FIBROMYALGIA

Disease Overview
Diagnosis
Management

Morris Papernik, MD, CCD, FACP
Assist. Clinical Prof. of Medicine
Uconn
Asst. Clinical Prof. of Medicine
Yale University
Assist. Clinical Prof. of Medicine
Quinnipiac University
Attending Physician, Hartford Hospital
'Oh terribly bad!' said the princess. 'I have hardly closed my eyes the whole night! Heaven knows what was in the bed. I seemed to be lying upon some hard thing, and my whole body is black and blue this morning. It is terrible!'
HISTORY

- 17th century descriptions of “muscular rheumatism”
- 1904 ‘fibrositis’ by Gower to describe lumbago
- 1960’s description of discrete illness involving diffuse pain, fatigue, poor sleep
- 1965 C.K. Meador “Art & Science of Nondisease”
  - NEJM. Disease is suspected but not found.
- 1975 Moldofsky described sleep EEG
- 1981 first controlled study of FMS by Yunus
- 1990 name changed to FMS
- 2010 Wolfe re-defines the FMS criteria
NOMENCLATURE

- NON ARTICULAR RHEUMATISM
- PSYCHOGENIC RHEUMATISM
- MYOFASCIITIS
- TENSION MYALGIA
- FIBROMYOSITS
- FIBROSITIS
- FIBROMYALGIA
- NEUROPATHIC PAIN SYNDROME
- PAIN AMPLIFICATION SYNDROME
Non-Diseases

- C K Meador, Rt of Non Diseases. NEJM; 1965

- When a specific disease is suspected but not found, that patient has a particular Non-Disease.
  - FMS, Migraine, Depression, CFS, Mono, IBS
FM Epidemiology and Risk Factors

- Prevalence of FM in United States is estimated to be 2% to 5% of the adult population\(^1,2\)
  - FM is often underdiagnosed/misdiagnosed\(^3\)
  - Diagnosis takes an average of 5 years\(^4\)
- Most common in individuals aged 25 to 60 years\(^5\)
- Risk factors include:
  - Genetic: increased incidence among first-degree relatives, associated with genetic markers\(^6,7\)
  - Environmental: physical trauma, infections (Lyme, EBV, Hep-C, Parvo), social stressors\(^8\)
  - Gender: more common in women (2-9)\(^1,5,9\)

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FM Is Characterized by Chronic Widespread Pain and Tenderness

- American College of Rheumatology (ACR) criteria for the classification of FM include:
  - Chronic widespread pain (core feature) for ≥3 months
    - Pain above and below the waist
    - Pain on left and right sides of body
    - Pain in the axial skeleton
  - Pain at ≥11 of 18 tender points when palpated with 4 kg/cm² of digital pressure
- Other proposed FM criteria, intended to complement ACR classification criteria, are in development

Diagram Showing 18 Tender Points

The ACR criteria are:
- Sensitive (88.4%) – proportion of patients correctly identified as having the condition
- Specific (81.1%) – proportion of patients correctly identified as not having the condition

3. Wolfe F et al. Arthritis Care Res. Accepted for publication.
The Clinical Challenge: Patient Cycling Contributes to Underdiagnosis

Obstacles to Earlier Diagnosis

- No definitive laboratory tests for diagnosis
- FM not suspected early in “cycling” process
- Multiple symptoms
- Confounding comorbidities
- Symptom descriptions do not always facilitate diagnosis

~5 million individuals with FM symptoms

94% present to HCP

In a practice with 30 patients/day, 1-3 may have FM symptoms

Overall diagnosis rate is low

Dx with comorbid condition

Refer or switch HCP

Cycling (average of 5 years)

Tx but then re-present

Switch/add Tx; switch/add Dx

HCP=health care provider.

Fibromyalgia is associated with functional disability.

Fibromyalgia patients frequently need help or have much difficulty with specific physical activities.*

N=2580

Chronic Pain and FM: Summary

- FM is a distinct chronic pain disorder characterized by widespread pain and tenderness\(^1\)
- In the United States, FM affects 2% to 5% of adults\(^2,3\)
- FM is challenging to diagnose; rate of diagnosis is low\(^4\)
- Diagnosis takes an average of 5 years\(^5\)

Fibromyalgia (FM) Is a Chronic Pain Condition and Is Distinct from Other Types of Pain\(^1\)

Pain is the most common reason for physician visits\(^2\)

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**Nociceptive Pain**

- Painful Stimuli
  - (eg, burns, cuts)

**Neuropathic Pain**

- Neuronal Damage
  - (eg, herpes zoster, pDPN)

**Inflammatory Pain**

- Inflammation
  - (eg, rheumatoid arthritis, psoriatic arthritis)

**Central Pain Amplification**

- Abnormal Pain Processing by CNS
  - (eg, FM)

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\(pDPN=\text{painful diabetic peripheral neuropathy.}\)

Pain Processing

- Pro-nociceptive pathway
- Anti-nociceptive pathway
Pain Processing

- **PRO-NOCICEPTIVE**
  - Stimulus sensed by the peripheral nerve
  - Extracellular Calcium diffuse into neurons causing the release of Pain Associated Neurotransmitters
    - Glutamate
    - Substance P
  - Impulses from afferents depolarize dorsal horn neurons via the NMDA receptors.
  - Signal then crosses contra laterally to carry the impulse cephalically via the ascending tract to the brain through the thalamus and finally the cortex.
FMS Pain Processing

- **Allodynia** resulting from CSS (Central Sensitization Syndrome)
  - Temporal Summation of painful stimuli (Wind Up)
  - Once there is CSS, glial cells are activated and cause hyperalgesia.
  - Glial cells release inflammatory cytokines (TNF, IL-6, NO, PGE,) which then further increase Dorsal Horn Excitability
  - Increase in Pro-Inflammatory products at trigger point sites. (High level of Mast Cells in dermis= increase in histamine and, potentially, the trigger for the pain augmentation.)
Pain Modulation

- **ANTI-NOCICEPTIVE**
- At the same time, the descending tract carries the impulses back down to the dorsal horn passing through the PAG (Periaqueductal Gray Matter).
- This pathway modifies or modulates the Pro-Nociceptive pathway
- Serotonin, NE
Allodynia

- There needs to be a balance between pro and anti-nociception to maintain normal perception of sensation.
- Chronic Overwhelming of anti-nociception by pro-nociception or, a lack of anti-nociception creates Allodynia.
- Overwhelming of pro-nociception by anti-nociception or the lack of pro-nociception produces no sensation.
- The FMS patient has both an increase in Pro-nociception and a decrease in Anti-nociceptive activity.
FM: An Amplified Pain Response

Subjective Pain Intensity vs. Stimulus Intensity

- **Pain in FM**
- **Hyperalgesia**: (eg, when a pinprick causes an intense stabbing sensation)
- **Allodynia**: (eg, hugs that feel painful)
- **Pain amplification response**
- **Normal Pain Response**

Normal Pain Pathways

Key:
RVM = rostroventral medulla
PAG = periaqueductal grey
C = cingulate cortex
F = frontal cortex
SS = somatosensory cortex
A = amygdala
H = hypothalamus

Ascending pathway
Descending pathway
Central Amplification: Leading Theory for Abnormal Pain Processing in FM

Perceived pain

Ascending input

Descending modulation

Nociceptive afferent fiber

Pain stimuli

Perceived pain (hyperalgesia/allodynia)

Increased release of glutamate and substance P

Pain amplification

Decreased release of norepinephrine and serotonin

Induction of central amplification leading to abnormal pain processing

Minimal stimuli

Elevated Substance P and Glutamate Are Found in CSF of FM Patients

Pain Neurotransmitter Levels

**Substance P**

<table>
<thead>
<tr>
<th></th>
<th>FM Patient (n=32)</th>
<th>Control (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration, fmoles/mL</td>
<td>42.8</td>
<td>16.3</td>
</tr>
<tr>
<td>P</td>
<td>P&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Glutamate

<table>
<thead>
<tr>
<th></th>
<th>FM Patient (n=20)</th>
<th>Control (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration, µg/mL</td>
<td>2.36</td>
<td>1.37</td>
</tr>
<tr>
<td>P</td>
<td>P&lt;.003</td>
<td></td>
</tr>
</tbody>
</table>

* CSF (cerebrospinal fluid) sample collected via lumbar puncture in FM and healthy controls and substance P levels assessed by radioimmunoassay.
† fmoles/mL = femtomole/mL = 10-15 mole/mL.

### Pro & Anti-Nociceptive Activity in FMS

<table>
<thead>
<tr>
<th>Pro-Nociceptive</th>
<th>Anti-Nociceptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subst. P</td>
<td>NE</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Dopamine</td>
</tr>
<tr>
<td>5HT 2a &amp; 3a</td>
<td>5HT 1a,b</td>
</tr>
<tr>
<td>NGF</td>
<td>GABA</td>
</tr>
<tr>
<td></td>
<td>Opioids</td>
</tr>
<tr>
<td></td>
<td>Adenosine</td>
</tr>
<tr>
<td></td>
<td>Cannabinoids</td>
</tr>
</tbody>
</table>
IMAGING
Medical Imaging

- fMRI
- ASL (arterial spin labeling)
- VBM (voxel based morphometry)
- DTI (diffusion tensor imaging)
fMRI

- Brain activation occurs in similar areas and with similar magnitude in FMS as normal controls, but at a lower threshold of pain
Evidence of Altered Pain Processing in Fibromyalgia: Neuroimaging Findings

STG = superior temporal gyri; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; arrows indicate changes in fMRI signal.

ASL (arterial spin labeling)

- rCBF by using magnetized blood as the contrast (decreased in FMS, pain and depression)

VBM (Voxel Based Morphometry)

- Measures differences in regional concentrations of brain tissue
- Decrease in gray matter found in patients with FMS, Chronic Pain and Stress Disorders
Pain = Neurodegenerative Disease?

- Via VBM studies:
  - Apkarian, A. 2004 J Neuroscience
    - Decreased gray matter in dorso-lateral PFC & thalamus
    - Related to length of pain
  - FMS have a 3.3x greater age associated decrease in gray matter volume compared to healthy controls.
  - Each year of FMS was equal to 9.5x the loss of gray matter observed in normal aging.
  - Resulting in impaired cognitive functioning and pain inhibition
  - Seen also in HA, IBS, FM, PTSD
- Is there value in testing FM patients earlier to prevent these gray matter changes?

DTI (diffusion tensor imaging)

- Quantifies micro-structural changes based on water mobility in brain tissue.
- Altered brain micro-circuitry are correlated with FMS symptom severity.

Thixotropy

- Increase in non-elastic connective tissue
  - Increases in FM patients and with age
- Results in ‘Stiffness’ in muscles and joints
- Stiffness increases with rest
- Stiffness decreases with movement
  - Vigorous exercise increases Thixotropy

Pathophysiology of FM: Summary

- Central amplification is a leading theory of FM pathophysiology\(^1\)
- fMRI data support FM as a disorder of central pain amplification\(^2\)
  - Areas activated by high-intensity stimuli in control patients were activated by low-intensity stimuli in patients with FM
- Elevated pain neurotransmitters (eg, substance P, glutamate) seen in patients with FM\(^3-5\)
  - May contribute to pain amplification

Consider FM in patients with chronic conditions who also suffer from chronic widespread pain, fatigue, and sleep disturbance.
Sleep Disruption

- Poor sleep causes decrease in energy, alertness, mood and cognition.
- Decrease anti-nociceptive pathway
- Moldofsky, 1975: alpha wave intrusion
- 4 hours of sleep vs 8 hours of sleep over 12 consecutive nights produce a 15% reduction in psychosocial behavior and a 3% increase in generalized pain. (Roehrs, T. Sleep, 2006)
- Predisposes individuals to CSS by interfering with the descending pathway and increasing sensitivity to non-painful stimuli (light, sounds, odors)
Sleep Architecture

- Sleep architecture disturbances characterized by:
  - Alpha wave intrusion on Delta Wave sleep
  - Prolonged sleep latency
  - Reduced sleep efficiency
  - Reduced slow wave sleep and REM sleep due to Alpha wave intrusion
  - Increased motor activity and restlessness during sleep (PLMs, RLS, OSA)

- Degree of disturbance correlates to severity of the FMS.

- Resultant:
  - Decrease growth hormone production
  - Negative effect on the HPA axis
  - Decreased 5HT synthesis
  - Increased substance P

- Repair of sleep architecture does not always result in decreased pain
Cognition

- Mimics older patients
- ? Premature aging?
- Also seen in chronic pain syndromes
- ? Increase in oxidative stress
- Increase in NGF in CSF of FMS patients
  - NGF is a trophic factor and increases in response to tissue damage
  - Elevated NGF in CSF of FMS patients may represent an attempt to repair brain tissue stimulated by the oxidative stress
- NGF: ↑ Subst. P: ↓ pain threshold
  - Interferes with sleep via NK receptors
  - Decreases cortisol level
  - Contributes to depression
Etiology

- **Infectious**
  - Viral (lyme, HIV)

- **Genetic**
  - 30% of FM patients have close relative with FM
  - Polymorphism in COMT (catecholamine o-methyl transferase) responsible for inactivating biogenic amines of descending pain inhibition (less NE, 5-HT)

- **Environmental**
  - Learned behavior

- **Psychological overlay**
  - Pain/stress during childhood

- **Auto-immune**
  - No data for this
Risk Factors for Fibromyalgia: The Role of Stress

- Patients experience stressful life events
  - More stressful, negative lifetime events than healthy controls
  - Significantly higher prevalence of all forms of childhood and adult victimization and trauma than patients with rheumatoid arthritis

Graph showing negative life events in fibromyalgia patients:
- Females with fibromyalgia (n=40)
- Controls (n=38)

Time of experience:
- Childhood or adolescence
- During the past year
- Prior to onset

Important Safety Information, including Boxed Warning, and full Prescribing Information provided at this presentation.

Clinical Presentation of FM

- Chronic widespread pain and tenderness are the defining features of FM\textsuperscript{1-3}
- FM is often accompanied by sleep disturbance and fatigue\textsuperscript{2}
- Patients with FM may also present with other co-morbid symptoms or conditions, including\textsuperscript{1,3,4}:
  - IBS
  - Cognitive dysfunction
  - Numbness or tingling
  - Mood disorders
  - Morning stiffness
  - Headaches/migraines

IBS, irritable bowel syndrome.

Telltales Descriptions of FM: Listening to Patients

Common descriptions of FM symptoms from patients\(^1,2\)

“I feel like I always have the flu.”

“I hurt all over.”

“No matter how much sleep I’ve had, I always feel like a truck ran me over when I wake up.”

“I’m always tired and run-down.”

Importance of “Seeing” the Whole Patient When Diagnosing FM

- Specialists often diagnose from the viewpoint of their training
- PCPs have the opportunity to look at the whole patient

The neurologist sees chronic headache
The gastroenterologist sees IBS
The otolaryngologist sees TMJ syndrome
The cardiologist sees noncardiac chest pain
The rheumatologist sees FM
The gynecologist sees PMS
The psychiatrist sees depression
The neurologist sees chronic headache

### Clinical Features of FM Pain

| Location                  | Pain in all 4 quadrants of the body, including:  
|                          | - Pain above and below the waist, on the left and right sides of the body, and in the axial skeleton |
| Duration                 | Chronic, lasting at least 3 months¹ |
| Quality                  | Allodynia: pain experienced from non-painful stimuli ²  
|                          | - eg, hugs, handshakes |
|                          | Hyperalgesia: an amplified response to painful stimuli ²  
|                          | - eg, pinprick, stubbed toe |
|                          | Patient descriptors of pain ³,⁴  
|                          | - “Flu-like,” “dull,” “aching” |
| Pain/Tenderness Measures | Manual Tender Point Survey (MTPS) exam ⁵  
|                          | Visual analog scale (VAS), numeric rating scale (NRS), pain diagram ²,³,⁶ |
| Other                    | Pain worsens with overactivity, stress, life events ²,³ |

Diagnosing FM: ACR Classification Criteria

According to ACR criteria, FM can be diagnosed if patient has:

1. Widespread pain for $\geq 3$ months in all 4 quadrants of body\(^1\)
   - Widespread pain is defined as:
     - Pain above and below the waist
     - Pain on the left and right sides of the body
     - Pain in the axial skeleton

2. Pain on palpation in $\geq 11$ of 18 tender points\(^1\)
   - MTPS provides standardized approach to tender point

The ACR criteria are\(^1\):

- Sensitive (88.4%) – proportion of patients correctly identified as having the condition
- Specific (81.1%) – proportion of patients correctly identified as not having the condition

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Identifying Widespread Pain in Possible FM Patients

Pain drawings can help identify widespread pain in possible FM patients.

Pain severity can be evaluated using assessment scales\(^2,3\).

**Visual Analog Scale (VAS)\(^2\)**

No pain  

Very severe pain

*Actual scale should be 10 mm in length.

**Numeric Rating Scale (NRS)\(^3\)**

No pain  

Most pain

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3. Precise Identification of Survey Sites

Control points 1, 16, and 17 are used to establish the patient’s baseline pain perception and do not count toward the total number of painful tender points.

New Tool for FMS Dx.

- CWSP index (0-19)
  - Self reported number of painful body sites
- Symptom severity score (0-12)
  - Fatigue (0-3)
  - Unrefreshed sleep (0-3)
  - Cognitive Dysfunction (0-3)
  - Somatic Symptoms (0-3)
- FMS present when:
  - CWSP index is 7 and Sx severity is 5 or more
  - CWSP index is 3-6 and Sx severity is 9 or more
- Exam not necessary
- Acknowledges multiple clinical domains
- Compliments the 1990 criteria

Wolfe, F. ACR 2009 Annual Scientific Meeting, Abstract 567. Arthritis Care & Rheum. Publication TBA.
Initial Evaluation

- Good History
- Good Physical
  - Att: trigger points
- X-Rays of joints
  - concomitant disease may co-exist
- Sleep Study

- Laboratory
  - ESR
  - TFT
  - ANA
  - RF
  - Ferritin
Causes of Muscle Pain

- Hypothyroidism
- Hyperthyroidism
- Menopause
- Testosterone deficiency (male menopause)
- Cushing’s
- Addison’s
- Parathyroid disease
- Autoimmune diseases
- PMR
- MS
- IC
- Tension
- Spasm
Conducting the Manual Tender Point Survey (MTPS)
Clinical Instructions
MTPS Exam Based on ACR Criteria for the Classification of FM

- The MTPS provides a standardized approach to assess tenderness per the ACR criteria\(^1,\,^2\)
- The MTPS involves 3 primary elements\(^1\)
  1. A specific pressure application technique
  2. A uniform procedure with specific patient instructions
  3. The precise identification of survey sites
- With practice, performing the MTPS should take approximately 5 minutes or less

1. Specific Pressure Application

- How to apply pressure
  - Locate each survey site visually and then with light palpation
  - Use the thumb pad of the dominant hand to apply 4 kg (8.8 lb) of pressure in a perpendicular direction
  - Gradually increase thumb pressure by 1 kg (2.2 lb) per second until you reach a pressure of 4 kg/cm², or enough to whiten the thumbnail
  - Each site should be pressed only once for a total of 4 seconds
- Note that some patients may not be able to tolerate the full force

1. Specific Pressure Application (cont.)

- Using a standard office scale
  - Set the scale to the weight of the practice subject
  - Add 4 kg (8.8 lb)
  - Apply perpendicular pressure to bring the scale back into balance

- Using a floor scale
  - Press on scale with thumb until it reads 4 kg (8.8 lb)

- Become familiar with how to apply 4 kgs of pressure

Learning the Feel of 4 kg

Control points 1, 16, and 17 are used to establish the patient’s baseline pain perception and do not count toward the total number of painful tender points.
MTPS Scoring Sheet for Clinicians

Assessing the presence of widespread pain

Directions for physicians: Present the following figures to your patients. Ask them to fill in the areas where they have felt pain for 3 months or longer.

Directions for patient: On the figures below, color in all areas where you have experienced pain for 3 months or longer.

Performing the Manual Tender Point Survey

Scoring sheet

Instructions for patient

Give the patient the following instructions:

"Various areas of your body will be examined for pain. Please say "yes" or "no" to indicate whether there is any pain when I press a specific point."

If a patient responds, "yes" to indicate a site is painful, the examiner should assess the patient’s perception of the pain severity by asking her/him to rate the pain on a 0 to 10 scale.

In addition, explain the pain rating scale to the patient:

"I want you to rate the intensity of the pain on a scale from 0 to 10, where 0 is no pain and 10 is the worst pain that you have ever experienced."

Directions: After palpating each tender point, ask the patient to assess the amount of pain on a scale of 0 to 10 (0=no pain; 10=worst pain). Record the patient’s response below.

<table>
<thead>
<tr>
<th>Seated position</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-forehead (control point)</td>
<td>1,____</td>
<td>2,____</td>
</tr>
<tr>
<td>Occiput: Suboccipital muscle insertions</td>
<td>3,____</td>
<td>4,____</td>
</tr>
<tr>
<td>Trapezius: Midpoint of upper border</td>
<td>5,____</td>
<td>6,____</td>
</tr>
<tr>
<td>Supraspinatus: Above medial border of scapular spine</td>
<td>7,____</td>
<td>8,____</td>
</tr>
<tr>
<td>Gluteal: Upper outer quadrant of buttocks</td>
<td>9,____</td>
<td>10,____</td>
</tr>
<tr>
<td>Low cervical: Anterior aspect of intertransverse space of C5-7</td>
<td>11,____</td>
<td>12,____</td>
</tr>
<tr>
<td>Second rib: Second costochondral junction</td>
<td>13,____</td>
<td>14,____</td>
</tr>
<tr>
<td>Lateral epicondyle: 2 cm distal to epicondyle</td>
<td>15,____</td>
<td>16,____</td>
</tr>
<tr>
<td>Right forearm (control point): junction of proximal ⅔ &amp; distal ⅓</td>
<td>17,____</td>
<td></td>
</tr>
<tr>
<td>Left thumb (control point)</td>
<td>17,____</td>
<td></td>
</tr>
<tr>
<td>Side position</td>
<td>17,____</td>
<td></td>
</tr>
<tr>
<td>Greater trochanter: Posterior to trochanteric prominence</td>
<td>18,____</td>
<td>19,____</td>
</tr>
<tr>
<td>Supine position</td>
<td>20,____</td>
<td>21,____</td>
</tr>
<tr>
<td>Knee: Medial fat pad proximal to the joint line</td>
<td>21,____</td>
<td></td>
</tr>
</tbody>
</table>

Number of positive tender points (those with a score of 2 or greater)

Note that tender points 1, 16 and 17 are control points and do not count toward the total number of positive tender points.
Fibromyalgia Identification and Diagnosis: Summary

- FM is one of the most common chronic widespread pain conditions¹

- ACR criteria for the classification of FM²:
  - History of widespread pain for ≥3 months; pain in all 4 quadrants and axial skeleton, ≥11 of 18 tender points

- The MTPS is a standardized procedure that enhances diagnostic reliability³

- Central amplification is a leading theory to explain FM⁴:
  - Associated with hyperalgesia, allodynia, and excessive release of pain neurotransmitters (eg, glutamate, substance P)⁴,⁵

- FM is commonly seen with other chronic pain-related conditions⁶

  FM diagnosis is the first step toward good management of FM.

Management of Fibromyalgia (FM)

**Nonpharmacologic**
- Aerobic exercise
- Cognitive behavioral therapy
- Patient education
- Strength training/PT
- Acupuncture
- Biofeedback
- Balneotherapy

**Pharmacologic**
- Antidepressants
- Analgesics
- Anticonvulsants
- Trigger Point Injections

*Until now there were no FDA-approved therapies for FM*

Nonpharmacologic Therapies*

- **Patient education**
  - Intensive patient education in FM has been shown to improve pain, sleep, fatigue, and quality of life in patients with FM

- **Aerobic exercise**
  - Exercise may increase aerobic performance and tender point pain pressure threshold, and improve pain

- **Cognitive behavioral therapy (CBT)**
  - Some evidence of improvements in pain, fatigue, mood, and physical function

*Only nonpharmacologic therapies with strong evidence are noted. 
# Commonly Prescribed Medications for Fibromyalgia

<table>
<thead>
<tr>
<th>Medication*</th>
<th>Experience in Fibromyalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs/COX-2s</td>
<td>No agents FDA approved for FM; Studies fail to confirm efficacy¹</td>
</tr>
<tr>
<td>TCAs</td>
<td>No agents FDA approved for FM; Short-term studies demonstrate some efficacy, but safety and tolerability concerns limit use²</td>
</tr>
<tr>
<td>Opioids</td>
<td>No agents FDA approved for FM; No demonstrated efficacy²; potential for abuse¹</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>No agents FDA approved for FM; Limited systematic studies of efficacy¹</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Not FDA approved for FM; May be somewhat efficacious²-⁴</td>
</tr>
<tr>
<td>SSRIs</td>
<td>No agents FDA approved for FM; Studies demonstrate mixed results in FM¹</td>
</tr>
<tr>
<td>Anticonvulsants/antiepileptics</td>
<td>Lyrica®: FDA approved for the management of FM⁵; One study demonstrates efficacy of gabapentin in FM⁶</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Cymbalta®: FDA approved for the management of FM⁷; Studies fail to establish efficacy of venlafaxine and desvenlafaxine in FM²,⁸</td>
</tr>
</tbody>
</table>

*The only FDA-approved medications for FM are Lyrica®, Cymbalta®, and Savella™

*With the exceptions of Savella™, Lyrica®, and Cymbalta®, these drugs do not have an indication for FM, but are often used off-label. Forest does not endorse the off-label use of these products to treat FM. NSAIDs = nonsteroidal anti-inflammatory drugs; COX-2s = cyclooxygenase-2 inhibitors; FM = fibromyalgia; FDA = Food and Drug Administration; TCAs = tricyclic antidepressants; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors.

# Approved Medications for Fibromyalgia: Pivotal Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>No. Patients</th>
<th>Primary Efficacy Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duloxetine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arnold et al(^1,2)</td>
<td>3-month, randomized, double-blind, placebo-controlled, fixed-dose study in female patients with FM</td>
<td>354</td>
<td>BPI average pain severity</td>
</tr>
<tr>
<td>Russell et al(^1,3)</td>
<td>6-month, randomized, double-blind, placebo-controlled, fixed-dose study</td>
<td>520</td>
<td>BPI average pain severity and PGI-I</td>
</tr>
<tr>
<td><strong>Milnacipran</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mease et al(^4)</td>
<td>6-month, double-blind, placebo-controlled, multicenter study</td>
<td>888</td>
<td>3-measure and 2-measure composite responders</td>
</tr>
<tr>
<td>Clauw et al(^5)</td>
<td>3-month, double-blind, placebo-controlled, multicenter study</td>
<td>1196</td>
<td>3-measure and 2-measure composite responders</td>
</tr>
<tr>
<td><strong>Pregabalin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arnold et al(^6,7)</td>
<td>14-week, double-blind, placebo-controlled, multicenter study</td>
<td>745</td>
<td>Pain reduction (VAS), PGIC, FIQ</td>
</tr>
<tr>
<td>Crofford et al(^6,8)</td>
<td>6-month, randomized withdrawal study</td>
<td>566</td>
<td>Time to loss of therapeutic response</td>
</tr>
</tbody>
</table>

BPI = Brief Pain Inventory. PGI-I = Patient Global Impression of Improvement.

## Analgesics*: Published Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>N</th>
<th>Study Duration (weeks)</th>
<th>Primary End Point</th>
<th>Significant Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett et al (2005)</td>
<td>Tramadol/acetaminophen vs PBO</td>
<td>313</td>
<td>13</td>
<td>SF-36, FIQ</td>
<td>Yes</td>
</tr>
<tr>
<td>Bennett et al (2003)</td>
<td>Tramadol/acetaminophen vs PBO</td>
<td>315</td>
<td>13</td>
<td>Time to discontinuation</td>
<td>Yes</td>
</tr>
<tr>
<td>Kemple et al (2003)</td>
<td>Opioid†</td>
<td>38</td>
<td>200</td>
<td>Improvement in pain</td>
<td>No</td>
</tr>
<tr>
<td>Russell et al (2000)</td>
<td>Tramadol vs PBO</td>
<td>100</td>
<td>9</td>
<td>Time to discontinuation</td>
<td>Yes</td>
</tr>
<tr>
<td>Biasi et al† (1998)</td>
<td>Tramadol vs PBO</td>
<td>12</td>
<td>1</td>
<td>VAS</td>
<td>Yes</td>
</tr>
<tr>
<td>Sorensen et al ‡ (1995)</td>
<td>Morphine (IV) vs PBO</td>
<td>9</td>
<td>1</td>
<td>Reduction in pain intensity</td>
<td>No</td>
</tr>
</tbody>
</table>

*No analgesic is currently FDA approved for FM.

† Doses of morphine equivalent per 24 hour were determined; ‡ Single-dose cross-over trial with 1 week washout period.

SF-36 = short-form 36; IV = intravenous; VAS = visual analog score.

### Anticonvulsants*: Published Trials†

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>N</th>
<th>Study Duration (weeks)</th>
<th>Primary End Point</th>
<th>Significant Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold et al (2007)</td>
<td>Pregabalin vs PBO</td>
<td>750</td>
<td>14</td>
<td>End point mean pain score</td>
<td>Yes</td>
</tr>
<tr>
<td>Crofford et al†‡(2007)</td>
<td>Pregabalin vs PBO</td>
<td>1051</td>
<td>32</td>
<td>Time to loss of therapeutic response</td>
<td>Yes</td>
</tr>
<tr>
<td>Arnold et al (2007)</td>
<td>Gabapentin vs PBO</td>
<td>150</td>
<td>12</td>
<td>BPI average pain severity</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Gabapentin is currently not FDA approved for FM.

†Published either in peer-reviewed journals or studies included in the Lyrica® package insert.

Includes open-label phase of trial.

Polypharmacy Is the Norm

~70% of fibromyalgia patients fill ≥2 relevant prescription drugs in a 3-month period

The only FDA-approved medications for FM are Lyrica®, Cymbalta®, and Savella™

Data on file, Forest Laboratories, Inc. SDI Longitudinal Patient Data, Ad hoc on patients with a diagnosis visit in May 2008 and related market drugs filled June to August 2008, n=8,344. Agent defined at the NDC code level of drug by form and strength.
Fibromyalgia and Polypharmacy

Patients with FM receive significantly more pain-related medications than non-fibromyalgia patients (P<0.001)

Impact of Fibromyalgia on Health Claims

Health claims per patient in 1998 by selected specialty provider

- Random 10% of employee population
- Fibromyalgia cohort (n=4,268)

- General Practice includes: General Practitioner, IM, and Ped.

Important Safety Information, including Boxed Warning, and full Prescribing Information provided at this presentation.

Summary

- FM is one of the most common CWSP conditions
- ACR criteria for Dx is sensitive and specific
- CSS/pain amplification is the leading theory to explain FM
- FM is seen with other pain conditions
- Getting the diagnosis right is essential
- Treatment needs to be individualized
PCP’s Role

- Understand that the illness exists and that it is evidence based

- Have empathy for these patients and be non-judgemental

- Understand that these patients will be treated with PolyPharmacy; using the medications together to augment the efficacy of each-other.


23. Crofford LJ, Clauw DJ. Fibromyalgia: where are we a decade after the American College of Rheumatology classification criteria were developed? *Arthritis Rheum*. 2002;46:1136-1138.


Bibliography (cont.)


