PainWeek®

Fibromyalgia Syndrome: Taking Another Look

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Disclosure

Speakers Bureau: Allergan, Amgen, Lilly, Salix

Learning Objectives

- Verbalize what is currently known about the pathophysiology of fibromyalgia.
- Prioritize the use of pharmacological management, through identification of risks, benefits, and side effects.
- Identify evidenced based, non-pharmacological strategies for management.

History

- 16th Century: Medical literature contains descriptions of clinical manifestations of musculoskeletal pain

- 1975: Dr. Harvey Moldofsky recommends redefining the disorder as
- "non-restorative sleep syndrome"

- 1981: "Fibromyalgia" for the first time in scientific literature

- 1987: American Medical Association acknowledges fibromyalgia as a true illness

History

- 1990: American College of Rheumatology (ACR) classification criteria used for diagnosis
- 1992: World Health Organization finally recognized fibromyalgia as a disease
- 2000+ fMRI findings demonstrate that neurobiological factors may contribute
- to the pathology of 'central' pain states such as fibromyalgia
- 2007-2009: New pharmaceutical agents approved by FDA
- 2010: ACR introduces new diagnostic criteria for fibromyalgia

Fibro (fibrous tissues) – myo (muscle) – algos (pain)

- A disorder characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory & mood issues. Researchers believe that fibromyalgia amplifies painful sensations by affecting the way your brain processes pain signals.
  - Mayo Clinic

- A chronic disorder characterized by widespread pain, tenderness, stiffness of muscles & associated connective tissue structures that is typically accompanied by fatigue, headache, and sleep disturbances. -Webster's

- A common neurologic health problem that causes widespread pain & tenderness. The pain and tenderness tend to come and go and move about the body. Most often, people with this chronic illness are fatigued and have sleep problems.
  - American College Rheumatology

Fibromyalgia (FM)

- 2-8% U.S. population, ♀ > ♂ 2:1 (7:1)
- Average 5 years to obtain a diagnosis
- Direct cost to healthcare budget and economy >$20 billion annually
- Indirect cost = years of suffering, poor quality of life, possible decreased life expectancy
- 2-4% managed in primary care; >95% referred to specialty care: orthopedics, pain medicine, rheumatology, neurology, gastroenterology, urology, etc.

Fibromyalgia

- A prevalent chronic pain syndrome:
  - pain all four quadrants of the body
  - tenderness @ 11+/18 specific muscle-tendon sites
- Diagnosis of exclusion/unknown cause
- Psychosomatic

Fibromyalgia Syndrome

- A prevalent chronic pain syndrome:
  - Dysregulation of neurotransmitters in the central nervous system
  - Increase in the brain's susceptibility to pain signals
- Genetic predisposition
- Environmental/psychological/physiological triggers

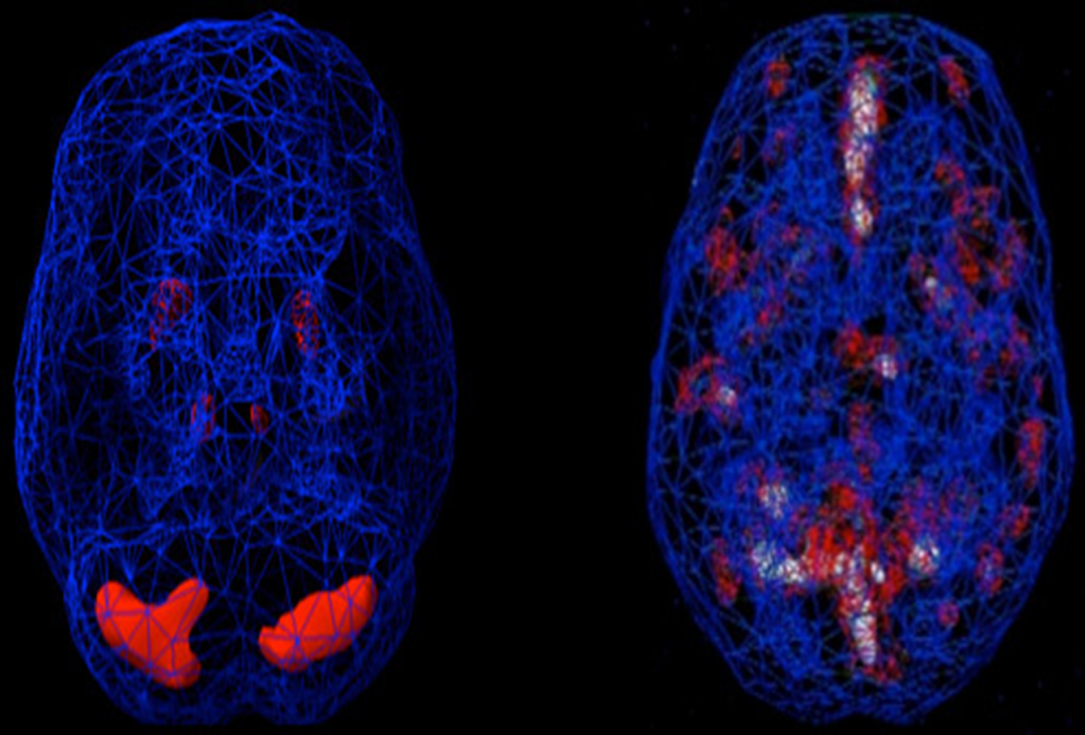
Proposed Pathophysiology

- 1976 Fibromyalgia →
  fibro (fibrous tissue) - my (muscles) - al (pain) - gia (condition of)
- 2000+ Fibromyalgia Syndrome
- Central Nervous System → central sensitization/wind-up (whole body hypersensitivity to pain)
- Maintained enhancement of temporal summation of second pain
- Biochemical
  (↓ inhibitory neurotransmitters, ↑excitatory neurotransmitters, dopamine dysregulation)
- Metabolic
  (↑oxidative stress, ↑cytokines, ↓ATP)
- Immuno-regulatory
  (dysfunction HPA, ↓ growth hormone, hypothyroidism)

MECHANISM	DESCRIPTION
Central sensitization	Amplification of pain in the spinal cord → spontaneous nerve activity, expanding receptive fields & augmented stimulus responses.
Abnormalities of descending inhibitory pain pathways	Dysfunction in brain center (or the pathways from these centers) that normally downregulate pain signaling in the spinal cord.
Neurotransmitter abnormalities	↓ serotonin in the central nervous system leading to aberrant pain signaling. ↓ dopamine transmission in the brain leading to chronic pain via unclear mechanisms.
Neurohumoral abnormalities	Dysfunction in the HPA axis, including blunted cortisol responses associated with (but not specific to) fibromyalgia.
Comorbid psychiatric conditions	Depression, anxiety, PTSD & somatization, which may predispose individuals to the development of fibromyalgia.

Use of fMRI to Identify Differences in Brain of FM Patient & Healthy Controls

- The first study to use fMRI in patients with FM. (Gracely, et al., 2002)
- Exposed 16 patients & 16 controls to painful pressures during MRI.
- Found increases in the blood oxygen-level (hyper-activation) in those with FM.
- Regions of increased activity included: primary & secondary somatosensory cortex, insula, & anterior cingulate.



Healthy Brain

Fibromyalgia

Central Sensitization in Fibromyalgia? A Systematic Review on Structural Brain MRI

- Changes in gray-matter volume.
- ↓ functional connectivity in descending pain modulating system.
- ↑ activity in the pain matrix related to central sensitization.

Cagnie B, Coppieters I, Denecker S, et al. *Seminars in Arthritis & Rheum*. 2014 Aug;44(1):68-75.

Chronic Overlapping Pain Syndromes

- Fibromyalgia, complex regional pain syndrome, other regional pain syndromes (restless leg, migraine, chronic fatigue).
- Conditions linked through dominant clinical features: pain, fatigue, allodynia, cognitive dysfunction poor sleep, dysesthesias & cutaneous circulatory changes.
- A key pathophysiological process behind each of these syndromes is central sensitization.
- "…have been made to appear separate because they have been historically described by different groups and with different criteria, but they are really phenotypically accented expressions of the same processes triggered by emotional distress and filtered or modified by genetics, psychology & local physical factors."

Littlejohn GO & Guymer E. Chronic pain syndromes: overlapping phenotypes with common mechanisms. *F1000Res.* 2019 Mar 5;8:F1000 Faculty Rev-255.

Endocannabinoid Deficiency Syndrome?

- Endocannabinoid system – endogenous homeostatic regulatory system inherited by all mammals.
- Regulates: sleep, appetite, mood, cognition, nociception, memory, motor control, etc.
- Signaling to ↔️ from the microbiome.
- Dysregulation (as a result of …) lead to disease – chronic/centralized pain syndromes – fibromyalgia/migraine/poor sleep/anxiety/IBS.

Russo EB. Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes. *Cannabis and Cannabinoid Research* 2016 1(1):154-165.

Diagnostic Guidelines

The ACR 1990 criteria for the classification of FM

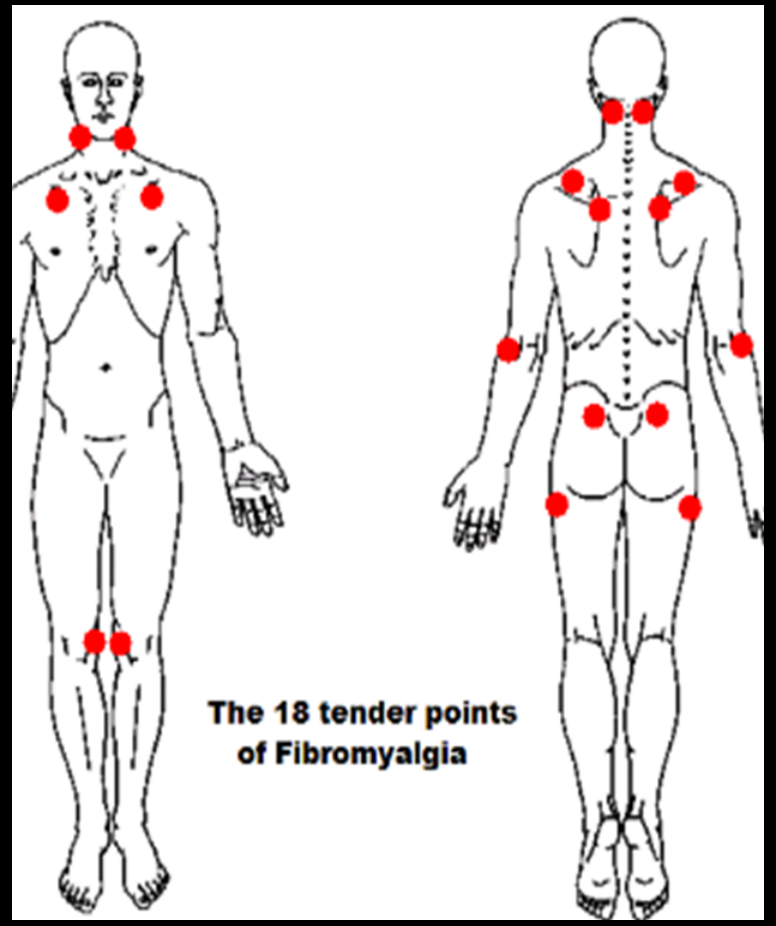
- Seminal article on classification criteria
- Gold Standard in FM diagnosis
- Continues to be used in research on FM/FMS

History of wide-spread pain (>3 months)

18 tender points to specific regions of muscle/tendon insertion sites

Pain in 11:18 tender points on digital palpation (4kg)

88.4% sensitivity / 81.1% specificity



Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis Rheum.* 1990;33:160-72.

Diagnostic Guidelines

American College of Rheumatology 2010 Preliminary Diagnostic Criteria

Objectives:

- Simple, practical diagnostic criteria
- Provide a severity scale FM symptoms
- Improve sensitivity/specificity of diagnosis

Widespread Pain Index (WPI) ≥ 7 &
Symptom Severity Scale (SS) ≥ 5
OR
WPI 3-6 & SS ≥ 9

- Correctly classifies 93% of FM cases
- Sensitivity = 96.6% / Specificity = 91.8%

Wolfe F, Clauw DJ, Fitzcharles M, et al. The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia & Measurement of Symptom Severity. *Arthritis Care & Research 2010*, 62(5):600-610.

ACR: 2010 Preliminary Diagnostic Criteria

Widespread Pain Index

Total (0-19) # of areas that the patient has had pain in the last week.

Symptom Severity Scale

Sum (0-12) of the severity of 4 symptoms, ranked over the past week from 0-3:

- fatigue
- waking unrefreshed
- cognitive symptoms
- level of somatic symptoms

Exclusion of other medical conditions that could account for pain/symptoms.

Patients at Risk

- Gender - female to male 2:1 to 7:1
- Genetics - strong familial component, 8-fold increase risk in a first degree relative, genetic polymorphisms serotonin & dopamine receptors.
- Environmental - physical trauma (especially involving the trunk), certain infections (hepatitis C, Epstein-Barr, Lyme disease), emotional stress, hormone alterations, drugs, vaccines.
- Psychological trauma - higher incidence in individuals with co-morbid history depression, anxiety, early childhood events, PTSD.

Genetic Influences

Serotonin-related genes:

Polymorphism also associated with

- anxiety-related personality traits
- diarrhea-predominant irritable bowel syndrome
- major depressive disorder (MDD)

Dopamine-related genes:

Alteration in D2 receptor gene

Catechol-O-methyltransferase (COMT gene):

One of several enzymes that degrade catecholamine's

- Dopamine
- Epinephrine
- Norepinephrine

Variant associated with:

- diminished μ-opioid system responses
- higher sensory & affective ratings of pain
- higher negative affective state

Obligatory Tests to r/o Other Disease

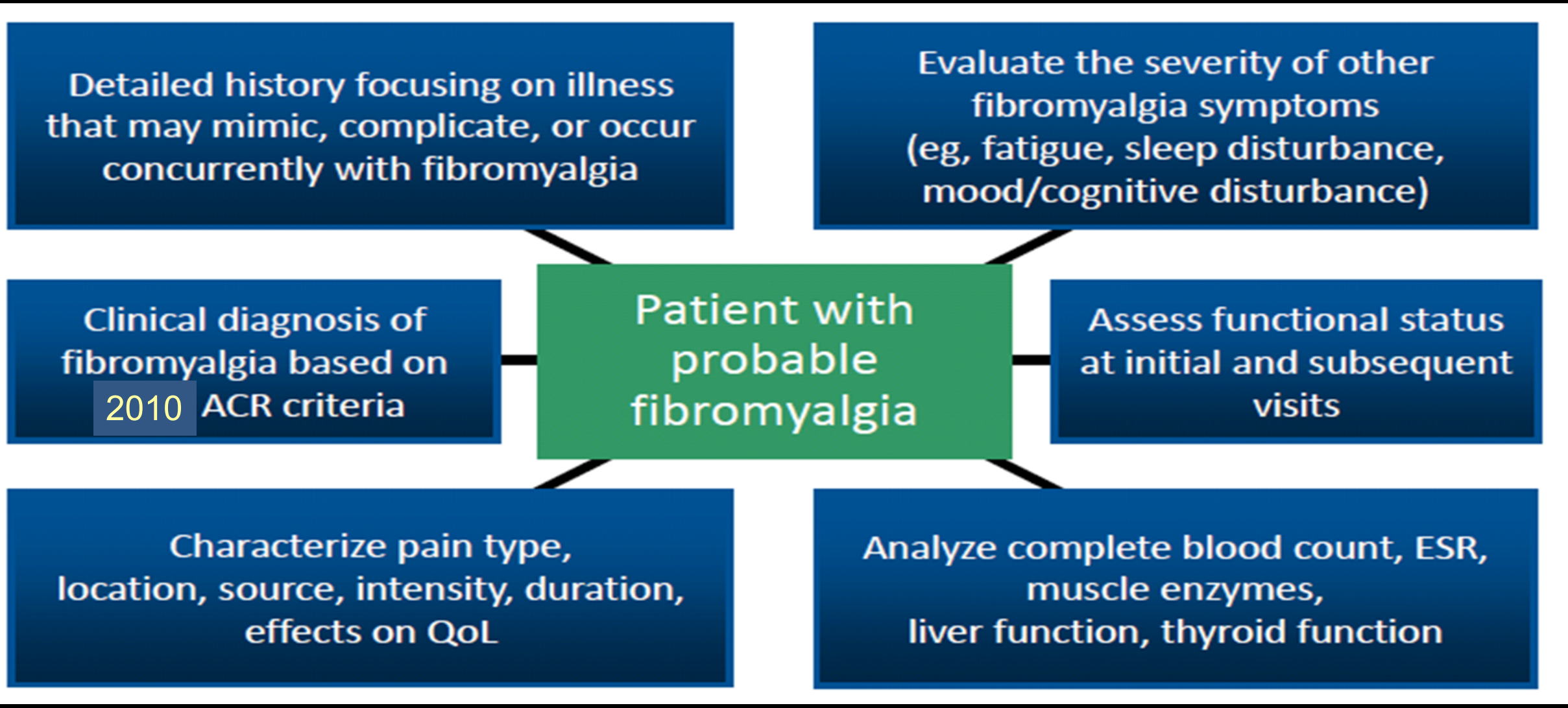
- Complete blood count w/differential (CBC)
- Iron studies
- Comprehensive metabolic panel (CMP)
- Thyroid stimulating hormone (TSH), T4
- Vitamin B12, D
- Erythrocyte sedimentation rate (ESR) & C-reactive protein (CRP)
- Creatinine kinase (CK)
- Other infectious disease (viral, bacterial, fungal)

Introducing Amy

- 35 y/o stay at home mother of three
- Presenting for evaluation of pain that started 4 months ago in her shoulders → recently spreading to hips, arms & back
- Pain level varies from 5-8/10
- Finding more difficult to complete household tasks
- History of symptoms consistent with IBS for past 4 years, migraine
- Recently diagnosed with mild depression, poor sleep and chronic fatigue.

- What formal diagnostic, laboratory and/or imaging tests may be helpful in narrowing your diagnosis?
- Any additional history that would be helpful?

Assessment for Fibromyalgia



Key Assessment Domains

Physical

- Pain
- Fatigue
- Disturbed sleep

Emotional & Cognitive

- Depression, anxiety
- Cognitive impairment
- Memory problems

Social

- Disrupted family relationships
- Disrupted relationships with friends
- Social isolation

Work & Activates

- Reduced activities of daily living
- Reduced leisure activities, avoidance of physical activity
- Loss of career, inability to advance career or education

Diagnosis

Based on comprehensive exam & normal serum/radiological studies:
(infectious, rheumatologic, other MSK disorders are ruled out)

- Meets criteria based on the ACR 2010
  - –WPI = 7
  - –SS score = 6

- Additional history significant early childhood discord/abuse
- +polymorphism enzyme catechol-O-methyltransferase (COMT gene)

Diagnosis – Fibromyalgia. Provide education, resources (including support group), discuss treatment.

Paradigms of Management

Behavioral

Psychotherapy, CBT, sleep hygiene, biofeedback, relaxation techniques

Pharmaceutical

Dual reuptake inhibitors, alpha-2-delta ligands, non-opioid analgesics, other

Physical

- Paced/graduated exercise
- Individualized physical therapy
- Warm pool

Nutritional

- Antioxidants
- Low fat
- Low glycemic index
- Weight control

The European Union League Against Rheumatism (EULAR) Revised Recommendations for the Management of Fibromyalgia

A multidisciplinary group of 18 members representing 12 countries

Reviewing systematic reviews & meta-analysis (through 2015):

- Pharmacological
- Non-pharmacological therapies

- Pharmacological:

amitriptyline (low-dose), tramadol, pregabalin, duloxetine/milnacipran, cyclobenzaprine

- Non-pharmacological:
  - Aerobic & strengthening exercises
  - Cognitive behavioral therapies & mindfulness stress reduction
  - Multicomponent therapies (combined educational & psychological)
  - Defined body therapies (acupuncture, hydrotherapy)
  - Meditative movement therapies (yoga, qigong, tai chi)

Practical Applications

- Realistic goals
- Financial considerations
- Personalize activities
- Consider physical therapy for education
- Reinforce positive behaviors/pacing

Practical Applications

- Education to avoid stigmatization
- Financial considerations
- Personalize therapy
- Reinforce positive behaviors/compliance

Pharmaceutical

- Tricyclic antidepressants (TCAs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- α2-δ ligands
- Only 1/3 of individuals will have meaningful improvement

Agents Currently FDA Approved for Fibromyalgia

Agent/Class/Dosing	Side Effects	Comments
Pregabalin – first approved agent for FM (1987) Antiepileptic – 150-300 mg BID	Ataxia, dizziness, sedation, peripheral edema Black box warning: increases risk of suicidal ideations	Additional FDA indications: seizures, post-herpetic neuralgia, diabetic peripheral neuropathy (DPN). Renal dosing; C-V drug
Duloxetine – 2008 SNRI – 60 mg daily	Anorexia, GI distress, nausea, dry mouth hyperhidrosis Black box warning: increases risk of suicidal ideations	Additional FDA indications: depression, anxiety, LBP/MSK pain, DPN. Renal dosing; avoid in severe hepatic disease.
Milnacipran – 2009 SNRI – 50-100 mg BID	Similar to duloxetine	Additional FDA indications: depression. Renal dosing; avoid in severe hepatic disease.

Class/Agent	Dose	Common Side Effects	Comments	EULAR/ American Pain Society
Tricyclic antidepressants amitriptyline desipramine nortriptyline	10-150 mg daily	Sedation, dry mouth, tachycardia, other anticholinergic effects	Dose desipramine during day and amitriptyline/nortriptyline at night	Strong efficacy for amitriptyline
Alpha 2 Delta (α2δ) Ligands gabapentin pregabalin	300-1200 mg TID 150-300 mg BID	Dizziness, sedation, edema, altered cognition	Renal dosing C-V	EULAR – strong efficacy APS – moderate efficacy
tramadol	50-100 mg BID	Nausea, sedation, ataxia, constipation	Weak mu agonist, decreases seizure threshold, risk of serotonin syndrome, renal dosing. C-V	EULAR – strong efficacy APS – moderate efficacy

Results of National Pain Foundation Survey Comparing Treatments for Fibromyalgia

Drug	% Very Effective	% Helps a Little	% Does Not Help at All
duloxetine	8	32	60
pregabalin	10	29	61
milnacipran	10	22	68
medical marijuana	66	35	5

Online survey of over 1,300 fibromyalgia patients conducted by the National Pain Foundation & National Pain Report

http://nationalpainreport.com/marijuana-rated-most-effective-for-treating-fibromyalgia-8823638.html

Pharmaceutical

Pramipexole

- Antiparkinsonian
  (dopamine receptor agonists)
- NOT FDA approved for FMS
- Clinical use for FM 4.5 mg qhs

Holman AJ & Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. *Arthritis Rheum.* 2005; 52: 2492-2505.

Pharmaceutical

Low-dose naltrexone (LDN)

- Proposed mechanism of action: opioid antagonist, glial cell modulator, anti-inflammatory
- NOT FDA approved for FMS
- Proposed dosing for FM 4.5 mg qhs

- Plesner KB, Weights HB & Handberg G. Pain Center South, Anesthesiology-Intensive Department, Odense University Hospital Weekly Doctors 2015; 177: V03150248
- Younger J, Noor N, McCue R, Mackey S. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. Arthritis Rheum. 2013 Feb;65(2):529-38.
- Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol. 2014 Apr;33(4):451-9.

Pharmaceutical

Muscle relaxants

- tizanidine, cyclobenzaprine, baclofen

Non-opioid analgesics

- NSAIDS, acetaminophen, tramadol, cannabinoids

Sleep aids

- amitriptyline, cyclobenzaprine,* doxepin, eszopiclone, melatonin, ramelteon, trazodone, zolpidem

*centrally acting, potentiates serotonin & norepinephrine (BESTFIT Study)

Sleep & Fibromyalgia

- Delayed sleep onset
- Decreased restorative sleep
- Frequent arousal
- Sleep disordered breathing
- EEG changes (α–EEG intrusions in non-REM sleep correlated with higher pain scores)

- Belt NK, Kronholm E, Kauppi MJ. Sleep problems in fibromyalgia and rheumatoid arthritis compared with the general population. Clinical and Experimental Rheumatology. 2009; 27: 35-41.
- González GLB, Fernández TVS, Rodríguez LA, et al. Sleep Architecture in Patients With Fibromyalgia. Psicothema. 2011 Aug;23(3):368-73.
- Roth T, Bhadra-Brown P, Pitman VW, Roehrs TA, Resnick EM. Characteristics of Disturbed Sleep in Patients With Fibromyalgia Compared With Insomnia or With Pain-Free Volunteers. Clin J Pain. 2016 Apr;32(4):302-7.

Arranz LI et al. Fibromyalgia and Nutrition, What do we know? Rheumatol Int. (2010)

Aim was to discover what was known from the scientific literature regarding FM and nutritional status.

- Medline 1998-2008 (174 articles)
- Vegetarian/vegan/low-allergenic diets
- Weight control
- Increased antioxidant intake
- low glycemic index (anti-inflammatory)
- Correct nutritional deficiencies:
  trace elements, Vit. D
- tryptophan (AA), melatonin, Vit. C

Nutraceuticals

- Food/fortified food product that not only supplements the diet but also assists in treating or preventing disease

- Not tested and regulated to the extent of pharmaceutical drugs

Nutraceuticals

Supplements that can be used empirically

- Fatigue – omega-3-oils, D-ribose
- Neuropathy – acetyl L-carnitine,
- alpha-lipoic acid
- Gastrointestinal – glutamine, probiotics
- Sleep – valerian root, melatonin
- Mood – SAMe, 5HTP, 1-tryptophan

- Other – magnesium, calcium, Vit. D, B-complex, Vit. C

Check for deficiencies

- Vit. D, B12, trace minerals, anemia

Check for allergies/sensitivities

- Gluten, diary, nuts

Diet/nutrition assessment

- Poor dietary choices?
- Pro-inflammatory diet?
- Weight control?

Dietary Aspects in Fibromyalgia Patients: Results of a Survey on Food Awareness, Allergies & Nutritional Supplementation

- Questionnaire (six questions: dietary habits, FAIs & supplement use)
- 101 ♀ suffering from FM, diagnosed for more than 6 months, mean age of 53.88 ± 7.78 years
- Investigate the dietary awareness, food allergies and/or intolerances (FAIs), & nutritional supplement (NS) consumption of FM patients. **Influence of advice from healthcare provider.**

Findings:

- Magnesium was one of the supplements most recommended specifically for FM.
- 74% of patients used NS following advice from health professionals.
- Once patients are diagnosed, they change their dietary habits and nutritional supplement intake, seeking nutritional strategies to improve their symptoms.

Arranz LI, Canela MA, Rafecas M. Dietary Aspects in Fibromyalgia Patients: Results of a Survey on Food Awareness, Allergies, and Nutritional Supplementation. *Rheumatol Int*. 2012 Sep;32(9):2615-21.

Treatment

Pharmaceutical:

- pregabalin 50 mg BID, titration to 150 mg BID
- LDN 4.5 mg 2hrs before bedtime

Physical:

- Referral to physical therapist for graduated, paced exercise program

Psychological:

- Referral to sleep medicine, r/o primary sleep disorder, CBT

Nutritional:

- Referral to nutritionist, food diary, portion control, low glycemic index (low-inflammatory) diet, supplements

Thought Provoking Questions

- Overlapping chronic pain (centralized pain) syndromes: could fibromyalgia be a symptom of/ or one disease in a broader diagnostic category of neuropathic/nociplastic pain?
- Should more focus be placed on correcting from within: health and wellbeing of the endocannabinoid system and the microbiome?
- Medication use as PRN versus daily? Reemergence of controversy, do opioids have a role? What about cannabinoids?

Summary

- Clinical support for FM being a chronic pain syndrome characterized by augmented central pain processing
- Existing diagnostic criteria based on comprehensive assessment, focus on symptom severity and QoL impact, exclusion of other potential disorders associated with wide-spread pain
- Evidence to support paradigm of management (multimodal): pharmacological, behavioral, psychological, nutritional therapies
- Because of its complexity, FM is best understood from a multidisciplinary perspective

Thank You

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Resources

- Fibromyalgia Information:
  http://fibromyalgia.ncf.ca
- National Fibromyalgia Association:
  http://www.fmaware.org
- American Pain Foundation:
  www.painfoundation.org
- www.webmd.com/fibromyalgia/guide/fibromyalgia-herbs-and-supplements
- www.centerwatch.com/ctrc/nationalfibromyalgia/
- www.fmaware.org/about-fibromyalgia/science-of-fm/latest-research/
- American College of Rheumatology: (search fibromyalgia)
  www.rheumatology.org/

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