Session 6: Fibromyalgia: Dispelling Myths, Improving Management

Learning Objectives

• Dispel misinformation about fibromyalgia and rely on scientific evidence to explain its causes, recognize its manifestations, and make an accurate diagnosis.
• Analyze current pharmacologic and nonpharmacologic therapies for fibromyalgia to devise tailored, evidence-based treatment plans.

Faculty

Philip J. Mease, MD
Seattle Rheumatology Associates
Chief of Rheumatology Research
Swedish Hospital Medical Center
Clinical Professor of Medicine
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Dr Philip J. Mease is a clinical rheumatologist and clinical professor of medicine. His research interests include pharmacotherapy of rheumatologic diseases and the methodology of disease assessment. He conducts clinical trials in emerging therapies for a number of conditions, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, fibromyalgia, systemic lupus erythematosus, osteoarthritis, and osteoporosis. Dr Mease has published extensively and is on the review boards of several rheumatic disease journals. He serves on the medical advisory boards of several pharmaceutical and biotechnology companies and foundations. He is a founding member of GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis), and chair/co-chair of 3 working groups of OMERACT (Outcome Measures in Rheumatology Clinical Trials). Dr Mease received his BA and MD degrees from Stanford University. He completed his residency in internal medicine at the University of Washington School of Medicine, where he was subsequently chief resident and fellow in rheumatology.

Richard Harris, PhD
Research Assistant Professor
University of Michigan
Ann Arbor, Michigan

Richard Harris is a research assistant professor in the Department of Anesthesiology at the University of Michigan. His background is in basic science and clinical research in alternative medicine. He received his BS degree in genetics from Purdue University in 1992 and his PhD in molecular and cellular biology from the University of California at Berkeley in 1997. Following his graduate work, he completed a postdoctoral fellowship at the National Institutes of Health, studying the rhythmic properties of neural cultures. He is a graduate of the Maryland Institute of Traditional Chinese Medicine and is currently investigating mechanisms of acupuncture in the treatment of chronic pain conditions.

Faculty Financial Disclosure Statements

The presenting faculty reported the following:

Dr Mease receives grants for clinical research from Pfizer Inc.; Cypress; Forest Pharmaceuticals, Inc.; Eli Lilly and Company; Fralex; Boehringer-Ingelheim Pharmaceuticals, Inc.; and Allergan. He also receives grants for educational activities, and serves as an advisor or consultant to Pfizer Inc.; Cypress; Forest Pharmaceuticals, Inc.; Eli Lilly and Company; Fralex; Boehringer-Ingelheim Pharmaceuticals, Inc.; Allergan; and Jazz Pharmaceuticals.
Dr Harris receives grants for clinical research and consultant fees from Pfizer Inc.
Education Partner Financial Disclosure Statement
The content collaborators at MedIQ Research & Education have reported the following:
Joyce Waskelo has nothing to disclose.

Drug List

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Investigational
milnacipran

Suggested Reading List


Today's Program
A presentation of facts and evidence to dispel several common myths related to fibromyalgia...

Part 1:
• Overview of Fibromyalgia
  – Epidemiology, disease classification, pathophysiology
• Diagnosis
  – Classic symptoms, clinical workup

Part 2:
• Management of Fibromyalgia
  – Treatment of pain and other symptom domains

Question
• Have you ever given a patient the diagnosis of fibromyalgia?
  1. Yes
  2. No

Overview of Fibromyalgia

Question
• How would you characterize fibromyalgia?
  1. Autoimmune disease
  2. Psychological disorder
  3. Rheumatic or inflammatory disorder
  4. Central nervous system disorder
  5. Musculoskeletal disorder

Myth 1:
Fibromyalgia is not a real illness—it is psychological
Case Study Preview: Darlene’s Story

Fibromyalgia diagnosis is not based on exclusion of other disorders

Fibromyalgia Often Associated with Other Disorders

Rheumatic disorders
- Lupus (SLE)
- Rheumatoid arthritis
- Sjögren’s syndrome
- Osteoarthritis

Infections and inflammation
- Hepatitis C
- Crohn’s disease
- Lyme disease
- Parvovirus infections

Psychological disorders
- Depression
- Anxiety states
- Posttraumatic stress disorder (PTSD)

Other pain states
- Irritable bowel syndrome
- Pelvic pain syndromes
- Sympathetic dystrophy
- Neuropathies
- Vascular headaches

What Causes Fibromyalgia?

- Genetics
- “Triggers”
- Potential mechanisms:
  - Central sensitization
  - Abnormalities of descending inhibitory pain pathways
  - Neurotransmitter abnormalities
  - Neurohumoral abnormalities
  - Psychiatric comorbid conditions

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Fibromyalgia “Triggers”

- Peripheral pain syndromes
- Infections (eg, parvovirus, Epstein-Barr, Lyme disease)
- Physical trauma (eg, automobile accidents)
- Psychological stress/distress
- Hormonal alterations (eg, hypothyroidism)
- Certain catastrophic events (eg, war)

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Pain Pathways

Facilitatory Ascending Pain Pathway

Descending Pain Pathway

Inhibitory

Ascending Pain Pathway

Descending Pain Pathway

Facilitatory

Inhibitory


Genetics of Fibromyalgia

- Strong familial predisposition
  - >8 odds ratio for first-degree relatives
- Possible genetic polymorphisms:
  - 5-HT(2A) receptor
  - Serotonin transporter
  - Dopamine D4 receptor
  - COMT (catecholamine-O-methyl transferase)

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Central Sensitization: Enhanced Processing of Pain Stimuli

- Amplified pain responses: abnormal "volume control"1
  - Increased response to painful stimuli (hyperalgesia)
  - Pain from normally innocuous stimuli (alldynia)
- Scientific evidence:
  - Temporal summation of second pain ("wind-up")
  - Increased activity on fMRI scans
    - "Left-shift" in stimulus-response function
  - Elevated cerebral spinal fluid levels of neurotransmitters (substance P, nerve growth factor)


Temporal Summation: The Concept of “Wind-Up” Pain

![Graph showing pain ratings over time](image)

Functional MRI: Objective Evidence of Augmented Pain Processing

![Graph showing stimulus intensity versus pain intensity](image)

Stimulus-Response Curve Shifts When Pressure-Induced Pain Is Reduced

- Placebo-controlled trial assessed effect of SNRI on pain-modulating systems in brain
- Visual analog scale measured pain produced by repeated application of blunt pressure
- At Week 12, a clinically relevant shift in stimulus-response for patients treated with SNRI

Elevated CSF Levels of Pain Modulator (Substance P) in Fibromyalgia Patients

![Graph showing CSF levels](image)
**Myth 2:**

*Fibromyalgia is a new and rare condition that affects only middle-aged women*

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**Fibromyalgia Prevalence**

- 2% of general population in the US; about 5 million adults ≥18 years of age\(^1\)
- 3.4% of female population\(^2\)
  - Female to male ratio 7:1
- All ages, from <10 years\(^3\) to elderly\(^2\)
  - Prevalence rises sharply in middle age, peaking at ages 70-79 years\(^2\)
- 5%-6% of general practice patients\(^4\)
- 10%-16% of rheumatology practice patients\(^5\)


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**Identifying Fibromyalgia: ACR Classification Criteria**

- Chronic widespread musculoskeletal pain for ≥3 months
- Tenderness at ≥11 of 18 tender points
  - Detected by digital palpation of soft tissue with approximate force of 4 kg/cm\(^2\)
- Sensitive (88.4%) and specific (81.1%) tool to differentiate fibromyalgia from other rheumatologic conditions
- Criteria need further refinement as knowledge about fibromyalgia evolves


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**Location of the Tender Points**

- Arterial aspects of the C5, C7 intertransverse spaces
- Second rib space – about 3 cm lateral to the internal border
- Medial 1/3 part of trapezius proximal to joint line
- Insertion of muscular fascia into scapula
- Upper border of infraspinatus, mid-portion
- Muscle attachments to lateral sacroiliac joint
- Muscle attachments to upper medial border of scapula
- Upper outer quadrant of pectoral muscles

Practical use of examination:
- Confirms diagnostic impression
- Serves as proxy for pain sensitivity
- Provides comparison with joint tenderness


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**Fibromyalgia: Constellation of Symptoms**

- Widespread pain with tender points
- Cognitive dysfunction
- Sleep disturbance
- Anxiety
- Fatigue
- Numbness and tingling
- Weakness
- Irritability
- Widespread muscle tenderness
- Headache
- Irritable bowel/bladder

Dysmenorrhea

Multiple chemical sensitivity syndrome

Depression/ anxiety

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Recommended Diagnostic Workup for Fibromyalgia

- History of chronic, widespread pain for ≥3 months
- Absence of other conditions that may present with chronic widespread pain
- General physical exam, neurologic exam, selected laboratory testing (ESR, thyroid tests; avoid screening serologic tests)
- Confirm presence of tender points (Fibromyalgia may be present, even if <11 of 18)

**Darlene’s Story:** Diagnosis and Hope for Relief

Patient Education: Common Patient Questions

- What is wrong with me?
- Why do I hurt all over?
- Why am I so exhausted?
- How did I get this?
- How is it treated?
- When will it go away?
- Why do people not believe me?

Educating About Fibromyalgia: Increasing Patient Self-Efficacy

- Consider group consultation
  - Didactic talk with patient Q&A
  - More time-saving than one-on-one education
- Include core information
  - Explain pathophysiologic mechanisms (biopsychological model)
  - Dispel notion that absence of organic disease means symptoms are psychogenic
  - Describe prognosis and clinical course
  - Reassure that fibromyalgia is not a prodrome of another disease
  - Emphasize that this condition can get better, but requires hard work and self-management by the patient
  - Warn that media and Internet are often sources of misinformation

Management of Fibromyalgia
**Continuing the Stepwise Approach**

- Confirm diagnosis of fibromyalgia
- Identify important symptom domains and their severity (eg, pain, sleep disturbance, fatigue, and level of function)
- Evaluate for comorbid medical and psychiatric disorders (eg, sleep apnea, osteoarthritis, depressive or anxiety disorders)
- Assess psychosocial stressors, level of fitness, and barriers to treatment
- May require referral to a specialist for full evaluation
- Provide education about fibromyalgia
- Review treatment options
- Adjunctive cognitive-behavioral therapy for patients with prominent psychosocial stressors and/or difficulty coping and/or functioning
- As first-line approach for patients with moderate-to-severe pain, trial with evidence-based medications
- Encourage exercise according to fitness level


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**Question**

• Which of the following nonpharmacologic therapies has no evidence-based support for treatment of fibromyalgia?
  1. Exercise regimen
  2. Cognitive-behavioral therapy
  3. Acupuncture
  4. Hypnosis
  5. Tender (trigger)-point injections

**Nonpharmacologic Strategies: Evidence of Efficacy**

**Strong Evidence**
- **Exercise**
  - Physical and psychological benefits
  - May increase tender point pain pressure threshold and improve pain
- **Cognitive-behavioral therapy**
  - Improvement in pain, fatigue, mood, and physical function often sustained for months
- **Patient education/self-management**
  - Improves pain, sleep, fatigue, and quality of life
- **Combination (multidisciplinary therapy)**

**Moderate Evidence**
- **Strength training**
- **Acupuncture**
- **Hypnotherapy**
- **EMG biofeedback**
- **Balneotherapy (medicinal bathing)**

**Weak Evidence**
- **Chiropractic**
- **Manual and massage therapy**
- **Electrotherapy**
- **Ultrasound**

**No Evidence**
- **Tender-point injections**
- **Flexibility exercise**


**Myth 3:**

Fibromyalgia causes unavoidable, progressive physical deterioration

**Managing Deconditioning: Rationale for Aerobic Exercise**

- Physical activity can increase fibromyalgia pain, leading to sedentary lifestyle
- Downward spiral of deconditioning can make symptoms worse at rest or with minimal exertion


**Aerobic Exercise Guidelines**

• Maximize tolerance and long-term compliance
  - Avoid high-intensity aerobic exercise (high dropout rates)
• Begin 1-2 months after start of drug therapy
  - Low-impact exercise, just below patient’s total capacity
  - Gradually increase duration to goal of 30 minutes

Improvements After Aerobic Fitness Training

**Managing Psychological Distress:**
*Cognitive-Behavioral Therapy (CBT)*

- Helps patients understand that fibromyalgia is manageable and teaches adaptive skills, including:
  - Relaxation techniques
  - Goal setting
  - Problem solving
  - Self-reinforcement
  - Substituting maladaptive thoughts with positive thoughts

Managing Psychological Distress: Cognitive-Behavioral Therapy (CBT)

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Managing Other Symptom Domains

**Sleep disturbance**

- Assess for primary sleep disorder; discuss sleep hygiene
- Minimize nocturnal pain and other sources of distress
- Recommend exercise at appropriate time of day
- Medications: TCA, short-acting hypnotic, muscle relaxant

**Psychological distress**

- Mood-altering medications as appropriate
- Cognitive-behavioral therapy
- Psychiatric referral for selected patients

Question

- What type of drug therapy would you initially prescribe for a patient you’ve diagnosed with fibromyalgia?
  1. Antidepressant
  2. Antiepileptic
  3. NSAID
  4. Opioid analgesic
  5. Sedative-hypnotic

Myth 4:

*Fibromyalgia is best managed with NSAIDs for inflammation and opioid analgesics for pain*
Pharmacologic Approaches

**Class** | **Agents** | **Randomized Controlled Trials**
--- | --- | ---
Antidepressants | SSRIs | ✓
Antidepressants | Tricyclic antidepressants | ✓
Antidepressants | SNRIs* | ✓
Antiepileptic Drugs | Gabapentin | ✓
Antiepileptic Drugs | Pregabalin* | ✓
Analgesics | NSAIDs | ✓
Muscle Relaxants | Cyclobenzaprine | ✓
Muscle Relaxants | Tizanidine | ✓
Sedative/Hypnotics | Tramadol | ✓
Sedative/Hypnotics | Zolpidem | ✓
Sedative/Hypnotics | Zopiclone | ✓
Sedative/Hypnotics | Sodium oxybate | ✓

* The SNRI duloxetine and the AED pregabalin are the only FDA-approved agents for the treatment of fibromyalgia.

**NSAIDs in Fibromyalgia**

- Nonsteroidal anti-inflammatory drugs constitute the number-one class of agents used to treat fibromyalgia
- No evidence of effectiveness as monotherapy for fibromyalgia
  - May be modestly helpful combined with a tricyclic antidepressant
- “Since fibromyalgia is not an inflammatory disease, it is not surprising we have a lot of treatment failures”
- Chronic analgesic use can set up cycle of rebound headaches, complicating fibromyalgia management


**Opiates in Fibromyalgia**

- No adequate, randomized, controlled clinical trials
- Opioids may heighten pain sensitivity (opioid-induced hyperalgesia)
  - Neuroadaptive changes lead to enhanced nociceptive output and decreased analgesic efficacy
  - Tramadol (central-acting narcotic) has some opioid activity, combined with SNRI activity
    - May be efficacious, but is associated with nausea and dizziness
    - Better tolerated in fixed-dose combination with acetaminophen
- Risk of seizures in patients using antidepressants, antiepileptics, or other drugs that decrease seizure threshold
- Long-term addiction or abuse potential


**Antiepileptics (Alpha-2-Delta Ligands): Pregabalin and Gabapentin**

- Mechanism:
  - Bind to α2δ subunit of voltage-gated calcium channels
  - Reduce calcium influx and inhibit release of neurotransmitters (eg, glutamate, substance P)
- Indications:
  - Postherpetic neuralgia (both agents)
  - Adjunctive therapy for partial onset seizures (both agents)
  - Pain associated with diabetic peripheral neuropathy (pregabalin)
  - Fibromyalgia (pregabalin)

**Pregabalin: Improvement in Weekly Fibromyalgia Pain Scores**

- Pooled analysis of 2 similarly designed randomized clinical trials (N=1493)
- Monotherapy: 2 doses per day
- Statistically significant improvement with all pregabalin doses vs placebo began at Week 1 and was sustained through endpoint

* For fibromyalgia indication. FDA-approved maximum dose is 450 mg/d.

**Pregabalin: Adverse Events**

- Discontinuations:
  - Peripheral edema
  - Fatigue
  - Headache
  - Nausea
- Due to all-cause AEs among all pregabalin patients, dizziness (5.4%) and somnolence (4.1%) were the AEs most commonly led to discontinuation.
Antidepressants for Fibromyalgia: Which To Choose?

- Most studies using antidepressants as analgesics for fibromyalgia demonstrate effects on pain that are distinct from effects on mood.
- Tricyclic antidepressants:
  - Block reuptake of serotonin and/or norepinephrine
  - Low doses may effectively treat pain, poor sleep, fatigue.
  - Tolerability issues; initiate therapy at very low doses, then titrate slowly.
- Selective serotonin reuptake inhibitors:
  - Better side-effect profile than TCAs
  - Used at higher doses, the older, less-selective SSRIs are generally more efficacious than "highly selective" agents.
- Dual receptor inhibitors:
  - Inhibit both serotonin and norepinephrine
  - Unlike TCAs, generally no significant activity at other receptors; better tolerability.
  - May have better analgesic effect than pure serotonergic drugs.
- Two SNRIs have undergone multicenter trials in fibromyalgia: duloxetine (FDA-approved therapy) and milnacipran.


Duloxetine: Phase III Study

- Male and female patients (N=520)
- Primary end points:
  - Brief Pain Inventory (average pain severity)
  - Patient Global Impression of Improvement
- Significant responses (secondary measures):
  - FIQ total score (only at 3 months)
  - CGI-S
  - SF-36 mental component
  - Certain MFI subscales
- Safety/tolerability similar to other clinical trials

Effect of Duloxetine on Average Pain Score: 30% Improvement

- Duloxetine 60 mg/d
- Duloxetine 120 mg/d
- Placebo

% of Patients

0 10 20 30 40 50

3 Month 6 Month

*P<0.01 vs placebo
†P<0.01 vs placebo

Milnacipran for Treatment of Fibromyalgia: Phase III Trials

- Two trials (N=888 and N=1196)
- Milnacipran 100 or 200 mg
- Primary end points: composite analysis
  - Pain: 30% improvement recorded in electronic diary
  - Global status: improvement on 7-point PGIC scale
  - Function: SF-36 Health Survey, physical component summary
- Additional, secondary end points:
  - FIO total score
  - Fatigue
  - Cognition

Milnacipran for Treatment of Fibromyalgia: Phase III Trials

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Composite End Points

% of Patients

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Milnacipran Outcomes: Composite Responder (Syndrome)

- Milnacipran 100 mg/d
- Milnacipran 200 mg/d
- Placebo

% of Patients

0 10 20 30 40

3 Months 6 Months

*P<0.05 vs placebo
†P<0.01 vs placebo
Clauw DJ, et al. Presented at the 2007 Annual Meeting of the American Society of Regional Anesthesia and Pain Medicine, Boca Raton, FL.

**References:**
Milnacipran Outcomes: Composite Responder (Pain)

*P<0.05 vs placebo.
†P<0.001 vs placebo.

Milnacipran Phase III Extension Study: 1-Year Maintenance of Pain Relief

Lead-in study, 27 weeks (N=888); extension study, 28 weeks (N=449). Data represent continuing cohort of patients at each visit. VAS=24-hour recall of pain measured on 10-cm visual analog scale.

Milnacipran AEs: Pooled Data

AEs reported in ≥5% of patients, and at least twice the incidence of placebo.

Summary of Findings: Studies in Fibromyalgia

- TCAs display efficacy but are poorly tolerated
- SNRIs improve pain, other symptom domains, function, quality of life, and global well-being
  - Effect on pain independent of effect on mood
  - Duloxetine is FDA-approved for the treatment of fibromyalgia
  - Milnacipran NDA filing under FDA review
- Alpha-2-delta ligands show similar improvements and improve slow-wave sleep
  - Pregabalin is FDA-approved for the treatment of fibromyalgia
- Combination therapy may be an option for patients with:
  - Incomplete response to single agent
  - Poor tolerance to higher doses

Summary: Practice Points

- Fibromyalgia is a common pain syndrome characterized by:
  - Widespread pain in peripheral tissues
  - Psychological distress
  - Central sensitization
- Pain component is consequence of disordered neurophysiology
  - Patients perceive more pain from nonpainful stimuli than do healthy controls and experience greater pain from painful stimuli
- Rationale for treatment involves 3 important strategies:
  - Reduction of peripheral nociceptive input
  - Improvement or prevention of central sensitization
  - Treatment of pain-related negative affect
Summary: Practice Points (Cont’d)

- Nonpharmacologic therapy includes:
  - Aerobic exercise
  - Improved sleep
  - Cognitive behavioral therapy

- Pharmacologic therapy includes neuromodulatory agents:
  - TCAs, NREs, dual reuptake inhibitors (SNRIs seem particularly efficacious for FM pain)
  - Anti-epileptic medications (eg, pregabalin)

- For optimal disease management, treatment should be customized to address the symptom domains of each patient: pain, global sense of well being, and physical function