FIBROMYALGIA: THE FIVE “MYTHS”
Is it real and can we help such patients?

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Learning objectives

- To review the history and controversy of fibromyalgia (FMS)
- To be introduced to emerging research in the pathophysiology of FMS
- To implement evidenced-based practical approaches in assessing and treating FMS

Fibromyalgia: what is it?

- WIDESPREAD PAIN
  - Chronic widespread pain is the defining feature of FMS
  - Allopathic pain with non-nociceptive input
  - The pain is all in your head
  - Tender points are often present, but are not a requirement to confirm diagnosis. 1990 ACR criteria is 11 or more of 18.

- SLEEP DISTURBANCES
  - Characterised by nonrestorative sleep and increased awakenings
  - Abnormalities in the continuity of sleep and deep architecture

- FATIGUE
  - Fatigue and cognitive dysfunction are common characteristics of FMS
  - Fatigue is a major problem for FMS patients.

- DYSAUTONOMIA
  - Vascular dysfunction includes Raynaud’s, migraine, TMI
  - Vascular abnormality may happen secondary to central nervous system dysfunction

Epidemiology of Fibromyalgia

Fibromyalgia is the most common chronic widespread pain condition

- 2% - 5% prevalence worldwide
- 0.7% - 1.4% in Denmark
- 3.3% in Canada
- 2% - 5% in the US

Gender and age differences

- This condition affects women 10 times more frequently than men
- Majority of patients are aged 35 to 60 years (working age)

- 900,000 Canadians

Proposed causes of Fibromyalgia

- Environmental factors that may trigger the onset of FMS
  - Physical trauma or injury
  - Infections (hepatitis C, Lyme disease)
  - Psychological stressors
  - Onset of FMS may occur without any trigger
  - Spontaneous

- FMS may occur concurrently with other diseases: osteoarthritis, autoimmune diseases (RA, SLE), neuromuscular diseases (post-polio, MS) and hypothyroidism

- Possible genetic component of FMS

- Specific gene mutations may predispose individuals to FMS

- Polymorphisms in the COMT enzyme and the serotonin transporter are potentially associated with FMS and other disorders

COMT = catechol-O-methyltransferase, RA = rheumatoid arthritis, OA = osteoarthritis, SLE = systemic lupus erythematosus

All traditional lab tests (blood work, X-Rays, MRI scans, electodiagnostic tests etc.) are all normal = “it is all in your head”

Fibromyalgia “syndrome” FMS = collection of symptoms and signs

“…the results of your tests were negative. Get lost!”
Controversies in FMS
George Ehrlich and Norton Hadler

- FMS is not a distinct entity
- It is a label – turning psychological symptoms into a disease
- FMS has no signs, imaging, diagnosis and modalities therefore non-verifiable
- FM is not diagnosed in some places
- Treatment does not work
- Bankrupt healthcare compensation
- Encourage chronic illness behaviour: if you are sick you cannot get better

Fibromyalgia: ACR classification criteria

- History of widespread pain > 3 months
  - above and below waist
  - left and right side
  - must include axial skeleton
- Pain in 11 / 18 tender points palpation <4 kg
  - occiput
  - low cervical (C5-6)
  - trapezius
  - supraspinatus (medial)
  - 2nd rib
  - lateral epicondyle (distal)
  - gluteal
  - greater trochanter (post)
  - knee (med. fat pad above joint line)

Fibromyalgia Pathophysiology

Central sensitization is emerging as a leading theory of FM pathophysiology
- Therapeutic agents that reduce neuronal hyperactivity by reducing the release of neurotransmitters (such as glutamate) may be one way to relieve the chronic pain of FM
- Agents that enhance DNIC (Descending Inhibitory Control) can also help.

Myth 1
TENDER POINTS ARE D______ AND UNIQUE FOR FIBROMYALGIA

Quantitative Sensory Testing: Key correlative physical exam findings...a brush, pin and a cold tuning fork!

Fibromyalgia Pathophysiology

- Loss of Pain Inhibition (DNIC) in FMS
- Patients with FM seem to have an impaired ability to inhibit muscle pain by descending inhibitory control
Myth #2: FM is caused by a slipped disc / pinched nerve?

- ____% of normal people have bulging discs
- ____% have actual disc herniations

Pseudoradicular symptoms: myofascial referral

Head forward, protracted shoulders

Thoracic Outlet syndrome

 “…compression of brachial plexus and subclavian artery by attached muscles in the region of the first rib and clavicle”

4 fingers forward....

Myth #3: FMS is “all in your head”?

- All traditional lab tests: normal
- Higher levels of childhood traumas, abuse, eating disorder
- Overlap with post-traumatic stress disorder
- Dr. H. Moldofsky 1976: Link with sleep alpha-delta intrusions

Validation: functional MRI evidence

1958 British Birth Cohort study PAIN 2009: 143:92-96
7571 subjects at 45 years: 12.3% with CWP → maternal death under age 7, MVA hospitalization; institutionalization; family $$ difficulty

Reduced Neuronal Activity in Rostral Anterior Cingulate Gyrus

Functional MRI for pain and depression

Major depressive disorder is found in 30-54% of chronic pain (tertiary care) patients.

fMRI revealed that depression level was NOT associated with magnitude of neuronal activation in pain sensory pathways (primary and secondary somatosensory cortices).

Depression was associated with affective pain processing (amygdala and contralateral anterior insula).

There are parallel, independent networks for sensory and affective pain.

**Treating depression will NOT necessarily have an impact on the sensory dimension of pain.

Fibromyalgia Cerebrospinal Fluid Substance P

- Normals
- Fibromyalgia syndrome

What hope is there?
- Brain Aging \( \rightarrow \) time \( \rightarrow \) Nerve Growth Factor

- Memory and sleep problems \( \uparrow \) Substance P

- pain \( \leftrightarrow \) biogenic amines

- poor stress response \( \downarrow \) Fibromyalgia

Dr. Jon Russell's theory
### Fibromyalgia Pathophysiology: Validation

- Recent data suggest alterations of the CNS may contribute to chronic widespread pain of FM
- Central 
- fMRI data provide supporting evidence that FM is a chronic pain processing disorder
- Loss of D- has been found in FM.
- qMRI suggests accelerated aging of the brain

**Therapeutic agents that reduce neuronal hyperactivity (glutamate)** by reducing the release of neurotransmitters may be one way to relieve the chronic pain of FM.


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### Myth #4: nothing can be done for this

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### Functional Medicine for FMS: pearls

- **PREVENT GREY MATTER ATROPHY:**
  - Omega 3 FA: **mg** EPA-DHA/day over 3 months or more aggressive neurotrophic formulas
  - Check omega 3 blood test and aim for AA:EPA ratio between 1.0-3.5
  - Serum B12 > **pmol/L**
  - Serum 25(OH) vitamin D3: **nmol/L** (40-64 ng/ml)

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### Cannabinoids: reduce glutamate neurotoxicity

- Total antioxidant capacity in fibromyalgia
- Lower than controls
- Need for antioxidants to decreased free radicals in FMS brains?

### Pregabalin Modulates Hyperexcited Neurons = reduces glutamate release

*Does not affect Ca++ influx in normal neurons; Does not affect cardiac calcium channels*
Pregabalin is the most studied drug and the first approved drug (USA and Canada) for fibromyalgia.

**Pregabalin Fibromyalgia (FM) Clinical Development Program**

- **Study A0081056**
  - 13 weeks
  - 300, 450, 600 mg/day (BID) N=748
  - Mease, 2008

- **Study 1008-033/197**
  - Open-label extension (N=413)

- **Study A0081100**
  - 14 weeks
  - 300, 450, 600 mg/day (BID; Pbo run-in) N=735

- **Study A0081077**
  - 14 weeks
  - 300, 450, 600 mg/day (BID; Pbo run-in) N=745
  - Arnold, 2008

- **Study A0081059**
  - 6 months
  - 300-600 mg/day (BID; durability) N=1051 total, N=566 DB
  - Crofford, 2008

- **Study 1008-105**
  - 8 weeks
  - 150, 300, 450 mg/day (TID) N=529
  - Crofford, 2005

- **Study A0081078**
  - Open-label extension (N=420)
  - 3 months

- **Study A0081101**
  - Open-label extension
  - DB lock: April 08
  - 3 months

- **4 Fixed Dose, Parallel Group Studies**

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**Myth #5: Diagnosis leads to disability and will ________ the system**

**Diagnosis of FM Is Associated With Reduced Health Care Costs**

**Health Economic Consequences Related to the Diagnosis of Fibromyalgia**

- Tests and imaging
- Referrals
  - GP visits
  - Drugs

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**Diagnosis Can Improve Patient Satisfaction**

- Diagram showing improvement in patient health satisfaction

**How do we manage fibromyalgia patients?**

**Reflections**

*That sinking feeling*

*Patient-doctor dialogue about rescuing patients from fibromyalgia culture*

**VALIDATION**

**HOPE**

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*Statistically significant versus baseline 95% Confidence Interval -1.2, -0.4*
Listen and get a Pain Diagram: a picture speaks a 1000 words!

Fibromyalgia Moldofsky Questionnaire:
to be validated and published

<table>
<thead>
<tr>
<th>Item</th>
<th>Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
<th>Don’t Know</th>
<th>Item total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain or stiffness in most of the parts of my body</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My body is sensitive to any tightness or pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel energetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My sleep is refreshing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel sad or nervous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am content with my life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total score for all items: __________

VALIDATION

- Example of Multiple Sclerosis patients before the advent of MRI scanning
- Functional MRI (dynamic, not static imaging of brain)
- Experimental Pain studies (loss of DNIC)
- Biochemical Laboratory studies
- Quantitative Sensory Testing
- Quantitative MRI

- Note: these are not “specific” for FMS but are also seen in other chronic neuropathic pain conditions

Antidepressants

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Documented Effectiveness</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertiary Amines</td>
<td>Secondary Amines</td>
<td>SSRIs, SNRIs and others</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>desipramine</td>
<td>nortriptyline</td>
</tr>
<tr>
<td>imipramine</td>
<td>paroxetine</td>
<td>citalopram</td>
</tr>
<tr>
<td>5-10 mg qhs</td>
<td>25 mg x 2 months</td>
<td>venlafaxine</td>
</tr>
</tbody>
</table>

Complications of treatment

AMITRIPTYLINE:

- Weight gain
- Anticholinergic effects:
  - dry mouth
  - constipation
  - urinary retention

Obesity: an epidemic without treatment

Amitriptyline: US General Account office list of 20 drugs that should NOT be prescribed in the elderly.

**Gabapentin pearls**

- Maximum single one time dose is 1200 mg (little absorbed beyond that)
- Titrate up to 1800 mg / day before deciding no therapeutic effect.
- Absorbed actively from duodenum. Less in disease: e.g. bypass surgery, elderly

**Gabapentin vs. Pregabalin: Differences**

<table>
<thead>
<tr>
<th>Gabapentin</th>
<th>Pregabalin</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Absorption: the percentage of absorption decreases with the dosage increase</td>
<td>• Absorption: proportional to the dose</td>
</tr>
<tr>
<td>• Divided doses improve absorption</td>
<td>• The dose-blood level curve is linear</td>
</tr>
</tbody>
</table>

**COST**

- Gabapentin 1800 mg/ day = $3.91
- Pregabalin 75 mg BID = $3.04
- 150/ 300 mg BID = $4.64

**HOPE**

- More than medications.ca:
  - SHINE: Sleep Hormones Infection Nutrition
  - Exercise (aerobic/aquatic, muscle core strengthen)
  - FCAMT physiotherapist at www.DrKoPRP.com
  - COPE: Cognitive- Behavioural therapy (doesn’t reduce pain) combined with EEG biofeedback (neurotherapy):
    - PhD Bob Gottfried 416 222 0004
  - Mindfulness-based Stress Reduction group program

- Medications:
  - Beyond the 5 “A’s”, muscle relaxants, T#3
  - Focus on pathophysiology mechanisms in central sensitization
  - Subtype patients → more specific treatment

**European League Against Rheumatism EULAR**


**Pharmacological Management**

<table>
<thead>
<tr>
<th>Recommended Agents</th>
<th>Gabapentin</th>
<th>Antidepressants, Antipsychotics, Doloraline*</th>
<th>Tramadol, pramipexole &amp; tropisetron **</th>
<th>Simple analgesics and weak opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rationale</td>
<td>Pain management</td>
<td>Pain management Function</td>
<td>Pain management</td>
<td>Can also be considered</td>
</tr>
<tr>
<td>Level of Evidence/ Strength</td>
<td>Ib A</td>
<td>Ib A</td>
<td>Ib A</td>
<td>IV D</td>
</tr>
<tr>
<td>Not Recommended (IV D)</td>
<td>Strong opioids</td>
<td>Corticosteroids</td>
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</tbody>
</table>

* Appropriate options: amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide, and prliftine**

**Decreased Central mu-opioid Receptor Availability in FMS**

<table>
<thead>
<tr>
<th>Right dorsal anterior cingulate</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ-opioid receptor binding potential</td>
</tr>
<tr>
<td>Healthy controls (n=17)</td>
</tr>
<tr>
<td>FM (n=17)</td>
</tr>
</tbody>
</table>

Harris RE et al. *J Neurosci* 2007;27:10000-6

**TRAMADOL**

**Synergistic Mechanisms of Action**

1. Mild mu opioid agonist → may or may not be helpful in fibromyalgia?
2. Mild inhibition of norepinephrine and serotonin reuptake → enhances DNIC

*Molecular structure is almost identical to venlafaxine*

**Duloxetine (SNRI) Inhibits 5-HT and NE Reuptake**

- The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways (DNIC) within the central nervous system.

For Fibromyalgia, start with 30mg/day with food and increase to 60mg/day after 1-2 weeks. (max 120mg/day).

- Warn about nausea and interactions with drugs that increase serotonin (including tramadol). And interact with Cytochrome P450 enzymes.

**FMS Subgroups**

- **Group 1 (n=50)**
  - Low tenderness
  - Moderate depression/anxiety
  - Moderate catastrophising
  - Moderate control over pain

- **Group 2 (n=31)**
  - High tenderness
  - High depression/anxiety
  - High catastrophising
  - Low control over pain

- **Group 3 (n=16)**
  - High tenderness
  - Low depression/anxiety
  - Low catastrophising
  - High control over pain

**Effects on sleep**

<table>
<thead>
<tr>
<th>Med</th>
<th>Sleep latency</th>
<th>Sleep efficiency</th>
<th>% SWS</th>
<th>% REM</th>
<th>a.m. sedation</th>
</tr>
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<tbody>
<tr>
<td>TCA</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SNRI</td>
<td>1/1</td>
<td>1/1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1</td>
<td>1/1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>1</td>
<td>1/1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1</td>
<td>1/1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Melatonin</td>
<td>1/3</td>
<td>1/3</td>
<td>n/a</td>
<td>n/a</td>
<td>---</td>
</tr>
</tbody>
</table>

MacFarlane, J. sleepnews.com

A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo

- RCT, 3-way crossover with 24 adults
- Pregabalin 150mg tid vs. alprazolam 1mg tid vs. placebo tid for 5 days; washout 7 days
- Both pregabalin and alprazolam increased total sleep time vs. placebo; decreased sleep latency
- Pregabalin: higher % SWS vs. alp, placebo
- Alprazolam: lower % SWS vs. placebo, pregab
- Pregabalin: fewer awakenings of > 1 minute vs. alp, placebo
How I prescribe Pregabalin...

- Warn about adverse effects:
  - Dizziness, Drowsiness 23%
  - dEma, weight gain 7%
  - Dry mouth
- Dose: 75 mg QHS x 3 nights
  - If not too drowsy or dizzy, increase to 75 mg BID or TID
  - If drowsy, dizzy; try 25 mg (afternoon) + 75 mg qhs
- Dizziness: 50% will resolve after 3 weeks
- Titrate up slowly — responders aim higher
- Arnold study: responders up to 450 mg/day
  (p value significant) VAS pain 300 mg; FIQ 450 mg/day.

Sensitive patients (e.g. FMS with multiple chemical sensitivities):

- start with 25 mg QHS.

Emerging Rx: Platelet-rich Plasma injections

- CTV newscast with Dr. Ko: http://www.ctv.ca/servlet/ArticleNews/story/20090707/blood_therapy_0907/2972637
- Video: http://watch.cntv.ca/news/Redirect/?Clipld=192043

Resources

- National Fibromyalgia Research Association, Mayo Clinic, NIH websites
- www.DrKoPRP.com
- www.FibromyalgiaIntegrativeTreatment.com (future Sunnybrook centre)
- www.NeuropathicPain.ca (for copy of powerpoint slides)
- Injection training: www.neurotoxinsforpain.org
- www.MoreThanMedications.ca

Summary

- FMS: 900,000 in Canada with diffuse pain: allodynia, hyperalgesia
  (11+/ 18 tender points) ≠ myth 1: more than tender points

- Validation of FMS
  - Traditional tests: normal ≠ myth 2: MRI disc
  - FMRI, DNIC, QST, qMRI ≠ myth 3: all in head
  - Lower costs after diagnosis made ≠ myth 5: bankrupt system

- Hope for FMS
  - ≠ myth 4: nothing can help

- Functional Medicine with science-based nutrition: omega 3, vitamin D3, B12
  - optimize diet and lifestyle; follow with objective laboratory markers
- SHINE: Sleep Hormones (MHR) Infection Nutrition Exercise
- Medications beyond the 5-A’s: Pregabalin for pain and sleep
- Subtypes: SNRI Duloxetine or Tramadol for pain and depression;
  Cannabinoids (opioid tolerance, PTSD)
- EXERCISE the body (cardio & core) and the mind (cbt & neurotherapy)
- Multidisciplinary: Psych – PT (FCAMT) – MD – MD RN (Pain)

- Education: patient, physician, public