Rupak Thapa, MD
Department of Rheumatology, Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC; Assistant Professor, Wake Forest University School of Medicine, Winston-Salem, NC

Dennis Ang, MD
Chair, Department of Rheumatology, Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC; Professor, Wake Forest University School of Medicine, Winston-Salem, NC

Nociplastic pain: A practical guide to chronic pain management in the primary care setting

ABSTRACT

Management of chronic pain is one of the most challenging medical issues in primary care. Effective pain management requires an understanding of nociplastic pain, a condition characterized by amplification of pain transmission and pain perception. Unlike nociceptive and neuropathic pain, nociplastic pain does not involve visible tissue injury or damage, which makes it difficult to understand and manage. This review discusses practical ways for primary care clinicians to identify and manage nociplastic pain at the point of care.

KEY POINTS

The most common barriers to effective pain management should be identified and addressed in the primary care setting, along with mitigation strategies, to achieve better pain control.

An alliance between the patient and primary care clinician is important because it increases treatment receptiveness, motivation, and adherence.

Nonpharmacologic treatment options are preferred because they have fewer side effects, greater availability, and sustained positive effects.

The views expressed in this review are those of the authors and do not represent an official position of any institution.

doi:10.3949/ccjm.92a.24101

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1] Pain that persists beyond the expected healing period of 3 months is defined as *chronic pain*.[2] Chronic pain can have a profound negative impact on a patient's emotional and social well-being[2] and exacts high societal costs as well. In the United States, the estimated societal cost of chronic pain is $560 to $635 billion per year, much higher than the economic impact of heart disease, diabetes mellitus, human immunodeficiency virus infection, Alzheimer disease, and even cancer,[3] and chronic pain accounts for 53% of indirect costs.[4] Moreover, 2.5% to 4.5% of gross domestic product in the United States is spent on chronic pain.[3]

More than half of patients receive care for chronic pain in the primary care setting.[5] Given that chronic pain is highly prevalent—more than the combined incidences of diabetes, heart disease, and cancer in the United States—a large percentage of primary care clinicians will manage chronic pain in their practices.[3] Thus, it is imperative that they understand how to manage pain safely and effectively.

PAIN CATEGORIZATION

Pain can be characterized into 3 mechanistic phenotypes.[6]

Nociceptive pain arises from tissue damage, injury, or degeneration caused by trauma, osteoarthritis, and joint inflammation (eg,

TABLE 1
Mechanistic types of pain

Pain type	Defining characteristics	Examples	Treatment
Nociceptive	Pain due to tissue injury, inflammation, damage, or degeneration	Osteoarthritis, rheumatoid arthritis, fracture, burns	Topical analgesics, nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, steroids
Neuropathic	Pain due to nerve injury or damage	Radiculopathy, diabetic neuropathy, chemotherapy-induced neuropathy	Topical or local therapy; systemic neuropathic medications such as gabapentin, pregabalin, and tricyclic antidepressants
Nociplastic	Pain arising from a sensitized nervous system (amplified processing of pain signals, decreased inhibition of pain, or both)	Fibromyalgia, chronic back pain, chronic temporomandibular pain disorders	Multimodal management approach

Based on information from reference 6.

rheumatoid arthritis). It is localized to the area of the damage, injury, or inflammation, and can respond to topical or systemic therapies, including nonsteroidal anti-inflammatory drugs, opioids, and corticosteroids.[7]

Neuropathic pain is a result of nerve injury or damage, such as traumatic nerve injury, diabetic neuropathy, sciatica or radiculopathy from mechanical nerve compression, or medication- or chemotherapy-induced neuropathy. The pain can be localized to the area of nerve injury or damage, or it can follow a dermatomal distribution, causing characteristic features of sharp, shooting, burning pain along with tingling and numbness.[7] It can respond to local therapy and systemic neuropathic medications like gabapentin, pregabalin, and tricyclic antidepressants.

Nociplastic pain, the third and less well-known category of pain, arises from a sensitized nervous system, a condition known as *central sensitization syndrome*.[7] Nociplastic pain involves dysfunction in the central nervous system pathways, including amplified pain-signal processing, decreased signaling of the descending pain inhibitory pathway, or both.[8] In contrast to nociceptive pain, there is no demonstrable tissue damage. Nociplastic pain is usually associated with more subjective symptoms rather than objective findings, which makes understanding and managing it a formidable task.

Table 1 summarizes the 3 mechanistic phenotypes of chronic pain.[6]

MECHANISMS OF NOCIPLASTIC PAIN

The basic mechanism of nociplastic pain is a heightened pain sensor with amplification of pain transmission and pain perception.[8] Specifically, nociplastic pain can be explained by **top-down pain amplification** (via alteration in the descending pain-modulatory pathway, causing diminished efficacy of the pain-inhibitory pathway and increased activity of the pain-facilitatory pathway) and **bottom-up pain facilitation** (the ascending pathways in the central nervous system become overstimulated by peripheral inputs), leading to hyperalgesia and allodynia (**Figure 1**).[7]

The heightened pain sensitivity and associated features in nociplastic pain conditions (eg, fatigue, poor sleep, brain fog) are driven by central nervous system and peripheral mechanisms.[9]

Supraspinal mechanisms

- Hyperactivity and connectivity in and between brain regions involved in pain, but decreased activity of regions involved in pain inhibition
- Altered size and shape of brain regions involved in pain processing
- Increased levels of neurotransmitters associated with pain signaling (substance P, glutamate) in cerebrospinal fluid and decreased gamma-aminobutyric acid neurotransmission
- Glial cell activation

Spinal mechanisms

- Clustering and convergence of signals from different pain loci
- Spinal cord reorganization
- Increased spinal reflex transmission and diminished spinal inhibition
- Temporal summation (repeated stimulus evokes increased pain sensation)
- Glial cell activation

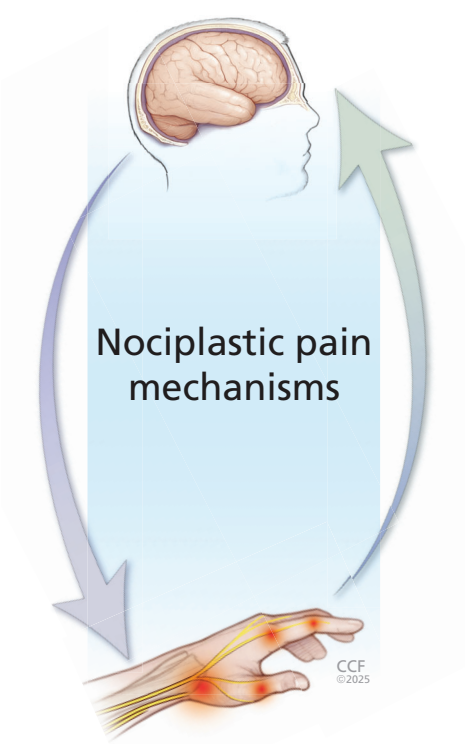

Figure 1. The mechanisms underlying nociplastic pain can be grouped into 2 broad categories: top-down (dysregulation in descending pathways involved primarily in pain inhibition) and bottom-up (dysregulation in ascending pathways primarily involved in pain facilitation).

Based on information from reference 7.

Peripheral mechanisms

- Minor local muscle pathology (eg, latent and active trigger points)
- Peripheral sensitization (eg, expansion of receptive fields, increased concentrations of cytokines and chemokines)
- Hyperalgesia, dysesthesia, and allodynia
- Localized or diffuse tenderness, or both

This pain-enhancement phenomenon may help explain how nociceptive and neuropathic pain lead to the evolution of nociplastic pain. For example, a patient with acute lower back pain and lumbar disc herniation often has nociceptive pain from the degenerated disc and neuropathic pain (radiculopathy) from nerve compression. Over time, the patient may also develop nociplastic pain. This highlights the importance of adequate and timely control of nociceptive and neuropathic pain in reducing the risk of developing coexisting chronic nociplastic pain.[10]

Chronic lower back pain is also an example of a condition in which nociceptive, neuropathic, and nociplastic pain can coexist, even though the 3 categories of pain remain distinct. Such conditions lend credence to the concept of a pain continuum,[9] as shown in **Figure 2.**[7] Given this pain continuum, effective management should address all 3 types of pain, as managing 1 type without addressing the others can result in inadequate pain control.

CHALLENGES AND MITIGATION STRATEGIES

Chronic pain is often frustrating to both patients and primary care clinicians because identifying nociplastic pain can be difficult and take time, and effective treatment modalities are limited. Further, when a patient visits their primary care clinician for chronic pain, they may worry about how their complaint will be perceived. Because nociplastic pain has no visible tissue injury or damage, patients may fear it will be mistakenly labeled by primary care clinicians as "made-up pain," "all in your head," "mental illness," or "drug-seeking behavior." This fear can prevent them from talking freely about their pain,[11] and can make them apprehensive about following the clinician's recommendations. Moreover, primary care clinicians often lack the knowledge and training needed to identify and manage nociplastic pain,

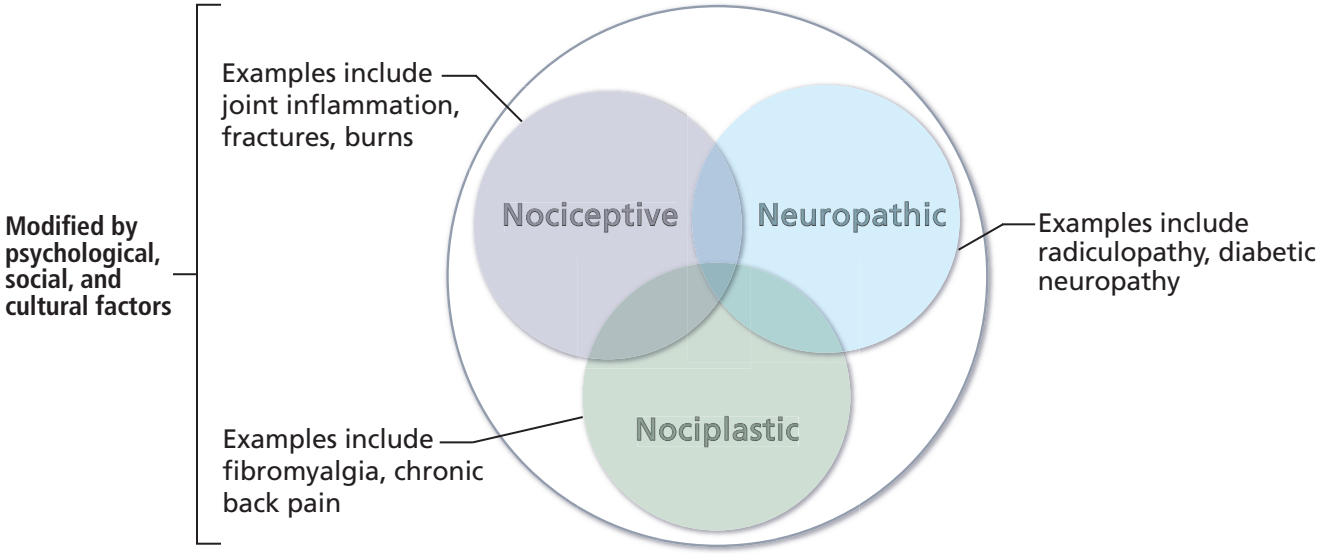

Figure 2. The pain continuum. There are 3 main categories of pain—nociceptive, neuropathic, and nociplastic—and these 3 types of pain can coexist.

Based on information from reference 7.

a problem compounded by the nature of the primary care setting, where multiple medical issues must be addressed within a short period of time. It is important to identify and address these barriers with patients to achieve better pain control. **Table 2**[10–15] outlines the most common barriers to effective pain management in primary care along with strategies to mitigate them.

Patients with chronic pain can fear having conditions like autoimmune arthritis, multiple sclerosis, or even malignancy. This fear can fuel the patient's anxiety and contribute immensely to the pain-amplification process, making it imperative that primary care clinicians explore and resolve any of these concerns. Explaining the symptom differences between inflammatory arthritis and osteoarthritis or mechanical arthritis and nociplastic or fibromyalgia-like pain can help reduce anxiety.[7] **Table 3** provides simple explanations of the 3 pain types that patients can understand easily.[7]

HOW TO IDENTIFY NOCIPLASTIC PAIN

Conditions that typically cause nociplastic pain can be localized (**Table 4**)[9] or widespread (eg, fibromyalgia) and are known as *chronic overlapping pain conditions*.[7] These conditions often occur together. Widespread nociplastic pain is often accompanied by diffuse tenderness, disabling fatigue, cognitive symptoms, and nonrestorative sleep.[16]

Concurrent symptoms

Nociplastic pain commonly occurs in combination with certain symptoms (**Table 5**).[9] Central sensitization, generalized hypersensitivity, and associated autonomic dysfunction possibly contribute to these concurrent symptoms.[8] Some patients with nociplastic pain may also have postural orthostatic tachycardia syndrome due to the same mechanisms.[17]

Standardized scales

Several standardized scales can be used to estimate the probability that nociplastic pain is present. The 2 scales that are most feasible to implement in the primary care setting are the Central Sensitization Inventory and the Central Aspects of Pain questionnaire.

The **Central Sensitization Inventory** is a simple, validated questionnaire developed to help identify patients with central sensitization, which would indicate they are also experiencing central sensitivity syndrome.[18] It has 2 sections. Part A measures 25 health-related symptoms common to central sensitivity syndrome, such as pain, hypersensitivity, mood, and energy, on a numeric scale; a score of 40 or higher out of 100 indicates central sensitivity syndrome. Part B lists previous diagnoses specific to central sensitivity syndrome. The more of these diagnoses a patient has, the greater the likelihood of central sensitization.[19] The questionnaire, including instructions, can be accessed at pridedallas.com/questionnaires/.

TABLE 2
Barriers and mitigation strategies for appropriate pain management

Barrier: *Previsit bias*
Mitigation: Eliminate any bias or negativity before the visit when the primary reason is "chronic pain" or "fibromyalgia" to improve clinician receptiveness and reduce frustration[13]
Avoid dismissive attitude toward the pain complaint[10,11]
Believe patient reports of the severity and adverse effects of pain
Barrier: *Difficulty connecting with patients and winning their confidence and trust*
Mitigation: Be empathetic and acknowledge that the pain is real; validating and legitimizing the pain can be emotional for patients and helps increase their trust and receptiveness[11]
Let patients narrate their symptoms and fully explain the impact of pain in their lives, which provides a crucial sense of being heard[10]
Debunk the myth that nociplastic pain is not a real condition and explain that the pain is not imagined or all in their head to make patients feel believed and heard[12,13]
Express to patients that we understand their pain and we will partner with them to help manage it as best we can
Share decision-making to reduce frustration toward clinicians and increase patient receptiveness, motivation, and adherence to therapeutic recommendations
Barrier: *Unrealistic or unreasonable expectations*
Mitigation: Patients may hope that a "magic pill" will fix the problem, and that can lead to frustration
Set realistic expectations upfront (eg, improve physical function), but be extremely empathetic[14]
Reassure patients that adequate pain control can be achieved, although the fix is not easy
Enable patients to take charge of their pain management, but provide assurance that they will always be supported
Barrier: *Overexpectation to completely eliminate the problem*
Mitigation: Focus on legitimizing and validating pain while also determining any acute causes of a pain flare
Accept that adequate pain management may not be curative, but even limited pain relief may enable patients to revive skills, renew social interactions, and improve quality of life
Modest gain in pain relief can significantly increase patient confidence in overcoming the pain and is a vital clinical accomplishment[11]
Focus on both the biological and psychosocial determinants of chronic pain (ie, mind–body dualism)[13]
Barrier: *Poor understanding of nociplastic pain and contributory factors*
Mitigation: Explain pain physiology to patients, which may improve health status (less worry about pain and long-term improvement in physical functioning, vitality, mental health) and increase endogenous pain inhibition in patients with fibromyalgia[15]
Barrier: *Appointment time constraints*
Mitigation: Schedule a separate appointment focused only on pain management; defer rest of care to another visit
Schedule a few extended appointments at first to allow time to really listen to patients
Barrier: *Diagnosis challenge and lack of knowledge and training*
Mitigation: Diagnosis is difficult due to inconsistent symptom recognition and diagnosis validity and lack of robust guidelines; even when guidelines are available, level of awareness may vary[11]
Learning about nociplastic pain and management principles is crucial
Barrier: *Referrals and resources*
Mitigation: Multidisciplinary approach can be helpful, but avoid unnecessary referrals that can lead to frustration
Create achievable short- and long-term pain management goals

The self-reported **Central Aspects of Pain** questionnaire consists of 8 items related to depression, anxiety, catastrophizing, cognition, sleep, and fatigue, and includes a body-pain manikin.[20] The questionnaire is a validated measure that assesses the centrality of chronic pain; it best assesses widespread pain in patients who mark 10 or more painful sites out of 26 on the body manikin. Studies have shown that a body manikin, or body map, can be the single most helpful tool to diagnose nociplastic pain.[21] The questionnaire, body manikin,

TABLE 3
Simplified ways to explain and compare different types of pain

Autoimmune inflammatory arthritis	Osteoarthritis or mechanical arthritis	Nociplastic pain or fibromyalgia
Autoimmune inflammation of the joints or tissue	Related to tissue injury or degeneration	Heightened pain sensitivity at the brain and spinal cord level
Presence of red, hot, swollen joints with palpable joint fluid and warmth	Can have transient morning pain and stiffness lasting less than 15 to 30 minutes	Pain is usually widespread with associated diffuse tenderness
Symptoms most pronounced in the morning and starts improving after 30 to 60 minutes of moving	Pain worsens with activity and joint use throughout the day	Related fatigue, poor sleep, brain fog, or irritable bowel symptoms
Rest aggravates pain and stiffness	Symptoms more prominent in the evenings, especially when joints were used more throughout the day	Worsens with poor sleep and stress
Responds to low-to-moderate dose of steroid; symptoms return after medication cessation	Rest makes the pain better except for transient pain and stiffness when getting up after a period of rest (ie, gelling phenomenon)	

Based on information from reference 7.

and scoring guide can be accessed at academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/keae342#supplementary-data

Beighton criteria

The Beighton criteria should be used to check for evidence of joint hypermobility.[22] Hypermobility arthralgia is a specific type of nociceptive pain that is more common in younger patients. It is often described as pain in multiple joints after overuse, especially after playing sports. Physical therapy and using splints to help prevent joint hyperextension can make a significant difference in the patient's quality of life.

UTILITY OF AUTOIMMUNE LABORATORY TESTS FOR CHRONIC PAIN

Because pain is a prominent symptom of autoimmune connective tissue diseases, primary care clinicians often order laboratory tests such as antinuclear antibody, rheumatoid factor, and inflammatory markers in patients with chronic pain. Notably, these tests can be nonspecific. For example, up to 20% of the general population test positive for antinuclear antibodies, and a positive test by itself is not sufficient to diagnose systemic lupus erythematosus.[23] Moreover, inflammatory markers can be elevated in conditions like infection, malignancy, high body mass index, and untreated obstructive sleep apnea.[24] We strongly discourage ordering these tests in the absence of appropriate clinical manifestations (eg, persistently swollen joints, photosensitive rash, unexplained cytopenia or proteinuria, or pleural effusions) given the potential negative outcomes such as increased psychological distress and unnecessary healthcare spending.

NOCIPLASTIC PAIN MANAGEMENT

Effective pain management starts with following barrier mitigation strategies (**Table 2**), exhibiting empathy, and securing the patient's trust.[7] An alliance between the patient and primary care clinician is important because it increases treatment receptiveness, motivation, and adherence.

Nonpharmacologic treatment options should be the first line of therapy because they have fewer side effects, are widely available, and have sustained positive effects.[25]

Self-care and management

Social support. When a patient has chronic pain, it affects not only the patient but also the family. Sharing frustrations and anxiety with family and support groups can provide catharsis and increase motivation to learn pain-coping skills.[11] Learning how other patients successfully manage similar pain can be helpful and inspiring.

Healthy lifestyle. Adopting general healthy lifestyle measures like regular exercise, good nutrition, proper sleep hygiene, smoking cessation, and ergonomic modifications can have a positive impact on pain control.[9]

Good communication skills and awareness of sensitive topics. For example, a discussion about weight loss, when appropriate, should be done in a nonthreatening manner because some patients may find it offensive, which could act as a barrier to further care.

Mental health. Seeking help from a mental health professional can enable patients to learn adaptive pain-coping skills in challenging situations. The timing of a referral to a mental health professional depends

TABLE 4
Localized conditions that cause nociplastic pain

Chronic primary headache and orofacial pain
Chronic migraine
Chronic tension-type headache
Trigeminal autonomic cephalalgias
Chronic temporomandibular pain disorders without anatomic abnormality or explanation
Chronic burning mouth
Chronic primary orofacial pain
Chronic visceral pain syndrome
Chronic primary bladder pain syndrome or interstitial cystitis
Chronic pelvic pain syndrome
Irritable bowel syndrome
Chronic chest pain
Chronic abdominal pain
Chronic primary musculoskeletal pain
Primary cervical, thoracic, lower back, and limb pain; extent of pain and suffering is greater than expected based on the underlying pathology[9]
Complex regional pain syndrome

TABLE 5
Symptoms and factors indicative of nociplastic pain

Difficulty localizing pain
Chronic fatigue
Memory problems (ie, brain fog)
Anxiety or depression
Poor sleep quality
Irritable bowel symptoms
Chronic headache
Chronic pelvic pain
Hypersensitivity to nonpainful stimuli (light sensitivity, sound sensitivity, allodynia or hyperalgesia)
Report of more comorbid illnesses
Intolerance to multiple medications without true allergy
Frequent use of healthcare services

Based on information from reference 9.

on the patient's receptiveness and degree of trust toward the primary care clinician. The topic should be introduced cautiously because a blunt presentation could sever the established relationship with the patient.

Graded aerobic exercise

Short-term aerobic training. Training at the intensity recommended to increase cardiorespiratory fitness provides important benefits, including improved physical function and possible pain relief.[16] Getting to the aerobic stage of exercise (with heart-rate increase and sweating) can result in activation of pain-inhibitory and endogenous endorphin pathways and release of "feel good" hormones.[26] Exercise can reduce fatigue, improve depression and fitness, and positively affect neuroplasticity, leading to improvements in sleep, memory, and emotional and cognitive functioning.[16,27]

When patients with nociplastic pain start exercising, they tend to hurt more initially due to their heightened pain sensitivity. Therefore, preparing patients psychologically, reiterating the importance of a graded approach and stressing the need to start slowly, can improve adherence to exercise.[28] Patients should be reassured that maintaining a consistent aerobic exercise program will make them feel better over time, which can also help with long-term adherence.

Even if patients are not able to achieve an aerobic level of exercise, movement itself can be beneficial for pain control. For patients with available resources, aquatic aerobics or water therapy (preferably in warm water due to temperature sensitivity) can be particularly helpful for those with underlying arthritis and high body mass index because it can be less painful than land-based exercise.

See the Resources section below for recommended forms of exercise.

Psychoeducational therapy

Different forms of psychotherapy can have a positive impact on nociplastic pain.[9] The main goal with these therapies is to "turn down the symptom dial" of the body's pain sensor (like turning down a volume dial). Options include the following:

- Cognitive behavioral therapy
- Mindfulness and acceptance-based interventions
- Psychodynamic therapies
- Biofeedback
- Hypnotherapy.

Table 6[29–36] outlines the components and benefits of various psychoeducational therapies. The Resources section also lists links to online resources that patients can access.

Physical and alternative therapies

Other nonpharmacologic therapies like acupuncture, massage therapy, virtual reality, transcutaneous electrical nerve stimulation, heat therapy, and cryotherapy have been shown to have some role in managing chronic pain and are thought to work by modulating chronic pain signals through physiologic mechanisms.[32]

TABLE 6
Psychoeducational therapies for nociplastic pain

Type and components	Description
Cognitive behavioral therapy	A technique to cope with pain and convert unpleasant stimuli to pleasant stimuli
	Focuses on reducing pain and distress by modifying physical sensations, catastrophic thinking, and maladaptive behaviors[29]
Distraction	Involves engaging in thoughts or activities (eg, finding joy, relaxation techniques, diaphragmatic or belly breathing, social activities) that distract from pain
	One of the most used and highly endorsed strategies for controlling pain[30]
Activity pacing	A 2-part strategy that involves spending just enough time on an activity to get the most out of it without pushing so far that patients experience more pain; over time, patients may be able to do more
	1. Conserve energy for activities patients value (eg, playing with their kids or undertaking a pleasurable recreational activity)
	2. Set graduated activity quotas to help increase ability to do activities (tolerance) and reduce disability
Cognitive restructuring	Helps reframe negative thoughts into more positive adaptive thoughts
Other	Includes relaxation, guided imagery, and meditation that can be helpful with pain management
	Telehealth can be an excellent resource, particularly for patients with inadequate access to mental health professionals[31]
Mind–body therapy	
Mindfulness	A nonelaborative, nonjudgmental awareness of the present-moment experience[32]
	Involves breathing methods, guided imagery, and other techniques to relax the body and mind and to help reduce stress
	Uses cognitive reappraisal to help separate the sensation of pain from the alarm reaction, which reduces the pain experience[33]
	A recent study on veterans with chronic pain showed telehealth-based mindfulness intervention improved pain-related function and biopsychosocial outcomes compared with standard care[34]
Tai chi	A mind–body activity that combines meditation with slow, gentle, graceful movements, as well as deep breathing and relaxation, to move vital energy (or qi) throughout the body
	A complex multicomponent intervention that integrates physical, psychosocial, emotional, spiritual, and behavioral elements[35]
	Evidence shows clinically important improvements in symptoms, disability, and quality of life in patients with chronic widespread pain[36]
Yoga	Evidence supports a role in reducing nociplastic pain[32]
Psychodynamic therapy	An in-depth form of talk therapy that focuses on unconscious processes based on previous unresolved conflicts or dysfunctional relationships that can shape present behavior
	Goal is to create self-awareness and understand how the past influences present behavior and then rectify it
	Focuses more on the patient's relationship with the external world rather than the patient–therapist relationship
Hypnosis and hypnotherapy	Explores the subconscious mind and causes an altered state of consciousness to prevent normally perceived experiences, such as pain, from reaching the conscious mind

Sleep hygiene

Nonrestorative or poor-quality sleep is associated with fatigue and tiredness and can contribute to pain amplification. Nonrestorative sleep is a strong predictor of chronic widespread pain because sleep is necessary to repair the body and decrease neuronal activity.[7]

Evaluation and treatment of obstructive sleep apnea and insomnia (difficulty falling asleep, staying asleep, or both) is vital to mitigate the pain amplification and fatigue that results from poor-quality sleep.

Sleep hygiene techniques like yoga, blue-light avoidance, changes to the sleeping environment (eg, removing televisions, screen-time reduction), avoiding exercise close to bedtime, and limiting caffeine can help patients achieve restorative sleep. Sleep-specific cognitive behavioral therapy can help improve insomnia and thereby improve pain.

As a last resort, low-dose trazodone, doxepin, or cyclobenzaprine can be considered for coexisting sleep disturbances that can amplify pain.[37,38]

Pharmacotherapy

Different medications are used on- and off-label to treat nociplastic pain. It is important to note that these medications have shown only modest efficacy and are fraught with adverse side effects[39] and a low adherence rate.[40]

Traditional analgesic treatments such as muscle relaxants, nonsteroidal anti-inflammatory drugs, acetaminophen, and opioids are less effective for nociplastic pain than for nociceptive pain, and the use of opioid analgesics is strongly discouraged.[9,41]

Low-dose naltrexone, an opioid antagonist, has shown some benefit for chronic back pain and complex regional pain.[9] It is thought to work by activating more opioid receptors, leading to increased response to endogenous opiates. Low-dose naltrexone may also improve memory problems commonly seen in patients with fibromyalgia.[42]

Duloxetine, milnacipran, and pregabalin are the 3 US Food and Drug Administration–approved medications for the treatment of fibromyalgia.[43] Duloxetine had greater efficacy in treating pain and depression. Pregabalin was effective in reducing pain and improving sleep and quality of life.[44]

Tricyclic antidepressants such as amitriptyline,[43] nortriptyline,[45] and cyclobenzaprine as well as the alpha 2 delta ligand gabapentin[43] are frequently used off-label. Amitriptyline has the most evidence for improving pain, sleep, fatigue, and overall quality of life.[43]

A summary of pharmacologic approaches is outlined in **Table 7.**[14,46]

COORDINATED CARE

The management of nociplastic pain involves a multidisciplinary approach, including referrals to other specialties (eg, pain specialists). Although referral to pain management can be helpful, the general management principle is to use nonpharmacologic and intervention techniques as described above. Referrals to several different healthcare professionals and time-consuming appointments, especially if not coordinated (ie, each professional trying to manage the disease in their own way), can be exhausting to patients and may hinder improvement. In contrast, coordinated care managed by a primary care clinician can have a favorable outcome.[12]

FINAL THOUGHTS

Management of chronic pain, particularly of the nociplastic type, is challenging and, at times, may seem like fighting an invisible enemy. We must use all available resources, and that starts with securing buy-in from patients with nociplastic pain. If patients are not invested, all management strategies are set to fail from the start.

The vast array of treatment modalities can be overwhelming for primary care clinicians. In our opinion, the best approach is to select a few options that are accessible to and practical for patients because they will be more likely to adhere to them. An initial approach could be starting with simpler self-management recommendations like regular exercise and pleasant activity scheduling followed by activity pacing. In more severe cases, healthcare professional–directed talk therapy or prescription medications can be considered.

RESOURCES

Primary care clinician training

- Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians (acpjournals.org/doi/10.7326/M16-2367)
- American Geriatrics Society guideline for the pharmacological management of persistent pain in older persons (agsjournals.onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2009.02376.x)

Exercise regimens

- Fibromyalgia-friendly exercises (www.webmd.com/fibromyalgia/ss/slideshow-fibromyalgia-friendly-exercises)

TABLE 7
Pharmacotherapy options for nociplastic pain

Drug class and medication	Predominant symptoms and dose	Potential side effects
Selective serotonin-norepinephrine reuptake inhibitors	Pain and depression	
Duloxetine	Start at 30 mg in morning; can increase to 60 mg daily in a few weeks as tolerated[14]	Nausea, headache, diarrhea; do not stop suddenly—taper off gradually
Milnacipran	Start at 12.5 mg in the morning, increase by 12.5 mg every few weeks to 50–100 mg once or twice daily as tolerated[14]	As above
Tricyclic antidepressants	Pain, sleep, fatigue, and overall quality of life	
Amitriptyline	Start at 5–10 mg 1 to 3 hours before bedtime; increase by 5 mg no more frequently than every 2 weeks; use lowest dose possible (20–30 mg)[46]	Dry mouth, dry eyes, blurred vision, flushing, constipation, urinary retention, dizziness, drowsiness, cardiac arrythmia
Nortriptyline	Start at 10 mg at bedtime; up to 75 mg maximum[46]	Like amitriptyline but preferred due to fewer anticholinergic side effects
Alpha 2 delta ligands	Prominent sleep disturbance	
Pregabalin	Start at 25–50 mg at bedtime; increase by 25–50 mg every 2 to 4 weeks to 300–450 mg daily (in 1 or 2 divided doses) as tolerated[14]	Dizziness, drowsiness, peripheral edema, weight gain, blurred vision
Gabapentin	Start at 100 mg at bedtime; increase by 100 mg every 2 to 4 weeks to 1,200–2,400 mg daily (usually in 2 or 3 divided doses) as tolerated[46]	As above

- Physical activity and self-management education program for persons with arthritis from the Centers for Disease Control and Prevention(www.cdc.gov/arthritis/programs)
- Pilates for persons with fibromyalgia (youtube.com/watch?v=PnKbwr5WuTw)
- *The FibroManual: A Complete Fibromyalgia Treatment Guide for You and Your Doctor* by Ginevra Liptan, MD (Ballantine Books, 2016)

Water therapy program

- Exercise and aquatic therapy videos from the Aquatic Exercise Association (aeawave.org/Arthritis/At-Home-Exercise-for-Arthritis)

Tai chi programs

- American Tai Chi and Qigong Association (amtaichi.org/tai-chi-qigong-classes-near-you)
- Tai chi for arthritis video lessons by Dr. Paul Lam (youtube.com/watch?v=tAOuEpa01j4)
- Tai chi health benefits (health.clevelandclinic.org/the-health-benefits-of-tai-chi)

Cognitive behavioral therapy

- Online cognitive behavioral therapy program; a referral is required and there is a fee to enroll (thiswayup.org.au/programs/chronic-pain-program)
- Society of Clinical Psychology cognitive behavioral therapy for fibromyalgia (div12.org/treatment/multi-component-cognitive-behavioral-therapy-for-fibromyalgia)
- Pacing resource from the Department of Health, Western Australia (painhealth.csse.uwa.edu.au/pain-module/pacing-and-goal-setting)
- Patient-perspective video about fibromyalgia and successful pain management (youtube.com/watch?v=tFDsdByqkM0)
- Cognitive restructuring (concordia.ca/cunews/offices/provost/health/topics/stress-management/cognitive-restructuring-examples.html)
- Psychodynamic therapy (psychologytoday.com/us/therapy-types/psychodynamic-therapy)
- Cognitive behavioral therapy for insomnia (sleepfoundation.org/insomnia/treatment/cognitive-behavioral-therapy-insomnia)

- Managing insomnia for those with chronic pain (health.clevelandclinic.org/managing-insomnia-for-those-with-chronic-pain)

University of Michigan pain guide

- Chronic pain management (painguide.com/pain-care)
- Self-care videos (painguide.com/pain-care/self-care)
- Cognitive behavioral therapy (painguide.com/pain-care/professional-care/therapies/cbt)
- Acupuncture (painguide.com/pain-care/professional-care/therapies/acupuncture)
- Acceptance and commitment therapy (painguide.com/pain-care/professional-care/therapies/act)
- Tai chi (painguide.com/pain-care/professional-care/therapies/tai-chi)
- Yoga (painguide.com/pain-care/professional-care/therapies/yoga)
- Massage and spa therapy (painguide.com/pain-care/professional-care/therapies/massage-spa)
- Emotional awareness and expression therapy (painguide.com/pain-care/professional-care/therapies/eaet)

Mindfulness

- American Mindfulness Association (goamra.org)
- Mindfulness for chronic pain from Extension Utah State University (extension.usu.edu/heart/files/mindfulnessforchronicpainmanagement.pdf)
- Mindfulness tips from Cleveland Clinic (health.clevelandclinic.org/what-is-mindfulness)
- Breathing, body scan, and compassion exercises (livinginthegap.org/blog/3-mindfulness-activities-to-use-in-your-new-daily-practice)
- Mindfulness exercises from the Mayo Clinic (mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/mindfulness-exercises/art-20046356)
- *Pain: Considering Complementary Approaches* eBook from the National Institutes of Health (nccih.nih.gov/health/pain-considering-complementary-approaches-ebook)

Acknowledgments: *The authors gratefully acknowledge the editorial assistance of Indra M. Newman, PhD, of the Wake Forest Clinical and Translational Science Institute (WF CTSI), which is supported by the National Center for Advancing Translational Sciences (NCATS) and National Institutes of Health under award number UM1TR004929.*

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Raja SN, Carr DB, Cohen M, et al.** The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain 2020; 161(9):1976–1982. doi:10.1097/j.pain.0000000000001939
2. **Treede RD, Rief W, Barke A, et al.** Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the international classification of diseases (ICD-11). Pain 2019; 160(1):19–27. doi:10.1097/j.pain.0000000000001384
3. **Gaskin DJ, Richard P.** The economic costs of pain in the United States. J Pain 2012; 13(8):715–724. doi:10.1016/j.jpain.2012.03.009
4. **Breivik H, Eisenberg E, O'Brien T; OPENMinds.** The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. BMC Public Health 2013; 13:1229. doi:10.1186/1471-2458-13-1229
5. **Johnson M, Collett B, Castro-Lopes JM.** The challenges of pain management in primary care: a pan-European survey. J Pain Res 2013; 6:393–401. doi:10.2147/JPR.S41883
6. **Kosek E, Cohen M, Baron R, et al.** Do we need a third mechanistic descriptor for chronic pain states? Pain 2016; 157(7):1382–1386. doi:10.1097/j.pain.0000000000000507
7. **Murphy AE, Minhas D, Clauw DJ, Lee YC.** Identifying and managing nociplastic pain in individuals with rheumatic diseases: a narrative review. Arthritis Care Res (Hoboken) 2023; 75(10):2215–2222. doi:10.1002/acr.25104
8. **Clauw DJ, Arnold LM, McCarberg BH; FibroCollaborative.** The science of fibromyalgia. Mayo Clin Proc 2011; 86(9):907–911. doi:10.4065/mcp.2011.0206
9. **Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W.** Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet 2021; 397(10289):2098–2110. doi:10.1016/S0140-6736(21)00392-5
10. **Dydyk AM, Conermann T.** Chronic pain. Updated May 6, 2024. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2024.
11. **Institute of Medicine 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; 2011.
12. **Doebl S, Macfarlane GJ, Hollick RJ.** "No one wants to look after the fibro patient". Understanding models, and patient perspectives, of care for fibromyalgia: reviews of current evidence. Pain 2020; 161(8):1716–1725. doi:10.1097/j.pain.0000000000001870
13. **Crowley-Matoka M, Saha S, Dobscha SK, Burgess DJ.** Problems of quality and equity in pain management: exploring the role of biomedical culture. Pain Med 2009; 10(7):1312–1324. doi:10.1111/j.1526-4637.2009.00716.x
14. **Arnold LM, Gebke KB, Choy EH.** Fibromyalgia: management strategies for primary care providers. Int J Clin Pract 2016; 70(2):99–112. doi:10.1111/ijcp.12757
15. **Van Oosterwijck J, Meeus M, Paul L, et al.** Pain physiology education improves health status and endogenous pain inhibition in fibromyalgia: a double-blind randomized controlled trial. Clin J Pain 2013; 29(10):873–882. doi:10.1097/AJP.0b013e31827c7a7d
16. **Busch AJ, Schachter CL, Overend TJ, Peloso PM, Barber KA.** Exercise for fibromyalgia: a systematic review. J Rheumatol 2008; 35(6):1130–1144. pmid:18464301
17. **Mueller BR, Robinson-Papp J.** Postural orthostatic tachycardia syndrome and migraine: a narrative review. Headache 2022; 62(7): 792-800. doi:10.1111/head.14365
18. **Mayer TG, Neblett R, Cohen H, et al.** The development and psychometric validation of the central sensitization inventory. Pain Pract 2012; 12(4):276–285. doi:10.1111/j.1533-2500.2011.00493.x
19. **Neblett R, Cohen H, Choi Y, et al.** The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. J Pain 2013; 14(5):438–445. doi:10.1016/j.jpain.2012.11.012

20. **McWilliams DF, Georgopoulos V, Patel J, Millar B, Smith SL, Walsh DA.** Validation of a questionnaire for Central nervous system Aspects of joint Pain: the CAP questionnaire. Rheumatology (Oxford) 2024; 63(12):3306–3314. doi:10.1093/rheumatology/keae342
21. **Clauw DJ.** Why don't we use a body map in every chronic pain patient yet? Pain 2024; 165(8):1660–1661. doi:10.1097/j.pain.0000000000003184
22. **Malfait F, Symoens S, Syx D.** Classic Ehlers-Danlos syndrome. Updated February 1, 2024. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. GeneReviews. Seattle, WA: University of Washington, Seattle; 1993–2024.
23. **Zanussi JT, Zhao J, Wei WQ, et al.** Clinical diagnoses associated with a positive antinuclear antibody test in patients with and without autoimmune disease. BMC Rheumatol 2023; 7(1):24. doi:10.1186/s41927-023-00349-4
24. **Wali SO, Manzar MD, Abdelaziz MM, et al.** Putative associations between inflammatory biomarkers, obesity, and obstructive sleep apnea. Ann Thorac Med 2021; 16(4):329–336. doi:10.4103/atm.atm_644_20
25. **Häuser W, Fisher E, Perrot S, Moore RA, Makri S, Bidonde J.** Non-pharmacological interventions for fibromyalgia (fibromyalgia syndrome) in adults: an overview of Cochrane Reviews. Cochrane Database Syst Rev 2022; 2022(1):CD015074. doi:10.1002/14651858.CD015074
26. **Harber VJ, Sutton JR.** Endorphins and exercise. Sports Med 1984; 1(2):154–171. doi:10.2165/00007256-198401020-00004
27. **Sanaeifar F, Pourranjbar S, Pourranjbar M, et al.** Beneficial effects of physical exercise on cognitive-behavioral impairments and brain-derived neurotrophic factor alteration in the limbic system induced by neurodegeneration. Exp Gerontol 2024; 195:112539. doi: 10.1016/j.exger.2024.112539
28. **Clauw DJ.** Fibromyalgia: a clinical review. JAMA 2014; 311(15): 1547–1555. doi:10.1001/jama.2014.3266
29. **Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A.** The efficacy of cognitive behavioral therapy: a review of meta-analyses. Cognit Ther Res 2012; 36(5):427–440. doi:10.1007/s10608-012-9476-1
30. **Johnson MH.** How does distraction work in the management of pain? Curr Pain Headache Rep 2005; 9(2):90–95. doi:10.1007/s11916-005-0044-1
31. **Menga G, Ing S, Khan O, et al.** Fibromyalgia: can online cognitive behavioral therapy help? Ochsner J 2014; 14(3):343–349. pmid:25249800
32. **Shi Y, Wu W.** Multimodal non-invasive non-pharmacological therapies for chronic pain: mechanisms and progress. BMC Med 2023; 21(1):372. doi:10.1186/s12916-023-03076-2
33. **Kabat-Zinn J.** An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. Gen Hosp Psychiatry 1982; 4(1):33–47. doi:10.1016/0163-8343(82)90026-3
34. **Burgess DJ, Calvert C, Hagel Campbell EM, et al.** Telehealth mindfulness-based interventions for chronic pain: the LAMP randomized clinical trial [published correction appears in JAMA Intern Med 2024; 184(10):1270]. JAMA Intern Med 2024; 184(10):1163–1173. doi:10.1001/jamainternmed.2024.3940
35. **Wayne PM, Kaptchuk TJ.** Challenges inherent to t'ai chi research: Part I—t'ai chi as a complex multicomponent intervention. J Altern Complement Med 2008; 14(1):95–102. doi:10.1089/acm.2007.7170a
36. **Wang C, Schmid CH, Rones R, et al.** A randomized trial of tai chi for fibromyalgia. N Engl J Med 2010; 363(8):743–754. doi:10.1056/NEJMoa0912611
37. **Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL.** Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2017; 13(2):307–349. doi: 10.5664/jcsm.6470
38. **Tofferi JK, Jackson JL, O'Malley PG.** Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. Arthritis Rheum 2004; 51(1):9–13. doi: 10.1002/art.20076
39. **Häuser W, Wolfe F, Tölle T, Uçeyler N, Sommer C.** The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis. CNS Drugs 2012; 26(4):297–307. doi:10.2165/11598970-000000000-00000
40. **Ben-Ami Shor D, Weitzman D, Dahan S, et al.** Adherence and persistence with drug therapy among fibromyalgia patients: data from a large health maintenance organization [published correction appears in J Rheumatol 2017; 44(11):1762]. J Rheumatol 2017; 44(10):1499–1506. doi:10.3899/jrheum.170098
41. **Derry S, Wiffen PJ, Häuser W, et al.** Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. Cochrane Database Syst Rev 2017; 3(3):CD012332. doi:10.1002/14651858.CD012332.pub2
42. **Due Bruun K, Christensen R, Amris K, et al.** Naltrexone 6 mg once daily versus placebo in women with fibromyalgia: a randomised, double-blind, placebo-controlled trial. Lancet Rheumatol 2024; 6(1):e31–e39. doi:10.1016/S2665-9913(23)00278-3
43. **Farag HM, Yunusa I, Goswami H, Sultan I, Doucette JA, Eguale T.** Comparison of amitriptyline and US Food and Drug Administration-approved treatments for fibromyalgia: a systematic review and network meta-analysis. JAMA Netw Open 2022; 5(5):e2212939. doi:10.1001/jamanetworkopen.2022.12939
44. **Arnold LM, Goldenberg DL, Stanford SB, et al.** Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum 2007; 56(4): 1336–1344. doi:10.1002/art.22457
45. **Heymann RE, Helfenstein M, Feldman D.** A double-blind, randomized, controlled study of amitriptyline, nortriptyline and placebo in patients with fibromyalgia. An analysis of outcome measures. Clin Exp Rheumatol 2001; 19(6):697–702. pmid:11791642
46. **Goldenberg DL, Kaplan M.** Fibromyalgia: treatment in adults. UpToDate. Updated August 15, 2024. https://www-uptodate-com.ccmain.ohionet.org/contents/fibromyalgia-treatment-in-adults. Accessed March 14, 2025.

Address: *Rupak Thapa, MD, Department of Rheumatology, Atrium Health Wake Forest Baptist Medical Center, 1 Medical Center Boulevard, Winston Salem, NC 27157; rthapa@wakehealth.edu*