Fibromyalgia for Primary Care Providers

Dana Villmore, PhD, PA-C
University of New England PA Program
Assistant Clinical Professor
Portland, Maine

Disclosure

- I have no relevant relationships with ineligible companies to disclose within the past 24 months. (Note: Ineligible companies are defined as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)
- My presentation will talk about the following medications that are used for indications that are not FDA-approved (off-label use)
  - Amitriptyline, despiramine, venlafaxine, gabapentin, cyclobenzaprine, tizanidine, baclofen, and tramadol for fibromyalgia

Learning Objectives

- At the conclusion of this session, participants should be able to:
  - Discuss pathophysiology of and identify triggers and comorbid conditions associated with fibromyalgia
  - Diagnose fibromyalgia utilizing current ACR and/or AAPT criteria
  - Formulate individualized treatment plans for patients with fibromyalgia using holistic approach and appropriate pharmacotherapy

Pre-test Question #1

- Which of the following neurological symptoms is characteristic of fibromyalgia?
  - Apraxia
  - Aphasia
  - Allodynia
  - Ataxia

Pre-test Question #2

- Which of the following is a first line treatment of fibromyalgia?
  - Exercise program
  - Low-dose opioids
  - Pregabalin
  - Acupuncture

Pre-test Question #3

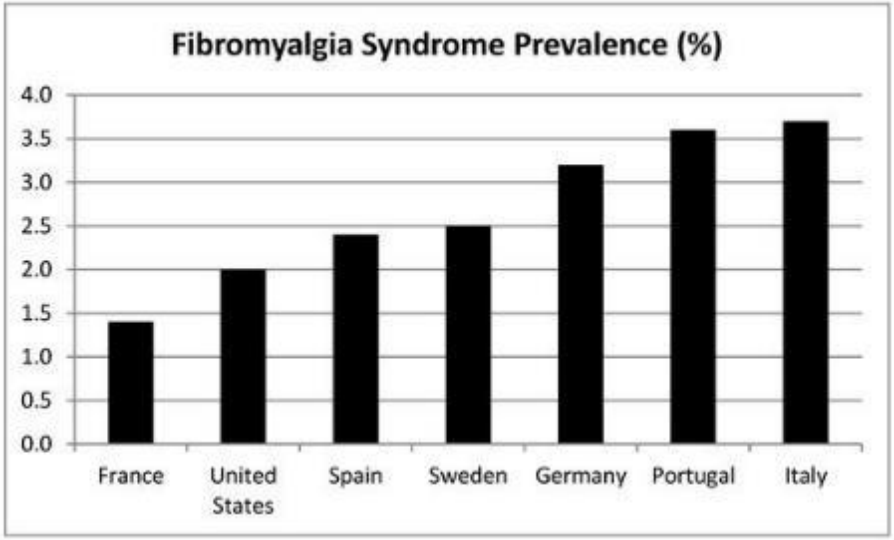
- Which of the following is an FDA-approved medication for the treatment of fibromyalgia?
  - Fluoxetine
  - Duloxetine
  - Paroxetine
  - Sertraline

Fibromyalgia Syndrome

- Chronic widespread pain disorder
- Migrating and multisite musculoskeletal pain
  - No evidence of inflammation!
- Somatic complaints
  - Fatigue and sleep disturbances
  - Cognitive and psychiatric disturbances
- Variable severity and outcomes → large spectrum

Epidemiology

- Prevalence 2-3%
  - Increases with age
  - Can happen in childhood/adolescence and persist into adulthood
- Female predominance
  - Most common cause of generalized MSK pain in women 20-55 years old



***J. Clin. Med.* 2020**, *9*(4), 1219.

Epidemiology

- Up to 30% of patients with inflammatory conditions have FMS
  - SLE, RA, etc.
- Half of patients with FMS have a mental health diagnosis
  - Anxiety, depression, etc.
  - Much higher than general population
- Commonly happens in people with other chronic pain syndromes
  - TMJD, chronic back pain, IBS, etc.

Epidemiology

- Up to 30% of patients with FMS report that they are work disabled
- More severe symptoms and more comorbidities = higher cost of care and greater morbidity
  - Many rate health as fair/poor
  - Average 1 outpatient visit/month!
  - Spend 3x more on healthcare
- Mortality rates not necessarily increased, but increased risk of suicide
  - More CVD and cancer (due to obesity and/or inactivity?)

Can't I just send them to rheum?!

- Rheumatologists are not always necessary
- PCPs can coordinate all aspects of care
  - Better patient outcomes than tertiary referral centers (rheum)!
- Continuous management: easier and closer follow up
- Reduced healthcare costs
  - 2+ years to get diagnosed with >3 different consults!

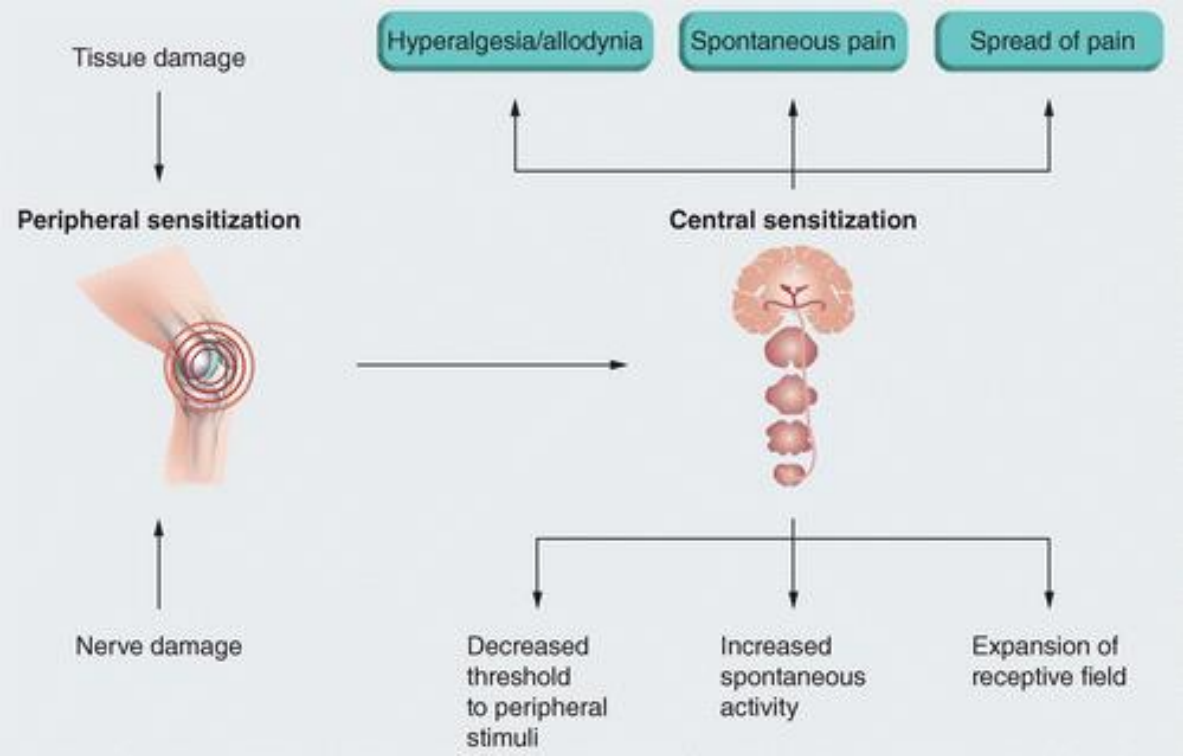
Why is this happening??

Pathophysiology of FMS

- Complex and still not understood
- Genetic predisposition (50%)
  - First degree relatives 8x more likely to have FMS
  - Multiple candidate genes
    - Serotonin, dopamine, and catecholamine metabolic or signaling pathways
  - Possible epigenetic contributions?
- Environmental triggers likely set it off
  - More later!

Pathophysiology of FMS

- Pain Processing Disorder: Central Sensitization
  - Hyperalgesia: feel more pain than normal
  - Allodynia: non-painful perceived as painful



Future Medicine 2014 14-37. https://doi.org/10.2217/fmeb2013.13.160

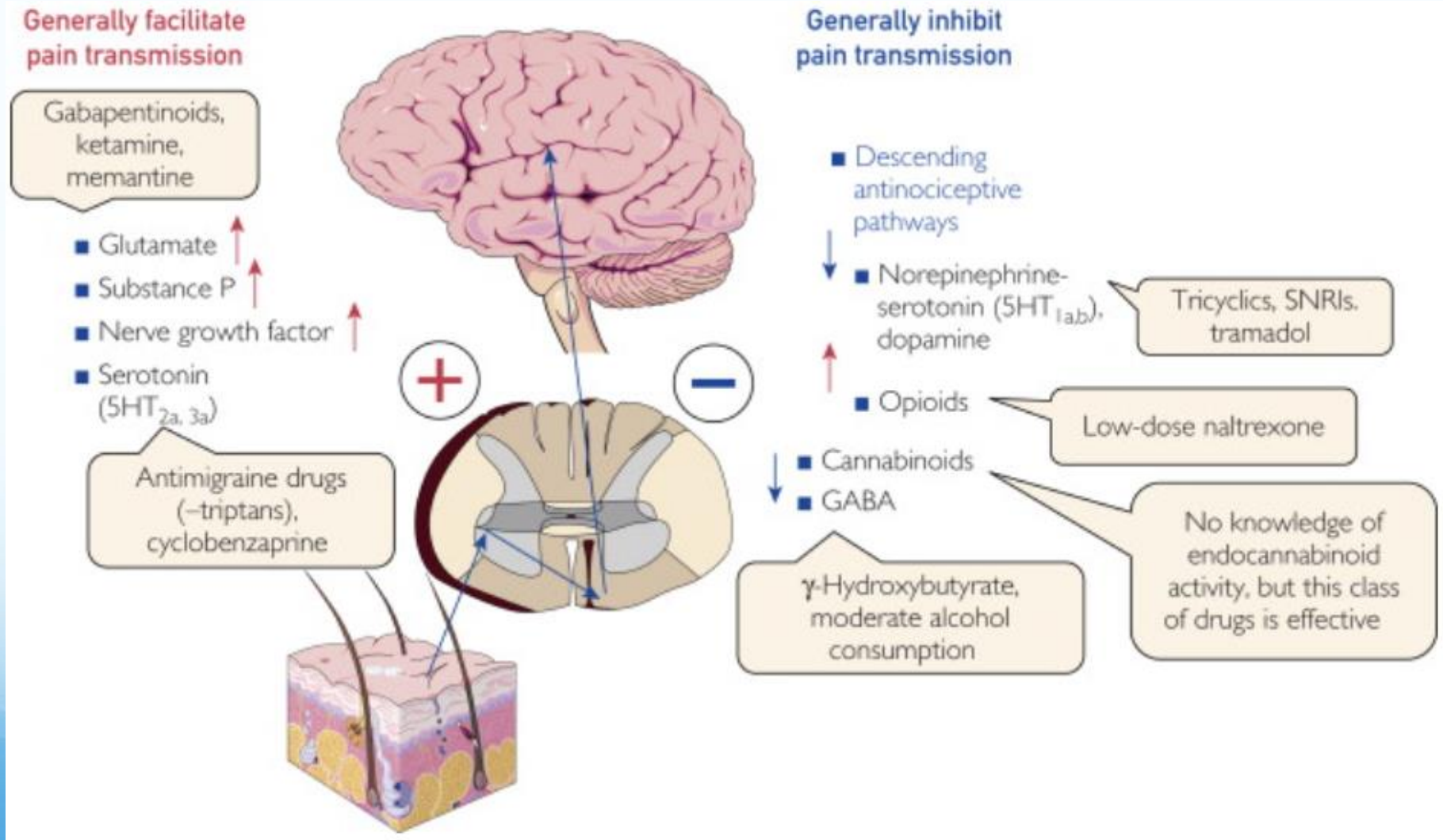
Pathophysiology of FMS

- Pain Processing Disorder: Central Sensitization
  - Decreased endogenous analgesic systems
    - Cannot turn off pain
  - Temporal summation of pain
    - Keep turning on pain and perceiving it as more severe

Pathophysiology of FMS

- Potential causes
  - Neurotransmitter alterations → increased excitatory state
    - High substance P and glutamate
    - Low GABA and dopamine
  - Brain structural and functional alterations
    - Overactivation of pain-sensitive and pain processing areas
    - Loss of gray matter brain volume → premature aging of brain
      - Cognitive function and stress/pain processing areas
      - Look similar to chronic pain and stress-related disorders
      - Worse with longer duration of disease

Pathophysiology of FMS



***SYMPOSIUM ON PAIN MEDICINE* 2015,** 90(5), P680-692.

Pathophysiology of FMS

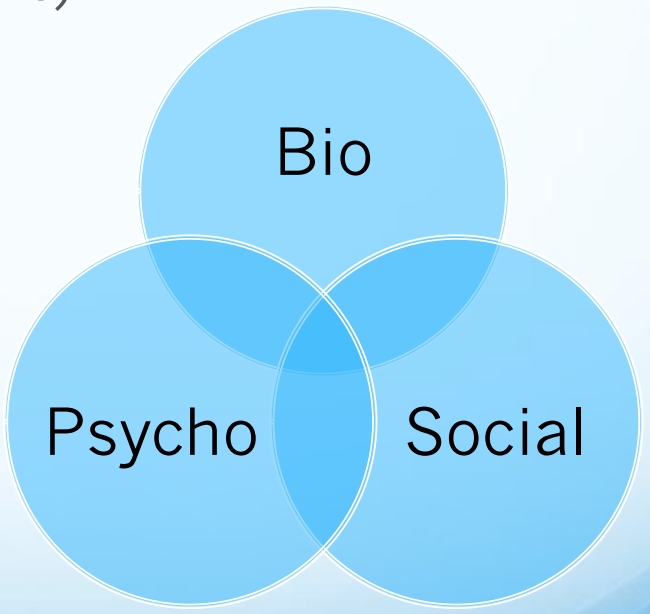
- Immune dysregulation
  - Role of cytokines is unclear
    - Altered but cannot find a consistent pattern
  - No autoimmunity, maybe…
- Sleep disorders
  - Alpha stage intrusion (hyperarousal)
  - Possibly precede the pain and then make pain worse
- Muscle dysfunction
  - Possible mitochondrial dysfunction → lower ATP
  - Overall capillary density lower – less blood flow
    - Inability to remove lactic acid?

Pathophysiology of FMS

- HPA axis and stress
  - Hyperactive stress response at baseline and with provocation → higher cortisol levels
  - Autonomic nervous system dysfunction
    - Increased heart rate and heart rate variability
    - Increased BP to stress
    - Catecholamine levels decreased
- May be accompanied by small fiber neuropathy
  - Could be up to 50% of patients
  - Cause or effect of FMS?

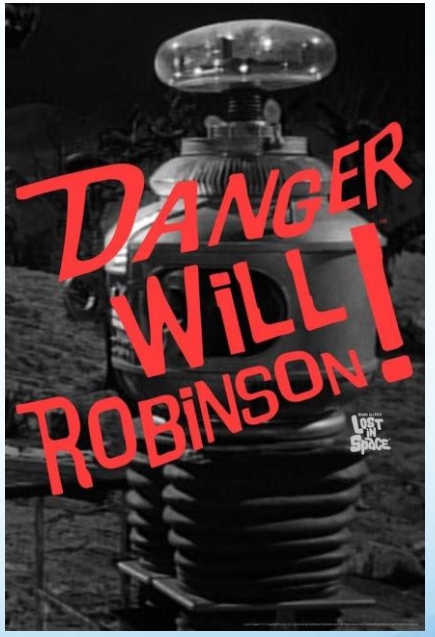
FMS Triggers

- Can happen gradually or right after a trauma
  - Emotional
    - Adverse Childhood Experiences (ACEs)
    - Abuse
    - Job dissatisfaction/burn out
    - Poor support system
    - Relationship problems
  - Physical
    - Injury
    - Deconditioning
  - Infectious or other severe illness
    - Viruses (maybe COVID)
    - Bacteria like *Borrelia burgdorferi*



Why did this condition evolve?

- My hypothesis: sense danger quicker than before to avoid it
- Hypersensors of environment
  - Hypervigilance
  - Sight – photophobia
  - Hearing – phonophobia
  - Smell – heightened
  - Taste – super tasters?
  - Touch – hyperalgesia and allodynia
    - Hyperreflexia?



This is NOT a diagnosis of exclusion

- Need a high index of suspicion
- Early diagnosis and treatment is important to prevent disability
- Keep active and involved in society → improve quality of life

HPI: Listen to your patient!

- Fatigue and exhaustion
- Cognitive dysfunction: “Fibro Fog”
  - Due to pain and/or depression
  - Poor concentration
  - Word-finding difficulties
  - Disorganized/slow thinking
- Poor quality of sleep and/or insomnia
  - Trouble falling asleep
  - Frequent awakenings: “light sleeper”
  - Waking unrefreshed

HPI: Listen to your patient!

- Migrating and multisite pain
  - Flu-like symptoms
  - “I hurt all over”
  - Arthralgias: TMJD, morning joint stiffness
  - Headaches: migraine and/or tension-type
- Paresthesias
  - Muscle twitching
  - Numbness
  - Tingling, burning, creepy/crawly sensations in extremities

HPI: Listen to your patient!

- Anxiety and depression
  - Chest pain
  - Catastrophizing
  - Perfectionism/neuroticism
  - Compulsive behavior
- Autonomic dysfunction
  - Raynaud's phenomenon
  - Dry eyes
  - Orthostatic hypotension
  - Heart rate variability

HPI: Listen to your patient!

- Other complaints
  - GI: nausea/vomiting, GERD, abdominal pain/cramping, IBS (any type)
  - GU: urinary frequency/urgency, pelvic pain
  - Atopy and Environmental sensitivity
    - Bright lights, loud noises, cold, perfumes, chemicals
  - Neuro: hearing loss common, dizziness, blurry vision

Comorbid Conditions

- IBS
- Interstitial Cystitis
- Dyspareunia/pelvic pain
- Migraines
- TMJD
- Joint hypermobility syndrome/EDS
- CFS/ME
- Sleep disorders
- Mood disorders
- Atopic disorders
- Raynaud's
- Autoimmunity
- Thyroid dysfunction
- OA
- GERD
- HTN
- Cardiac disorders/arrhythmias
- Hyperlipidemia
- Obesity/physical inactivity

Differential Diagnosis

- RA – joint swelling, high ESR/CRP
- SLE – malar rash, renal/cardiac/pulmonary/neuro features
- PMR – older onset age, high ESR/CRP, rapid response to GCs
- Myositis/myopathies – muscle weakness/fatigue, less muscle pain, high muscle enzymes, biopsy findings
- Spondyloarthritis – restricted motion, high ESR/CRP, imaging abnormalities
- OA – joint specific pain, PE and imaging abnormalities
- Lyme – bullseye rash, joint swelling, serologic tests
- Hypothyroidism – high TSH, pain not prominent
- Neuropathies – sensory/motor deficits, abnormal EMG/NCV

Diagnosis

- Physical exam
  - Soft tissue is very tender to palpation
    - Muscles, ligaments, tendons especially
  - Evaluate for other possible disorders that have similar symptoms
    - Joint assessment for synovitis or arthritis: should be none!
      - No overlying erythema, warmth, or swelling
    - Neurologic exam normal: no focal deficits
      - Might see findings suggestive of peripheral neuropathy or small-fiber neuropathy
      - Might see evidence of autonomic nervous system dysfunction: tachycardia, orthostasis

Diagnosis

- No specific lab abnormalities are diagnostic for FMS
- Do labs only to rule out other things
  - **CBC**
  - **CRP or ESR to rule out inflammatory processes**
  - RF, ANA, etc. not necessary
  - TSH for suspected thyroid disease
  - CK for suspected myositis
  - Vitamin deficiencies if suspected:
    - B12, folate for paresthesias
    - D3 for depression/fatigue

Diagnosis

- No characteristic radiographic findings in FMS
  - Imaging not necessary unless you are sure it's something else!
- Might consider sleep study to check for comorbid sleep disorders
- Might consider psych referral for undiagnosed comorbid mental health problems

Gold standard for diagnosis?

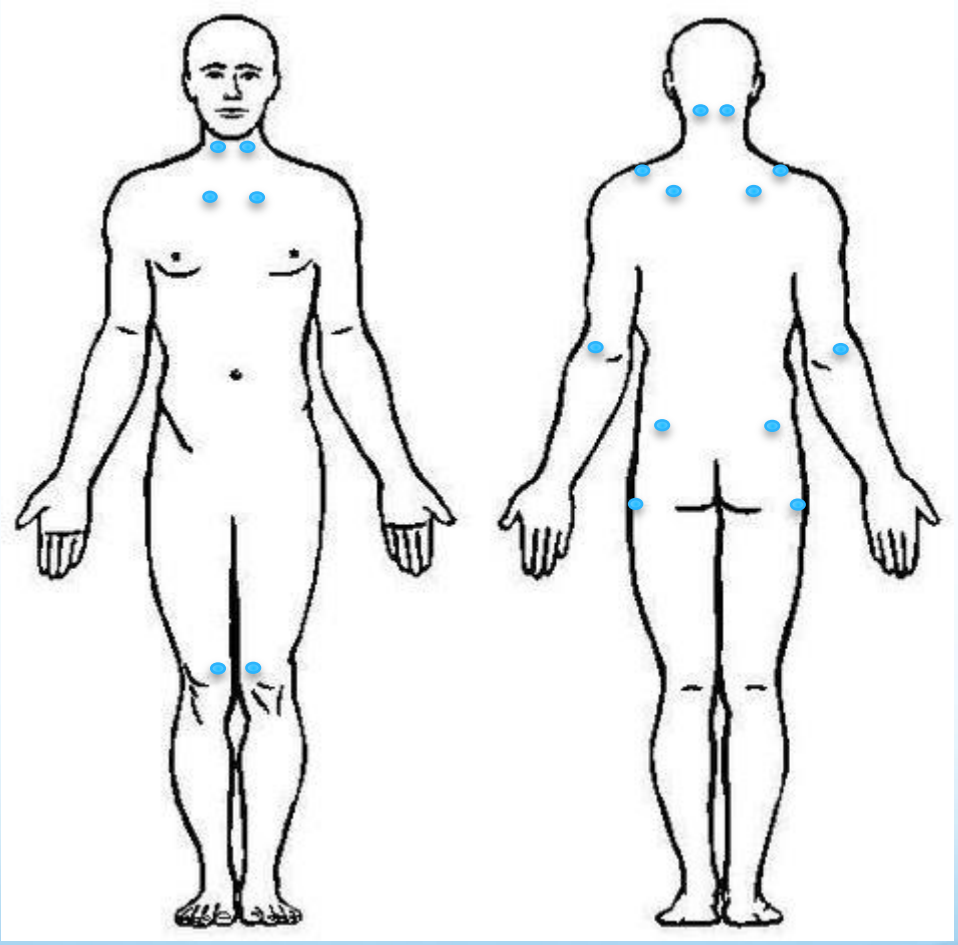
- There is none here…
- It's YOUR CLINICAL JUDGEMENT!
- Consult rheum if you have doubts…
  - More of them are comfortable making the diagnosis of FMS than PCPs
- Tools to help you out coming next!

Diagnostic Criteria for FMS: Old ACR Model

Widespread pain >3 months

≥11/18 tender points are positive

Presence of other clinical disorder does not exclude dx of FMS



CONS:
Males have higher pressure pain threshold than females → skewed towards females

Tender points often incorrectly assessed or not assessed at all in primary care

No mention of non-pain symptoms

Diagnostic Criteria for FMS: New ACR Model

- New ACR criteria (revised in 2010/11 and 2016)
  - Prevalence more equal between men and women, similar to other pain conditions
  - Generalized pain in ≥4/5 body regions
  - Symptoms present at similar level ≥3 months
  - Widespread Pain Index (WPI): number of areas patient has pain over the last week (score 0-19)
  - Symptom Severity Scale (SSS): severity of fatigue, waking unrefreshed, and cognitive symptoms + severity of general somatic symptoms (score 0-12)
  - WPI ≥7 and SSS ≥5
    - or WPI 4-6 and SSS 9
  - Fibromyalgia Severity (FS) scale = WPI + SSS

Widespread Pain Index (WPI): Note the number of areas in which patient has had pain over the last week. In how many areas has the patient had pain? Score range is 0-19.

L Upper Region
L jaw
L shoulder girdle
L upper arm
L lower arm

R Upper Region
R jaw
R shoulder girdle
R upper arm
R lower arm

Axial Region
Neck
Upper back
Lower back
Chest
Abdomen

L Lower Region
L hip (buttock/trochanter)
L upper leg
L lower leg

R Lower Region
R hip (buttock/trochanter)
R upper leg
R lower leg

Symptom Severity Scale (SSS) score (range is 0-12)

Fatigue
Waking unrefreshed
Cognitive symptoms

For each of the 3 symptoms above, indicate the level of severity over the last week using the following scale:

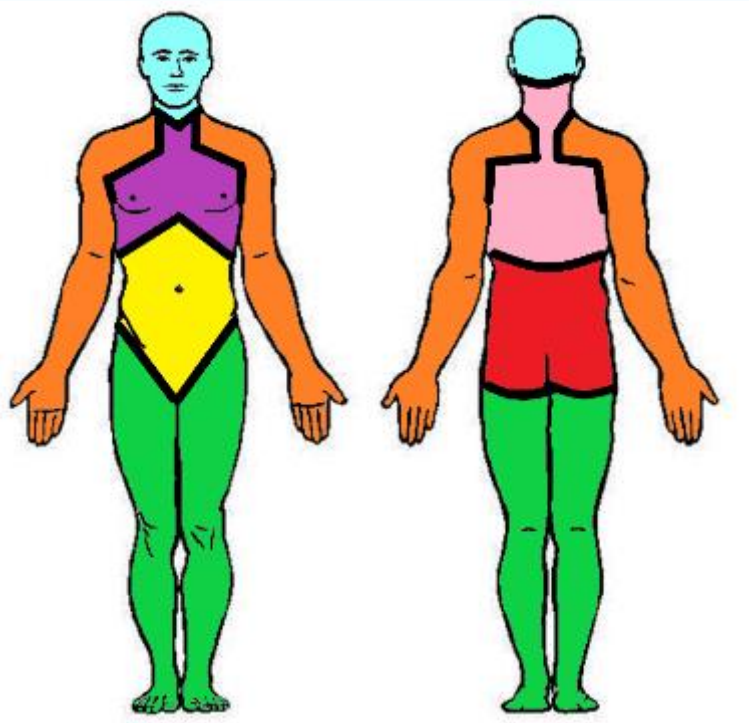
0 = No problem
1 = Slight or mild problems, generally mild or intermittent
2 = Moderate, considerable problems, often present and/or at moderate level
3 = Severe: pervasive, continuous, life-disturbing problems

The SSS score is the sum of the severity score of the 3 symptoms (0-9) plus the sum of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 months (0-3):

1) Headaches (0-1)
2) Pain or cramps in lower abdomen (0-1)
3) Depression (0-1)

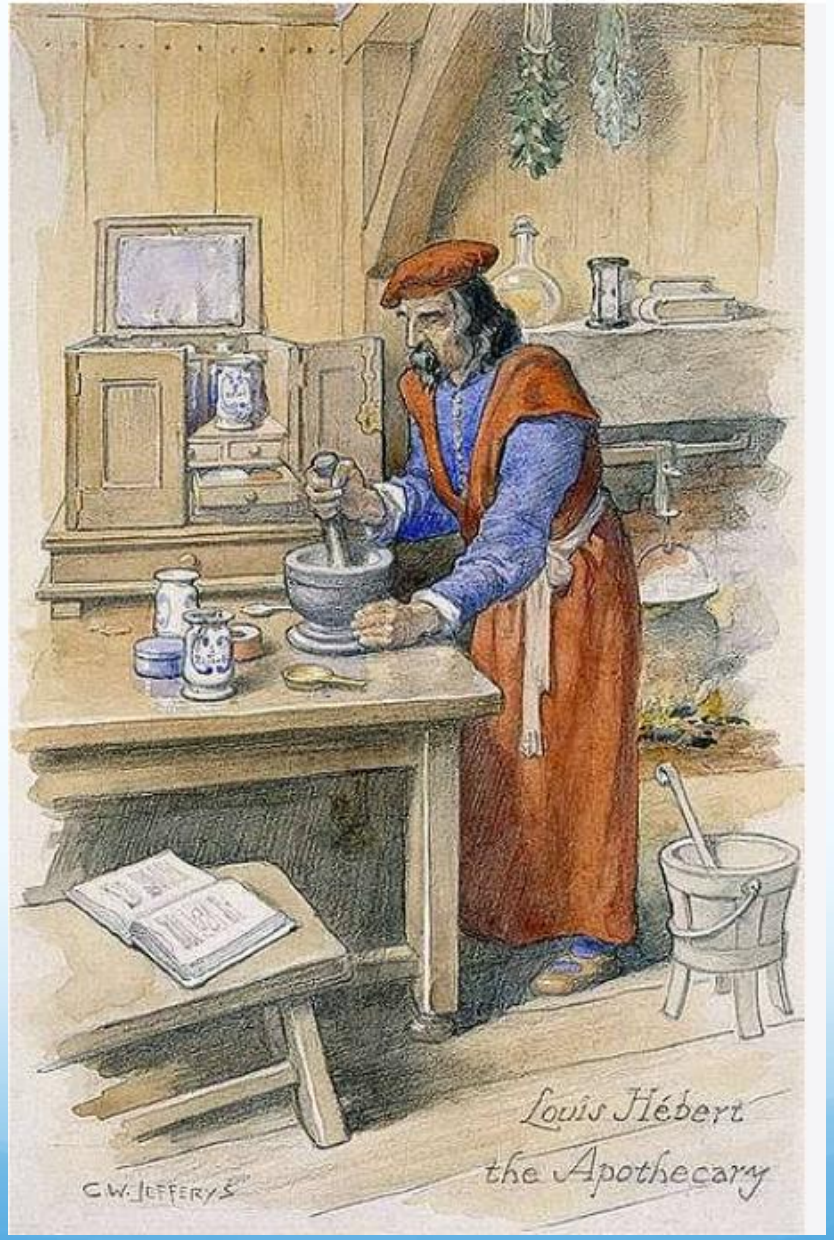
Newest Diagnostic Criteria for FMS

- AAPT (ACTTION-APS Pain Taxonomy) working group
- ≥3 months of BOTH multisite pain at ≥6/9 possible sites AND moderate/severe problems with sleep OR fatigue
- Does not require tender point assessment
- Other disorders that cause pain or related symptoms does not exclude the possibility of FMS



Sites: Head, L arm, R arm, Chest, Abdomen, Upper back and spine, Lower back and spine, L leg, R leg

The Art of Medicine



Treatment

- Need multimodal approach tailored for individual patient
  - Patient Education!
  - Non-pharmacologic – exercise program, CBT, sleep hygiene
  - Treat comorbid psych/sleep disorders
  - Pharmacologic – most patients will need this
- Goals: maintain/improve function, improve quality of life, manage symptoms

  - Teal = shown to significantly improve FMS symptoms and recommended by EULAR (European League Against Rheumatism)

FIRST: Patient Education

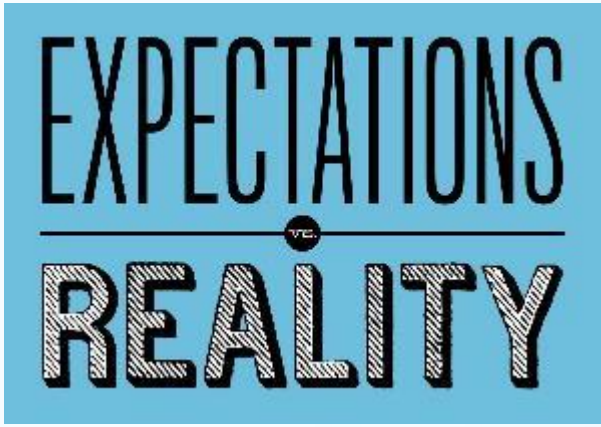
- Real illness!! Not “all in your head”
  - Validation, empathy, compassion
- Prognosis: benign, not progressive, infectious
- Pathophysiology of central sensitization and neurotransmitter alterations
  - Increased pain perception, fatigue, abnormal sleep, and mood disturbances
- Symptoms wax and wane, but pain/fatigue may persist
- Can have normal life with some modifications
  - Activity pacing, knowing your limits, listening to your body

Patient Education

- Treatment approaches
  - Patient's role in their treatment plan: taking ownership
  - Start with treating worst symptoms first
  - No "magic bullet" to cure it
  - No "one size fits all" approach either
  - Understand that meds help a little, not a lot
- Sleep hygiene and effects of poor sleep on function and pain
  - Treat any underlying sleep-associated disorders
    - OSA, PLMD, or RLS

Patient Education

- Importance of treating comorbid mental disorders
  - Mood disorders especially
  - Managing physical and emotional stress to reduce flares and pain
  - Fix maladaptive chronic illness behavior – CBT



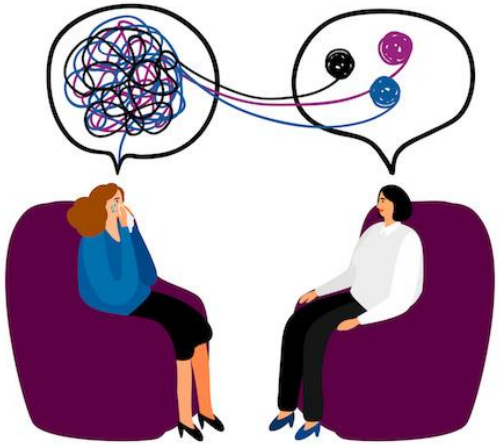
- Good to educate family members as well
- No time to educate? Refer to internet-based programs!

SECOND: Exercise is key!

- Low-impact Aerobic and Strengthening Exercise
  - Start with low to moderate intensity
    - Walking, swimming, cycling, water aerobics
  - Graded exercise programs: increase intensity over time to goal of 30-60 minutes of moderate exercise ≥3 times weekly
- Strength training and stretching
  - Low weight and high reps
- May have temporary increase in myalgias, but will get better!
- Improves: pain, overall function, sleep, mood, and quality of life

THIRD: Psychotherapy

- Cognitive Behavioral Therapy (CBT)
  - Understand, recognize, and modify maladaptive thinking/behavioral patterns
  - Great for concurrent mood disorders
  - Face to face, online, books/CDs
  - Psych referral if possible



- Usually better and cheaper than medication!
- Improves: pain, overall function, sleep, mood, and QOL with lasting effects!

FOURTH: Improve Sleep

- Restore sleep
  - Sleep hygiene
  - CBT for insomnia (CBT-I)
  - Treatment of comorbid sleep disorders
    - OSA, RLS, PLMD…
- Improves: pain, overall function, sleep, mood, and QOL

FIFTH: Pharmacologic Therapy

- No strong evidence that they work well, only modest benefit
  - Very few continue meds due to lack of efficacy, side effects, or both
- May help with pain and sleep, not so much for fatigue or QOL
- Choice depends on predominating symptoms, clinical experience, and patient preference
  - Only 3 FDA-approved for FMS
- Start low and slow!!
  - Titrate to effectiveness and patient tolerability

Tricyclics

- Amitriptyline
  - First line treatment (maybe)
  - Low cost
  - Start at 10mg at bedtime
  - Careful of side effects, especially in elderly
    - Anticholinergic side effects!
  - Improves: pain, fatigue, sleep, QOL

- Despiramine is alternative with fewer anticholinergic side effects

SNRIs

- Next step in therapy
- Great for patients with severe fatigue and depression
- Duloxetine – FDA-approved for FMS
  - Start at 20 or 30mg and double every 1-2 weeks
  - Goal is 60mg daily
    - No further improvement with higher doses
  - Improves: pain and depressive symptoms, maybe fatigue

SNRIs

- Milnacipran – FDA-approved for FMS
  - Start at 12.5mg daily and double weekly
  - Goal is 100mg daily
  - Improves: pain and fatigue
- Venlafaxine
  - Lower cost, but short half-life causing withdrawal symptoms if missed dose
  - Unsure if effective

Anti-convulsants

- Great for patients with sleep disturbances
- Pregabalin – FDA-approved for FMS
  - Start at 75mg bid and double every 1-2 weeks
  - Goal is 300-450mg daily
  - Improves: sleep and pain (maybe fatigue and QOL)

Anti-convulsants

- Gabapentin
  - Low cost alternative to pregabalin
  - Start at 100-300mg at bedtime
  - For patients with poor sleep only
  - Careful of side effects
  - Improves: sleep and pain (maybe fatigue and QOL)

What if those sort of work, but not enough?

COMBO MEDS!

Combination Medications

- Low dose SSRI/SNRI in am + low dose tricyclic in pm
  - SSRI: fluoxetine
  - SNRI: duloxetine or milnacipran
  - Tricyclic: amitriptyline
- Low dose SNRI in am + low dose anticonvulsant in pm
  - SNRI: duloxetine, milnacipran, or venlafaxine
  - Anticonvulsant: pregabalin
- These combos work better than monotherapy for pain, sleep, and function

What if those don't work?

- Referral to specialists
  - Psychiatry: needing more CBT, mood symptoms, meds
  - PT: failed exercise program
  - Physiatry: failed exercise program or PT, need trigger point injections
  - Rheumatology: confirm dx, combo meds, MSK issues
  - Sleep specialists: RLS or OSA testing
  - Pain management: only if comprehensive center that will not rx opioids or do interventional procedures on FMS pts
- Alternative and complementary therapies
  - Limited evidence for these modalities

Adjunct Medications

- Acetaminophen and/or tramadol for temporary pain relief
  - Tramadol is weak opioid with SNRI activity, but be wary
- Muscle Relaxants as needed for flares
  - Cyclobenzaprine
    - Similar to a TCA with minimal antidepressant effect
    - Good for mild/moderate symptoms
    - Improves: sleep mainly, small effect on pain
  - Tizanidine
    - Fewer DDIs than cyclobenzaprine
  - Baclofen

Other Substances

- Alcohol
  - Works to increase CNS GABA levels
  - Low-moderate consumption improved pain, function, and QOL
  - Heavy drinking did not help
- Cannabinoids
  - Inconsistent with effectiveness
  - Canadian guidelines for FMS management includes it for sleep problems
  - EULAR does not recommend them

Inconsistent/Insufficient Evidence

- SSRIs
- MAOIs
- NSAIDs
- Memantine
- NRIs (reboxetine or esreboxetine)
- Pramipexole
- Melatonin
- Antipsychotics
- Corticosteroids
- Opioids
- Growth hormone
- Sodium oxybate
- Cannabinoids
- Ketamine
- Vitamin D

Not Recommended by EULAR

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- MAOIs
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- Corticosteroids
- Opioids
- Growth hormone
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- Cannabinoids
- Ketamine
- Vitamin D

Effective Complementary/Alternatives

- Mindfulness-based stress reduction
  - Improve coping with pain
  - Improves: sleep, symptom severity, and perceived stress
- Meditation, hypnosis, or guided imagery
- Meditative movement therapies
  - Yoga
  - Tai chi
- EMG Biofeedback
- Hydrotherapy/balneotherapy

Ineffective Complementary/Alternatives

- Qigong
- Acupuncture
- Chiropractic
- EEG Biofeedback
- Supplements (SAMe)
- Homeopathy
- Phytotherapy
- Transcranial Magnetic Stimulation (TMS)?
- TENS units?
- Massage?
- Cannabinoids?
- Topical capsaicin?
- Naltrexone?

Not Recommended by EULAR

- Qigong
- Acupuncture
- Chiropractic
- Biofeedback (any)
- Supplements (SAMe)
- Homeopathy
- Phytotherapy
- Transcranial Magnetic Stimulation (TMS)
- TENS units
- Massage
- Cannabinoids?
- Topical capsaicin
- Naltrexone?
- Hypnotherapy/guided imagery

You can try these and see if they help!

Consider This…

- Weight Loss
  - Obesity increases FMS symptoms and reduces QOL
  - Gluten-free diet
    - Improves: GI symptoms
    - Not for everyone
  - Hypocaloric diet
    - Improves: symptom severity and pain (joints especially!)
    - Might be from IL-10 increase (anti-inflammatory)
  - Low FODMAP diet
    - Improves: GI symptoms (abdominal pain)

Close Monitoring

- Regular follow ups
  - Weekly or monthly
  - Symptom severity, functioning, response to treatment, adherence, and adverse effects
  - Greater outpatient engagement is protective against suicide in FMS patients
- Track daily or weekly symptoms to see progress
  - Can use the ACR Widespread Pain Index and Symptom Severity Score to track progress
  - Numbers have power!

Set backs

- “Frequent fliers” can be emotionally overwhelming
  - Unrealistic expectations
  - Inability to cope
  - Noncompliance/non-adherance
- Flares happen, so be prepared
  - Find triggers, reduce stress, relaxation exercises, pleasant activities, resting, adjunct meds (maybe)
- Feeling discouraged because you “can’t fix them”
  - Not all treatments work for every fibro patient
  - You just have to find your patient’s “cocktail”
  - Some have better outcomes than others

You can do it!!

- Most are thankful for help and that you listened
- Treating FMS is a marathon, not a sprint
- You can change their lives for the better!! ☺

Take Home Points

- Fibromyalgia is a chronic widespread pain disorder characterized by dysfunctional CNS pain processing
- Clinicians need to have a low index of suspicion for fibromyalgia and not treat it as a diagnosis of exclusion
- Utilize non-pharmacological treatment regimens that are tailored to each patient first, then pharmacological
- Close follow up, empathy, and support are key for an effective provider-patient relationship and treatment success

Post-test Question #1

- Which of the following neurological symptom is characteristic of fibromyalgia?
  - Apraxia
  - Aphasia
  - Allodynia
  - Ataxia

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Questions?

- Email me at dvillmore@une.edu

Mt. Katahdin in Baxter State Park, Maine