

Fibromyalgia

- A clinical syndrome characterized by chronic widespread pain and tenderness to palpation at specific body sites
- Fibromyalgia has no target tissue but an easily recognizable clinical presentation

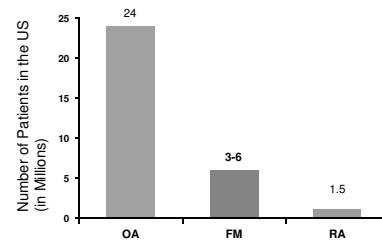
The Evolution of the Fibromyalgia Concept

- Muscular Rheumatism: c.1700
- Valliex (1841) tender points
- Fibrositis (Gowers): 1904
- Fibromyalgia (Yunus): 1981
- ACR Classification Criteria: 1990
- ACR Diagnostic Criteria (Preliminary): 2010

The Prevalence of Fibromyalgia

- General medicine clinics: 5-10%
- Rheumatology practice: 15%
- General population: 2%
 - Incidence estimated at 3-6 million
- Women: 3% Men: 0.5%
 - At least 6 x more prevalent in women in a clinic setting
 - 9x more likely in most rheumatology clinics
- Wolfe (1995): prevalence increases with age, most common in women >50

Fibromyalgia More Prevalent than Rheumatoid Arthritis



The Paradox of Fibromyalgia: No Target Tissue

- Normal passive range of joint motion
- Minimal mechanical disability
- Absence of muscle weakness or atrophy
- Normal ESR
- Normal radiographs, electromyogram, etc

ACR 1990 Fibromyalgia Classification Criteria

From History: widespread pain of 3 months duration

From Examination: tender points defined by digital palpation with a force of 4 kg pain experienced in at least 11 of 18 tender point sites

Wolfe F, et al. Arthritis Rheum 1990;33:160-72

Case Presentation

- Ms. JD is a 51 year-old female who complains of severe pain and swelling of her hands and generalized stiffness lasting over an hour in the morning. Her joints do not move well and she cannot grip objects without pain.
- Q: what would lead you to suspect a diagnosis of FM (fibromyalgia) rather than early rheumatoid arthritis (ERA) or another inflammatory arthritis?

Differential Diagnosis

- What symptoms would lead us towards FM?
- Pain
 - Symptoms start insidiously but then maintain consistent severity for at least 3 months
 - Widespread symmetrical pain: axial and truncal, jaw, shoulder and hip girdles, upper and lower arms and legs
- The other major symptoms:
 - Fatigue (I feel like I always have the flu)
 - Waking unrefreshed (no matter how much sleep I have had I feel exhausted as if I have not slept at all)
 - Cognitive symptoms (I cannot focus my thoughts, I have trouble remembering, I cannot do simple math)

Differential Diagnosis

- What other symptoms would lead us towards FM?
- General Somatic symptoms:
 - Irritable bowel syndrome: abdominal pain and cramping, food intolerance, constipation, diarrhea, nausea, heartburn, vomiting
 - Neurologic: headaches, muscle cramps and weakness, numbness and tingling, loss or change of taste, ringing in the ears, dizziness, seizures
 - Irritable bladder symptoms: frequent urination, painful urination, bladder spasms

Differential Diagnosis

- What other symptoms would lead us towards FM?
- General Somatic symptoms:
 - Depression, insomnia, many allergies, chemical sensitivity, nervousness
 - Raynaud's Phenomenon, cold and heat intolerance, sun sensitivity, dry skin, dry eyes and throat
 - Hives/welts, easy bruising, hair falling out
 - Loss or change of taste, loss of appetite

Physical examination

- General examination is normal.
- Musculoskeletal examination is normal.
 - Joints are NOT swollen, range of motion is normal.
 - Strength is limited by pain; no muscle atrophy or fasciculation; reflexes are normal; sensation is intact
 - Widespread tender points are seen in the majority of patients but a formal tender point examination to diagnose FM is no longer used for diagnosis
 - Should we accept a diagnosis of FM in the absence of ANY tender points?

Differential Diagnosis

- Past medical history is variable
 - Many have symptoms dating back to childhood; others claim an abrupt change, previously healthy and productive
 - Many claim symptoms started after physical trauma, infection, social stressors (e.g. divorce)
- Family history often positive
 - First degree relatives are 8.5x more likely to have FM than relatives of RA patients
- Many drug allergies but mostly intolerance rather than rashes, hives, difficulty breathing or wheezing

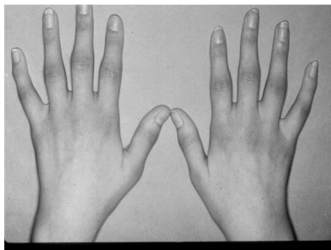
Differential Diagnosis

- Is age 51 too old for either FM or ERA?
 - No for both. FM commonly occurs in individuals aged 25 to 60; highest incidence age 50. Durations of symptoms at diagnosis about 5 years.
 - Early RA trials (disease within 6 months) mean age 50.
- Does morning stiffness of over an hour distinguish inflammatory arthritis from FM?
 - No. Severe morning stiffness that may last hours is a hallmark of both FM and ERA.

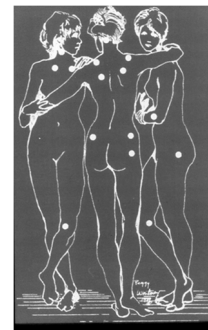
Differential Diagnosis

- Does joint swelling distinguish FM from RA?
 - Yes but only if confirmed by physical examination.
 - FM patients often complain of joint swelling but there are no objective signs of synovitis
- Would the absence of pain in other areas than her hands exclude FM?
 - Yes. FM patients should complain of widespread pain and not pain confined to one region of the body.
 - This is one way to distinguish FM from Myofascial Pain Syndrome

RA Symmetrical synovitis



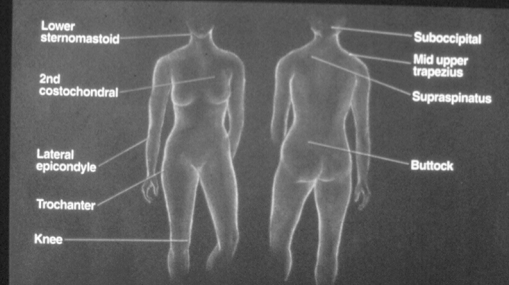
Fibromyalgia tender points



Fibromyalgia tender points



Map of 18 Possible Tender-Points in Fibromyalgia



Source: Panel Consensus; Wolfe et al, 1990.

The Tender Point: Key to Fibromyalgia Diagnosis



- Excessively tender, discrete area of soft tissue
- Palpated with thumb or first two fingers
- Palpation pressure: ~ 4 kg/cm, enough to whiten nail

Source: Wolfe et al, 1990.

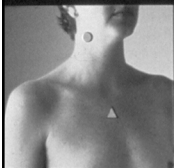
Tender-Point Palpation: I. Head



● Insertion of suboccipital muscle



Tender-Point Palpation: IV. Neck and Chest



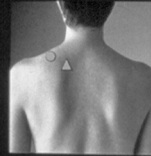
● Lower sternomastoid



▲ Second costochondral junction



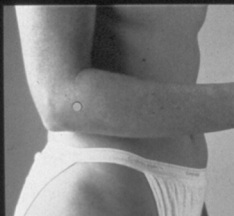
Tender-Point Palpation: II. Upper Back



● Mid upper trapezius
▲ Origin of supraspinatus



Tender-Point Palpation: V. Arms



● Lateral epicondyle



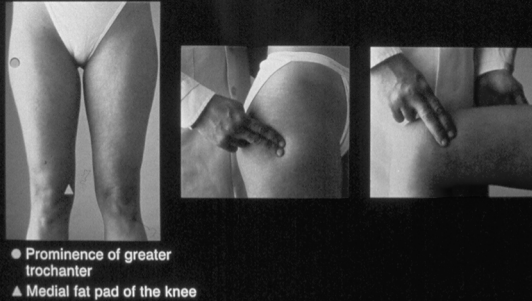
Tender-Point Palpation: III. Lower Back



● Upper outer buttock quadrant



Tender-Point Palpation: VI. Legs



ACR 2010 Preliminary Diagnostic Criteria for Fibromyalgia

3 components:

1. Widespread pain index (WPI) > 7 and Symptom severity (SS) scale score ≥ 5 or WPI 3-6 and SS scale score ≥ 9
2. Symptoms have been present at this level for at least 3 months
3. The patient does not have a disorder that would otherwise explain the pain.

Wolfe F, et al. Arthritis Care Res 2010; 62: 600-10

ACR 2010 Preliminary Diagnostic Criteria for Fibromyalgia

WPI: count the number of areas in which the patient had pain in the last week. Score is 0 to 19

| | | |
|--------------------------------------|----------------------|-------------------------|
| Jaw L or R (2) | Neck (1) | Back Upper or Lower (2) |
| Shoulder girdle L or R (2) | Chest (1) | Abdomen (1) |
| Upper Arm L or R (2) | Lower Arm L or R (2) | |
| Hip (buttock, trochanter) L or R (2) | | |
| Upper Leg L or R (2) | Lower Leg L or R (2) | |

Wolfe F, et al. Arth Care Res 2010; 62: 600-10

ACR 2010 Preliminary Diagnostic Criteria for Fibromyalgia

SS scale score: 0 = no problem
1 = mild or slight or intermittent, few
2 = moderate, frequent, moderate number
3 = severe, continuous, great number

1. Fatigue
2. Waking unrefreshed
3. Cognitive symptoms (fibro-fog)*
4. General somatic symptoms (physician component)**

Total score for SS scale is between 0 and 12

Wolfe F, et al. Arth Care Res 2010; 62: 600-10

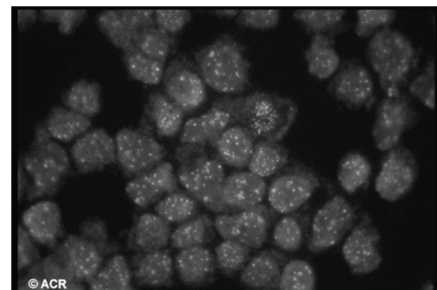
*Does not portend Alzheimer's disease. ACR 2013

** removed in modified Criteria. J Rheum 2011; 38:1113-22

Differential Diagnosis

- What laboratory studies should we perform?
- All laboratory studies are normal in FM. Tests are performed to screen for other systemic illnesses:
 - CBC, comprehensive metabolic panel, ESR, CRP, CK, TSH
 - Do NOT perform RF or ANA as screening studies
 - Serum 25 (OH) D probably not helpful unless very low
Vitamin D (< 9 ng/ml) mimics FM

ANA: speckled pattern



15-23% of FMS and CFS patients have a positive ANA

Don't use ANA as a screening test

Sensitivity 99+ %, specificity 85%
Lupus is a rare disease: highest prevalence (AA women) is 400/100,000
(or 4/1000) = *base rate*
If 1000 women were screened,
4 would be true positive (all SLE positive)
But 150 would be false positive (15% false positive)

A patient with a positive ANA has $4/154 = 2.6\%$ chance of having lupus

In a primary care setting 232 patients referred with positive ANA and
widespread pain – 2.1% had lupus, 9.1% had any ANA-associated
rheumatic disease; no patient with ANA < 1:160.
Abeles, Abeles. Am J Med 126:342, 2013.

Clinical Features of Fibromyalgia

| Criterion | % positive |
|-----------------------------------|------------|
| Widespread Pain | 97.6 |
| Tenderness 11 of 18 tender points | 90.1 |
| Fatigue | 81.4 |
| Morning stiffness > 15 minutes | 77.0 |
| Sleep disturbance | 74.6 |
| Parasthesias | 62.8 |
| Headache | 52.8 |
| Anxiety | 47.8 |
| Dysmenorrhea | 40.6 |
| Sicca symptoms | 35.8 |
| Prior depression | 31.5 |
| Irritable bowel syndrome | 29.6 |
| Urinary urgency | 26.3 |
| Raynaud's phenomenon | 16.7 |

Data from the first 305 patients in the Cleveland Clinic Fibromyalgia Clinic cohort

| | |
|---|-------|
| Fatigue | 98.7% |
| Widespread pain for three months or more | 97.1% |
| Current depression (PHQ-9 score > 10) | 88.6% |
| Unrefreshing sleep | 85.8% |
| Headaches | 82.5% |
| Difficulty concentrating | 79.5% |
| Memory difficulty | 75.5% |
| Urinary frequency | 67.5% |
| Constipation alternating with diarrhea | 61.8% |
| Current severe or moderate-to-severe depression (PHQ-9 score ≥ 15) | 45.8% |
| Anxiety | 41.8% |

PHQ-9 = Patient Health Questionnaire-9

Syndromes That Overlap with Fibromyalgia

The neurologist sees chronic headache, the gastroenterologist
sees IBS, the otolaryngologist sees TMJ syndrome, the
cardiologist sees costochondritis, the rheumatologist sees
fibromyalgia, and the gynecologist sees PMS.

The Spectrum of “Medically Unexplained Symptoms”

- Fibromyalgia
- CFS / SEID
- Somatic symptom disorder
- Illness anxiety
- Conversion disorder
- Hypochondriasis
- Factitious disorder
- Malingering

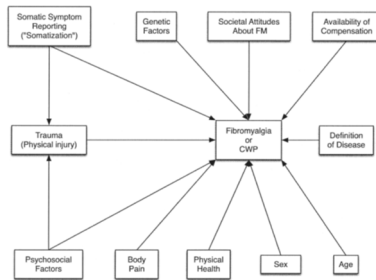
- Depression
- Generalized anxiety disorder

Proposed Pathogenesis of Fibromyalgia

- Emotional trauma
- Physical trauma
- Chiari malformation, syringomyelia, spinal stenosis
- Genetic predisposition
- Low serotonin production and levels
- High CSF nerve growth factor levels
- High CSF Substance P levels
- Dysfunctional sleep
- Neuroendocrine dysfunction
- Low production of growth hormone and insulin-like
growth factor-1

Russell IJ. Am J Med Sci 1998;315:377-84

Does Physical Trauma cause FM?



Wolfe et al. J Rheum 2014; 41:1737-45

Proposed Pathogenesis of Fibromyalgia

- Fan: The sensitive to everything syndrome
- Current working hypothesis: FM is a problem of central sensitization.
 - Peripheral and internal (autonomic) sensory inputs are heightened by the brain so that “normal” sensations are experienced as unpleasant
- Caveat: “central sensitivity is an evolving concept”
- Criticized as too broad and non-falsifiable (Wolfe 2015)*

Wolfe, F. Arth Rheum 2015;67:2553-4

Fm as a problem of Central Sensitization

Persistent activation of C-fiber sensory nerves

Sensitized neurons in the dorsal horn of the spinal cord

Exaggerated neuronal response to normal input

Physical manifestations include

- ◆ Increased receptive field
- ◆ Hyperalgesia
- ◆ Allodynia

Woolf CJ, Mannion RJ. *Lancet*. 1999;353:1959-64.

Neuronal plasticity in FM

- Neural plasticity: the capacity of neurons to change their function, chemical profile, or structure
- Primary sensory and dorsal horn neurons undergo activation, modulation and modification.
- Gain is increased and results in hypersensitivity

Woolf CJ, Salter MW. *Science* 2000;288:1765-68

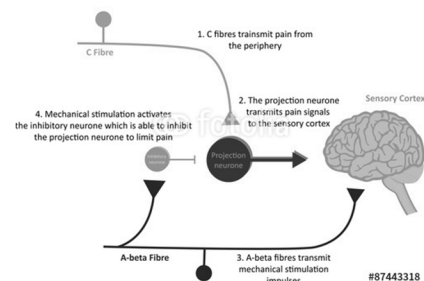
Pathophysiology of Pain

Transmission of pain sensation

- ◆ A fibers: large myelinated
 - α motor
 - β touch
 - γ position
 - δ pain and temperature
- ◆ B fibers: myelinated – autonomic
- ◆ C fibers: small, unmyelinated
 - Pain and temperature

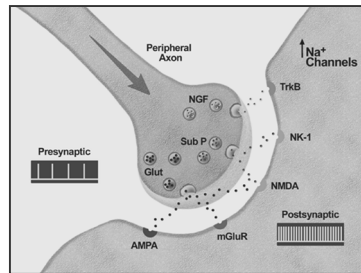
Melzack and Wall

Gate Control Theory of Pain



Mechanisms of Pain

Central Sensitization



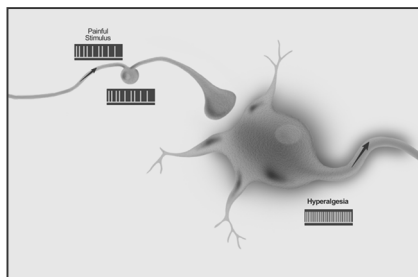
Mechanisms of Pain

Expansion of Receptive Field



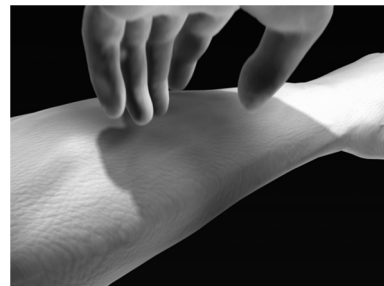
Mechanisms of Pain

Hyperalgesia



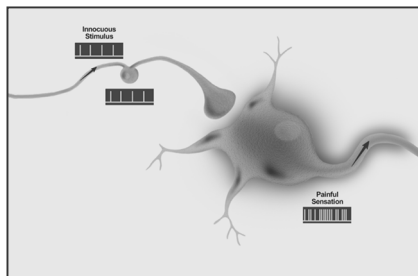
Mechanisms of Pain

Hyperalgesia



Mechanisms of Pain

Allodynia



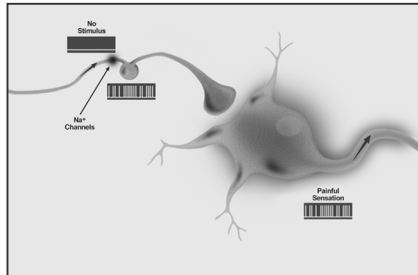
Mechanisms of Pain

Allodynia

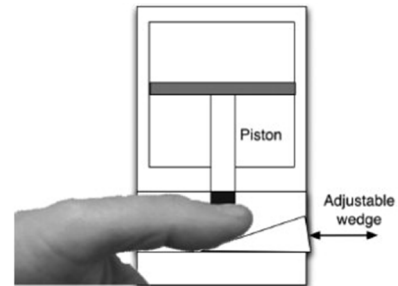


Mechanisms of Pain

Neuropathic

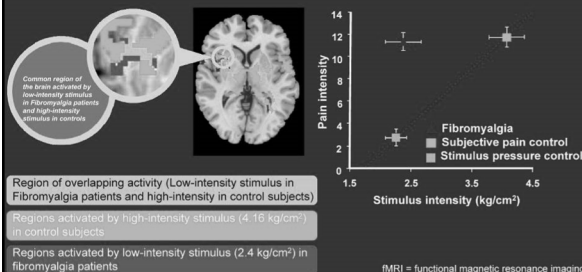


Pneumatic pain stimulator for fMRI studies

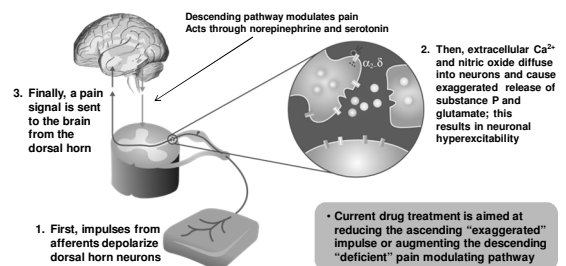


Fibromyalgia May Be a Central Pain Processing Disorder: fMRI Evidence

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



Pathophysiology of Fibromyalgia: The Role of Central Sensitization



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.

Staud. Arthritis Res Ther [serial online]. 2006;8:208; Henriksson. J Rehabil Med. 2003;41(suppl 41):89-94.

The Fibromyalgia Complex: Central Sensitivity Syndromes

- Chronic Fatigue Syndrome
- Fibromyalgia
- Irritable bowel syndrome
- Temporomandibular joint disorder
- Migraine and tension headaches
- Multiple allergies syndrome
- Multiple chemical sensitivities
- Idiopathic low back pain
- Irritable bladder syndrome
- Restless leg syndrome
- Primary dysmenorrhea
- Interstitial cystitis/ chronic prostatitis/ painful bladder syndrome
- Myofascial pain syndrome
- Regional soft tissue pain syndrome
- Many similarities to generalized anxiety disorder

Treatment of Fibromyalgia

- Relieve pain
- Education
- Improve sleep
- Exercise
- Improve sense of well-being and overall function

The Key Elements to managing Fibromyalgia

- Cognitive behavioral therapy
 - Includes education of her illness
- Graduated exercise program
 - Perform daily
- Restful Sleep
 - Quiet environment, no distraction

Treatment of Fibromyalgia / CFS

- Cognitive behavioral therapy

A psychological treatment to modify thoughts and beliefs about FM and modify behavior by teaching coping skills and more effective use of rest, sleep and activity

Components of the cognitive behavior therapy approach

- Education
- Meditation
- Cognitive restructuring
- Distraction
- Pacing
- Laughter

Treatment of Fibromyalgia

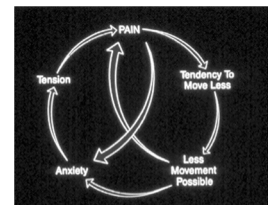
- Education:
 - Fibromyalgia is a well-recognized disorder
 - Stop further diagnostic studies
 - Reassure benign nature of complaints
 - Amelioration of symptoms is possible although there is no cure

Treatment of Fibromyalgia

- Exercise: needs to be sustained
 - Aerobic exercise, Tai-Chi, mineral baths, spa therapy proven effective
 - Emphasize that exercises improves energy and well-being but does NOT reduce pain

Pain, stress and fatigue

Fatigue ↓
Inactivity ↓
Deconditioning ↓ ↑
Susceptibility to DOMS ↓
Muscle Pain → Inactivity

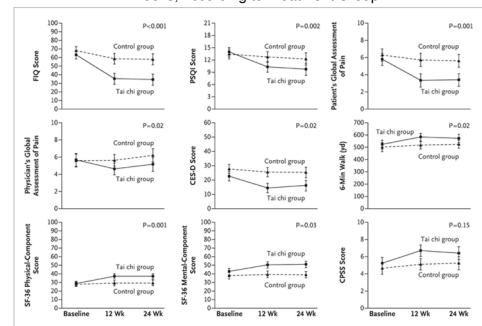


Nonpharmacologic Treatment

Aquatic Exercise
Tai-Chi
Program
Stretching
Low impact aerobics



Tai-Chi Exercises: Mean Changes in Nine Secondary Outcomes at 12 and 24 Weeks, According to Treatment Group



Wang C et al. N Engl J Med 2010;363:743-754



FIGURE 2: Pharmacological Therapies

| | |
|------------------------|--|
| Strong Evidence | <ul style="list-style-type: none"> > Dual reuptake inhibitors such as: <ul style="list-style-type: none"> > Tricyclic compounds (amitriptyline, cyclobenzaprine) > SNRIs and NSRIs (milnacipran, duloxetine, venlafaxine?) > Anticonvulsants (e.g., pregabalin, gabapentin) |
| Modest Evidence | <ul style="list-style-type: none"> > Tramadol > Selective serotonin reuptake inhibitors (SSRIs) > Gamma hydroxybutyrate > Dopamine agonists |
| Weak Evidence | <ul style="list-style-type: none"> > Growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe) |
| No Evidence | <ul style="list-style-type: none"> > Opioids, corticosteroids, nonsteroidal antiinflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics, guanifenesin |

Modified from Goldenberg et al. JAMA. 2004;292:2388-2395.

Pharmacologic treatment of Fibromyalgia

- Improve sleep:
 - Pediatric doxepin 10mg/ml, start with 6 drops at bedtime = 3mg
 - Alternative is low-dose amitriptyline 10mg nightly with slow increase to 50mg
 - Cyclobenzaprine 5 – 10mg nightly

Pharmacologic Treatment of Fibromyalgia

- Depression:
 - 30% have major depression at time of diagnosis
 - Lifetime prevalence of depression is 74% and anxiety disorder 60%
 - SSRIs are not effective in reducing pain by themselves
 - Teach simple relaxation techniques
 - Formal stress-reduction program
 - Sleep hygiene
 - Correct sleep disorder

Pharmacologic Treatment of Fibromyalgia

- General rules:
 - Start with a low dose and build up slowly
 - Build upon a tricyclic at bedtime to improve sleep
 - For patients with prominent sleep problems add pregabalin (alternative gabapentin) to tricyclic
 - For patients with poor energy and exhaustion add duloxetine or milnacipran to tricyclic
 - Combining SNRIs with either pregabalin or gabapentin offers synergistic benefit

Pharmacologic Treatment of Fibromyalgia

- Anticonvulsants: pregabalin and gabapentin
- Pregabalin: start with 25mg at bedtime
- Warn patient about dizziness and somnolence
- Gradually build the dose up to 150mg to 225mg twice a day (300 - 450mg daily)
- Aim for 50% pain reduction; also improved sleep, fatigue and quality of life
- Weight gain of over 7% seen in 8 – 10%
- Alternative is gabapentin
- Start at 100mg nightly, build up to 1200 to 2400mg

Pharmacologic Treatment of Fibromyalgia

- SNRIs: duloxetine, milnacipran and venlafaxine
- Aim for 50% pain reduction
- Duloxetine: start with 20-30mg in the morning
- Gradual increase to 60mg once a day
- Improves pain within 1 week and also mental fatigue
- Side effects are nausea, headache and dry mouth

Pharmacologic Treatment of Fibromyalgia

- Milnacipran: start with 12.5mg in the evening
- Gradual increase with twice a day dosing to 100mg daily; rarely beneficial at 200mg daily
- Improves pain, global status and physical function
- Side effects nausea, headache, constipation
- SNRIs may cause rapid heart rate
- Venlafaxine: final mean dose of 167mg daily was effective in one study

Pharmacologic Treatment of Fibromyalgia

- Others
 - Fluoxetine 20mg in the morning combined with amitriptyline 25mg at bedtime
 - Acetaminophen-tramadol combination up to four times a day
 - Dopamine receptor agonists: ropinirole, pramipexole¹
 - GHB (γ-hydroxybutyrate) sodium oxybate
 - Nabilone – synthetic cannabinoid
 - Naltrexone 4.5mg daily²
 - Memantine 20mg/d (+/- pregabalin)³
 - NSAIDs and prednisone do not work better than placebo

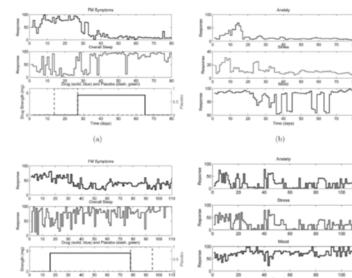
1. Holman AJ, Myers RR. Arthritis Rheum. 2005 Aug;52(8):2495-505
 2. Younger J, Parkitny L, McLain D. Clin Rheumatol. 2014 Apr;33(4):451-9
 3. Olivan-Blasquez, et al. Pain 2014;155:2157

Treatment of Fibromyalgia

- **Multicomponent therapy**
 - Education, physical therapy, psychological component, pharmacotherapy
 - **Meta-analysis:**
 - reduced pain, fatigue, depressive symptoms and limitations on QOL scales
 - improved self-efficacy pain and physical fitness
 - * no sustained benefit at 4-15 months
- Hauser W, Arthritis Care Res 2009; 61:216
- **Control systems engineering approach –**
 - Intervention with drug and behavioral modification based on intense frequent monitoring and frequent decision making – low-dose naltrexone model.

Deshpande, S, et al. TBM 2014;4:275-89

Adaptive Intervention to treat FM

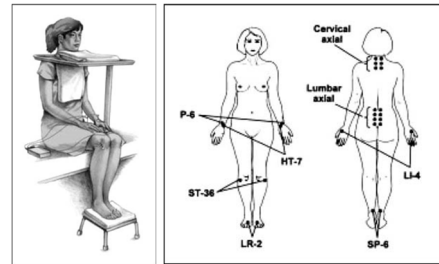


Drug used was naltrexone 4.5mg. Deshpande, et al

Treatment of Fibromyalgia / CFS

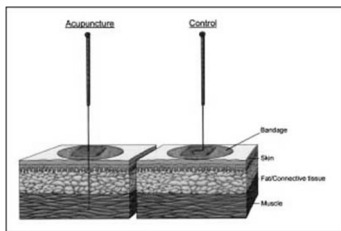
- **Dubious treatments:**
 - growth hormone
 - pressors: fludrocortisone
 - **Alternative Medicine:** NADH, SAM-e, malic acid, acupuncture
 - Botulinum toxin, nerve blocks, trigger point injections, rhizotomies, facet blocks, etc

Acupuncture for Fibromyalgia



Martin DP,et. Mayo Clin Proc 2006;81:749-57

Acupuncture for Fibromyalgia



Martin DP,et. Mayo Clin Proc 2006;81:749-57

References: General

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- Nabilone: Skrabek, *J Pain* 2008; 9:164
- Pramipexole: Holman, *Arthritis Rheum* 2005; 52: 2495
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