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

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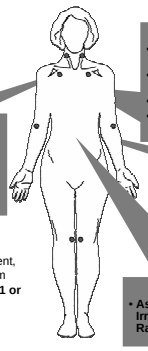
Sunnybrook HEALTH SCIENCES CENTRE

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**
- **Allodynia: pain with non-noxious stimuli**
- **Hyperalgesia: increased pain response with noxious stimuli**

SLEEP DISTURBANCES
- **Characterized by nonrestorative sleep and increased awakenings**
- **Abnormalities in the continuity of sleep and sleep architecture**
- **Reduced slow-wave sleep**
- **Abnormal alpha wave intrusion in non-REM sleep**

FATIGUE/ FIBROFOG
- **Fatigue and cognitive dysfunction are common characteristics of FMS**

DYSAUTONOMIA
- **Associated syndromes include Irritable Bowel, Bladder, PMS, Raynaud's, Migraine, TMJ**

Tender points are often present, but are not a requirement to confirm diagnosis. **1990 ACR criteria is 11 or more of 18.**

Wolfe et al. *Arthritis Rheum.* 1995;38:19-28; Leavitt et al. *Arthritis Rheum.* 1986;29:775-781; Wolfe et al. *Arthritis Rheum.* 1990;33:160-172; Roizenblatt et al. *Arthritis Rheum.* 2001;44:222-230; Harding. *Am J Med Sci.* 1998;315:367-376.

Epidemiology of Fibromyalgia

Fibromyalgia is the most common chronic widespread pain condition

2% - 5% prevalence worldwide

Between 16 and 40 million people worldwide have Fibromyalgia

- **0.7% - 1.4% in Denmark**
- **2.4 % in Spain**
- **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

Burckhardt et al. APS Clinical Practice Guidelines Series, No. 4. Glenview, Ill: American Pain Society; 2005. Neumann et al. *Curr Pain Headache Rep.* 2003;7:362-368. Wolfe et al. *Arthritis Rheum.* 1995;38:19-28. Lawrence et al. *Arthritis Rheum.* 1998;41:778-799. Wolfe. *Am J Med.* 1986;81(suppl 3A):7-14. Weir et al. *J Clin Rheumatol.* 2006;12:124-128.

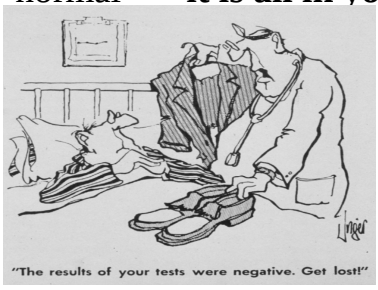
Proposed causes of Fibromyalgia

- 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

Zubieta et al. *Science.* 2003;299:1240-1243; Arnold et al. *Arthritis Rheum.* 2004;50:944-952; Clauw and Crofford. *Best Prac Res Clin Rheumatol.* 2003; 17:685-701; Burckhardt et al. APS Clinical Practice Guideline Series, No.4. Glenview, IL: 2005.

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



Fibromyalgia "syndrome" FMS = collection of symptoms and signs

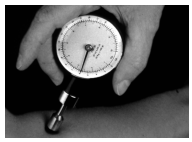
Controversies in FMS

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

Myth 1

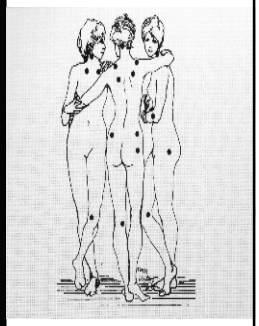
TENDER POINTS ARE D_____ AND UNIQUE FOR FIBROMYALGIA



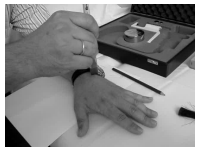
Fibromyalgia: ACR classification criteria

Wolfe F, Smythe HA, Yunus MB et.al: *Arthritis Rheum* 1990; **33:19-31**

- 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)

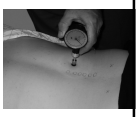


Quantitative Sensory Testing: Key correlative physical exam findings…a brush, pin and a cold tuning fork!



Canadian Tire brush: $1.09

MEDOC QST technology: $30,000 part of the electrodiagnostic work-up at Dr. Ko's Markham centre



Algometer (Sammons-Preston) $450

Tender points (pressure hyperalgesia): are one part of Quantitative Sensory testing for neuropathic pain. R.Rolke et.al. PAIN 2006; 123:231-43.

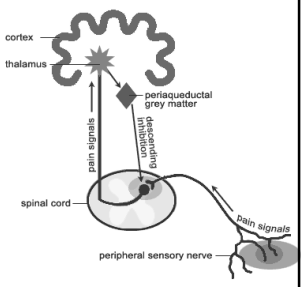
Neuropen (Surgo surgical supplies) $40

Fibromyalgia Pathophysiology

Central sensitization is emerging as a leading theory of FM pathophysiology

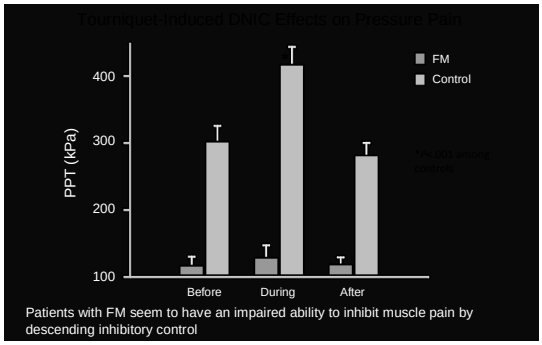
Therapeutic agents that reduce **neuronal hyperactivity** by reducing the release of neurotransmitters (such as glutamate) may be one way to relieve the chronic pain of FM

Agents that enhance **DNIC (D_____ N_____ Inhibitory Control)** can also help.



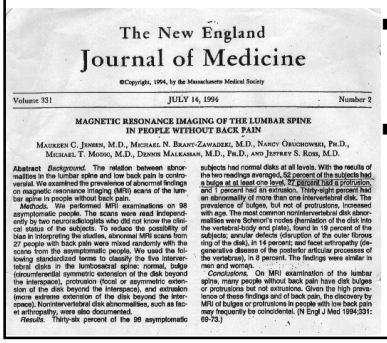
Staud and Rodriguez. *Nat Clin Pract Rheumatol*. 2006;2:90-98; Henriksson. *J Rehabil Med*. 2003;41(suppl 41):89-94; Gracely et al. *Arthritis Rheum*. 2002;46:1333-1343; Campbell and Meyer. *Neuron*. 2006;52:77-92; Rao. *Rheum Dis Clin N Am*. 2002;28:235-259; Maneuf and McKnight. *Br J Pharmacol*. 2001;134:237-240; Cedena et al. *J Neurochem*. 2005;94:1131-1139.

Loss of Pain Inhibition (DNIC) in FMS



Kosek E et al. *Pain*. 1997;70(1):41-51.

Myth #2: FM is caused by a slipped disc / pinched nerve ?



The New England Journal of Medicine

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Volume 331 JULY 14, 1994 Number 2

MAGNETIC RESONANCE IMAGING OF THE LUMBAR SPINE IN PEOPLE WITHOUT BACK PAIN

MAUREEN C. JENSEN, M.D., MICHAEL N. BRANT-ZAWADZKI, M.D., NANCY OBUCHOWSKI, PH.D., MICHAEL T. MODIC, M.D., DEBNOM MALKASIAN, M.D., PH.D., AND JEFFREY S. ROSS, M.D.

Abstract *Background.* The relation between abnormalities in the lumbar spine and low back pain is controversial. We examined the prevalence of abnormal findings on magnetic resonance imaging (MRI) scans of the lumbar spine in people without back pain.

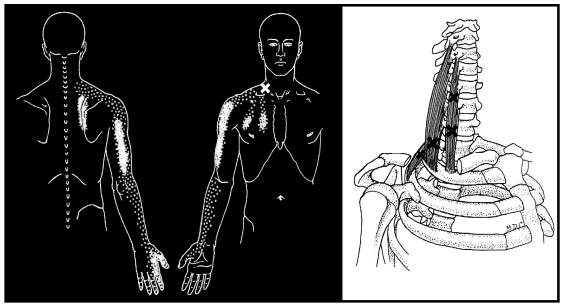
Methods. We performed MRI examinations on 98 asymptomatic people. The scans were read independently by two neuroradiologists who did not know the clinical status of the subjects. To reduce the possibility of bias in interpreting the studies, abnormal MRI scans from 27 people with back pain were mixed randomly with the scans from the asymptomatic people. We used the following standardized terms to classify the five intervertebral disks in the lumbosacral spine: normal, bulge (circumferential symmetric extension of the disk beyond the interspace), protrusion (focal or asymmetric extension of the disk beyond the interspace), and extrusion (more extreme extension of the disk beyond the interspace). Noninvertebral disk abnormalities, such as facet arthropathy, were also documented.

Results. Thirty-six percent of the 98 asymptomatic subjects had normal disks at all levels. With the results of the two readings averaged, 52 percent of the subjects had a bulge at at least one level, 27 percent had a protrusion, and 1 percent had an extrusion. Thirty-eight percent had an abnormality of more than one intervertebral disk. The prevalence of bulges, but not of protrusions, increased with age. The most common noninvertebral disk abnormalities were Schmorl's nodes (herniation of the disk into the vertebral-body end plate), found in 19 percent of the subjects; annular defects (disruption of the outer fibrous ring of the disk), in 14 percent; and facet arthropathy (degenerative disease of the posterior articular processes of the vertebrae), in 8 percent. The findings were similar in men and women.

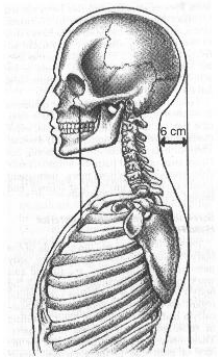
Conclusions. On MRI examination of the lumbar spine, many people without back pain have disk bulges or protrusions but not extrusions. Given the high prevalence of these findings and of back pain, the discovery by MRI of bulges or protrusions in people with low back pain may frequently be coincidental. (N Engl J Med 1994;331: 69-73.)

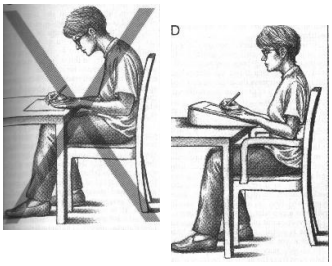
- ___% of normal people have bulging discs
- ___% have actual disc herniations

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"

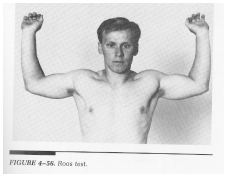


FIGURE 4–36. Roos test.

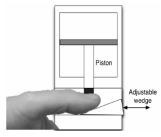
4 fingers forward….

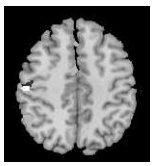
Myth #3: FMS is "all in your head"?

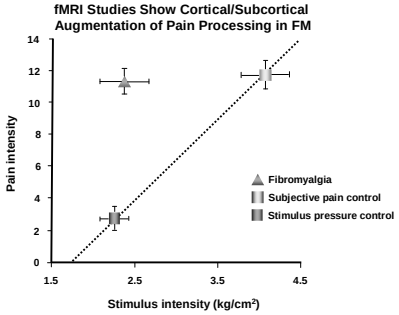
- All traditional lab tests: normal
- Higher levels of childhood traumas, abuse, eating disorder
- Overlap with post-traumatic stress disorder
- Dr. H. Moldofsky 1976: Link with sleep alpha-delta intrusions

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

Validation: functional MRI evidence

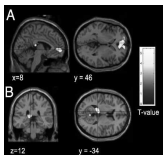


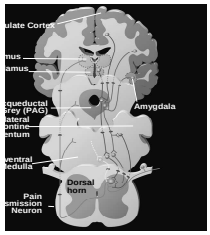


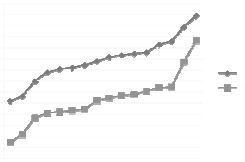


Gracely et al. *Arthritis Rheum.* 2002,46:1333-1343; Cook et al. *J Rheumatol*, 2004. 31(2): p. 364-78; Mailis-Gagnon et al. *Neurology* 2003, 60(9): p. 1501-7.

Reduced Neuronal Activity in Rostral Anterior Cingulate Gyrus







Anatomical region	Cluster size	Peak T-value	Peak Z-value	p-value
rACC	1330	4.67	4.02	p<0.007 *

Jensen KB *et al*. PAIN 2009;144:95-100

Functional MRI for pain and depression

- Giesecke T, Gracely RH et.al. The relationship between depression, chronic pain, and experimental pain in a chronic pain cohort. Arthritis & Rheumatism May 2005; 52:1577-84

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).

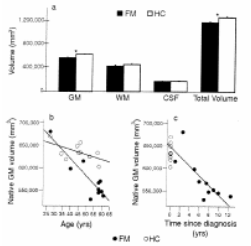
Depression was associated with affective pain processing (amygdalae and contralateral anterior insula).
There are parallel, independent networks for sensory and affective pain.

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

Brief Communications

Accelerated Brain Gray Matter Loss in Fibromyalgia Patients: Premature Aging of the Brain?

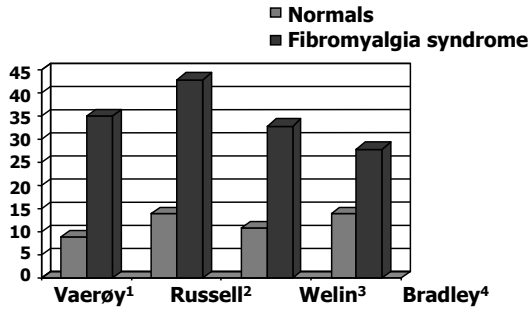
Anil Kuchinad,[1,2] Petra Schweinhardt,[1] David A. Seminowicz,[1] Patrick B. Wood,[1] Boris A. Chizh,[3] and M. Catherine Bushnell[1,2,3]
[1]McGill Centre for Research on Pain, [2]Department of Neurology and Neurosurgery, and [3]Department of Anesthesia and Faculty of Dentistry, McGill University, Montreal, Quebec, Canada H3A 2B2, and [3]GlaxoSmithKline, Addenbrooke's Centre for Clinical Investigation, Addenbrooke's Hospital, Cambridge CB2 2QG, United Kingdom



- ___x greater loss in FMS
- ___x loss per year

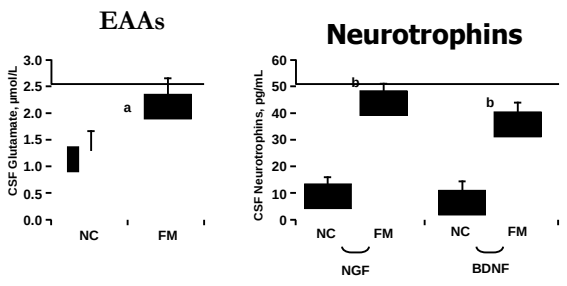
PAIN June 2009 (Hsu MC, 143:262-7) indicates that FMS patients with major affective disorder are only at risk for this!

Fibromyalgia Cerebrospinal Fluid Substance P



1. Vaeroy H, et al. *Pain*. 1998;32:21-26. 2. Russell IJ, et al. *Arthritis Rheum*. 1994;37:1593-1601. 3. Liu Z, et al. *Peptides*. 2000;21:853-860. 4. Bradley LA, et al. *Arthritis Rheum*. 1999;42:2731-2732.

Increased CSF Levels of Glutamate and Neurotrophins



[a] *P*<0.003; [b] *P*<0.001.
BDNF, brain-derived neurotrophic factor; EAA, excitatory amino acid; NGF, nerve growth factor.
N=20 patients with fibromyalgia and 20 control subjects.
Sarchielli et al. *J Pain*. 2007;8:737-745.

What hope is there?

Brain Aging → (time) → ↑ Nerve Growth Factor
↓
Memory and sleep problems
+
pain ← (time) ← ↓ biogenic amines
depression
poor stress response
↓
↑ Substance P
↓
→ **Fibromyalgia**

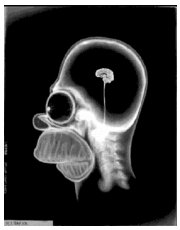
Dr. Jon Russell's theory

Fibromyalgia Pathophysiology: Validation

- Recent data suggest alterations of the CNS may contribute to chronic widespread pain of FM
- Central _____ is emerging as a leading theory of FM pathophysiology
- fMRI data provide supporting evidence that FM is a central 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

Staud and Rodriguez. *Nat Clin Pract Rheumatol*. 2006;2:90-98; Henriksson. *J Rehabil Med*. 2003;41(suppl 41):89-94; Gracely et al. *Arthritis Rheum*. 2002;46:1333-1343; Campbell and Meyer. *Neuron*. 2006;52:77-92; Rao. *Rheum Dis Clin N Am*. 2002;28:235-259; Maneuf and McKnight. *Br J Pharmacol*. 2001;134:237-240; Cedera et al. *J Neurochem*. 2005;94:1131-1139.

Myth #4: nothing can be done for this


Altinadag C. Redox Rep 2006; 11:131-5

Total antioxidant capacity and the severity of the pain in patients with fibromyalgia

Ozlem Altindag[1], Hakim Celik[2]

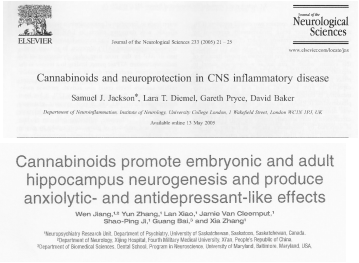
Departments of [1]Physical Medicine and Rehabilitation, and [2]Biochemistry, Harran University, Sanliurfa, Turkey

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

Functional Medicine for FMS: pearls

- **PREVENT GREY MATTER ATROPHY:**
- Omega 3 FA: _____mg EPA+DHA/ day over 3 months or more aggressive 1200mg/ 50 lbs body weight → check omega 3 blood test and aim for AA:EPA ratio between 1.0-3.5
  → [Ko G, Arseneau L, Nowacki N, Mrkoboda, S. *Omega 3 fatty acids for neuropathic pain: literature review and case series.* Practical Pain Manage 2008; 8(7):21-31 and Clin J Pain 2009 (in press)]
  Ozgocmen S et.al. Effect of omega-3 fatty acids in the management of fibromyalgia syndrome. Int J Clin Pharmacol Therap 2000;38:362-3
- Serum B12 > ____pmol/L →[Teitelbaum J. From Fatigued to Fantastic p227]
  - SHINE approach: Teitelbaum J, Bird B, Greenfield R et.al Effective treatment of chronic fatigue syndrome and fibromyalgia: a randomized, double-blind, placebo-controlled, intent to treat study. J Chronic Fatigue Syndrome 2001; 8(2)
- Vogiatzolou A et.al. Vitamin B12 status and rate of brain volume loss in community-dwelling elderly. Neurology 2008; 71:826-32. (brain loss with level < 309 pmol/L)
- Serum 25(OH) vitamin D3: ____ nmol/L (40-64 ng/ml)
  → [Ko G, Arseneau L. Vitamin D (letter to the editor) Pract Pain Manage 2008;8(7):12-13.
  Turner MK et.al. Prevalence and clinical correlates of Vitamin D inadequacy among patients with chronic pain. Pain Medicine 2008; 9:979-84

Cannabinoids: reduce glutamate neurotoxicity


ELSEVIER — Journal of the Neurological Sciences 233 (2005) 21–25 — Journal of the Neurological Sciences — www.elsevier.com/locate/jns

Cannabinoids and neuroprotection in CNS inflammatory disease

Samuel J. Jackson*, Lara T. Diemel, Gareth Pryce, David Baker

Department of Neuroinflammation, Institute of Neurology, University College London, 1 Wakefield Street, London WC1N 1PJ, UK

Available online 15 May 2005

Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects

Wen Jiang,[1,3] Yun Zhang,[1] Lan Xiao,[1] Jamie Van Cleemput,[1] Shao-Ping Ji,[1] Guang Bai,[2] and Xia Zhang[1]

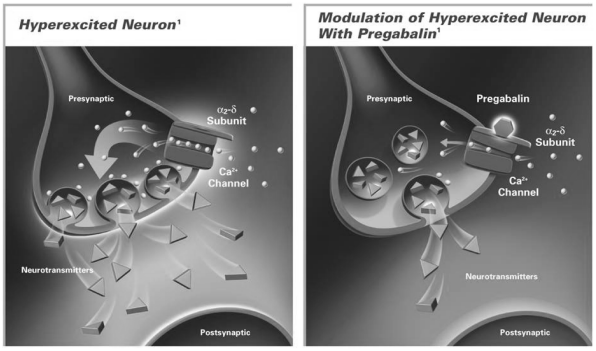
[1]Neuropsychiatry Research Unit, Department of Psychiatry, University of Saskatchewan, Saskatoon, Saskatchewan, Canada. [2]Department of Neurology, Xijing Hospital, Fourth Military Medical University, Xi'an, People's Republic of China. [3]Department of Biomedical Sciences, Dental School, Program in Neuroscience, University of Maryland, Baltimore, Maryland, USA.

Pharmaceutical cannabinoid FMS studies: Skrabek RQ, Galimova L, Ethans K. A randomized double-blind placebo controlled trial assessing the effect of the oral cannabinoid Nabilone on pain and quality of life in patients with Fibromyalgia. J Pain 2008;9:164-73.

Ko G, Hum A, Eitel M, Tumarken E. *A retrospective chart review of add-on nabilone in the clinical management of fibromyalgia.* Pain Res Manage 2009; 14(2):152.

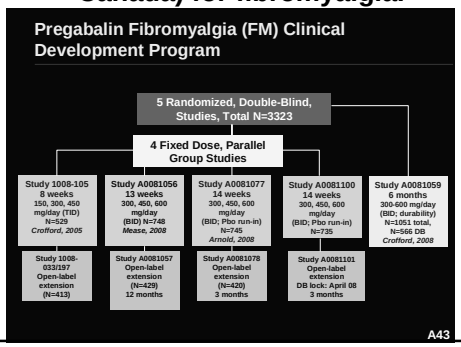
Ko G, Wine W, Tumarken E. Case series of fibromyalgia patients with neuropathic pain improved with the sublingual cannabinoid Sativex. *European J Pain* 2007; 11:145-6
Ko GD, Wine W. *Chronic pain and cannabinoids.* Practical Pain Management 2005(May); 5:28-39.

Pregabalin Modulates Hyperexcited Neurons = reduces glutamate release

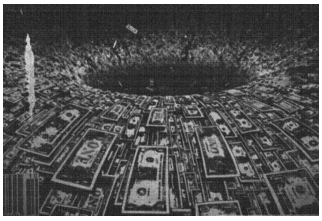


*Does not affect Ca^{2+} influx in normal neurons; Does not affect cardiac calcium channels

Pregabalin is the most studied drug and the first approved drug (USA and Canada) for fibromyalgia.

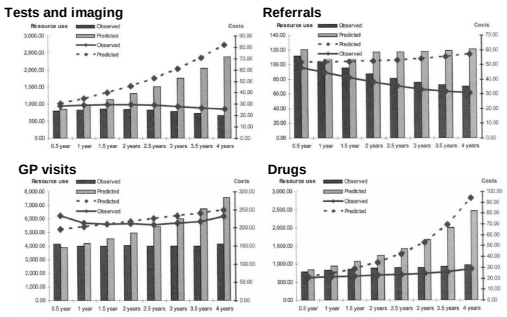


Myth #5: Diagnosis leads to disability and will _____ the system



Diagnosis of FM Is Associated With Reduced Health Care Costs

Health Economic Consequences Related to the Diagnosis of Fibromyalgia

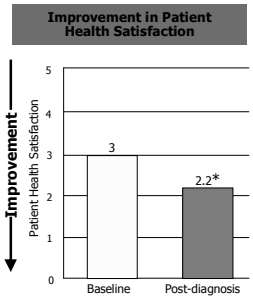


Annemans et al. *Arthritis Rheum* 2008;58:895-902.

Diagnosis Can Improve Patient Satisfaction

Diagnosis of Fibromyalgia improves health satisfaction

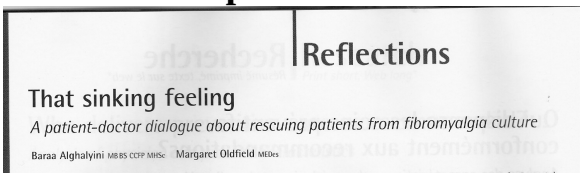
- White et al conducted a prospective, community comparison of Fibromyalgia patients in Canada that revealed significantly improved scores 36 months post-diagnosis
- Patient self-reported health satisfaction on a 5-point scale



White et al. *Arthritis Rheum.* 2002;47:260-265.

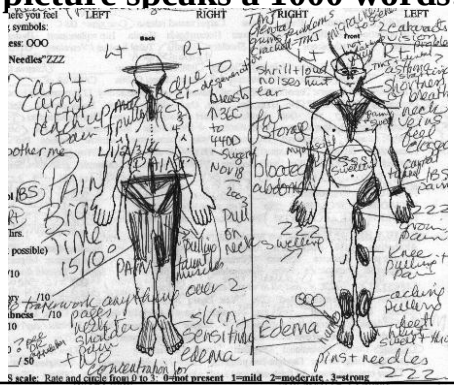
*Statistically significant versus baseline (95% Confidence Interval -1.2, -0.4).

How do we manage fibromyalgia patients?



VALIDATION HOPE

Listen and get a Pain Diagram: a picture speaks a 1000 words!



Fibromyalgia Moldofsky Questionnaire: to be validated and published

	Never	Sometimes	Often	Always	Don't Know	Item score
Pain or stiffness in most of the parts of my body						
My body is sensitive to any tightness or pressure						
I feel energetic						
My sleep is refreshing						
I feel sad or nervous						
I am content with my life						

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

WHAT PATIENTS TAKE FOR FIBROMYALGIA? The 5 A's

Wolfe F, Anderson J Arthritis Rheum 1997; 40:1560-70.

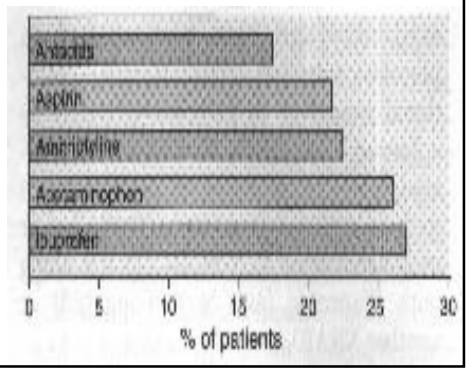
A _____

A _____

Amitriptyline

A_____

A____



Antidepressants

+ Documented Effectiveness -

Tertiary Amines	Secondary Amines	SSRIs, SNRIs and others
amitriptyline	desipramine	paroxetine
imipramine	nortriptyline	citalopram
		bupropion
5-10 mg qhs → 25 mg x 2 months		venlafaxine

+ Side Effects -

Nishishinya B et.al. Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy. RHEUMATOLOGY 2008; 47:1741-6.

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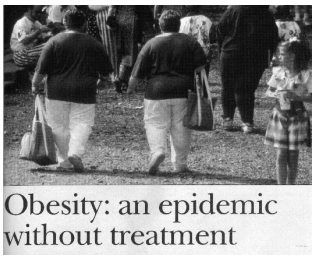
Complications of treatment

AMITRIPTYLINE:

Weight gain

Anticholinergic effects:

- dry mouth
- constipation
- urinary retention



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

Gabapentin

- Absorption: the percentage of absorption decreases with the dosage increase
- Divided doses improve absorption

Pregabalin

- Absorption: proportional to the dose
- The dose-blood level curve is linear

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

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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

Carville et al. **EULAR** evidence based recommendations for the management of fibromyalgia syndrome. ***Ann Rheum Dis*** *published online* ***20 July 2007***.

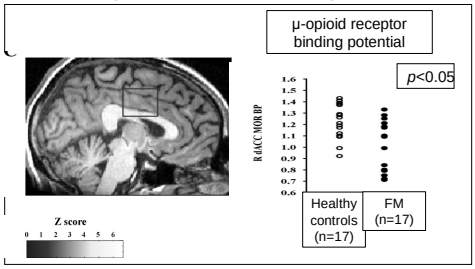
Pharmacological Management

Recommended Agents	**Pregabalin**	Antidepressants Amitriptyline **Duloxetine***	**Tramadol,** pramipexole & tropisetron **	Simple analgesics and weak opioids
Rationale	Pain management	Pain management Function	Pain management	Can also be considered
Level of Evidence/ Strength	Ib A	Ib A	Ib A	IV D
Not Recommended (IV D)	***Strong opioids***	***Corticosteroids***		

*** Appropriate options: amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide, and pirlindole****
**** Tropisetron, milnacipran, pirlindole not available in Canada**

Decreased Central mu-opioid Receptor Availability in FMS

Right dorsal anterior cingulate



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

TRAMADOL

Synergistic Mechanisms of Action

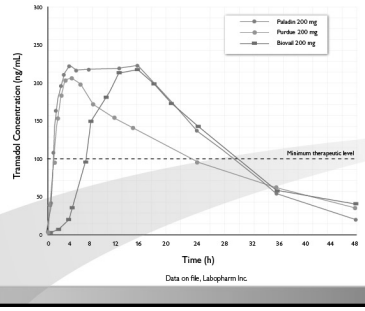
1. Mild mu opioid agonist → may or may not be helpful in fibromyalgia?
2. Mild inhibition of norepinephrine and serotonin reuptake → enhances DNIC

Molecular structure is almost identical to venlafaxine

Muth-Selbach US, et al. *Anesthesiology* 1999;91:231
Bjorkman R, et al. *Pain* 1994;57:259

PHARMACOKINETICS

PK PROFILE OF THE 3 ONCE-DAILY TRAMADOL FORMULATIONS

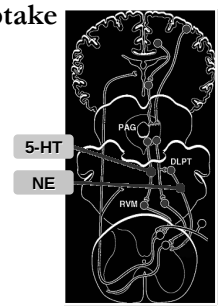


Data on file, Labopharm Inc.

Duloxetine (SNRI) Inhibits 5-HT and NEp 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



PAG – periaqueductal grey
DLPT – dorsolateral pontine tegmentum
RVM – rostral ventromedial medulla

1. Cymbalta® Product Monograph, Eli Lily Canada Inc., October 31, 2007.
2. Figure adapted from: Fields HL and Basbaum AI. Central nervous system mechanisms of pain modulation. In: Wall PD and Melzack R, eds. Textbook of Pain, 5th ed. Churchill Livingstone: London, UK;1999,310.

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Duloxetine Potential Drug Interactions

CNS drugs	• Caution is advised when Duloxetine is taken in combination with other centrally acting drugs and substances, especially those with a similar mechanism of action, including alcohol. • Concomitant use of other drugs with serotonergic activity (e.g. SNRIs, SSRIs, triptans, or tramadol) may result in serotonin syndrome.
Serotonergic drugs	• Based on the mechanism of action of Duloxetine and the potential for serotonin syndrome, caution is advised when Duloxetine is co-administered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as **tryptophan, triptans, serotonin reuptake inhibitors, lithium, tramadol, or St. John's Wort**.
Triptans ($5HT_1$ agonists)	• Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. • If concomitant treatment with Duloxetine and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
Drugs that affect gastric acidity	• Caution is advised in using Duloxetine in patients with conditions that may slow gastric emptying (e.g. some diabetics).
Tricyclic antidepressants (TCA)	■Caution is advised in the co-administration of tricyclic antidepressants (TCAs) (e.g. amitriptyline, desipramine, nortriptyline) because Duloxetine may inhibit TCA metabolism. ■Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Duloxetine.
Warfarin	• Increases in INR have been reported when Duloxetine was co-administered with warfarin.

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Adapted from Cymbalta® Product Monograph, Eli Lily Canada Inc., October 31, 2007.

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

Giesecke T, et al. *Arthritis Rheum* 2003;48:2916-2922
Subgroups studied with fMRI: The Effect of Milnacipran on Pain Modulatory Systems in FMS: an fMRI Analysis by Gracely R, Jensen K, Petzke F etal.

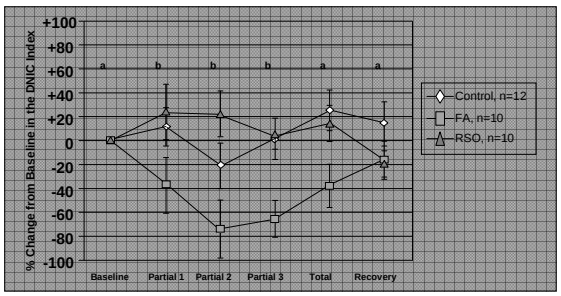
Effects on sleep MacFarlane, J. sleepreviewmag.com

Med	Sleep latency	Sleep efficiency	% SWS	% REM	a.m. sedation
TCA	↓↓	↑	↑	↓	↑↑
SNRI	↑/↓	↑/↓	↓	↓	↑ (esp. paroxetine and fluoxetine)
Benzo	↓↓	↑	↓↓	↓↓	↑
Zopicolone	↓↓	↑	↑/ ---	---	---
Gabapentin	↓	↑	↑	↑	---
Melatonin	↓ / ---	↑ / ---	n/a	n/a	---

A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo Hindmarch I. SLEEP 2005;28:187-93

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

Sleep Continuity Disturbances Impair DNIC



Partial sleep deprivation day 1, 2, and 3
FA and RSO underwent total sleep deprivation for 36 hours

*DNIC Index=PPTh during cold pressor/PPTh before cold pressor *100.
Smith MT et al. *Sleep*. 2007;30(4):494-505.

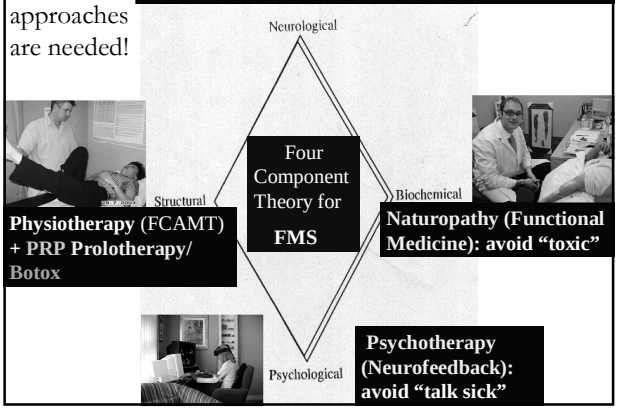
How I prescribe Pregabalin…

- Warn about adverse effects:
- Dizziness, Drowsiness 23%
- eDema, 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 qam (qafternoon) + 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.

Multiple approaches are needed!

Pain control: nerve blocks, acupuncture, TENS, TCAs, pregabalin, SNRIs, tramadol, cannabinoids

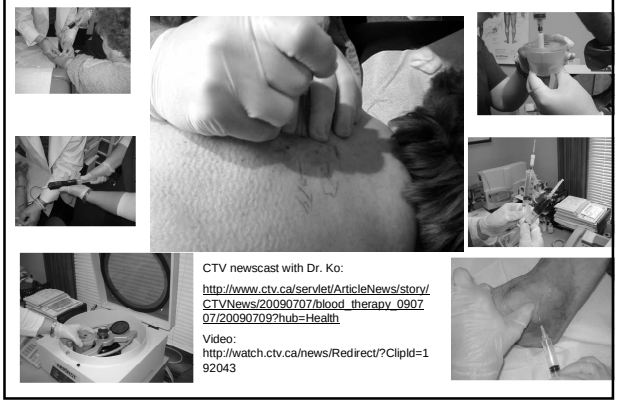


Physiotherapy (FCAMT) **+ PRP Prolotherapy/ Botox**

Naturopathy (Functional Medicine): avoid "toxic"

Psychotherapy (Neurofeedback): avoid "talk sick"

Emerging Rx: Platelet-rich Plasma injections



CTV newscast with Dr. Ko:
http://www.ctv.ca/servlet/ArticleNews/story/CTVNews/20090707/blood_therapy_090707/20090709?hub=Health

Video:
http://watch.ctv.ca/news/Redirect/?ClipId=192043

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 (bHRT) 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) – ND – MD/ RN (Pain)
- Education: patient, physician, public

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