OFFICE OF WOMEN'S HEALTH, VHA

Etiology, Evaluation and Management of Widespread Musculoskeletal Pain in Women

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Presenters

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Susan Garstang, M.D. is a Clinical Associate Professor of Physical Medicine & Rehabilitation (PM&R) at University of Utah Medical School, and the Associate Chief of Staff for Academic Affiliations at the Veterans Affairs (VA) Salt Lake City (SLC) Healthcare System, where she is also a staff physician in PM&R. Dr. Garstang received her medical degree from Washington University School of Medicine, followed by residency in PM&R at Baylor College of Medicine in Houston and a fellowship in spinal cord injury medicine at Kessler Institute of Rehabilitation at Rutgers-New Jersey Medical School. She is certified in PM&R and also holds subspecialty certification in spinal cord injury medicine and brain injury medicine. She worked in academia until 2009, when she transferred to the VA New Jersey Healthcare System to provide care for Veterans and continue teaching residents and students.

Dr. Garstang is a founding member of the Salt Lake City Women's Musculoskeletal Training Team, who with support of the Office of Women's Health (WH) developed a WH Musculoskeletal (MSK) training for Primary Care Providers (PCPs), which has been taught nationally since 2017. She teaches MSK care to Nurse Practitioners (NP), NP students, and NP residents, medical students and PM&R residents, and our primary care providers. In her clinical practice, Dr. Garstang's focus is musculoskeletal medicine (including a women veterans MSK clinic), treatment of widespread pain syndromes, headache management, and the care of Veterans with as spinal cord injury, stroke, spasticity, and amyotrophic lateral sclerosis (ALS).

Jamie Clinton-Lont, M.S., A.N.P.-B.C.

Jamie Clinton-Lont, M.S., A.N.P.-B.C. is an Adult and Geriatric Nurse Practitioner at the Salt Lake City VA Healthcare system, where she has worked in various roles since 1991. Her background includes many years as a Primary Care Provider specializing in women's health, musculoskeletal pain, and overdose prevention. She has held leadership roles as the Women's Health Medical Director; Program Director for Pain Education and Overdose Prevention; and she has led the development of the Women's Health Musculoskeletal Training curriculum since 2016 funded by the Office of Women's Health.

Ms. Clinton-Lont is published in Pain Medicine (2020); The Journal of Opioid Management (2020); and Translational Behavioral Medicine (2019). Her focus remains in women's health, musculoskeletal curriculum and training process development, and teaching Musculoskeletal care to primary care providers.

Disclosures

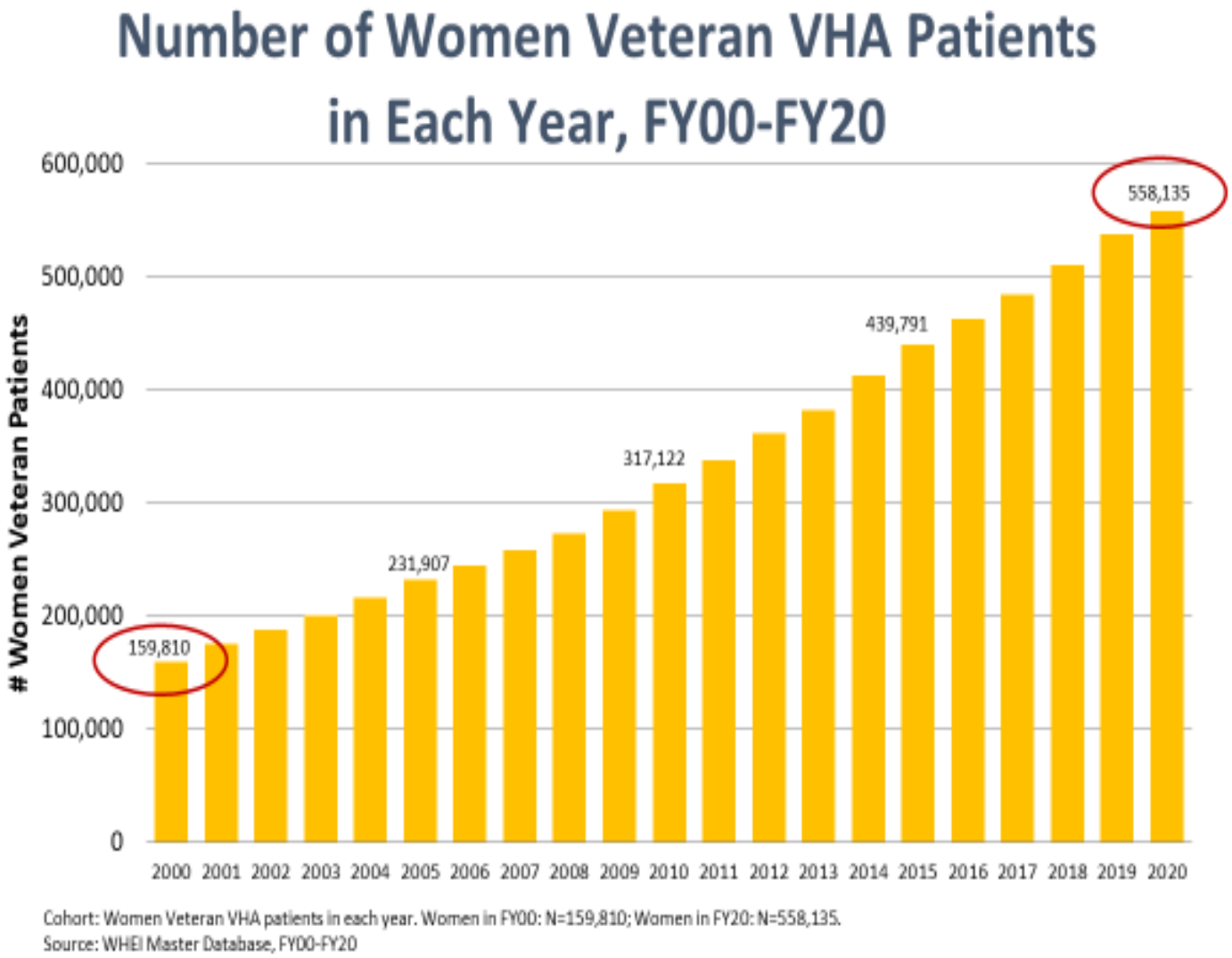
- Ms. Jamie Clinton-Lont has no relevant financial or non-financial relationships to disclose relating to the content of this activity.
- Dr. Susan Garstang has no relevant financial or non-financial relationships to disclose relating to the content of this activity.
  - Presenter will discuss the use of several medications that are “off-label” for the conditions presented. This includes gabapentin, amitriptyline, tramadol, loratadine, famotidine, tizanidine, and cromolyn.
- The views expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of the Department of Veterans Affairs, nor the U.S. Government.
- This continuing education activity is managed and accredited by the Defense Health Agency, J-7, Continuing Education Program Office (DHA, J-7, CEPO). DHA, J-7, CEPO and all accrediting organizations do not support or endorse any product or service mentioned in this activity.
- Commercial support was not received for this activity.

Learning Objectives

At the conclusion of this activity, participants will be able to:

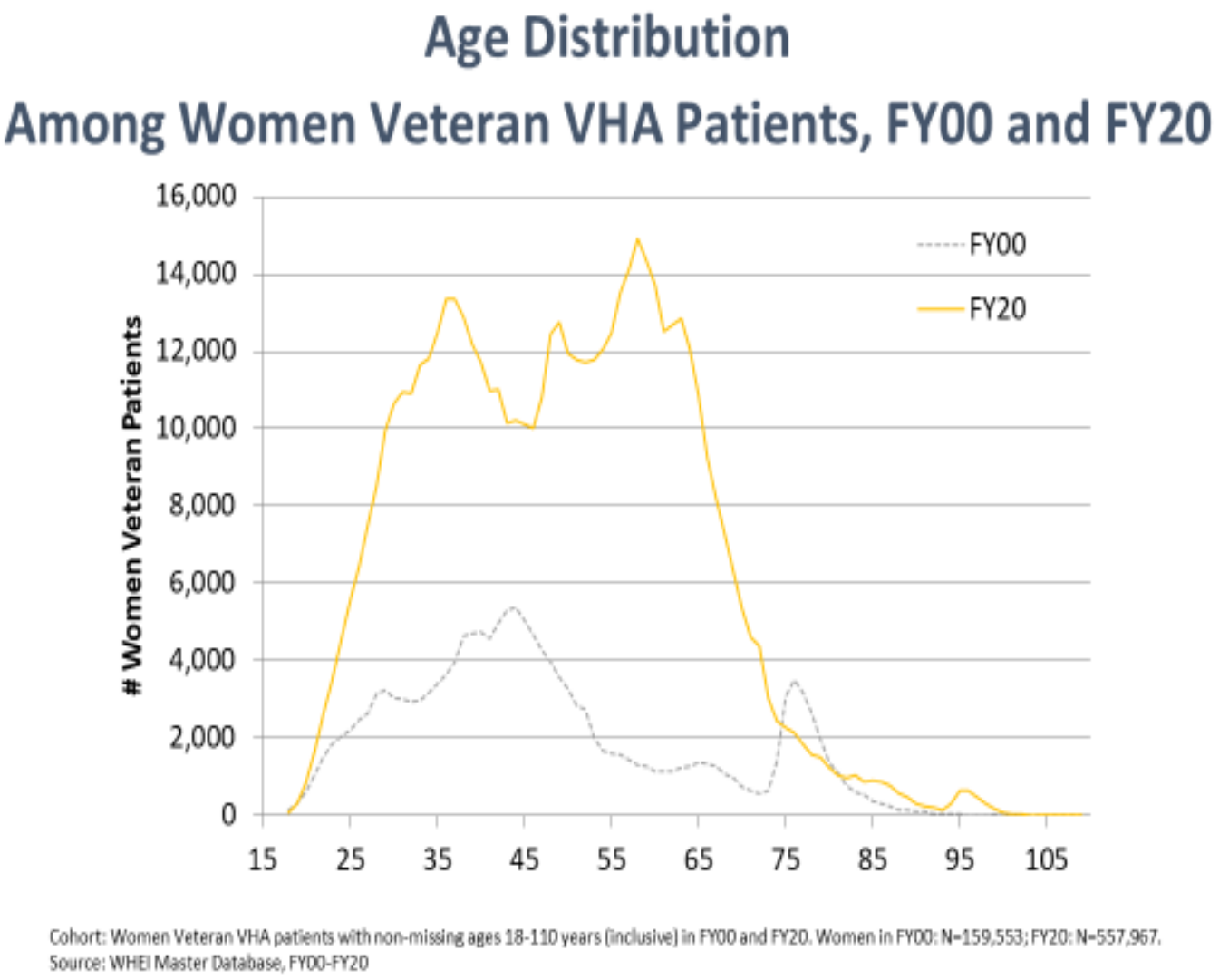
1. Identify the population of women Veterans who will utilize primary care services for Musculoskeletal (MSK) conditions.
2. Explain gender differences related to pain.
3. Summarize the way to evaluate widespread MSK pain and eliminate organic etiologies.
4. Differentiate between the common types of Ehlers-Danlos Syndrome, including phenotypes and associated conditions.
5. Describe the American College of Rheumatology criteria for the diagnosis of fibromyalgia.
6. Discuss management options for connective tissue disorders and fibromyalgia.

Number of Women Veteran VHA Patients



(VHA, 2020)

Age Distribution Among Woman Veteran VHA Patients



(VHA, 2020)

Utilization of Primary Care Services

Primary Care:

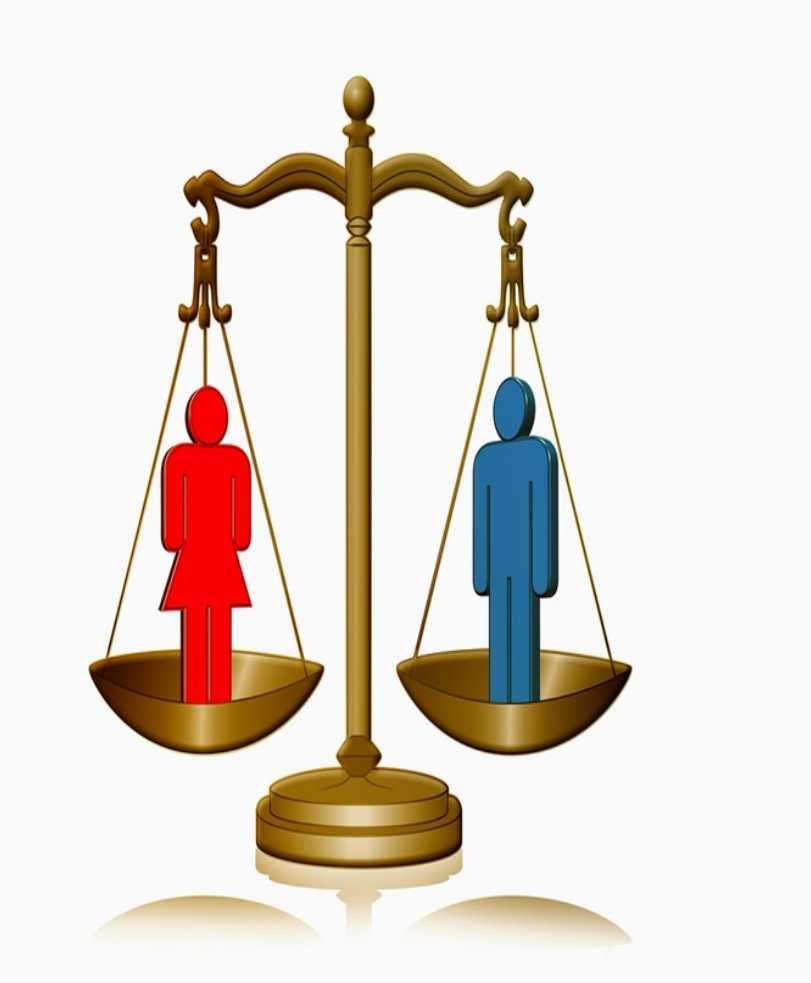
- **Nearly 90% of women Veterans see a VHA primary care provider.**
- **Women are heavy users of primary care** (12% of women vs. 10% of men had at least six primary care visits in FY12).
- **45–64-year-old age group use outpatient services particularly heavily.**

Comprehensive Women's Health Care: VHA policy now sets the expectation that women will receive Comprehensive Women's Health Care (i.e., having both gender-neutral primary care services and gender-specific primary care services from a single designated women's health provider) to reduce fragmentation of care.

Ambulatory Visits

In the past decade in the U.S.:

- MSK conditions are the most frequent diagnoses in primary care clinic encounters.
- Pain accounts for nearly 20% of ambulatory visits.
- Overuse injuries account for ~7% of all injury-related physician office visits.



(istockphoto.com, n.d.)

Genders Differ: Threshold to Seek Care

- Women have a **lower threshold to seek medical care** and to visit their primary care provider for functionally limiting pain.
  - 74% vs 62%
  - 65+ years have an 86% - 90% likelihood
- **Rationale:**
  - Women are conditioned from a young age to report how they feel, while boys and men are discouraged from doing so.

Genders Differ: How Pain is Described

- Women tend to **describe** pain as widespread, chronic, and functionally limiting; greater pain-related emotional distress.
- Men tend to **describe** pain based on recounting facts and observations; descriptors like ‘anger’, ‘angry’ and swear words are used more frequently at the time of a painful event.

Different Coping Strategies

- **Emotion-focused coping - Women**
  - Modifying how they think about the problem/pain i.e.; Distancing themself from pain through denial or humor
- **Problem-focused coping - Men**
  - Understand the pain
  - Treat the underlying cause

Gender Differences Impacting Pain

- Women have diminished pain pressure thresholds (so lesser stimulus needed to cause pain).
- Women have a higher incidence of trauma.
- Women have more estrogen.
- Women are biomechanically different which predisposes them to certain types of injury.

Higher Incidence of Trauma

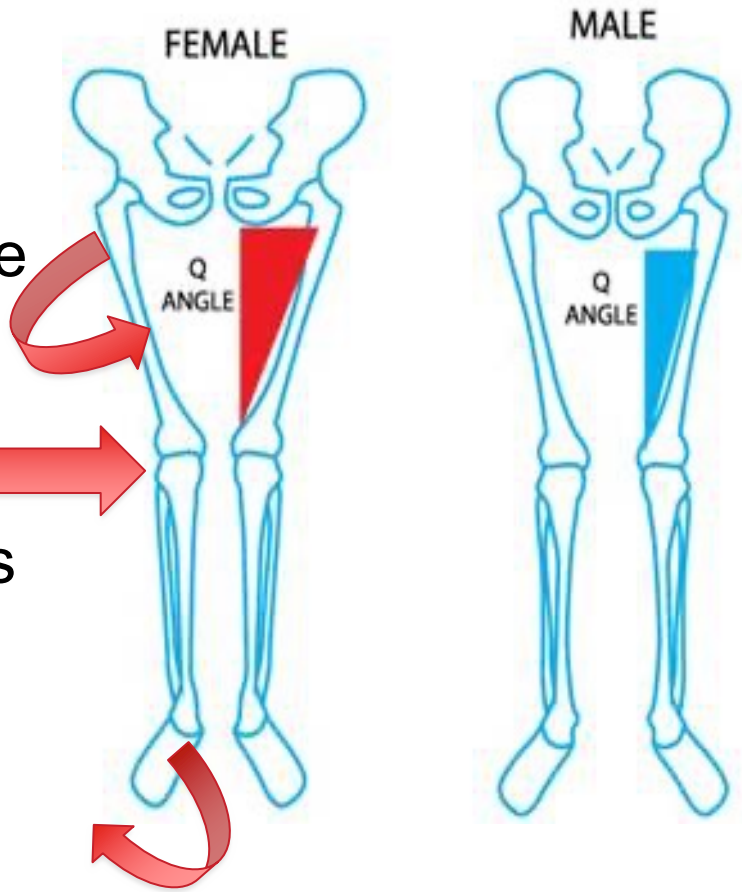
- Rape ~ 17% vs 3%
- Childhood Sexual Trauma ~ 20% vs 8%
- **Higher incidence of Trauma-Related Diagnoses:**
  - Post-traumatic Stress Disorder (PTSD)
  - Anxiety
  - Major Depressive Disorder
- Pain, Depression, & Anxiety co-exist **30-50% of the time**

Estrogen and Pain

- **Pain Severity:** varies during phases of the menstrual cycle.
- **Estrogen's relationship with MSK conditions:**
  - Lean-to-fat ratio
  - Flexibility
  - Bone structure
  - Alignment
  - Musculature
  - Injury Type

Gender Differences: Biomechanical

- Wider Pelvis with increased Q-angle
- Miserable Malalignment Syndrome
- Propensity for knee & foot problems



(sciencedirect.com, n.d.)

Gender Differences: MSK Conditions

- **Foot Pain:** **9.0 times** more common in women
- **Osteoporosis:** **4.0 times** more common in women
- **Headaches (HA):** **2.6 times** more common in women
- **Shoulder Pain:** 1.8 times more common in women
- **Pain in arms/leg:** 1.3 times more common in women
- **Back Pain:** 1.2 times more common in women

Are Providers Ready?

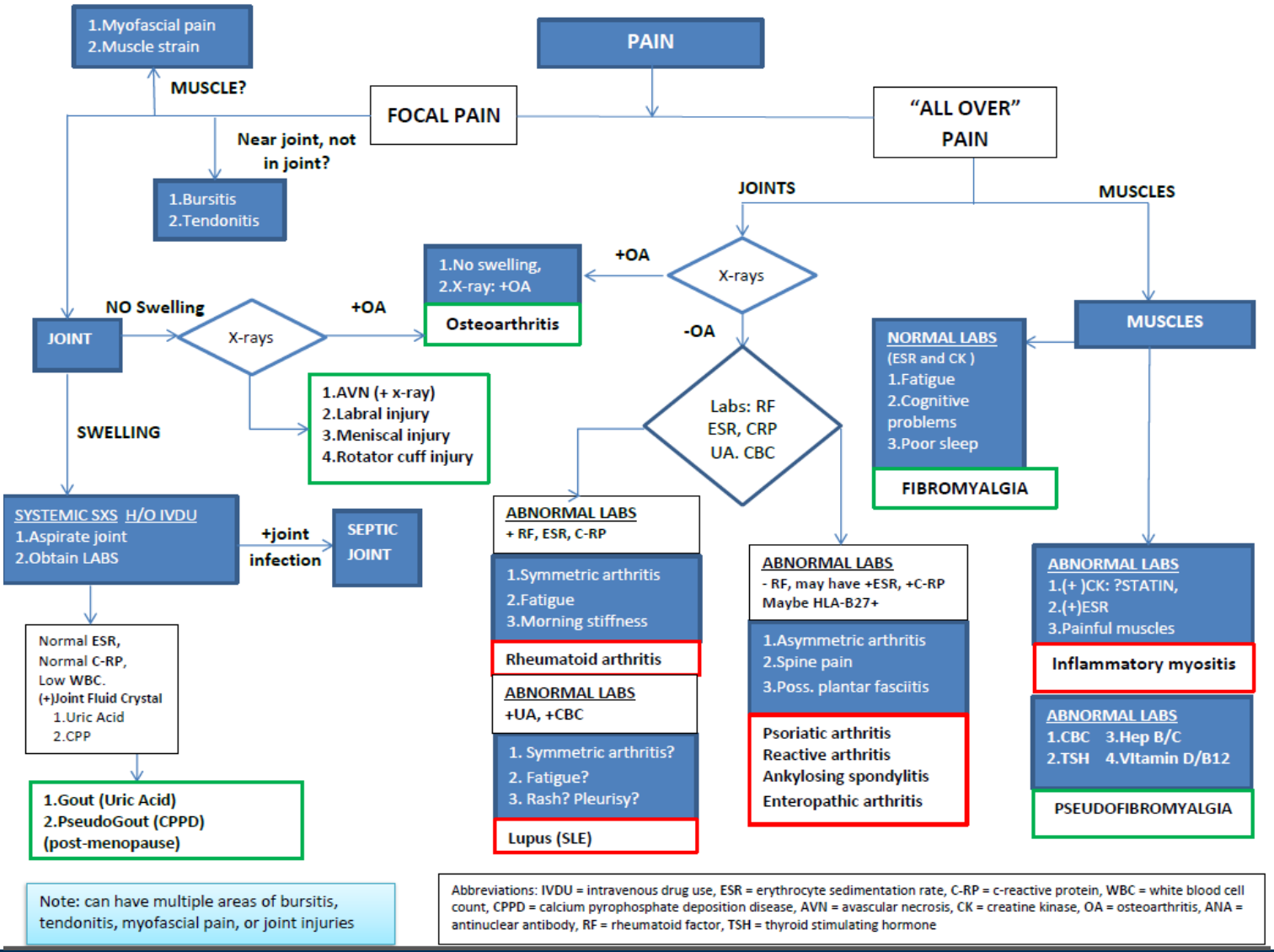
- MSK conditions are in the top five diagnoses for women Veterans in all three age cohorts (18-44, 45-64, and 65+ years of age).
- Despite the high prevalence, primary care providers are often ill-prepared to effectively address common MSK Problems.

Evaluation of Widespread Pain

How do we approach it?

- Pain all over :
  - Muscles
    - Normal labs? Fibromyalgia
    - Abnormal labs? Rheumatologic or pseudofibromyalgia
  - Joints
    - Normal labs? Osteoarthritis (OA)
    - Abnormal labs? Rheumatologic
      - Symmetric: Rheumatoid Arthritis (RA) or Systemic Lupus Erythematosus (SLE)
      - Asymmetric: psoriatic arthritis, reactive/enteropathic arthritis, ankylosing spondylitis (all may also have spine pain)

Diagnostic Approach to Pain



(VA, n.d.)

Fatigue and Widespread Pain

- Differential diagnosis of fatigue and widespread pain:
  - Fibromyalgia (FM): 2%
    - Diagnosis of exclusion
  - "Pseudofibromyalgia" (a.k.a. "secondary FM"): 98%
    - Organic diseases
    - Connective tissue disorders or rheumatologic diseases
    - Musculoskeletal disorders
- Note: if pain is in multiple joints *but not muscles*, less likely FM and more likely inflammatory arthritis.

"Pseudofibromyalgia"

"I hurt all over"

- Organic:
  - Anemia (iron deficiency)
  - Infectious: Lyme disease, Hepatitis B/C
  - Endocrine: dysglycemia, hypothyroidism
  - Multiple sclerosis
  - Nutritional deficiencies: Vitamin D, B12, C, iron
  - Electrolyte imbalances: Ca^{++}, K^{+}, Mg^{+} (see with Proton Pump Inhibitors [PPI] use)

"Pseudofibromyalgia"

"I hurt all over"

- Sleep apnea (esp. untreated)
- Medications
  - Statins
  - Bisphosphonates
  - Aromatase inhibitors
  - HAART (highly active antiretroviral therapy)
- Depression and other mental health disorders
- Chronic fatigue syndrome/Gulf War syndrome

“Pseudofibromyalgia”

“I hurt all over”

- Connective tissue disorders
  - Ehlers Danlos Syndrome (hypermobile and other types) or Marfan Syndrome
- Musculoskeletal:
  - Myopathy
  - Rheumatologic: RA 3x more likely, SLE 10x more likely in women
  - Myofascial pain syndrome

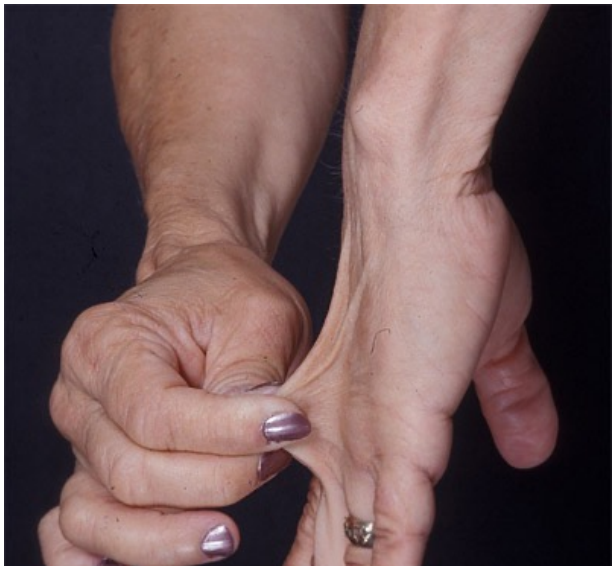
Connective Tissue Disorders

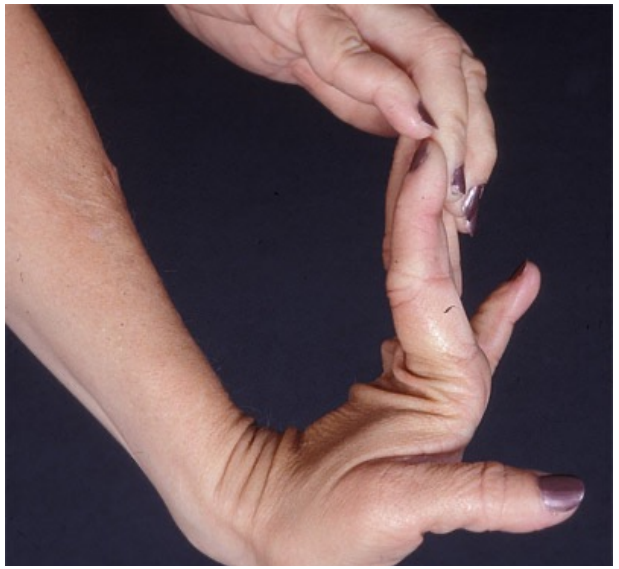
Connective Tissue Diseases

- Ehlers-Danlos Syndrome (EDS)
  - A group of disorders that affect the connective tissues that support the skin, bones, blood vessels, and many other organs and tissues.
    - Defects in connective tissues cause the signs and symptoms of Ehlers-Danlos syndrome, which vary from mildly loose joints to life-threatening complications.
  - Prevalence is 1:5,000 – 1:10,000 for all types (classic and hypermobile are most common).

Connective Tissue Diseases: EDS

- Many types; all have some degree of joint hypermobility and hyperextensible skin.
- Other common issues include impaired wound healing, ocular complications, and vascular complications.





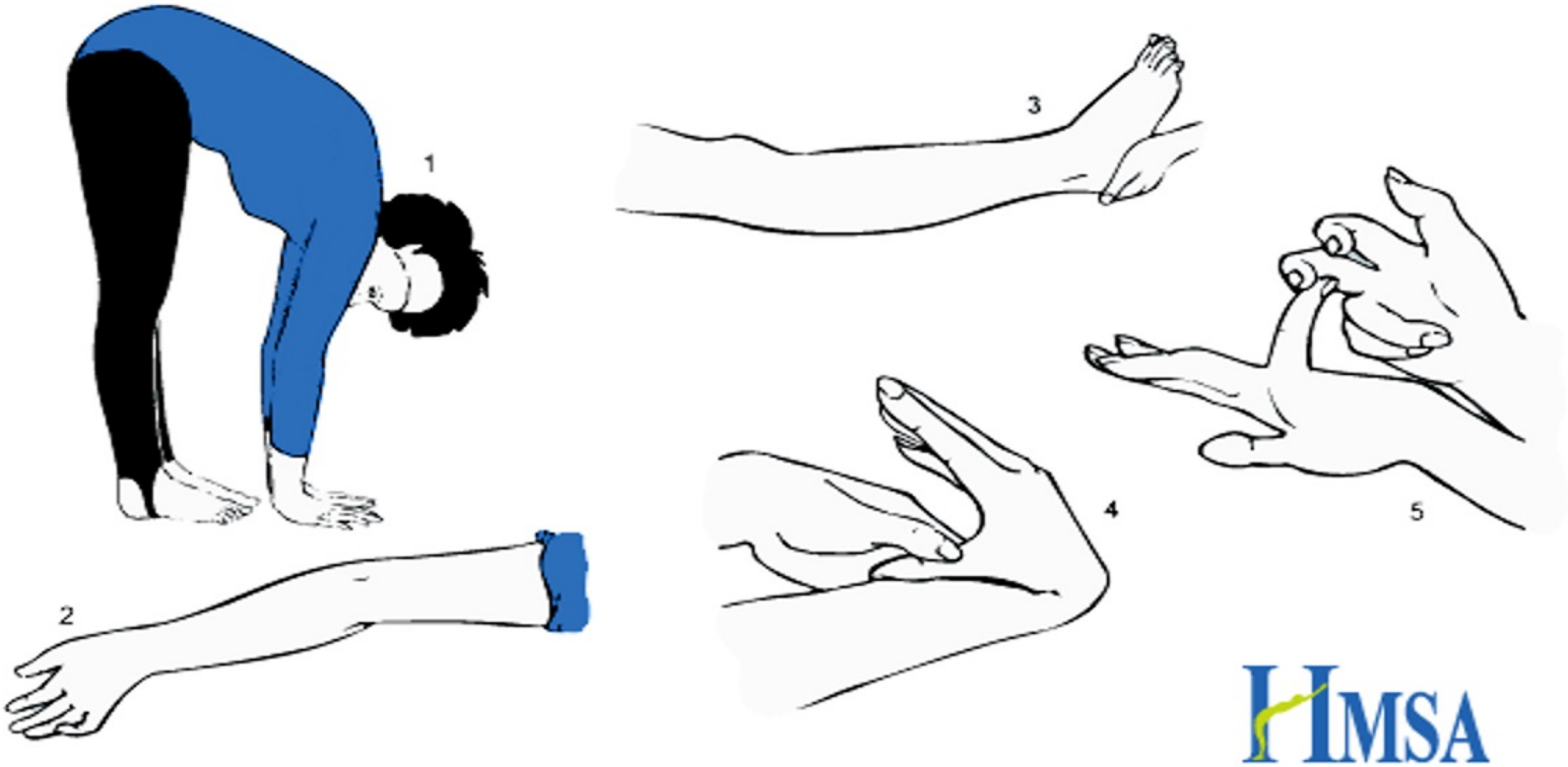
(mayoclinic.org, n.d.)

Ehlers-Danlos Syndrome

- Ehlers-Danlos Syndrome:
  - Hypermobile type usually have widespread joint pain, history of sprains and dislocations.
    - Often misdiagnosed with fibromyalgia
    - Other common issues include impaired wound healing, ocular complications, and vascular complications.
- Most dangerous type of Ehlers-Danlos Syndrome is Vascular EDS; family history of aneurysms and early death.
  - Send to Geneticist for diagnosis.

Beighton Score

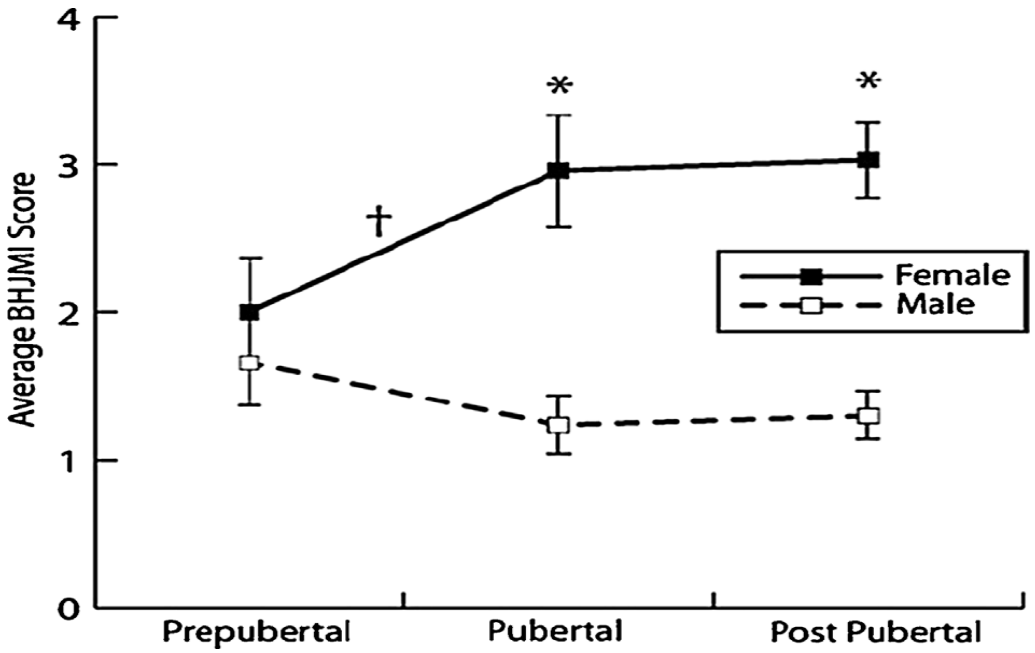
- Used to screen for hypermobility
- + if >5 , or >4 if over age 50



(hypermobility.org, n.d.)

Hypermobility and Gender

(BHJMI- Beighton and Horan Joint Mobility Index)



- Female to male ratio for hypermobile EDS is 9:1.
- Hypermobility declines with age (50+).

(Journal of Science and Medicine in Sport, 2008)

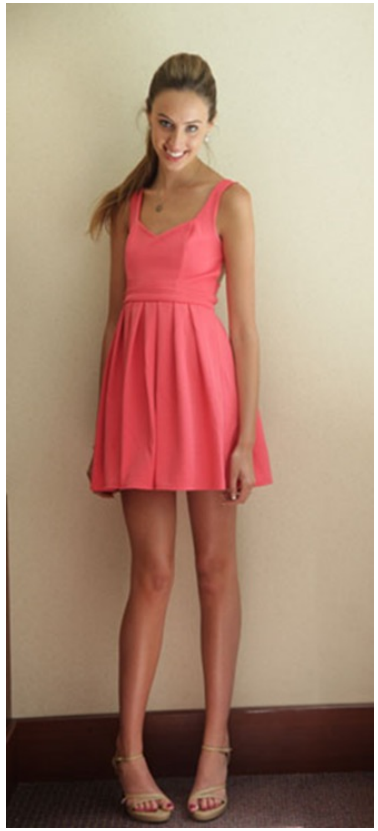
Connective Tissue Diseases: Marfan's

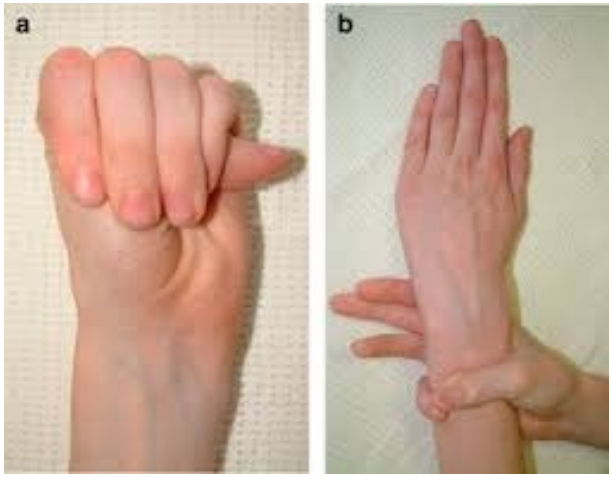
Marfan's Syndrome:

- Connective tissue disorder with joint hypermobility, associated with cardiac valvular and ocular (lens) problems.
- Characterized by arachnodactyly and arm span > height.

About 1 in 5,000 people have Marfan syndrome, including men and women of all races and ethnic groups.

- Needs referral to genomic medicine, cardiology, ophthalmology.
- www.Marfan.org (scoring algorithm)





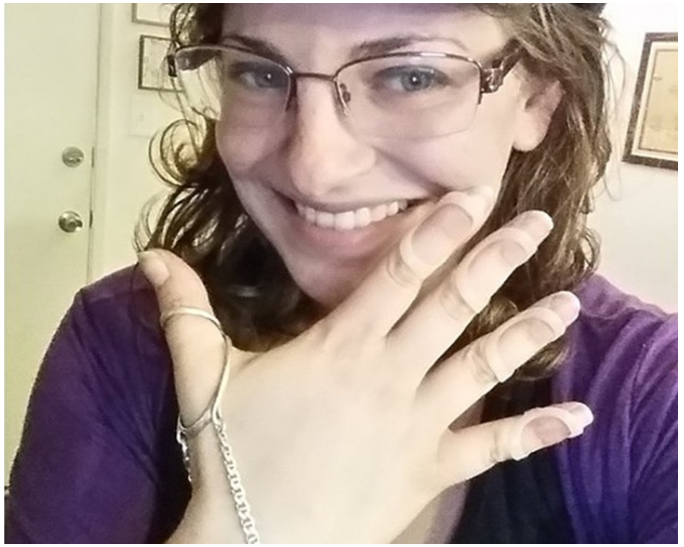
(marfan.org, n.d.)

EDS: Clinical Management Overview

- Chronic pain and mobility impairment (kinesiophobia)
  - Joint stabilization-Occupational Therapy (OT), Physical Therapy (PT) and Orthotics.
- Autonomic Dysregulation and Fatigue
  - Mast Cell Activation Disorder targeted therapies.
  - Florinef, midodrine, abdominal binders, fluids, etc.
- Pregnancy
  - Counseling and consultation, close follow-up.

OT Treatments

- Wrist splints for carpal tunnel syndrome
- Opponens splints for carpometacarpal or wrist issues
- Ring splints for hypermobility
- Education



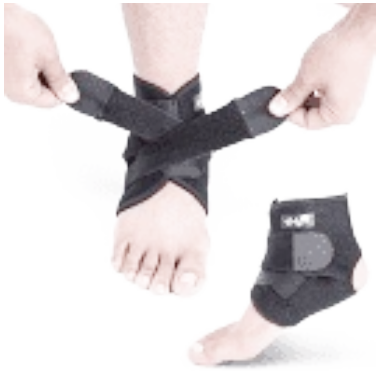
(marfan.org, n.d.)

Physical Therapy

- Non weight-bearing exercises, such as swimming or cycling, may be beneficial in promoting strength and balance.
- High impact sports and excessive weight-lifting should be avoided, because these activities may produce undue strain on hypermobile joints.
- Proprioceptive and strengthening exercises may help prevent injury.
- Do NOT focus on range of motion and stretching.

Orthoses

- Feet: custom rigid orthoses for pes planus, and ankle supports (figure-8)
- Knees: Anterior Cruciate Ligament (ACL) brace with extension stop
- Sacroiliac (SI) belt (especially pregnant women)
- Elbow braces sometimes helpful
- Few good options for shoulder stabilization



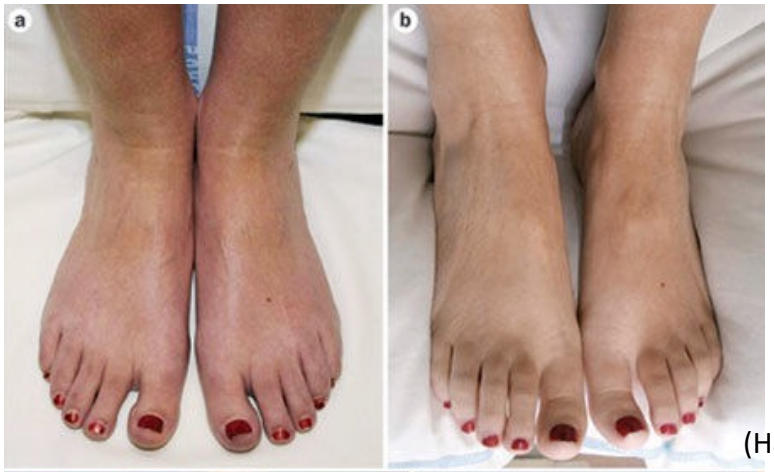
(adobestock.com, n.d.)

Pain in EDS

- Chronic pain: highly prevalent in EDS, associated with analgesic use.
- More prevalent and severe in hypermobile EDS.
- Pain severity correlates with hypermobility, dislocations, and previous surgery.
- Pain correlates with low sleep quality.
- Pain contributes to functional impairment in daily life (independent of fatigue).

Postural Tachycardia Syndrome (PoTS)

- Elevation in heart rate of >30 beats per minute (bpm) with standing, can take 5-30 minutes of standing (tilt table testing) to manifest.
- Symptoms are due to excessive venous pooling from abnormal connective tissue in the vessels.
- Is considered “secondary” or peripheral in EDS; see orthostatic acrocyanosis and tachycardia.



(Handbook of Clinical Neurology, 2019)

Postural Tachycardia Syndrome (PoTS)

- Can cause tachycardia with palpitations, also associated with dysautonomia and orthostasis with syncope/pre-syncope
- If mostly tachycardic, can use low dose beta-blocker (propanolol 10mg twice a day [BID]) or clonidine.
- If also hypotensive, use florinef and/or midodrine. Serotonin and norepinephrine reuptake inhibitors (SNRIs) can also be effective.
- Hydration with 2L fluid a day, and 3-5 grams salt. Sometimes need intravenous fluid (IVF): 1 liter normal saline (NS) weekly.
- Compression stockings (30mm Hg).
- Exercise! 30 minutes 3x/week.

Mast Cell Activation Syndrome (MCAS)

- Seen in EDS, also may play a role in fibromyalgia, chronic fatigue syndrome, and even possibly chronic Lyme disease and Gulf War syndrome, ?long-COVID.
- Characterized by episodic allergic reactions.
  - Usually have skin allergies, asthma/reactive airways to stimuli, a plethora of medication and food allergies.
- Thought to be primarily histamine mediated, but mast cells also release prostaglandins (which cause joint pain), Interleukin (IL)-1, IL-6, Nerve Growth Factor (NGF), and Tumor Necrosis Factor (TNF)-α which is implicated in inflammatory conditions, and other mediators.

Mast Cell Activation Syndrome(MCAS)

- Refer to allergy/immunology for work-up for severe cutaneous reactions or history of anaphylaxis.
- Mainstay of treatment is Histamine-2 (H-2) blocker (e.g. famotidine) and Histamine-1 (H-1) blocker (e.g. loratadine, many need 2-4x usual does), oral cromolyn can also be useful for gastrointestinal (GI) symptoms.
- Luteolin and quercetin can be helpful for symptoms, as can Vitamin C (also true in EDS and in FM).
  - Note that Vitamin C is a mast cell stabilizer (as is amitriptyline).

Fibromyalgia

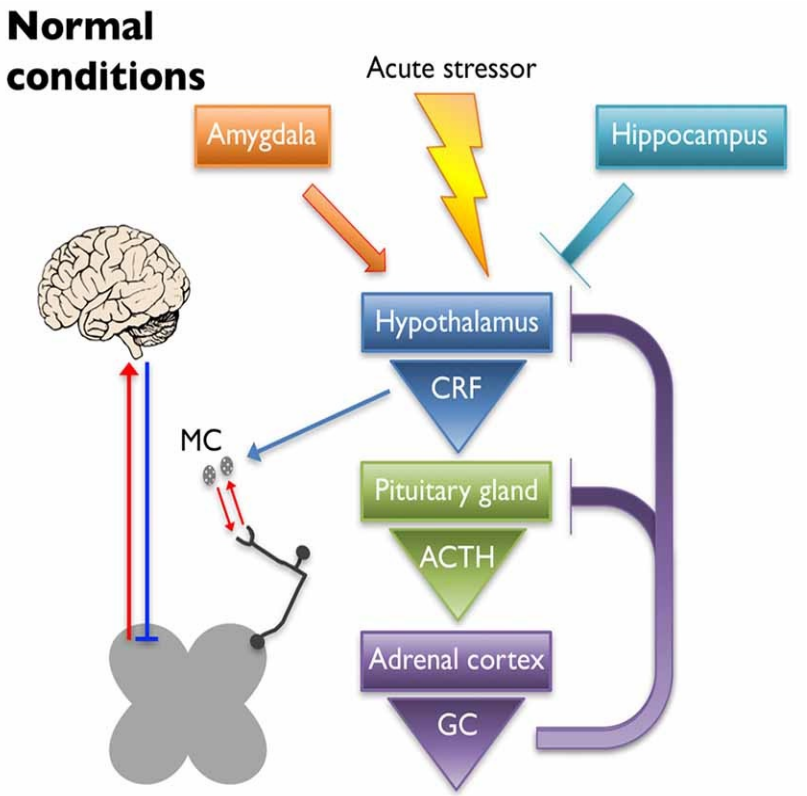
Fibromyalgia

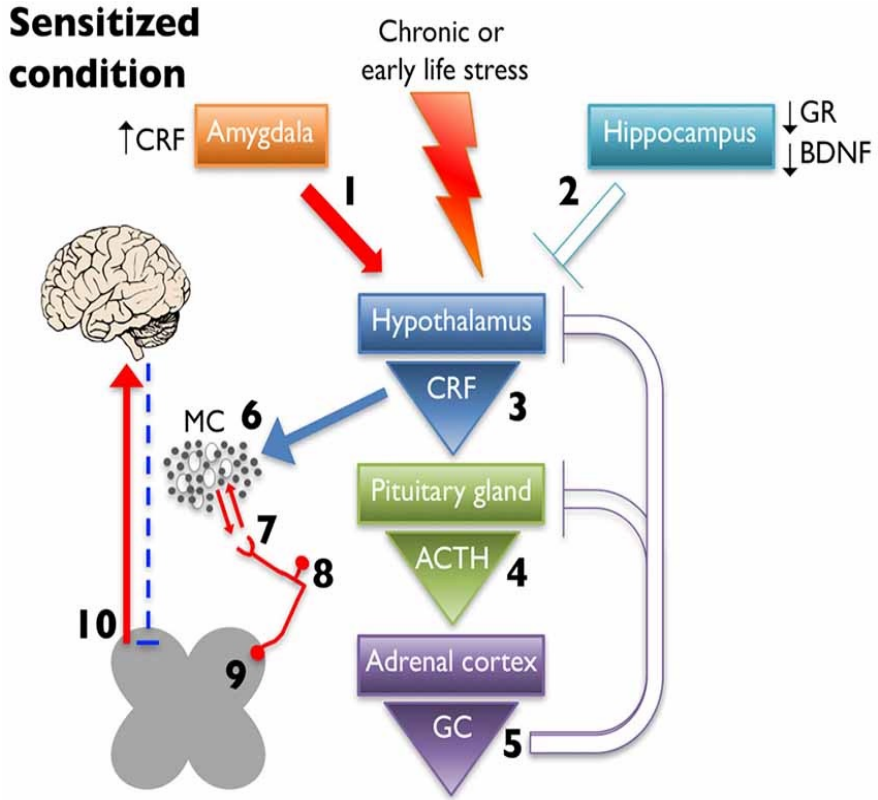
- More common in women than men (3.4% vs. 0.5%).
- Commonly presents at ages 50-70.
- Characterized by widespread pain (axial and appendicular, above and below the waist)
- Can be primary, or secondary ("pseudofibromyalgia") to other conditions such as sleep apnea or chronic hepatitis.
- May overlap or co-exist with other regional pain syndromes, as well as anxiety and mood disorders, irritable bowel syndrome, chronic fatigue syndrome, interstitial cystitis, migraines, and others.

Fibromyalgia

- Syndrome manifested by widespread pain, stiffness, fatigue, cognitive difficulties (“fibrofog”), and non-refreshing sleep.
- Central Sensitivity Syndrome: neurosensory disorder associated with difficulties in pain processing by the Central Nervous System (CNS), including changes in the spinal cord.
- Chronic/early life stress can “set up” the CNS for a more robust response to pain.

The role of stress in sensitization



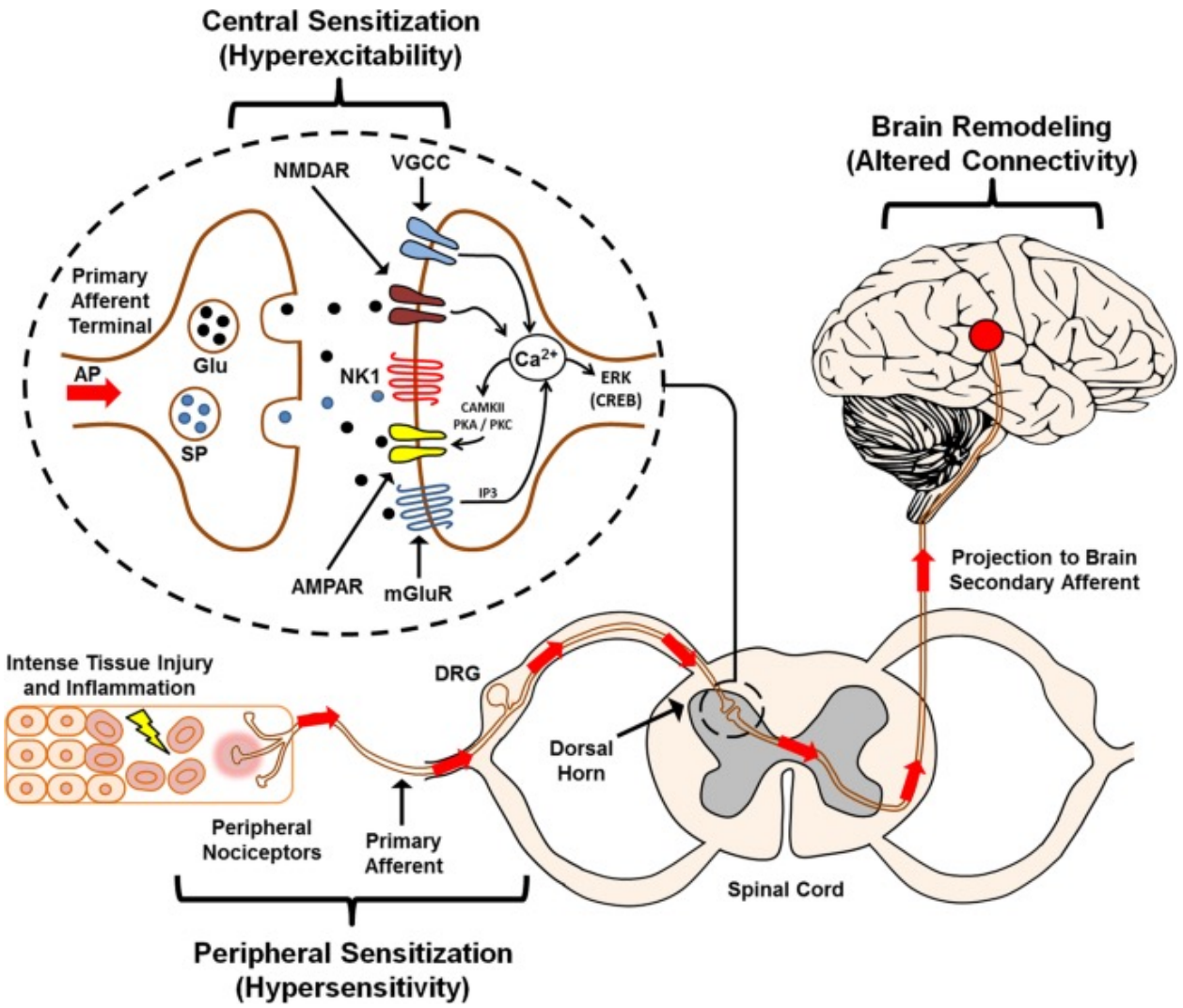


(Frontiers in Cellular Neuroscience, 2018)

Fibromyalgia Etiology

- Often follows a peripheral pain stimulus such as a focal injury, Temporomandibular joint (TMJ) pain, or irritable bowel syndrome.
- Presence of trauma (either pre-existing or concurrent) is thought to play a role in "wind up" of the Central Nervous System, in combination with peripheral injury.
- This leads to "central sensitization".
  - Increased synaptic efficacy and pain amplification in the spinal cord.
  - Loss of descending inhibition, so the painful state is maintained.
  - Alteration in neurochemicals; abnormally high levels of substance P, glutamate, low levels of CNS serotonin, and elevated levels of nerve growth factor.

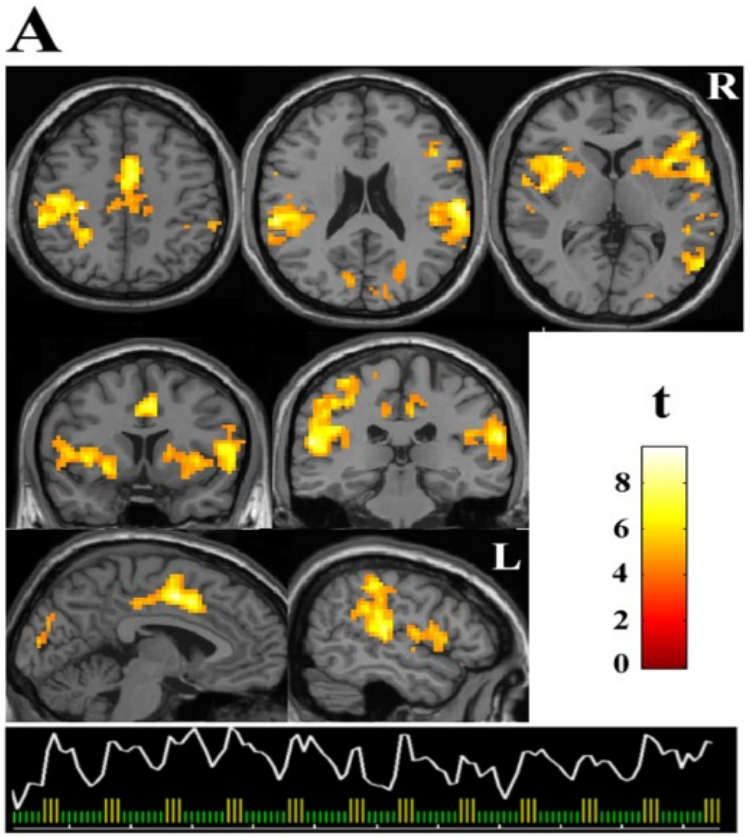
Central Sensitization



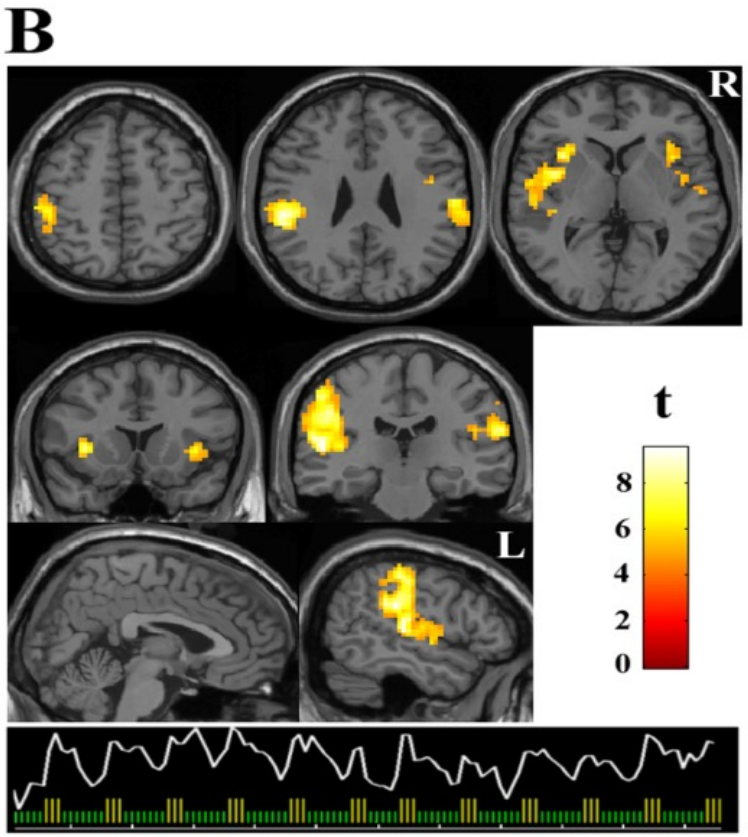
(Egyptian Journal of Neurology, Psychiatry, and Neurosurgery, 2022)

Fibromyalgia Pathophysiology

Altered Pain Processing in the Brain



FM; response duration



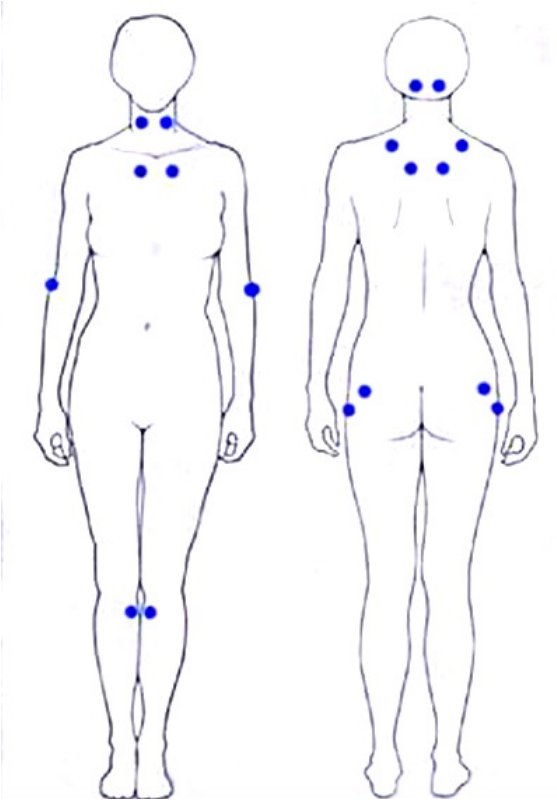
Normal; response duration

(Pujol et al., 2009)

Fibromyalgia Diagnosis

- American College of Rheumatology (ACR) 1990 Criteria
  - Widespread pain, in combination with at least 11 of 18 tender points.
    - *Difficult to standardize.*
  - No other diagnoses that can explain symptoms.

- ACR 2010 Criteria
  - Eliminated tender point exam.
  - Added 2 patient scales (Wide-spread Pain Index [WPI] and Symptom Severity Score [SSS]).



(mayoclinic.org, n.d.)

Fibromyalgia Classification

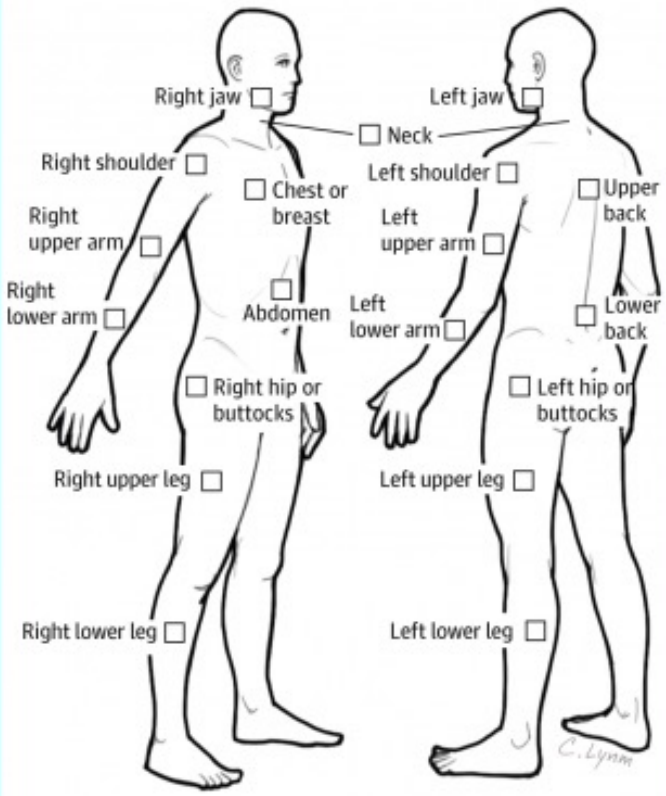
ACR 2011 Classification of Fibromyalgia

- Wide-spread Pain Index (WPI): 19 painful areas, patient counts how many hurt.
- Symptom Severity Score (SSS): from 0-12; 0-3 scale for fatigue, difficulty sleeping, and poor cognition; and 0-3 for list of “other symptoms” which includes headache, depression, and abdominal pain.
- **FM symptom scale of ≥13 is diagnostic (0-31 possible).**

WPI and SSS

Widespread Pain Index
(1 point per check box; score range: 0-19 points)

(1) Please indicate if you have had pain or tenderness **during the past 7 days** in the areas shown below.
Check the boxes in the diagram for each area in which you have had pain or tenderness.



Symptom Severity
(score range: 0-12 points)

(2) For each symptom listed below, use the following scale to indicate the severity of the symptom **during the past 7 days**.

- **No problem**
- **Slight or mild problem**: generally mild or intermittent
- **Moderate problem**: considerable problems; often present and/or at a moderate level
- **Severe problem**: continuous, life-disturbing problems

	No problem	Slight or mild problem	Moderate problem	Severe problem
Points	0	1	2	3
A. Fatigue	☐	☐	☐	☐
B. Trouble thinking or remembering	☐	☐	☐	☐
C. Waking up tired (unrefreshed)	☐	☐	☐	☐

(3) During the **past 6 months** have you had any of the following symptoms?

	Points	0	1
A. Pain or cramps in lower abdomen		☐ No	☐ Yes
B. Depression		☐ No	☐ Yes
C. Headache		☐ No	☐ Yes

Additional criteria (no score)

(4) Have the symptoms in questions 2 and 3 and widespread pain been present at a similar level for at **least 3 months**?

☐ No ☐ Yes

(5) Do you have a disorder that would otherwise explain the pain?

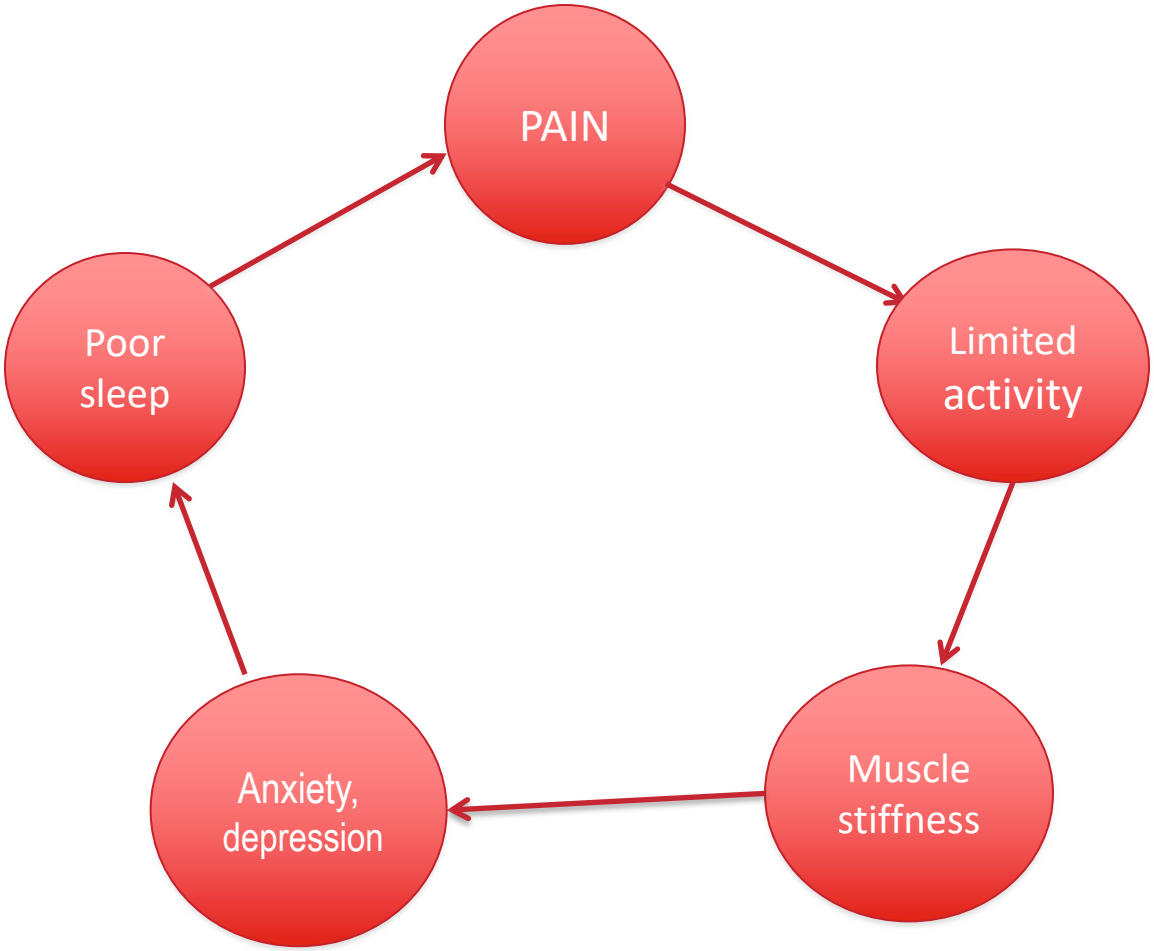
☐ No ☐ Yes

(physio-pedia.com., n.d)

Fibromyalgia Work-Up

- **No diagnostic test for fibromyalgia.**
- **No x-rays or Magnetic Resonance Images (MRIs) needed.**
  - Unless for reassurance or to rule out other etiologies.
- DIAGNOSIS OF EXCLUSION:
  - Not rheumatologic or neurologic
  - Not organic
  - Not connective tissue disorder (hypermobility)

Fibromyalgia: Cycle of Pain



Fibromyalgia Treatment Overview

- **Best evidence is for graded aerobic exercise (try aquatic therapy) and amitriptyline (off-label).**

- Food and Drug Administration (FDA)-approved medications: milnacipran, duloxetine, and pregabalin.
  - Pregabalin; alters Ca++ dependent neurotransmission, Gamma-aminobutyric acid agonist.
  - Milnacipran and duloxetine (SNRIs); both 5-HT and norepinephrine (NE) are antinociceptive and involved in descending inhibition.

Medications for Fibromyalgia

- Other medications (off-label) aimed at symptoms.
- Tricyclics; fix sleep architecture (see alpha intrusion into stage IV sleep in FM).
- Tizanidine; alpha-2 agonist, decreases activation of afferent fibers and substance P release. Also muscle relaxant and sedating, so useful at night.
- Cyclobenzaprine; tricyclic structure, acts at the brain stem to reduce tonic somatic motor activity, also sedating muscle relaxant so useful at night.

Fibromyalgia Pharmacotherapy

Tricyclic Antidepressants (TCA) (blocks NE & 5HT reuptake)	Start at 5-10 mg at bedtime; increase by 5 mg every 2 wks. Final dose determined by efficacy/side effects.
Cyclobenzaprine	Start 10 mg in evening, titrate to 10 mg three times a day (TID) (side effects may limit)
SNRIs	Duloxetine: start 30 mg/d, up to 60mg/day in morning
Tramadol	50 mg four times a day (QID)
Selective Serotonin Reuptake Inhibitor (SSRIs)	Less effective, can use activating SSRI like paroxetine
Gabapentin	Start with 100mg at bedtime; titrate as tolerated to 1200-2400 mg/day
*Pregabalin (FDA-approved)	Up to 450 mg/day
Tizanidine	Start at 2mg every night (qHS), and titrate up to 4mg TID (max is 8mg TID but side effects may limit)

Fibromyalgia: Treatment Pearls

- May need several types of medications, and frequent rotation.
  - Start at low dose and titrate up slowly.
- Focus on symptoms; address co-existing sleep problems and depression
  - For patients with exhaustion, consider duloxetine at breakfast.
  - For sleep disturbance, try TCA or gabapentin at night.
- Can also try;
  - Energy conservation techniques
  - Transcutaneous electrical nerve stimulation (TENS), massage, modalities, topical analgesics
  - Biofeedback, Cognitive Behavioral Therapy (CBT), relaxation
  - Complementary therapies; Tai chi, Acupuncture
- **No opioids!!!!**

Key Takeaways

1. MSK conditions are in the top five diagnoses for women Veterans in all three age cohorts (18-44, 45-64, and 65+ years of age).
2. There are gender differences in how women describe pain, and how they cope with pain.
3. Women have both biomechanical and hormonal differences that predispose them to MSK pain.
4. Widespread pain can best be evaluated by a systemic approach, including ruling out organic etiologies, and evaluating for joint pain (polyarthralgia) or muscle pain (myalgias).
5. Ehlers-Danlos Syndrome is 9x more common in women and can be screened for using the Beighton Score.
6. Core treatments for EDS include bracing, PT and OT, and awareness of coexisting conditions such as POTS and Mast Cell Activation Disorder.
7. Fibromyalgia is a central sensitization disorder, often with a peripheral trigger in the context of prior trauma.
8. Patients with fibromyalgia respond well to aerobic exercise, and medications including pregabalin, duloxetine, and milnacipran.

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QUESTIONS?

(Defense.gov, n.d.)

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