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 women 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
2010 ACR 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)

1. Mid-forehead (control point)
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
10, 11. Low cervical: Anterior aspect of intertransverse space of C5-7
12, 13. Second rib: Second costochondral junction
14, 15. Lateral epicondyle: 2 cm distal to epicondyle
16. Right forearm (control point): Junction of proximal ⅔ & distal ⅓
17. Left thumbnail (control point)
18, 19. Greater trochanter: Posterior to trochanteric prominence
20, 21. Knee: Medial fat pad proximal to the joint line
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
**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).
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 hypothalamic-pituitary-adrenal axis
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\(^5\)

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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)

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

Central sensitization produces abnormal pain signaling

After nerve injury, increased input to the dorsal horn can induce central sensitization. Perceived pain (hyperalgesia/allodynia) is induced with minimal stimuli. Induction of central sensitization results in increased release of pain neurotransmitters glutamate and substance P, leading to pain amplification and increased pain perception.
FM: AN AMPLIFIED PAIN RESPONSE

Subjective pain intensity vs. Stimulus intensity graph showing:
- **Normal pain response**
- **Hyperalgesia** (when a pinprick causes an intense stabbing sensation)
- **Allodynia** (hugs that feel painful)

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

**Patients with FM experienced high pain with low grade stimuli**

- 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)

Patients with FM experienced high pain with low grade stimuli.

\[ \text{Pain intensity versus Stimulus intensity (kg/cm}^2) \]

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

**fMRI** = functional magnetic resonance imaging

FM PATHOPHYSIOLOGY: SUMMARY

- Central sensitization is a leading theory of FM pathophysiology
  
- Elevated pain neurotransmitters in CSF of patients with FM
  - 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
  - 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
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
1. Mid-forehead (control point)
2, 3. Occiput: Suboccipital muscle insertions
4, 5. Trapezius: Midpoint of upper border
6, 7. Supraspinatus: Above medial border of scapular spine
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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%,
  • Myalgia 15%,
  • Pruritis 15%,
  • Sicca Syndrome 11%

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!!
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
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_2delta calcium channel ligand
  – Pregabalin (Lyrica) 75mg bid, titrate to 150-225mg bid
**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)
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 antinociception
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\(^2\)

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\(^2\)

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
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