Fibromyalgia
Primary vs Speciality Care

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Fibromyalgia Questions

• Is fibromyalgia a real problem?
  - Yes - Not a disease - central amplification

• What is the pathophysiology?
  - Pain generators, spinal cord, central processing

• What causes fibromyalgia?
  - Multifactorial - genetics, rheum diseases, sleep, emotions

• How is fibromyalgia best treated?
  - What & by whom - PCP vs spec. - conditioning, sleep, meds
There are over 100 named musculoskeletal disorders.

**Pain** is the most common musculoskeletal symptom.
Arthritis Vital Statistics

Prevalence of various types of arthritis

Low back pain – 59 million
Neck pain – 30.1 million
Osteoarthritis – 27 million
Fibromyalgia – 5 million
Gout – 3 million
Spondyloarthropathy – 0.6 - 2.4 million
Rheumatoid arthritis – 1.3 million
SLE – 161,000 - 322,000
Juvenile arthritis - 294,000
Systemic sclerosis - 49,000
Pain:

- Opposite of pleasure - philosophical
- Punishment for wrongdoing - moral
- Suffering - psychological
- Warning system to protect the body - pathophysiologic
Pain is a subjective sensation that cannot be attributed only to the incoming nociceptive information. Indeed, pain is modulated by a variety of cognitive and emotional factors as well as by a number of sensory inputs.
Acute Pain:
Associated with acute disease or traumatic injury and subsides as healing occurs.
e.g. low back pain, gout
Chronic Pain

- Persisting after healing is complete.
- Associated with an ongoing disease process. (e.g. OA, RA).
- Begins with an uncertain precipitating event or organic cause. (e.g. FM).
Complexities of Pain

- Reliance on the patient’s perception and description
- Individual variability of pain
- Role of psychological and social factors
“The following is a test of the fire-alarm system. It is only a test. Please ignore the intense heat and combustion.”
Fibromyalgia (FM) Is a Chronic Pain Condition and Is Distinct from Other Types of Pain

Pain is the most common reason for physician visits.

- **Nociceptive Pain**: (eg, burns, cuts)
- **Neuropathic Pain**: (eg, herpes zoster, DPN)
- **Inflammatory Pain**: (eg, rheumatoid arthritis, psoriatic arthritis)
- **Central Pain Amplification**: (eg, FM)

pDPN = painful diabetic peripheral neuropathy

Pain Sensitivity in the General Population

- We all have a "volume control" setting for how our brain and spinal cord processes pain.
- This is likely set by genetic influences and modified by environmental influences.
- The higher the volume control setting, the more pain we will experience, irrespective of nociceptive input.

Figure 1. Bell curve illustrating the distribution of pain tenderness in the general population.
Figure 2 Annual scientific publications on fibrositis or fibromyalgia as identified in PubMed

Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2013.96
Fibromyalgia:

1. **Widespread** musculoskeletal pain present for at least 3 months.

2. Pain in 11 of 18 **tender point** sites with digital palpation.

Somatic symptomatology—autonomic nervous system
FM Epidemiology and Risk Factors

- Prevalence of FM in United States is estimated to be 2% to 5% of the adult population
- FM is often underdiagnosed/misdiagnosed
  - Diagnosis takes an average of 5 years
- Most common in individuals aged 25 to 60 years
- Risk factors include:
  - Genetic: increased incidence among first-degree relatives, associated with genetic markers
  - Environmental: physical trauma, infections, social stressors
  - Gender: more common in women- 70-80%
“Central” Pain Prone Phenotype

- Female
- Genetics
- Early life trauma
- Family history of chronic pain and mood disturbances
- Personal history of chronic centrally-mediated symptoms (multifocal pain with neuropathic descriptors, fatigue, sleep disturbances, psychological distress, memory difficulties)
- Cognitions such as catastrophizing
- Lower mechanical pain threshold and descending analgesic activity

Exposure to “stressors” or acute, peripheral nociceptive input

Psychological and behavioral response to pain or stressor

New or different region of chronic pain
THE AMERICAN COLLEGE OF RHEUMATOLOGY 1990 CRITERIA FOR THE CLASSIFICATION OF FIBROMYALGIA

Report of the Multicenter Criteria Committee

FREDERICK WOLFE, HUGH A. SMYTHE, MUHAMMAD B. YUNUS, ROBERT M. BENNETT, CLAIRE BOMBARDIER, DON L. GOLDENBERG, PETER TUGWELL, STEPHEN M. CAMPBELL, MICHA ABELES, PATRICIA CLARK, ADEL G. FAM, STEPHEN J. FARBER, JUSTUS J. FIECHTNER, C. MICHAEL FRANKLIN, ROBERT A. GATTER, DANIEL HAMATY, JAMES LESSARD, ALAN S. LICHTBROUN, ALFONSE T. MASI, GLENN A. McCAIN, W. JOHN REYNOLDS, THOMAS J. ROMANO, I. JON RUSSELL, and ROBERT P. SHEON
Fibromyalgia is a common but contested illness. Its definition and content have changed repeatedly in the 110 years of its existence. The most important change was the requirement for multiple tender points and extensive pain that arose in the 1980s, features that were not required previously. By 2010, a second shift occurred that excluded tender points, allowed less extensive pain, and placed reliance on patient-reported somatic symptoms and cognitive difficulties ('fibro fog') that had never been part of past definitions or content.
Tender-Point Pain: Fibromyalgia Patients versus Controls

Percent positive

- Mid upper trapezius
- Lateral epicondyle
- 2nd costochondral
- Knee
- Anterior cervical (lower sternomastoid)
- Supraspinatus
- Suboccipital
- Buttock
- Trochanter

The “Systemic” Conditions That Overlap With Fibromyalgia

- Tension/migraine headache
- Affective disorders
- Temporomandibular joint syndrome
- Memory and cognitive difficulties
- ENT complaints (sicca syndrome, vasomotor rhinitis, accommodation problems)
- Vestibular complaints
- Multiple chemical sensitivity, “allergic” symptoms
- Esophageal dysmotility
- Neuromediately hypotension, mitral valve prolapse
- Noncardiac chest pain, dyspnea due to respiratory mm. dysfunction
- Interstitial cystitis, female urethral syndrome, vulvar vestibulitis, vulvodynia
Abnormalities During Restorative (non-REM) Sleep in Fibromyalgia Patients

Healthy Subject

Fibromyalgia Patient

Pain/Fatigue Cycle

- Disease
- Tense Muscles
- Poor Sleep
- Stress & Anxiety
- Difficult Emotions
- Depression
- Medication Problems
Psychological findings in Fibromyalgia

• Only 25% to 35% have a current psychiatric (DSM) diagnosis, most often major depression.
• As in most other chronic disorders, most patients report some mood disturbances such as feeling anxious or depressed.
Widespread Pain Index
(1 point per check box; score range: 0-19 points)
1. Please indicate if you have had pain or tenderness during the past 7 days in the areas shown below. Check the boxes in the diagram for each area in which you have had pain or tenderness.

Symptom Severity
(score range: 0-12 points)
2. For each symptom listed below, use the following scale to indicate the severity of the symptom during the past 7 days:
- No problem
- Slight or mild problem: generally mild or intermittent
- Moderate problem: considerable problems; often present and/or at a moderate level
- Severe problem: continuous, life-disturbing problems

<table>
<thead>
<tr>
<th>Points</th>
<th>No problem</th>
<th>Slight or mild problem</th>
<th>Moderate problem</th>
<th>Severe problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Fatigue</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>B. Trouble thinking or remembering</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>C. Waking up tired (unrefreshed)</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

3. During the past 6 months have you had any of the following symptoms?

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Pain or cramps in lower abdomen</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>B. Depression</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>C. Headache</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Additional criteria (no score)
4. Have the symptoms in questions 2 and 3 and widespread pain been present at a similar level for at least 3 months?
   - No [ ] Yes [ ]

5. Do you have a disorder that would otherwise explain the pain?
   - No [ ] Yes [ ]

ACR indicates American College of Rheumatology. Scoring information is shown in blue. The possible score ranges from 0 to 31 points; a score ≥13 points is consistent with a diagnosis of fibromyalgia. Additional scoring information and a printer-ready version of this survey that patients can complete are available online (eFigure 1 and eFigure 2 in the Supplement).
Pain is a subjective sensation that cannot be attributed only to the incoming nociceptive information. Indeed, pain is modulated by a variety of cognitive and emotional factors as well as by a number of sensory inputs.
What is a Pain Generator?
20% of patient’s with RA have fibromyalgia

**Pain mechanisms through the natural history of RA**

FM: An Amplified Pain Response

Subjective Pain Intensity

Stimulus Intensity

Hyperalgesia (eg, when a pinprick causes an intense stabbing sensation)

Allodynia (eg, hugs that feel painful)

Pain in FM

Normal Pain Response

fMRI Study Supports the Amplification of Normal Pain Response in Patients With FM

Patients with FM experienced high pain with low-grade stimuli

Stimulus Intensity, kg/cm²

Pain Intensity

Overlapping regions of brain activation were seen in patients with FM after low pain stimuli and in normal subjects after high pain stimuli

- **Red**: Activated by low-intensity stimulus in FM patients
- **Blue**: Activated only by high-intensity stimulus in controls
- **Yellow**: Area of overlapping activation

- **Δ**: FM (n=16)
- **Subjective pain control**
- **Stimulus pressure control** (n=16)

fMRI= functional magnetic resonance imaging.
An individual’s “set point” or “volume control setting” for pain is set by a variety of factors, including the levels of neurotransmitters on the left that either facilitate pain transmission (turn up the gain or volume control) or those on the right that reduce pain transmission. Thus high levels of neurotransmitters on the left, or low levels of those on the right, would be capable of causing the diffuse hyperalgesia (increased volume control) seen in a variety of chronic pain states.
Fibromyalgia Autonomic Nervous System Symptomatology
The ability to perceive noxious stimuli is critical for an animal’s survival in the face of environmental danger, and thus pain perception is likely to be under stringent evolutionary pressure. Pathways, processes and gene sets that share a role in a biological process were pooled into functional classes while the underlying genes that constitute them are depicted with a connection to their respective functional class.
Summary of Findings From the Family Study of Fibromyalgia

- Fibromyalgia is strongly familial (the odds ratio [OR] is 8.5 for first-degree relatives)\(^1\)
  - Fibromyalgia in probands associated with decreased pressure pain threshold in relatives\(^1\)
  - Genetic factors may be involved in etiology of fibromyalgia and pain sensitivity\(^1\)
  - Shared environmental factors also very likely to play a role in fibromyalgia\(^2\)
- Fibromyalgia coaggregates with major mood disorder in families\(^1\) (OR=1.8 [95% CI, 1.1-2.9] \(P=\).01)
  - Mood disorders and fibromyalgia may share some inherited factors


Figure 2. Arnold et al performed genome-wide linkage studies of patients with fibromyalgia.
Treatment of Fibromyalgia

Individualization is essential
Establish rapport with the patient

- Ask the patient to tell you in order all of the problems that bring them to see you.
- I am going to ask you two sets of questions to help determine how we will work together.
- Who is in charge of your care? - you are the captain, significant others in your life are the 1st mates and we your health care professionals are you navigators.
- Are your symptoms real? Do you think I believe you? Do you want to have the problem? What is your diagnosis?
## Stepwise fibromyalgia therapy

<table>
<thead>
<tr>
<th>Initial approach in every patient</th>
</tr>
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<tbody>
<tr>
<td>Confirm the diagnosis</td>
</tr>
<tr>
<td>Education: explain the condition</td>
</tr>
<tr>
<td>Evaluate and treat comorbidities, such as mood and sleep disturbances</td>
</tr>
</tbody>
</table>

### Most patients

- Trial with low-dose tricyclic antidepressants or selected antidepressants or anticonvulsants proven effective in fibromyalgia
- Exercise program

### Patients not responding to above

- Specialty referral (e.g., rheumatologist, physiatrist, psychiatrist, pain management)
- Combinations of drug therapies
- Physical therapy measures
- Psychological interventions, such as cognitive behavioral therapy
- Multidisciplinary programs

Nonpharmacologic Strategies: Evidence of Efficacy

Strong Evidence

- **Exercise**
  - Physical and psychological benefits
  - May increase aerobic performance and tender-point pain pressure threshold, and improve pain
  - Efficacy not maintained if exercise stops

- **Cognitive-behavioral therapy**
  - Improvements in pain, fatigue, mood, and physical function
  - Improvement often sustained for months

- **Patient education/self-management**
  - Improves pain, sleep, fatigue, and quality of life

- **Combination (multidisciplinary therapy)**


Modest Evidence

- Strength training
- Acupuncture
- Hypnotherapy
- EMG biofeedback
- Balneotherapy (medicinal bathing)
- Transcranial electrical stimulation

Weak Evidence

- Chiropractic
- Manual and massage therapy
- Ultrasound

Table 1  Overview of results from selected systematic reviews of placebo-controlled pharmacological trials

<table>
<thead>
<tr>
<th>Treatment (review reference)</th>
<th>No. of trials (no. of participants)</th>
<th>Review quality</th>
<th>Dosages; durations of treatment</th>
<th>Overall trial quality*</th>
<th>Safety and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline^12</td>
<td>10 (767) AMSTAR=6</td>
<td></td>
<td>10–50 mg/day; 8–24 weeks</td>
<td>Low</td>
<td>There was no analysis of safety but no difference in discontinuation rates compared with patients on placebo was reported.</td>
</tr>
<tr>
<td>Anticonvulsants—pregabalin^24</td>
<td>5 (3256) AMSTAR=10</td>
<td></td>
<td>Three studies with fixed doses of 300, 450 and 600 mg/day; one with fixed doses of 150, 300 or 450 mg/day; one flexible dosing study of 300 or 450 mg/day; 8–14 weeks</td>
<td>High</td>
<td>Increased likelihood of withdrawal due to adverse events, RR 1.68, 95% CI 1.36 to 2.07; NNH 12 95% CI 9 to 17. No difference in likelihood of serious adverse events.</td>
</tr>
<tr>
<td>Cyclobenzaprine^25</td>
<td>5 (312) AMSTAR=7</td>
<td></td>
<td>10–40 mg; 2–24 weeks</td>
<td>Moderate</td>
<td>There was no analysis of adverse outcomes in the trials reviewed although dropout across trials was large (cyclobenzaprine 29%, placebo 43%). Only two studies conducted ITT.</td>
</tr>
</tbody>
</table>

EULAR revised recommendations for the management of fibromyalgia
### EULAR revised recommendations for the management of fibromyalgia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Size</th>
<th>AMSTAR</th>
<th>Duration</th>
<th>Overall Trial Quality</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>2 (242)</td>
<td>AMSTAR=7</td>
<td>Ibuprofen 600 mg four times a day, tenoxicam 20 mg/day; 6-8 weeks</td>
<td>Low</td>
<td>The adverse event profile, although not considered in this review, is well established for this class of drugs.</td>
</tr>
<tr>
<td>SNRIs—duloxetine</td>
<td>6 (2249)</td>
<td>AMSTAR=10</td>
<td>20-120 mg/day; 12-28 weeks</td>
<td>Moderate</td>
<td>Dropout rates due to side effects across studies higher than with placebo. No difference in serious adverse events.</td>
</tr>
<tr>
<td>SNRIs—milnacipran</td>
<td>5 (4118)</td>
<td>AMSTAR=10</td>
<td>100 or 200 mg/day; 12-27 weeks</td>
<td>High</td>
<td>Dropout rates due to side effects across studies were double compared with placebo, but there was no difference in serious adverse events.</td>
</tr>
<tr>
<td>SSRIs</td>
<td>7 (322)</td>
<td>AMSTAR=8</td>
<td>20-40 mg/day citalopram, 20-80 mg/day fluoxetine, 20-60 mg/day paroxetine; 6-16 weeks</td>
<td>Moderate to high</td>
<td>Acceptability and tolerability were similar to placebo NNH 40, 95% CI 19 to 66. Although several studies excluded patients with depression/anxiety, Häuser et al showed a small effect of SSRIs in improving depressed mood (SMD −0.37, 95% CI −0.66 to −0.07).</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>5 (1535)</td>
<td>AMSTAR=5</td>
<td>4.5-6 g/day; 8-14 weeks</td>
<td>NE</td>
<td>There is the potential for abuse and central nervous system effects associated with abuse such as seizure, respiratory depression and decreased levels of consciousness.</td>
</tr>
<tr>
<td>Tramadol</td>
<td>1 (313)</td>
<td>AMSTAR=3</td>
<td>37.5 mg tramadol/325 mg paracetamol 4x/day; 3 months</td>
<td>High</td>
<td>No significant difference in discontinuation due to adverse events (RR 1.62, 95% CI 0.94 to 2.80). A high-quality review (AMSTAR score 7) identified a single study, which, among persons who tolerated and benefitted from tramadol, demonstrated a lower discontinuation rate in a double-blind phase compared with placebo.</td>
</tr>
</tbody>
</table>

*According to the method of quality evaluation used in the review.
<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approval</th>
<th>Mechanism of action</th>
<th>Efficacy studies</th>
<th>Primary end-points</th>
<th>Dosing</th>
<th>Adverse events*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>21 June 2007</td>
<td>Non-selective $\alpha_2$ ligand</td>
<td>• 14 weeks, randomised, double-blind, placebo-controlled&lt;br&gt;• 6 months, randomised, withdrawal</td>
<td>Pain reduction, improvements in PGIC and FIQ</td>
<td>300–450 mg/day; start at 75 mg bid (might increase to 150 mg bid within 1 week); max dose 225 mg bid</td>
<td>Dizziness, somnolence, dry mouth, oedema, blurred vision, weight gain, abnormal thinking</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>16 June 2008</td>
<td>SNRI</td>
<td>• 3 months, randomised, double-blind, placebo-controlled&lt;br&gt;• 6 months, randomised, double-blind, placebo-controlled</td>
<td>Pain reduction, improvements in PGIC and FIQ</td>
<td>60 mg/day; start 30 mg/day for 1 week then increase to 60 mg/day</td>
<td>Nausea, dry mouth, somnolence, constipation, decreased appetite, hyperhidrosis</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>14 January 2009</td>
<td>SNRI</td>
<td>• 3 months, randomised, double-blind, placebo-controlled&lt;br&gt;• 6 months, randomised, double-blind, placebo-controlled</td>
<td>Composite end-point that concurrently evaluated improvement in pain (VAS), physical function (SF-36 PCS) and patient global assessment (PGIC)</td>
<td>100 mg/day; start 12.5 mg/day, increasing incrementally to 50 mg bid in 1 week; maximum dose 100 mg bid</td>
<td>Nausea, constipation, hot flush, hyperhidrosis, vomiting, palpitations, increased heart rate, dry mouth, hypertension</td>
</tr>
</tbody>
</table>
Mortality in fibromyalgia: A study of 8,186 patients over thirty-five years

Mortality does not appear to be increased in patients diagnosed with fibromyalgia, but the risk of death from suicide and accidents was increased.

Arthritis Care & Research 63, January 2011
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