

# Chronic Pain

## How to Approach These 3 Common Conditions

Fibromyalgia, osteoarthritis, and low back pain require multimodal, evidence-based treatment plans. Tailoring those plans to the underlying mechanisms of pain is key.

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### PRACTICE RECOMMENDATIONS

Recommend cognitive behavioral therapy for most patients with chronic pain. **A**

Recommend movement and exercise therapies for all patients with chronic pain. **A**

Prescribe anti-inflammatory medications for patients with peripheral nociceptive pain and centrally-acting agents (eg, tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, and alpha 2 delta ligands) for patients with centralized pain. **A**

### STRENGTH OF RECOMMENDATION

**A** Good-quality patient-oriented evidence

**B** Inconsistent or limited-quality patient-oriented evidence

**C** Consensus, usual practice, opinion, disease-oriented evidence, case series

**Case 1** Lola, 28, has a history of muscular aches and joint pain throughout her body, fatigue, and mental foggy. A rheumatologist diagnosed fibromyalgia, but Lola just moved to your town and is establishing care. She is feeling desperate because her pain has worsened and the medication previously prescribed (gabapentin 300 mg tid) is no longer working. She asks to try oxycodone.

**Case 2** Matt is a 59-year-old truck driver with severe hip osteoarthritis (OA). His orthopedist recommended against hip replacement at this time because of his young age and a heart

condition that makes him high risk. His pain makes sitting for long periods very difficult. He presents to you for help because he is worried he will be unable to continue working.

**Case 3** Keith is a 56-year-old construction worker who has been experiencing back pain for many years. The pain has become more debilitating over time; it is now constant, and Keith can hardly make it through his work day. He has been getting hydrocodone/acetaminophen from urgent care centers and emergency departments, but he isn't sure it is helping and is coming to you to assume his pain management.

**C**hronic pain (defined as > 3 mo in duration) is a complex, heterogeneous condition affecting an estimated 116 million US adults.<sup>1</sup> Much of the management of chronic pain occurs in primary care settings, placing family practice providers (FPPs) on the frontlines of two epidemics: that of chronic pain and that of the abuse and misuse of opioid pain medications.

To improve communication about the risks and benefits of opioid therapy and the safety and effectiveness of pain treatments in general, many professional organizations, health care institutions, and recently the CDC, have published guidelines on the use of opioids for nonmalignant chronic pain.<sup>2</sup> With these guidelines in mind—and in light of the latest evidence—we propose the following paradigm for the treatment of chronic pain. A critical aspect is deter-

**TABLE 1**  
**Mechanisms of Pain**

Peripheral nociceptive pain	Central neuropathic pain or central sensitization	Combination of peripheral and central mechanisms
Inflammation or mechanical damage in tissues Responds to NSAIDs, opioids Responds to procedures Classic examples: Osteoarthritis Rheumatoid arthritis Cancer pain	Characterized by central disturbance in pain processing (diffuse hyperalgesia/ allodynia) Responds to neuroactive compounds that alter levels of neurotransmitters involved in pain transmission Responsive to nonpharmacologic therapies such as exercise and CBT Classic examples: Fibromyalgia Irritable bowel syndrome TMJD Tension headache	Involvement of both inflammatory or mechanical damage to the tissues along with dysfunction in central pain processing Need to treat all contributing mechanisms Classic examples: Low back pain Rheumatologic diseases that develop into comorbid fibromyalgia
Peripheral neuropathic pain		
Damage to, or dysfunction of, peripheral nerves Responds to both peripheral and centrally acting pharmacologic therapies Classic examples: Diabetic neuropathic pain Postherpetic neuralgia		

Abbreviations: CBT, cognitive behavioral therapy; TMJD, temporomandibular joint disorder.  
 Source: Clauw. *Best Pract Res Clin Rheumatol*. 2015.<sup>4</sup> Adapted with permission from Dr. Daniel Clauw, University of Michigan.

mining the underlying pathophysiology of a patient’s pain in order to develop a well-rounded, multimodal, evidence-based treatment plan. Detailed here is the application of this approach to the treatment of three common diagnoses: fibromyalgia, osteoarthritis, and low back pain.

**LOOK TO THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM**

Acute pain begins with activation of peripheral nociceptors at the site of injury. This causes depolarization up the spinal cord and through the brain stem to higher cortical centers where the pain is perceived and localized. Descending neural pathways transport both excitatory and inhibitory information from the brain to the periphery via the spinal cord, which either increases or decreases the perception of pain.<sup>3</sup>

**When damage/injury doesn’t correlate with the perception of pain**

Until recently, it was assumed that chronic pain worked much the same way as acute pain and was caused by ongoing nociceptive input in the periphery, but research has

shown us that the central nervous system (CNS) can play a large role in the modulation of nociception. This new understanding comes from the lack of evidence pointing to any pain state in which the degree of nociceptive input correlates with the degree of pain experienced.

For most patients with chronic pain, regardless of their diagnosis, there is some degree of alteration in the processing of nociceptive signals by the CNS contributing to the experience of pain.<sup>4</sup> This alteration is thought to result from peripheral nociceptive signaling persisting past the point of tissue healing, leading to a hypersensitivity of nerve fibers, which then continue to respond to low, or absent, sensory stimuli.

*Central sensitization* is when this hypersensitivity develops in the superficial, deep, and ventral cord nerves. When this happens, pain is often accompanied by systemic symptoms such as fatigue and slowed cognitive processing, often with little to no actual stimulation of the peripheral nociceptors.<sup>3</sup>

Table 1 lists the possible mechanisms of pain, which can be broken down into four categories: peripheral nociceptive

**TABLE 2**  
**Treatment Options for Fibromyalgia: What Works?**

Treatment	Specifics	SOR*	Adverse effects
<b>Nonpharmacologic therapies</b>			
Patient education <sup>25</sup>	Incorporate principles of self-management into patient teaching, including a multimodal approach.	A	
Graded exercise <sup>26</sup>	Aerobic exercise has been studied the most, but strengthening and stretching have also been shown to be of value.	A	Worsening of symptoms when program is begun too rapidly
CAM therapies <sup>27</sup>	Most CAM therapies have not been rigorously studied, but there is emerging evidence that CAM treatments such as Tai Chi, yoga, balneotherapy, and acupuncture might be effective.	A	Generally safe
CBT <sup>29</sup>	Pain-based CBT programs have been shown to be effective in one-on-one settings, small groups, and via the Internet.	A	No significant adverse effects per se, but patient acceptance is often poor when CBT is viewed as a “psychologic intervention.”
<b>Pharmacologic therapies<sup>†</sup></b>			
Tricyclic compounds	Amitriptyline 10-70 mg at bedtime <sup>30</sup> Cyclobenzaprine 5-20 mg at bedtime <sup>31</sup>	A	Dry mouth, weight gain, constipation, “groggy” or drugged feeling
SNRIs <sup>32</sup>	Duloxetine 30-120 mg/d Milnacipran 100-200 mg/d	A	Nausea, palpitations, headache, fatigue, tachycardia, hypertension
SSRIs <sup>32</sup>	Fluoxetine, sertraline, paroxetine	A	Nausea, sexual dysfunction, weight gain, sleep disturbance
Gaba-pentinoids <sup>33</sup>	Gabapentin 800-2,400 mg/d in divided doses Pregabalin up to 600 mg/d in divided doses	A	Sedation, weight gain, dizziness
Opioid receptor agonists <sup>34</sup>	N/A	No evidence for use	Sedation, constipation, addiction, opioid-induced hyperalgesia
Combined opioid receptor agonist/SNRI <sup>35</sup>	Tramadol 50-100 mg 2-3x/d; prn dosing	B	Sedation, constipation
Low-dose naltrexone <sup>36</sup>	4.5 mg/d	B	N/A

Abbreviations: CAM, complementary and alternative medicine; CBT, cognitive behavioral therapy; N/A, not applicable; prn, as needed; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

\*See page 38 for an explanation of the SOR (strength of recommendation) ratings.

(inflammatory or mechanical), peripheral neuropathic (underlying damage to a peripheral nerve), central (when the CNS is the primary entity involved in maintaining the pain), or any combination of the three.<sup>4</sup>

**As pain becomes chronic, multiple mechanisms overlap**

It is important to remember that for any single pain diagnosis, there is likely to be—at least initially—a principle underlying mechanism generating the pain. But as the

**Clinical pearls**

Following initial diagnosis, spend several visits (or use separate educational sessions) explaining the condition and setting treatment expectations.

Counsel patients to “start low, go slow.”  
For many patients, focusing first on increasing daily activity is helpful before starting a formal exercise routine.

Allowing patients to choose which CAM therapies to incorporate into an active treatment program can increase self-efficacy.<sup>28</sup>

Internet-based programs are gaining acceptance and are more convenient for patients who work.

When effective, these agents can improve a wide range of symptoms including pain, sleep, and bowel and bladder symptoms. Taking these drugs several hours prior to bedtime improves the adverse effect profile.

Warning patients about transient nausea, advising them to take the drug with food, and slowly increasing the dose can increase tolerability.

Milnacipran might be slightly more noradrenergic than duloxetine and thus potentially more helpful for fatigue and memory problems, but milnacipran is also more likely to cause hypertension.

Older, less selective SSRIs may have some efficacy in improving pain, especially at higher doses that have more prominent noradrenergic effects.

Newer SSRIs (citalopram, escitalopram, desvenlafaxine) are less effective or ineffective as analgesics.

Giving most or the entire dose at bedtime can increase tolerability.

Occasionally needed for patients with a mixed inflammatory or nociceptive pain component

Only recommended as second-line agent  
Less effective than SNRIs alone

Available only as a compounded medication

<sup>†</sup>Pharmacologic therapy is best chosen based on the predominant symptoms and initiated in low doses with slow dose escalation. Some practitioners find that getting patients on a drug regimen that helps improve symptoms prior to initiating nonpharmacologic therapies helps improve compliance.

pain becomes chronic, an overlap of multiple mechanisms develops, with central sensitization often playing a more dominant role than peripheral stimulation (regardless of the diagnosis).

For example, in a patient with rheuma-

toid arthritis (RA), peripheral nociceptive input (in the form of inflammation) is likely the initial mechanism at work, but as time goes on, central processing becomes more involved. The patient may then begin to experience pain that is disproportionate to

**TABLE 3**  
**Treatment Options for Osteoarthritis: What Works?**

Treatment	Specifics	SOR*	Adverse effects
Patient education and self-management programs <sup>46,47</sup>	Can boost adherence to exercise modalities	A	
Exercise (eg, land-based, aquatic, Tai Chi) <sup>48,49</sup>	Prevents progression, decreases pain, and increases function	A	Adherence can be a problem
Acetaminophen <sup>50</sup>	Evidence does not support its use for OA.	A	Liver and kidney damage
NSAIDs <sup>50</sup>	Diclofenac 150 mg/d in divided doses	A	Cardiac complications, GI bleeding
Opioid agonists <sup>51</sup>	Recent meta-analysis showed almost no improvement over NSAIDs for pain and function. <sup>52</sup>	B	Sedation, constipation, addiction, opioid-induced hyperalgesia
SNRIs <sup>51</sup>	Duloxetine 30-60 mg/d	B	
Intra-articular injections	1. Hyaluronic acid 2. Steroids 3. Platelet-rich plasma 4. Botulism toxin	A B B B	2. Alters glucose regulation
Glucosamine and chondroitin	No statistically significant evidence showing reductions in pain alone or in combination, but trends toward positive findings exist for both <sup>53,54</sup>	B	No significant AEs in studies. Glucosamine theoretically can cause GI upset, headache, and tachyarrhythmia.
Dietary interventions to reduce inflammation	1. Turmeric (curcumin) 2. Plant-based diet	B B	
Acupuncture		B	Few to none

Abbreviations: AEs, adverse events; GI, gastrointestinal; OA, osteoarthritis; SNRI, serotonin norepinephrine reuptake inhibitors.

what is generally expected with RA and may develop other somatic symptoms. The diagnosis then becomes pain primarily related to RA with central sensitization, and both need to be addressed in a treatment plan. In rheumatic conditions, comorbid fibromyalgia (indicative of central sensitization) is thought to occur in 15% to 30% of patients.<sup>5</sup>

FPPs can utilize the underlying mechanisms to cut across diagnostic labels and

tailor treatments to those that are most likely to be effective. For a patient with more prominent peripheral involvement, a procedural intervention such as injections or surgery alone may suffice, whereas a broader approach including psychotherapy, medications, exercise, and other lifestyle interventions may be necessary for a patient with pain caused predominantly by central sensitization.

Clinical pearls
Following initial diagnosis, spend several visits (or use separate educational sessions) explaining the condition and setting treatment expectations.
Likely most beneficial in the setting of acute flare-ups of pain Topical preparations are more effective than placebo and have fewer adverse effects than oral preparations.
Risk-benefit discussion is needed before initiation. Should be used as a second-line therapy only in patients for whom other strategies are not sufficient
Can be used as first-line therapy for patients with a centralized pain component
<ol style="list-style-type: none"> <li>1. Likely to have a longer duration of effect than steroid injections (based on heterogeneous data)<sup>42</sup></li> <li>2. Short-term improvement in pain, but no efficacy after 26 wk<sup>43</sup></li> <li>3. Significant reductions in pain for up to 12 mo<sup>44</sup></li> <li>4. Short-term studies (up to 12 wk) show reduction in pain in refractory OA cases.<sup>45</sup></li> </ol>
Trends toward pain <sup>55</sup> and function <sup>56</sup> benefit for glucosamine Chondroitin has shown some effects on radiologic disease progression in knee OA. <sup>57</sup>
<ol style="list-style-type: none"> <li>1. Heterogeneous data showing overall improvement in inflammatory biomarkers and function along with decreased pain. Dosing not consistent among studies.<sup>58</sup></li> <li>2. Showed improvement in functionality<sup>59</sup></li> </ol>
Statistically significant: <ul style="list-style-type: none"> <li>• decrease in pain • improvement in functional status</li> <li>• improvement in quality of life<sup>60,61</sup></li> </ul>

\*See page 38 for an explanation of the SOR (strength of recommendation) ratings

**Addressing both peripheral and central components is essential.** One prospective, observational cohort study of more than 600 patients scheduled for unilateral total knee or total hip arthroplasty found that patients with a higher degree of centralization of pain (measured by widespread pain index and modified fibromyalgia screening scales) were less likely to report improvement in the affected body part and in overall

body pain following surgery.<sup>6,7</sup>

There is a high degree of overlap among many of the chronic pain syndromes (fibromyalgia, irritable bowel syndrome, interstitial cystitis, chronic headaches) that have been found to have a central sensitization component.<sup>8</sup> Providers of primary care are aptly positioned to recognize central sensitization as the underlying pathology and target treatment effectively.

### TAILOR TREATMENT TO THE UNDERLYING MECHANISMS OF PAIN

As with any chronic condition, a thorough workup (complete with history, physical exam, and diagnostic testing, as appropriate) is indicated. In the setting of chronic pain, it's important to identify the primary mechanism, as well as secondary factors that may contribute to the patient's pain, before developing your treatment plan. These secondary factors may include co-occurring affect disorders, a history of trauma, poor sleep, and tobacco use.<sup>9-12</sup> A history of trauma, for example, co-exists with many pain syndromes. For these patients, central sensitization is responsible for much of their pain. As a result, traditional cognitive behavioral therapy (CBT) may not be the best option because of its focus on accepting pain as a chronic diagnosis; more trauma-focused treatments, such as

those dealing in emotional awareness and understanding of the CNS's role in chronic pain, need to be considered.<sup>13</sup>

**Three common conditions.** Below we present evidence-based treatment approaches for conditions typically associated with each of the major mechanisms of chronic pain: fibromyalgia (central sensitization), OA (peripheral nociceptive), and low back pain (mixed pain state).

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### Fibromyalgia: a case of central sensitization

Fibromyalgia is a hallmark diagnosis for patients in whom central sensitization is the dominant cause of pain. They usually present with widespread, diffuse pain and somatic symptoms such as fatigue, memory difficulties, and poor sleep quality.<sup>8</sup> When explaining the pain mechanism to patients, it may be useful to use the analogy of a volume control dial that is stuck in the “high” position and can’t be turned down.

**Genes, the environment, and neurotransmitters play a role.** The origin of the pain amplification process is believed to be multifactorial.

**Genetic factors** are thought to contribute to a predisposition for amplification. To date, five sets of genes have been implicated in increased sensitivity to pain leading to increased risk of the development of chronic pain during a patient’s lifetime.<sup>14-19</sup>

**Environmental factors** (eg, early life trauma, physical trauma especially to the trunk, certain infections such as Lyme disease and Epstein-Barr virus, and emotional stress) may trigger or exacerbate symptoms.<sup>8</sup> Of note: Only about 5% to 10% of people who experience these triggers actually develop a chronic pain state, while the rest regain their baseline health.<sup>4</sup> This raises the question of whether there is a point during an acute pain episode in which one can intervene and prevent the acute pain from becoming chronic in those at higher risk.<sup>4</sup>

**Imbalances of neurotransmitters** (high glutamate; low norepinephrine, serotonin, and gamma-aminobutyric acid [GABA]) play a role in central amplification.<sup>20-22</sup> These substances not only affect sensory transmission, but also control levels of alertness, sleep, mood, and memory.

**The diagnostic criteria for fibromyalgia** were modified in 2011 to remove the tender point examination and to add somatic symptoms.<sup>6</sup> These criteria can be useful in the clinical setting in identifying not only fibromyalgia itself but also the degree of “fibromyalginess” a patient has, which is an indicator of how large a role the centralization process plays in the maintenance of chronic pain.<sup>23,24</sup>

**Treatment: multimodal and patient empowering.** Evidence-based treatment options for fibromyalgia, as well as other conditions for which there is a high degree of centralized pain, can be found in Table 2 (page 40).<sup>25-36</sup> Multimodal treatment, with an emphasis on patient knowledge and empowerment, is generally thought to be the most beneficial.<sup>25,37</sup> Treatment should almost always include CBT and exercise/activity therapies, which have high degrees of efficacy with few adverse effects.<sup>26,29</sup>

In terms of medication, centrally-acting agents (tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors [SNRIs], and alpha 2 delta ligands) are the most effective. There is little to no data showing benefit from anti-inflammatories or opioids in the setting of fibromyalgia. There is some data to suggest that combination therapy, for example with an SNRI (milnacipran) and an alpha 2 delta ligand (pregabalin), may provide more benefit than treating with pregabalin alone.<sup>38</sup>

Complementary and alternative therapies (eg, yoga, chiropractic care, acupuncture, massage) are being studied more, and while evidence is only preliminary in terms of efficacy, there is increasing emphasis being placed on the need for patients with chronic pain to shift their treatment expectations to greater acceptance of pain and the need for ongoing self-care.<sup>28</sup>

### OA: an example of peripheral nociceptive pain

OA is a condition long thought to be characterized by damage to the cartilage and bone; however, as with many other pain diagnoses, there is frequently little correlation between damage seen on radiographs and the amount of pain that patients experience.

One study analyzed data on almost 7,000 patients from the National Health and Nutrition Examination Survey (NHANES I) and found that between 30% and 50% of OA patients with moderate to severe radiographic changes were asymptomatic, and 10% of those with moderate to severe pain had normal radiographs or only mild changes.<sup>39</sup> Research is showing that many factors may contribute to this discrepancy,

including the typical “wear and tear” of the disease, subacute levels of inflammation that can lead to peripheral sensitization, and, in some patients, a centralized pain component.<sup>40</sup> The patients with more centralized pain often have pain that is disproportionate to radiographic evidence, as well as more somatic symptoms, such as fatigue, sleep disturbance, and memory issues.<sup>41</sup>

**Treatment should be multimodal** and include interventions targeted at halting the progression of damage as well as palliation of pain. All treatment plans for OA should also include exercise, weight reduction, and self-management, in addition to pharmacologic interventions, to reduce both the micro-inflammation and the centralized pain component (when present). Intra-articular injections of various types have been studied with some having more efficacy in pain reduction and functional improvement than others.<sup>42-45</sup> See Table 3 (page 42) for a summary of evidence-based treatment options.<sup>42-61</sup>

### Low back pain: a mixed pain state

Low back pain (LBP) has been recognized as a mixed pain state for quite some time. While some patients may experience purely nociceptive and/or neuropathic pain, most cases are nonspecific, with patients experiencing varying degrees of nociceptive (myofascial LBP), neuropathic (lumbar radiculopathy), and central sensitization pain.<sup>62,63</sup> Evidence for centralized pain is demonstrated in studies showing hyperalgesia, augmented central pain processing, involvement of the emotional brain, and delayed recovery influenced by poor coping strategies.<sup>64-67</sup>

**When developing a treatment plan** for a patient with chronic LBP, remember that the pain derives from a complex combination of pathophysiologic contributors. Identifying where a patient lies on the pain centralization spectrum can help you tailor treatment.

In one study of 548 patients presenting to a tertiary pain clinic with primary spine pain diagnoses, 42% met diagnostic criteria for fibromyalgia.<sup>68</sup> Compared to criteria-negative patients, these patients tended to be young-

er, unemployed, and receiving compensation; they had greater pain intensity, pain interference, and used stronger words to describe their neuropathic pain, as well as having higher levels of depression/anxiety and a lower level of physical function.

Because LBP is a condition with high prevalence and associated disability, many clinical boards have created guidelines for management. These guidelines tend to vary in the strength of evidence used, and the extent to which they are followed in clinical practice remains largely unknown. Recommendations frequently discourage the use of ultrasound/electrotherapy, but many encourage *short-term* use of medications, supervised exercise therapy, CBT, and multidisciplinary treatment.

Guidelines tend to differ most widely with regard to recommendations for spinal manipulation and specific drug therapies.<sup>69</sup> The classes of drugs that may be most useful when centralized pain is present include the SNRIs and the alpha 2 delta calcium channel ligands.<sup>4</sup> See Table 4 (page 46) for a summary of evidence-based treatment options.<sup>70-89</sup>

**Case 1** Lola is started on amitriptyline 25 mg at bedtime, which improves her fatigue and cognitive symptoms. During monthly office visits, her FPP educates her about the pathophysiology of fibromyalgia and uses motivational interviewing to get her slowly moving and increasing her activity level. She is weaned off the gabapentin previously prescribed, as her symptoms stabilize and improve.

**Case 2** Matt is sent for a steroid injection, which decreases his pain temporarily. During this time, he begins physical therapy; slowly, with increased movement, his function improves. A trial of duloxetine provides pain relief; that combined with intermittent NSAIDs has allowed Matt to maintain his function and his job.

**Case 3** Because Keith was only taking the narcotics intermittently and wasn't certain they were helping, CBT was sufficient to wean him off the medication without any worsening of his pain in the process. By participating in



**TABLE 4**  
**Treatment Options for Chronic Low Back Pain: What Works?**

Treatment	Specifics	SOR*	Adverse effects
Self-management <sup>70</sup> Patient education <sup>71</sup>	Zero to small benefit	B	None
Exercise	Mean decrease in pain of 13.3% and increase in function of 6.9% <sup>72</sup>	B	There were no adverse events reported.
Heat/cold application <sup>73</sup>	Heat reduces pain/disability for up to 3 mo. Cold not helpful	B B	There were no adverse events reported.
OMT	Improves pain and function when used alone <sup>74</sup> or added to other interventions <sup>75</sup>	B	Serious adverse events associated with lumbar spine manipulation are rare (< 1 in 1,000,000). <sup>76</sup>
Massage	Unlikely helpful <sup>77</sup>	B	Increased pain
US and TENS	There is no evidence to support the use of TENS <sup>78</sup> or therapeutic ultrasound. <sup>79</sup>	B	Severe rash with TENS unit rare. No safety
Acupuncture	May have additive effect on pain relief and function when used in addition to other therapies <sup>80</sup>	B	Serious complications are rare. Patients could experience pain or bleeding. <sup>81</sup>
Yoga	More effective than a self-care book for improving function and reducing pain <sup>82</sup>	B	No serious adverse events
Behavioral therapy	More effective with longer lasting results than usual care <sup>83</sup>	A	No reported adverse events with therapy
Injection therapy (sites reviewed included epidural, facet, and local)	No strong evidence for or against the use of any type of injection therapy <sup>84</sup>	B	Headaches, dizziness, pain, numbness, cauda equina, septic arthritis, paraplegia, paraspinal abscesses
Surgery	Fusion is no more effective than intensive rehabilitation, but is associated with small benefits compared to standard therapy. <sup>85</sup>	B	Major adverse effects include deep wound infection, bleeding, thrombosis, ARDS, pulmonary edema, and heart failure.
Acetaminophen	No improvement in pain or function <sup>86,87</sup>	A	COX inhibition at high doses; increased risk of MI, HTN, renal failure, decreased hemoglobin
NSAIDs	Slightly more effective than placebo for pain and disability reduction <sup>88</sup>	B	Gastropathy, renal impairment, drug-drug interactions Extra care required in individuals at risk for CVD/VTE
Antidepressants	Not more effective than placebo with respect to pain or functional status <sup>89</sup>	A	No specific data
Opioids	No benefit over NSAIDs with regard to pain and disability <sup>89</sup>	B	Dependence, constipation

Abbreviations: AEs, adverse events; ARDS, acute respiratory distress syndrome; CBT, cognitive behavioral therapy; COX, cyclooxygenase; CVD/VTE, cardiovascular disease/venous thromboembolism; HTN, hypertension; LBP, low back pain; MBSR, mindfulness-based

**Clinical pearls**

More evidence for education in acute back pain

In subacute low back pain, there is some evidence that a graded activity program improves absenteeism outcomes.

Heat treatments include warm packs, hot baths/steam, and infrared heat lamps.

OMT can include a range of manual techniques, is not standardized between practitioners, and can be delivered by osteopathic physicians, chiropractors, and physical therapists.

Improvements observed, but only in short term

Alert patients that they must be wary if these modalities make up the bulk of a physical therapy session.

Benefit over no therapy or sham therapy observed for up to 3 mo

No significant differences between MBSR and CBT

Cannot rule out potential benefit of specific agents (steroids, NSAIDs, opioids, and local anesthetics) to specific subgroups of patients

Formal shared decision-making aids have been shown to decrease the proportion of patients who choose spine surgery, without adversely affecting clinical outcomes.

Occasional use is safe, and marginal effect is not statistically significant. High-dose acetaminophen should be avoided, given its limited efficacy and risk of toxicity.

NSAIDs considered first-line treatment by many guidelines

Patients with a previous history of LBP had improved psychosocial outcomes (including anxiety and depression).

Rate of AEs significantly greater than placebo

stress reduction; OMT, osteopathic manipulation therapy; TENS, transcutaneous electrical nerve stimulation; US, ultrasound.

\*See page 38 for an explanation of the SOR (strength of recommendation) ratings.

physical therapy, he has learned how to perform certain tasks at his job without pain or injury. He uses NSAIDs as needed for pain. **CR**

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## REFERENCES

- Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington (DC): National Academies Press (US); 2011.
- Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. *MMWR Recomm Rep*. 2016;65:1-49.
- Aronoff GM. What do we know about the pathophysiology of chronic pain? Implications for treatment considerations. *Med Clin North Am*. 2016;100:31-42.
- Clauw DJ. Diagnosing and treating chronic musculoskeletal pain based on the underlying mechanism(s). *Best Pract Res Clin Rheumatol*. 2015;29:6-19.
- Clauw DJ, Katz P. The overlap between fibromyalgia and inflammatory rheumatic disease: when and why does it occur? *J Clin Rheumatol*. 1995;1:335-342.
- Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol*. 2011;38:1113-1122.
- Brummett CM, Urquhart AG, Hassett AL, et al. Characteristics of fibromyalgia independently predict poorer long-term analgesic outcomes following total knee and hip arthroplasty. *Arthritis Rheumatol*. 2015;67:1386-1394.
- Ablin K, Clauw DJ. From fibrositis to functional somatic syndromes to a bell-shaped curve of pain and sensory sensitivity: evolution of a clinical construct. *Rheum Dis Clin North Am*. 2009;35:233-251.
- Giesecke T, Gracely RH, Williams DA, et al. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis Rheum*. 2005;52:1577-1584.
- Tesarz J, Eich W, Treede RD, et al. Altered pressure pain thresholds and increased wind-up in adult chronic back pain patients with a history of childhood maltreatment: a quantitative sensory testing study. *Pain*. 2016;157:1799-1809.
- Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J Pain*. 2013;14:1539-1552.
- Shi Y, Weingarten TN, Mantilla CB, et al. Smoking and pain: pathophysiology and clinical implications. *Anesthesiology*. 2010;113:977-992.
- Burger AJ, Lumley MA, Carty JN, et al. The effects of a novel psychological attribution and emotional awareness and expression therapy for chronic musculoskeletal pain: a preliminary, uncontrolled trial. *J Psychosom Res*. 2016;81:1-8.
- Zubieta JK, Heitzeg MM, Smith YR, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science*. 2003;299:1240-1243.
- van Meurs JB, Uitterlinden AG, Stolk L, et al. A functional polymorphism in the catechol-O-methyltransferase gene is associated with osteoarthritis-related pain. *Arthritis Rheum*. 2009;60:628-629.
- McLean SA, Diatchenko L, Lee YM, et al. Catechol O-methyltransferase haplotype predicts immediate musculoskeletal neck pain and psychological symptoms after motor vehicle collision. *J Pain*. 2011;12:101-107.
- Costigan M, Belfer I, Griffin RS, et al. Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. *Brain*. 2010;133:2519-2527.
- Tegeeder I, Costigan M, Griffin RS, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nat Med*. 2006;12:1269-1277.
- Amaya F, Wang H, Costigan M, et al. The voltage-gated sodium channel Na(v)1.9 is an effector of peripheral inflammatory pain hypersensitivity. *J Neurosci*. 2006;26:12852-12860.
- Harris RE, Napadow V, Huggins JP, et al. Pregabalin rectifies aberrant brain chemistry, connectivity, and functional responses in chronic pain patients. *Anesthesiology*. 2013;119:1453-1464.
- Russell IJ, Vaeroy H, Javors M, et al. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. *Arthritis Rheum*. 1992;35:550-556.
- Foerster BR, Petrou M, Edden RAE, et al. Reduced insular gamma-aminobutyric acid in fibromyalgia. *Arthritis Rheum*. 2012;64:579-583.
- Clauw DJ. Fibromyalgia: a clinical review. *JAMA*. 2014;311:1547-1555.
- Wolfe F. Fibromyalgianess. *Arthritis Rheum*. 2009;61:715-716.
- Hauser W, Bernardy K, Arnold B, et al. Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. *Arthritis Rheum*. 2009;61:216-224.
- Hauser W, Klose P, Langhorst J, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther*. 2010;12:R79.
- Porter NS, Jason LA, Boulton A, et al. Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia. *J Altern Complement Med*. 2010;16:235-249.
- Eaves ER, Sherman KJ, Ritenbaugh C, et al. A qualitative study of changes in expectations over time among patients with chronic low back pain seeking four CAM therapies. *BMC Complement Altern Med*. 2015;15:12.
- Bernardy K, Fuber N, Kollner V, et al. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome: a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol*. 2010;37:1991-2005.
- Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics*. 2000;41:104-113.
- Moldofsky H, Harris HW, Archambault WT, et al. Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: a double-blind randomized placebo-controlled study. *J Rheumatol*. 2011;38:2653-2663.
- Arnold LM. Duloxetine and other antidepressants in the treatment of patients with fibromyalgia. *Pain Med*. 2007;8(Suppl 2):S63-S74.
- Häuser W, Bernardy K, Uceyler N, et al. Treatment of fibromyalgia syndrome with gabapentin and pregabalin—a meta-analysis of randomized controlled trials. *Pain*. 2009;145:69-81.
- Gaskell H, Moore RA, Derry S, et al. Oxycodone for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2014;Jun 23:CD010692.
- MacLean AJ, Schwartz TL. Tramadol for the treatment of fibromyalgia. *Expert Rev Neurother*. 2015;15:469-475.
- Younger J, Noor N, McCue R, et al. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. *Arthritis Rheum*. 2013;65:529-538.
- Camerini L, Schulz PJ, Nakamoto K. Differential effects of health knowledge and health empowerment over patients' self-management and health outcomes: a cross-sectional evaluation. *Patient Educ Couns*. 2012;89:337-344.
- Mease PJ, Farmer MV, Palmer RH, et al. Milnacipran combined with pregabalin in fibromyalgia: a randomized, open-label study evaluating the safety and efficacy of adding milnacipran in patients with incomplete response to pregabalin. *Ther Adv Musculoskeletal Dis*. 2013;5:113-126.
- Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. *J Rheumatol*. 2000;27:1513-1517.
- Daghestani HN, Kraus VB. Inflammatory biomarkers in osteoarthritis. *Osteoarthritis Cartilage*. 2015;23:1890-1896.
- Fingleton C, Smart K, Moloney N, et al. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2015;23:1043-1056.
- Strand V, Molnlyre LF, Beach WR, et al. Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: a systematic review and meta-analysis of randomized, saline-con-

- trolled trials. *J Pain Res.* 2015;8:217-228.
43. Jüni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database Syst Rev.* 2015:CD005328.
  44. Meheux CJ, McCulloch PC, Lintner DM, et al. Efficacy of intra-articular platelet-rich plasma injections in knee osteoarthritis: a systematic review. *Arthroscopy.* 2016;32:495-505.
  45. Wu T, Song HX, Dong Y, et al. Intra-articular injections of botulinum toxin A for refractory joint pain: a systematic review and meta-analysis. *Clin Rehabil.* 2017;31(4):435-443.
  46. Jordan JL, Holden MA, Mason EE, et al. Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev.* 2010:CD005956.
  47. Bodenheimer T, Lorig K, Holman H, et al. Patient self-management of chronic disease in primary care. *JAMA.* 2002;288:2469-2475.
  48. Fransen M, McConnell S, Hernandez-Molina G, et al. Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev.* 2014:CD007912.
  49. Bartels EM, Juhl CB, Christensen R, et al. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database Syst Rev.* 2016;3:CD005523.
  50. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet.* 2016;387:2093-2105.
  51. Myers J, Wielage RC, Han B, et al. The efficacy of duloxetine, non-steroidal anti-inflammatory drugs, and opioids in osteoarthritis: a systematic literature review and meta-analysis. *BMC Musculoskelet Disord.* 2014;15:76.
  52. Berthelot JM, Darrieutort-Lafitte C, Le Goff B, et al. Strong opioids for noncancer pain due to musculoskeletal diseases: not more effective than acetaminophen or NSAIDs. *Joint Bone Spine.* 2015;82:397-401.
  53. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med.* 2006;354:795-808.
  54. Wandel S, Jüni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ.* 2010;341:c4675.
  55. Sawitzke AD, Shi H, Finco MF, et al. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. *Ann Rheum Dis.* 2010;69:1459-1464.
  56. Wu D, Huang Y, Gu Y, et al. Efficacies of different preparations of glucosamine for the treatment of osteoarthritis: a meta-analysis of randomised, double-blind, placebo-controlled trials. *Int J Clin Pract.* 2013;67:585-594.
  57. Kahan A, Uebelhart D, De Vathaire F, et al. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2009;60:524-533.
  58. Perkins K, Sahy W, Beckett RD. Efficacy of curcuma for treatment of osteoarthritis. *J Evid Based Complementary Altern Med.* 2017;22:156-165.
  59. Clinton CM, O'Brien S, Law J, et al. Whole-foods, plant-based diet alleviates the symptoms of osteoarthritis. *Arthritis.* 2015;2015:708152.
  60. Manyanga T, Froese M, Zarychanski R, et al. Pain management with acupuncture in osteoarthritis: a systematic review and meta-analysis. *BMC Complement Altern Med.* 2014;14:312.
  61. Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Intern Med.* 2012;172:1444-1453.
  62. Nijs J, Apeldoorn A, Hallegraaff H, et al. Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. *Pain Physician.* 2015;18:E333-E346.
  63. Fishbain DA, Cole B, Lewis JE, et al. What is the evidence that neuropathic pain is present in chronic low back pain and soft tissue syndromes? An evidence-based structured review. *Pain Med.* 2014;15:4-15.
  64. Hübscher M, Moloney N, Rebeck T, et al. Contributions of mood, pain catastrophizing, and cold hyperalgesia in acute and chronic low back pain: a comparison with pain-free controls. *Clin J Pain.* 2014;30:886-893.
  65. Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum.* 2004;50:613-623.
  66. Baliki MN, Chialvo DR, Geha PY, et al. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *J Neurosci.* 2006;26:12165-12173.
  67. Wertli MM, Eugster R, Held U, et al. Catastrophizing—a prognostic factor for outcome in patients with low back pain: a systematic review. *Spine J.* 2014;14:2639-2657.
  68. Brummett CM, Goesling J, Tsodikov A, et al. Prevalence of the fibromyalgia phenotype in patients with spine pain presenting to a tertiary care pain clinic and the potential treatment implications. *Arthritis Rheum.* 2013;65:3285-3292.
  69. Koes BW, van Tulder M, Lin CW, et al. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. *Eur Spine J.* 2010;19:2075-2094.
  70. Oliveira VC, Ferreira PH, Maher CG, et al. Effectiveness of self-management of low back pain: systematic review with meta-analysis. *Arthritis Care Res.* 2012;64:1739-1748.
  71. Engers A, Jellema P, Wensing M, et al. Individual patient education for low back pain. *Cochrane Database Syst Rev.* 2008:CD004057.
  72. Hayden JA, van Tulder MW, Malmivaara A, et al. Exercise therapy for treatment of non-specific low back pain. *Cochrane Database Syst Rev.* 2005:CD000335.
  73. French SD, Cameron M, Walker BF, et al. Superficial heat or cold for low back pain. *Cochrane Database Syst Rev.* 2006:CD004750.
  74. Franke H, Franke JD, Fryer G. Osteopathic manipulative treatment for nonspecific low back pain: a systematic review and meta-analysis. *BMC Musculoskelet Disord.* 2014;15:286.
  75. Franke H, Fryer G, Ostelo RW, et al. Muscle energy technique for non-specific low back pain. *Cochrane Database Syst Rev.* 2015:CD009852.
  76. Oliphant D. Safety of spinal manipulation in the treatment of lumbar disk herniations: a systematic review and risk assessment. *J Manipulative Physiol Ther.* 2004;197-210.
  77. Furlan AD, Giraldo M, Baskwill A, et al. Massage for low-back pain. *Cochrane Database Syst Rev.* 2015:CD001929.
  78. Khadilkar A, Odebiyi DO, Brosseau L, et al. Transcutaneous electrical nerve stimulation (TENS) versus placebo for chronic low back pain. *Cochrane Database Syst Rev.* 2008:CD003008.
  79. Ebadi S, Henschke N, Nakhostin Ansari N, et al. Therapeutic ultrasound for chronic low back pain. *Cochrane Database Syst Rev.* 2014:CD009169.
  80. Furlan AD, van Tulder MW, Cherkov DC, et al. Acupuncture and dry-needling for low back pain. *Cochrane Database Syst Rev.* 2005:CD001351.
  81. Chou R, Huffman LH. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med.* 2007;147:492-504.
  82. Sherman KJ, Cherkov DC, Erro J, et al. Comparing yoga, exercise, and a self-care book for chronic low back pain: a randomized, controlled trial. *Ann Intern Med.* 2005;143:849-856.
  83. Cherkov DC, Sherman KJ, Balderson BH, et al. Effect of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care on back pain and functional limitations in adults with chronic low back pain: a randomized clinical trial. *JAMA.* 2016;315:1240-1249.
  84. Staal JB, de Bie R, de Vet HC, et al. Injection therapy for subacute and chronic low back pain. *Cochrane Database Syst Rev.* 2008:CD001824.
  85. Chou R, Baisden J, Carragee EJ, et al. Surgery for low back pain: a review of the evidence for an American Pain Society Clinical Practice Guideline. *Spine.* 2009;34:1094-1109.
  86. Felson D. Paracetamol is ineffective for spinal pain and knee and hip osteoarthritis. *Evid Based Med.* 2015;20:205.
  87. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ.* 2015;350:h1225.
  88. Enthoven WT, Roelofs PD, Deyo RA, et al. Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database Syst Rev.* 2016;2:CD012087.
  89. White AP, Arnold PM, Norvell DC, et al. Pharmacologic management of chronic low back pain: synthesis of the evidence. *Spine (Phila Pa 1976).* 2011;36:S131-S143.