

Fibromyalgia for Primary Care Providers

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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, reboxetine, esreboxetine, gabapentin, cyclobenzaprine, tizanidine, baclofen, naltrexone, memantine, ketamine, tramadol, quetiapine, and pramipexole for fibromyalgia

Learning Objectives

- At the conclusion of this session, participants should be able to:
 - Discuss pathophysiology of fibromyalgia
 - 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
 - Utilize appropriate pharmacotherapy for patients with fibromyalgia

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

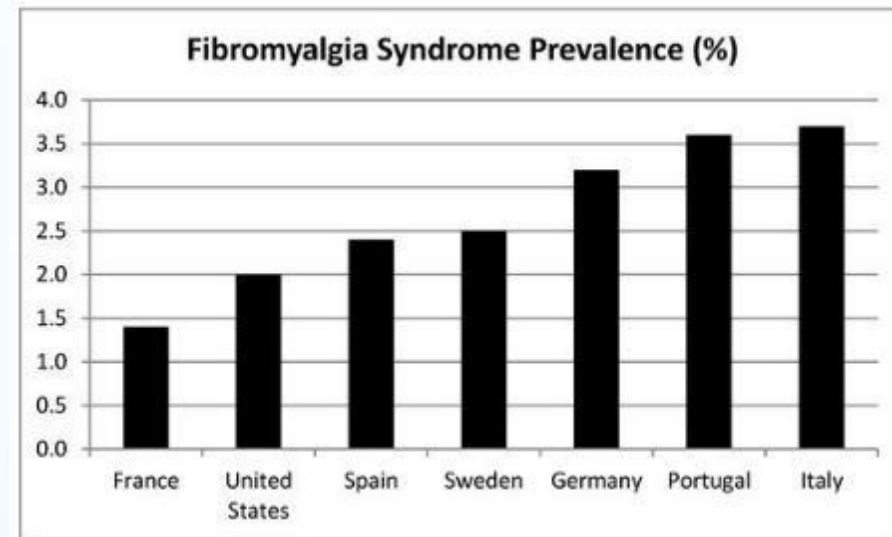
Fibromyalgia Syndrome

- 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



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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??

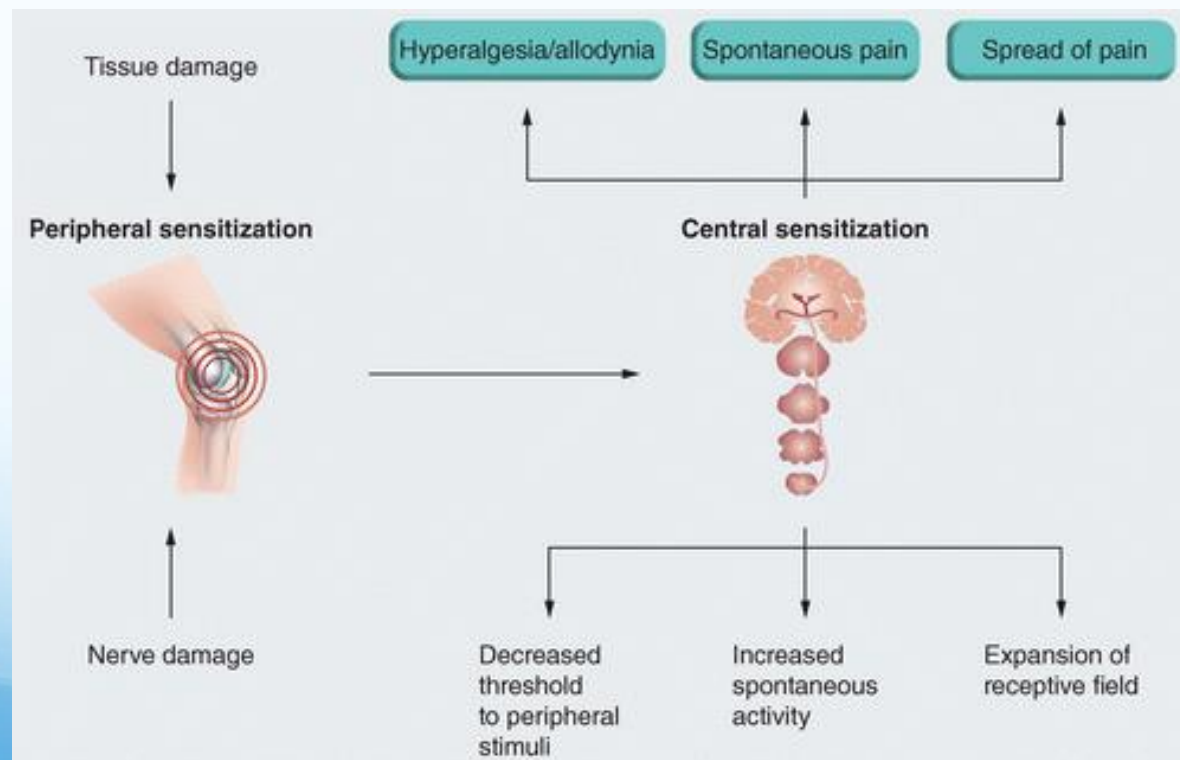


Pathophysiology of FMS

- 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



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

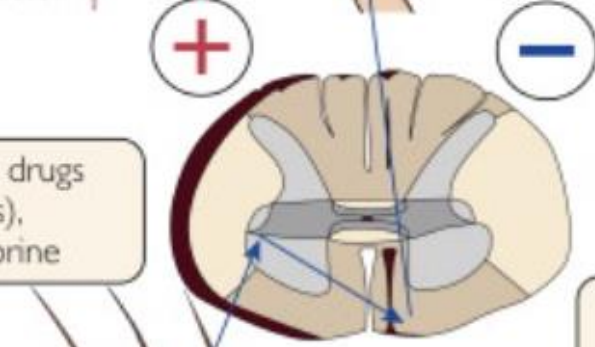
Pathophysiology of FMS

Generally facilitate pain transmission

Gabapentinoids, ketamine, memantine

- Glutamate ↑
- Substance P ↑
- Nerve growth factor ↑
- Serotonin (5HT_{2a, 3a}) ↑

Antimigraine drugs (-triptans), cyclobenzaprine



Generally inhibit pain transmission

■ Descending antinociceptive pathways

■ Norepinephrine-serotonin (5HT_{1ab}), dopamine

Tricyclics, SNRIs, tramadol

■ Opioids

Low-dose naltrexone

■ Cannabinoids
■ GABA

γ-Hydroxybutyrate, moderate alcohol consumption

No knowledge of endocannabinoid activity, but this class of drugs is effective

Pathophysiology of FMS

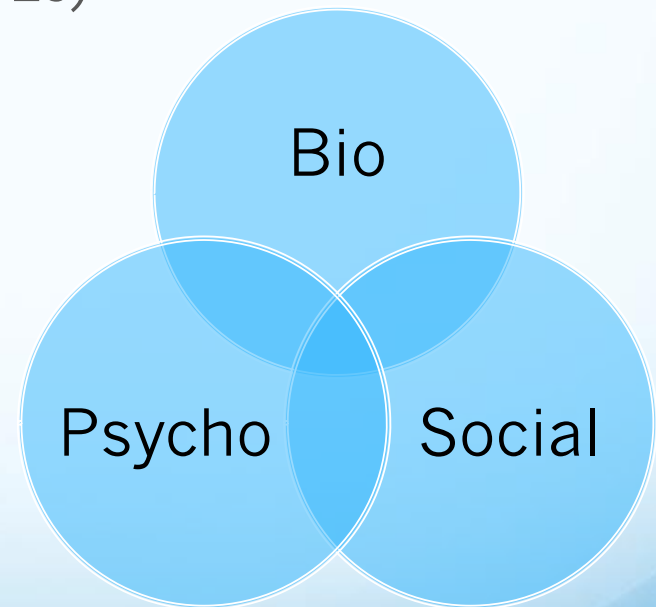
- Immune dysregulation
 - Role of cytokines is unclear
 - Altered but cannot find a consistent pattern
 - No autoimmunity, maybe...
- Sleep disorders
 - Alpha stage intrusion (hyperarousal)
 - Possibly precede the pain and then make pain worse
- Muscle dysfunction
 - Possible mitochondrial dysfunction → 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?

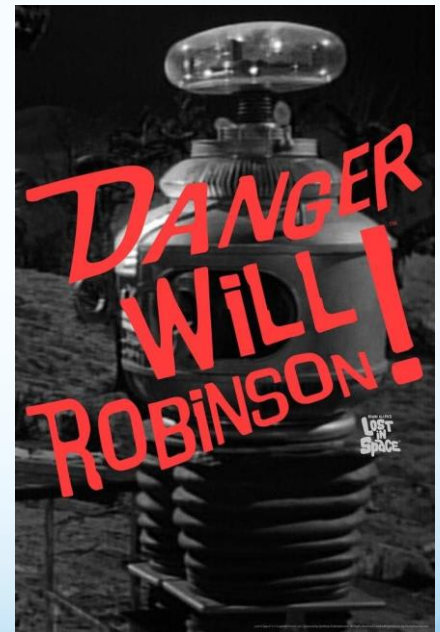
FMS Triggers

- 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

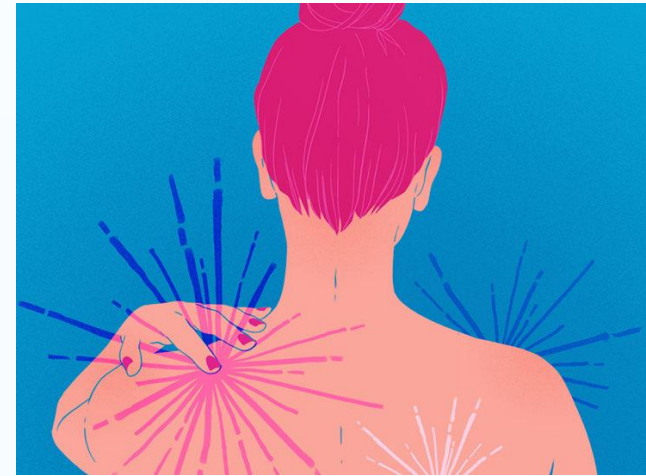
HPI: Listen to your patient!

- 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?

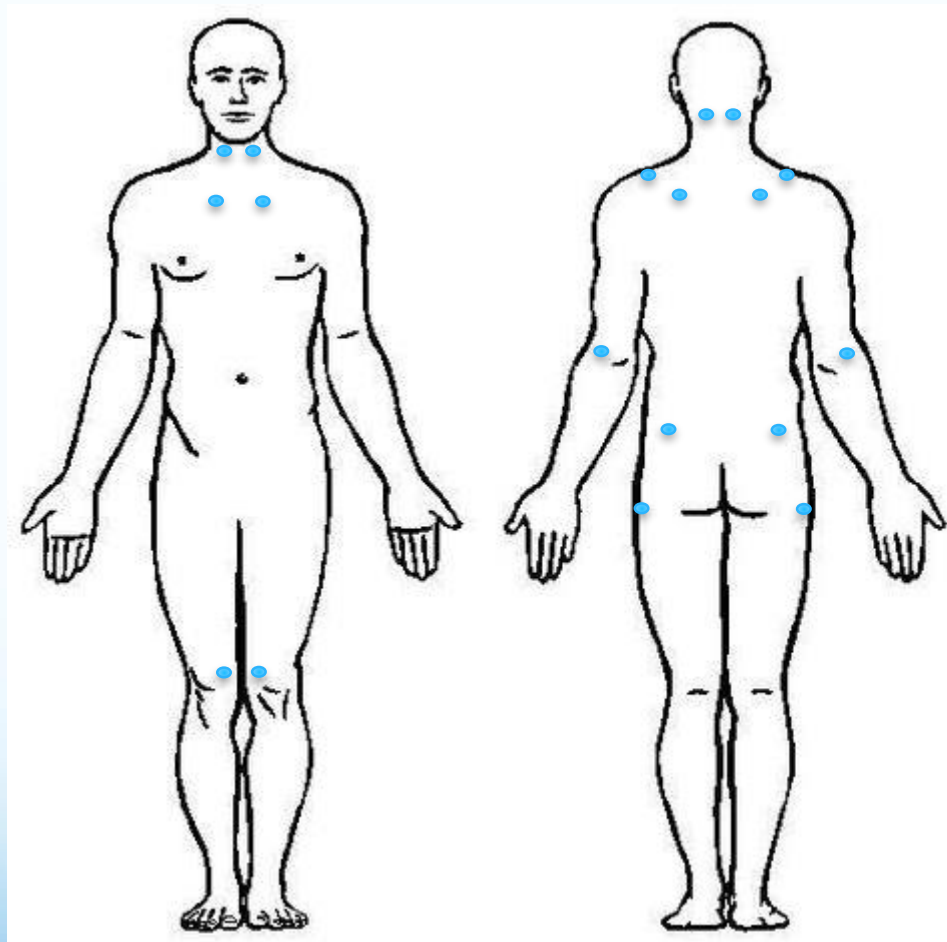
- There is none here...
- It's YOUR CLINICAL JUDGEMENT!
- Consult rheum if you have doubts...
 - More of them are comfortable making the diagnosis of FMS than PCPs
- Tools to help you out coming next!

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 $\geq 4/5$ 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):

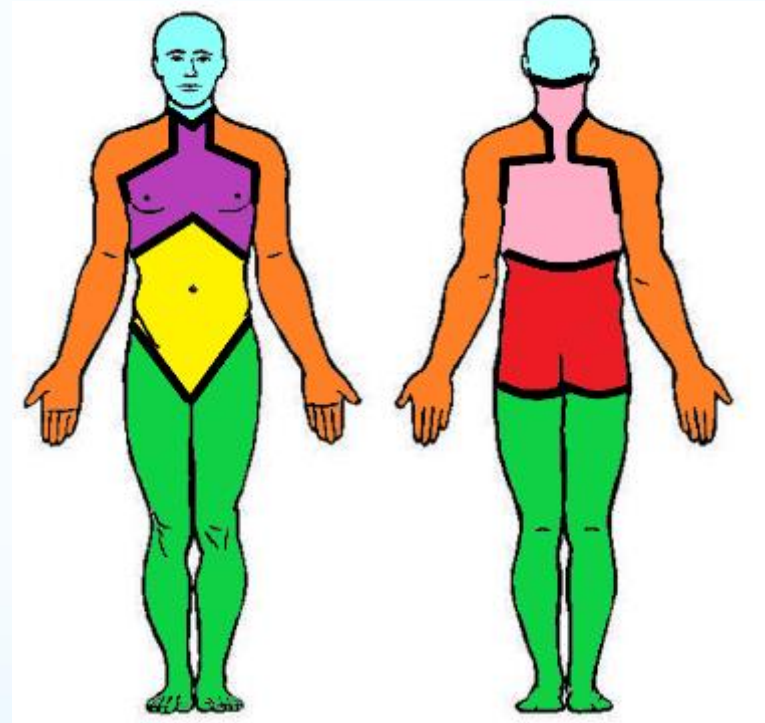
1) Headaches (0-1)

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

3) Depression (0-1)

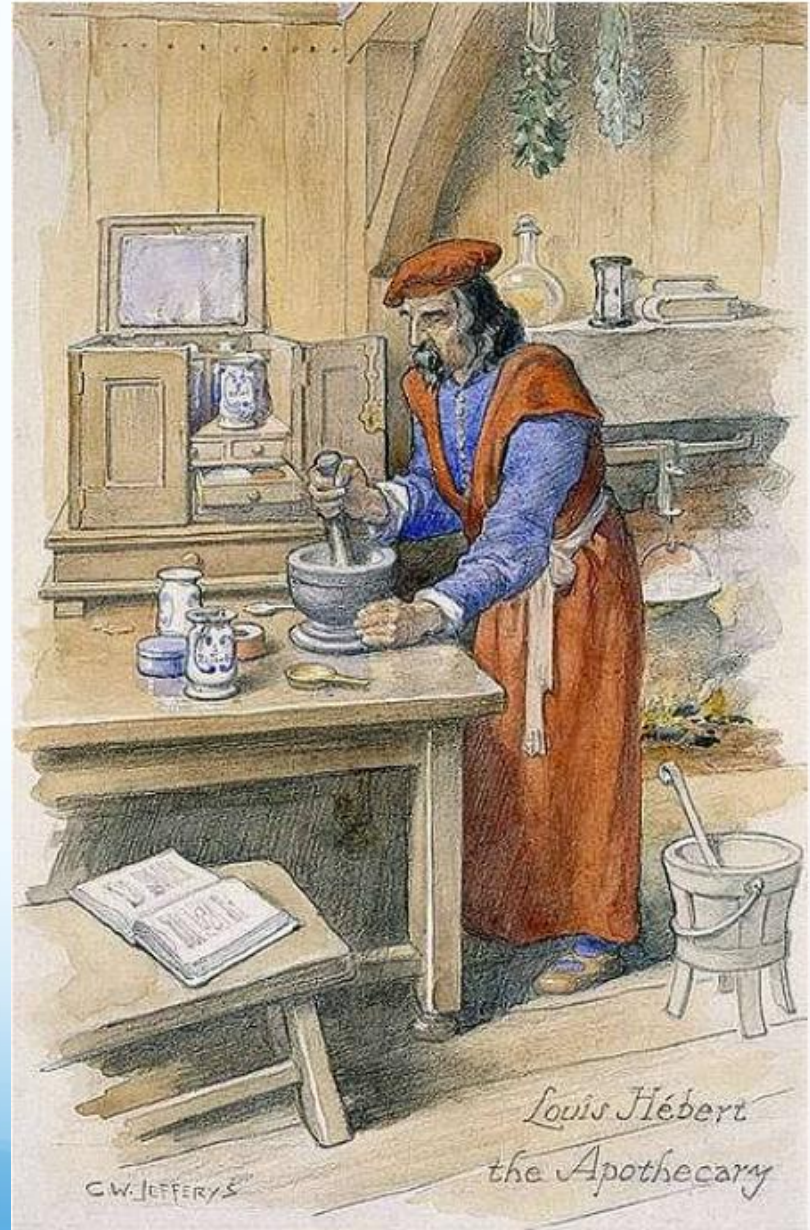
Newest Diagnostic Criteria for FMS

- AAPT (ACTION-APS Pain Taxonomy) working group
- ≥ 3 months of BOTH multisite pain at $\geq 6/9$ 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



Knowledge is
Power

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!

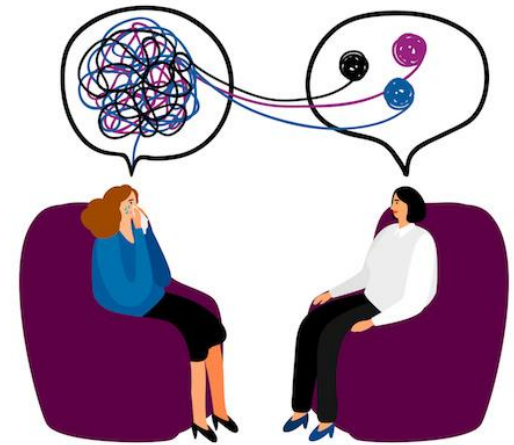


SECOND: Exercise is key!

- 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

- SSRI
- MAOI
- NSAID
- Memantine
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- Pramipexole
- Melatonin
- Antipsychotics
- Corticosteroids
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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

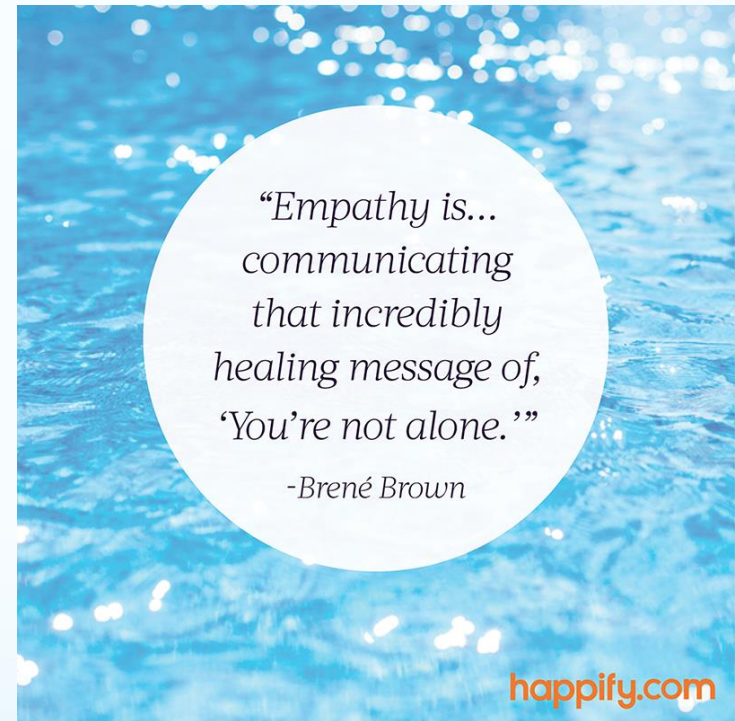
- Regular follow ups
 - Weekly or monthly
 - Symptom severity, functioning, response to treatment, adherence, and adverse effects
 - Greater outpatient engagement is protective against suicide in FMS patients
- Track daily or weekly symptoms to see progress
 - Can use the ACR Widespread Pain Index and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

Set backs

- “Frequent fliers” can be emotionally overwhelming
 - Unrealistic expectations
 - Inability to cope
 - Noncompliance/non-adherence
- 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?

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