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Pathogenesis and Treatment of Fibromyalgia

Daniel J. Clauw M.D.

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Associate Dean for Clinical and Translational Research
The University of Michigan

Fall 2008
M2 Musculoskeletal
# Mechanistic Characterization of Pain

## Peripheral (nociceptive)
- Primarily due to inflammation or mechanical damage in periphery
- NSAID, opioid responsive
- Responds to procedures
- Behavioral factors minor
- Examples
  - Osteoarthritis
  - Rheumatoid arthritis
  - Cancer pain

## Neuropathic
- Damage or entrapment of peripheral nerves
- Responds to both peripheral and central pharmacological therapy

## Central (non-nociceptive)
- Primarily due to a central disturbance in pain processing
- Tricyclic, neuroactive compounds most effective
- Behavioral factors more prominent
- Examples
  - Fibromyalgia
  - Irritable bowel syndrome
  - Tension headache
  - Idiopathic low back pain

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D. Clauw
Paradigm Shift in Fibromyalgia

American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Psychologic and behavioral factors nearly always present and negative

- Chronic widespread pain
- Tenderness in ≥11 of 18 tender points
- Final common pathway
- Part of a larger continuum
- Many somatic symptoms, diffuse tenderness
- Psychologic and behavioral factors play roles in some individuals
Overlap Between Fibromyalgia and Related Syndromes

**Fibromyalgia**
- 2%-4% of population
- Defined by widespread pain and tenderness

**Regional Pain Syndromes**
- eg, irritable bowel [IBS]
- Painful bladder / interstitial cystitis [PBS/IC]
- TMD
- Tension HA
- Vulvodynia

**Chronic Fatigue Syndrome (CFS)**
- 1% of population
- Fatigue and 4 of 8 “minor criteria”

**Psychiatric Disorders**
- Major depression
- OCD
- Bipolar
- PTSD
- GAD
- Panic attack

**Somatoform Disorders**
- 4% of population
- multiple unexplained symptoms — no “organic” findings

Shared features

• Characterized by multiple somatic symptoms and high rates of comorbidities with other related syndromes
• 1.5 – 2X more common in females
• Strong familial/genetic underpinnings
• Triggered or exacerbated by “stressors”
• Pain and/or sensory amplification most reproducible pathophysiological feature
• Dysautonomia, neuroendocrine dysfunction, and neurogenic inflammation also commonly noted, but of unclear physiological significance
“Stressors” Capable of Triggering These Illnesses (Supported by Case-Control Studies$^{1,2}$)

- Early life stressors$^3$
  - Children born in 1958 who had experienced a motor traffic accident or who were institutionalized were 1.5 – 2X more likely to have CWP 42 years later
- Peripheral pain syndromes (e.g. RA, SLE, osteoarthritis)$^4$
- Physical trauma (automobile accidents)$^5$
- Certain catastrophic events (war but not natural disasters)$^6$
- Infections
- Psychological stress/distress

Genetics of Fibromyalgia

• Familial predisposition\(^1\)
  – Most recent work by Arnold, et al suggests >8 odds ratio (OR) for first-degree relatives, and much less familial aggregation (OR 2) with major mood disorders
  – Much stronger with bipolarity, obsessive compulsive disorder

• Genes that may be involved
  – 5-HT2A receptor polymorphism T/T phenotype\(^2\)
  – Serotonin transporter\(^3\)
  – Dopamine D4 receptor exon III repeat polymorphism\(^4\)
  – COMT (catecholamine o-methyl transferase)\(^5\)

Conditions Characterized by Widespread Secondary Hyperalgesia / Allodynia

- Fibromyalgia
- Temperomandibular disorder\(^1,2\)
- Headache (tension > migraine)\(^3,4\)
- Idiopathic low back pain\(^5,6\)
- Vulvodynia/vulvar vestibulitis\(^7\)
- Whiplash associated disorder\(^8\)
- IBS\(^9,10\)

Supraspinal Influences on Pain and Sensory Processing

Facilitation
- Substance P
- Glutamate and EAA
- Serotonin (5HT$_{2a, 3a}$)
- Nerve growth factor
- CCK

Inhibition
- Descending antinociceptive pathways
- Norepinephrine-serotonin (5HT$_{1a,b}$), dopamine
- Opioids
- GABA
- Cannabinoids
- Adenosine

Source Undetermined (All Images)

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Fibromyalgia Cerebrospinal Fluid Substance P

Increased Spinal Fluid Levels Of Glutamate and Neurotrophins

EAAs

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<th>NC</th>
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<td>Glutamate, µmol/L</td>
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**P<0.003; **P<0.001.

Neurotrophins

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<td>50</td>
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<tr>
<td>BDNF</td>
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</table>

N=20 patients with fibromyalgia and 20 control subjects.


BDNF, brain-derived neurotrophic factor; EAA, excitatory amino acid; NGF, nerve growth factor.

*D. Clauw*
Decreased Spinal Fluid Levels Of Biogenic Monoamines

5-HIAA, 5-hydroxyindole acetic acid; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenethylene glycol.

N=17 patients with fibromyalgia, 5 patients with rheumatoid arthritis, and 7 control subjects.

*P=0.028; **P=0.057; ***P=0.005 vs nonfibromyalgia controls.

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“Pain Matrix” – Pain is Processed in at Least Three Domains in CNS

- **Sensory**: where it is and how much it hurts
  - Primary and secondary somatosensory cortices
  - Thalamus
  - Posterior insula

- **Affective**: emotional valence of pain
  - Anterior cingulate cortex
  - Anterior insula
  - Amygdala

- **Cognitive**: similar to affective plus prefrontal regions

**Source:**
fMRI of Evoked Pressure Pain in Fibromyalgia and Related Conditions

- Is there objective evidence of augmented pain processing in fibromyalgia?¹
- Role of depression in pain processing in FM²
- Role of cognitive factors in pain processing in FM
  - Locus of control
  - Catastrophizing³
- fMRI changes of augmented central processing of pain also seen in idiopathic low back pain⁴

Sources:
Stimuli and Responses During Pain Scans

Stimulus Pressure Control

Pain Intensity

Stimulus Pressure Control

Fibromyalgia

Subjective Pain Control

Stimulus Pressure Control

STG=superior temporal gyri; SI=primary somatosensory cortex; SII=secondary somatosensory cortex; IPL=inferior parietal lobule.

Specific Underlying Mechanisms in Fibromyalgia

- Global problem with sensory processing (i.e. interoception)
  - FM patients equally sensitive to loudness of auditory tones\(^1\)
  - Insular hyper-reactivity consistently seen\(^2-4\)
  - H-MRS studies of glutamate levels in posterior insula\(^5\)

Sources:
Reduction in Glu is Associated with Reduced Experimental Pressure Pain in FM

$r=-0.95; P<0.001.$

Specific Underlying Mechanisms in Fibromyalgia

- Decreased descending analgesic activity
  - Absent or attenuated DNIC in FM and IBS
  - Brainstem activations with conditioning stimulus seen in controls but not in FM patients

Source:
There is a Deficiency of Descending Analgesic Activity in FM:\(^1,^2\) Which one?

**Opioids**
- Normal or high levels of CSF enkephalins\(^3\)
- Never been administered in RCT but most feel that opioids are ineffective or marginally effective
- Harris recently used PET to show decreased mu opioid receptor binding in FM\(^4\)

**Noradrenergic/Serotonergic**
- Low levels of biogenic monoamines in CSF in FM\(^5\)
- Nearly any class of drug that raises both serotonin and norepinephrine has demonstrated efficacy in FM

Sources:
### FM Patients Have Reduced MOR Availability

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<td>31.1(7.0)</td>
<td>21.5(6.4)</td>
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*corrected

Is Chronic Pain a Neurodegenerative Disease?

• Apkarian\(^1\) was first to show that chronic pain may be a neurodegenerative disease, showing
  – Decreased gray matter density in DLPFC and thalamus
  – Related to length of pain

• More recently seen in other pain states including
  – Headache (insula and ACC)\(^2\)
  – IBS (insula and ACC)\(^3\)
  – Fibromyalgia\(^4\) (multiple regions)
  – PTSD\(^5\) (insula)

Sources:
The Biopsychosocial Continuum

Population

- Abnormal sensory processing
- Autonomic dysfunction
- HPA dysfunction
- Psychiatric disorders
- ? Peripheral nociceptive input

Primary Care

- General “distress”
- Psychiatric comorbidities
- Cognitive factors
- Maladaptive illness behaviors
- Secondary gain issues

Tertiary Care

This is a polygenic disorder

There will be subgroups of FM needing different treatments

There is a deficiency of noradrenergic-serotonergic activity and/or excess levels of excitatory neurotransmitters

Drugs that raise norepinephrine and serotonin, or lower levels of excitatory neurotransmitters, will be efficacious in some

Lack of sleep or exercise increase pain and other somatic sx, even in normals

Exercise, “sleep hygiene,” and other behavioral interventions are effective therapies for biological reasons

How FM patients think about their pain (cognitions) may directly influence pain levels

Cognitive therapies are effective in FM and have a biological substrate
So How Do I Really Diagnose Fibromyalgia? The History – I

• Pain
  – Current and lifetime history of widespread pain
  – The more widespread, the more likely it is fibromyalgia
  – “I hurt all over”
  – Pain felt in any area of musculoskeletal and non-musculoskeletal regions
  – Often “unpredictable”, worsened by stress
  – Often accompanied by stiffness, non-dermatomal paresthesias
So How Do I Really Diagnose Fibromyalgia? The History – II

- Other somatic symptoms
  - Fatigue
    - Not made better by rest or exercise
  - Memory difficulties
    - Difficulty with memory and concentration
  - Insomnia and sleep disturbances
  - Co-morbid syndromes
    - Irritable bowel
    - Interstitial cystitis
    - Headache
    - TMJ/TMD
So How Do I Really Diagnose Fibromyalgia?

**Family History**
- Family history of other pain syndromes

**Past Medical History**
- Regional somatic and visceral pain syndromes
- Psychiatric disorders

**Social History**
- Symptoms often triggered or exacerbated by “stressors”

**Physical Exam**
- Normal except for diffuse tenderness
- Tenderness not just confined to the joints
Diagnostic Work-up

- Intensity of evaluation depends largely on history
  - If symptoms acute or sub-acute extensive evaluation necessary
  - If symptoms have lasted for many years and history is classic virtually no work-up is necessary
- Laboratory evaluation at some point in illness
  - ESR, CRP
  - CBC and chemistry profile
  - TSH, Vitamin D
  - Avoid serological studies e.g. ANA, RF
Treatment of Fibromyalgia and Other Central Pain Syndromes

- Education
- Pharmacological Therapy
- Aerobic Exercise
- Cognitive Behavioral Therapy (CBT)
Summary

Increased
- Neurotransmitters
  - Serotonin
  - Norepinephrine
  - Opioids
- Exercise
- Sleep

Decreased
- Neurotransmitters
  - Glutamate
  - Substance P
  - Nerve growth factor
- Cognitions
  - Catastrophizing
  - External locus of control

Pain Threshold
## Pharmacological Therapies

| Strong Evidence | Dual reuptake inhibitors such as  
|                  | Tricyclic compounds (amitriptyline, cyclobenzaprine)  
|                  | SNRIs and NSRIs (milnacipran, duloxetine, venlafaxine?)  
|                  | Anticonvulsants (e.g., pregabalin, gabapentin) |
| Modest Evidence | Tramadol  
|                  | Selective serotonin reuptake inhibitors (SSRIs)  
|                  | Gamma hydroxybutyrate  
|                  | Dopamine agonists |
| Weak Evidence    | Growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe) |
| No Evidence      | Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics, guanifenesin |

Supraspinal Influences on Pain Processing

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- Neurotensin
- Nerve growth factor
- CCK

Inhibition
- Descending anti-nociceptive pathways
  - Norepinephrine-serotonin (5HT$_{1a,b}$), dopamine
  - Opioids
  - GABA
  - Cannabinoids
  - Adenosine

Source Undetermined (All Images)

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Likely MOA of Dual-Reuptake Inhibitors

**Facilitation**
- Substance P
- Glutamate and EAA
- Serotonin (5HT$_{2a, 3a}$)
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Source: Undetermined (All Images)

D. Clauw
Possible MOA of Pregabalin/Gabapentin

Facilitation
- Substance P
  - Decrease SP release in inflammatory states\(^1\)
- Glutamate and EAA
  - Inhibit SP-induced glutamate release\(^2\)

Inhibition
- Descending antinociceptive pathways
  - Norepinephrine-serotonin (5HT\(_{1a,b}\)), dopamine
  - Opioids
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There is a Deficiency of Descending Analgesic Activity in FM:¹,² Which one?

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**Noradrenergic/Serotonergic**
- Low levels of biogenic monoamines in CSF in FM⁵
- Nearly any class of drug that raises both serotonin and norepinephrine has demonstrated efficacy in FM

Sources:
Relative Activity on Serotonin and Norepinephrine Reuptake Among Antidepressants

Citalopram  Venlafaxine  Amitriptyline  Maprotiline
Fluvoxamine  Duloxetine  Milnacipran  Desipramine
Sertraline  Imipramine  Nortriptyline
Paroxetine  
Fluoxetine  Reboxetine

Antidepressant  Analgesic/Antidepressant

Nonpharmacological Therapies

<table>
<thead>
<tr>
<th>Strong Evidence</th>
<th>Modest Evidence</th>
<th>Weak Evidence</th>
<th>No Evidence</th>
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<tbody>
<tr>
<td>Education</td>
<td>Strength training</td>
<td>Acupuncture, chiropractic, manual and massage therapy, electrotherapy, ultrasound</td>
<td>Tender (trigger) point injections, flexibility exercise</td>
</tr>
<tr>
<td>Aerobic exercise</td>
<td>Hypnotherapy, biofeedback, balneotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive behavior therapy</td>
<td></td>
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</tbody>
</table>
Symptoms of Pain, Fatigue, etc.

- Nociceptive processes (damage or inflammation of tissues)
- Disordered sensory processing

Functional Consequences of Symptoms

- Increased Distress
- Decreased activity
- Isolation
- Poor sleep
- Maladaptive illness behaviors

Dually Focused Treatment

- Pharmacological therapies to improve symptoms
- Nonpharmacological therapies to address dysfunction

Exercise

• Aerobic exercise nearly universally beneficial; tolerance, compliance, adherence are biggest issues

• To maximize benefits
  – Begin several months after pharmacologic therapy
  – Begin with low-impact exercises; avoid strength training until late
  – Both physician and patient should consider this as a “drug”

• Less evidence supporting strengthening, stretching
Exercise for Treating Fibromyalgia: Cochrane Review

34 RCTs
47 Interventions

20 RCTs Met ACSM Guidelines

Aerobic training (17)
Aerobic only: 6 moderate to high-quality RCTs

Strength training (3)
Strength only: 2 low-quality RCTs

Flexibility (2)

ACSM Guidelines
2 days/week
40% to 85% HR reserve
55% to 90% maximum HR
20 minutes
6 weeks

ACSM=American College of Sports Medicine; HR=heart rate.

Cognitive Behavioral Therapy

- A program designed to teach patients techniques to reduce their symptoms, to increase coping strategies, and to identify and eliminate maladaptive illness behaviors
- Shown to be effective for nearly any chronic medical illness
- Not all CBT is created equally; very dependent on content, therapist and program
Improvements Noted in CBT vs Standard Care Over 12 Months (n=122)

*Clinically significant. OR 2.9, $P<.05$. 

Recommended Approach

- Education
- Identify and treat “peripheral” pain generators
- For patients who need or want medications, start with low doses of mixed tricyclic antidepressants (amitriptyline, cyclobenzaprine); start low, go slow
- If patient has depression, memory problems, fatigue as most prominent symptoms
  - Add mixed reuptake inhibitor (eg, duloxetine, milnacipran, venlafaxine)
    or SSRI (may need high doses)
- If patient has sleep disturbance as most prominent symptom
  - Use pregabalin or gabapentin first, give higher % of dose at night

Recommended Approach - II

- If no response, consider use of dopamine agonist, sodium oxybate
- For additional analgesic effect, add tramadol, tizanidine, opioids
- For sleep, if patient doesn’t tolerate TCA, use zolpidem, zaleplon, trazodone
- Aggressively introduce non-pharmacological therapies

Conclusions

• Fibromyalgia has strong neurobiological underpinnings
• This is a polygenic disorder characterized by pain and sensory amplification
• There is evidence of increased levels of pro-nociceptive neurotransmitters (e.g. Substance P, glutamate) and decreased levels of anti-nociceptive neurotransmitters (e.g. serotonin, norepinephrine)
• The condition can be easily diagnosed in clinical practice based primarily on the patient history
Additional Source Information

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