

# Fibromyalgia

**Tarvez Tucker, M.D.**

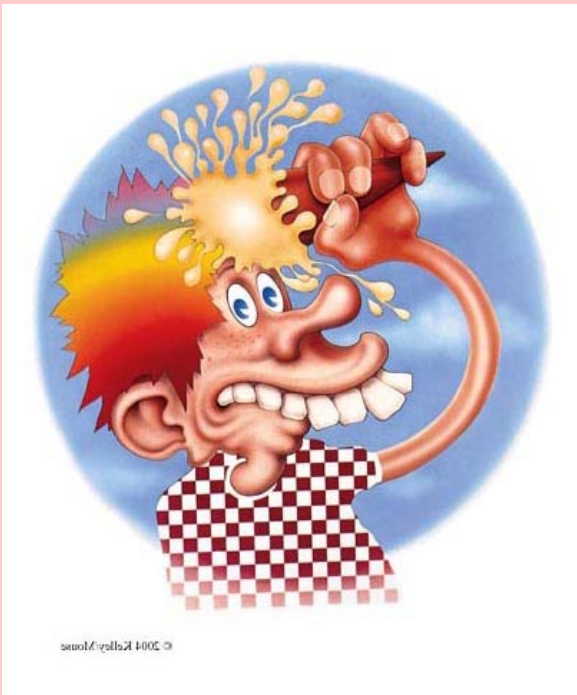
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# Fibromyalgia Quiz

- Fibromyalgia: more prevalent in women or men?
- ACR criteria
  - Widespread pain > 3 months
  - How many of 18 tender points present?
- What should FM patients NOT do in bed?
  - Sleep
  - Watch TV
  - Make love
  - Observe the moonlight

# Which of the Following are Fibromyalgia “Triggers?”



- Zucchini
- Whiplash
- Childhood sexual abuse
- Godiva chocolate
- Mononucleosis
- Closed head injury

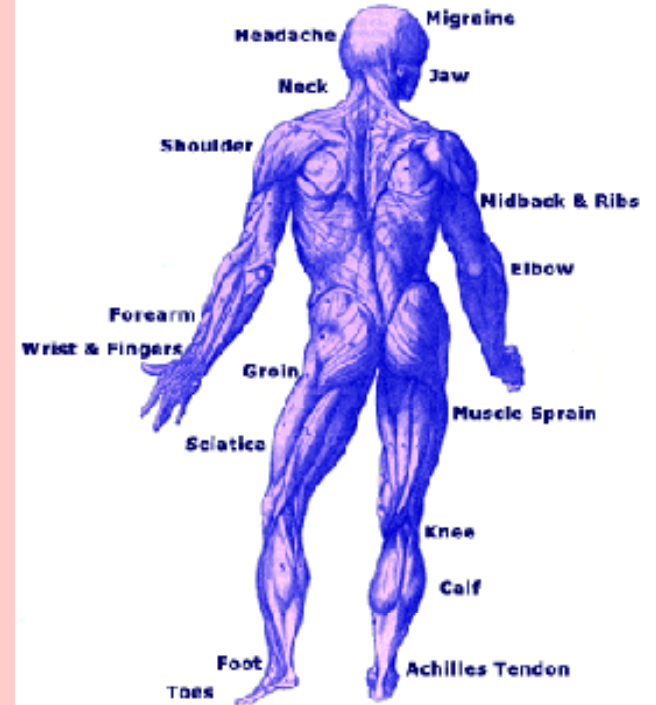
# Fibromyalgia “Quiz”



- What time of day are symptoms most severe?
  - Upon awakening
  - After exercise
  - Waning mid-afternoon hours
  - After dinner

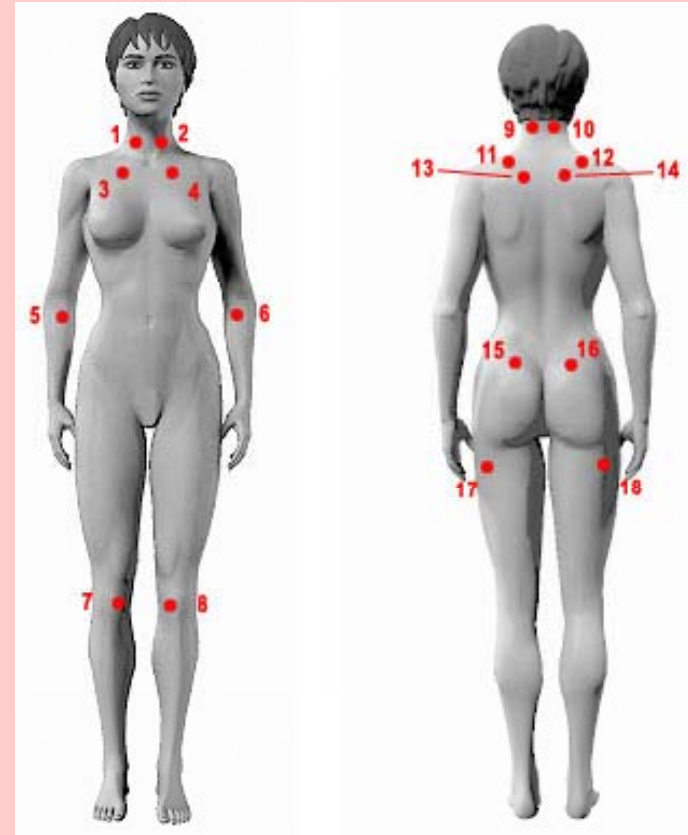
# Clinical Features

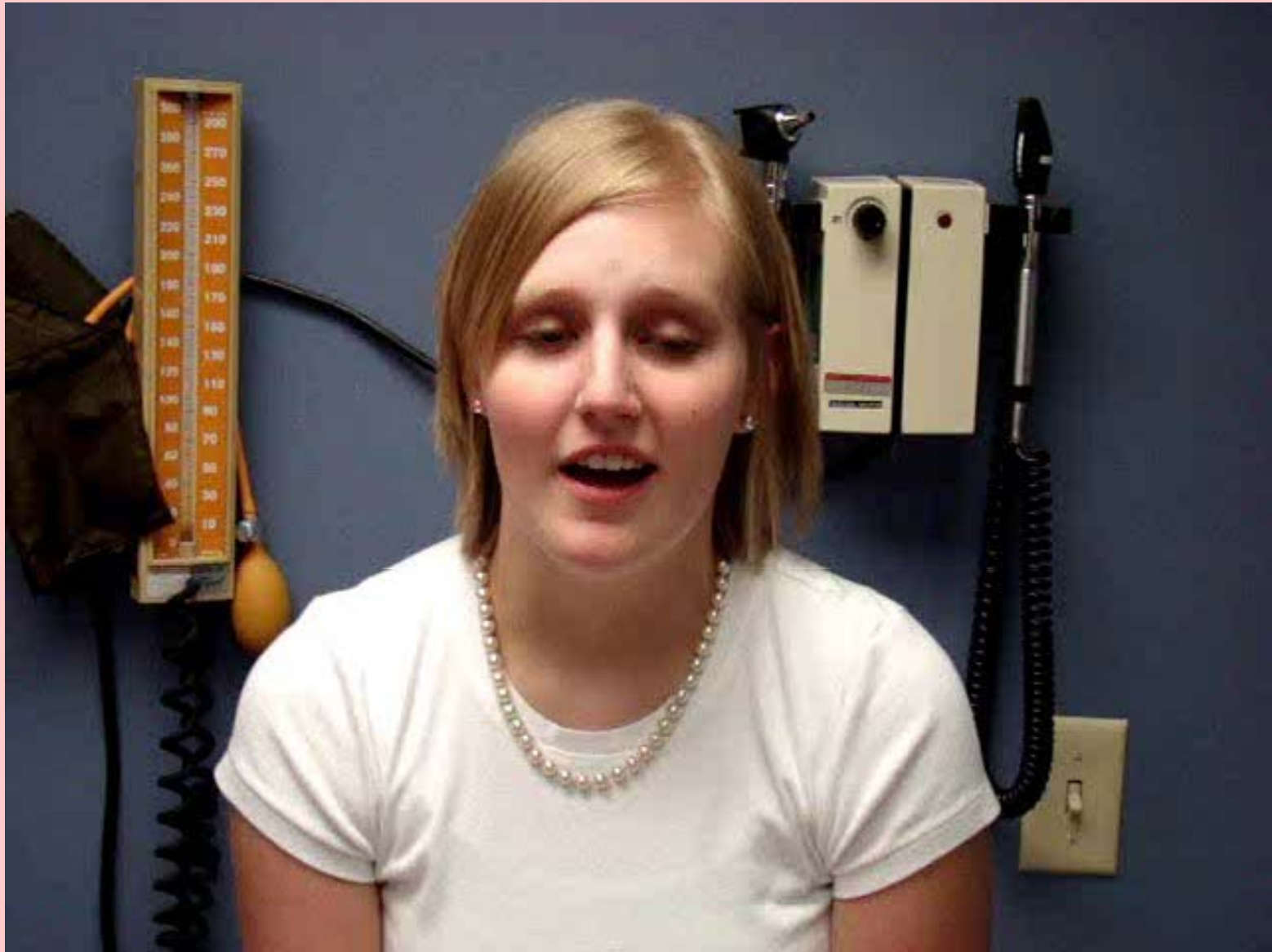
- Muscle and joint pain
- Fatigue (persistent “flu”)
- Sleep disturbance
- Cognitive dysfunction (“fibro-fog”)
  
- Tender Points



# Diagnosis: Tender Points

- American College of Rheumatology
  - 11 of 18 tender points
  - Many patients have less than 11 (or more than 18 at other locations on the body)





# Epidemiology of Fibromyalgia

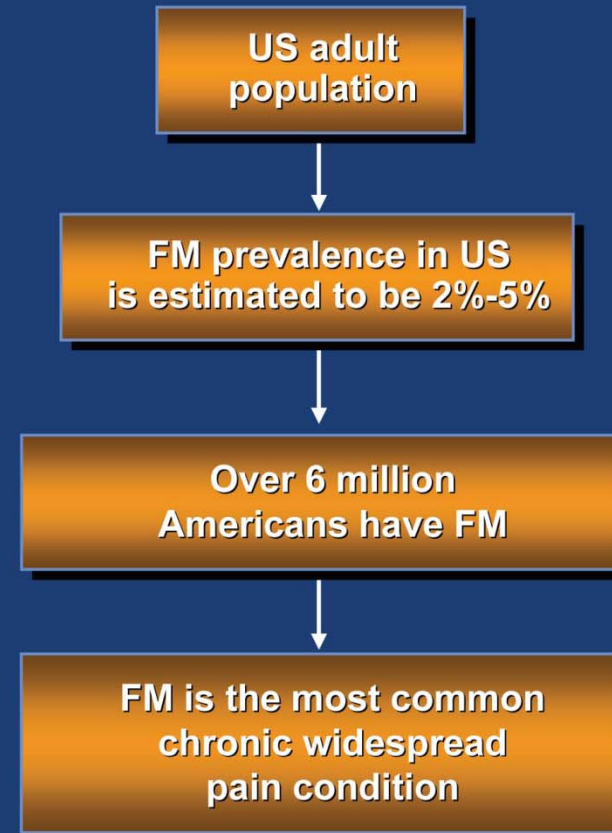
- Prevalence

- FM is common worldwide and affects 2%-5% of US adult population
- Majority of patients between the ages of 35 and 60 years

- Gender differences

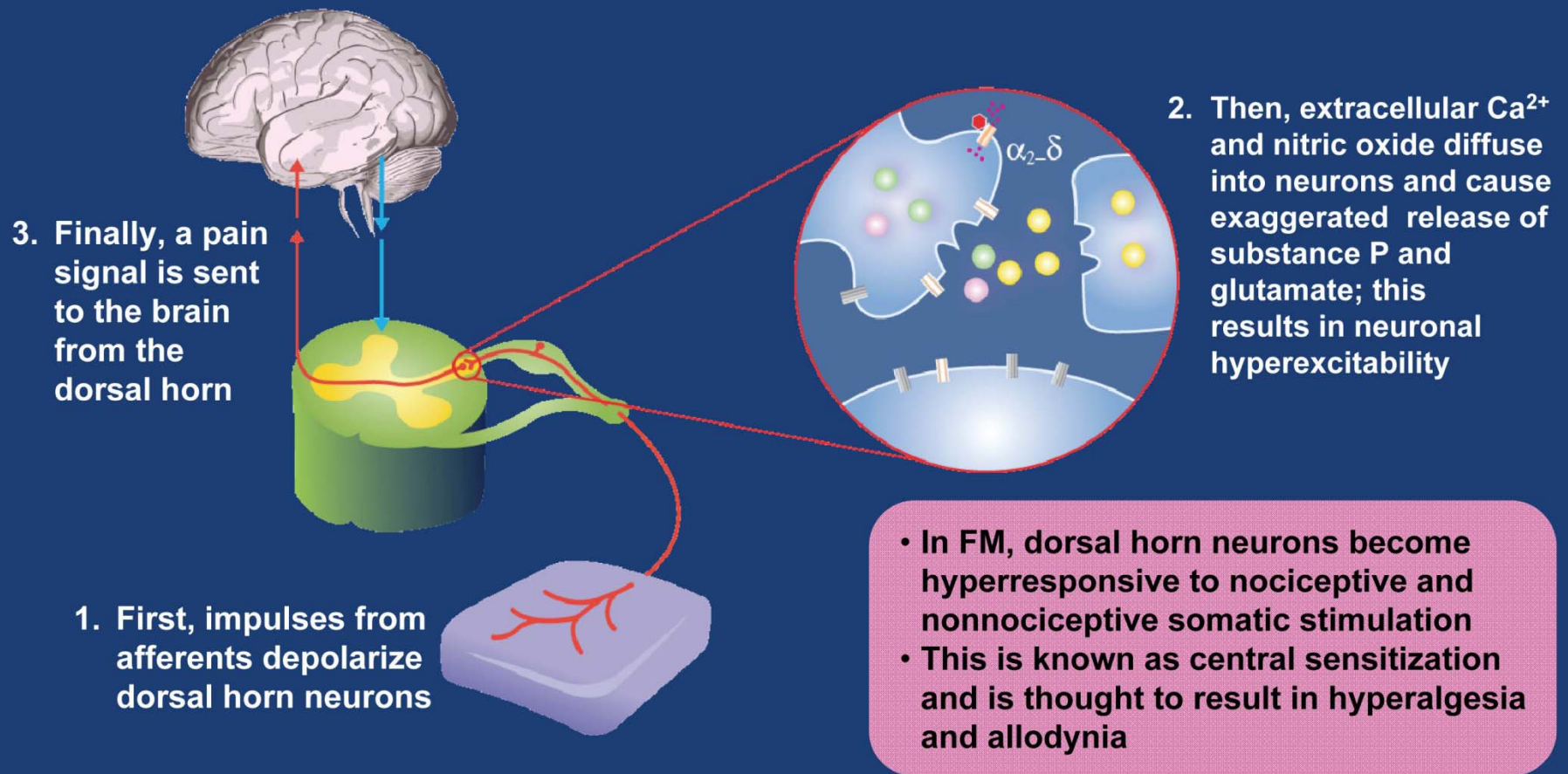
- Women are more likely to be diagnosed with FM than men

## Determining FM Prevalence





# Pathophysiology of Fibromyalgia: The Role of Central Sensitization



*Despite extensive research, the pathogenesis of pain in FM is not clearly understood. However, central sensitization has emerged as a leading theory of disease mechanism.*

# Exclusions/Co-Conditions

- Systemic lupus erythematosus, rheumatoid arthritis, hypothyroidism, ankylosing spondylitis/ seronegative spondyloarthropathy
- Recommend: CBC, ESR, muscle enzymes, LFTs, TFTs, ANA, anti-DNA

# Associated Conditions

- Nonrestorative sleep
  - Alpha intrusion in NREM Stage 4
- Irritable Bowel Syndrome
- Cognitive Dysfunction
  - SPECT caudate, thalamic CBF/memory
- Headache, TMJ pain
- Neurally mediated hypotension, RLS
- Chronic Fatigue

# Central Sensitivity Syndromes

- Irritable Bowel
- Overactive Bladder
- Low Back Pain, TMJ Disorder
- Migraine and Chronic Tension Headaches
  
- Comorbid: mood disturbance
- Associated: Chronic Fatigue, Sleep Disturbance, “Fibro-Fog,” Endocrine Dysfunction

# Central Sensitization

- Nociception *plus*
  - Modulation in the CNS
  - Emotional and affective components
  - Temporal summation (“wind up”)
    - Second pain (C fibers stim > q 3 sec); inh by NMDA rec antagonists
- Pain amplification syndromes
  - Heightened sensitivity to non-painful stimuli as well: touch, heat, cold, light, sound, smell
  - HPA, high levels of sub P/ EAAs in CSF

# Central Sensitization

- Excitability of spinal cord neurons after injury
  - Dorsal Horn neurons transmit nociceptive input to the brain
- Enlargement of receptive fields of sc neurons
- Reduction in pain threshold
- Recruitment of novel afferent inputs
  - A-beta fibers normally have no role in pain
- Pain generation by low threshold mechanoreceptors normally silent in pain processing

# Peripheral Sensitization

## Muscle as Source of Nociceptive Input

- Increased levels of substance P in muscle tissue
- NMR Spectroscopy: lower phosphorylation potentials in quadriceps
- DNA fragmentation of muscle fibers
- Increased IL-1 in cutaneous tissues
- Muscle perfusion deficits
  
- Peripheral tissue nociceptive activity need not be extensive: central sensitization requires little sustained input to maintain a chronic pain state

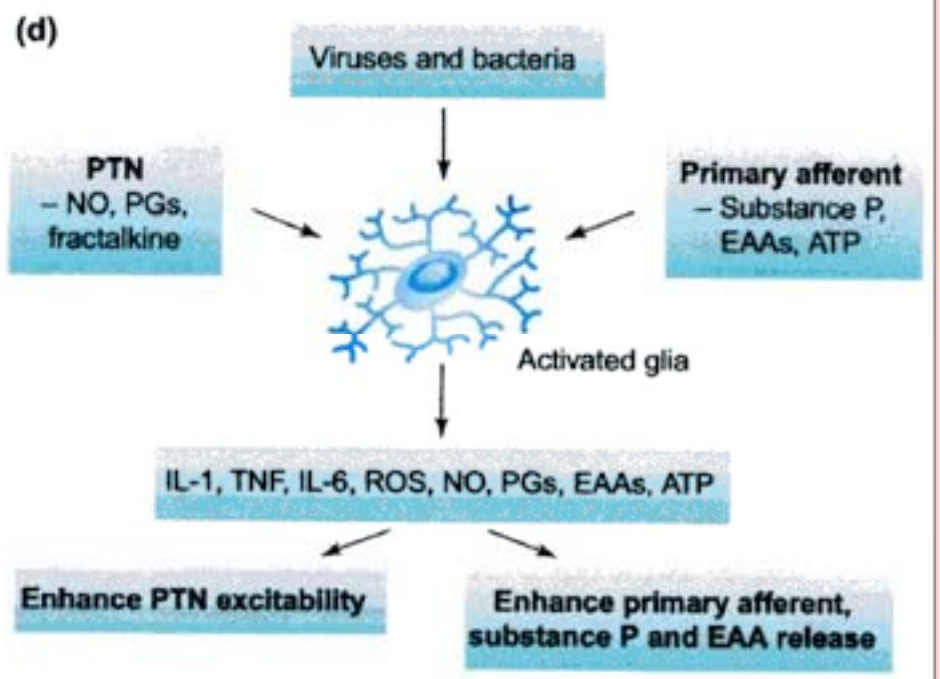
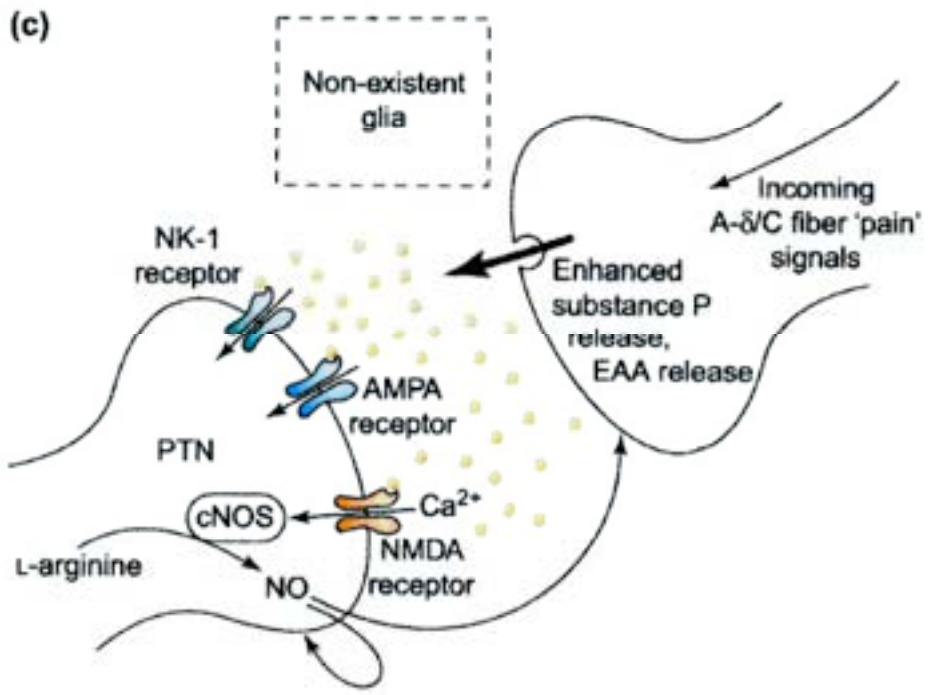
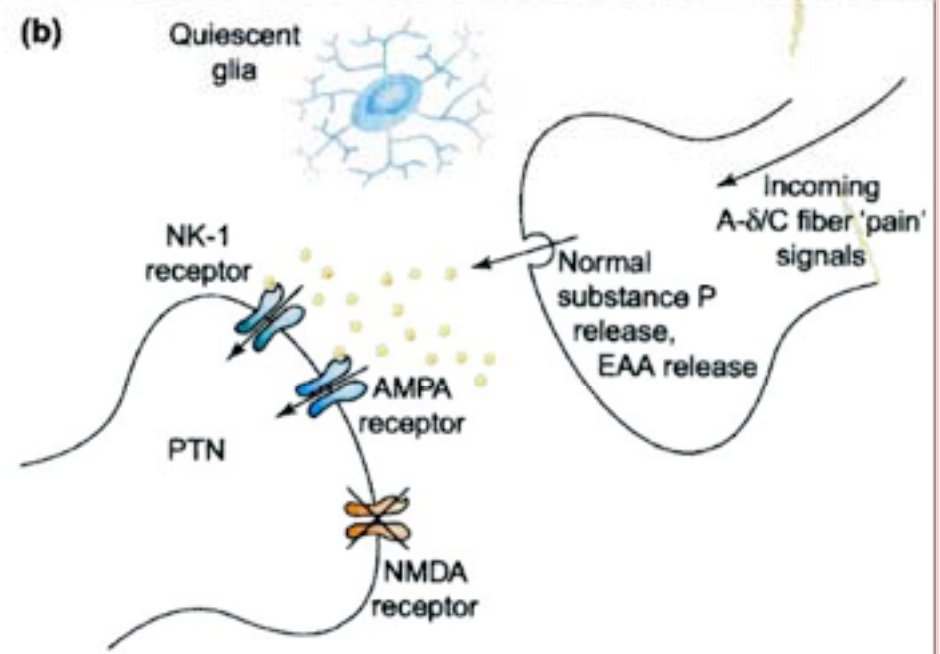
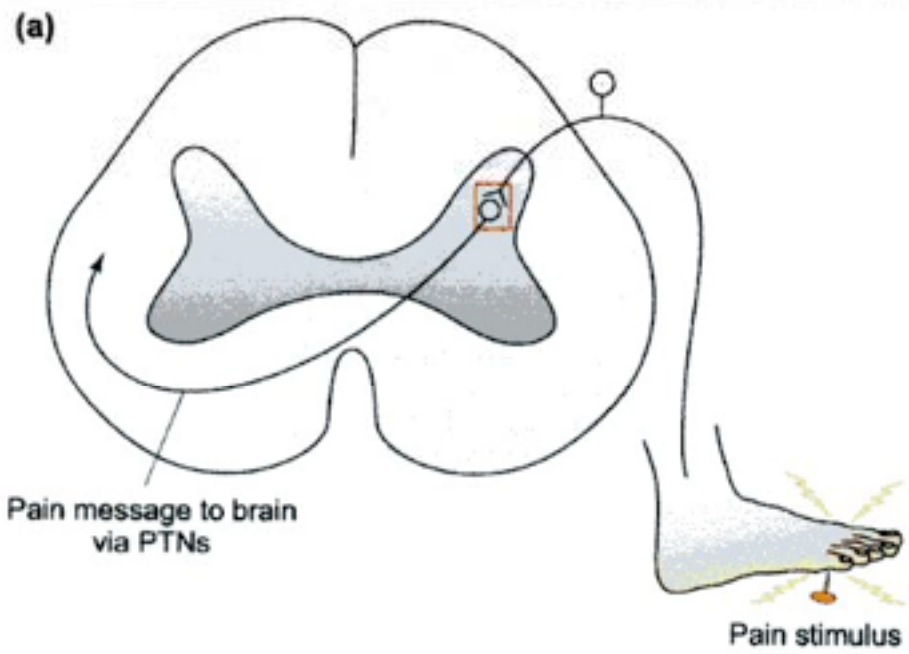
# CNS in Fibromyalgia

- CNS
  - Hyperexcitable spinal cord neurons w/ ascending projections to higher centers
  - Descending system, facilitatory as well as inhibitory “bottom up” and “top down” regulation
    - Mediators: 5HT and NE
  - Abnormal pain processing produces a self-sustained pain state in the absence of peripheral disease



# CNS Mechanisms

- Voltage gated calcium channels in plasma membrane of all excitable cells
  - Release of neurotransmitters and neuropeptides
  - Five families of Ca Channels
    - Alpha2-delta subunit as treatment target (gabapentin and pregabalin)/upregulation of this subunit causes path pain in animals
    - Gabapentin abolishes brainstem activation in hyperalgesia

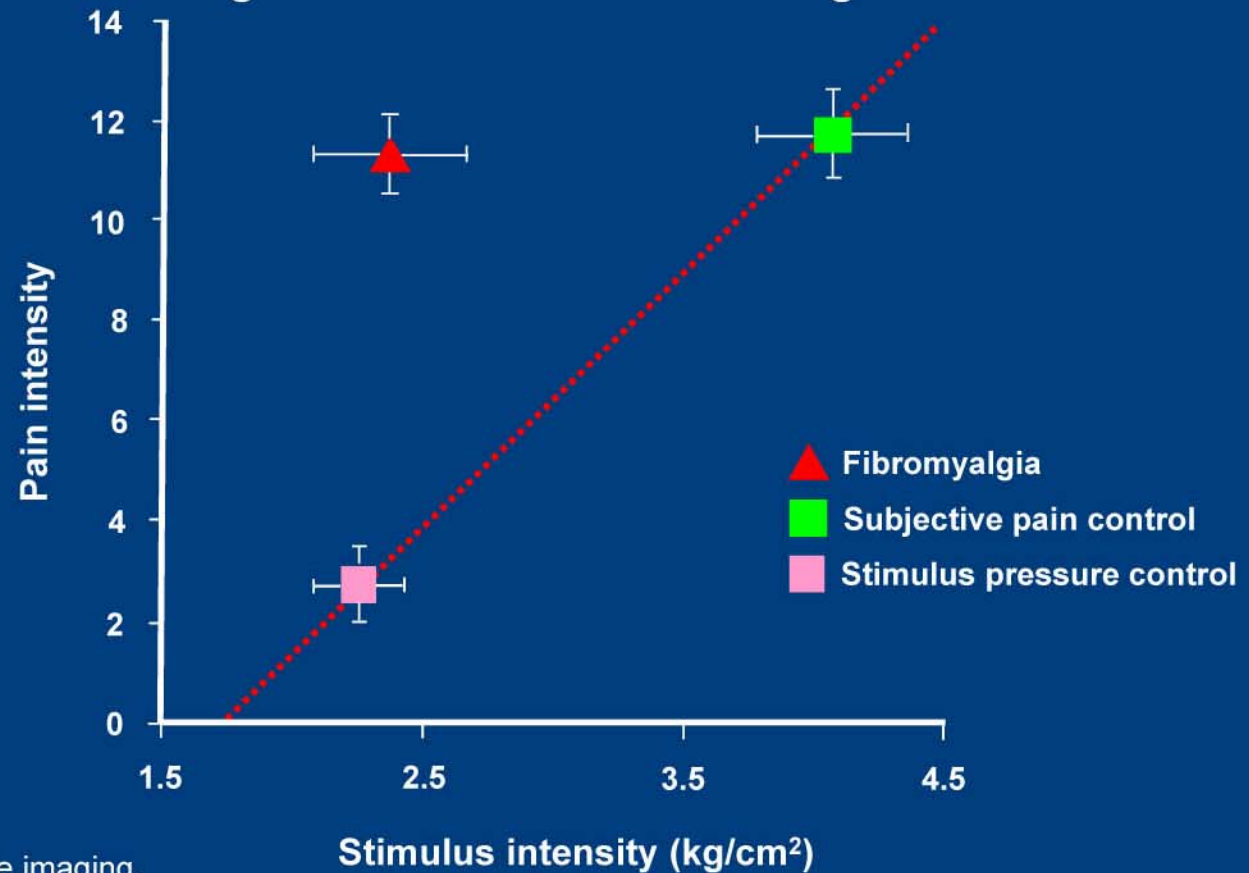
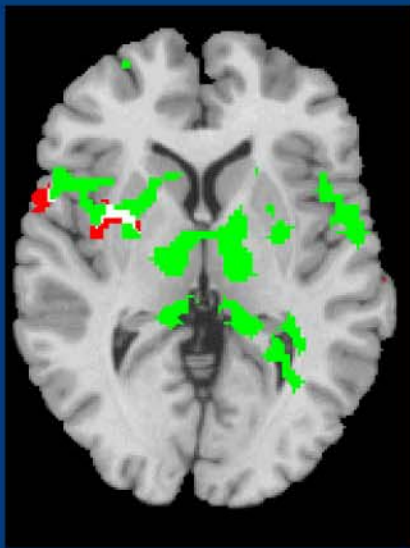


# Glia

- Express receptors for neurotransmitters and neuromodulators (incl subP)
- Synthesize and release transmitters
- Dorsal horn astrocytes and microglia are activated by inflammation, bacteria, spinal nerve transection, spinal cord trauma, and chronic (not acute) morphine Rx / morphology changes
- Activated glia release proinflammatory cytokines (IL-1,6 and TNF)- like immune cells

# Fibromyalgia May Be a Central Pain Processing Disorder: fMRI Evidence

fMRI Studies Show Cortical/Subcortical Augmentation of Pain Processing in FM



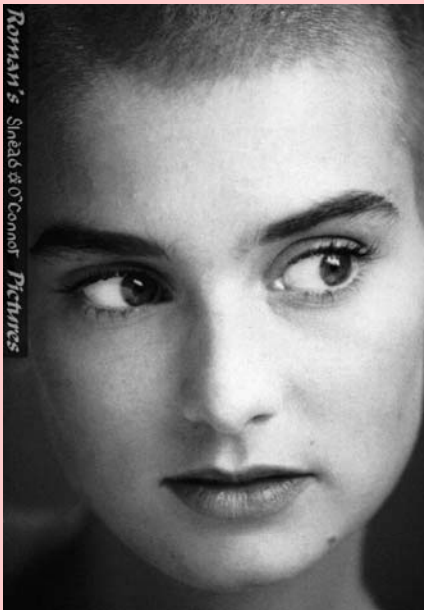
fMRI = functional magnetic resonance imaging.  
Gracely et al. *Arthritis Rheum.* 2002;46:1333-1343.

# Precipitants of FM

- One severe exposure or several repeated exposures: *physical/emotional trauma*
  - War
  - Torture
  - Childhood abuse
  - Rape
  - Natural disasters
  - Terrorist attacks
- Nothing

# PAIN: Acute vs Chronic

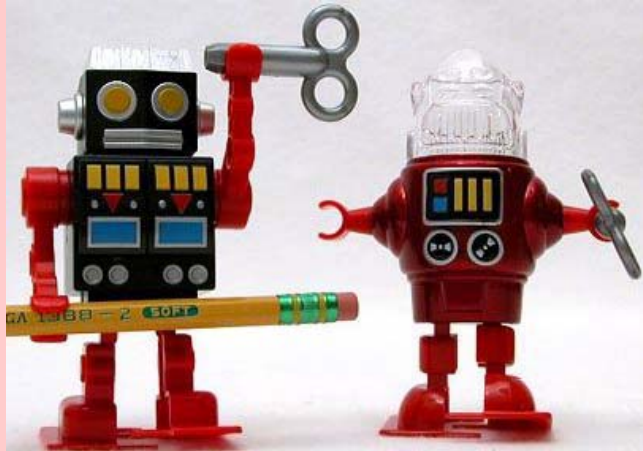
**Most fibromyalgia patients look normal**



- **Acute pain manifestations are absent**
- **Tachycardia, diaphoresis, grimace, elevated BP**
- **A single simple painful stimulus (such as a needle prick) does not produce a stereotypic response**

# Which are Correct in Fibromyalgia?

- a) Inhibitory pathways are inhibited
- b) Excitatory pathways are super-excited
- c) Excitatory neurotransmitters are elevated in CSF
  - a) Substance P
  - b) Glutamate
  - c) Biogenic amines

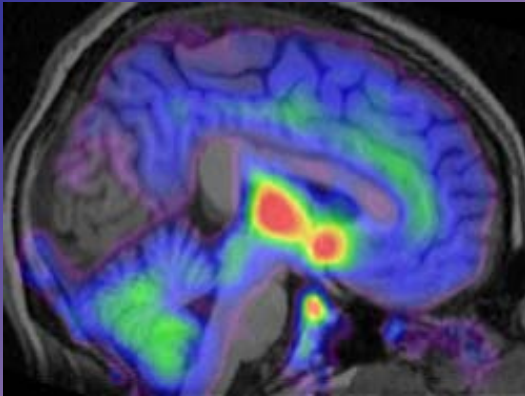


# “Wind-Up”

Mendell and Wall, 1965

- Stimulation of peripheral nerves repetitively led to a progressive build-up of amplitude of the electrical response in the corresponding dorsal horn neurons of the spinal cord.
- Wind-Up leads to increased pain susceptibility called “Central Sensitization”





## PAIN: Mechanisms

- Activation of peripheral nociceptors leads to release of neurotransmitters in the spinal cord
- Substance P and Calcitonin Gene Related Peptide (CGRP) are increased in CSF of patients with fibromyalgia



# Pain in Fibromyalgia

- “Fibromyalgia” means “pain of muscles and other fibrous tissue”
  - “algia” = pain
  - “fibro” = fibrous, connective tissue
  - “myo” = muscle



# Pain in Fibromyalgia

- Description
  - Burning, gnawing, throbbing, stabbing, aching
- Location
  - Neck, shoulders, chest, rib cage, lower back and thighs
- Severity
  - Worse with relaxation and early morning (with stiffness); less noticeable with activity

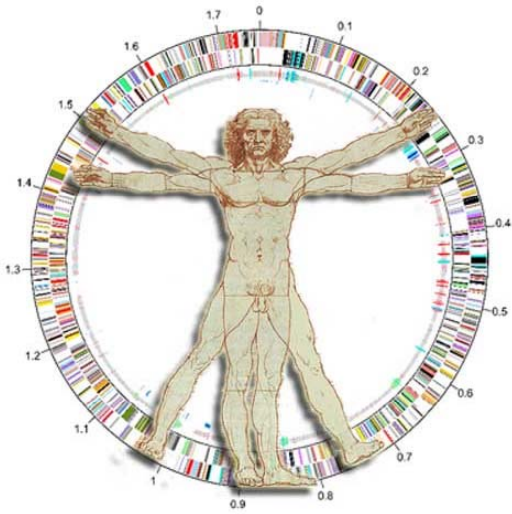
# Clinical Features and Diagnosis of Fibromyalgia: Overview

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- Clinically, FM presents with chronic widespread pain in addition to a wide range of symptoms, including tenderness, sleep disturbances, fatigue, and morning stiffness
- Patients with FM are more likely to have comorbidities such as painful neuropathies and circulatory disorders
- ACR and Canadian criteria may be used to diagnose FM
- Symptoms may overlap with other conditions (IBS, MDD, CFS, SLE, RA, OA, Lyme disease); differentiation is essential for optimal management

ACR = American College of Rheumatology; IBS = irritable bowel syndrome; MDD = major depressive disorder; CFS = chronic fatigue syndrome; SLE = systemic lupus erythematosus.

Wolfe et al. *Arthritis Rheum.* 1995;38:19-28; Wolfe et al. *Arthritis Rheum.* 1990;33:160-172; Berger et al. *Int J Clin Pract.* In press; Jain et al. *J Musculoskelet Pain.* 2003;11(4):3-107; Burckhardt et al. APS Clinical Practice Guideline Series, No.4.



# Causes of Fibromyalgia

- Genetics
  - Polymorphism in COMT gene
- Trauma: physical or emotional
- Infection
  - Hepatitis C, Lyme, EBV, parvovirus



# Management of Fibromyalgia (FM)

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## Nonpharmacologic

- Aerobic exercise
- Cognitive behavioral therapy
- Patient education
- Strength training
- Acupuncture
- Biofeedback
- Balneotherapy
- Hypnotherapy

## Pharmacologic

- Antidepressants
- Analgesics
- Anticonvulsants

***Until now there were no FDA-approved therapies for FM***

# Pharmacologic Treatments

- SNRIs
  - Duloxetine 60 mg bid
  - Milnacipran (recently FDA-approved)
- Atypical Opioids
  - 37.5 tramadol/325 acetaminophen
- TCAs
- Alpha2-delta ligand pregabalin and gabapentin
  - Crofford et al. Arthritis Rheum. 2006; A six month, double-blind, placebo-controlled, durability study of pregabalin for pain associated with fibromyalgia.
  - Arnold et al. Arthritis Rheum. 2007; Gabapentin in the treatment of fibromyalgia



# FDA-Approved

- Lyrica
- Cymbalta
- Savella

# Analgesics\*: Published Trials

Study	Agent	N	Study Duration (weeks)	Primary End Point	Significant Improvement with Tramadol
Bennett et al (2005)	Tramadol/acetaminophen vs PBO	313	13	SF-36, FIQ	Yes
Bennett et al (2003)	Tramadol/acetaminophen vs PBO	315	13	Time to discontinuation	Yes
Kemple et al (2003)	Opioid <sup>†</sup>	38	200	Improvement in pain	No
Russell et al (2000)	Tramadol vs PBO	100	9	Time to discontinuation	Yes
Biasi et al <sup>‡</sup> (1998)	Tramadol vs PBO	12	1	VAS	Yes
Sorensen et al (1995)	Morphine (IV) vs PBO	9	1	Reduction in pain intensity	No

**\*No analgesic is currently FDA approved for FM.**

<sup>†</sup>Doses of morphine equivalent per 24 hour were determined; <sup>‡</sup>Single-dose cross-over trial with 1 week washout period.

SF-36 = short-form 36; IV = intravenous; VAS = visual analog score.

Bennett et al. *Arthritis Rheum.* 2005;53:519-527; Bennett et al. *Am J Med.* 2003;114:537-545; Kemple et al. *Arthritis Rheum.* 2003;48:S88; Russell et al. *J Clin Rheumatol.* 2000;6:250-257; Biasi et al. *Int J Clin Pharmacol Res.* 1998;18:13-19; Sorensen et al. *Scand J Rheumatol.* 1995;24:360-365.

# Tricyclic Antidepressants (TCAs)\*: Published Trials ≥8 Weeks Duration

Study	Agent	N	Duration (weeks)	Primary End Point	Significant Improvement
Carette et al (1986)	AMI vs PBO	70	9	Morning stiffness, pain analog score	No
Carette et al (1994)	AMI vs CBP vs PBO	208	24	VAS (pain, sleep, stiffness, fatigue)	No
Ginsberg et al (1996)	AMI vs PBO	46	8	Pain VAS, TP score	Yes
Hannonen et al (1998)	AMI vs Moclobemide vs PBO	130	12	VAS (pain, sleep, fatigue) NHP, Sheehan disability	Yes
Heyman et al (2001)	AMI vs Nortriptyline vs PBO	118	8	NTP, FIQ, VSIG	No
Caruso et al (1987)	AMI vs Nortriptyline	60	8	Manual TP count	Yes
Bennett et al (1988)	CBP vs PBO	120	12	CGIC	Yes

**\*No TCAs are currently FDA approved for FM.**

AMI = amitriptyline; VAS = visual analog score; PBO = placebo; CBP = cyclobenzaprine; TP = tender points; NHP = Nottingham Health Profile; NTP = number of tender points; FIQ = Fibromyalgia Impact Questionnaire; VSIG = verbal scale global improvement; CGIC = clinician global impression of change; FDA = United States Food and Drug Administration.

Carette et al. *Arthritis Rheum.* 1986;29:655-659; Carette et al. *Arthritis Rheum.* 1994;37:32-40; Ginsberg et al. *J Musculoskelet Pain.* 1996;4(3):37-47; Hannonen et al. *Br J Rheumatol.* 1998;37:1279-1286; Heymann et al. *Clin Exp Rheumatol.* 2001;19:697-702; Caruso et al. *J Int Med Res.* 1987;15:154-159; Bennett et al. *Arthritis Rheum.* 1988;31:1535-1542; Arnold LM. In: Wallace & Clauw's *Fibromyalgia and Other Central Pain Syndromes.*

## Anticonvulsants\*: Published Trials†

Study	Agent	N	Study Duration (weeks)	Primary End Point	Significant Improvement
Arnold et al (2007)	Pregabalin vs PBO	750	14	End point mean pain score	Yes
Crofford et al‡ (2007)	Pregabalin vs PBO	1051	32	Time to loss of therapeutic response	Yes
Crofford et al (2005)	Pregabalin vs PBO	529	8	End point mean pain score	Yes
Arnold et al (2007)	Gabapentin vs PBO	150	12	BPI average pain severity score	Yes

\*Gabapentin is currently not FDA approved for FM.

†Published either in peer-reviewed journals or studies included in the Lyrica® package insert.

Includes open-label phase of trial.

Arnold et al. *APS*, 2007; Crofford et al. *APS*, 2007; Crofford et al. *Arthritis Rheum.* 2005;52:1264-1273; Arnold et al. *Arthritis Rheum.* 2007;56:1336-1344.

# Nonpharmacologic Therapies\*

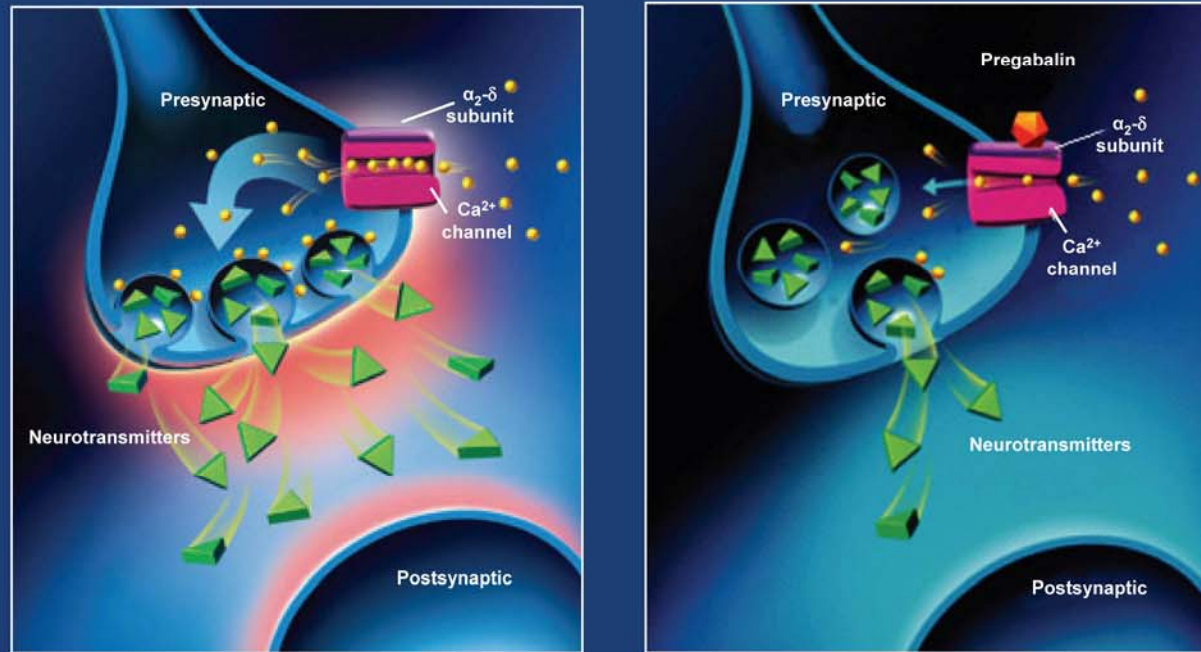
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- Patient education
  - Intensive patient education in FM has been shown to improve pain, sleep, fatigue, and quality of life in patients with FM
- Aerobic exercise
  - Exercise may increase aerobic performance and tender point pain pressure threshold, and improve pain
- Cognitive behavioral therapy (CBT)
  - Some evidence of improvements in pain, fatigue, mood, and physical function

**\*Only nonpharmacologic therapies with strong evidence are noted.**

Williams et al. *J Rheumatol*. 2002;29:1280-1286; Karper et al. *Rehabil Nurs*. 2006;31:193-198; Busch et al. *Cochrane Database Syst Rev*. 2002;CD003786; Goldenberg et al. *JAMA*. 2004;292:2388-2395.

# Pregabalin Binds to the $\alpha_2$ - $\delta$ Subunit of Voltage-Gated $\text{Ca}^{2+}$ Channels in the Central Nervous System

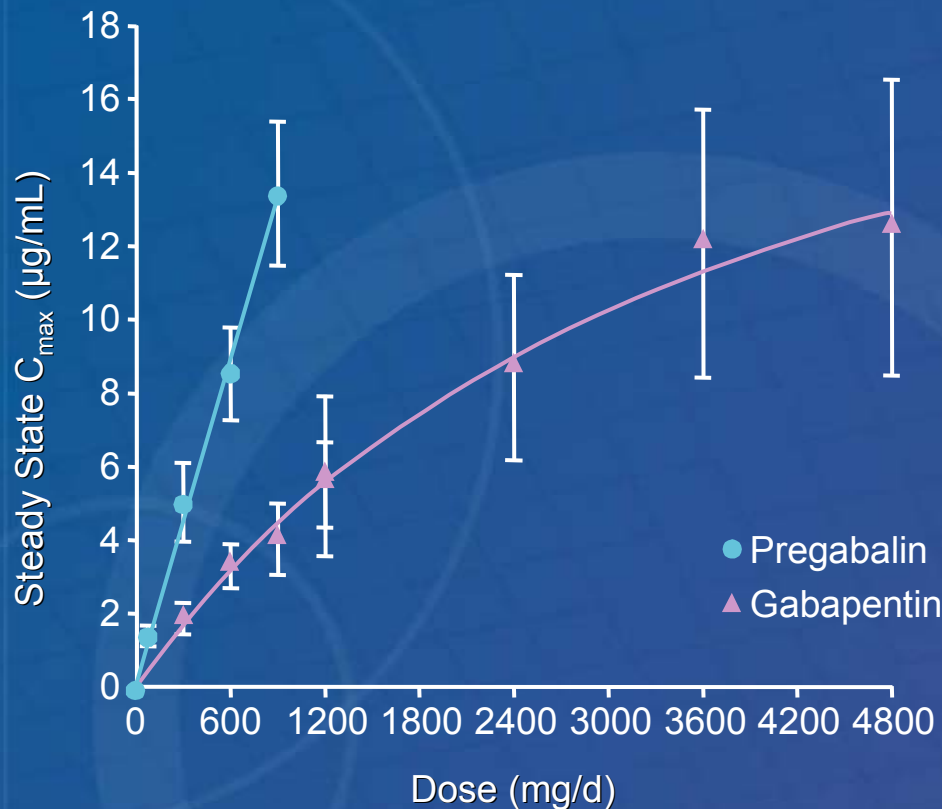


Schematic representation of pregabalin's proposed mechanism of action

- Pregabalin selectively binds to  $\alpha_2$ - $\delta$  subunit of voltage-gated calcium channels
  - Modulates calcium influx in hyperexcited neurons
  - Reduces neurotransmitter release (glutamate, substance P, norepinephrine)
  - Pharmacologic effect requires binding at this site in animal models
  - The clinical significance of these observations in humans is currently unknown

# Pregabalin: Predictable Response Versus Gabapentin

## Linear PK Profile



## High Bioavailability

### Pregabalin

### Gabapentin

All doses  
≥90%

900 mg, 60%

1200 mg, 47%

2400 mg, 34%

3600 mg, 33%

1800 mg  
Recommended  
dose

Lyrica® (pregabalin) Capsules CV [package insert]. New York, NY: Pfizer Inc; 2005; Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc; 2004; Wesche, Bockbrader. Presented at: 24th Annual Scientific Meeting of the American Pain Society; 2005.

# Additional Therapies

- Tricyclic antidepressants, SNRIs and NMDA receptor blockade are beneficial; SSRIs only minimally so
  - NE primarily inhibitory
  - 5HT both inhibitory and facilitative
- Weak opioid agonists reduce reuptake of 5HT and NE
- Heated pool therapy, aerobic exercise, CBT — *2006 European League Against Rheumatism (EULAR)*



# Treatment

- Topical Creams and Patches
  - Zostrix (capsaicin)
    - Reduces levels of Substance P
  - Lidoderm transdermal patch
- Narcotics
- Synthetic Opioids
- Nerve Blocks
- TENS/ Trigger Point Injections

# Lifestyle Management of the Chronic Pain of Fibromyalgia

- **Stress Management**
  - Thermal biofeedback
  - Sequential relaxation
  - Yoga and Tai Chi
- Acupuncture and Acupressure
- Massotherapy, Craniosacral Therapy
- **Cognitive-Behavioral Therapy**