Fibromyalgia for PCPs:

Not Just for Rheumatology Anymore

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

Disclosure

- No relevant commercial relationships to disclose
- The activity is not supported by a grant
- 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 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 is NOT an FDA approved medication for the treatment of fibromyalgia?
  - Venlafaxine
  - Duloxetine
  - Milnacipran
  - Pregabalin

Pre-test Question #2

- Which of the following does NOT contribute to the symptoms of fibromyalgia?
  - Aberrant pain processing in CNS
  - Dysfunctional sleep patterns
  - Neurotransmitter alterations
  - Immune dysregulation
  - These all contribute to fibromyalgia symptoms

Pre-test Question #3

- Which of the following is NOT a main symptom of fibromyalgia?
  - Migrating widespread pain
  - Cognitive dysfunction
  - Non-restorative sleep/waking unrefreshed
  - Fatigue
  - Joint swelling

Fibromyalgia

- Chronic widespread pain disorder characterized by aberrant central pain processing and central sensitization
- Migrating and multisite musculoskeletal pain
  - Muscle, ligaments, tendons especially, but no evidence of inflammation
- Somatic complaints: mainly fatigue and sleep disturbances
- Cognitive and psychiatric disturbances
- Etiology unknown
- Variable severity and outcomes → large spectrum

Epidemiology

- Prevalence 2-4% and increases with age
  - Can happen in children and adolescents and persist into adulthood
- 2:1 female predominance
  - Most common cause of generalized musculoskeletal pain in women between 20-55 years of age
- Up to 30% of patients with inflammatory conditions (SLE or RA) have FMS
- Up to 65% of patients with FMS have a mental health diagnosis (anxiety, depression)
  - Much higher than general population
- Commonly happens in people with other chronic pain syndromes (TMJD, chronic back pain, IBS)

Epidemiology

- Up to 30% of patients with FMS report that they are work disabled
- Worse outcomes: low socioeconomic status, obesity, comorbid mental illness, history of abuse, catastrophizing, and excess somatic concern
- More severe symptoms and more comorbidities = higher cost of care and greater morbidity
  - Many rate health as fair/poor and have average of 1 outpatient visit/month!
  - Spend 3x more on healthcare
- Mortality rates not necessarily increased, but increased risk of suicide
  - More cardiovascular disease and cancer (obesity, inactivity)?

Can’t I just send them to rheum?!

- Rheumatologists are not always necessary
- PCPs can coordinate all aspects of care
  - Comprehensive management with medical home model
  - **PCPs have better patient outcomes than tertiary referral centers!**
- Continuous management: easier and closer follow up
- Reduced healthcare costs
  - Often takes 2+ years to get diagnosed with >3 different consults!

Pathophysiology of FMS

- Pathophysiology is complex and not quite understood
  - Likely genetic predisposition with environmental triggers
  - Possible epigenetic contributions?
- Strong genetic association
  - First degree relatives of patients with FMS 8x more likely to have FMS
  - Multiple candidate genes in serotonin, dopamine, and catecholamine metabolic or signaling pathways
    - Not always consistent results with SNPs

Pathophysiology of FMS

- Dysfunction of CNS pain processing
  - Central sensitization and/or central augmentation of pain/stimuli
    - Heat, cold, auditory, electrical stimuli
    - Feel pain instead of just touch (allodynia)
    - Feel more pain than normal (hyperalgesia)
  - Decreased endogenous analgesic systems
    - Downregulation of opioid receptors in brain – decreased analgesia
    - Inability to inhibit irrelevant sensory stimuli
    - Do not reduce pain felt after second painful stimulus

Pathophysiology of FMS

- Neurotransmitter alterations
  - High substance P – hyperalgesia, induces inflammation, increased anxiety/depression
  - High glutamate and lower GABA – increased excitatory state
  - Low serotonin and dysregulation of dopamine – changes in mood
  - High nerve growth factor – more sensitive to nociceptive stimuli

Pathophysiology of FMS

- Brain function alterations
  - Pain-sensitive areas in brain over-activated on fMRI
    - Amygdala, insula, somatosensory cortex
      - Insula includes emotional processing of sensations (unpleasantness)
  - New connections between areas not normally involved in pain transmission
  - Reduction in total gray matter volume and increase in age-associated loss of gray matter → premature aging of brain
    - Worse with longer duration of disease, similar to depressed brains

Pathophysiology of FMS

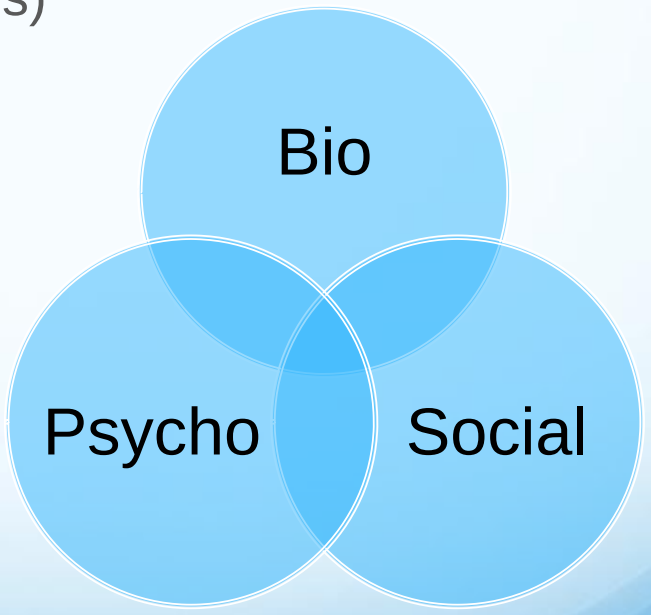
- Muscle dysfunction
  - Lactic acid buildup and mitochondrial dysfunction (lower ATP)
  - Overall capillary density lower – less blood flow
- Immune dysregulation
  - Pro-inflammatory cytokines (IL-6 and IL-8 elevated in sera)
  - Immune cell hyper-responsiveness: microglia in CNS
  - No autoimmunity, maybe…
- Sleep disorders
  - Alpha stage intrusion
  - Stage IV and REM reduced

Comorbid Conditions

- IBS
- Interstitial Cystitis
- Dyspareunia/pelvic pain
- Migraines
- TMJD
- Joint hypermobility syndrome/EDS
- CFS/Myalgic Encephalomyelitis
- OSA, RLS, other sleep disorders
- Mood disorders: anxiety, depression, PTSD, OCD…
- Atopic disorders
- Raynaud's
- Autoimmunity – RA, SLE, AnkSpond, Sjögren's
- Thyroid dysfunction
- OA
- GERD
- HTN
- Cardiac disorders/arrhythmias
- Hyperlipidemia
- Obesity/physical inactivity

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



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

Differential Diagnosis

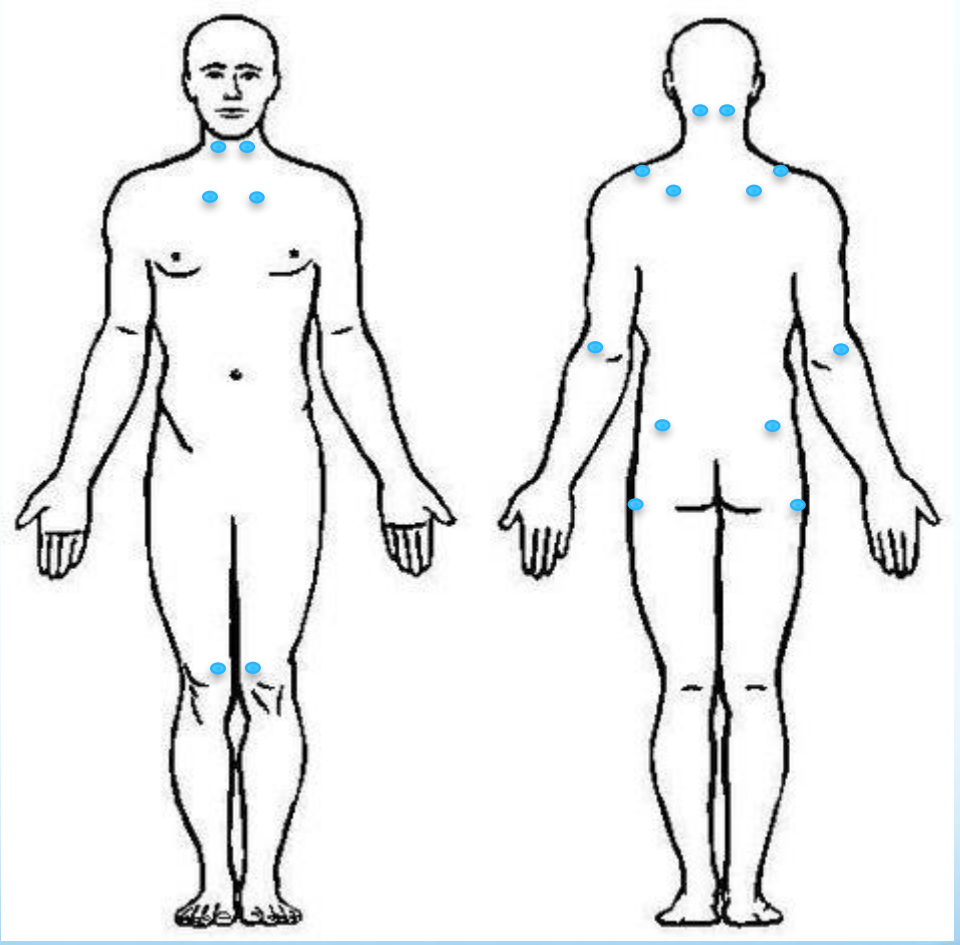
- RA – joint swelling, elevated ESR/CRP
- SLE – malar rash, renal/cardiac/pulmonary/neuro features
- PMR – older age at onset, elevated ESR/CRP, rapid response to glucocorticoids
- Polymyositis – muscle weakness, elevated muscle enzymes, abnormal EMG
- Spondyloarthritis – restricted spinal motion, elevated ESR/CRP
- Lyme – bullseye rash, joint swelling, serologic tests
- Hypothyroidism – abnormal TSH, pain not prominent
- Neuropathies – sensory/motor deficits, abnormal EMG

Diagnostic Criteria for FMS: Old Model

Widespread pain > 3 months

FMS if >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 female prevalence

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

No mention on non-pain symptoms

Diagnostic Criteria for FMS: New Model

- New ACR criteria (revised in 2010/11 and 2016)
  - Prevalence more equal between men and women, similar to other pain conditions
  - Generalized pain (at least 4/5 body regions)
  - Symptoms present at similar level ≥ 3 months
  - Diagnosis of FMS is valid irrespective of other diagnoses (can have FMS *AND* another disorder)
  - **Widespread Pain Index (WPI)**: number of areas patient has pain over the last week (score 0-19)
  - **Symptom Severity Scale (SSS)**: sum of severity of fatigue, waking unrefreshed and cognitive symptoms plus severity of general somatic symptoms (score 0-12)
  - WPI ≥ 7 and SSS ≥ 5
    - or WPI 4-6 and SSS ≥ 9
  - Fibromyalgia Severity (FS) scale is the sum of WPI and 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 (1)
L jaw
L shoulder girdle
L upper arm
L lower arm

R Upper Region (2)
R jaw
R shoulder girdle
R upper arm
R lower arm

Axial Region (3)
Neck
Upper back
Lower back
Chest
Abdomen

L Lower Region (4)
L hip (buttock, trochanter)
L upper leg
L lower leg

R Lower Region (5)
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:

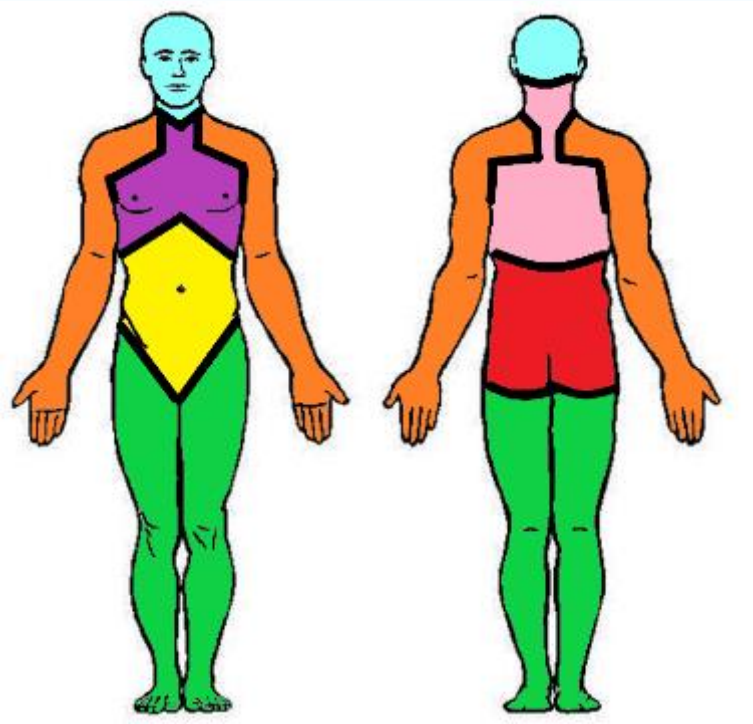
0 = No problem
1 = Slight or mild problems, generally mild or intermittent
2 = Moderate, considerable problems, often present and/or at moderate level
3 = Severe: pervasive, continuous, life-disturbing problems

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
- History of at least 3 months of BOTH multisite pain at 6/9 possible sites AND moderate to severe problems with sleep or fatigue
- Do not require enumeration of tender points at defined sites by physical exam
- Other disorders that cause pain or related symptoms does not exclude the possibility of FMS
  - Must fully evaluate any other condition that could be causing those related symptoms or pain



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

HPI: Listen to your patient!

- FATIGUE
  - Flu-like symptoms
  - “I hurt all over”
- Cognitive dysfunction: “Fibro Fog”
  - Working memory impairment
  - Poor concentration
  - Word-finding difficulties
  - Disorganized/slow thinking
- Poor quality of sleep and/or insomnia
- Migrating pains and paresthesias
  - Muscle twitching
  - Arthralgias: TMJD, morning joint stiffness

HPI: Listen to your patient!

- Neuro complaints: headaches, migraines, dizziness, blurry vision
- GI complaints: nausea/vomiting, GERD, abdominal pain/cramping, diarrhea, constipation
- GU complaints: urinary frequency, urinary urgency
- Anxiety and depression
  - Chest pain
  - Catastrophizing
  - Perfectionism/neuroticism
  - Compulsive behavior
- Atopy and Environmental sensitivity
  - Bright lights, loud noises, cold, perfumes, chemicals

Diagnosis

- Physical exam
  - Soft tissue is tender to palpation
  - Evaluate for other possible disorders that have similar symptoms
    - Joint assessment for synovitis (should be no joint damage!)
      - 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, palpitations

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 process
  - RF, ANA, etc. not necessary for FMS patients
  - Vitamin deficiencies: B12, folate for paresthesias, D3 for depression/fatigue
  - TSH for thyroid disease
  - CK for inflammatory muscle disease
  - Iron studies?
  - CMP?

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 sleep disorders
- Might consider psych referral for undiagnosed mental health problems
- Other referrals: physiatry, physical therapy, pain specialists

Treatment

- Need multimodal approach tailored for individual patient
  - Patient Education!!!
  - Non-pharmacologic – exercise program, CBT, sleep hygiene
  - Pharmacologic (2nd line, only if needed)
- **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

- Disease process: KNOWLEDGE IS POWER
  - Real illness!! Not “all in your head”
    - Validation, empathy, compassion
  - Prognosis: benign, not progressive, not infectious
  - Talk about pathophysiology of central sensitization
    - 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
  - Fix maladaptive chronic illness behavior – CBT
- Good to educate family members as well
- No time to educate? Refer to internet-based programs!
- EXPECTATIONS VS. REALITY

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 at least 3 times weekly
- Strength training and stretching
  - Low weight and high reps
- Increases blood flow to release lactic acid buildup
- 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

Add-ons: Holistic Medicine

- Mindfulness-based stress reduction
  - Improve coping with pain
  - Improves: sleep, symptom severity, and perceived stress
- Meditative movement therapies
  - Yoga
  - Tai chi
  - Qigong
- Defined physical therapies
  - Acupuncture
  - Hydrotherapy

Add-ons: Holistic Medicine

- Weight Loss
  - 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)

Not Recommended by EULAR

- Biofeedback
- Hypnotherapy
- Guided imagery
- Transcranial Magnetic Stimulation (TMS)
- Topical capsaicin
- Massage
- Chiropractic
- Supplements (SAMe)
- Homeopathy

You can always try these and see if they help!

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 quality of life
- 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
- Good 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
- Milnacipran – FDA approved for FMS
  - Start at 12.5mg daily and double weekly
  - Goal is 100mg daily
  - Improves: pain and fatigue

SNRIs

- Venlafaxine
  - Lower cost, but short half-life causing withdrawal symptoms if missed dose
  - Unsure if effective
- Reboxetine
  - Inconsistent effectiveness
- Esreboxetine
  - Improves: pain, fatigue, and QOL

Anti-convulsants

- Pregabalin – FDA approved for FMS
  - Start at 75mg bid and double every 1-2 weeks
  - Goal is 300-450mg daily
  - Can uses with duloxetine – shown to be more effective than either alone
  - Improves: sleep and pain (maybe fatigue and QOL)
- 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)

Others

- Muscle Relaxants
  - 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
- Alcohol
  - Works to increase CNS GABA levels
  - Low-moderate consumption improved pain, function, and QOL
  - Heavy drinking did not help

Others

- Naltrexone
  - Competitive opioid receptor antagonist and blocks innate immune receptor TLR-4
    - Might be anti-inflammatory in CNS
  - 4.5mg daily
  - Needs to be specially compounded
  - Improves: pain and depressive symptoms
- Anti-Parkinson's (NMDA Antagonists)
  - Memantine
    - 20mg/day (10mg bid)
    - Start at 5mg daily then increase by 5mg weekly
    - Improves: pain
  - Ketamine
    - Improves: pain
- Sleep aids
  - Melatonin
- Pramipexole
  - Comorbid RLS

Not Recommended by EULAR

- SSRIs – usually not effective
  - Small improvements in pain, fatigue, QOL
  - Can try if cost is issue
- Cannabinoids
  - Inconsistent effectiveness
  - Canadian guidelines for FMS management do include it for sleep problems
- MAO inhibitors
- Antipsychotics
- Corticosteroids
- Growth hormone
- Sodium oxybate

What about opioids?

- NO!!!
- Opioids are ineffective for FMS pain
- Worse outcomes in FMS patients than those not taking opioids
  - Gradually taper them off (might take years)
- Some use tramadol as adjunct
  - Weak opioid with SNRI activity
  - Be wary of abuse
  - Improves: pain

What about benzos or z-drugs?

- NO!!!
- Tolerance and dependence
- Zolpidem and other sleep meds not recommended long term
- Benzos are not first line for mood disorders!
  - Also not recommended long term

What about OTC analgesics?

- Many patients self-medicate: NSAIDs especially
- Acetaminophen and NSAIDs are not effective for FMS pain
- Often prescribed as adjuncts, but no evidence they work
- If they do help your patient, make sure they are taking them safely

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
- Flares happen so be prepared
  - Find triggers, reduce stress, relaxation exercises, pleasant activities, resting
- 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 is NOT an FDA approved medication for the treatment of fibromyalgia?
  - Venlafaxine
  - Duloxetine
  - Milnacipran
  - Pregabalin

Post-test Question #1

- Which of the following is NOT an FDA approved medication for the treatment of fibromyalgia?
  - Venlafaxine
  - Duloxetine
  - Milnacipran
  - Pregabalin

Post-test Question #2

- Which of the following does NOT contribute to the symptoms of fibromyalgia?
  - Aberrant pain processing in CNS
  - Dysfunctional sleep patterns
  - Neurotransmitter alterations
  - Immune dysregulation
  - These all contribute to fibromyalgia symptoms

Post-test Question #2

- Which of the following does NOT contribute to the symptoms of fibromyalgia?
  - Aberrant pain processing in CNS
  - Dysfunctional sleep patterns
  - Neurotransmitter alterations
  - Immune dysregulation
  - These all contribute to fibromyalgia symptoms

Post-test Question #3

- Which of the following is NOT a main symptom of fibromyalgia?
  - Migrating widespread pain
  - Cognitive dysfunction
  - Non-restorative sleep/waking unrefreshed
  - Fatigue
  - Joint swelling

Post-test Question #3

- Which of the following is NOT a main symptom of fibromyalgia?
  - Migrating widespread pain
  - Cognitive dysfunction
  - Non-restorative sleep/waking unrefreshed
  - Fatigue
  - Joint swelling

Questions?

- Email me at dvillmore@une.edu

Mt. Katahdin in Baxter State Park, Maine

References

- Ablin JN, Buskila D. Update on the genetics of the fibromyalgia syndrome. *Best Pract Res Clin Rheumatol* 2015; 2920-8.
- Aman MM, Yong RJ, Kaye AD, Urman RD. Evidence-based non-pharmacological therapies for fibromyalgia. *Curr Pain Headache Rep* 2018; 22: 33.
- Arnold LM, Bennett RM, Crofford LJ, et al. AAPT diagnostic criteria for fibromyalgia. *Pain* 2019; 20: 611-28.
- Arnold LM, Gebke KB, Choy EHS. Fibromyalgia: management strategies for primary care providers. *Int J Clin Pract* 2016; 70: 99-112.
- Arnold LM, Hudson JI, Hess EV, et al. Family study of fibromyalgia. *Arthritis Rheum* 2004; 50: 944-52.
- Arnold LM, Chatamra K, Hirsch I, Stoker M. Safety and efficacy of esreboxetine in patients with fibromyalgia: an 8-week, multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* 2010; 32: 1618-32.
- Bair Mjand Krebs EE. In the clinic: fibromyalgia. *Ann Intern Med* 2020; 172(5): ITC33-48.
- Bidonde J, Busch AJ, Schachter CL, et al. Aerobic exercise training for adults with fibromyalgia. *Cochrane Database Syst Rev* 2017; 6: CD012700.
- Branco J, Atalaia A, Paiva T. Sleep cycles and alpha-delta sleep in fibromyalgia syndrome. *J Rheumatol* 1994; 21: 1113-7.
- Fitzcharles MA, Ste-Marie PA, Goldenberg DL, et al. 2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. *Pain Res Manag* 2013; 18(3): 119-126.
- Fitzcharles MA, Da Costa D, Poyhia R. A study of standard care in fibromyalgia syndrome: a favorable outcome. *J Rheumatol* 2003; 30: 154-9.
- Gerdle B, Forsgren MF, Bengtsson A, et al. Decreased muscle concentrations of ATP and PCR in the quadriceps muscle of fibromyalgia patients – a 31P-MRS study. *Eur J Pain* 2013; 17: 1205-15.
- Gerdle B, Larsson B, Forsberg F, et al. Chronic widespread pain: increased glutamate and lactate concentrations in the trapezius muscle and plasma. *Clin J Pain* 2014; 30: 409-20.
- Gilron I, Chaparro LE, Tu D, et al. Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial. *Pain* 2016; 157: 1532-40.
- Haliloglu S, Carlioglu A, Akdeniz D, et al. Fibromyalgia in patients with other rheumatic diseases: prevalence and relationship with disease activity. *Rheumatol Int* 2014; 34: 1275-80.
- Harris RE, Clauw DJ, Scott DJ, et al. Decreased central mu-opioid receptor availability in fibromyalgia. *J Neurosci* 2007; 27: 10000-6.
- Hauser W, Jones G. Psychological therapies for chronic widespread pain and fibromyalgia syndrome. *Best Pract Res Clin Rheumatol* 2019; 33(3): 101416.

References

- Julien N, Goffaux P, Arsenault P, Marchard S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain* 2005; 114: 295-302.
- Khoury S, Piltonen MH, Ton AT, et al. A functional substitution in the L-aromatic amino acid decarboxylase enzyme worsens somatic symptoms via a serotonergic pathway. *Ann Neurol* 2019; 00:1-13.
- Knijnik LM, Dussan-Sarria JA, Rozisky JR, et al. Repetitive transcranial magnetic stimulation in fibromyalgia: systematic review and meta-analysis. *Pain Pract* 2016; 16: 294-304.
- Kuchinad A, Schweinhardt P, Seminowicz DA, et al. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? *J Neurosci* 2007; 27: 4004-7.
- Lan CC, Tseng CH, Chen JH, et al. Increased risk of suicide event in patients with primary fibromyalgia and in fibromyalgia patients with concomitant comorbidities: A nationwide population-based cohort study. *Medicine (Baltimore)* 2016; 95: e5187.
- Loge-Hagen JS, Saele A, Juhl C, et al. Prevalence of depressive disorder among patients with fibromyalgia: systematic review and meta-analysis. *J Affect Disord* 2019; 245: 1098-1105.
- Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis* 2017; 76(2): 318-328.
- MacLean AJ, Schwartz TL. Tramadol for the treatment of fibromyalgia. *Expert Rev Neurother* 2015; 15: 469-75.
- Martinez-Jauand M, Sitges C, Rodriguez V, et al. Pain sensitivity in fibromyalgia is associated with catechol-O-methyltransferase (COMT) gene. *Eur J Pain* 2013; 17: 16-27.
- McLean SA, Williams DA, Harris RE, et al. Momentary relationship between cortisol secretion and symptoms in patients with fibromyalgia. Arthritis Rheum 2005; 52: 3660-9.
- McLean SA, Williams DA, Stein PK, et al. Cerebrospinal fluid corticotropin-releasing factor concentration is associated with pain but not fatigue symptoms in patients with fibromyalgia. Neuropsychopharmacology 2006; 31: 2776-82.
- Montoya P, Sitges C, Garcia-Herrera M, et al. Reduced brain habituation to somatosensory stimulation in patients with fibromyalgia. *Arthritis Rheum* 2006; 54: 1995-2003.
- Napadow V and Harris RE. What has functional connectivity and chemical neuroimaging in fibromyalgia taught us about the mechanisms and management of “centralized” pain? *Arthritis Res Ther* 2014; 16: 425.
- Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S. Alpha sleep characteristics in fibromyalgia. *Arthritis Rheum* 2001; 44: 222-30.
- Sanchez-Dominguez B, Bullon P, Roman-Malo L, et al. Oxidative stress, mitochrondrial dysfunction, and inflammation common events in skin of patients with fibromyalgia. *Mitochondrion* 2015; 21: 69-75.
- Srikuea R, Symons TB, Long DE, et al. Association of fibromyalgia with altered skeletal muscle characteristics which may contribute to postexertional fatigue in postmenopausal women. *Arthritis Rheum* 2013; 65: 519-28.

References

- Tsilioni I, Russell IJ, Stewart JM, et al. Neuropeptides CRH, SP, HK-1, and inflammatory cytokines IL-6 and TNF are increased in serum of patients with fibromyalgia syndrome, implicating mast cells. *J Pharmacol Exp Ther* 2016; 356: 664-72.
- Tzadok R and Ablin JN. Current and emerging pharmacotherapy for fibromyalgia. *Pain Res Manag* 2020; 6541798.
- Walitt B, Nahin RL, Katz RS, et al. The prevalence and characteristics of fibromyalgia in the 2012 National Health Interview Survey. *PLoS One* 2015; 10: e0138024.
- Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis Rheum* 1990; 33(2): 160-172.
- 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: 600-10.
- Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol* 2011; 38: 1113-22.
- Wolfe F, Claw DJ, Fitzcharles MA, et al. 2016 revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Sem Arthritis Rheum* 2016; 46: 319-329.
- Lyrica (pregabalin) capsules, CV; Lyrica (pregabalin) oral solution, CV, [package insert]. New York, NY: Pfizer Pharmaceuticals, 2013.
- Cymbalta (duloxetine delayed-release capsules) for oral use [package insert]. Indianapolis, IN: Lilly USA, LLC, 2012.
- Savella (milnacipran HCl) tablets [package insert]. St. Louis, MO: Forest Laboratories, Inc., 2013.
- UpToDate: Clinical manifestations and diagnosis of fibromyalgia in adults. Goldenberg, DL.
- UpToDate: Pathogenesis of fibromyalgia. Goldenberg, DL.
- UpToDate: Differential diagnosis of fibromyalgia. Goldenberg, DL.
- UpToDate: Initial treatment of fibromyalgia in adults. Goldenberg, DL.