University of Massachusetts Medical School
UMASS

Understanding and Managing Fibromyalgia

I HAVE NO FINANCIAL DISCLOSURES RELATIVE TO THIS TALK. HOWEVER, I WOULD LIKE TO DISCLOSE THAT I AM NOT A FIBROMYALGIA EXPERT AND THIS DISORDER IS NOT A MAJOR FOCUS OF MY CLINICAL PRACTICE

Learning Objectives

- Discuss the pathophysiology of fibromyalgia
- Summarize the history and physical exam findings in FM patients
- Review pharmacologic and non-pharmacologic treatments for FM

Case Presentation

- 49 yo female with >10 year h/o widespread pain diagnosed as FM
- Comes to visit with journal of symptoms
- Has been treated with multiple medications including tricyclics, muscle relaxants and NSAIDS. Currently on duloxetine-feels current meds not working but afraid to try anything new because she doesn't want to gain weight
- Reports increased stress due to discontinuation of child support from ex-husband
- PMH: Anxiety and depression

ROS

- Severe Fatigue (prevents her from working even part time)
- Poor sleep
- Pain in every joint, neck and back (7/10 baseline)
- Achy “from head to toe”, feels like she has the flu all the time
- Poor concentration
- Symptoms of IBS
- Diffuse numbness and tingling
- Even light exercise exacerbates her pain

Exam

- Patient is tearful throughout the visit
- Gait is normal, doesn't appear to be in distress
- Verbalizes pain wherever she is touched: FM tender points as well as all control points
- Joints, neurological and general exam normal

FIBROMYALGIA

- A common clinical syndrome characterized by diffuse pain and tender points
- There is no diagnostic test, and no radiographic or pathologic findings
- Currently felt to be a disorder of pain regulation also known as central sensitization

FIBROMYALGIA

- Affects 2-3% of the general population (15% of rheumatology practice)
- Prevalence increases with age (most common in women >50)
- Six times more common in females
- Age range 20-65 years
- It is the most common cause of generalized musculoskeletal pain in woman ages 20-55
- >40% of patients referred to a tertiary pain clinic meet the diagnostic criteria for FM

1990 ACR CLASSIFICATION CRITERIA

- Symptoms of widespread pain, occurring both above and below the waist and affecting both the right and left sides of the body
- Physical findings of at least 11 out of 18 tender points

These criteria had >85% sensitivity and specificity for differentiating patients with FM from those with other rheumatic diseases

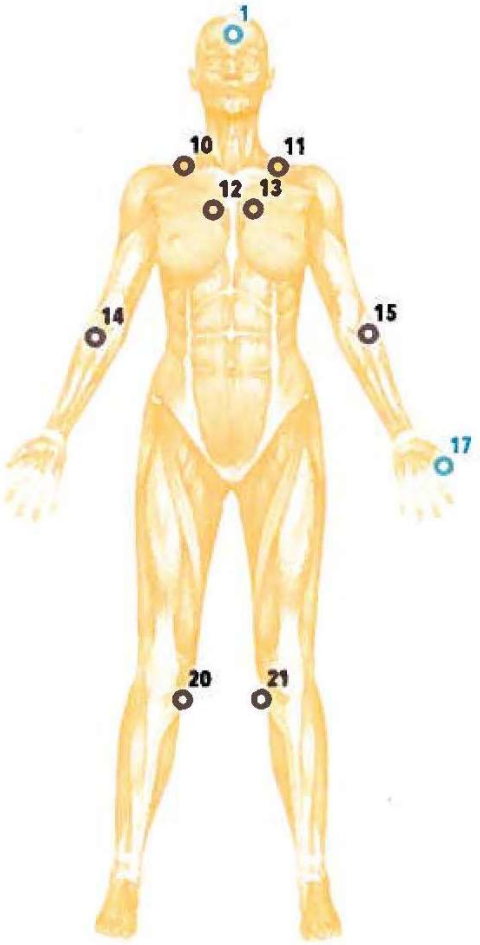
A&R 1990; 33:160

2010ACR CLASSIFICATION CRITERIA
(Still in Draft Form)

- **The 2010 ACR Criteria require the assessment of 3 key elements:**
  - Presentation of widespread pain and symptoms for 3 months or more
  - Widespread Pain Index that assesses the number of painful body areas (HCP-administered questionnaire)
  - Symptom Severity Scale that assesses the severity of fatigue, waking unrefreshed, and cognitive symptoms, as well as the extent of other somatic symptoms (HCP-administered questionnaire)

Wolfe F, Clauw DJ, Fitzcharles M-A, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res. 2010;62:600-610.

Manual Tender Point Survey Sites[2]



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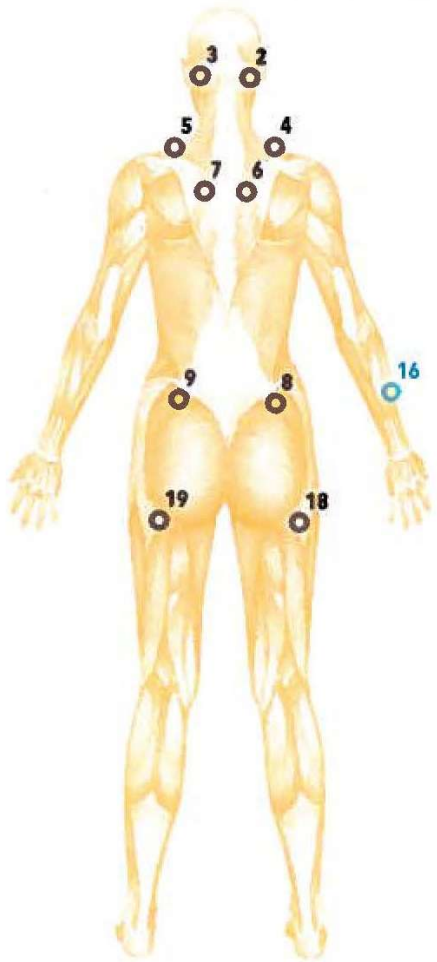

Back

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2, 3 **Occiput:** Suboccipital muscle insertions
4, 5 **Trapezius:** Midpoint of upper border
6, 7 **Supraspinatus:** Above medial border of scapular spine
8, 9 **Gluteal:** Upper outer quadrant of buttocks
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Characteristic Features

- Fatigue
- Sleep disturbance
- Stiffness
- Paresthesias
- Headache
- Weakness
- Raynaud's-like symptoms
- Depression
- Anxiety
- Mood disturbance
- Cognitive difficulties

Other symptoms

- Subjective joint swelling (no true synovitis)
- Abdominal and chest wall pain
- Irritable Bowel Syndrome (50-80% FM pts)
- Temporomandibular Joint Syndrome
- Pelvic pain
- Interstitial cystitis/painful bladder syndrome
- Multiple chemical sensitivities
- Palpitations

OTHER SYMPTOMS CONTINUED

- Vulvodynia
- Dysmenorrhea
- Sexual dysfunction
- Weight fluctuations
- Night sweats
- Orthostatic intolerance
- Chronic Fatigue Syndrome: 70% of CFS patients meet criteria for FM

Overlapping Disorders

- Depression is present in 25-60% of patients; Anxiety disorders also very common
- Sleep Apnea can be found in up to 40% of males with Fibromyalgia
- Repetitive leg movements or nocturnal myoclonus may contribute to Fibromyalgia

FM: Modulating Factors

- Aggravating Factors:
  - Cold or humid weather
  - Nonrestorative sleep
  - Physical/mental fatigue
  - Excess physical activity
  - Physical inactivity
  - Anxiety/stress

FM: Modulating Factors

- Relieving Factors:
  - Warm/dry weather
  - Hot shower/bath
  - Restful sleep
  - Moderate activity
  - Massage

Pathogenesis of FM

- Genetic
- Central Sensitization
- Sleep Abnormalities

Ann Int Med 2007; 146:726-734
Current Opinion in Rhem 2010; 22:59-63

Pathogenesis of FM: Genetics

- Evidence for familial aggregation indicates that genetic risk factors might contribute to the etiology of FM
- Genetic Risk Factors: recent A&R study using large-scale candidate gene approach was used to evaluate >350 genes known to be involved in nociception, inflammation and affect by Smith et al
- Found variations in 4 genes that may be involved (serotonin transporter gene, catechol-O-methyltransferase gene,dopamine D4 receptor gene, HLA-region)

A&R 2012;64:584

Biologic Contributions

- Abnormalities in pain perception at the level of the brain and spinal cord
- Decreased blood flow to the areas of the brain that control pain (thalamus and caudate nucleus)
- Alterations in neurohormones: low plasma serotonin, high CSF substance P, abnormal level of growth hormone
- Abnormalities in the hypthalamic-pituitary-adrenal axis

Ann Int Med 2007;146:726-734
Mayo Clin Proc 2011; 86(9): 907-911

Central Sensitization: A Theory for Neurological Pain Amplification in FM

- Central sensitization is believed to be an underlying cause of the amplified pain perception that results from dysfunction in the CNS[1]
  - May explain hallmark features of generalized heightened pain sensitivity[2]
    - Hyperalgesia – Amplified response to painful stimuli
    - Allodynia - Pain resulting from normal stimuli
- Theory of central sensitization is supported by:
  - Increased levels of pain neurotransmitters[3,4]
    - Glutamate
    - Substance P
- fMRI data demonstrates low intensity stimuli in patients with FM comparable to high intensity stimuli in controls[5]

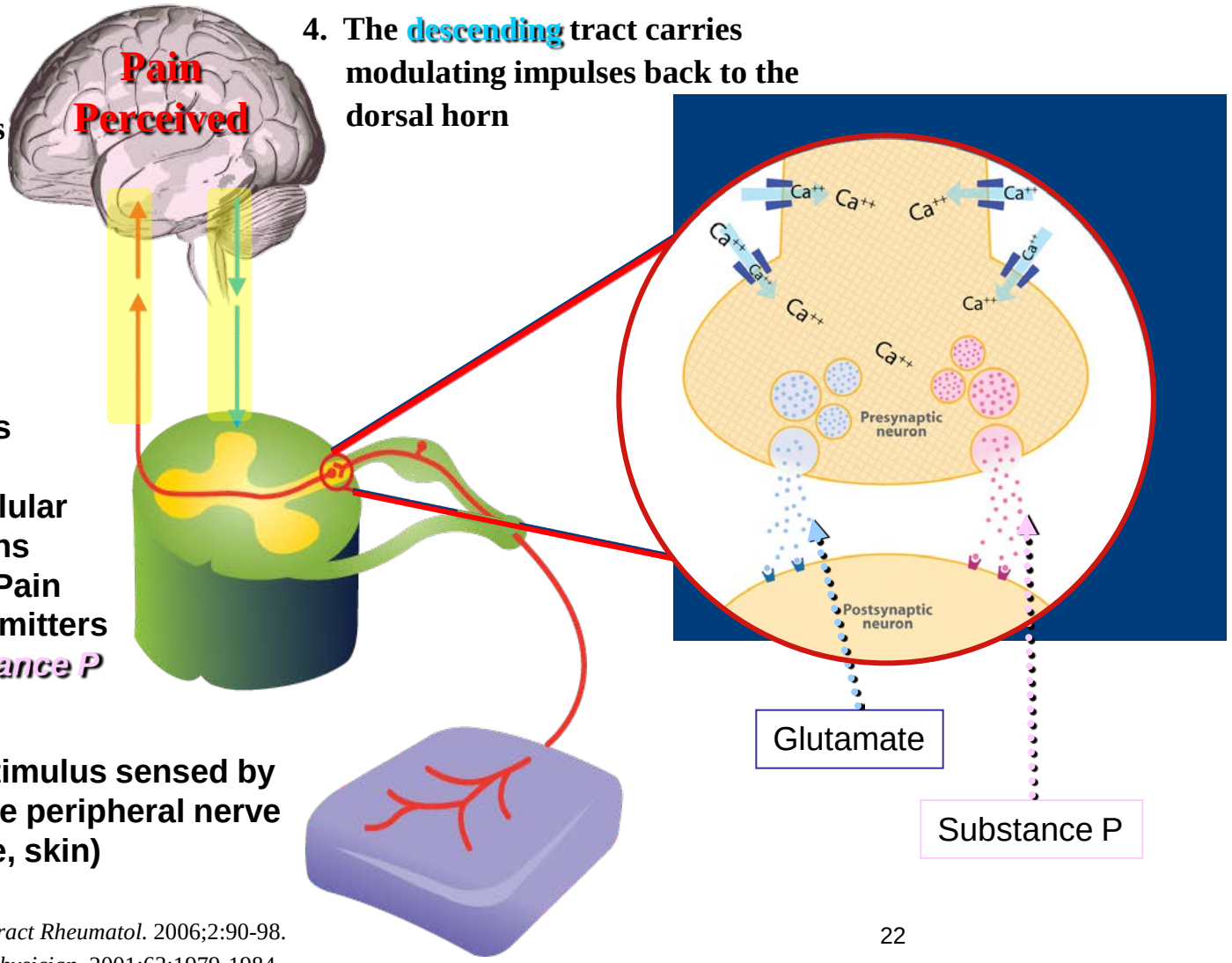
fMRI = functional magnetic resonance imaging

1. Staud R and Rodriguez ME. *Nat Clin Pract Rheumatol*. 2006;2:90-98.
2. Williams DA and Clauw DJ. *J Pain*. 2009;10(8):777-791.
3. Sarchielli P, et al. *J Pain*. 2007;8:737-745.
4. Vaerøy H, et al. *Pain*. 1988;32:21-26.
5. Gracely RH, et al. *Arthritis Rheum*. 2002;46:1333-1343.

The Normal Pain Processing Pathway

3. A signal is sent via the ascending tract to the brain, and perceived as pain

4. The descending tract carries modulating impulses back to the dorsal horn

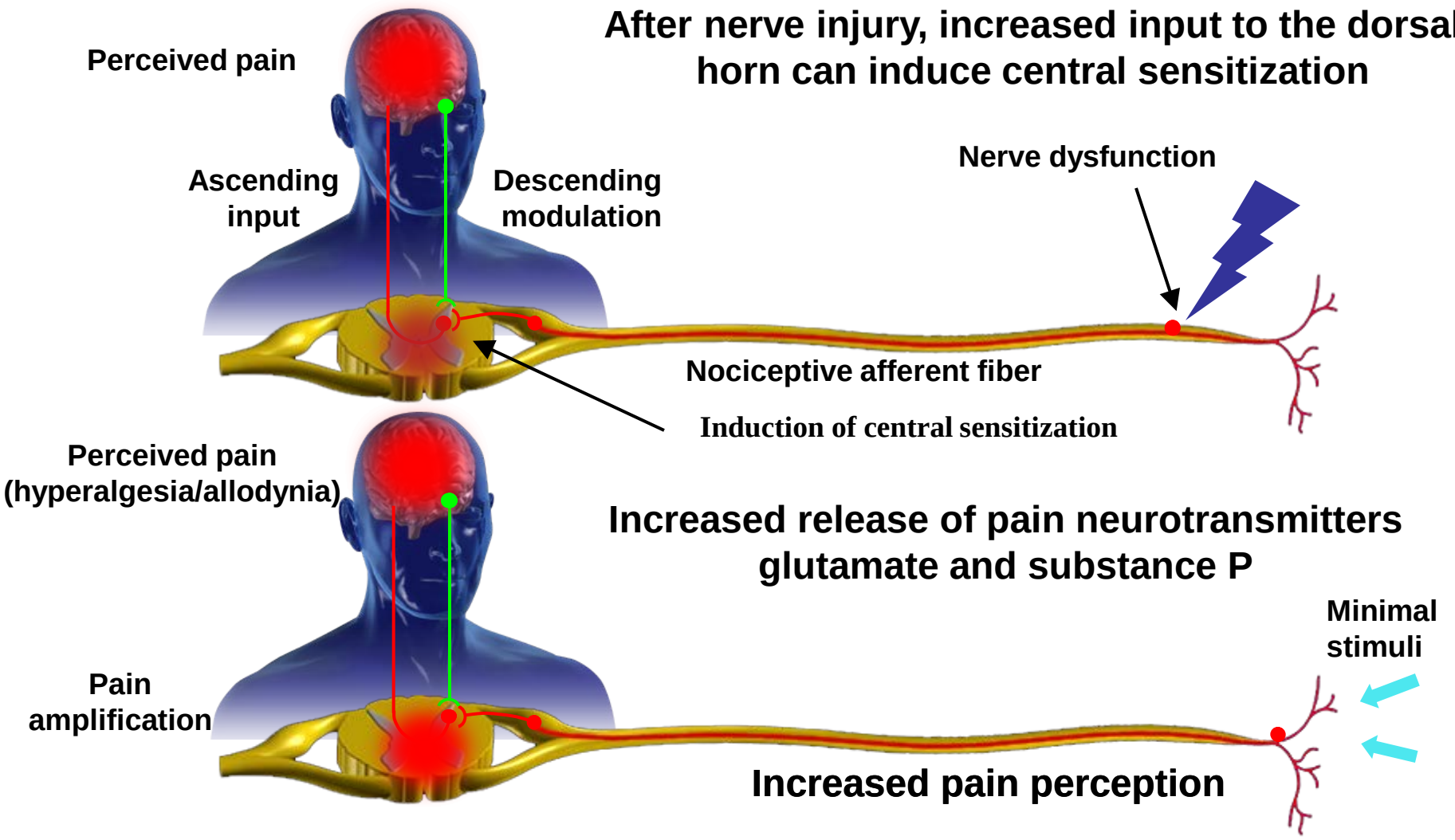


2. Impulses from afferents depolarize dorsal horn neurons, then, extracellular Ca^{2+} diffuse into neurons causing the release of Pain Associated Neurotransmitters – Glutamate and Substance P

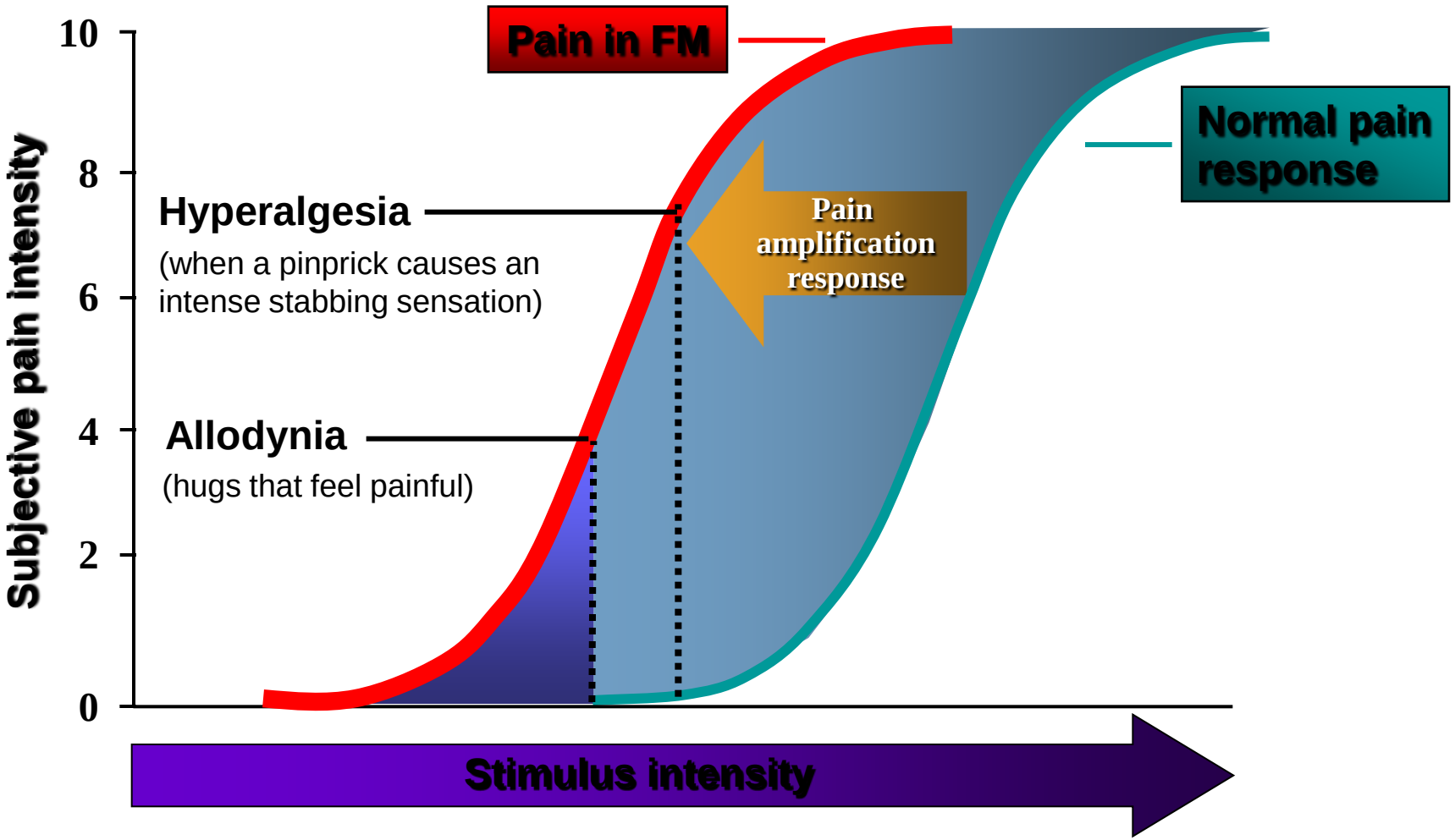
1. Stimulus sensed by the peripheral nerve (ie, skin)

1. Staud R and Rodriguez ME. *Nat Clin Pract Rheumatol*. 2006;2:90-98.
2. Gottschalk A and Smith DS. *Am Fam Physician*. 2001;63:1979-1984.

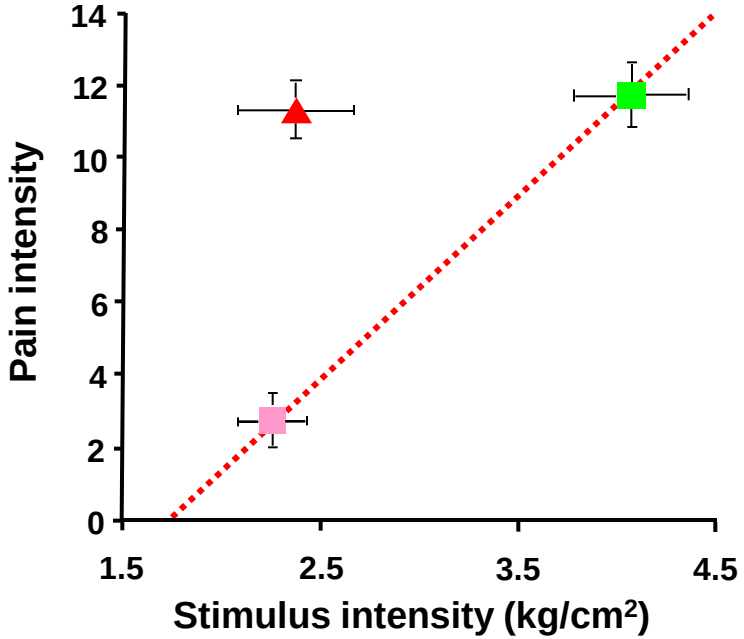
Central Sensitization Produces Abnormal Pain Signaling



FM: An Amplified Pain Response



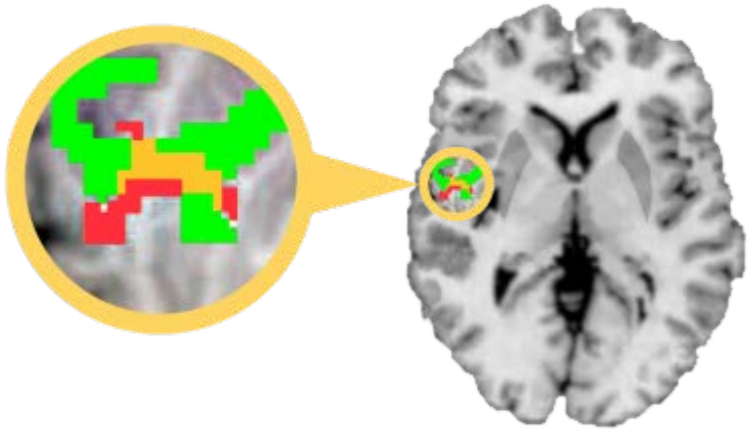
fMRI Study Supports the Amplification of Normal Pain Response in Patients With FM



Patients with FM experienced high pain with low grade stimuli

- ▲ FM (n=16)
- Subjective pain control
- Stimulus pressure control

} (n=16)



Red: Activation at low intensity stimulus in patients with FM

Green: Activated only at high intensity stimulus in controls

Yellow: Area of overlap (ie, area activated at high intensity stimuli in control patients was activated by low intensity stimuli in patients with FM)

fMRI = functional magnetic resonance imaging

Gracely RH, et al. *Arthritis Rheum*. 2002;46:1333-1343.

FM Pathophysiology: Summary

- Central sensitization is a leading theory of FM pathophysiology[1]
- Elevated pain neurotransmitters in CSF of patients with FM[2-4]
  - Several studies showed elevated levels of glutamate and substance P
  - Elevated levels suggest that this may contribute to pain amplification
- fMRI data supports FM as a disorder of central pain amplification[5]
  - Areas activated by high intensity stimuli in control patients were activated by low intensity stimuli in patients with FM

CSF = cerebrospinal fluid
fMRI = functional magnetic resonance imaging

1. Staud R and Rodriguez ME. *Nat Clin Pract Rheum*. 2006;2:90-98.
2. Russell IJ, et al. *Arthritis Rheum*. 1994;37:1593-1601.
3. Bradley LA, et al. *Arthritis Rheum*. 1996;suppl 9:212. Abstract 1109.
4. Sarchielli P, et al. *J Pain*. 2007;8:737-745.
5. Gracely RH, et al. *Arthritis Rheum*. 2002;46:1333-1343.

Sleep Abnormalities

- Found in 75-100% of patients
- Reproducible non-REM Stage 4 sleep disturbance by alpha intrusion
- GABA and serotonin are important in non-REM sleep
- Decreased serotonin precursors are found in the CSF
- Inhibition of serotonin reproduces pain
- Reproducing sleep disturbance results in pain

Moldofsky: Rheum Dis Clin NA 2009: 35:275

Cognitive Behavioral Variables

- Pain beliefs and attributions
- Hypervigilance
- Coping strategies
- Depression and anxiety
- Personality traits/disorders
- Pain behaviors

Environmental and Sociocultural Variables

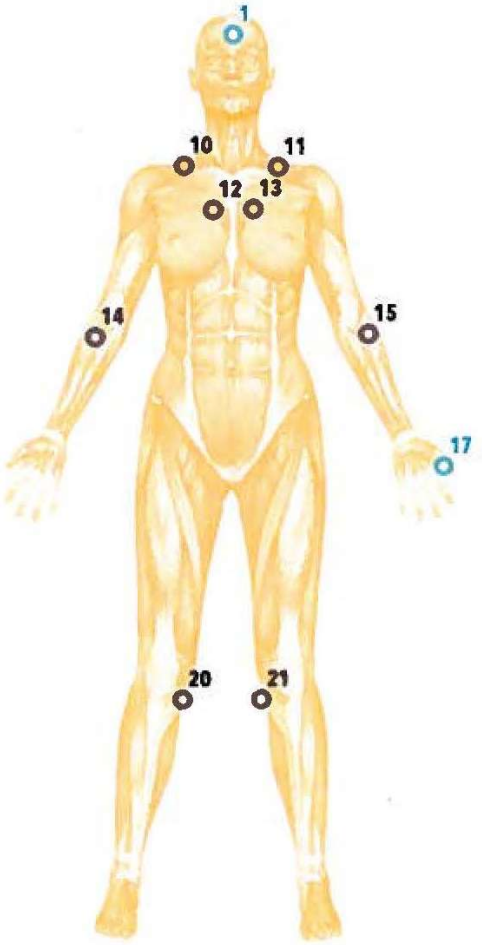
- Abuse during childhood
- Recurrent abuse during adulthood
- Domestic Violence

Annals IM 2001; 134:917
Sem A&R 2002;32:38

PHYISICAL EXAMINATION

- Assessment of pain in the 18 tender points
- Assessment of pain in control points
- Joint exam looking for true synovitis
- Complete neurologic exam

Manual Tender Point Survey Sites[2]



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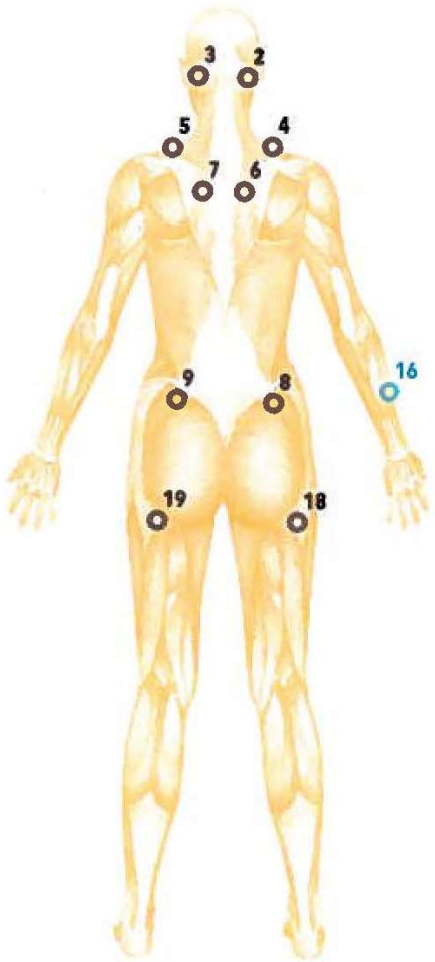

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DIAGNOSTIC TESTING

- Assessment of mood and functional impairment
- Normal lab exam (including CPK, ESR & CRP)
- Consider ordering thyroid studies
- Consider sleep study based on history
- 8-10% of the general population is ANA positive- only order if you have a high suspicion for inflammatory, systemic rheumatic illness (same is true for RF)

Differential Diagnosis

- Connective Tissue Diseases
  - SLE
  - RA
  - Sjogren's
  - Spondyloarthropathy
  - Inflammatory myopathy
  - PMR

Differential Diagnosis

- Nonrheumatic illness
  - CFS
  - Myofascial pain syndromes
  - Drugs
  - Electrolyte disturbances
  - Endocrine disorders (Hypoparathyroid, hyperthyroid, hypothyroid)
  - Malignancy

Differential Diagnosis

- Nonrheumatic illness (continued)
  - Neuropathies
  - Entrapment syndromes
  - Chronic infections (Hepatitis C)
  - Psychiatric (especially somatization disorder or major depression)

Areas of Controversy

- Hepatitis C: some data support association but not proven
- Lyme: association unclear
- Chronic fatigue: overlap in symptoms
- Myofascial pain: some consider this to be a localized form of FM

Chronic Hepatitis C

- Five Extrahepatic Manifestations had a prevalence >10%
- Arthralgia 23%
- Paresthesia 17%,
- Myalgia15%,
- Pruritis 15%,
- Sicca Syndrome11%

Cacoub, et.al. A&R, 1999;42:10

Treatment of Fibromyalgia

- There is no "Magic bullet"
- Can be managed by the Primary Care Provider after initial Rheumatology consult
- Multi-disciplinary approach usually required
- NSAIDS-not a very effective form of therapy (there is no inflammation) when used alone but may be synergistic with other meds

J Rheum 2004; 31:2468-71

Focus

- Focus on improvement of function and not elimination of symptoms
- Focus on identifying and treating associated depression/anxiety
- Focus on empowering patients to take control through life style modification and exercise
- Focus on connecting drug therapy to tangible outcomes

Treatment of Fibromyalgia

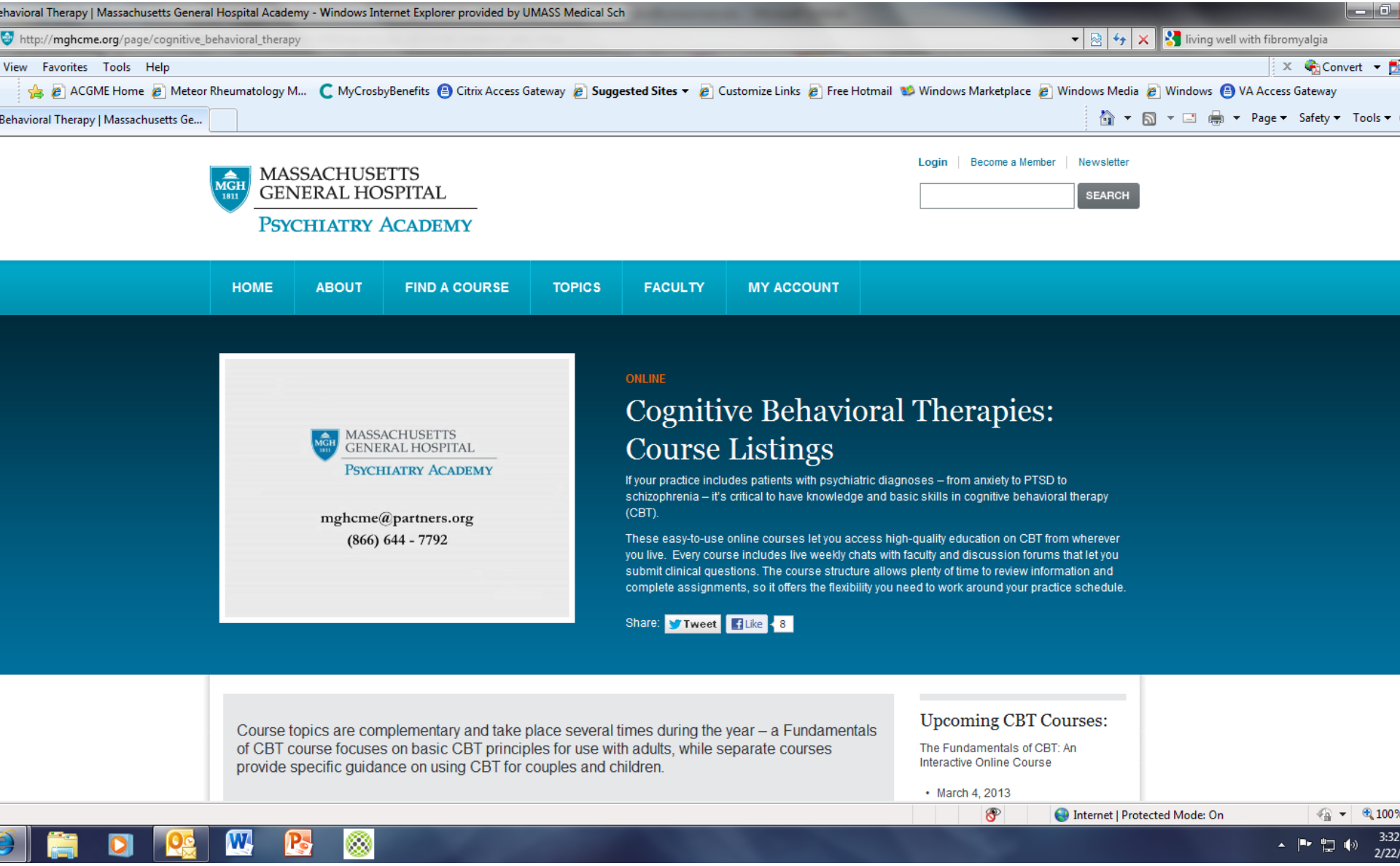
- Education and Reassurance
- Set realistic treatment goals/assess impact on all aspects of life
- Stress Reduction/Pain Management
- Behavioral modification*
- Gradual, Graded Low Impact Exercise*
- Treat sleep disorder if present
- Mental health referral if indicated
- Medication to assist with pain, sleep and fatigue
- TENS/Injections: NOT HELPFUL!!

Mayo Clin Proc 2012; 87(5): 488-496
Jl Pain Res 2012; 5: 425
Jl Pain2011;12 Suppl: 49
Europ J Pain 2010; 14:5

Stress/Pain Management

- Stress Reduction Programs
- Individual Counseling (Cognitive Behavioral Therapy)* with exercise
- EMG Biofeedback and Hypnotherapy
- Acupuncture, Massage and Chiropractic
- Yoga, Tai Chi, Spirituality and Prayer

Ann Rheum Dis 2007; 66:571-581
J Rheum 2002;29:1280



Next course starts May 6, 2013

FDA-Approved Medications for FM

- Serotonin and norepinephrine reuptake inhibitors
  - Duloxetine (Cymbalta) 30mg/d, titrate to 60mg
  - Milnacipran (Savella) 12.5mg/d, titrate to 50mg bid
- Combination with tricyclic (qhs) may be more efficacious
- $Alpha_2$delta calcium channel ligand
  - Pregabalin (Lyrica) 75mg bid, titrate to 150-225mg bid

Pain 2005; 119 (1-3);5-15
Pain 2008; 136(3): 419-431
Clin Ther 2008; 30(11): 1988-2004
J Pain 2008; 9 (9); 792-805

Dual Reuptake Inhibitors Multiple studies showed improvement in symptoms

- Chemically novel and unrelated to other groups of antidepressants
- Strongly inhibit neuronal serotonin and norepinephrine reuptake
- Weakly inhibit dopamine reuptake
- No affinity for muscarinic cholinergic, H1-histaminergic or alpha1-adrenergic receptors
- Duloxetine, milnacipran, venlafaxine (effexor)

J Pain 2010; 11:505
JAMA 2009; 301:198
Pain 2008; 136:432
CNS Drugs 2012;26:297

Treatment

- Avoid stimulants:Caffeine, Nicotine
- Tricyclic Medications (use is limited by lack of uniform efficacy and relatively high incidence of side effects)-clinically important improvement shown in 25-45% of patients
  - Amitryptyline
  - Imipramine
  - Doxepin
  - Desipramine

Treatment

- Muscle relaxants: minimal data for efficacy
  - Cyclobenzaprine (Flexeril)
  - Methocarbamol(Robaxin)
  - Orphenadrine (Norflex)
  - Metaxalone (Skelaxin)

Treatment of Sleep Disturbance

- Clonazepam (Klonopin): .5mg-1mg qhs
- Alprazolam (Xanax): .5 – 1mg qhs
- Zolpidem (Ambien): 5-10mg qhs

Treatment

- Tramadol HCL (Ultram) is FDA approved for chronic use in moderate-severe pain
- Tramadol decreases pain by
  - Binding to the mu opiate receptor
  - Inhibiting the reuptake of serotonin and norepinephrine
- Both mechanisms contribute to anti-nociception

Treatment

- Tramadol Disadvantages
  - Effectiveness is variable
  - Sedation
  - Nausea
  - Potential for abuse/addiction
  - Drug interactions ex. SSRI's, St. John's Wort, with the risk of precipitating seizures

Gabapentin & Pregabalin

- Published beneficial effect in Idiopathic Restless Leg Syndrome, Postherpetic Neuralgia and Diabetic Neuropathy
- Generally well tolerated
- Data show significant improvement in pain
- Excellent safety profile

Natural History of FM

- No conversion to another condition
- Response to treatment is possible
- No known cure

THEREFORE THERE IS A NEED TO SET REALISTIC TREATMENT EXPECTATIONS WITH PATIENTS

Prognosis

- 538 patients from 6 referral centers experienced little improvement in symptoms over a 14 year period[1]
- Observational study of 1555 patients followed for up to 11 years by American rheumatologists: little change in symptoms[2]

1. Wolfe, et.al. A&R, 1997;40:1571
2. Walitt, et al. J Rheum 2011; 38:2238

Prognosis

- Patients treated by primary care providers in the community have a better prognosis than those treated in tertiary care centers
  - One small community based study showed 35% experiencing resolution of symptoms at 2 years[1]
  - In a community survey of 141 FM patients, only 35% were still symptomatic 2 years later[2]

1.White, et.al. A&R, 1999;42:76
J Rheum 2003; 30:154

A Few Words on Disability…

- 25-42% receive some type of disability
- 14.8% receive SSDI
- Only 20% return to the work place
- Only 1% had complete resolution of symptoms
- Age, Duration of Symptoms and Psychological Distress did not predict outcome

When to Refer to Rheum?

- To confirm diagnosis/provide support
- To evaluate the contribution of coexistent disease
- To answer a specific concern or exam finding
- To review interventions to date and assist in other treatment options

Mayo Clinic Proc 2012; 87(5): 488-96

Facilitate Wellness..... Use "CARE"

- Connect with the patient
- Assess for abuse and distress
- Encourage the patient to Run or get some type of aerobic exercise
- Educate the patient to Enhance self-efficacy