy **Excluded:** patients < 18 years of age, pregnant women, specific causes of LBP (eg, surgical conditions, referred pain, inflammatory diseases, infections, degenerative and anatomical alternations, fractures, neoplasm, metabolic bone disease)
Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain **(VA/DoD; 2017)**[1,2] [c, d]	Clinical practice guidance for the diagnosis, and pharmacologic and nonpharmacologic therapies, including dietary supplements for the management of LBP **Excluded:** surgical procedures	**Adults (≥ 18 years of age)** with acute, subacute, and chronic nonspecific LBP with or without radiculopathy **Excluded:** patients <18 years of age, pregnant women
Adult Acute and Subacute Low Back Pain **(ICSI; 2018)**[5] [d]	Assist in recommendations for the diagnosis, and pharmacologic and nonpharmacologic treatment options for LBP	**Adults (≥ 18 years of age)** with acute and subacute nonspecific LBP or radiculopathy **Excluded:** patients with chronic LBP, patients < 18 years of age

Table 6. Scope and Target Population of Reviewed Guidelines for Nonspecific Low Back Pain[a]

Guideline (Professional Organization; Year)	Guideline Scope	Target Population
Diagnosis and Treatment of Low Back Pain **(NASS; 2020)[4] [e]**	Informational guidance to assist healthcare practitioners for the diagnosis, and pharmacologic, including invasive interventions (eg, steroid joint injections) and nonpharmacologic treatment of LBP	**Adults (≥ 18 years of age)** with acute, subacute, and chronic nonspecific LBP with stomatic referred pain/**non-radicular** pain restricted to above the knee **Excluded:** patients with leg pain extending below the knee (eg, sciatica), patients < 18 years of age, pregnant women, LBP in the context of neurological deficits, patients who had undergone lumbar surgery, or LBP due to deformities (eg, spondylolisthesis, spondylolysis and scoliosis) or extra-spinal conditions

Abbreviations: ACP, American College of Physicians; DoD, Department of Defense; ICSI, Institute for Clinical Systems Improvement; LBP, low back pain; NASS, North American Spine Society; NICE, National Institute for Health and Care Excellence; TOP, Toward Optimized Practice; VA, Department of Veterans Affairs

[a] The NICE (United Kingdom) and TOP (Canadian) guideline recommendations are provided within the body text of the report to provide additional insight on the treatment approach for nonspecific low back pain

*[b] Acute and subacute is defined as pain lasting ≤ 3 **months** and chronic is defined as pain lasting > 3 months [c] Chronic is defined as >12 weeks of pain [d] Acute is defined as pain lasting < 4 weeks and subacute is defined as 4—12 weeks of pain [e] Acute is defined as pain lasting < 6 weeks and subacute is defined as 6—12 weeks of pain*

4.1 Guideline Recommendations for Nonpharmacologic Treatments

Some nonpharmacologic therapies recommended by guidelines include education, superficial heat, exercise, psychotherapy, spinal manipulation, and acupuncture. Nonpharmacologic treatment may vary based on the duration of symptoms.

The following subsections include nonpharmacologic therapies with evidence to support their use for nonspecific LBP with or without radiculopathy, which were frequently mentioned within reviewed guidelines. **Appendix D** includes a glossary and summary table of conventional nonpharmacologic inventions for nonspecific LBP.

Nonpharmacologic therapies that were commonly lacking a recommendation or were recommended against due to insufficient evidence or lack of benefit for nonspecific LBP with or without radiculopathy include the following:[1,3-5]

- Electrical muscle stimulation
- Lumbar support
- Ultrasound
- Transcutaneous electrical nerve stimulation (TENS)
- Short-wave diathermy
- Lumbar traction

Table 7 outlines select nonpharmacologic recommendations from the reviewed US guidelines.

Table 7. Select Nonpharmacologic and Self-care Guideline Recommendations for Nonspecific Low Back Pain With or Without Radiculopathy

Professional Organization (Year) and Guideline Recommendations	
North American Spine Society [NASS] (2020)[4]	**Recommendation Strength (LOE)[a]**
Psychotherapy	
• Cognitive behavioral therapy (CBT) with physical therapy (PT) is recommended in patients with chronic LBP to improve pain	Recommended ***(A)***
○ May improve the ability to return to work and functionality	Suggested ***(B)***
○ During the first 6 months of LBP onset, PT with treatments focused on fear-avoidant behaviors (eg, CBT) are recommended	Recommended ***(A)***
▪ Kinesiophobia is a negative indicator of LBP treatment response	Suggested ***(B)***
Physical Activity	
• For improvements in chronic LBP and functionality, back school is recommended	Recommended ***(A)***
○ McKenzie exercise may be used for chronic LBP	May be considered ***(C)***
• Exercise in combination with laser therapy (low level or high level) provides improved short-term pain relief, unlike either therapy used alone	Suggested ***(B)***
○ Compared to exercise alone, laser therapy (low level or high level) provides no short-term benefit	Suggested ***(B)***
• Aerobic exercise is recommended to decrease pain, prevent disability, and improve psychological health at short-term follow-up (eg, 12 weeks)	Recommended ***(A)***
• Patients with acute LBP that exercise at baseline and use it to aid recovery are more likely to have better outcomes than those that do not exercise or use bed rest	Suggested ***(B)***
Heat Therapy	
• Heat may be used to provide transient pain relief for patients with acute LBP	Suggested ***(B)***
Acupuncture	
• In patients with chronic LBP, laser acupuncture provides no additional benefit (short-term or medium-term) compared to sham acupuncture	Recommended ***(A)***
• Acupuncture in combination with usual care is recommended for short-term pain relief and to enhance functionality in patients affected by chronic LBP	Recommended ***(A)***
Spinal Manipulation	
• Consider for patients affected by acute or chronic LBP	May be considered ***(C)***
○ Provides periodic, short-term improvement in patients with acute LBP, but clinical impact is unclear and overall results may be comparable to no treatment	Recommended ***(A)***

Table 7. Select Nonpharmacologic and Self-care Guideline Recommendations for Nonspecific Low Back Pain With or Without Radiculopathy

Professional Organization (Year) and Guideline Recommendations	
Institute for Clinical Systems Improvement [ICSI] (2018)[5]	**Recommendation Strength (LOE)[a]**
Education	
• All patients presenting with acute or subacute LBP should receive education about treatment and recovery expectations	Strong ***(moderate-high)***
Physical Activity	
• Patients should be encouraged to remain active, including performing activities of daily living within the parameters allowed by their symptoms	Strong ***(moderate)***
Heat/Cold Therapy	
• For pain, heat may be used for patients with acute or subacute LBP	Weak ***(moderate)***
• For pain, cold may be used for patients with acute or subacute LBP	Consensus ***(N/A)***
Acupuncture	
• For treatment of subacute LBP, acupuncture may be considered	Weak ***(low)***
Spinal Manipulation	
• For acute and subacute LBP, spinal manipulation should be considered as an early intervention	Strong ***(low-moderate)***
The Department of Veterans Affairs/Department of Defense [VA/DoD] (2017)[1,2]	**Recommendation Strength (LOE)[a, b]**
Education	
• Evidence-based information regarding anticipated progress, counseling to remain physically active, and education on self-care options should be provided to patients affected by chronic LBP	Strong for [Recommend]
○ An additional educational element (eg, neurophysiology) may be considered	Weak for [Suggest offering]
Psychotherapy	
• Recommended for patients with chronic LBP	Strong for [Recommend]
○ Consider mindfulness-based stress reduction (MBSR) (eg, meditation)	Weak for [Suggest offering]
Physical Activity	
• Clinician-directed exercises (eg, motor control, physical therapy) should be considered for patients with chronic LBP	Weak for [Suggest offering]
• Consider an exercise program (eg, Pilates, yoga, tai chi) for patients with chronic LBP	Weak for [Suggest offering]
Heat Therapy	
• Patients with acute LBP may use heat to increase symptom relief	NL

Table 7. Select Nonpharmacologic and Self-care Guideline Recommendations for Nonspecific Low Back Pain With or Without Radiculopathy

Professional Organization (Year) and Guideline Recommendations	
Acupuncture	
• Consider in patients with chronic LBP	Weak for [Suggest offering]
Spinal Manipulation	
• Consider in patients with acute or chronic LBP	Weak for [Suggest offering]
American College of Physicians [ACP] (2017)[3]	**Recommendation Strength (LOE)[a]**
Psychotherapy	
• Recommend for patients with chronic LBP	Strong ***(low)***
○ Recommend MBSR (eg, meditation)	Strong ***(moderate)***
Physical Activity	
• Exercise is recommended in patients with chronic LBP	Strong ***(moderate)***
○ Exercise program (eg, yoga, tai chi)	Strong ***(low)***
○ Clinician-directed exercises (eg, motor control)	Strong ***(low)***
Heat Therapy	
• For pain, heat therapy may be used for patients with acute or subacute LBP	Strong ***(moderate)***
Acupuncture	
• Patients with acute or subacute LBP	Strong ***(low)***
• Patients with chronic LBP	Strong ***(moderate)***
Spinal Manipulation	
• Patients with acute or subacute, and chronic LBP	Strong ***(low)***
Massage	
• Patients with acute or subacute LBP	Strong ***(low)***

Abbreviations: CBT, cognitive behavioral therapy; CT, computed tomography; LBP, low back pain; LOE, level of evidence; MBSR, mindfulness-based stress reduction; N/A, not applicable; NL, not listed (ie, not a graded statement in the guideline); PT, physical therapy

[a] See Appendix C for interpretation of level of evidence (LOE) and strength of recommendations

[b] The 2017 VA/DoD guideline does not report the LOE for their recommendations

4.1.1 Self-care

Education on self-care is recommended for all patients with nonspecific LBP with or without radiculopathy, regardless of symptom duration or severity.[1,5] Active management strategies (eg, remaining active, exercise techniques) are preferred to passive approaches (eg, educational materials) for educating patients with acute LBP.[8,37] Education oriented towards chronic LBP should still include self-care advice, such as remaining active,[1] but may include additional education on pain neurophysiology.[1,37] Patient education regarding anticipated symptom duration, treatment interventions, and appropriate self-care guidance may improve patient outcomes by easing anxiety and setting realistic, patient-centered goals.[1,5] Self-management materials such as *"The Back Book",* may be used to supplement physician guidance.[9,11]

Patients should be encouraged to return-to-work based on physician judgement, which may include accommodations in activities, and may occur before complete resolution of pain.[5,8,12] Performing daily activities such as going to work, assist in preventing fear-avoidant behaviors (eg, kinesiophobia) and feelings of disability.[5] The self-care recommendation of continuing to be active, as tolerated, may reduce pain and decrease recovery time for those affected with acute and chronic LBP.[1,5]

4.1.2 Heat or Cold Therapy

The application of heat (eg, heating pad, heated blankets) for transient pain relief is recommended in patients with acute or subacute nonspecific LBP.[1-5] The application of cold therapy (eg, ice packs) is generally not recommended due to a lack of evidence;[1,2,4,5] however, due to the minimal risk of harm, cold therapy may be used short-term to provide symptomatic relief.[5,9] To prevent burns, direct application to the skin of either heat or cold should be avoided,[5,8] and should be limited to 15 to 20 minutes intervals.[8]

4.1.3 Exercise Therapy

Exercise therapy may consist of clinician-directed (eg, physical therapy, McKenzie method) or home-based programs targeted towards physical fitness, aerobic exercise, strength training (eg, motor control), or flexibility (eg, yoga).[11] NASS (2020) recommends patients with nonspecific LBP, particularly chronic, to participate in aerobic exercise (eg, cycling, walking, swimming) to improve short-term pain, disability, and psychological health.[4] Physical therapy, as an early-intervention, may result in reduced medication use (eg, opioids), prevent invasive procedures (eg, surgery, injections), and decrease physician visits.[5] Additionally, exercise may be combined with other interventions such as laser therapy (low or high level) to gain synergistic transient pain relief.[4] In contrast to the self-care recommendation of returning to work or remaining active, which are recommend for all patients with LBP,[1,5] exercise therapy is generally recommend exclusively for the management of chronic LBP.[1,3,4]

Clinician-directed exercise programs (eg, back school) are recommended to improve pain and functionality.[1,3,4,12] Motor control exercise, which targets the activation and coordination of the spine muscles (ie, transversus abdominis and multifidus),[38] has been shown to be effective at reducing pain,[3,38] and disability.[1] Yoga, tai chi, and Pilates are supported by guidelines due to the potential for improved outcomes with minimal risk of harm.[1,3] VA/DoD (2017) mentions that yoga generally improved short-term pain, disability, and quality of life compared to education; however, evidence was uncertain for yoga versus exercise or usual care.[1] NASS and ACP (2020, 2017) suggest that yoga may offer

improvements for pain and function versus usual care,[3,4] but the results may not be clinically relevant due to better baseline functionality.[4] Tai chi and Pilates are also associated with improved pain outcomes among patients with chronic nonspecific LBP.[1,3] Motor control exercise, yoga, tai chi, and Pilates may be beneficial for patients with chronic nonspecific LBP, but extensive heterogeneity exists between studies.[1,3] There is insufficient evidence to support the use of these exercises in acute nonspecific LBP with or without radiculopathy.[1,3,5] Ultimately, the type of exercise should be based on patient preference, tolerability, previous response, and accessibility.[8,9]

For patients with more severe or complicated chronic nonspecific LBP with or without radiculopathy, unresponsive to other "limited approaches", a multidisciplinary biopsychosocial rehabilitation (MBR) method may be recommended according to VA/DoD (2017).[1,2] This method focuses on physical (eg, exercise) and behavioral/psychological (eg, occupational therapy, massage, education) aspects to manage chronic symptoms.[1] NICE (2016) more narrowly recommends this approach for individuals that have substantial psychosocial hindrances (eg, inaccurate beliefs regarding physical capabilities) that are impacting recovery, or experienced failure with previous treatments.[12] Due to the multidisciplinary approach, MBR programs require significant commitment and resource utilization on behalf of the patient and healthcare organization, but offer a low-risk nonpharmacologic option for complicated chronic pain management.[1]

Regardless of symptom duration, guidelines recommend patients experiencing LBP to continue physical activity, as tolerated, to diminish recovery time, prevent disability, and alleviate symptoms.[1,5] Physical activity should be reintroduced as light-duty activities (eg, walking), and gradually escalated to prevent worsening symptoms.[5] Bedrest should be limited (< 2–3 days) during recovery.[1,4,5,34] Additionally, exercise may help prevent recurrent episodes.[5,8]

4.1.4 Psychological Therapies

Cognitive behavioral therapy (CBT) uses a psychotherapeutic approach to modify perceptions and behaviors related to pain, and promote relaxation techniques to manage symptoms.[1,9] A licensed psychological clinician is required to conduct the therapy, typically in private sessions ranging from 8 to 12 visits.[1] Another psychological therapy used for the management of LBP is mindfulness-based stress reduction (MBSR). MBSR programs are structured to focuses on intentionally being in the present through relaxation techniques, such as medication and yoga.[1,9] A mindfulness trainer, usually an independent physician, specialized in MBSR is required to perform the therapy.[1] By utilizing CBT and MBSR, individuals gain better coping mechanisms for pain management.[9]

Guidelines support CBT and MBSR exclusively for chronic nonspecific LBP due to the conflicting evidence about the management of acute or subacute nonspecific LBP, with or without radiculopathy.[1,3-5] CBT and MBSR may be used alone or in combination with other nonpharmacologic therapies.[4,9,12] In contrast to US guidelines, NICE (2016) recommends the use of CBT only as part of a combined approach that includes exercise, with or without manual interventions (eg, spinal manipulation, massage).[12] Evidence suggests CBT in combination with physical therapy (PT) improves disability and the ability of patients to return to work, versus PT alone.[4] For patients experiencing persistent LBP (> 12 months), CBT is recommended in addition to PT to improve pain severity.[4] According to VA/DoD (2017), evidence is lacking regarding the long-term (> 12 months) advantages of MBSR and CBT.[1]

Several patient barriers may exist regarding the feasibility of CBT and MBSR. The availability of specialized physicians to facilitate CBT or MBSR may be limited based on the geographic location or healthcare organization, or may not be reimbursed (or have barriers to reimbursement) by health insurance.[1] Additionally, the time commitment required for the therapy may be inconvenient for some individuals.[1]

4.1.5 Acupuncture

Guidelines are conflicting about the therapeutic utility of acupuncture depending on symptom duration, which may be due to the substantial heterogeneity of the evidence.[1] ACP (2017) recommends acupuncture for acute, subacute, and chronic nonspecific LBP;[3] ICSI (2018) recommends acupuncture only for subacute nonspecific LBP,[5] VA/DoD and NASS (2017, 2020) recommends acupuncture only for chronic nonspecific LBP.[1,4]

Patients presenting with subacute LBP with a higher risk for developing chronic LBP, or presenting with severe symptoms may benefit from short-term acupuncture therapy.[9] The majority of reviewed guidelines support the use of acupuncture for chronic nonspecific LBP.[1,3,4] NASS (2020) highlights that compared to usual care, the addition of acupuncture improved short-term pain and functionality among those with chronic LBP; however, mixed evidence exists regarding improved outcomes versus sham acupuncture for patients with any duration of LBP.[4] In contrast to US guidelines, NICE does not recommend the use of acupuncture for patients with LBP.[12] A 2017 Canadian guideline recommends offering acupuncture as adjunctive therapy to an "active rehabilitation program" or as temporary treatment for patients with chronic LBP, noting the minimal risk of adverse events (AEs).[8]

4.1.6 Massage

Similar to acupuncture, massage is a "passive" technique used for the management of pain and as a method to increase patient participation in active interventions (eg, exercise).[9] Guidelines favor massage for pain reduction among patients with subacute or chronic LBP, but rarely provide recommendations regarding its use.[1,3,5]

US guidelines lack a uniform consensus regarding the short-term benefit of massage for pain in combination with an exercise program among those with subacute or chronic nonspecific LBP with or without radicuopathy.[3-5] NASS (2020) states there is a lack of evidence to make a recommendation for the combination use of massage and exercise for short-term pain relief,[4] whereas ICSI (2018) provides evidence to support massage with exercise, but does not state a recommendation on its use.[5] ACP mentions low-quality evidence supporting massage in combination with another therapy (eg, exercise, education, usual care) offers additional benefits for short-term pain over the comparative therapy (eg, exercise with or without education, usual care) alone.[3] It is noted that for long-term symptom relief, a combined exercise and massage program provides no additional benefit compared exclusively to an exercise program.[4] Massage has not been proven to be an effective intervention for acute nonspecific LBP according to ICSI.[5] However, the 2017 Canadian guideline recommends massage therapy for acute and subacute nonspecific LBP and physical therapists may consider massage for short-term pain reduction for acute LBP.[8,37]

4.1.7 Spinal Manipulation

Similar to massage and acupuncture, spinal manipulation is a "passive" technique used for short-term pain management.[9] It is recommended for acute, subacute, and chronic nonspecific LBP,[1,3-5] particularly as an early intervention for acute conditions.[5]

Overall, the evidence for spinal manipulation shows a modest effect for pain and short-term improvement in function among patients with acute nonspecific LBP.[1,3,5] Compared to sham manipulation, spinal manipulation provided minimal benefit in pain and functionality at up to 6 weeks.[5] Additionally, no differences in functional outcomes were observed at week 1 or 3 months for spinal manipulation versus an inert treatment.[3] Spinal manipulation in combination with other therapies (exercise or guidance) yielded a greater response in functionality at one week versus either therapy used alone; however, the response was not sustained at one or three months.[3,5] Among patients with radicular LBP, a combination of nonpharmacologic therapies (spinal manipulation, home exercise, and guidance) resulted in a greater effect for leg and back pain at 12 weeks compared solely to home exercise and guidance, but over time the effect diminished and was no longer statistically significant by week 52.[5] Spinal manipulation may provide intermittent, short-term benefits in patients with acute nonspecific LBP, but the clinical relevance remains unclear.[4]

For chronic LBP, evidence suggests no clinically relevant differences exist between spinal manipulation compared to sham manipulation[1], including pain relief at one month.[3] According to NASS (2020), spinal manipulation combined with exercise results in comparable outcomes to spinal manipulation alone;[4] however, other evidence has demonstrated that spinal manipulation resulted in greater long-term (up to one year) pain reduction and improved function when used concurrently with another active intervention (eg, exercise, psychological therapies) versus the active intervention alone.[3,9] Additionally, low quality evidence suggests that the combined use may offer long-term benefits in perceived recovery, reduce medication use, and improve care gratification.[1]

4.2 Guideline Recommendations for Pharmacologic Therapies

A variety of pharmacologic treatment options may be considered for patients with LBP, including nonsteroidal anti-inflammatory drugs (NSAIDs), skeletal muscle relaxants (SMRs), and opioids.[1,3-5] Medication selection depends on patient specific factors such as age, renal and hepatic function, risk-benefit assessment, and duration of pain (chronic vs acute).

Pharmacologic interventions should be prescribed at the lowest effective dose, for the shortest amount of time.[1,3,12] Additionally, patient education that incorporates shared decision-making and addresses potential harms, especially with opioid therapy, and alternative options should be provided.[1] Patients already on benzodiazepines, antiepileptics, including gabapentinoids, or opioids should have a discussion about the risks associated with continued use, and the potential for withdrawal if inappropriately tapered.[12] Risks versus benefits of continuation should be considered, and if there is a lack of benefit in pain reduction or functional improvement, those pharmacologic interventions should be discontinued with an appropriate taper.[8] Patients should be aware that optimal medication use may not bring complete resolution of pain symptoms, especially for chronic nonspecific LBP, in which a 30% or 40% reduction in pain is considered successful.[8]

The following subsections include pharmacologic therapies with evidence to support their use for nonspecific LBP with or without radiculopathy that were frequently mentioned within reviewed guidelines.

Medications that were commonly recommended **against** in the reviewed guidelines for nonspecific LBP with or without radiculopathy include the following:

- Benzodiazepines
- Systemic corticosteroids

Medications for which a recommendation is not provided *for or against* in the reviewed guidelines for nonspecific LBP with or without radiculopathy include antiepileptics (Canada and US guidelines only) (including **gabapentinoids** gabapentin, pregabalin) and lidocaine patches. For example,

- NASS (2020), a recent guideline, did not discuss potential supportive information for gabapentinoids or topical lidocaine for LBP with neuropathic features; this may be due to the guideline's focus on non-radicular LBP.[4]
- Other guidelines and expert reviews that address neuropathic pain (which may include radiculopathy), recommended gabapentinoids and topical lidocaine for consideration.[13-17] Additionally, pregabalin, a controlled V substance, is FDA approved for neuropathic pain associated with spinal cord injury.[39]
- NICE recommends **against** the use of **gabapentinoids** for patients with sciatica[12] due to a lack of supporting evidence and the greater risk of harm from adverse effects (eg, dry mouth, problems with paying attention and memory, blurred vision).[1,39]

Additionally, some guidelines support non-surgical invasive pharmacologic treatments (eg, steroid injections) not reviewed in this report for patients with nonspecific LBP with radiculopathy, in which initiation is based on symptom severity.[1,5,12]

Table 8 outlines select pharmacologic recommendations from the reviewed US guidelines.

Table 8. Select Pharmacologic Guideline Recommendations for Nonspecific Low Back Pain With or Without Radiculopathy

Professional Organization (Year) and Guideline Recommendations	
North American Spine Society [NASS] (2020)[4]	**Recommendation Strength (LOE)[a]**
Topical Therapies	
• Topical capsaicin is recommended for short-term use (≤ 3months) for the treatment of LBP	Recommended ***(A)***
○ Not enough evidence exists to make a recommendation *for or against* the use of lidocaine patch	Insufficient or Conflicting Evidence ***(I)***
Antidepressants	
• Recommended against for the management of LBP	Recommended ***(A)***
Antiepileptics	
• A lack of evidence exists to make a recommendation *for or against* the use of antiepileptics	Insufficient or Conflicting Evidence ***(I)***
NSAIDs	
• Consider **non-selective** NSAIDs for the management of LBP	Suggested ***(B)***
• A lack of evidence exists to make a recommendation *for or against* **selective** NSAID use for the management of LBP	Insufficient or Conflicting Evidence ***(I)***
Steroids	
• There is a lack of efficacy for the use of systemic steroids for the management of LBP	Suggested ***(B)***
Opioids	
• Should be limited to a short duration of use in patients with LBP	Suggested ***(B)***
Institute for Clinical Systems Improvement [ICSI] (2018)[5, b]	**Recommendation Strength (LOE)[a]**
NSAIDs	
• Recommended for short-term pain reduction in patients affected by acute and subacute LBP • Patients should be educated on the potential adverse effects	Strong ***(moderate)***
Acetaminophen	
• May consider for pain reduction in patients affected by acute and subacute LBP • Patients should be educated on the potential adverse effects	Consensus ***(N/A)***
Muscle Relaxants	
• For patients with acute LBP, consider for short-term (less than 7 days) use ○ Although use of sedative hypnotics (eg, benzodiazepines) should be seldom, if used, it should be limited to < 7 days for acute pain related muscle spasms	Weak ***(moderate)***

Table 8. Select Pharmacologic Guideline Recommendations for Nonspecific Low Back Pain With or Without Radiculopathy

Professional Organization (Year) and Guideline Recommendations	
○ Non-sedative hypnotic muscle relaxants should be restricted to < 4 weeks if used	
• Carisoprodol should not be used for pain	NL
Opioids	
• For patients with acute and subacute LBP, opioids are usually not recommended	
• At the clinicians discretion after failure of non-opioid agents in select patients with severe acute pain, an initial short-acting opioid may be tried at the lowest effective dose (≤ 100 morphine milligram equivalents [MME] total) for ≤ 3 days	Consensus ***(N/A)***
The Department of Veterans Affairs/Department of Defense [VA/DoD] (2017)[1,2]	**Recommendation Strength (LOE)[a, b]**
Topical Therapies	
• Not enough evidence exists to make a recommendation *for or against* the use of topical therapies	N/A
Antidepressants	
• Consider duloxetine in patients affected by chronic LBP, taking into consideration individualized risks	Weak for [Suggest offering]
Antiepileptics	
• An inadequate amount of evidence exists to make a recommendation *for or against* the use of antiepileptics, including **gabapentin and pregabalin** for the treatment of acute or chronic LBP with or without radiculopathy	N/A
NSAIDs	
• Recommended for patients with acute or chronic LBP, with special consideration to individualized risks	Strong for [Recommend]
Acetaminophen	
• Long-term use should be avoided in patients with chronic LBP	Strong against [Recommend against]
• A paucity of evidence exists to make a recommendation *for or against* short-term (< 1 week) use in patients with acute or chronic LBP	N/A
Muscle Relaxants	
• A non-benzodiazepine muscle relaxant (eg, cyclobenzaprine, tizanidine) may be offered for short-term use in patients with chronic LBP experiencing a flare or patients with acute LBP	Weak for [Suggest offering]
○ Among patients with chronic LBP, **not** experiencing an acute exacerbation, a non-benzodiazepine muscle relaxant should not be recommended	Weak against [Suggest not offering]

Table 8. Select Pharmacologic Guideline Recommendations for Nonspecific Low Back Pain With or Without Radiculopathy

Professional Organization (Year) and Guideline Recommendations	
• Benzodiazepines are not recommended for the treatment of LBP	Strong against [Recommend against]
Steroids	
• Systemic corticosteroids are not recommended for the treatment of acute or chronic LBP with or without radiculopathy	Strong against [Recommend against]
Opioids	
• Patients with LBP should not be started on long-term opioid therapy	Strong against [Recommend against]
○ Opioid therapy should be used for the shortest duration and at the lowest effective dose	N/A
American College of Physicians [ACP] (2017)[3]	**Recommendation Strength (LOE)[a]**
Antidepressants	
• Consider duloxetine as second-line therapy for patients with chronic LBP, unresponsive to nonpharmacologic interventions and NSAIDs	Weak ***(moderate)***
NSAIDs	
• Recommended in patients with acute or subacute LBP	Strong ***(moderate)***
• Consider as first-line therapy for patients with chronic LBP, unresponsive to nonpharmacologic interventions	Weak ***(moderate)***
Muscle Relaxants	
• Skeletal muscle relaxants (eg, cyclobenzaprine, tizanidine) are recommended in patients with acute or subacute LBP	Strong ***(moderate)***
Opioids	
• Tramadol may be used as second-line therapy for patients with chronic LBP, unresponsive to nonpharmacologic interventions and NSAIDs	Weak ***(moderate)***
○ Among patients with chronic LBP, other opioids (excluding tramadol) should be considered only after failure of first-and second-line agents	Weak ***(moderate)***

Abbreviations: IV, intravenous; LBP, low back pain; LOE, level of evidence; MME, morphine milligram equivalents; N/A, not applicable; NL, not listed (ie, not a graded statement in the guideline); NSAIDs, nonsteroidal anti-inflammatory drugs;

[a] See Appendix C for interpretation of level of evidence (LOE) and strength of recommendations

[b] The 2017 VA/DoD guideline does not report the LOE for their recommendations

4.2.1 Topical Therapies

NASS (2020) makes recommendations about topical pharmacologic therapies, specifically capsaicin and lidocaine for the treatment of LBP.[4] Other guidelines neither address topical therapies nor make recommendations about their use, due to insufficient evidence.[1,3,5]

NASS recommends topical capsaicin for short-term use (≤ 3 months) for the treatment of LBP, likely chronic, based on two randomized controlled trials (RCTs).[4] These studies evaluated the efficacy and tolerability of topical capsaicin among patients with chronic (≥ 3 months) nonspecific LBP.[4,40,41] Both studies showed a significant reduction in pain (either a compound score, or sum of 3 different pain scores) versus placebo after 3 weeks of treatment.[4,40,41] Additionally, the capsaicin arm produced a more robust responder rate of ≥ 30% pain reduction compared to the placebo group.[4,40,41] The area of pain was exposed to topical capsaicin plaster for a range of 4 to 8[40] or 4 to 12[41] hours per day. Among both studies, AEs were reported numerically more often for capsaicin versus placebo.[40,41] Common AEs reported for topical capsaicin plaster were local heat sensation or erythema, and pruritus.[4,40,41]

Despite an open-label study (level III evidence) supporting the use of lidocaine 5% patch for the treatment of LBP, NASS states there is a lack of evidence to make a recommendation *for or against* its use.[4] In this open-label nonrandomized single-arm study, patients with varying symptom duration (3 months to 12 months) applied a 5% lidocaine patch to the area of pain up to four times per day for 6 weeks.[4,42] Significant improvements in pain scores, including pain intensity, and quality of life were observed by week 2 and week 6 compared to baseline.[4,42] Common AEs reported for lidocaine were skin reactions (eg, rash), dizziness, and headache.[4,42] The study authors indicated that high quality studies (RCTs) are needed to provide additional insight on the efficacy and safety of lidocaine patches for the treatment of LBP.[4,42]

4.2.2 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

US guidelines recommend oral NSAIDs for short-term pain management in patients with acute, subacute, and chronic nonspecific LBP with or without radiculopathy, with special consideration to individualized risks (eg, gastrointestinal [GI], renal, cardiovascular).[1,3-5] Except NASS, most guidelines favor cyclooxygenase-2s (COX-2s) over conventional NSAIDs; NASS favors non-selective NSAIDs due to inconclusive evidence for the use of selective NSAIDs.[4] Most guidelines prefer selective NSAIDs due to statistically fewer AEs, and absence of clinically relevant differences in pain reduction between selective and conventional NSAIDs.[1,3]

Table 9 includes initial dosing recommendations for NSAIDS, categorized by COX selectivity. Full prescribing information should be reviewed for patient-specific dosing of individual NSAIDs due to dosing variabilities based on patient age, hepatic and renal function, and formulation.

Table 9. Initial Dose for Select NSAIDs, organized by COX-Selective Inhibition[1]

Cox Selectivity	Generic	Initial Oral Dose *(max dose)*[a]	Half-life (hrs)[a]
More Cox 1 Selective	Ibuprofen	200—400 mg q 4—6 hrs *(3200 mg)*	~ 2
	Naproxen	250 mg BID *(1500 mg)*	12—17
< 5-fold COX-2 Selective	Diclofenac potassium or sodium	50—75 mg BID *(150—200 mg)*	~ 2

Table 9. Initial Dose for Select NSAIDs, organized by COX-Selective Inhibition[1]

Cox Selectivity	Generic	Initial Oral Dose *(max dose)*[a]	Half-life (hrs)[a]
5—50 fold COX-2 Selective	Celecoxib	200 mg BID *(400 mg)*	~ 11
	Meloxicam	5—7.5 mg QD *(15 mg)*	~ 15—22
	Etodolac	200—400 mg q 6—8 hrs *(1000 mg)*	6.4

Abbreviations: BID, twice per day; COX-2, cyclooxygenase-2; hrs, hours; max, maximum; mg, milligram; NSAIDs, nonsteroidal anti-inflammatory drugs; q, every; QD, daily

[a] Prescribing information should be reviewed for patient-specific dosing of individual drugs; dosing and half-life may change based on patient age, renal and hepatic function, and drug formulation. Chronic use should be avoided in geriatric patients (≥ 65 years), except if alternatives are ineffective and a gastroprotective agent (eg, proton pump inhibitor or misoprostol) is used.

4.2.3 Acetaminophen

Due to consistent evidence demonstrating a lack of efficacy, concerns of harm predominates recommendations about acetaminophen, which results in conflicting recommendations in acute nonspecific LBP.[1,3,5] ACP (2017) no longer recommends it for acute nonspecific LBP with or without radiculopathy due to a lack of superiority vs placebo.[3] A large RCT (N=1,652) indicated that scheduled or as-needed acetaminophen produced a similar effect as placebo for recovery time, as well as pain intensity or function among patients with acute LBP.[1,3,43] In addition, a low quality SR found similar findings with acetaminophen being comparable to placebo for pain, disability, quality of life, or function at 12 weeks.[1,5] NICE recommends acetaminophen in combination with other agents, such as "weak opioids" for acute nonspecific LBP; but is against monotherapy with acetaminophen, likely due to a lack of efficacy.[12] Insufficient evidence exists to ascertain the effect of acetaminophen for chronic nonspecific LBP.[3,44]

Patient education should be provided about the potential harms and risks of accidental misuse of acetaminophen, particularly given its effortless accessibility and inexpensive cost.[1] Long-term use at high doses should be avoided because of the dose-related liver toxicity (limit use in adults with no other risk factors for liver toxicity to < 4 grams per day),[20] particularly in older individuals and those with chronic LBP.[1] However, acetaminophen may present a minimal risk of serious harm compared to other agents for the treatment of LBP; and thus, ICSI (based on consensus) recommends acetaminophen for pain in patients with acute and subacute nonspecific LBP.[5] Furthermore, a Canadian guideline (revised in 2017) recommends scheduled acetaminophen as first-line, preferred over NSAIDs, for analgesic relief in acute, subacute, or chronic LBP due to the favorable side effect profile.[8]

4.2.4 Antidepressants

NASS (2020) recommends against antidepressants for nonspecific LBP, but does not address their use for radiculopathy.[4] While NICE recommends against antidepressants for nonspecific LBP, they advise that this therapy should be investigated further for the management of sciatica since clinical experience suggests they may provide benefit.[12] VA/DoD and ACP support the use of duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI) for chronic nonspecific LBP with or without radiculopathy, based on at least 1 RCT.[1-3] According to the VA/DoD guideline, duloxetine is the only SNRI that has been evaluated for LBP; nevertheless, the other agents within the drug class may produce a comparable benefit given the similar mechanism of action.[1] A 2017 Canadian guideline recommends duloxetine for

LBP patients with neuropathic pain and concurrent musculoskeletal issues, but states there is inconclusive evidence in chronic nonspecific LBP.[8]

VA/DoD (2017) states that a low dose tricyclic antidepressant (TCA) or selective serotonin reuptake inhibitor (SSRI) may be considered for select patients with other underlying psychiatric comorbidities.[1] The 2017 Canadian guideline includes amitriptyline and nortriptyline as third-line options (after acetaminophen and NSAIDs fail) for patients with chronic nonspecific LBP or spinal pain.[8] UpToDate describes that experts may select a TCA for evening use in patients with pain that interferes with sleep (ie, to take advantage of the somnolence adverse effect), or if duloxetine is ineffective or cost-prohibitive.[9] ICSI, a guideline that focuses on acute and subacute treatments, did not address antidepressants for the management of LBP.[5]

4.2.5 Skeletal Muscle Relaxants (SMRs)

Guidelines recommend non-benzodiazepine skeletal muscle relaxants (SMRs) (eg, cyclobenzaprine, tizanidine) for short-term (< 1 week) use in nonspecific LBP with or without radiculopathy.[1,3,5] VA/DoD recommends that muscle relaxants should only be used for acute exacerbations in chronic nonspecific LBP;[1] this is likely due to an unfavorable side effect profile, which outweighs any benefit with long-term use.[5]

The potential benefits of different agents within the SMR class appear similar,[3,5] but the side effect profiles vary significantly between agents.[1] It is recommended to avoid the SMR carisoprodol, a Schedule IV controlled substance, due to the higher risk for central nervous system (CNS) depression and dependence relative to other non-benzodiazepine SMRs.[1,5]

There is no evidence to support an advantage of using SMRs on a continuous, long-term basis for chronic LBP.[1] When selecting a SMR, physicians should evaluate patient specific factors that would impact the side effect profile, such as the concomitant use of other CNS depressant agents (eg, opioids).[1,5]

Benzodiazepines: There is a paucity of evidence regarding the use of benzodiazepines for LBP.[1] Given the known potential harms, including addiction, dependence, respiratory depression, and overdose, they are generally not recommended.[1,12] Furthermore, these risks are intensified when combined with opioid therapy.[1] If benzodiazepines are used, it is recommended not to exceed more than one week of use.[5]

4.2.6 Opioids

US guidelines only recommend a short-course of opioids as a last-line option in most LBP conditions, especially chronic nonspecific LBP with inadequate relief from other medications (eg, NSAIDs, duloxetine), and only when therapeutic benefits outweigh the risks.[3] However, some guidelines provide a separate recommendation for tramadol, perhaps due to its slightly different mechanism of action. Tramadol differs from traditional opioids (oxycodone, hydrocodone) in that it also has some neuromodulatory action, inhibiting serotonin and norepinephrine reuptake.[13] ACP (2017) lists tramadol as a second-line agent for chronic nonspecific LBP.[3] NICE does not recommend routine use of opioids for acute or chronic nonspecific LBP, but may advise consideration of “weak opioids” with or without acetaminophen for acute nonspecific LBP if a contraindication, intolerance, or lack of efficacy exists to NSAIDs.[12]

Typically, opioids are not recommended for acute or subacute nonspecific LBP.[5] ICSI recommends a trial of short-acting opioids in patients with severe acute pain that has not responded to non-opioids; in such cases, clinicians should use the lowest effective dose (≤ 100 morphine milligram equivalents [MME] total) for ≤ 3 days.[5,8]

The small short-term benefits of opioids for nonspecific LBP may be offset by the increased risk of AEs (eg, nausea, dizziness, constipation), usually observed with short-course therapy.[1,5] Of importance, some of the reviewed guidelines mentioned that included trials did not evaluate the risks of overdose, abuse, addiction, or long-term detriments;[3,5] but a dose-dependent relationship between opioid use for chronic pain and serious AEs has been suggested by observational studies.[3] To minimize the risk of AEs, opioids should be prescribed for the shortest duration and at the lowest effective dose.[1,4,8] The continuous requirement of opioid therapy may be a sign for patient reassessment.[8]

5.0 SPECIAL POPULATIONS

Given the increased awareness in selecting appropriate pharmacologic therapy in pregnant women and older adults, the following subsections provide additional details for these special populations.

5.1 Pregnancy

LBP, or in combination with pelvic pain, is a common symptom experienced during pregnancy.[1,2,5,45] Approximately 50–80% of pregnant people experience LBP,[5] with up to 25% experiencing severe pain and 8% reporting severe disability.[45] Typically, symptoms develop during the second trimester and progressively worsen over the course of pregnancy.[1,2,5] Despite symptoms worsening as pregnancy progresses, pregnancy-related LBP usually resolves during the post-partum period.[1,2,5] Although majority of cases resolve after pregnancy, up to 20% of people experience chronic LBP following delivery.[5,45]

The physical examination should be conducted in the same manner as nonpregnant individuals, with consideration to spinal anatomical limitations as the pregnancy progresses.[5] Imaging is usually avoided during pregnancy; however, MRI (usually without contrast)[46] is preferred for severe cases of LBP.[5]

Nonpharmacologic therapy: Exercise is a preferred nonpharmacologic intervention for pregnancy-related LBP.[5] According to a 2015 SR, exercise provided pain relief among pregnant women with LBP.[5] Compared to standard prenatal care, evidence suggests that any exercise may produce better outcomes regarding disability and sick absences.[5] The American College of Obstetricians and Gynecologists (ACOG) also suggest using heat or cold therapy, resting a foot on a stool or box if standing for prolonged periods of time, avoiding high heels, and wearing maternity clothing that contains abdominal support.[47]

NSAIDs: NSAIDs may be used in pregnancy; however, use should be avoided/limited starting at 20 weeks due to the risk of oligohydramnios/ fetal renal dysfunction.[18,48] If NSAID therapy is required, use may be restricted to the lowest effective dose for the shortest duration between 20 to 30 weeks.[18,48] NSAIDs should be avoided at 30 weeks or later in pregnancy due to the increased risk of premature closure of the fetal ductus arteriosus.[18,48]

Acetaminophen: The use of acetaminophen at recommended doses during pregnancy is generally considered safe and an appropriate treatment for pain relief.[20] Among pregnant women exposed to oral acetaminophen during the first trimester, no increased risk of congenital malformations was observed beyond the baseline inherent risk within the general population.[21] However, in cases of maternal

overdose with delayed treatment, fetal death or spontaneous abortion may occur.[20] Acetaminophen does cross the placenta.[20] To minimize the potential risks to the fetus, acetaminophen should be used for a short duration at the lowest effective dose.[20]

Antidepressants: Duloxetine should be avoided in pregnant women during the later phase of pregnancy to minimize maternal and fetal risks.[22] The use of duloxetine during the third trimester, specifically in the month before delivery may cause an increased risk of postpartum hemorrhage.[22] Additionally, newborns exposed to duloxetine and other antidepressants (eg, SNRIs, SSRIs) during the later phase of the third trimester have developed difficulties resulting in extended hospitalization, respiratory distress, and feeding complications.[22] Symptoms experienced by the newborn such as convulsions, respiratory distress, tremor, irritability, vomiting, and inadequate temperature regulation may either be a result of direct toxicity or withdrawal of an SNRI or SSRI.[22]

Regarding the management of depression, the potential risks of untreated depression with discontinuing antidepressants or changing treatment during pregnancy and postpartum should be considered.[22] Pregnant women that discontinue antidepressants during pregnancy have an increased chance of experiencing a relapse of major depression versus women that continue therapy.[22]

Skeletal muscle relaxants (SMRs): In general, there is a paucity of human data to guide the use of preferred non-benzodiazepine SMRs (eg, cyclobenzaprine, tizanidine) during pregnancy.[9,24,25] Additionally, maternal/ fetal risk of the muscle relaxants differs by agent, with cyclobenzaprine having the most favorable risk profile.[23] Case reports have not shown an increased risk of major birth defects, miscarriages, or other maternal or fetal adverse outcomes with cyclobenzaprine use during pregnancy.[24] Animal data has shown no adverse embryofetal outcomes in mice and rabbits administered cyclobenzaprine at doses up to 15 times the maximum human recommended dose during organogenesis; however, a decreased offspring weight and survival was observed in rats administered ≥ 3 times the maximum human recommended dose during pregnancy and lactation.[24]

Opioids: Similar to non-pregnant patients, nonpharmacologic and non-opioid agents are preferred in pregnancy, especially for chronic pain management given that opioids cross the placenta and may produce fetal complications.[28,29,49] Before starting opioid therapy in pregnant women, a careful consideration of the potential benefits and risks should be evaluated to ensure the therapy is appropriately indicated.[49,50] Opioid use during pregnancy has been associated with stillbirth, inadequate fetal growth, early delivery, and birth defects, including neural tube and congenital heart defects, and gastroschisis.[29,50] Long-term use of opioids during pregnancy may cause neonatal opioid withdrawal syndrome, respiratory depression, and physical dependence that manifests soon after delivery.[28,29,49,50] The onset, duration, and severity of withdrawal depends on the particular opioid ingested, length of use, timing and amount of last administration, and the elimination rate of the newborn.[28,29] Physicians should monitor newborns for withdrawal symptoms (eg, irritability, tremor, high pitched crying, hyperactivity, irregular sleep pattern) in pregnant woman that use opioids chronically during pregnancy.[28,29] Naloxone, an opioid antagonist may need to be administered to reverse opioid-induced respiratory depression in the newborn.[28,29]

5.2 Older Adults

For older individuals, additional considerations are needed before selecting a pharmacologic agent for the treatment of LBP. Due to age-associated changes, geriatric patients may experience alterations in efficacy, tolerability, and adverse effects (AEs), which may impact the overall benefit-risk profile.[51,52]

Nonpharmacologic therapy: Age-related recommendations for nonpharmacologic therapy were not provided by guidelines,[1,3-5,8,12] but selection is presumably similar to younger adults, with consideration of patient preference, tolerability, and accessibility.[9]

NSAIDs: Chronic NSAID use should be avoided in patients ≥ 65 years of age due to the increased risk of GI bleed or peptic ulcer disease (PUD), particularly among high-risk groups, such as those > 75 years of age, or those taking corticosteroids, anticoagulants, or antiplatelet therapies.[52] However, chronic use may be permitted for those that are taking a gastroprotective medication (eg, proton pump inhibitor [PPI] or misoprostol) in which alternative therapies have failed.[52] The gastroprotective medication does not eradicate the risk for NSAID-related GI ulcers, bleeding, or perforation, but may help to reduce it.[52] In addition, dose-related effects on hypertension and drug-induced kidney injury have been reported with NSAID use.[52] Indomethacin and ketorolac should be avoided due to greater risks of AEs compared to other NSAIDs.[52]

Acetaminophen: The maximum dose limit (≤ 4 grams per day in healthy adults) for acetaminophen is the same regardless of age,[51] which helps to prevent potential hepatic failure and death due to liver injury.[20,21] However, in the presence of hepatic impairment or history of alcohol abuse, a maximum of 2–3 grams per day is recommend by the American Geriatrics Society (AGS) for persistent pain.[51]

Antidepressants: According to the AGS 2019 Updated Beers Criteria, TCAs should be avoided in individuals ≥ 65 years of age due to the extensive anticholinergic activity (eg, dry mouth, constipation), sedation, and orthostatic hypotension.[52] Additionally, other classes of antidepressants (SSRIs and SNRIs) should be avoided in older adults with a history of falls or fracture. If TCAs, SSRIs, or SNRIs are cautiously used in this patient population, special consideration should be made to monitor sodium levels due to the increased risk of developing syndrome of inappropriate antidiuretic hormone (SIADH) or hyponatremia.[52] The potential for additive CNS-depression between antidepressants and other medications should be considered; use of 3 or more drugs with CNS-depression effects should be avoided.[52]

Skeletal muscle relaxants (SMRs): The Updated 2019 AGS Beers Criteria mentions that majority of SMRs are not tolerated by older individuals due to the anticholinergic side effects (eg, cyclobenzaprine), CNS depression (eg, sedation), and increased risk of fractures.[1,52] Reduced dosages are often required to enhance tolerability but as a result, the effectiveness is decreased, making the overall benefit questionable.[52] Thus, SMRs should be avoided in older individuals.[52] Additionally, benzodiazepines should be avoided for LBP in older individuals due to the increased risk of falls, fractures, delirium, and cognitive impairment.[52]

Opioids: Opioids should be used cautiously in older adults on a "trial basis with clearly defined therapeutic goals".[51] Of note, meperidine should be avoided in older adults due to the increased risk of neurotoxicity including delirium compared to other opioids.[52] Furthermore, it is recommended to avoid the use of opioids in older adults that have a history of falls or fractures, except for cases of severe acute

pain management (eg, recent fractures, joint replacement).[52] Due to the increased risk of overdose, opioids with the concurrent use of benzodiazepines should be avoided.[52] Additionally, the simultaneous use of three or more medications that affect the CNS (eg, antidepressants, opioids, benzodiazepines, antiepileptics) should be avoided due to the increased likelihood of falling and fractures.[52]

6.0 SAFETY

6.1 Adverse Events

AEs for nonpharmacologic interventions were rarely reported in clinical trials, but generally muscle aches and/or slight increases in pain were reported for exercise, tai chi, massage, and spinal manipulation, with no serious AEs reported.[3]

Table 10 provides a summary of select adverse events (AEs) for pharmacologic agents or drug classes used for the treatment of LBP as reported in the guidelines, prescribing information, or Lexicomp drug compendia.

Table 10. Select Adverse Events for Pharmacologic Interventions used for the Treatment for Nonspecific Low Back Pain

Drug Class	Adverse Events
Acetaminophen[a]	Skin reactions (eg, AGEP, SJS, TEN); hepatotoxicity (overdose or with long-term high-dose intake);[8] hearing loss; increased serum ALT[53]
NSAIDs	Edema; rash; abdominal pain or cramps; dyspepsia; diarrhea; dizziness; heartburn; tinnitus; headache; GI bleeding and/or perforation[3,8]
SMRs	Sedation; nausea; dizziness; headache; drowsiness[1,3]
Duloxetine[b]	Nausea; dry mouth; sleepiness; constipation; reduced appetite and/or weight; hyperhidrosis[22]
Opioids	Nausea, dizziness, constipation, vomiting, drowsiness, dry mouth[3]

Abbreviations: AGEP, acute generalized exanthematous pustulosis; ALT, alanine transaminase; GI, gastrointestinal; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; SJS, Stevens-Johnson Syndrome; SMRs, skeletal muscle relaxants; TEN, toxic epidermal necrolysis

[a] *Excludes adverse events related to the IV formulation*

[b] *Adverse events for adults only*

6.2 Warnings and Precautions

The pharmacologic therapies carry a variety of labeled warnings and precautions. **Table 11** contains select contraindications, warnings, and precautions for agents or drug classes used for the treatment of nonspecific LBP with or without radiculopathy. Additional details related to black box warnings or serious precautions are provided below, *except for the SMRs*. Warnings and precautions differ between SMRs, with some agents having the potential to cause anticholinergic side effects (eg, cyclobenzaprine, orphenadrine),[23] while the majority tend to increase the risk of CNS depression (eg, sedation), especially with concomitant use of other CNS depressants (eg, alcohol, opioids).[24-27] Given the variety of adverse effects between SMRs, the agent-specific prescribing information should be consulted.

NSAIDs, regardless of selectivity, carry a black box warning for increased risk of serious cerebrovascular events (myocardial infarction [MI] and stroke) and GI events (bleeding, ulceration, and perforation).[18] CV

thrombotic event risks may vary across the NSAIDs, but such risks are thought to occur early, and to increase with prolonged use.[18] Older adults and patients with a previous history of peptic ulcer disease (PUD) and/or ulcers have increased risks for serious GI events; these events may occur at any time during NSAID use, with or without warning symptoms.[18] For patients 45 years of age and older or with a higher CV/ GI risk requiring NSAID therapy, the addition of a proton pump inhibitor (PPI) may be considered.[1,8]

Acetaminophen has the potential to cause rare but serious, potentially fatal skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN).[19] These reactions may occur with first-time use or at any time during use.[19] NSAIDs and duloxetine also carry the risk of causing serious skin reactions; however, cross-sensitivity between acetaminophen and NSAIDs does not seem to exist.[19] Acetaminophen in higher doses is known to cause toxicity that can result in hepatic failure and death due to liver injury.[20,21] To avoid potential liver injury, acetaminophen should not exceed the recommended daily dosage (< 4 grams per day for healthy adults), including acetaminophen from combination products and various dosage forms.[20,21] It is recommended to use caution in patients with alcoholism, liver dysfunction or active hepatic illness.[20,21]

Duloxetine carries a black box warning for increased risk of suicidality, including emergent thoughts and behaviors among pediatrics, adolescents, and young adults, particularly during the initial period of therapy.[22] This warning is supported by a pooled analyses from placebo-controlled trials assessing antidepressant agents among pediatrics, adolescents, and adults, aged ≤ 24 years with major depressive disorder (MDD) and other mental health conditions.[22] Patients on antidepressants should be monitored for worsening depression, suicidality, and bizarre alterations in behavior, particularly during the months following initiation, or after dosage modifications.[22] Patients that experience consistent worsening depression, or develop suicidal thoughts or behaviors, should consider discontinuing the medication.[22] Duloxetine should not be discontinued abruptly due to the potential for withdrawal symptoms (eg, irritability, dizziness, confusion, anxiety); the dose should be tapered to minimize the chance of experiencing this type of symptoms.[22] Patients at risk for bipolar disorder who are starting an antidepressant should be screened for symptoms suggestive of the disorder prior to use to avoid triggering a mixed/manic episode.[22]

Opioids have several warnings and precautions including the development of respiratory depression and the potential for addiction.[28,29] Opioids carry a black box warning for addiction, abuse and misuse, mandatory participation by the Food and Drug Administration (FDA) in a Risk Evaluation and Mitigation Strategy (REMS) program, increased risk for fatal respiratory depression, overdose with accidental consumption, the possibility for neonatal opioid withdrawal syndrome *(see pregnancy section)*, and the potential for drug-drug interactions, including with benzodiazepines and other CNS depressants.[28,29] Given the risk for addiction, abuse, or misuse, patients should be evaluated for the emergence of concerning behaviors, especially in those with a family history of substance abuse or psychological conditions.[28,29] The FDA requires opioid products to be part of the REMS program, which includes conducting patient education to ensure opioids are appropriately indicated based on the risk/benefit assessment.[28,29] Significant respiratory depression, which may result in respiratory arrest and death has occurred with opioid use.[28,29] Drug-drug interactions (DDIs) affecting cytochrome (CYP) P450 enzymes may cause alterations in opioid levels, which can result in adverse effects, including respiratory depression, or trigger withdrawal symptoms in those with a physical dependence.[28,29] Potential additive CNS effects must also be considered with alcohol and other CNS depressants (eg, muscle relaxants,

benzodiazepines).[28,29] Due to these risks, opioids with CNS depressants should be reserved for patients in which other treatments are insufficient.[28,29] In the presence of CNS depressants, the initial opioid dose should be reduced and adjusted based on response, and vice versa.[28,29] Patients should be monitored for respiratory depression for 1–3 days after starting or escalating opioid therapy. Careful dosing, particularly when switching from another opioid, and appropriate titration may help mitigate the risk of respiratory depression.[28,29] Accidental consumption of even a single dose may cause overdosing, particularly in pediatrics.[28,29] Naloxone, an opioid antagonist may be prescribed for emergency use in patients with an increased risk of overdose (eg, children, history of opioid use disorder or previous overdose, taking CNS depressants).[28,29] To minimize these risks, opioids should be prescribed for the shortest needed duration at the lowest effective dose.[1,4,8]

Table 11. Select Contraindications, Warnings, and Precautions for Pharmacologic Interventions used for Nonspecific Low Back Pain[a]

Acetaminophen[20] [b]	NSAIDs[1,18,48] [c]	Duloxetine[22]	Cyclobenzaprine[24] [d]	Opioids[28,29] [e]
Contraindications				
Hypersensitivity to active substance or any product components			**Hypersensitivity** to active substance or any product components	
Combination acetaminophen products The maximum daily dose of 4 grams of acetaminophen (in healthy adults), including combination products and all dosage forms should not be exceeded due to the risk of hepatic failure	**CABG surgery** Increased incidence of MI and stroke has been reported for individuals using NSAIDs post CABG surgery	**MAO inhibitors** Simultaneous use of MAO inhibitors or within the 14 days after stopping their use		**Respiratory depression** Contraindicated in patients with substantial respiratory depression
	Allergic-type reactions after taking aspirin or other NSAIDs • Contraindicated in patients with aspirin-sensitive asthma • Monitor for changes in asthma in patients without preexisting known aspirin sensitivity • Contraindicated in patients with urticaria after taking aspirin or other NSAIDs	**Linezolid- or IV methylene blue** Contraindicated to start duloxetine in patients treated with linezolid- or IV methylene blue	**Heart conditions** • During the acute recovery period after an MI • In patients with arrhythmias, heart block or conduction impairments • Congestive heart failure	**Acute or Severe Bronchial Asthma** In an unmonitored setting, contraindicated in patients with acute or severe bronchial asthma or in the absence of resuscitative devices
			Hyperthyroidism	**GI Obstruction** Contraindicated in patients with established or suspected GI obstruction, including paralytic ileus
Warnings and Precautions				
Hepatic injury • Acetaminophen in higher doses than recommended, including combination products may result in hepatic injury	**Serious CV thrombotic events** • An increased risk of serious CV thrombotic events, including MI and stroke have been reported with NSAID use • May occur early and increase with prolonged NSAID use	**Suicidal thinking and behaviors** • Increased risk of suicidal thoughts and behaviors in adults and pediatrics • Monitor for signs of suicidal thoughts and behaviors, including worsening depression	**Structural TCA-related events** • Cyclobenzaprine may cause arrythmias, tachycardia, and conduction prolongation resulting in MI and stroke	**Addiction, abuse and misuse** Evaluate risk before starting opioid therapy and monitor for the development of addiction, abuse, and misuse behaviors during use

Table 11. Select Contraindications, Warnings, and Precautions for Pharmacologic Interventions used for Nonspecific Low Back Pain[a]

Acetaminophen[20] [b]	NSAIDs[1,18,48] [c]	Duloxetine[22]	Cyclobenzaprine[24] [d]	Opioids[28,29] [e]
○ Overdose may result in hepatic failure and death • The maximum daily dose (4 g in adults), including combination products and all dosage forms, should not be exceed	• To minimize risk, treat for the shortest duration at the lowest effective dose	• Do not abruptly discontinue *(see withdrawal syndrome)*	due to the structural similarity to TCAs • May increase the effects of CNS depressants (eg, alcohol, barbiturates) • Consider stopping in the event clinically relevant CNS symptoms occur	
Allergy and hypersensitivity • Discontinue if signs of anaphylaxis occur and seek medical treatment • Avoid use in patients with an acetaminophen allergy	**Serious GI events** • An increased risk of serious GI events, including bleeding, ulceration, and perforation of the stomach or intestines have been reported with NSAID use • May occur at any time during NSAID use, with or without warning symptoms • Geriatric patients and patients with a previous history of PUD and/or ulcers are at increased risk	**Withdrawal syndrome** • Monitor for symptoms such as irritability, dizziness, anxiety, insomnia, seizures, and fatigue when discontinuing treatment • Recommended to taper dose to minimize the risk of withdrawal symptoms	**Avoid use in older adults** Due to the increased blood concentrations and half-life, cyclobenzaprine should be avoided older adults	**Mandatory REMS** The FDA requires a REMS for opioid products given the risks of addiction, abuse, and misuse, potentially leading to overdose and death
Dangerous skin reactions • Cases of AGEP, SJS, erythema multiforme, DRESS (***NSAIDs only***), or TEN have been reported Stop immediately if any symptoms of skin reactions develop (eg, skin rash, redness, blisters, skin separation), or other hypersensitivity reactions			**Avoid use in liver dysfunction** Avoid in patients with mild, moderate, or severe liver impairment	**Respiratory Depression** • Fatal respiratory depression has occurred with opioid therapy, even with recommended use • Monitor for serious respiratory depression when starting and with dose escalation, especially in patients with chronic lung disease or wasting syndrome,

Table 11. Select Contraindications, Warnings, and Precautions for Pharmacologic Interventions used for Nonspecific Low Back Pain[a]

Acetaminophen[20] [b]	NSAIDs[1,18,48] [c]	Duloxetine[22]	Cyclobenzaprine[24] [d]	Opioids[28,29] [e]
				older adults, or weakened patients

When to seek medical care
• New symptoms occur or symptoms worsen
• Appearance of redness or swelling
• Fever for > 3 days (all ages)
• Extended period of pain (excluding sore throat)
  ○ > 10 days (≥ 12 years of age)
  ○ >5 days (< 12 years of age)
• Severe, constant (> 2 days) sore throat in children or fever, headache, rash, nausea, or vomiting occurs after treatment
	Renal toxicity
	• Renal decompensation may occur with NSAID use
	• Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia
	• Discontinuation of NSAID usually results in recovery of renal function
		Serotonin syndrome:
		• Increased risk of serotonin syndrome has been observed with SNRIs, including duloxetine, SSRIs, and cyclobenzaprine, especially in combination with other serotonergic agents (eg, tramadol, TCAs)
		• Monitor for signs such as mental changes (eg, irritability, confusion, hallucinations), neuromuscular and gastrointestinal symptoms (eg, tremor, clonus, diarrhea)
		• Discontinue and provide supportive treatment if symptoms occur
				Accidental consumption and CYP P450 interactions
				• Accidental consumption of even a single dose may cause an overdose, particularly in children
				• Opioid concentrations may be affected by CYP P450 inhibitors and inducers
				• Monitor for side effects or symptoms of withdrawal at regular intervals, and adjust dose accordingly

	Hyperkalemia Potassium should be monitored with NSAID use due to the increased risk of hyperkalemia, especially in patients aged ≥ 65 years, patients with diabetes or renal impairment, and other contributing agents (eg, ACE inhibitors)	**Caution in select populations** Use caution in patients with a previous experience of urinary retention and angle-closure glaucoma ***Cyclobenzaprine only***: elevated intraocular pressure and using anticholinergic agents		**Use with CNS depressants** • Potential for additive adverse effects when combined with other CNS depressants. Restrict combination use for patients that have failed alternative therapies • Consider prescribing naloxone in case of an emergency
	Liver enzyme elevations • Elevations of liver enzymes (ALT and AST) have occurred, with cases of liver failure reported with duloxetine use			**Neonatal opioid withdrawal syndrome**

Table 11. Select Contraindications, Warnings, and Precautions for Pharmacologic Interventions used for Nonspecific Low Back Pain[a]

Acetaminophen[20] [b]	NSAIDs[1,18,48] [c]	Duloxetine[22]	Cyclobenzaprine[24] [d]	Opioids[28,29] [e]
	• Discontinue if signs of hepatotoxicity develop (eg, jaundice, "flu-like" symptoms, URQ soreness), or liver tests continue to be elevated or worsen • Avoid duloxetine in patients with significant alcohol use or preexisting liver disease			Neonatal opioid withdrawal syndrome has been observed in pregnant women that use long-term opioid therapy during pregnancy
	Hematologic abnormalities • NSAIDs and duloxetine may increase the risk of bleeding • Monitor hemoglobin or hematocrit in patients that develop anemia with NSAID use • Monitor for signs of bleeding in patients with coagulation disorders or patients also taking anticoagulants, antiplatelets, SSRIs, and SNRIs			**Adrenal deficiency** • Adrenal deficiency has been associated with opioid use • Taper opioid and treat with corticosteroids if adrenal deficiency is confirmed
	Hypertension • May cause new onset hypertension or worsen preexisting hypertension • ACE inhibitors, thiazide or loop diuretics may have decreased efficacy with concurrent NSAID therapy • Monitor BP before starting and during treatment			**Serious hypotension** • May cause hypotension, including orthostatic and fainting • Monitor BP after starting an opioid or escalating the dose
		Hyponatremia • Cases of hyponatremia have been reported, likely due to SIADH • Older adults, patients taking diuretics or hypovolemic may be at increased risk • Seems to be reversible after stopping duloxetine		**Caution in patients with head complications** • Patients with high intracranial pressure or brain tumors may experience increased intracranial pressure with opioid use
		Sexual impairment • SNRIs, including duloxetine may cause sexual impairment (eg, decreased libido, ED)		

Table 11. Select Contraindications, Warnings, and Precautions for Pharmacologic Interventions used for Nonspecific Low Back Pain[a]

Acetaminophen[20] [b]	NSAIDs[1,18,48] [c]	Duloxetine[22]	Cyclobenzaprine[24] [d]	Opioids[28,29] [e]
		Risk of orthostatic hypotension, falls and fainting: Consider dose adjustments or stopping if these events occur		

*Grey shading indicates it is a **black box warning***

Abbreviations: ACE, angiotensin converting enzyme; AGEP, acute generalized exanthematous pustulosis; BP, blood pressure; CNS, central nervous system; CV, cardiovascular; CYP, cytochrome; DRESS, drug reaction with eosinophilia and systemic symptoms; ED, erectile dysfunction; FDA, Food and Drug Administration; g, grams; GI, gastrointestinal; IV, intravenous; MAO, monoamine oxidase; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; REMS, Risk Evaluation and Mitigation Strategy; SJS, Stevens-Johnson Syndrome; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCAs, tricyclic antidepressants; TEN, toxic epidermal necrolysis; URQ, upper right quadrant

[a] *Prescribing information should be reviewed for individual drugs; this contains select warnings and precautions. Additionally, contraindications, warnings, and precautions may vary for specific agents within a drug class or drug formulation*

[b] *Contraindications, warnings, and precautions regarding the IV formulation of acetaminophen was excluded due to the unlikely use for the treatment of low back pain*

[c] *Safety information for the drug class was extrapolated from the ibuprofen and celecoxib prescribing information*

[d] *Due to the vast differences between skeletal muscle relaxants, contraindications, warnings, and precautions were only provided for cyclobenzaprine. Please refer to the agent-specific prescribing information for the appropriate safety information*

[e] *Safety information for the drug class was extrapolated from the tramadol and oxycodone prescribing information*

7.0 SUMMARY OF THE TREATMENT APPROACH FOR NONSPECIFIC LOW BACK PAIN WITH OR WITHOUT RADICULOPATHY

US guidelines tend to recommend education on self-care as the first-line option for patients presenting with nonspecific LBP with or without radiculopathy, regardless of symptom duration or severity.[1,5,9] Self-care includes maintaining physical activity, patient education, and appropriate physician advice.[9] Self-management materials such as *"The Back Book",* may be used to supplement physician guidance.[9,11]

Nonpharmacologic interventions are preferred over pharmacologic treatments for acute, subacute, and chronic nonspecific LBP due to the lower inherent risks;[3] however, a combination of both modalities are often used in clinical practice to gain better symptom control.[9] Some guidelines recommend offering "passive" nonpharmacologic interventions (eg, acupuncture, massage, and spinal manipulation) as adjunctive therapy for patients with an inadequate response to active nonpharmacologic interventions (eg, exercise, self-care).[1,2,8] NICE (2016) recommends manual therapies (eg, massage, spinal manipulation) only as part of a comprehensive program that includes exercise, and perhaps psychological therapy.[12]

Due to the usual self-limiting nature of acute and subacute nonspecific LBP with or without radicular pain, pharmacologic treatment is reserved for patients presenting with more severe symptoms that fail to produce an adequate response to nonpharmacologic interventions.[3,9] Treatments should be initiated based on shared decision-making between patients and providers,[1,3,5] especially among older individuals who are more predisposed to medication risks.[52] Before initiating any pharmacologic treatment, physicians should review the prescribing information, including black box warnings.[50]

Generally, oral NSAIDs are considered the first-line pharmacologic option for the treatment of nonspecific LBP with or without radiculopathy (acute, subacute, and chronic).[9] A 2017 Canadian guideline preferred acetaminophen to NSAIDs due to the more favorable adverse effect profile;[8] however, acetaminophen has not been proven to be more effective than placebo for outcomes related to LBP.[1,3,5] Due to consistent evidence demonstrating a lack of efficacy, concerns of harm predominates recommendations about acetaminophen, which results in conflicting recommendations in acute nonspecific LBP.[1,3,5] Acetaminophen may be considered as an alternative in patients that are not appropriate candidates for NSAIDs.[9]

Guidelines recommend non-benzodiazepine skeletal muscle relaxants (SMRs) (eg, cyclobenzaprine, tizanidine) for short-term (< 1 week) use in the management of nonspecific LBP.[1,3,5] Typically, SMRs are reserved as second-line agents when therapy with NSAIDs or acetaminophen has failed;[9] however, ACP (2017) recommends SMRs as first-line agents for acute or subacute nonspecific LBP, with the decision to select an NSAID or SMR based on patient specific factors (eg, benefit/risk, preference).[3]

NASS and NICE recommend against antidepressants for nonspecific LBP.[4,12] VA/DoD and ACP recommend consideration of duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI) for chronic nonspecific LBP with or without radiculopathy.[1-3] According to the VA/DoD guideline, duloxetine is the only SNRI that has been evaluated for LBP; nevertheless, the other agents within the drug class may produce a comparable benefit given the similar mechanism of action.[1] ACP lists duloxetine as a second-line agent for individuals with chronic nonspecific LBP that previously failed nonpharmacologic interventions and NSAIDs.[1,3] Tramadol is also recommended as a second-line agent for the treatment of

chronic nonspecific LBP by ACP, whereas other opioids are reserved as last-line agents.[3] Duloxetine may be preferred over tramadol in individuals with a history of substance use disorders, or concurrent depression or neuropathic pain.[8,9]

Opioids are considered a last-line option (except tramadol), generally for chronic nonspecific LBP after failure of all other alternative therapies (nonpharmacologic and pharmacologic).[3,8] Guidelines tend to discourage the use of opioids for acute or subacute nonspecific LBP;[3,5] however, ICSI recommends a trial of short-acting opioids in patients with severe acute pain that has not responded to non-opioids.[5] Due to the greater risk of overdose and morality with extended-release opioids,[28] short-acting opioids are preferred.[5] Given the significant adverse events (eg, overdose, respiratory depression, abuse, addiction) generally outweighing the potential small improvement in pain relief, it is recommended that opioid therapy should be prescribed for the shortest needed duration at the lowest effective dose.[1,4,5]

Based on the limited evidence for topical capsaicin, and a majority of US guidelines not including recommendations for topical preparations,[1,3-5] a place in therapy for these products is uncertain. However, topical capsaicin plaster may be an option for acute exacerbations in chronic nonspecific LBP, as suggested by the 2017 Canadian guideline.[8]

Table 12 outlines the treatment approach for managing non-specific LBP with or without radiculopathy, based on symptom duration (acute/subacute or chronic).[1,3-5,8,10,12]

Table 12. Treatment of Nonspecific Low Back Pain With or Without Radiculopathy

Treatment Method	Symptom Duration	
	Acute/Subacute (≤ 12 weeks)	**Chronic (> 12 weeks)**
Recommended for all patients:		
Guidance, education, self-care, encouragement of physical activity and returning to work		
Nonpharmacologic	• Superficial Heat • Spinal manipulation • Acupuncture • Massage[a]	• Structured exercises, including clinician-directed or yoga, tai chi • Psychological therapies (CBT, MBSR) • Spinal manipulation • Acupuncture • Massage[a] **Severe or more complex:** Multidisciplinary treatment (eg, exercise combined with psychological therapies)

Pharmacologic (*consider after failure of nonpharmacologic treatment*)	• **First-line:**
	  ○ NSAIDs[b]
	• **Second-line:**
	  ○ SMRs[c] (*only for acute/subacute or acute exacerbations in chronic nonspecific LBP*)
	  ○ Duloxetine (*chronic nonspecific LBP pain)*[d]
	• **Third-line:**
	  ○ Opioids[e] (*only when other medications have failed, contraindicated, or intolerant; usually for chronic nonspecific LBP)*	

Abbreviations: CBT, cognitive behavioral therapy; LBP, low back pain; MBSR, mindfulness-based stress reduction; NSAID, nonsteroidal anti-inflammatory drug; SMRs, skeletal muscle relaxants

[a] *Guideline recommendations are rarely provided; however, guidelines tend to provide evidence supporting massage for subacute and chronic nonspecific LBP with or without radiculopathy*

[b] ***Acetaminophen*** *may be used as an alternative to NSAIDs if an intolerance or contraindication exists, but only for acute nonspecific LBP with or without radiculopathy or as first-line per the 2017 Canadian guideline[8]*

[c] *Generally preferred as second-line agents but the 2017 ACP guideline lists them as first-line agents for patients with acute or subacute nonspecific LBP with or without radiculopathy*

[d] *May be used first-line for neuropathic pain with co-emergent musculoskeletal complaints in patients with nonspecific LBP per the 2017 Canadian guideline[8]*

[e] *According to the 2017 ACP guideline,* ***tramadol*** *is recommended as a second-line agent for chronic nonspecific LBP with or without radiculopathy*

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APPENDIX A – LITERATURE SEARCH

The following search was performed in OVID Medline and Epistemonikos on January 28, 2022.

Table 13. Ovid Medline Literature Search Strategy for Low Back Pain Guidelines

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to January 28, 2022>
Search strategy (date of search: January 28, 2022)

#	Searches	Results
1	Practice guideline.pt.	29569
2	Guide*.pt.	16486
3	(guidance or guideline*).ti.	104637
4	Position statement*.ti.	3523
5	Consensus.ti.	28699
6	1 or 2 or 3 or 4 or 5	152124
7	"low back pain".ti.	15502
8	Low Back Pain/	24460
9	7 or 8	28269
10	6 and 9	485
11	Limit 10 to yr= "2017 — Current"	**152**

Table 14. Epistemonikos Literature Search Strategy for Low Back Pain Guidelines

Database(s): Epistemonikos Session Results
Search strategy (date of search: January 28, 2022)

#	Searches	Results
1	Title: ((practice guideline) OR (guide*) OR (guidance OR guideline*))	13564
2	**AND** Title OR abstract: Low back pain	132
Filter publication year	From 2017 to 2022	**42**

APPENDIX B – CLINICAL GUIDELINES

Guidelines used for the preparation of this report:

- 2007 ACP, APS Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline[11]
- 2016 NICE Low Back Pain and Sciatica in over 16s: Assessment and Management[12]
- 2017 TOP Evidence-Informed Primary Care Management of Low Back Pain: Clinical Practice Guideline[8]
- 2017 VA/DoD Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain *(published in literature in 2019)*[1,2]
- 2017 ACP Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline[3]
- 2018 ICSI Adult Acute and Subacute Low Back Pain[5]
- 2020 NASS Evidence-Based Clinical Guidelines for Multidisciplinary Spine Care: Diagnosis and Treatment of Low Back Pain[4]
- 2021 ACR Appropriateness Criteria Low Back Pain[35]
- 2021 AOPT, APTA Interventions for the Management of Acute and Chronic Low Back Pain[37]

APPENDIX C – BASIS FOR GUIDELINE RECOMMENDATIONS

Evidence rating from NASS 2020:

- Recommendation strength: determined based on the LOE
- LOE:
    - **A** ("Good evidence"): based on well-designed randomized clinical trials, or well-conducted systematic review of randomized controlled trials with consistent findings for or against recommendation (level I studies)
    - **B** ("Fair evidence"): based on lesser quality randomized clinical trials, observational studies (cohort or case-control), or systematic review of observational studies with consistent findings for or against recommendation (level II or III studies)
    - **C** ("Poor quality evidence"): based on inadequately controlled or uncontrolled studies, or expert opinion for or against recommendation (level IV or V studies)
    - **I** ("Insufficient clinical evidence"): unable to make a recommendation due to lacking or conflicting evidence

Evidence rating from ICSI 2018:

- Recommendation strength (based on LOE): strong or weak
- LOE (high, moderate, or low): based on GRADE criteria. Consensus recommendations were made using the best available evidence.

Evidence rating from VA/DoD 2017:

- Recommendation strength: strong or weak
    - GRADE determined based on LOE, balance of desired and undesired effects, values/preferences, other factors as appropriate (eg, costs, feasibility), relative strength, and direction (for or against). Recommendation categorization was used to identify recommendations that were modified, new, or unchanged from the previous guideline.
- LOE (high, moderate, low, or very low)

Evidence rating from ACP

- Recommendation strength: strong or weak
- LOE (high, moderate, or low): based on GRADE criteria
    - High-quality evidence: based on well-designed randomized clinical trials
    - Moderate-quality evidence: based on lesser quality randomized clinical trials, or well-conducted observational studies
    - Low-quality evidence: observational studies (eg, case series)

APPENDIX D – SUPPLEMENTARY TABLES

Table 15. Glossary of Nonpharmacologic Interventions

Nonpharmacological Intervention	Description[1,11,37]
Acupuncture	Manual insertion of needles at precise locations on the body to alleviate pain
Back school	Program conducted by a paramedical therapist or medical specialist focusing on education and exercise therapy
Clinician-direct exercise	Consists of supervised or home-based programs targeted for physical activity or aerobic exercise to improve muscle strength, and/or flexibility
Cognitive behavioral therapy (CBT)	A psychotherapeutic approach to modify perceptions and behaviors related to pain, and promote relaxation techniques to manage symptoms
Lumbar traction	Manual or mechanical manipulation of the spine by using force to stretch the spine
Massage	Manual manipulation of soft tissue using hand techniques or devices to promote relaxation of affected muscles
Mindfulness-based stress reduction (MBSR)	A psychotherapeutic approach focused on intentionally being in the present through relaxation techniques, such as medication and exercise
Motor control exercise	A rehabilitative exercise that targets the activation and coordination of the spine muscles. Muscle control is challenged with more complex activities as patient capabilities improve.
Multidisciplinary biopsychosocial rehabilitation (MBR)	A collaborative approach from multiple healthcare disciplines that combines physical (eg, exercise) and behavioral/psychological (eg, occupational therapy, massage, education) aspects to manage symptoms
Pilates	A mind-body exercise that concentrates on strength training, flexibility, and posture
Short-wave diathermy	Heat is produced using electromagnetic energy (10—100 MHz) to reduce pain
Spinal manipulation	Manual application of controlled force that is applied to the spinal joints, either within or extending beyond the joint range
Tai chi	A meditative exercise that uses concentrated breathing and slow movements
Transcutaneous electrical nerve stimulation (TENS)	Constant electrical impulses (low voltage) are delivered via a device to modify pain sensitivity
Yoga	A mind-body exercise that focuses on particular body positions and breathing techniques

Table 16. Summary of Selected Nonpharmacologic and Self-care Interventions for Nonspecific Low Back Pain, Specified by Duration of Symptoms

Nonpharmacological Intervention(s)	Type of Low Back Pain			Reference US Guideline(s) (Sponsoring Organization, Year)[d]
	Acute[a]	Subacute[b]	Chronic[c]	
Psychological therapies (CBT)			✓	(NASS; 2020)[4] (VA/DoD; 2017)[1] (ACP; 2017)[3]
Exercise[e]	✓	✓	✓	(VA/DoD; 2017)[1]
	✓	✓		(ICSI; 2018)[5]
			✓	(ACP; 2017)[3] (NASS; 2020)[4]
Clinician-directed exercise (eg, back school, motor control, McKenzie)			✓	(NASS; 2020)[4] (VA/DoD; 2017)[1] (ACP; 2017)[3]
Yoga			✓	(NASS; 2020)[4] (VA/DoD; 2017)[1] (ACP; 2017)[3]
Heat	✓			(NASS; 2020)[4] (VA/DoD; 2017)[1]
	✓	✓		(ICSI; 2018)[5] (ACP; 2017)[3]
Acupuncture			✓	(NASS; 2020)[4] (VA/DoD; 2017)[1]
		✓		(ICSI; 2018)[5]
	✓	✓	✓	(ACP; 2017)[3]
Spinal manipulation	✓		✓	(NASS; 2020)[4] (VA/DoD; 2017)[1]
	✓	✓		(ICSI; 2018)[5]
	✓	✓	✓	(ACP; 2017)[3]

Abbreviations: ACP, American College of Physicians; CBT, cognitive behavioral therapy; DoD, Department of Defense; ICSI, Institute for Clinical Systems Improvement; North American Spine Society; VA, Veteran Affairs

*[a] Defined as < 4 weeks of pain for included guidelines **except NASS,** which defines acute as <6 weeks*

*[b] Defined as pain lasting 4 to 12 weeks by included guidelines **except NASS,** which defines subacute as 6—12 weeks*

[c] Defined as > 12 weeks of pain

[d] Guideline names are as follows: ACP: Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain; NASS: Diagnosis and Treatment of Low Back Pain; ICSI: Adult Acute and Subacute Low Back Pain; VA/DoD: Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain

[e] Includes self-care recommendations for exercise (eg, remaining active)

Table 17. Summary of Selected Pharmacologic Interventions for Nonspecific Low Back Pain, Specified by Duration of Symptoms

Pharmacological Intervention(s)	Type of Low Back Pain			Reference US Guideline(s) (Sponsoring Organization, Year)[d]
	Acute[a]	Subacute[b]	Chronic[c]	
Antidepressants (duloxetine)*			✓	(VA/DoD; 2017)[1] (ACP; 2017)[3]
NSAIDs	✓	✓	✓	(ACP; 2017)[3]
	✓	✓		(ICSI; 2018)[5]
	✓		✓	(NASS; 2020)[4] (VA/DoD; 2017)[1]
Acetaminophen	✓	✓		(ICSI; 2018)[5]
Muscle relaxants	✓	✓		(ACP; 2017)[3]
	✓			(ICSI; 2018)[5]
	✓		✓**	(VA/DoD; 2017)[1]
Opioids			✓	(ACP; 2017)[3] (ICSI; 2018)[5]

Abbreviations: ACP, American College of Physicians; DoD, Department of Defense; ICSI, Institute for Clinical Systems Improvement; NSAIDs, nonsteroidal anti-inflammatory drugs; North American Spine Society; SMRs, skeletal muscle relaxants; VA, Veteran Affairs;

**The NASS guideline (does not address radiculopathy) recommends against antidepressants (as a drug class) for the treatment of LBP, while other guidelines (VA/DoD and ACP) mention a specific agent, duloxetine as recommended.*

***Only for acute exacerbations of chronic low back pain; not for long-term use*

[a] *Defined as < 4 weeks of pain for included guidelines **except NASS,** which defines acute as <6 weeks*

[b] *Defined as pain lasting 4 to 12 weeks by included guidelines **except NASS,** which defines subacute as 6—12 weeks*

[c] *Defined as > 12 weeks of pain*

[d] *Guideline names are as follows: ACP: Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain; NASS: Diagnosis and Treatment of Low Back Pain; ICSI: Adult Acute and Subacute Low Back Pain; VA/DoD: Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain*