Practical Updates in Primary Care

Navigating Fibromyalgia in Primary Care: From First Symptoms to Personalized Management

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Faculty Disclosures

- **Andrea Chadwick, MD, MSc, FASA:** Consultant—Axsome Therapeutics, Swing Therapeutics, Tonix Medicines; Speaker's Bureau—Tonix Medicines

- **Jennifer Zuccarelli, MD** has nothing to disclose in relation to this activity

Disclosure

The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

This activity has been independently reviewed for balance.

Learning Objectives

- Recognize the interconnected symptom patterns and comorbidities of FM, including pain, sleep disturbance, and psychiatric symptoms, to support early diagnosis and effective management
- Assess the efficacy, safety, and indications of current and emerging pharmacologic therapies for FM
- Implement evidence-based, nonpharmacologic, and multidisciplinary strategies for FM management in primary care, including appropriate use of patient-reported outcome measures and referral pathways

FM = fibromyalgia.



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Early Recognition and Diagnosis of FM in Primary Care

Fibromyalgia Overview

- Chronic nociplastic pain syndrome with widespread pain and associated symptoms
- Accompanied by
  - Mood alterations
  - Sleep disruption
  - Cognitive difficulties
- Prevalence: 2-8%
- Despite advances, remains challenging and difficult to treat
  - Pharmacologic therapy rarely works as monotherapy
  - Medications often do not provide significant relief and cause side effects

Clauw DJ. *JAMA*. 2014;311(15):1547-1555.

What Is Nociplastic Pain?

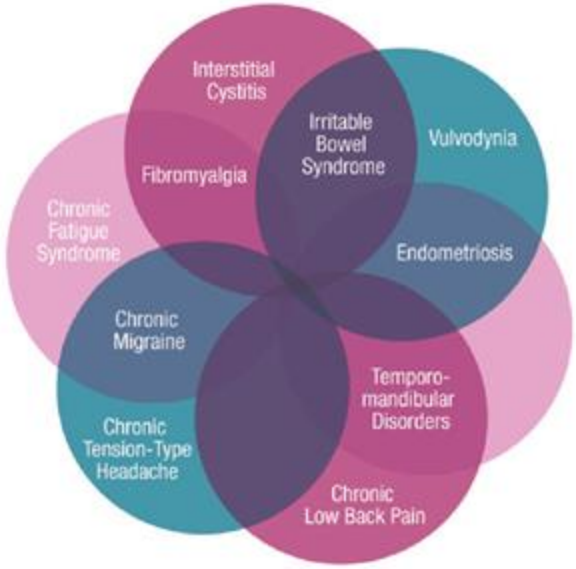
- “Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors, or evidence for disease or lesion of the somatosensory system causing the pain”
- Introduced in 2016 through International Association for the Study of Pain Terminology Task Force
- Best exemplified in conditions such as: fibromyalgia, irritable bowel syndrome, migraine and tension headache, chronic low back pain, and others
  - Nociplastic pain is thought to be predominant pain mechanism
  - “Chronic overlapping pain conditions”
  - “Primary pain”

International Association for the Study of Pain. Accessed September 10, 2026. https://www.iasp-pain.org/resources/terminology/. Kaplan CM, et al. *Nat Rev Neurol.* 2024;20:347-363.

Centralized Pain Syndromes

Figure 1. Venn Diagram of Chronic Overlapping Pain Conditions

The complexity of overlap among COPCs is demonstrated in this figure. Any combination of conditions is possible. Some people may develop two disorders – either simultaneously or over the course of their lives – while others may develop three or more.



- Centralized pain syndromes have distinct adaptations within the central nervous system (CNS) known as central sensitization
  - Amplify peripheral input
  - Generate the perception of pain in the absence of peripheral input
- Chronic overlapping pain conditions
  - Recognized by the NIH as a set of conditions where there is substantial overlap thought to be secondary to similar pathophysiology

Maixner W, et al *J Pain*. 2016;17(9 Suppl):T93-T107.

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Understanding the Interrelationship

- Pain
- Sleep disturbance
- Fatigue
- Psychiatric symptoms

Brain network enmeshment

Neurotransmitter alterations

Dysfunctional reward processing

Microglial and astrocyte dysregulation

Deficits in descending pain modulation

Clauw DJ, et al. *Mayo Clin Proc*. 2011;86(9):907-911.

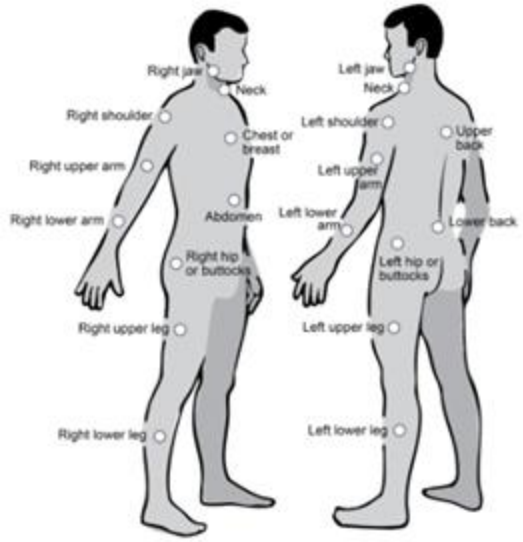
Why Primary Care Is on the Front Lines

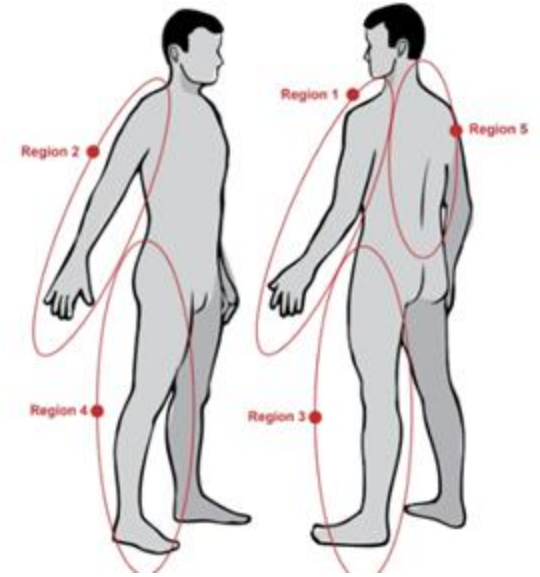
Average delay to diagnosis: 2-7 years from symptom onset in many studies

Reasons include

- Fluctuating symptoms over time
- No confirmatory lab or imaging test
- Patients often present with multiple seemingly unrelated symptoms
- Overlap with autoimmune, endocrine, neurologic, and psychiatric disorders
- Persistent misconceptions that symptoms are “psychological”
- Multiple specialist referrals before diagnosis
- Limited clinician familiarity with updated diagnostic criteria

2016 ACR Diagnostic Criteria





The 2016 update to the ACR guidelines sought to refine the diagnosis criteria for fibromyalgia to reduce the number of false positives

The diagnosis of other chronic pain disorders does not preclude a diagnosis of fibromyalgia

- Generalized pain in at least 4 out of 5 body regions
- Widespread Pain Index (WPI) score ≥7
- Symptom Severity (SS) scale score ≥5
- Or WPI score between 4-6 and SS score ≥9 with symptoms for at least 3 months
- A diagnosis of fibromyalgia does not need to exclude other clinically important conditions

ACR = American College of Rheumatology.

Wolfe F, et al. *Semin Arthritis Rheum*. 2016;46(3):319-329. Ablin JN, Wolfe F. *J Rheumatol*. 2017;44(8):1271-1276.

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The ACTTION-American Pain Society Pain Taxonomy (AAPT)

The framework organizes pain conditions using 5 distinct dimensions

- Dimension 1: Core Diagnostic Criteria
- Dimension 2: Common Features
- Dimension 3: Common Medical Comorbidities
- Dimension 4: Neurobiological, Psychosocial, and Functional Consequences
- Dimension 5: Putative Neurobiological and Psychosocial Mechanisms, Risk Factors, and Protective Factors

Fillingim RB, et al. *J Pain*. 2014;15(3):241-249.

The Fibromyalgia Rapid Screening Tool (FiRST)

A brief, 6-question self-administered questionnaire designed to help identify fibromyalgia in patients with chronic pain

The questionnaire uses simple yes/no questions targeting key symptoms of fibromyalgia

- Widespread pain: Do I have pain all over my body?
- Fatigue: Is my pain accompanied by continuous and very unpleasant general fatigue?
- Pain character: Does my pain feel like burns, electric shocks, or cramps?
- Other sensations: Is my pain accompanied by unusual sensations like pins and needles, tingling, or numbness?
- Associated problems: Is it accompanied by digestive issues, urinary problems, headaches, or restless legs?
- Daily impact: Does it significantly impact sleep, concentration, or overall slowness?

Perrot S, et al. *Pain*. 2010;150(2):250-256.

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Defining PCP's Role in Management

- Most specialists will refer patient back to PCP for treatment (eg, rheumatology, neurology)

- Recommend educational resources
  - Newly diagnosed: *Fibromyalgia for Dummies* by Dr. Roland Staud and Christine Adamec
  - More comprehensive: *The Fibro Manual* by Dr. Ginevra Liptan

- Engage other clinicians to assist in management
  - Physical therapy – consider warm water aquatic PT
  - Behavioral therapist specializing in chronic pain for acceptance and commitment therapy

Differentiating FM from Overlapping Conditions

- Irritable bowel syndrome
- Myalgic encephalomyelitis/chronic fatigue syndrome
- Migraine
- Depression/anxiety disorders
- Somatic symptom disorder



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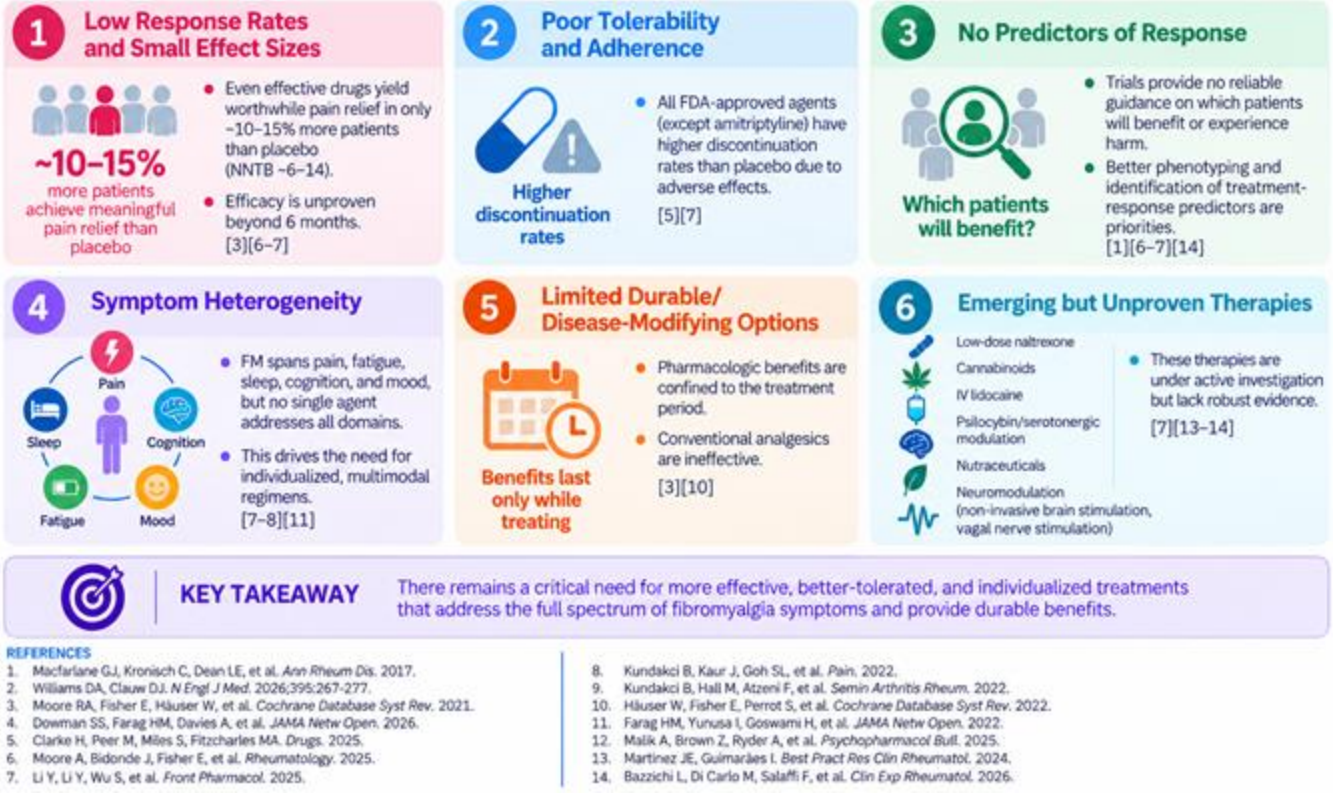
Current and Emerging Pharmacologic Therapies for FM

Current Treatment Overview

- Historically, 3 FDA-approved therapies
  - Duloxetine
  - Milnacipran
  - Pregabalin
- Late 2025 came first new FDA-approved pharmacotherapy in ~15 years
  - Sublingual cyclobenzaprine
- FDA-approved therapies tend to focus on modulation of
  - Reduction of facilitatory neurotransmission
  - Augmenting inhibitory (noradrenergic/serotonergic) signaling
- Non-FDA-approved therapies (off-label) are widely used

Williams DA, Clauw DJ. *N Engl J Med*. 2026;395(3):267-277.

Unmet Needs and Gaps in the Pharmacotherapy of Fibromyalgia: Current Pharmacotherapy Provides Modest, Short-Term Benefits and Does Not Fully Address the Complex, Multifaceted Nature of FM

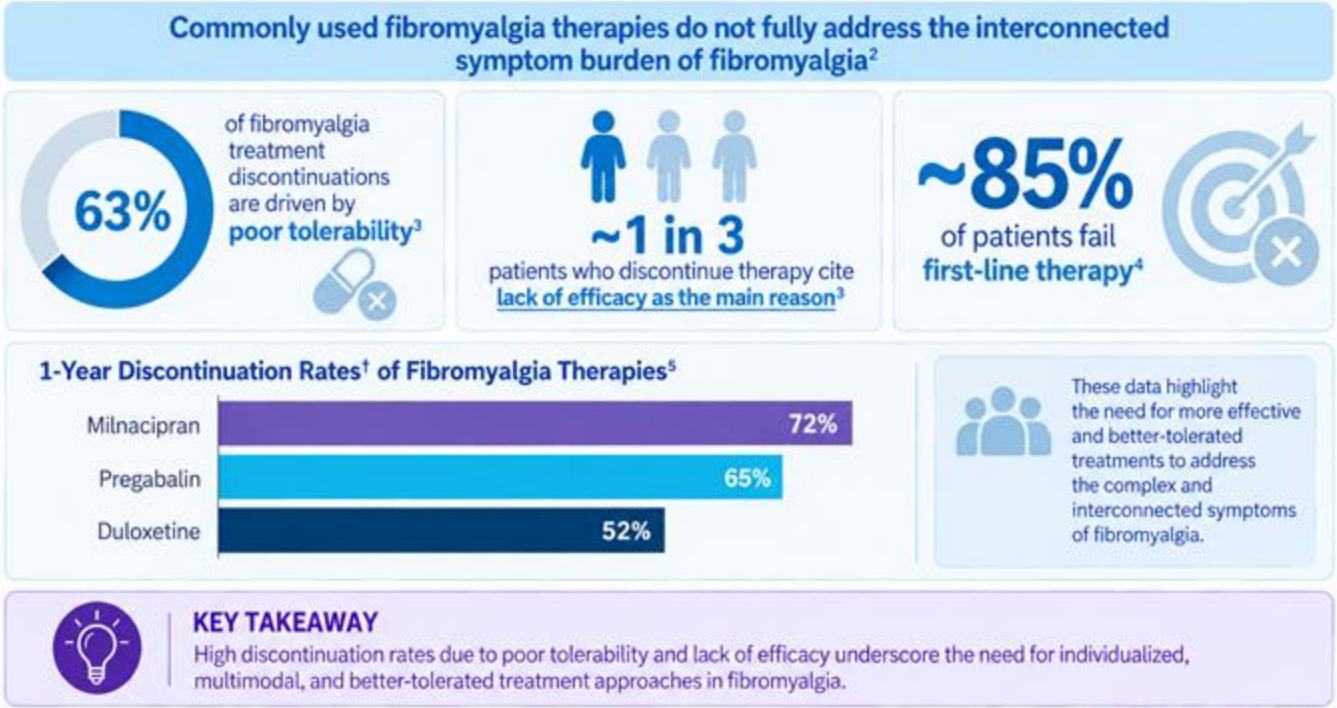


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14. Bazzichi L, Di Carlo M, Salaffi F, et al. *Clin Exp Rheumatol*. 2026.

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Despite Available Treatment Options, Many Patients Still Struggle with Substantial Disease Burden



1. Schaefer CP, et al. *Open Rheumatol J.* 2016;10:109-121. 2. Giorgi V, et al. *Curr Pain Headache Rep.* 2024;28(12):1349-1363.
3. Robinson RL, et al. *Pain Med.* 2013;14:1400-1415. 4. Williams DA, et al. *New Engl J Med.* 2026;395:267-277.
5. Liu Y, et al. *J Manag Care Spec Pharm.* 2016;22(3):263-271.

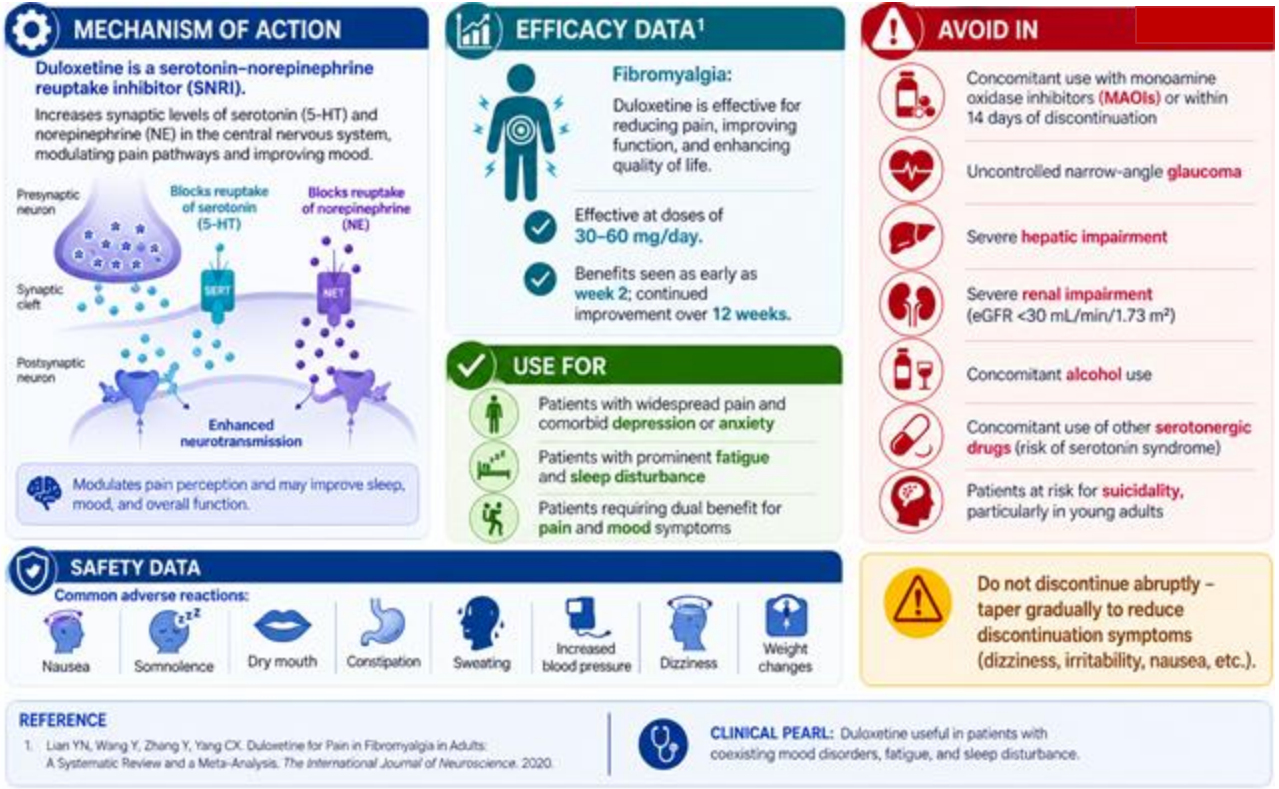
† Discontinuation defined as stopping therapy for any reason within 1 year.

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Duloxetine, Pregabalin, and Milnacipran

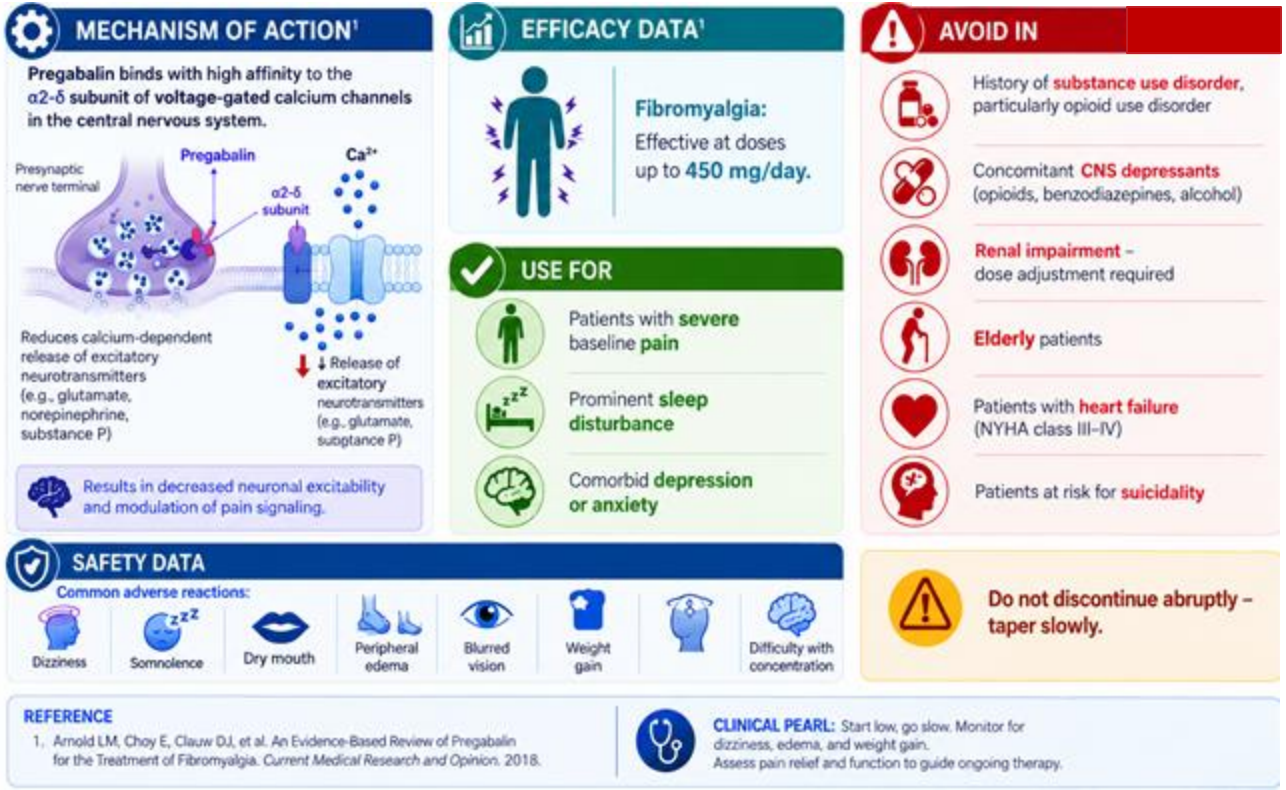
Duloxetine: An Evidence-Based Option for Fibromyalgia Management – Approved for FM in 2008



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Pregabalin: An Evidence-Based Option for Fibromyalgia Management – Approved for FM in 2007



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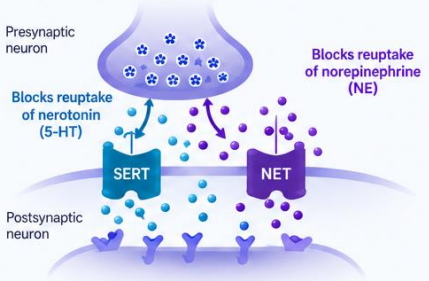
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Milnacipran: An Evidence-Based Option for Fibromyalgia Management – Approved for FM in 2009

MECHANISM OF ACTION

Milnacipran is a serotonin–norepinephrine reuptake inhibitor (SNRI).

Increases synaptic levels of serotonin (5-HT) and norepinephrine (NE) in the central nervous system, modulating pain pathways and improving mood and function.



Enhances descending inhibitory pathways and modulates pain perception.

EFFICACY DATA[1]

Fibromyalgia:

Milnacipran is effective for reducing pain, improving function, and enhancing quality of life.

- Effective at doses of **100–200 mg/day**.
- Benefits observed as early as **week 1–2**; continued improvement over **12 weeks**.
- Improves pain, physical function, fatigue, and overall quality of life.

USE FOR

- Patients with widespread pain and comorbid **depression** or **anxiety**
- Patients with prominent **fatigue** and **sleep disturbance**
- Patients requiring dual benefit for **pain** and **mood** symptoms

AVOID IN

- Concomitant use with other **serotonergic drugs** (risk of serotonin syndrome)
- Uncontrolled **hypertension**
- Severe **hepatic impairment**
- Severe **renal impairment** (eGFR <30 mL/min/1.73 m²)
- Concomitant **alcohol** use
- Patients at risk for **suicidality**, particularly in young adults

SAFETY DATA

Common adverse reactions:

Nausea · Somnolence · Sweating · Dizziness · Constipation · Dry mouth · Increased heart rate · Urinary retention

Do not discontinue abruptly – taper gradually to reduce discontinuation symptoms (dizziness, headache, nausea, irritability, etc.).

REFERENCE

1. Cording M, Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for Pain in Fibromyalgia in Adults. *The Cochrane Database of Systematic Reviews*. 2015.

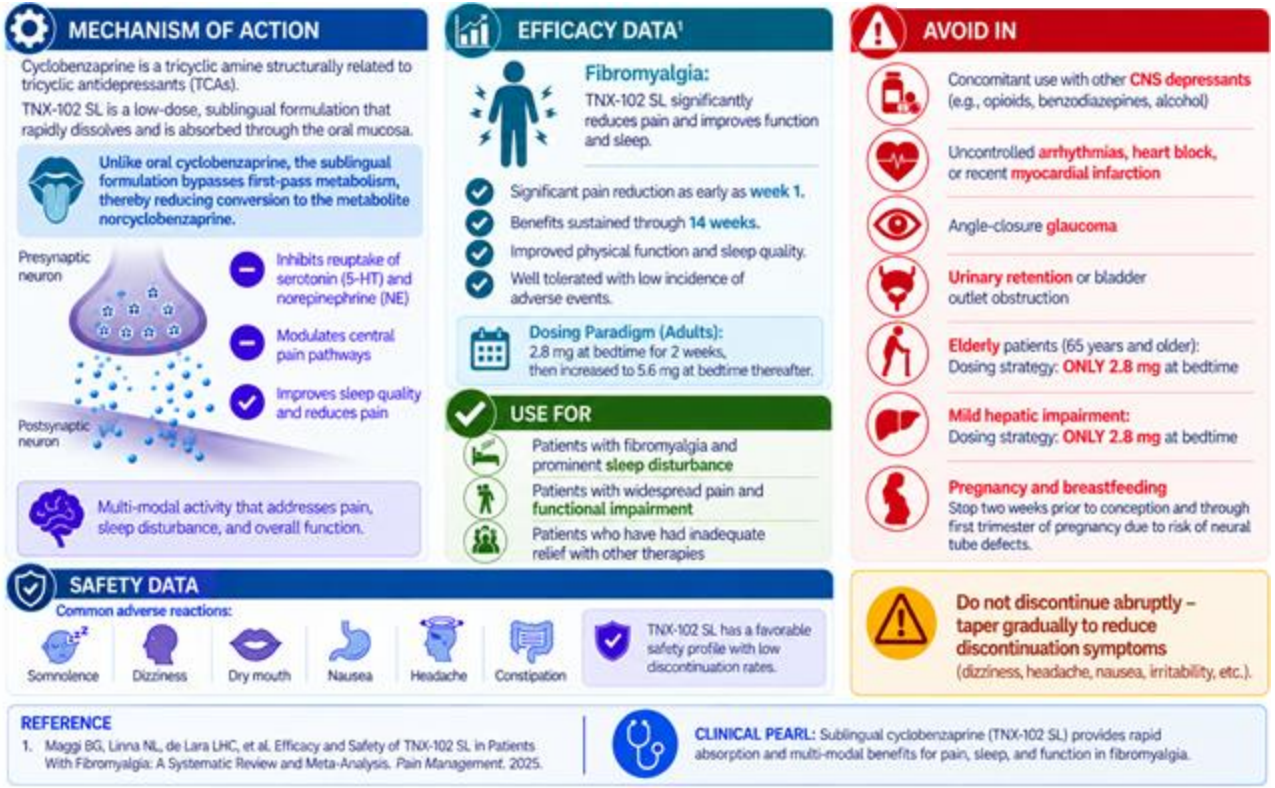
CLINICAL PEARL: Milnacipran can be particularly useful in patients with coexisting mood disorders, fatigue, and sleep disturbance.

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New and Emerging Therapies

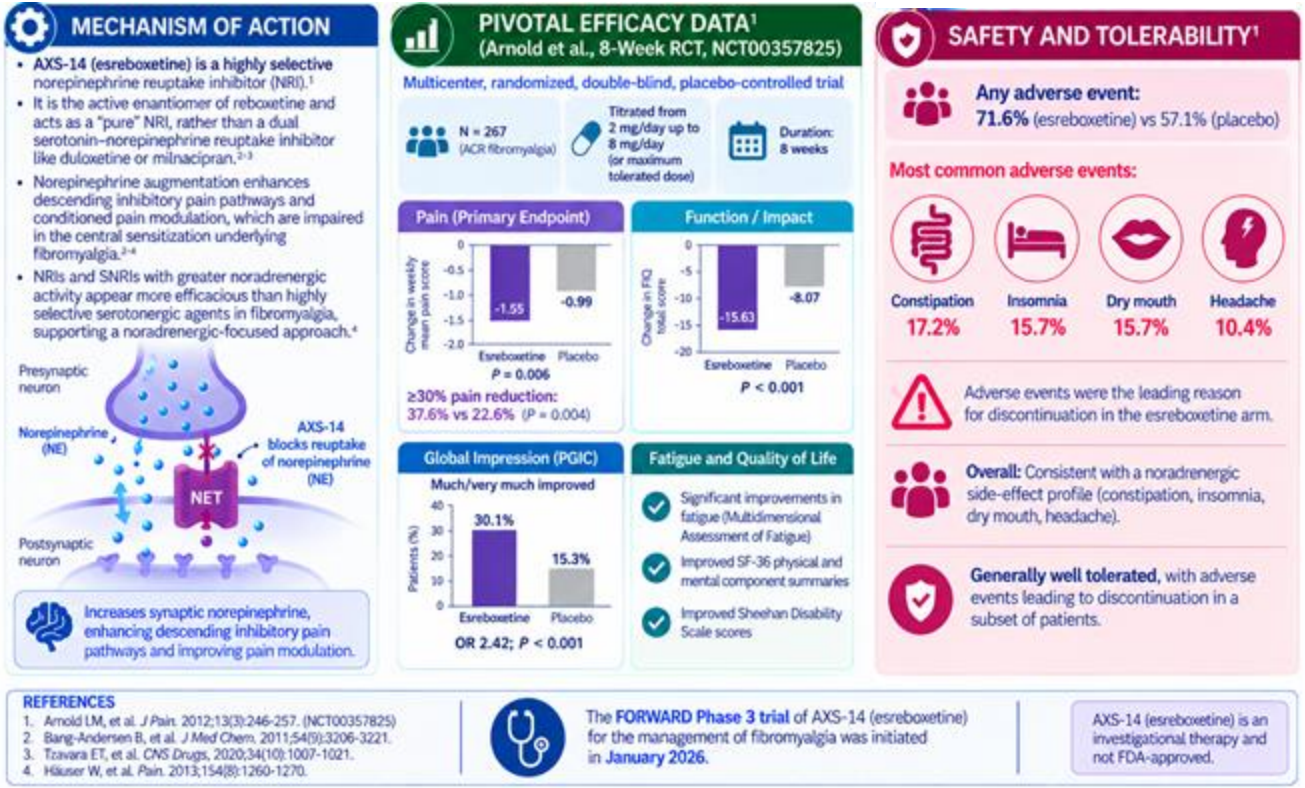
Sublingual Cyclobenzaprine (TNX-102 SL): An Evidence-Based Option for Fibromyalgia Management – Approved for FM in 2025



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AXS-14 (Esreboxetine): Investigational Therapy for Fibromyalgia – A Selective Norepinephrine Reuptake Inhibitor for FM

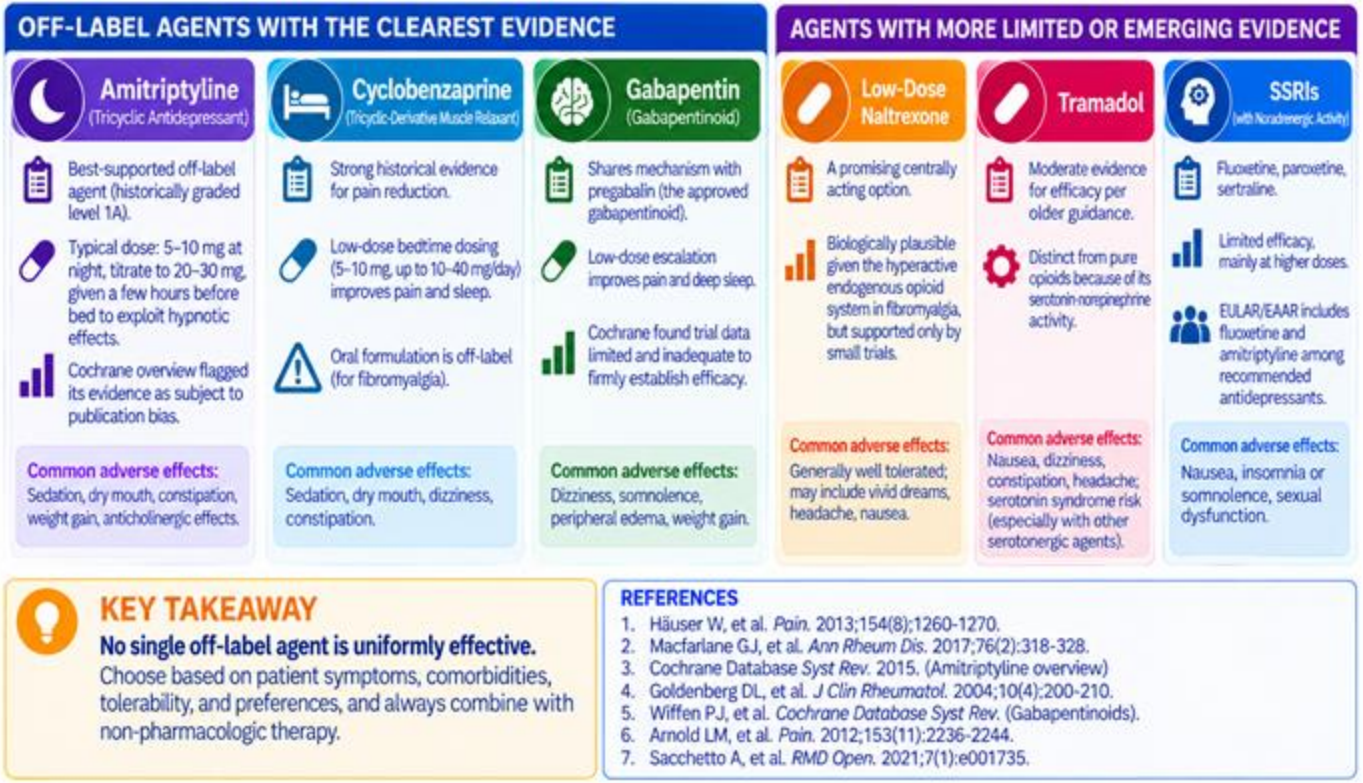


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Off-Label Therapies (Strong Evidence Base)

Off-Label Pharmacotherapy for Fibromyalgia: Evidence-Based Options to Individualize Care



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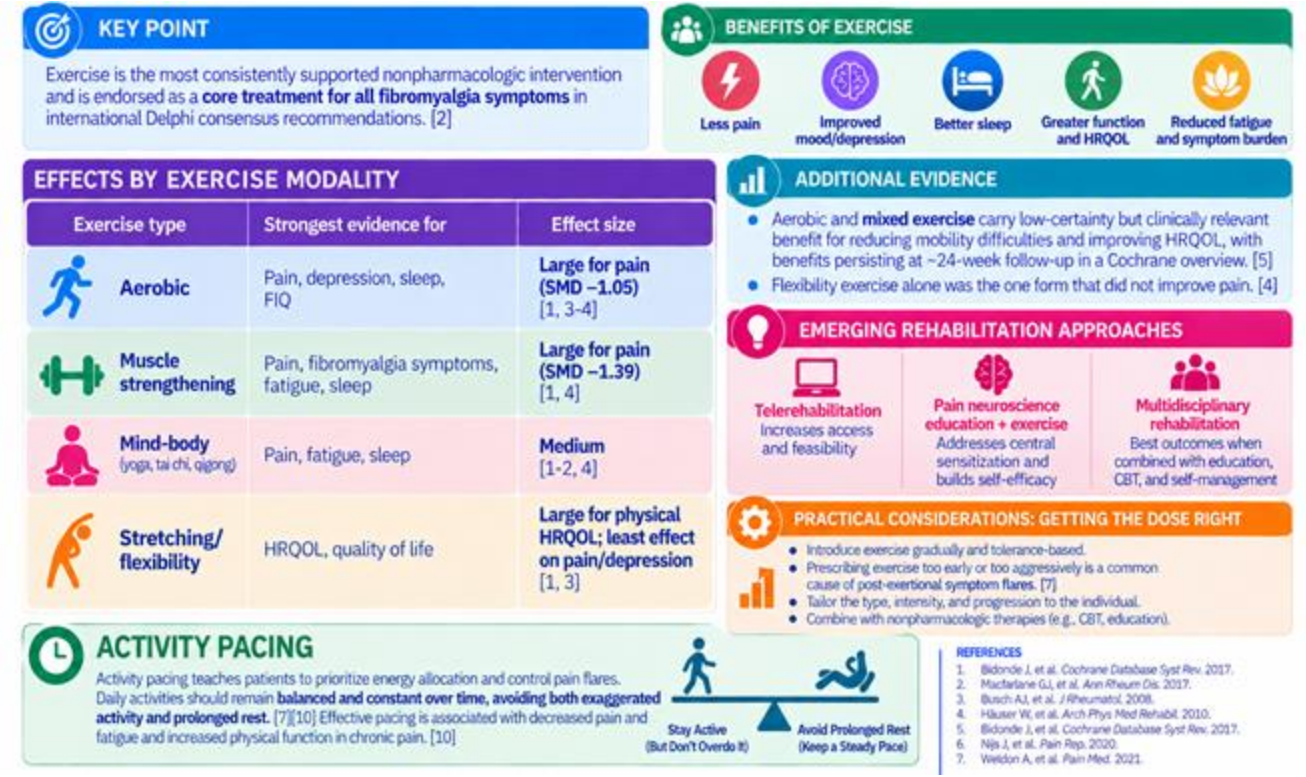


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Patient-Centered Non-Pharmacologic and Multidisciplinary FM Management

Exercise and Rehabilitation Therapies

Exercise, Rehabilitation Therapies, and Activity Pacing: A Core Treatment for All FM Symptoms

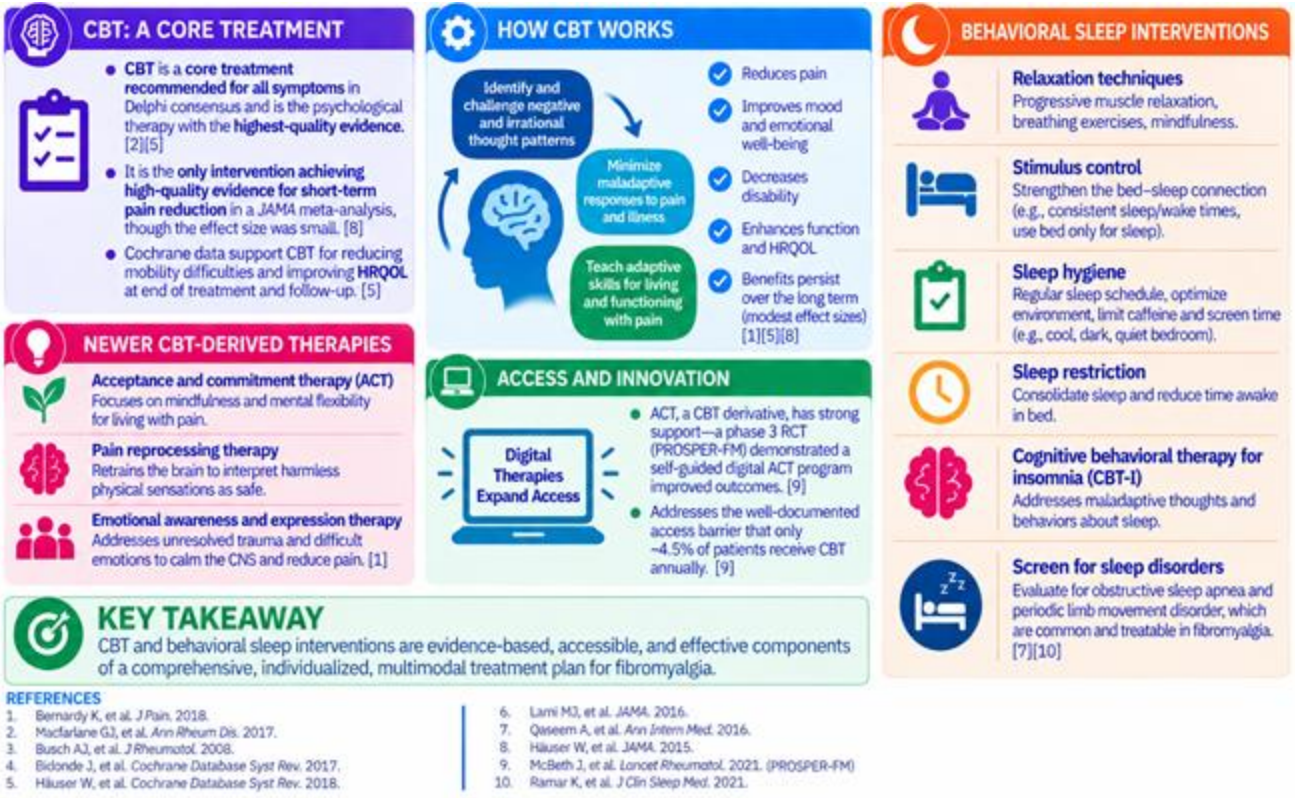


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Behavioral Interventions and Sleep Interventions

Cognitive Behavioral Therapy and Behavioral Sleep Interventions: Improving Coping, Sleep, and Quality of Life in Fibromyalgia



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Self-Management and Education Strategies

Self-Management Education and Care Strategies for Fibromyalgia: Building Skills for a Better Tomorrow

Pain education

Pain education aims to clarify the known scientific underpinnings of fibromyalgia (e.g., central sensitization and nociplastic mechanisms), assure patients about the legitimacy and prognosis of the condition, and engage patients in taking an active role in care. This foundation helps provide a rational framework for understanding why specific medications, nonpharmacologic treatments, and self-care approaches can provide benefit.

Social support

Support for living with fibromyalgia can come from interactions with others, including family, friends, workplace colleagues, and health care providers. Effective management of these relationships can be challenging but is key to successful self-care.

Pleasant activity scheduling and activity pacing

Pleasant activity scheduling is a structured method of incorporating something pleasant for a brief time each day in order to improve mood and increase function. Activities can include seeing a friend or watching a show, but they must be scheduled in advance and completed.

Activity pacing teaches patients to prioritize energy allocation and control pain flares. Daily activities should remain **balanced and constant over time, avoiding both exaggerated activity and prolonged rest.** [7][10] Effective pacing is associated with decreased pain and fatigue and increased physical function in chronic pain. [10]



Stress management

Stress management combines a number of coping skills to achieve physiological and mental calmness. Skills include relaxation techniques (e.g., progressive muscle relaxation and visual imagery), mindfulness practices, time management skills, and cognitive reappraisal or reframing (structured reevaluation of negative thinking and emotions).

Individualized self-management

Self-management education is foundational: patients should understand fibromyalgia is a **real, non-progressive condition** not due to peripheral tissue damage, and should be positioned to develop individualized coping techniques, since patients rarely improve substantially without adopting core self-management strategies. [13]

KEY TAKEAWAY

Self-management education is foundational: patients should understand fibromyalgia is a real, non-progressive condition not due to peripheral tissue damage, and should be positioned to develop individualized coping techniques, since patients rarely improve substantially without adopting core self-management strategies. [13]

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How to Individualize Therapy?

Pharmacologic

- Tailor by symptom and side effect profile
  - Most drugs have small effect sizes
- Sublingual cyclobenzaprine/TCAs
  - Useful in sleep-predominant phenotypes
- Gabapentinoids
  - Similarly useful for sleep-predominant phenotypes
  - Patients with significant neuropathic pain symptoms and allodynia
- SNRIs
  - Useful in those with predominant depression/anxiety

Non-pharmacologic

- Again, tailoring to predominant symptoms
- Pain and depression
  - Exercise, CBT/mindfulness
- Fatigue
  - Mind-body, strengthening exercises
- Sleep
  - Aerobic, strengthening exercises
  - CBT-I
- Overall symptom burden
  - Exercise, behavioral interventions, multidisciplinary care

TCAs = tricyclic antidepressants; SNRIs = serotonin-norepinephrine reuptake inhibitors; CBT = cognitive behavioral therapy.

Williams DA, Clauw DJ. *N Engl J Med*. 2026;395(3):267-277. Bidonde J, et al. *Semin Arthritis Rheum*. 2023;63:152248.

How to Integrate: Multidisciplinary Care

- Parallel vs sequential treatment paradigms
- EULAR's revised recommendations frame individualization with a sequential graduated approach built on shared decision-making
  - Start all patients with education and nonpharmacologic therapy (exercise is the only "strong for" recommendation)
  - Then, for non-responders, add tailored options: psychological therapy for mood disorders and unhelpful coping, pharmacotherapy for severe pain or sleep disturbance, and multimodal rehabilitation for severe disability/functional impairment
- An alternative parallel model has also been proposed, applying all 4 "pillars"
  - Education, psychotherapy, pharmacotherapy, and fitness simultaneously from the outset
  - Modifying whichever pillar underperforms, always individualized to patient preference and shared decision-making

EULAR = European Alliance of Associations for Rheumatology.
Macfarlane GJ et al. *Ann Rheum Dis*. 2017;76(2):318-328. Sarzi-Puttini P, et al. *Nat Rev Rheumatol*. 2020;16(11):645-660.

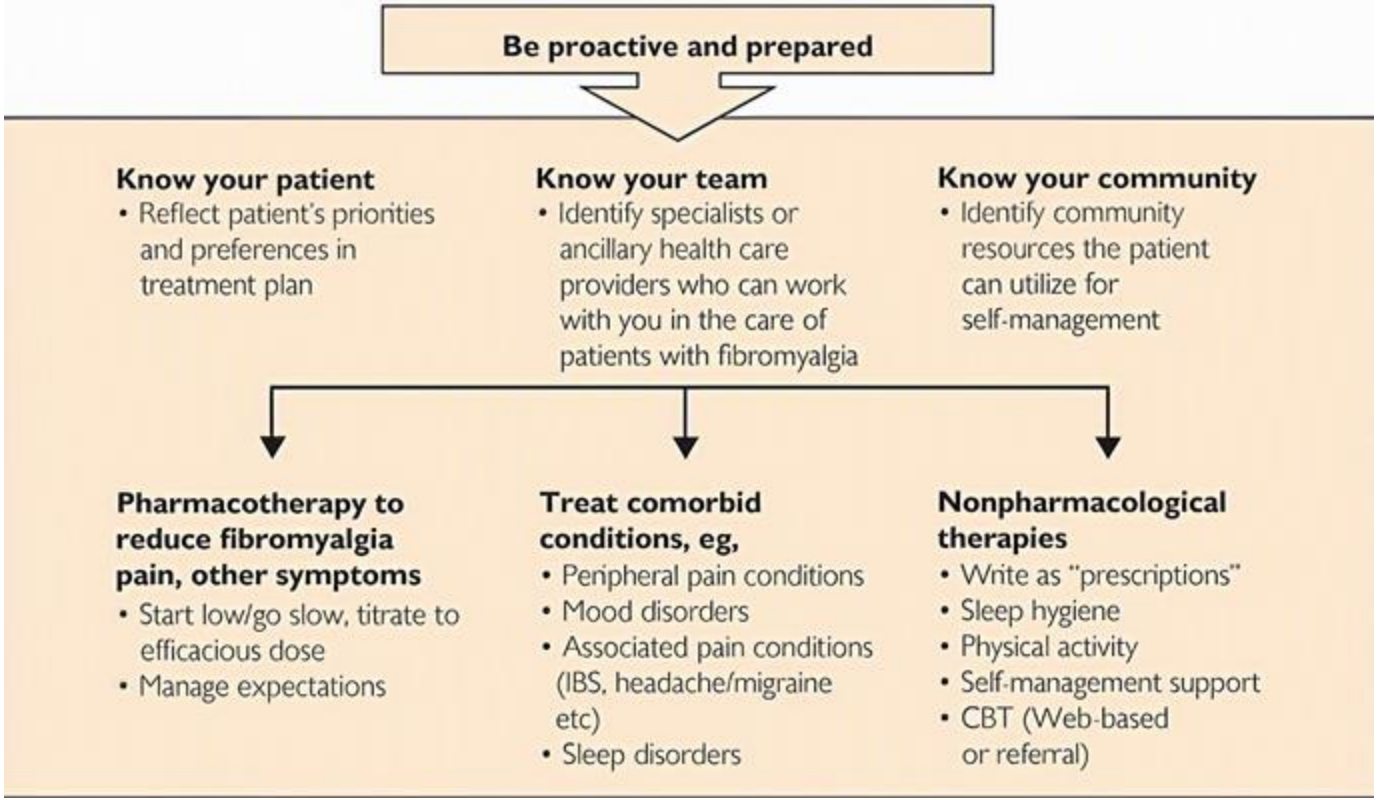
Streamlined Referral Pathways

- For further evaluation
  - Sleep medicine
  - Rheumatology
  - Neurology

- For further treatment
  - Physical therapy
  - Behavioral therapy

Williams DA, Clauw DJ. *N Engl J Med*. 2026;395(3):267-277.

Coordinating Longitudinal Care in Primary Care



IBS = irritable bowel syndrome.

Arnold LM, Clauw DJ, et al. *Mayo Clin Proc*. 2012;87(5):488-496.

Key Learning Points



- Fibromyalgia is a nociplastic pain disorder characterized by widespread pain, fatigue, sleep disturbance, cognitive symptoms, and mood changes
- Early recognition in primary care is critical, as diagnosis is often delayed by several years due to symptom overlap with other medical and psychiatric conditions, and the absence of definitive laboratory or imaging biomarkers
- Diagnosis should be based on established clinical criteria, including the 2016 ACR criteria, and can be supported by screening tools such as the Fibromyalgia Rapid Screening Tool (FiRST)
- Effective fibromyalgia management requires a multimodal approach; pharmacologic therapies alone typically provide modest benefit and should be selected based on a patient's predominant symptoms and comorbidities
- Nonpharmacologic therapies are foundational components of treatment and should be initiated early
- Long-term care is best delivered through a patient-centered, multidisciplinary model that emphasizes education, shared decision-making, individualized treatment plans, and appropriate referral pathways when alternative diagnoses or specialized interventions are needed