RHEUMATOLOGY FOR PRIMARY CARE

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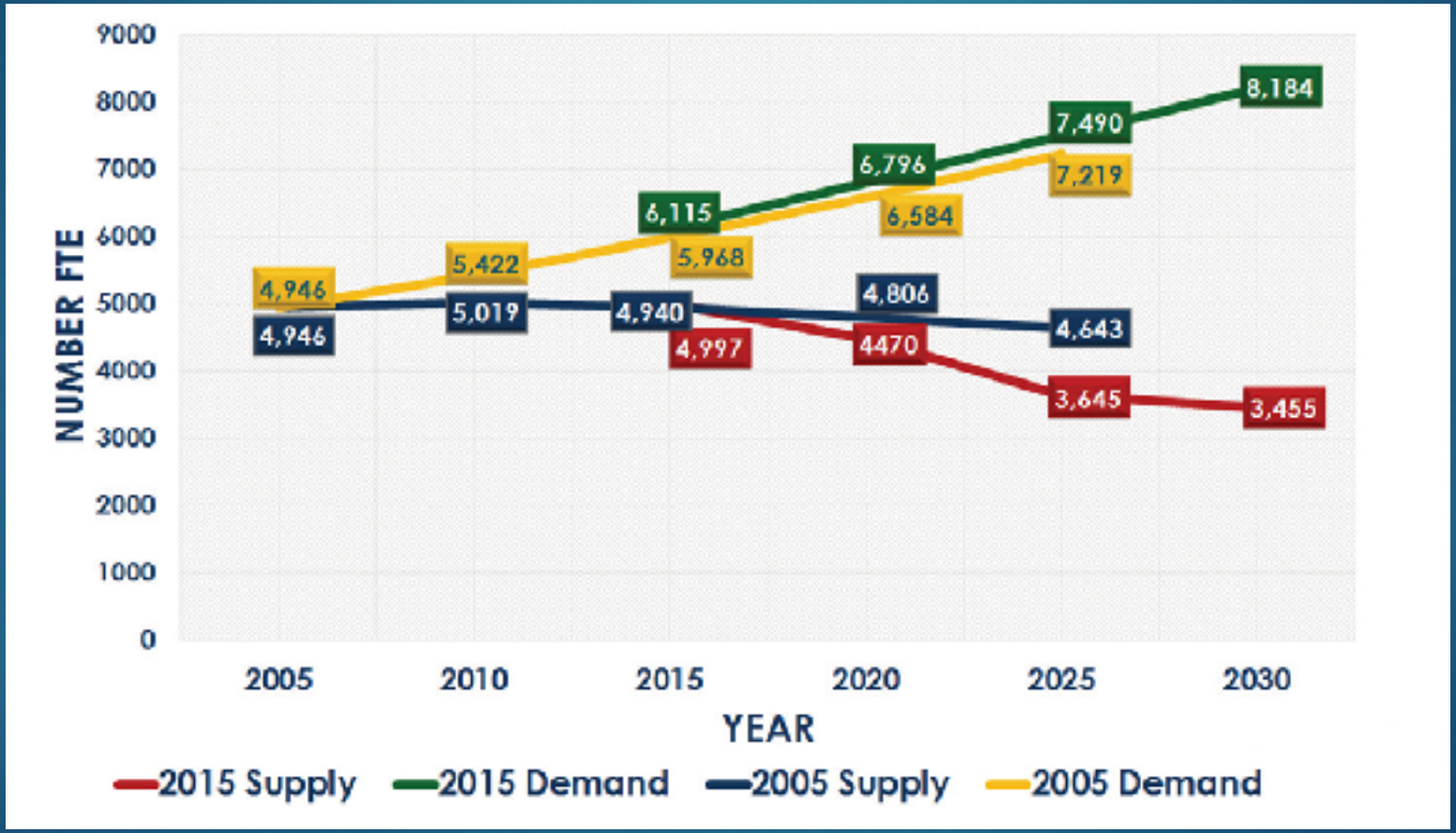
Disclosures

- I do have financial/business relationships with Novartis, Sanofi/ Genzyme, Janssen, Horizon, UCB, Amgen, Abbvie, Astrazeneca, Aurinia, Pfizer
- I do no intend to discuss specific products related to the content of this presentation

Overview

- Rheumatology Shortage
- Role of referring providers
- Clinical Pearls
- Lab Pearls with focus on ANA and RF
- Overview of role of imaging
- Brief review of Fibromyalgia
- Why it matters

Rheumatology Shortage



Rheumatology Shortage in WV

- WV compares poorly to other regions of country
  - In 2015:
    - Northeast—1 Rheumatologist per 32,000
    - Our region—1 Rheumatologist per 42,000
  - Projections in 2025:
    - Northeast—1 Rheumatologist per 62,000
    - Our region—1 Rheumatologist per 81,000
- WV averages are worst because region includes PA, VA, Carolinas
- WV more likely to be similar to TN, KY; 1 per 70,000 with projections 1 per 137,000

Role of Referring Providers

- Screen and differentiate between inflammatory disease and non-inflammatory disease
  - Judicial use of testing
  - Early referral for acute inflammatory disease
- Education to better manage non-inflammatory conditions
  - Fibromyalgia
  - Straightforward osteoarthritis

Role of Referring provider: What makes an appropriate referral?

- I.e. "Joint pain"—poor referral, too general and often poorly documented
- Better options to improve triage:
  - Inflammatory joint pain with history of psoriasis
  - Inflammatory joint pain with morning stiffness, joint swelling
  - Describe distribution of joint pain/specific concerns or exam findings
- Referral issues—the highlights
  - Majority of referrals are for non-specific complaints
  - Low positive ANA or RF with patient having being told they have "lupus" or "RA" respectively by referring office
  - Fibromyalgia and OA (often while seeing orthopedics/pain clinic, etc)

Clinical Pearls

- A good history is everything!
  - Inflammatory joint pain features
    - Prolonged am stiffness lasting >30 minutes
    - Joint or digit swelling
    - Joint redness/warmth
    - Pain that is worse at rest, improves with activity
    - Joint distribution helps differentiate between types of arthritis
  - Associated features of inflammatory disease
    - Eye inflammation
    - Weight loss
    - Rashes—what type? i.e. psoriasis, photosensitive, etc
    - Dry eyes, dry mouth, etc

Lab Pearls

- Arthritis Panels are overused
  - Clinical history should direct testing, i.e. little clinical use in ASO titer in adult with pain
- Knowing how to interpret a test is of utmost importance
- Routine lab work is often a better clue than expensive specialty tests
  - Leukopenia, thrombocytopenia, thrombocytosis, hematuria, proteinuria

Rheumatoid factor—A more in depth look

- Rheumatoid factors are antibodies against Fc region of Immunoglobulin G
  - First detected in RA approximately 70 years ago
  - Prior to that, as early as 1920s, found to be positive in liver cirrhosis and chronic bronchitis
  - Named Rheumatoid factor in 1950s due to association with RA, likely leading to much of the persistent confusion

Rheumatoid factor—A more in depth look

- Disease associations are fairly broad
  - Rheumatic diseases with positive rheumatoid factor
    - Rheumatoid arthritis
    - Juvenile idiopathic arthritis
    - Psoriatic arthritis
    - Reactive arthritis
    - Connective tissue diseases—Primary Sjogren's syndrome, Systemic lupus erythematosus, Systemic sclerosis, Inflammatory myopathy, vasculitis

Rheumatoid f actor—A more in depth look

- Non-rheumatic disease association
  - Hepatitis C
    - Found in 40-50% of patients but can be up to 76%
    - Screening for Hepatitis C should be done in all patients with increased RF
- Other infections: Tb, mononucleosis, malaria, syphilis, endocarditis, HIV
- Liver diseases: Cirrhosis, hepatitis (including but not limited to HCV)
- Cancers—Leukemia, etc,
- Pulmonary disease—ILD, infections
- Cryoglobulinemia, including HCV related
- Healthy subjects
    - 4% of young Caucasions have RF positive
      - Usually low/moderate titer
    - Up to 20% of patients over 65

Rheumatoid factor—What do we do now?

- With multiple causes of RF, it is important to understand when to order and how to interpret
  - "Your rheumatoid arthritis test is positive"—misleading and creates more work and confusion for both the patient and provider that receives referral
  - Low positive titers—usually either normal or false positive from lab
  - More specific/sensitive testing is available for RA; however, a pertinent history needs to be taken rather than blind testing
    - I.e. if symptoms are consistent with Sjogren's syndrome—directed testing is more beneficial than broad testing for RA
- Pearl: Rheumatoid arthritis is only present in 1% of US population

Antinuclear antibody—A more in depth look

- Soto et al. published article in 2013 in Results in Immunology regarding utility of positive ANA
- Retrospective study assessing predictive value of positive ANA
  - Correlated ANA results ordered across a variety of specialties to patients's final diagnosis
- Findings showed low PPV and high NPV
- Overview of methods used:
  - Included ANA positive on IIF at a titer of 1:40 or greater
  - Also looked at other antibodies via ELISA—Sm, RNP/Sm, SSA/Ro, SSB/La, Anti-Scl70 and anti-centromere
  - Rheumatologist reviewed each chart to assess clinical correlation with symptoms and if the reason for referral was found in final diagnosis

Antinuclear antibody—A more in depth look

- Soto et al. Results
- 373 requests for positive ANA where evaluated
  - 299 women, mean age 40 +/- 15 and 74 men, mean age 37+/- 17
  - 364 had positive antibodies with dilutions of at least 1:40
    - 9 cases were negative upon repeat testing
  - 193/364 (52%) had antibodies against specific antigens
- Net findings
  - 40% had no clinical criteria applied prior to test
  - Other rheumatic and autoimmune diseases where seen in the tested population
  - Testing improper population resulted in low PPV and high NPV to ANA test

Antinuclear antibody—A more in depth look

- ANA—how do we test?
  - Indirect immunofluorescence if often best—using Hep2 cells
    - Positives—better sensitivity, different possible patterns, and titers
    - Negatives—
      - More expensive so commercial labs—tend prefer other methods
      - Important to understand the fundamental aspects of testing as well as classification criteria of diseases linked to ANA
    - Positive predictive value 11%, negative predictive value of 97%
    - Sensitive and specificity of 42% and 85% respectively

Antinuclear antibody—A more in depth look

- Enzyme immunoassay (EIA)/enzyme linked immunosorbent assay (ELISA)
  - Subdivided into two categories
    - ANA only—reported as positive/negative
    - Multiple antigen detection—Sm, Sm/RNP, SSA, SSB, Scl70, dsDNA, Jo1, etc
  - Positive—if a patient is positive on IIF at a titer 1:160 or greater, sensitivity and specificity is high, rapid test, less expensive
  - Negatives—high proportions of false positives, not as effective as screening test

Antinuclear antibody—NOT THE "LUPUS TEST"

- Healthy population
  - 20-30% have positive ANA at a titer of 1:80 or greater; positivity increases with age
- Rheumatic disease—present in a wide variety
  - Systemic lupus erythematosus—caveat is virtually 100% of SLE patients have positive ANA but converse not true. Very small minority of positive ANA represents SLE
  - Sjogren's syndrome—can see positive ANA but can be negative with positive SSA
  - MCTD/UCTD
  - Rheumatoid arthritis
  - Inflammatory myopathy
  - Scerloderma
  - Juvenile idiopathic arthritis
  - Ankylosing spondylitis
  - Vasculitis
  - Drug induced lupus

Antinuclear antibody—NOT THE "LUPUS TEST"

- Non-rheumatic disease
  - Hashimoto's thyroiditis (46%)
  - Graves'disease (50%)
  - Autoimmune hepatitis (100%)
  - Primary autoimmune cholangitis (100%)
  - Primary pulmonary hypertension (40%)
  - Medications
  - Infections

Antinuclear antibody—NOT THE "LUPUS TEST"

New EULAR/ACR criteria for the classification of SLE

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis or tenderness in at least 2 joints	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria > 0.5 g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG > 40 GPL *or* anti-β2GP1 IgG > 40 units *or* lupus anticoagulant	2
Complement proteins domain	
Low C3 *or* low C4	3
Low C3 *and* low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Sm antibody	6

REFERENCE: Aringer et al. Abstract #2928. 2018 ACR/ARHP Annual Meeting

- ✓ **Classification criteria are not diagnosis criteria**
- ✓ All patients classified as having SLE must have ANA ≥ 1:80 (entry criterion)
- ✓ **Patients must have ≥ 10 points to be classified as SLE**
- ✓ Items can only be counted for classification if there is no more likely cause
- ✓ Only the highest criterion in a given domain counts
- ✓ SLE classification requires points from at least one clinical domain

@Lupusreference

Imaging Pearls

- Arthritis is NOT a lab diagnosis—imaging is extremely important and markedly underutilized
- X-rays in appropriate context can be a cheap and simple way to assess for inflammatory versus degenerative disease
  - Plain films can detect a variety of findings seen in OA, RA, PsA, AS, Gout and CPPD arthropathy
- U/S represents a relatively cheap and rapid modality to get better imaging
  - Great at detecting early inflammation
  - Can detect enthesitis, tendonitis, tophi
  - Good test for carpal tunnel syndrome
- MRI is expensive but when used judiciously, can detect early inflammatory disease

Fibromyalgia Introduction

- Is it real?
- Syndrome definition
  - A group of symptoms that collectively indicate or characterize a disease, psychological disorder, or other abnormal condition

Fibromyalgia Background

- It is postulated that Florence Nightingale had fibromyalgia
  - After serving as a nurse from 1854-1856 under stressful conditions, she became bedridden for much of the rest of her life with pain and fatigue
- Documentation of similar symptoms noted since mid 1800s
- Multiple names have been used to describe including hysterical paroxysm, muscular rheumatism, fibrositis
- "Fibromyalgia" was coined in 1976
- Diagnostic criteria developed in 1990

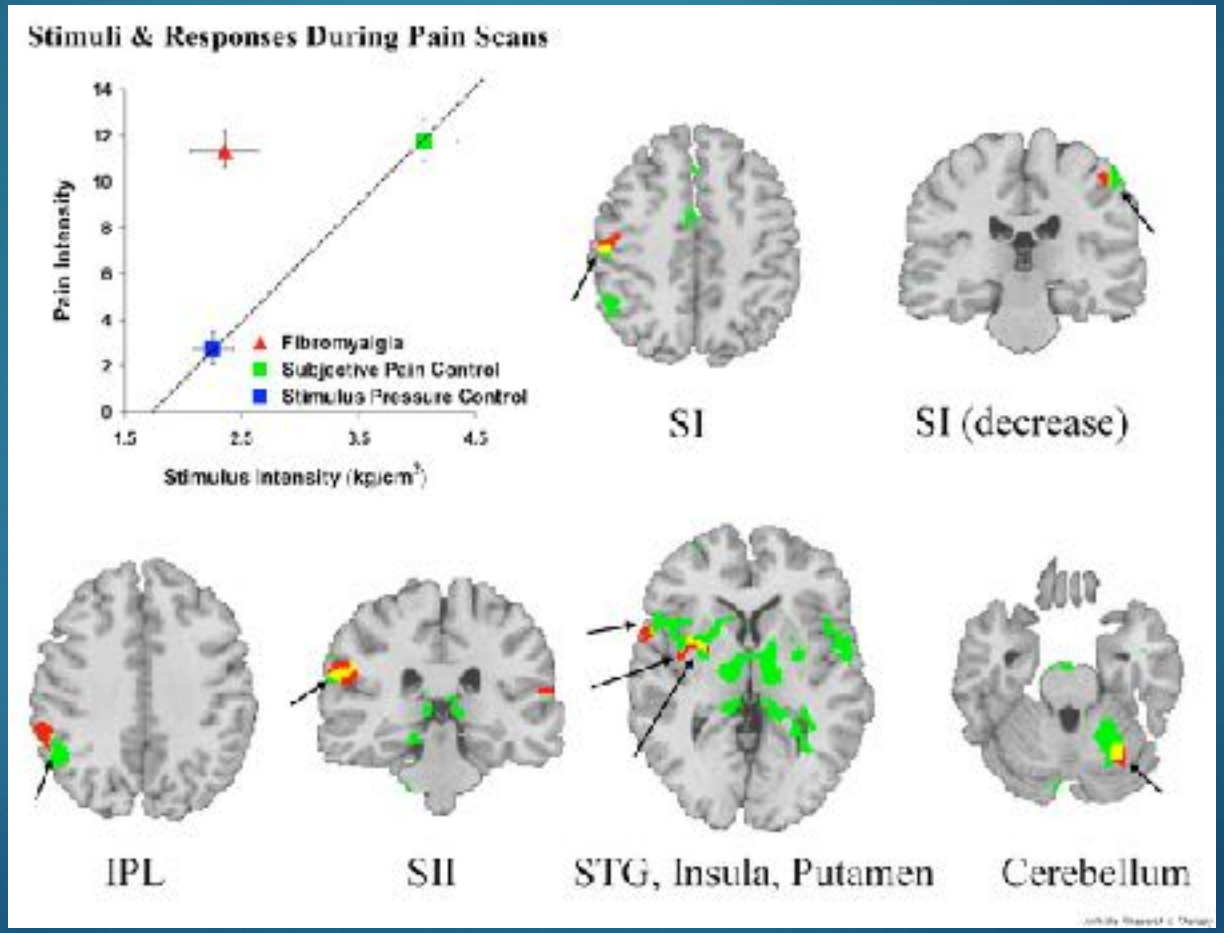
Fibromyalgia Pathogenesis

- Disorder of pain regulation--multifactorial
- There may be some genetic component
  - First degree relatives of FMS patients have significant likelihood of developing
  - No gene firmly identified as of yet
- Altered pain processing is at the core
  - Noxious stimuli including heat, electric current or pressure is perceived as painful at lower levels of stimulation then controls

Fibromyalgia Pathogenesis

- Alteration of pain processing
  - Changes in opioid receptors
    - Upregulation in periphery, particularly skin
    - Downregulation in CNS
  - Increase in substance P, glutamate
  - Decrease in serotonin, norepinephrine
  - Functional MRI studies demonstrate greater activity after stimuli compared to controls
    - Especially in secondary somatosensory cortex, insula, and anterior cingulate cortex

Fibromyalgia Functional MRI



Fibromyalgia By the Numbers

- Females:Males—7:1
- Age 20-60
  - Can occur in children and older adults
  - Average age 35
- 2.2 million ambulatory care visits yearly
- CDC estimates annual cost at $5,945/patient
  - $59 billion yearly

Fibromyalgia Symptoms

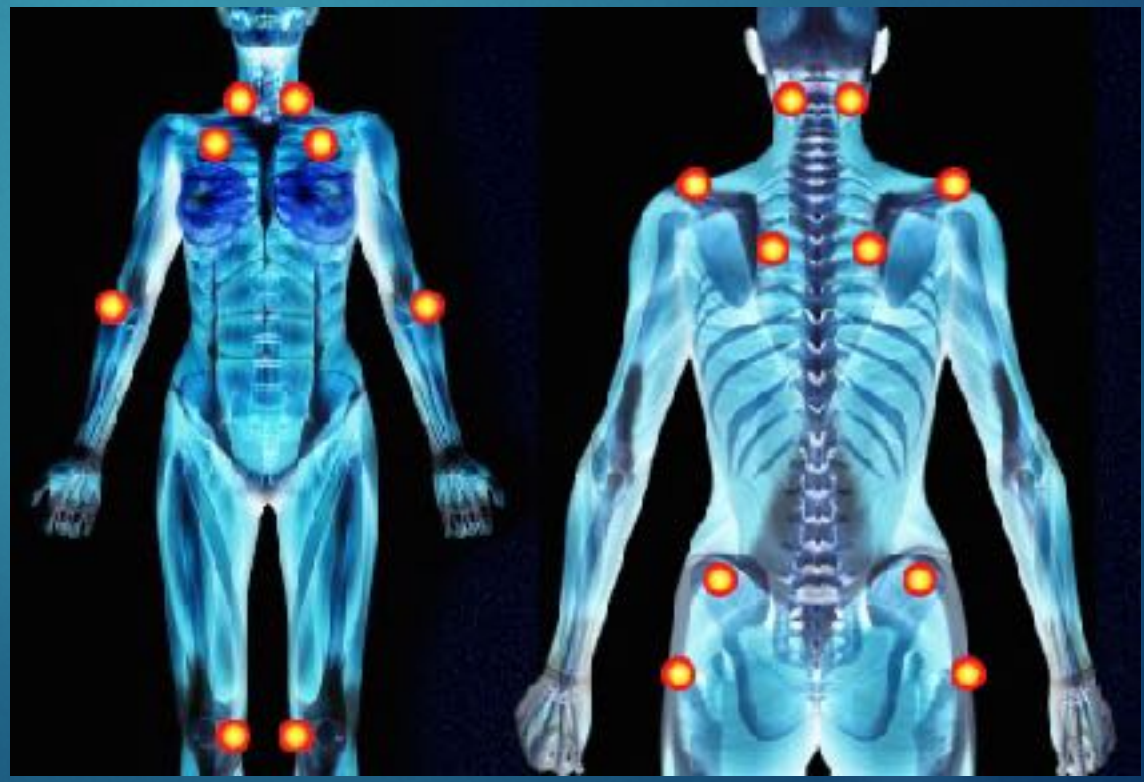
- Cardinal symptom is chronic, widespread pain
  - Can include joints and muscles
  - Often will complain of joint stiffness/swelling but no synovitis on exam
- Fatigue is common
- Paresthesia described as numbness, tingling, burning, creeping sensations
  - Physical exam, testing negative
- Poor sleep that is nonrestorative
- Mood disorders are common including depression and anxiety

Fibromyalgia Symptoms

- Multiple disease associations, primarily localized pain disorders
  - Interstitial cystitis
  - Irritable bowel syndrome
  - Pelvic pain syndrome
  - Migraine or tension headaches
- Variety of other complaints can be seen
  - Ocular sicca
  - Palpitations
  - Chest pain
  - Dyspnea
  - Dysmennhorea
  - Night sweats
  - Weight fluctuations

Fibromyalgia Physical Exam

- Essentially normal exam with the exception of tender points



Fibromyalgia
Making the Diagnosis

- Diagnosis of exclusion
- Can mimic multiple diseases
  - Including RA, SLE, degenerative disc disease, inflammatory myopathies, thyroid disease
- Do not chase every symptom
  - Cost can be exorbitant
- Screening tests should include CBC, CMP, TSH, ESR, CRP
  - Vitamin D level should be considered
  - Other testing should be done if physical exam findings dictate

American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity

Criteria
A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:
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 a similar level for at least 3 months.
3) The patient does not have a disorder that would otherwise explain the pain.
Ascertainment
1) **WPI**
Note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? The WPI will be between 0 and 19.
Neck
Jaw, left
Jaw, right
Shoulder girdle, left
Shoulder girdle, right
Upper arm, left
Upper arm, right
Lower arm, left
Lower arm, right
Chest
Abdomen
Upper back
Lower back
Hip (buttock, trochanter), left
Hip (buttock, trochanter), right
Upper leg, left
Upper leg, right
Lower leg, left
Lower leg, right
2) **SS scale score**
For each of the 3 symptoms below, indicate the level of severity over the past week using the following scale:
0 = no problem / 1 = slight or mild problems, generally mild or intermittent / 2 = moderate, considerable problems often present and/or at a moderate level / 3 = severe, pervasive, continuous, life-disturbing problems
- Fatigue (0-3)
- Waking unrefreshed (0-3)
- Cognitive symptoms (0-3)
Considering somatic symptoms in general, indicate whether the patient has:*
- No symptoms (0)
- Few symptoms (1)
- A moderate number of symptoms (2)
- A great deal of symptoms (3)
The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

* Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms

Wolfe, F, Clauw, DJ, Fitzcharles, MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 2010; 62:600. Copyright © 2010 American College of Rheumatology. Reproduced with permission of John Wiley & Sons.

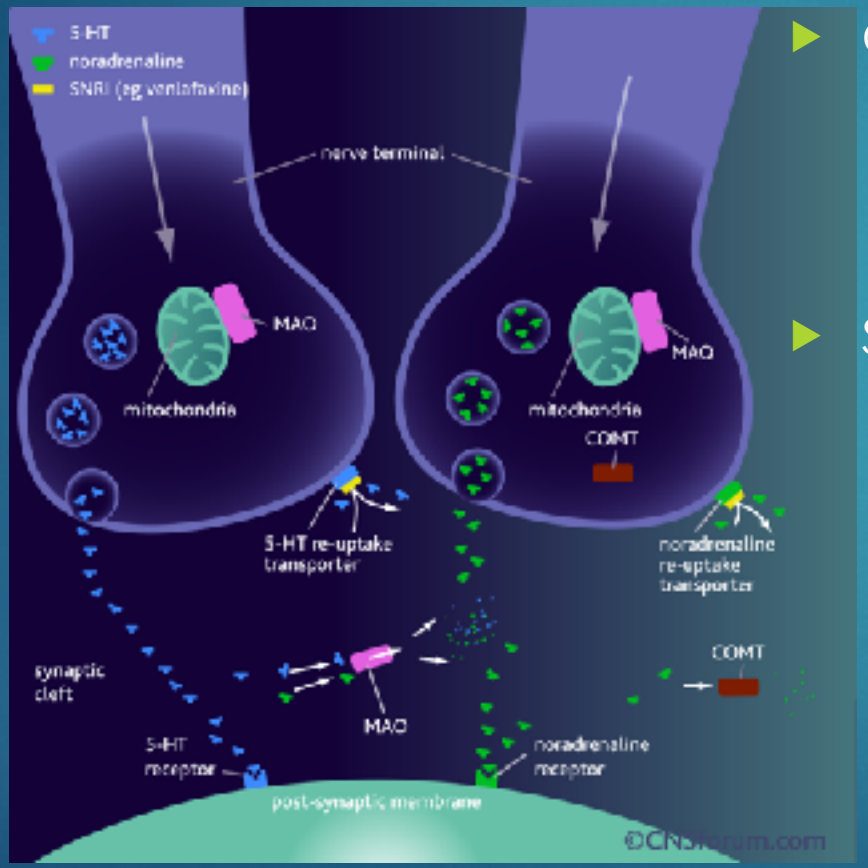
Fibromyalgia Treatment Non-pharmacologic

- Take the time to counsel patient early in diagnosis
  - Full pain relief is rarely attainable
  - Importance of sleep and good sleep hygiene
  - Non-pharmacologic therapies can be effective
- Exercise
  - Graded exercise program
  - Water aerobics
  - Tai Chi, encourage starting at beginner levels
- Cognitive behavior therapy
- Various other modalities have mixed results
  - Massage, biofeedback, acupuncture, ultrasound
- Trigger point injections
  - Anecdotal only

Fibromyalgia Treatment Pharmacologic

- 3 FDA approved medications
  - Serotonin norepinephrine (dual) reuptake inhibitors
    - Cymbalta (Duloxetine)
    - Savella (Milnacipran)
  - Lyrica (Pregabalin)
- Of note, two other SNRIs are on the market but not FDA approved for use
  - Pristiq (Desvenlafaxine)
  - Effexor (Venlafaxine)

Fibromyalgia Treatment
SNRI



- Cymbalta dosing
  - Starting dose of 30mg daily
  - Can increase to target dose of 60mg after 1 week
- Savella dosing
  - Starting dose of 12.5mg
  - Increase gradually over several weeks to target dose of 50mg BID
  - Can increase to 100mg BID if needed

Fibromyalgia Treatment
SNRI Side Effects

- Cymbalta
  - Nausea
  - Headache
  - Dry mouth
  - Carries black box warning of SSRIs in regards to suicide risk
- Savella
  - Nausea
  - Headache
  - Constipation
  - Carries SSRI black box warning

Fibromyalgia Treatment Pregabalin

- Mechanism of action is unknown
  - Reduces neurotransmitter release
  - Anti-nociceptive properties
  - Antiseizure properties
- Dosing
  - Typical starting dose is 75mg BID
  - Increase gradually to 150mg BID
  - Maximum dose is 450mg daily
  - Taper off to discontinue
- Side Effects
  - Peripheral edema
  - Weight gain
  - Somnolence
  - Dizziness
  - Ataxia

Fibromyalgia Treatment Other Medications

- Tricyclic antidepressants (Amitriptyline)
  - Frequently used first line
  - Side effects frequently limit dosing
- Cyclobenzaprine (Flexeril)
  - Very similar to TCA in structure and action
- Gabapentin (Neurontin)
  - Works similar to Pregabalin but much cheaper
  - Increasing dose very gradually makes this better tolerated
- Tramadol
  - Binds to mu opiod receptors, weakly inhibits norepinephrine and serotonin reuptake
- SSRIs
  - Works for some patients, particularly those with concomitant depression

Fibromyalgia Treatment Approach to Medications

- Do not start multiple medications concomitantly
  - Side effects can include excessive sedation
- Start at lowest doses and increase slowly
  - Medications are better tolerated
  - Increases compliance
- Combination therapy can be used but do so cautiously
- Patient's comorbities should be taken into consideration
  - i.e. concomitant psychiatric illness
- Narcotics are a bad idea in FMS
  - Risk of dependency with only minimal pain relief

Fibromyalgia Questions

- Is it real?
  - Yes, meets the definition of a syndrome
  - In practice, reproducible with wide variety of patients have virtually identical symptoms
- Is it a rheumatic disease?
  - No, this is a disorder of pain processing
  - There is no evidence of joint or muscle pathology
  - No evidence of autoimmunity or inflammatory disease

Fibromyalgia Conclusions

- This is an increasingly common disease
- Many different types of providers need to be familiar and comfortable with diagnosis and treatment
  - Primary care
  - Psychiatry
  - Pain specialists
  - Etc.
- Rheumatologist can confirm diagnosis but no specialty care is necessary for chronic management

Why does it matter?

- Early diagnosis of inflammatory disease can change outcomes
  - Prevent disability
  - Decrease risk of long term complications
    - Cardiac disease
    - Pulmonary disease
    - Renal disease
    - Orthopedic complications
- Wise utilization of resources
  - Rheumatologists are best equipped to prescribe and monitor for toxicity of various DMARDs and immunomodulators
  - Finite resource and need to be available for patients who need it the most

Communication is Key!

- A simple phone call between providers can decrease confusion
- Letting Rheumatologist know prior work-up, previous opinions decrease confusion and saves money/time for patient/system

THANK YOU!

QUESTIONS?