Fibromyalgia

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Fibromyalgia Quiz

- Fibromyalgia: more prevalent in women or men?
- ACR criteria
  - Widespread pain > 3 months
  - How many of 18 tender points present?
- What should FM patients NOT do in bed?
  - Sleep
  - Watch TV
  - Make love
  - Observe the moonlight
Which of the Following are Fibromyalgia “Triggers?”

- Zucchini
- Whiplash
- Childhood sexual abuse
- Godiva chocolate
- Mononucleosis
- Closed head injury
Fibromyalgia “Quiz”

• What time of day are symptoms most severe?
  – Upon awakening
  – After exercise
  – Waning mid-afternoon hours
  – After dinner
Clinical Features

• Muscle and joint pain
• Fatigue (persistent “flu”)
• Sleep disturbance
• Cognitive dysfunction (“fibro-fog”)

• Tender Points
Diagnosis: Tender Points

- American College of Rheumatology
  - 11 of 18 tender points
  - Many patients have less than 11 (or more than 18 at other locations on the body)
Epidemiology of Fibromyalgia

Prevalence
- FM is common worldwide and affects 2%-5% of US adult population
- Majority of patients between the ages of 35 and 60 years

Gender differences
- Women are more likely to be diagnosed with FM than men

Determining FM Prevalence

- US adult population
- FM prevalence in US is estimated to be 2%-5%
- Over 6 million Americans have FM
- FM is the most common chronic widespread pain condition

Pathophysiology of Fibromyalgia: The Role of Central Sensitization

1. First, impulses from afferents depolarize dorsal horn neurons

2. Then, extracellular Ca$^{2+}$ and nitric oxide diffuse into neurons and cause exaggerated release of substance P and glutamate; this results in neuronal hyperexcitability

3. Finally, a pain signal is sent to the brain from the dorsal horn

- In FM, dorsal horn neurons become hyperresponsive to nociceptive and nonnociceptive somatic stimulation
- This is known as central sensitization and is thought to result in hyperalgesia and allodynia

Despite extensive research, the pathogenesis of pain in FM is not clearly understood. However, central sensitization has emerged as a leading theory of disease mechanism.

Exclusions/Co-Conditions

- Systemic lupus erythematosus, rheumatoid arthritis, hypothyroidism, ankylosing spondylitis/ seronegative spondyloarthropathy

- Recommend: CBC, ESR, muscle enzymes, LFTs, TFTs, ANA, anti-DNA
Associated Conditions

- Nonrestorative sleep
  - Alpha intrusion in NREM Stage 4
- Irritable Bowel Syndrome
- Cognitive Dysfunction
  - SPECT caudate, thalamic CBF/memory
- Headache, TMJ pain
- Neurally mediated hypotension, RLS
- Chronic Fatigue
Central Sensitivity Syndromes

- Irritable Bowel
- Overactive Bladder
- Low Back Pain, TMJ Disorder
- Migraine and Chronic Tension Headaches

- Comorbid: mood disturbance
- Associated: Chronic Fatigue, Sleep Disturbance, “Fibro-Fog,” Endocrine Dysfunction
Central Sensitization

• Nociception *plus*
  – Modulation in the CNS
  – Emotional and affective components
  – Temporal summation (“wind up”)
    • Second pain (C fibers stim > q 3 sec); inh by NMDA rec antagonists

• Pain amplification syndromes
  – Heightened sensitivity to non-painful stimuli as well: touch, heat, cold, light, sound, smell
  – HPA, high levels of sub P/EAAs in CSF
Central Sensitization

- Excitability of spinal cord neurons after injury
  - Dorsal Horn neurons transmit nociceptive input to the brain
- Enlargement of receptive fields of sc neurons
- Reduction in pain threshold
- Recruitment of novel afferent inputs
  - A-beta fibers normally have no role in pain
- Pain generation by low threshold mechanoreceptors normally silent in pain processing
Peripheral Sensitization

Muscle as Source of Nociceptive Input

- Increased levels of substance P in muscle tissue
- NMR Spectroscopy: lower phosphorylation potentials in quadriceps
- DNA fragmentation of muscle fibers
- Increased IL-1 in cutaneous tissues
- Muscle perfusion deficits

- Peripheral tissue nociceptive activity need not be extensive: central sensitization requires little sustained input to maintain a chronic pain state
CNS in Fibromyalgia

- CNS
  - Hyperexcitable spinal cord neurons with ascending projections to higher centers
  - Descending system, facilitatory as well as inhibitory "bottom up" and "top down" regulation
    - Mediators: 5HT and NE
  - Abnormal pain processing produces a self-sustained pain state in the absence of peripheral disease
CNS Mechanisms

• Voltage gated calcium channels in plasma membrane of all excitable cells
  – Release of neurotransmitters and neuropeptides
  – Five families of Ca Channels
    • Alpha2-delta subunit as treatment target (gabapentin and pregabalin)/upregulation of this subunit causes path pain in animals
    • Gabapentin abolishes brainstem activation in hyperalgesia
Glia

• Express receptors for neurotransmitters and neuromodulators (incl subP)
• Synthesize and release transmitters
• Dorsal horn astrocytes and microglia are activated by inflammation, bacteria, spinal nerve transection, spinal cord trauma, and chronic (not acute) morphine Rx / morphology changes
• Activated glia release proinflammatory cytokines (IL-1, 6 and TNF)-like immune cells
Fibromyalgia May Be a Central Pain Processing Disorder: fMRI Evidence

fMRI Studies Show Cortical/Subcortical Augmentation of Pain Processing in FM

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fMRI = functional magnetic resonance imaging.
Precipitants of FM

• One severe exposure or several repeated exposures: *physical/emotional trauma*
  – War
  – Torture
  – Childhood abuse
  – Rape
  – Natural disasters
  – Terrorist attacks

• Nothing
PAIN: Acute vs Chronic

Most fibromyalgia patients **look normal**

- Acute pain manifestations are absent
- Tachycardia, diaphoresis, grimace, elevated BP
- A single simple painful stimulus (such as a needle prick) does not produce a stereotypic response
Which are Correct in Fibromyalgia?

a) Inhibitory pathways are inhibited
b) Excitatory pathways are super-excited
c) Excitatory neurotransmitters are elevated in CSF
   a) Substance P
   b) Glutamate
   c) Biogenic amines
“Wind-Up”
Mendell and Wall, 1965

- Stimulation of peripheral nerves repetitively led to a progressive build-up of amplitude of the electrical response in the corresponding dorsal horn neurons of the spinal cord.

- Wind-Up leads to increased pain susceptibility called “Central Sensitization”
PAIN: Mechanisms

- Activation of peripheral nociceptors leads to release of neurotransmitters in the spinal cord
- Substance P and Calcitonin Gene Related Peptide (CGRP) are increased in CSF of patients with fibromyalgia
Pain in Fibromyalgia

- "Fibromyalgia" means "pain of muscles and other fibrous tissue"
  - "algia" = pain
  - "fibro" = fibrous, connective tissue
  - "myo" = muscle
Pain in Fibromyalgia

• Description
  – Burning, gnawing, throbbing, stabbing, aching

• Location
  – Neck, shoulders, chest, rib cage, lower back and thighs

• Severity
  – Worse with relaxation and early morning (with stiffness); less noticeable with activity
Clinical Features and Diagnosis of Fibromyalgia: Overview

- Clinically, FM presents with chronic widespread pain in addition to a wide range of symptoms, including tenderness, sleep disturbances, fatigue, and morning stiffness.
- Patients with FM are more likely to have comorbidities such as painful neuropathies and circulatory disorders.
- ACR and Canadian criteria may be used to diagnose FM.
- Symptoms may overlap with other conditions (IBS, MDD, CFS, SLE, RA, OA, Lyme disease); differentiation is essential for optimal management.

ACR = American College of Rheumatology; IBS = irritable bowel syndrome; MDD = major depressive disorder; CFS = chronic fatigue syndrome; SLE = systemic lupus erythematosus.
Causes of Fibromyalgia

- Genetics
  - Polymorphism in COMT gene
- Trauma: physical or emotional
- Infection
  - Hepatitis C, Lyme, EBV, parvovirus
Management of Fibromyalgia (FM)

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

**Pharmacologic**
- Antidepressants
- Analgesics
- Anticonvulsants

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

Pharmacologic Treatments

• SNRIs
  – Duloxetine 60 mg bid
  – Milnacipran (recently FDA-approved)

• Atypical Opioids
  – 37.5 tramadol/325 acetaminophen

• TCAs

• Alpha2-delta ligand pregabalin and gabapentin
  – Arnold et al. Arthritis Rheum. 2007; Gabapentin in the treatment of fibromyalgia
FDA-Approved

- Lyrica
- Cymbalta
- Savella
### 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 with Tramadol</th>
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<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>
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<tr>
<td>Kemple et al (2003)</td>
<td>Opioid†</td>
<td>38</td>
<td>200</td>
<td>Improvement in pain</td>
<td>No</td>
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<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>
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<tr>
<td>Biasi et al (1998)</td>
<td>Tramadol vs PBO</td>
<td>12</td>
<td>1</td>
<td>VAS</td>
<td>Yes</td>
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<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.
<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>N</th>
<th>Duration (weeks)</th>
<th>Primary End Point</th>
<th>Significant Improvement</th>
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</thead>
<tbody>
<tr>
<td>Carette et al (1986)</td>
<td>AMI vs PBO</td>
<td>70</td>
<td>9</td>
<td>Morning stiffness, pain analog score</td>
<td>No</td>
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<td>Carette et al (1994)</td>
<td>AMI vs CBP vs PBO</td>
<td>208</td>
<td>24</td>
<td>VAS (pain, sleep, stiffness, fatigue)</td>
<td>No</td>
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<td>Ginsberg et al (1996)</td>
<td>AMI vs PBO</td>
<td>46</td>
<td>8</td>
<td>Pain VAS, TP score</td>
<td>Yes</td>
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<tr>
<td>Hannonen et al (1998)</td>
<td>AMI vs Moclobemide vs PBO</td>
<td>130</td>
<td>12</td>
<td>VAS (pain, sleep, fatigue) NHP, Sheehan disability</td>
<td>Yes</td>
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<td>Heyman et al (2001)</td>
<td>AMI vs Nortriptyline vs PBO</td>
<td>118</td>
<td>8</td>
<td>NTP, FIQ, VSGI</td>
<td>No</td>
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<td>Caruso et al (1987)</td>
<td>AMI vs Nortriptyline</td>
<td>60</td>
<td>8</td>
<td>Manual TP count</td>
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<td>Bennett et al (1988)</td>
<td>CBP vs PBO</td>
<td>120</td>
<td>12</td>
<td>CGIC</td>
<td>Yes</td>
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</table>

*No TCAs are currently FDA approved for FM.*

AMI = amitriptyline; VAS = visual analog score; PBO = placebo; CBP = cyclobenzaprine; TP = tender points; NHP = Nottingham Health Profile; NTP = number of tender points; FIQ = Fibromyalgia Impact Questionnaire; VSGI = verbal scale global improvement; CGIC = clinician global impression of change; FDA = United States Food and Drug Administration.

# 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>
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<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>
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<tr>
<td>Crofford et al (2005)</td>
<td>Pregabalin vs PBO</td>
<td>529</td>
<td>8</td>
<td>End point mean pain score</td>
<td>Yes</td>
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<tr>
<td>Arnold et al (2007)</td>
<td>Gabapentin vs PBO</td>
<td>150</td>
<td>12</td>
<td>BPI average pain severity score</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.
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.
Pregabalin Binds to the $\alpha_2\delta$ Subunit of Voltage-Gated Ca$^{2+}$ Channels in the Central Nervous System

- Pregabalin selectively binds to $\alpha_2\delta$ subunit of voltage-gated calcium channels
  - Modulates calcium influx in hyperexcited neurons
  - Reduces neurotransmitter release (glutamate, substance P, norepinephrine)
  - Pharmacologic effect requires binding at this site in animal models
  - The clinical significance of these observations in humans is currently unknown

Pregabalin: Predictable Response Versus Gabapentin

**Linear PK Profile**

**High Bioavailability**

<table>
<thead>
<tr>
<th>Dose (mg/d)</th>
<th>Pregabalin</th>
<th>Gabapentin</th>
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<tbody>
<tr>
<td>600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1200</td>
<td>900 mg, 60%</td>
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</tr>
<tr>
<td>1800</td>
<td>1200 mg, 47%</td>
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<tr>
<td>2400</td>
<td>2400 mg, 34%</td>
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<tr>
<td>3000</td>
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<td>3600 mg, 33%</td>
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<td>3600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4200</td>
<td>1800 mg</td>
<td></td>
</tr>
<tr>
<td>4800</td>
<td></td>
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</tr>
</tbody>
</table>

All doses ≥90%

Additional Therapies

• Tricyclic antidepressants, SNRIs and NMDA receptor blockade are beneficial; SSRIs only minimally so
  – NE primarily inhibitory
  – 5HT both inhibitory and facilitative

• Weak opioid agonists reduce reuptake of 5HT and NE

• Heated pool therapy, aerobic exercise, CBT – 2006 European League Against Rheumatism (EULAR)
Treatment

• Topical Creams and Patches
  – Zostrix (capsaicin)
    • Reduces levels of Substance P
  – Lidoderm transdermal patch

• Narcotics

• Synthetic Opioids

• Nerve Blocks

• TENS/ Trigger Point Injections
Lifestyle Management of the Chronic Pain of Fibromyalgia

- **Stress** Management
  - Thermal biofeedback
  - Sequential relaxation
  - Yoga and Tai Chi
- Acupuncture and Acupressure
- Massotherapy, Craniosacral Therapy
- Cognitive-Behavioral Therapy