

# Fibromyalgia

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**The following potential conflict of interest relationships are germane to my presentation.**

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NA/Non-Clinical

**Status of off-label use of devices, drugs or other materials that constitute the subject of this presentation**

NA/Non-Clinical

# Fibromyalgia



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# Incidence of Chronic Fatigue Syndrome and Fibromyalgia

- CFS is present in 522 women per 100,000 and 291 men per 100,000
- Fibromyalgia is present in 3,400 women per 100,000 and 500 men per 100,000
- In comparison:
  - Breast cancer: 26 women per 100,000
  - Diabetes: 900 women per 100,000
  - Heart disease: 3,400 women per 100,000
  - Arthritis: 3,800 women per 100,000

Bested, A, et al., Rev on Env Health. 2015; 30:223.

Sumpton, JE, et al., Fibromyalgia. Handb Clin Neurol. 2014;119:513-27.

# Fibromyalgia

- Affects 6-12 million Americans
- Causes more disability than rheumatoid arthritis
- Similar symptoms have been described in the medical literature since the 1800s with names like muscular rheumatism. In 1904, the term fibrositis was coined to describe pain associated with fibrous or connective tissue.

# Current Paradigms for Diagnosing and Treating Chronic Pain are Obsolete

- Multiple non-psychological neurobiological factors can increase or decrease sensitivity to pain
  - Operative in many chronic pain states
- We must modify our diagnostic and therapeutic paradigms to better identify and treat the CNS contributions to chronic pain

# Mechanistic Characterization of Pain

## Peripheral (nociceptive)

- Primarily due to inflammation or mechanical damage in periphery
- NSAID, opioid responsive
- Responds to procedures
- Behavioral factors minor
- Examples
  - Osteoarthritis
  - Rheumatoid arthritis
  - Cancer pain

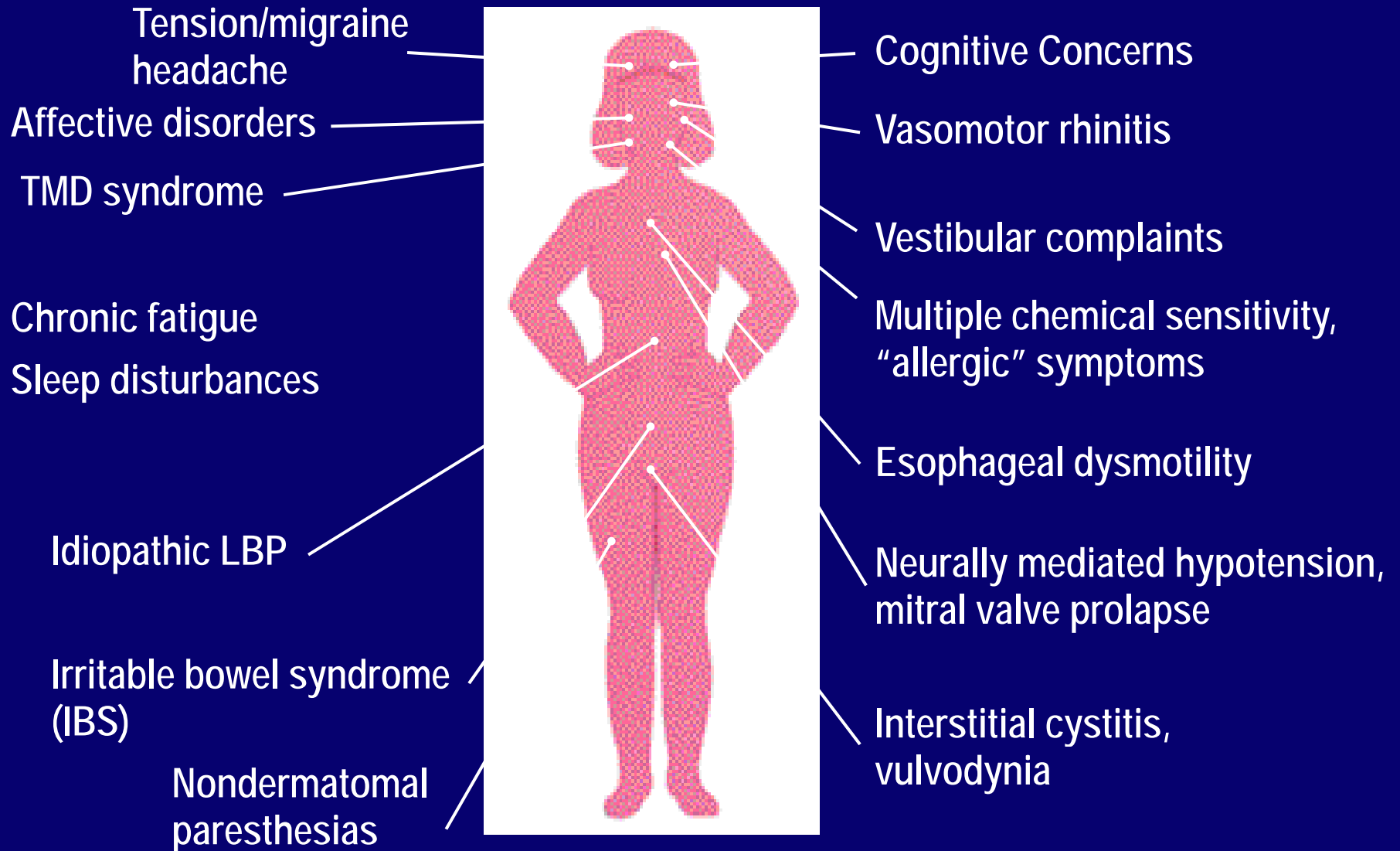
## Neuropathic

- Damage or entrapment of peripheral nerves
- Responds to both peripheral and central pharmacological therapy

## Central (non-nociceptive)

- Primarily due to a central disturbance in pain processing
- Tricyclic, neuroactive compounds most effective
- Behavioral factors more prominent
- Examples
  - Fibromyalgia
  - Irritable bowel syndrome
  - Tension headache
  - Idiopathic low back pain

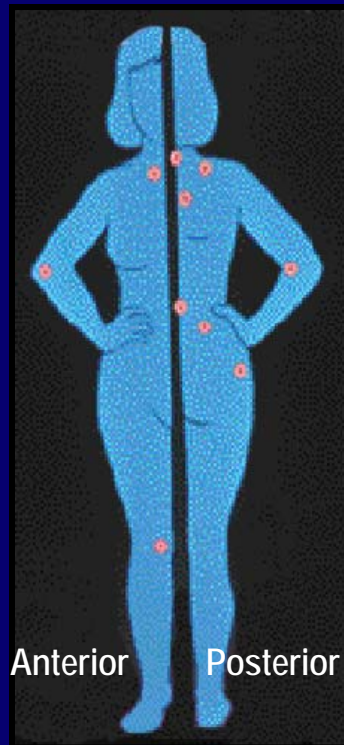
# Related Symptoms and Syndromes



# Paradigm Shift in Fibromyalgia

## American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Psychologic and behavioral factors nearly always present and negative



- One or more common widespread pain
- Tender points
- Many somatic symptoms, diffuse tenderness
- Psychologic and behavioral factors play roles in some individuals





# Neuroendocrine Disturbances in CFS/FM Patients

- ▶ Almost all patients have low cortisol levels
  - Hypothalamus does not secrete enough CRH
  - ACTH then does not stimulate the adrenals
  - Adrenal glands get smaller due to lack of stimulation
    - One study revealed adrenal glands to be 50% smaller

Bested, A., *Chronic Fatigue Syndrome and Fibromyalgia*. Nashville, TN: Cumberland House, 2006, p. 35.

- ▶ 54% FM patients have hypothyroidism
- ▶ FM patients have elevated TPO antibody and anti-TSH receptor antibody

Lowe, J., et al., "Thyroid disease and fibromyalgia syndrome," *Lyon Mediterranee Medical: Medicine du Sud-Est* 2000; 35: 15-7.

Suk, J., et al. "Association between thyroid autoimmunity and fibromyalgia," *Exp Clin Endocrinol Diabetes*. 2012;120(7):401-4.

Nishioka, K., et al. "High prevalence of anti-TSH receptor antibody in fibromyalgia syndrome," *Int J Rheu, Dis*. 2017;20(6):685-90.

# Neuroendocrine Disturbances in CFS/FM Patients (Cont.)

- ▶ DHEA levels are frequently suboptimal in CFS/FM

Teitelbaum, J., "Effective treatment of chronic fatigue syndrome," *Integrative Med* 2005; 4(4):24-9.

- ▶ Estrogen deficiency may coincide with the onset of CFS/FM.

*Ibid.*, Teitelbaum.

- ▶ Low testosterone is also common in both men and women with CFS/FM.

*Ibid.*, Teitelbaum.



Primary Care Physician

Rheumatologist

Gastroenterologist

Neurologist Specialist

# Overlap Between Fibromyalgia and Related Syndromes

## Fibromyalgia

- 2%-4% of population
- Defined by widespread pain and tenderness

## Regional Pain Syndromes

- eg, irritable bowel [IBS]
- Painful bladder / interstitial cystitis [PBS/IC]
- TMD
- Tension HA
- Vulvodynia

## Chronic Fatigue Syndrome (CFS)

- 1% of population
- Fatigue and 4 of 8 “minor criteria”

## Psychiatric Disorders

- Major depression
- OCD
- Bipolar
- PTSD
- GAD
- Panic attack

## Somatoform Disorders

- 4% of population



**Pain and/or  
sensory  
amplification**

# “Central Pain” Clinical Characteristics

- Multifocal pain (use pain diagram)
- Higher current and lifetime history of pain
- Multiple other somatic symptoms (fatigue, memory difficulties, sleep disturbances)
  
- Not “yes” or “no” - occurs over a wide continuum
  - Labels (e.g. fibromyalgia, IBS, TMJD) mostly irrelevant<sup>1</sup>
  - “Fibromyalgia-ness” predicts pain intensity, symptoms and disability (RA, OA, etc.)<sup>2</sup>

(1) Ablin K, Clauw DJ. Rheum Dis Clin North Am 2009; 35(2):233-51.

(2) Wolfe F, et. al. J Rheumatol 2006; 33(11):2291-9.

# “Central Pain” Clinical Characteristics

- 1.5 – 2X more common in females
- Strong familial/genetic underpinnings<sup>1</sup>
  - Take family history of pain
- Triggered or exacerbated by “stressors”<sup>2</sup>
- Generally normal physical examination except for diffuse tenderness and nonspecific neurological signs”<sup>3</sup>

(1) Kato K, et. al. Psychol Med 2008;1-9.

(2) Ablin K, Clauw DJ. Rheum Dis Clin North Am 2009; 35(2):233-51.

(3) Watson NF, et. al. Arthritis Rheum 2009; 60(9):2839-44.

# Genetics of Fibromyalgia

- Familial predisposition<sup>1</sup>
  - Work by Arnold, et al suggests 8.5 odds ratio (OR) for first-degree relatives, and much less familial aggregation (OR 2) with major mood disorders
  - Much stronger with bipolarity, obsessive compulsive disorder
- Genes that may be involved:
  - 5-HT<sub>2A</sub> receptor polymorphism C/T or C/C phenotype<sup>2</sup>
  - 5-HTT Serotonin transporter<sup>3</sup>
  - Dopamine D<sub>4</sub> receptor exon III repeat polymorphism<sup>4</sup>
  - COMT (catecholamine o-methyl transferase)<sup>5</sup>

1. Arnold et al. *Arthritis Rheum.* 2004;50:944-52.

3. Offenbaecher et al. *Arthritis Rheum.* 1999;42:2482-8.

5. Martínez-Jauand M et al. *Eur J Pain.* 2013;17(1):16-27.

2. Bondy et al. *Neurobiol Dis.* 1999;6:433-9.

4. Buskila et al. *Mol Psychiatry.* 2004;9:730-1.

# Genetics of Pain

- Three specific genes have been shown to play major roles in pain sensitivity thus far:
  - $\text{Na}_v1.7$ 
    - A genetic mutation that leads to loss of function of the  $\text{Na}_v1.7$  channel is associated with insensitivity to pain, whereas mutations (1.8, 1.9) that lead to increased function leads to erythromelalgia or paroxysmal extreme pain disorder<sup>1</sup>
  - GTP cyclohydrolase 1 (GCH1)<sup>2</sup>
  - Catechol-O-methyltransferase (COMT) rs4680<sup>3</sup>

1. Vargas-Alarcon G et. al. BMC Musculoskelet Disord. 2012;13:23

2. Tegeder et.al., NatMed. 2006;12(11):1269-77.

3. Tammimäki A. et. al. Pharmacogenet Genomics. 2012;22(9):673-91.



# “Stressors” as Triggers

- Early life stressors<sup>1</sup>
  - » Children born in 1958 who had experienced a motor traffic accident or who were institutionalized were 1.5 – 2X more likely to have CWP 42 years later
- Peripheral pain syndromes (e.g. RA, SLE, osteoarthritis)<sup>2</sup>
- Physical trauma (automobile accidents)
- Certain catastrophic events
  - (War but not natural disasters)<sup>3</sup>
- Infections
- Psychological stress/distress

1. Jones et. al. 2007 ACR meeting.

2. Clauw et. al. JCR 1997.

3. Clauw et. al. J Occup Environ Med. 2003 Oct;45(10):1040-8.

# “Pain Matrix” – Three Domains in CNS

- **Sensory:** where it is and how much it hurts
  - Primary and secondary somatosensory cortices
  - Thalamus
  - Posterior insula
- **Affective:** emotional valence of pain
  - Anterior cingulate cortex
  - Anterior insula
  - Amygdala
- **Cognitive:** what we think and do about pain
  - Many of above regions plus prefrontal regions

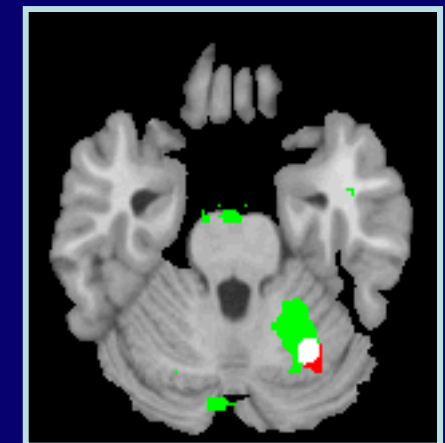
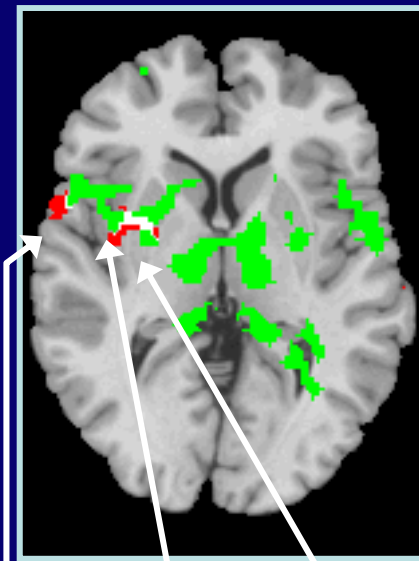
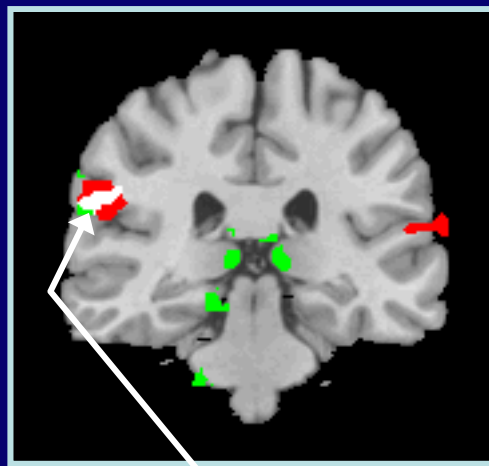
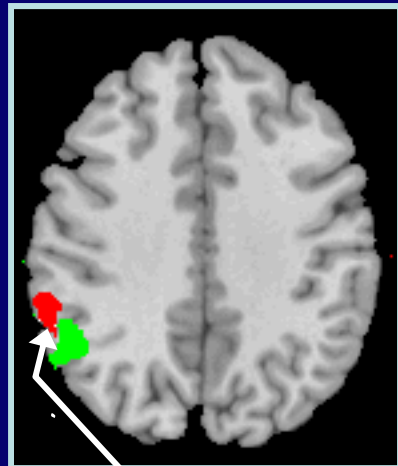
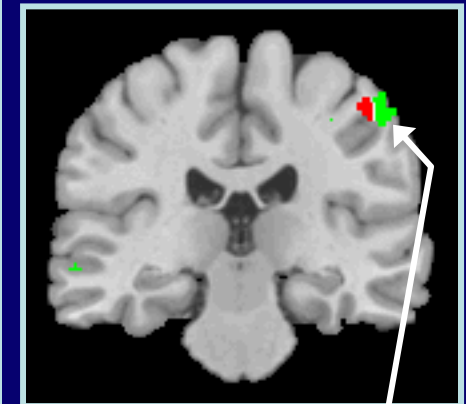
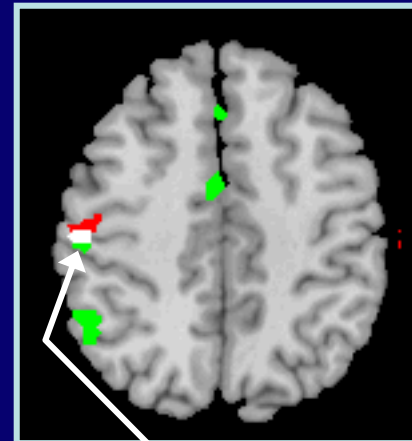
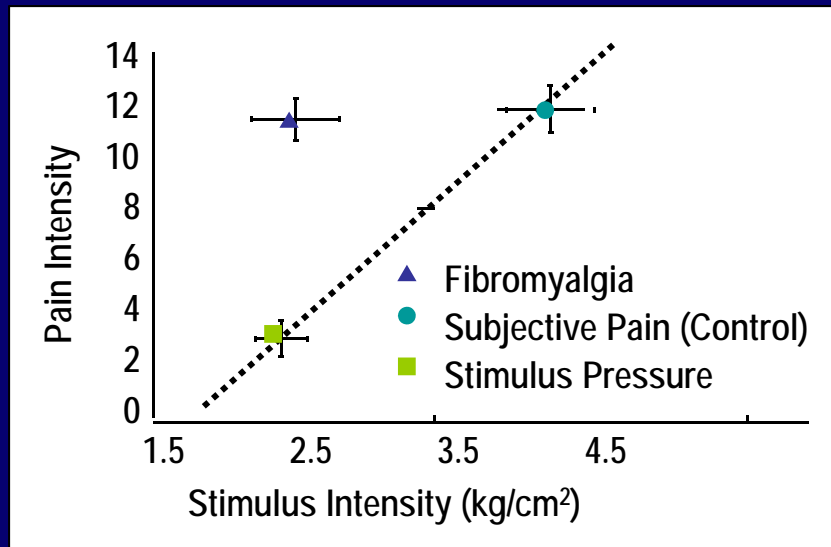
# fMRI in Chronic Pain States

- Augmented pain processing in a broad range of hyperalgesic pain states<sup>1-4</sup>
- Depression and pain are overlapping neurobiological processes<sup>5</sup>
- How individuals think about their pain can affect both the sensory and affective processing of pain<sup>6</sup>

1. Gracely et al. *Arthritis Rheum.* 2002;46:1333-43.  
3. Giesecke et al. *Arthritis Rheum.* 2004;50:613-23.  
5. Gracely et al. *Brain.* 2004;127:835-43.

2. Mayer et al. *Gastroenterology* 2006(131):1925-31.  
4. Giesecke et al. *Arthritis Rheum.* 2003;48:2916-22.

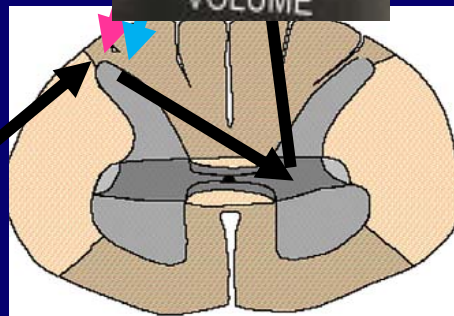
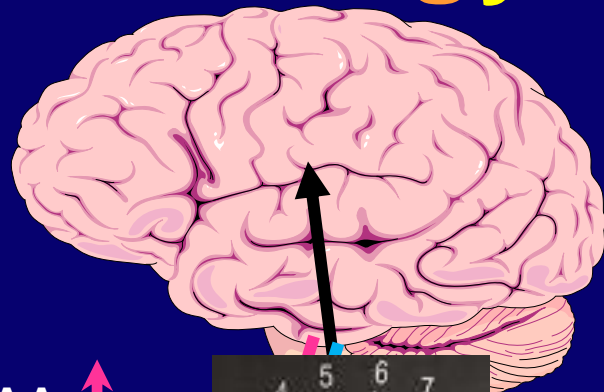
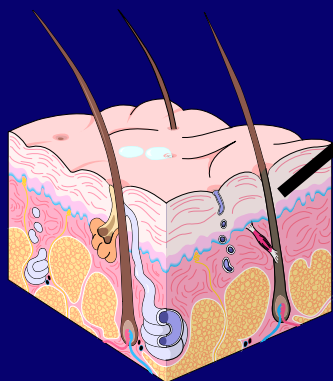
# Stimuli and Responses



# Essential Hypertension of Pain Processing Pathways

## Facilitation

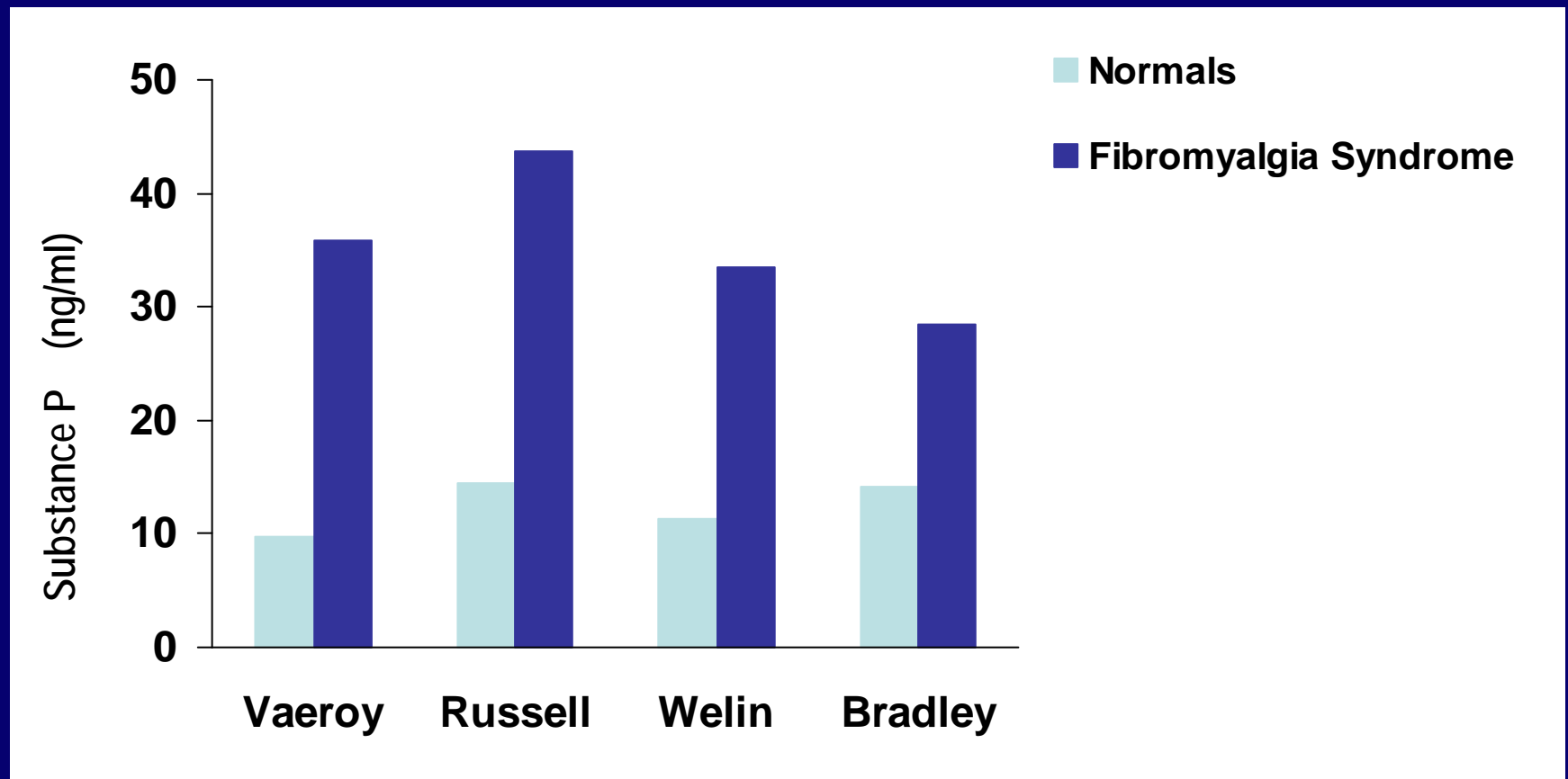
- Substance P ↑
- Glutamate and EAA ↑
- Serotonin (5HT<sub>2a, 3a</sub>) ↑
- Nerve growth factor ↑



## Inhibition

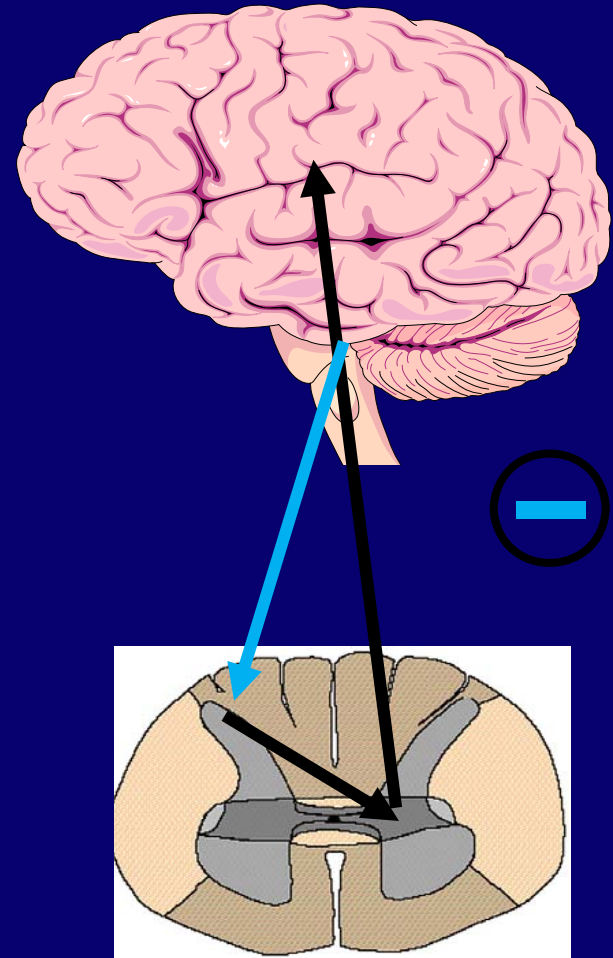
- Descending anti-nociceptive pathways ↓
- Norepinephrine-serotonin (5HT<sub>1a,b</sub>), dopamine ↓
- Opioids ↑
- GABA
- Cannabinoids
- Adenosine

# Fibromyalgia CSF Substance P



# Specific Underlying Mechanisms in Chronic Pain

- Decreased descending analgesic activity
  - Absent or attenuated descending inhibitory function in FM, IBS, OA, and other pain states<sup>1-3</sup>
  - Brainstem activations with conditioning stimulus seen in controls but not in FM patients<sup>4</sup>



# Deficiency of Descending Analgesic Activity in FM<sup>1,2</sup>

## Opioids

- Normal or high levels of CSF enkephalins<sup>3</sup>
- No RCT
- Opioids are ineffective or marginally effective
- Reduced Mu opioid receptor binding in FM<sup>4</sup>

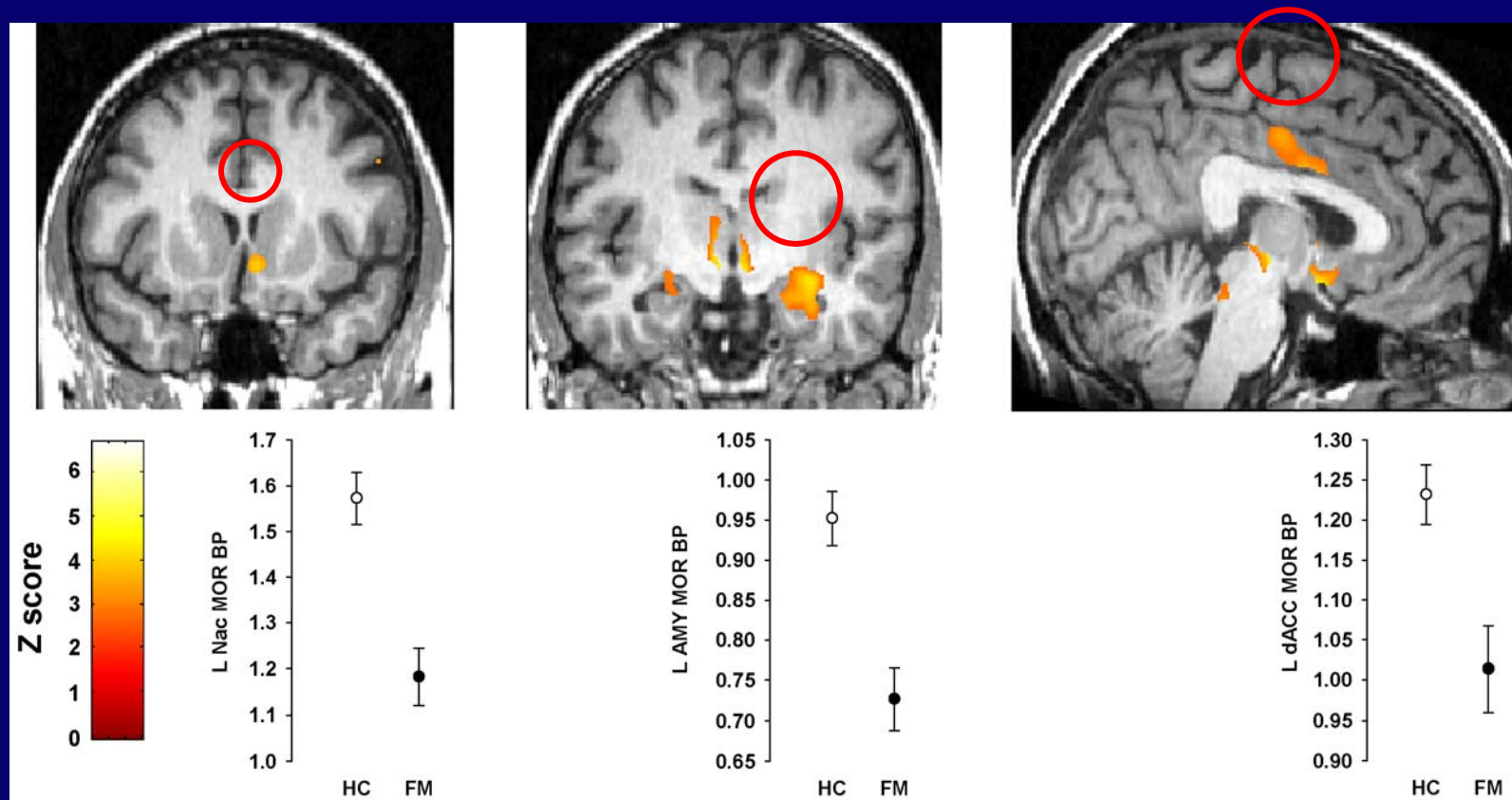
## Noradrenergic/ Serotonergic

- Low levels of monoamines in CSF in FM<sup>5</sup>
- Drugs that raise both serotonin or norepinephrine demonstrate efficacy in FM

1. Kosek and Hansson. *Pain*. 1997;70:41-51. 2. Julien et al. *Pain*. 2005;114:295-302.  
3. Baraniuk et al. *BMC Musculoskelet Disord*. 2004;5:48. 4. Harris et al. *J Neurosci*. 2007;27:10000-6.  
5. Russell et al. *Arthritis Rheum*. 1992;35:550-6.



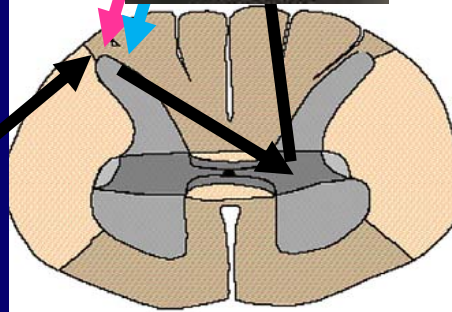
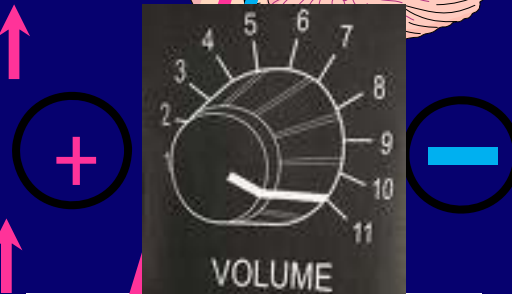
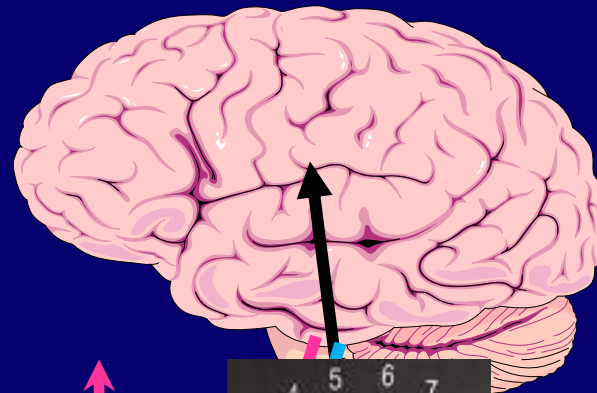
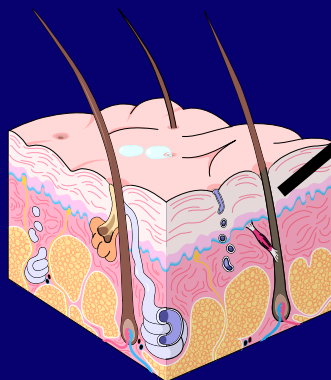
# FM Patients Have Reduced mu-Opioid Receptor Availability



# Any of These Neurotransmitters Are Potential “Targets” in Central Pain

## Facilitation

- Substance P ↑
- Glutamate
- Serotonin (5HT<sub>2a</sub>, 3a)
- Nerve growth factor ↑



## Inhibition

- Descending anti-nociceptive pathways ↓
- Norepinephrine-serotonin (5HT<sub>1a,b</sub>), dopamine ↓
- Opioids ↑
- GABA
- Adenosine

# Osteoarthritis of the knee

- Poor relationship between structural abnormalities and symptoms<sup>1</sup>. In population-based studies:
  - 30 – 40% of individuals who have grade 3/4 K/L radiographic OA have no symptoms
  - 10% of individuals with severe pain have normal radiographs
- Psychological factors explain very little of the variance between symptoms and structure<sup>2</sup>
- Therapies are inadequate
  - NSAIDs, acetaminophen, and even opioids have small effect sizes
  - Arthroplasty does not predictably relieve pain, especially long-term

(1) Creamer P, et. al. Br J Rheumatol 1997; 36(7):726-8.

(2) Creamer P, et. al. Arthritis Care Res 1998; 11(1):60-5.

# Toxins

- There is a suggestion in the literature that mercury toxicity plays a role in the etiology of fibromyalgia.

Kotter, I., et al., "Mercury exposure from dental amalgam fillings in the etiology of primary fibromyalgia: a pilot study," *Jour Rheumatol* 1995; 22:2194-95.

# Nonpharmacological Therapies for Fibromyalgia

## Strong Evidence

- Education
- Aerobic exercise
- Cognitive behavior therapy

## Modest Evidence

- Strength training
- Hypnotherapy, biofeedback, balneotherapy

## Weak Evidence

- Acupuncture, chiropractic, manual and massage therapy, electrotherapy, ultrasound

## No Evidence

- Tender (trigger) point injections, flexibility exercise

# Cognitive Behavioral Therapy and Exercise for Chronic Pain

- Effective over a wide range of pain states
- May be more effective than medication<sup>1</sup>
- Despite wide agreement that these help, barriers to implementation have been:
  - Physicians do not strongly recommend this
  - Not generally reimbursed by third parties
  - Not enough trained therapists to give one-on-one CBT to all chronic pain patients

# Pharmacological Therapies for FM

## Strong Evidence

- Dual reuptake inhibitors such as
  - Tricyclic compounds (amitriptyline, cyclobenzaprine)
  - SNRIs and NSRIs (milnacipran, duloxetine, venlafaxine?)
- Anticonvulsants (e.g., pregabalin, gabapentin)

## Modest Evidence

- Tramadol
- Selective serotonin reuptake inhibitors (SSRIs)
- Gamma hydroxybutyrate
- Dopamine agonists

## Weak Evidence

- Growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe)

## No Evidence

- Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics, guanifenesin

# Integrative Treatment

- Diet
- Hormonal therapies
- Treating infections
- Nutritional Therapies
  - Fueling the mitochondria
- Pain control gels
- Guaifenesin



# Diet

- Studies have shown that vegetarian or vegan diets have helpful in treating fibromyalgia.

Donaldson, M., et al., "Fibromyalgia syndrome improved using a mostly raw vegetarian diet: in observational study," BMC Complement Alter Med 2001; 1:7.

Kaartinen, K., et al., "Vegan diet alleviates fibromyalgia symptoms," Scand Jour Rhematol 2000; 29(5):308-13.

# Diet (Cont.)

- Avoid dietary excitotoxins
  - MSG
  - Aspartame

Smith, J., et al., "Relief of fibromyalgia symptoms following discontinuation of dietary excitotoxins," *Ann Pharmacother* 2001; 35 (6):702-06.

# Hormonal Therapies

## ▶ Adrenal

- Adrenal dysfunction may be a result of hypothyroidism or may be a separate issue.

## ▶ Thyroid

- Inadequate thyroid supplementation or cellular resistance to thyroid hormone may be the underlying cause to:
  - Chronic pain
  - Increased tenderness
- Hypothyroidism can impair the anti-nociceptive system and lead to pain, tenderness, and hyperalgesia.

# Hormonal Therapies (Cont.)

- Thyroid hormone replacement lowers substance P levels in the brain.

Lam, K., et al., "Vasoactive intestinal peptide in the anterior pituitary is increased in hypothyroidism," *Endocrinology* 1989; 124:1077-84.

Savard, P., et al., "Influences of both thyroid and bovine growth hormones on substance P, thyrotropin-releasing hormone, serotonin and 5-hydroxyindoleacetic acid contents in the lumbar spinal cord of developing rats," *Brain Res* 1984; 315:105-10.

# Hormonal Therapies (Cont.)

- Thyroid hormone (Cont.)
  - T3 plays a crucial role in the synthesis of dopamine and NE.
    - The locus ceruleus has the heaviest concentration of T3 in the brain.
    - Thyroid hormone regulates tyrosine hydroxylase (catalyzes conversion of tyrosine to dopa) and dopamine-beta-hydroxylase (catalyzes conversion of dopamine to NE).

# Hormonal Therapies (Cont.)

- Melatonin
  - Fibromyalgia patients have decrease melatonin levels in the evening.
    - Wikner, J., et al., “Fibromyalgia: a syndrome associated with decreased nocturnal melatonin secretion,” Clin Endocrinol (Oxf). 1998; 49:179-83.
  - Helps with sleep
  - Is an antioxidant thus limiting the loss of intramitochondrial glutathione which prevents damage to mitochondrial protein and DNA
  - Reduces LPS mitochondrial impairment

# Hormonal Therapies (Cont.)

- Melatonin (cont.)
  - Increases the activity of complexes 1 and 4 of the electron transport chain which increases ATP synthesis
    - Leon, J., et al., “Melatonin mitigates mitochondrial malfunction,” *Jour Pineal Res* 2005; 38:1-9.
  - Has been shown in clinical trials to improve sleep, help with pain and fatigue, and alleviate other symptoms of fibromyalgia(3-6 mg qhs)
    - Acuna-Castroviejo, D., et al., “Melatonin therapy in fibromyalgia,” *Jour Pineal Res* 2006; 40:98-9.

# Fibromyalgia Is A Mitochondrial Disease

- Study measured the ATP levels in patients with fibromyalgia
  - Found a 20% reduction in the level of ATP in muscle biopsies taken from patients diagnosed with fibromyalgia
  - There were lower levels of ATP inside the cells and in their reservoirs
  - Normal tissue showed no ATP deficits



# Fibromyalgia Is A Mitochondrial Disease

- Study measuring ATP and Phosphocreatinine in the quad muscle in fibromyalgia patients
- Fibromyalgia patients had 28-29% lower levels of ATP and PCR
- Quadriceps muscle fat content was significantly higher in Fibromyalgia patients

# Fibromyalgia Is A Mitochondrial Disease (Cont.)

- References

- Bengtsson, A., et al., “The muscle in fibromyalgia: a review of Swedish studies,” *Jour of Rheumatology* 1989: 16(Suppl 19):144-49.
- Bengtsson, A., et al., “Reduced high-energy phosphate levels in the painful muscles of patients with primary fibromyalgia,” *Arthritis and Rheumatism* 1986: 29(7):817-21.

# Nutritional Therapies

- Coenzyme Q-10
- D-Ribose
- NADH
- Alpha lipoic acid
- Magnesium
- B vitamins

# Nutritional Therapies (Cont.)

- Acetyl-L-carnitine
- Tryptophan/5-HTP
- SAMe
- Chlorella
- Ginkgo biloba
- Probiotics
- Vitamin D

# Co-Enzyme Q10

- Key component of cellular respiratory chain
- Statins disrupt krebs cycle and deplete levels of CoQ10
- Preliminary evidence that common side effects of myopathies and liver inflammation are in part due to CoQ10 depletion
- Some patients supplement with CoQ10 to alleviate symptoms
- Used in various neurological disease treatments, cardiovascular, and diabetes
- Dose 100-300mg per day in AM

# D-Ribose

- Study of 41 patients with fibromyalgia using 5 grams TID of D-ribose revealed an improvement in energy, sleep mental clarity, pain intensity, and well-being.
  - Teitelbaum, J., et al., “The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study,” *Jour Altern complement Med* 2006; 12:857-62.
- Increases mitochondrial ATP production

# NADH

- Improves the production of cellular energy by boosting the levels of ATP
- Is an antioxidant
- Dose: 10 mg QD

# Alpha Lipoic Acid

- Is a cofactor for mitochondrial enzymes
- Acts as a metal chelator for cadmium, copper, and iron
- Increases glutathione
- Is an antioxidant
- Recycles coenzyme Q-10, vitamins C and E  
Stops activation of NF-Kappa B
- Stops the adhesion of macrophages to the arterial wall
- Improves the immune system



# Magnesium and Malic Acid

- ▶ Magnesium deficiency makes the symptoms of fibromyalgia worse by decreasing the production of ATP.
- ▶ Malic acid is a fruit acid that in high amounts in apples
- ▶ Dose: 900 mg magnesium and 2,400 mg of malic acid
- ▶ A clinical trial revealed improvement with magnesium and malic acid.

Russell, I., et al., "Treatment of fibromyalgia syndrome with Super Malic: a randomized, double-blind, placebo controlled, crossover pilot study," *Jour Rheumatol* 1995; 22:953-58.

# B Vitamins

- High levels of homocysteine have been found in both FMS and CFS.

Ibid., Bsted, p. 131-32.

# Acetyl-L-Carnitine

- Double-blind study of 102 patients with fibromyalgia were treated with acetyl-L-carnitine or placebo. After three weeks saw improvements in depression, musculoskeletal pain, number of tender points, and total symptom scores.
  - Rossini, M., et al., “Double-blind, multicenter trial comparing acetyl-L-carnitine with placebo in the treatment of fibromyalgia patients,” *Clin Exp Rheumatol* 2007; 25:182-88.

# Tryptophan/5-HTP

- Patients with fibromyalgia have low levels of tryptophan.
- The lower the level of tryptophan the worse the pain with fibromyalgia

Yumus, M., et al., "Plasma tryptophan and other amino acids in primary fibromyalgia: a controlled study," Jour Rheumatol 1992; 19:90-4.

Russell, I., et al., "Serum amino acids in fibrositis/fibromyalgia syndrome," Jour Rheumatol Suppl. 1989; 19:158-63.

# Tryptophan/5-HTP (Cont.)

- Patients with fibromyalgia also frequently have low serotonin levels.

Wolfe, F., et al., "Serotonin levels, pain threshold, and fibromyalgia symptoms in the general population," *Jour Rheumatol* 1997; 24:555-59.

# Tryptophan/5-HTP (Cont.)

- Studies have shown that supplementation with 5-HTP has been helpful.
  - One study looked at 50 patients with fibromyalgia for 3 months. Treatment with 5-HTP showed significant improvement in tender points, anxiety, pain intensity, quality of sleep and fatigue after taking 5-HTP in nearly 50% of the patients.

Sarzi Puttini, P., et al., "Primary fibromyalgia syndrome and 5-hydroxy-L-tryptophan: a 90 day open study," J Int Med Res 1992; 20:182-89.

# Tryptophan/5-HTP (Cont.)

- In another trial (double-blind, placebo-controlled), using 5-HTP in 50 patients with fibromyalgia showed significant improvement in all symptoms.

Caruso, I., et al., "Double-blind study of 5-hydroxytryptophan versus placebo in the treatment of primary fibromyalgia syndrome," *Jour Int Med Res* 1990; 18:201-09.

# Tryptophan/5-HTP (Cont.)

- Treatment
  - Magnesium (deficiency impairs the conversion of 5-HTP to serotonin)
  - 50-300 mg of 5-HTP
    - If using larger doses –divide throughout the day
  - Tryptophan
    - Take on an empty stomach with carbohydrate



# SAMe

- Found to be beneficial in the treatment of fibromyalgia

Leventhal, I., "Management of fibromyalgia," *Ann Intern Med* 1999; 131:850-58.

- Helps maintain mitochondrial function by preserving glutathione
- Methyl donor
- Dose: 800 mg QD

# Chlorella pyrenoidosa

- Is a fresh water green algae
- Contains many nutrients especially vitamin D (500 IU vitamin D per 1.35 g Chlorella)
- Detoxifies xenobiotics

Nakano, S., et al., "Chlorella (Chlorella pyrenoidosa) supplementation decreases dioxin and increases immunoglobulin a concentration in breast milk," J Med Food 2007; 10:134-42.

- Used with other treatments for fibromyalgia

# Ginkgo Biloba

- Antioxidant
- Anti-inflammatory
- Vasodilator
- Protects the mitochondria
- Clinical trial using Ginkgo biloba (200 mg) with coenzyme Q-10 (200 mg) daily found benefit in 64% of the patients.

Lister, R., et al., "An open, pilot study to evaluate the potential benefits of coenzyme Q-10 combined with Ginkgo biloba extract in fibromyalgia syndrome," *Jour Int Med Res* 2002; 30:195-99.

# Probiotics

- 90% to 100% of patients with fibromyalgia have small bowel overgrowth.

Vasquez, A., Musculoskeletal Pain: Expanded Clinical Strategies. "Clinical Focus: Fibromyalgia," Gig Harbor, WA: Institute for Functional Medicine, 2008, p. 102.

- In a study of 42 patients with fibromyalgia, all of them had SBO.

Pimental , M., et al., "A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath test," Ann Rheumatol Dis 2004; 63:450-52.

# Vitamin D

- Vitamin D deficiency has been shown to be linked with depression and anxiety in patients with fibromyalgia.
- Measure level of 25 OH vitamin D and replace with vitamin D3.

Armstrong, D., et al., "Vitamin D deficiency is associated with anxiety and depression in fibromyalgia," Clin Rheumatol 2007; 26:551-54.

# Pain Control Gels

- Compounded by the compounding pharmacy

# Treatment (Cont.)

- Guaifenesin
  - Works by helping the kidneys increase excretion of phosphate
  - Fibromyalgic kidneys have excess phosphate
  - Retention of phosphate interferes with energy production by the cells
  - Excess phosphate also forces retention of calcium, swelling develops and causes pain

Bennet, R., et al., "A 1-year double-blind, placebo-controlled study of guaifenesin in fibromyalgia," (Abstract). *Arthritis Rheum* 1996; 39(Suppl 9):112.

# Treatment (Cont.)

- Initially patient may feel worse as the excess phosphate leaves the body
- Eliminate all sources of salicylates since they block guaifenesin's access to the receptor sites in the kidneys. It is NOT necessary to avoid salicylates that are in foods.
  - Lipsticks
  - Muscle balms
  - Nutritional and herbal supplements
  - Cosmetics
  - Sunscreens



# Treatment (Cont.)

- Guaifenesin (cont.)
  - For every two months on guaifenesin it reverses one year of fibromyalgia
  - This only works if the patient avoids all salicylates
  - No side effects except rarely transient nausea
  - Do not use liquid guaifenesin since it contains sugar and many patients with fibromyalgia are hypoglycemic and then later insulin resistant. As insulin increases, more phosphate is released into the cells.
  - Suggest having it made by compounding pharmacy so there is no dyes
  - Do not use in pregnancy

# Treatment (Cont.)

## ▶ Guaifenesin (cont.)

- Dose: 300 mg BID
- The patient should feel worse at first if the guaifenesin is working.
- If the patient does not feel bad during the first week then double the dose.
- There should be an increase in symptoms in 10-14 days. If this does not occur, then increase the dose to 1800 mg qd.
- If the patient does not feel worse in one month then increase the dose to 1200 mg BID.
- In 95% of the patients you will not have to go higher than 1200 mg BID.

# Treatment (Cont.)

- Guaifenesin (cont.)
  - How long does the patient take guaifenesin—forever. It only works while they are taking it. The genetic defect that caused the problem to begin with is not fixed so the symptoms will reoccur if the guaifenesin is discontinued.

# Common Medications Containing Natural Salicylates

- Aloe vera
- Celestial Seasonings Throat Drops
- Dong Kwai
- Ephedra
- Feverfew
- Gas-X
- Gingko biloba

# Common Medications Containing Natural Salicylates (Cont.)

- Naxixx (Chinese herbs)
- Pau D/Arco
- Preparation H Ointment (thyme oil)
- Purge (caster oil)
- St. John's wort
- Saw palmetto
- Valerian
- Vicks Cough Drops (eucalyptus oil)

# Common Topical Preparations Containing Natural Salicylates

- Absorbine Jr. (calendula, echinacea, wormwood)
- Aloe Vera Gel
- Arthricare
- Cortaid Maximum Strength Cream (Aloe vera)
- Dolorac Cream (capsaicin)
- Gum and Toothache Medications (clove oil)
- Hemorid (Aloe barbadensis extract)

# Common Medications Containing Natural Salicylates (Cont.)

- Milk of magnesia (cascara)
- Vaseline Intensive Care Sunless Tanning Lotion (Aloe)
- Vicks Vaporub Cream (eucalyptus oil)
- Zostrix Cream (capsicum)

# Common Medications Containing Synthetic Salicylates

- ▶ Alka Seltzer
- ▶ Anacin
- ▶ Asacol
- ▶ Ascriptin
- ▶ Aspergum
- ▶ ASA
- ▶ Bayer Arthritis Pain formula
- ▶ Bengay
- ▶ Bufferin
- ▶ Darvon compound
- ▶ Disalcid
- ▶ Doan's pills
- ▶ Ecotrin



# Common Medications Containing Synthetic Salicylates (Cont.)

- ▶ Empirin Compound
- ▶ Excedrin (except aspirin-free formula)
- ▶ Fiorinal
- ▶ Halfprin
- ▶ Lortab ASA
- ▶ Monogesic
- ▶ Myoflex
- ▶ Pepto-Bismol
- ▶ Percodan
- ▶ Soma Compound
- ▶ Trilisate
- ▶ Zorprin

# Common Topical Products Containing Synthetic Salicylates

- Almay Fragrance-Free Oil Free Lotion
- Clearasil Double Textured Pads Maximum Strength (and other Clearasil products)
- Compound W Gel/Liquid
- Coppertone Shade Sunblock Stick
- Fostex Regular Strength Medicated Cleansing Bar (and other products)
- Freshburst Listerine
- Listerex Golden Scrub Lotion (and other products)

# Natural Salicylates

- See lists of Natural Salicylates
  - Previous slides on most common things containing salicylates
  - Also extensive list of over 1000 items that contain salicylates

Amand, R., What Your Doctor May Not Tell You About Fibromyalgia. New York: Warner Books, 1999.

Amand, R., What Your Doctor May Not Tell You About Fibromyalgia Fatigue. New York: Time Warner Books, 2003.

# Interstitial Cystitis

- Some patients with fibromyalgia will have interstitial cystitis.
  - Do not use cranberry tablets in these patients because it can block the guaifenesin
  - Urised and Prosed contain phenyl salicylate and they will therefore block guaifenesin
  - Elmiron will not block guaifenesin.

# Fibro Fog

- The cognitive symptoms of fibromyalgia are also helped by guaifenesin.

# Exercise

## ▶ Mild exercise is important in patients with fibromyalgia

Ambrose, K., et al., "Applying exercise to the management of fibromyalgia," *Curr Pain Headache Rep* 2003; 7:348-54.

Rooks, D., et al., "Managing fibromyalgia: the role of exercise," *Jour Musculoskel Med* 2002; 19:439-48.

Jones, K., et al., "Individualizing the exercise prescription for persons with fibromyalgia," *Rheum Dis Clin North Amer* 2002; 28:419-36.

Mannerkorpi, K., et al., "Six and 24-month follow-up of pool exercise therapy and education for patients with fibromyalgia," *Scand Jour Rheumatol* 2002; 31:306-10.

# Yoga

- Pilot study to evaluate pain, psychological variables, mindfulness, and cortisol in women with fibromyalgia
- 75 min yoga class twice weekly for 8 weeks
- Results:
  - Yoga reduced pain and catastrophizing
  - Increased acceptance and mindfulness
  - Altered total cortisol levels

# Tai Chi

- Study comparing Tai Chi to aerobic exercise in an RCT
- 226 adults (92% women) were divided into four tai chi groups and one aerobic exercise group
- Primary outcome was a change in FIQR questionnaire
- Results: Tai Chi had a greater reduction in FIQR score and should be considered as a possible adjunct/alternative therapy to aerobic exercise



# Medical Marijuana

- Data from 56 patients with fibromyalgia were obtained from two hospitals
- Compared cannabis users vs non-cannabis users
- After 2 hours of cannabis use, VAS scores showed a statistically significant reduction of pain and stiffness, enhancement of relaxation, and an increase in well being
- Cannabis users had a significantly higher mental health score in the SF-36.

# Summary

- The most effective therapies for chronic pain are often not used in clinical practice
  - Education
  - Exercise
  - Cognitive therapy
- Medications are limited in their benefit for chronic pain
- Chronic pain may be both “peripheral” and “central”

