Fibromyalgia:
Current Concepts 2017

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Fibromyalgia: Broadly Defined

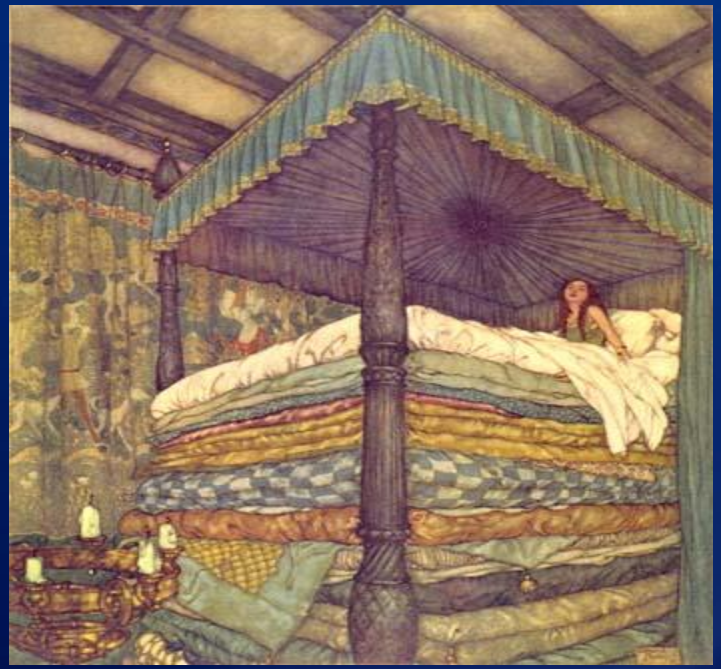
- A common and complex condition of widespread musculoskeletal pain accompanied by nonrestorative sleep, fatigue, psychological dysfunction, and regions of localized tenderness
- More recent insights have suggested that fibromyalgia is a syndrome caused by disordered sensory processing by the nervous system

Wolfe, et al. *Arthritis Rheum* 1990;33:160–72; Smith HS. *Pain Physician* 2011; 14:E217-E245

In the morning they asked her how she slept.

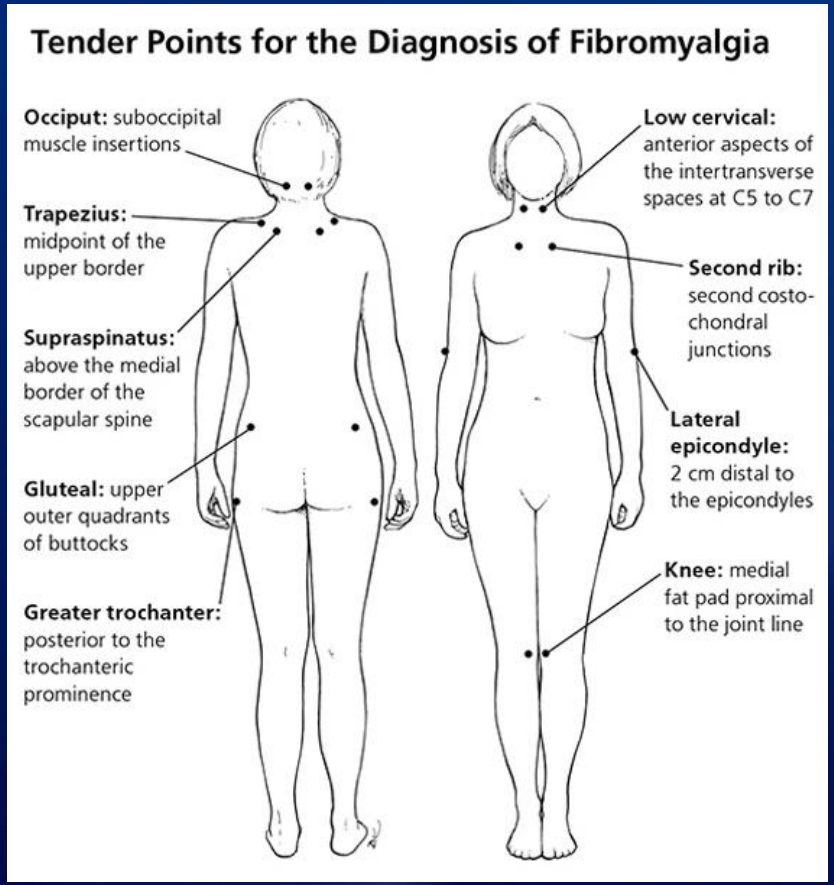
“Oh terribly bad!” said the princess. “I have hardly closed my eyes the whole night! … and my whole body is black and blue this morning. It is terrible!”

- Hans Christian Andersen, 1835



Diagnostic Considerations

- Using ACR criteria, the prevalence of fibromyalgia in most studies from industrialized nations ranges from 0.5 to 4%
- Chronic widespread pain (CWP) diagnosed in the absence of tender points has a 10-11% prevalence in industrialized nations
- FMS may be diagnosed without requisite numbers of tender points; they do not capture the complexity of FMS
- Tender points may add specificity to diagnosis, but diagnostic criteria are always improving



Symptoms are typical, even stereotypical

- **Pain and sensory**
  - Generalized symptoms, articular and non-articular
  - Aching, deep, sore, bruised, "lactic acid," "in the bones"
  - Hypersensitive to: light, sound, temperature, humidity, odors etc.
- **Fatigue**
  - Poor stamina
  - Poor recovery from efforts
- **Sleep disturbance**
  - Nonrestorative: waking up tired
  - Problems in both induction and maintenance phases of sleep
- **Cognitive**
  - Poor short-term memory
  - Poor focus/concentration
  - Word-finding problems
  - Forgotten facts/events/conversations
- **Affective**: depression, anxiety
- **Pain behaviors**

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Diagnostic Criteria: American College of Rheumatology (2016 Revision)

- A diagnosis of Fibromyalgia may be made if the patient exhibits the following:

(1) Generalized pain, defined as pain in at least 4 of 5 regions, is present

(2) Symptoms have been present at a similar level for at least 3 months

(3) Widespread pain index (WPI) > 7 and symptom severity scale (SSS) score > 5 OR WPI of 4–6 and SSS score > 9

(4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses

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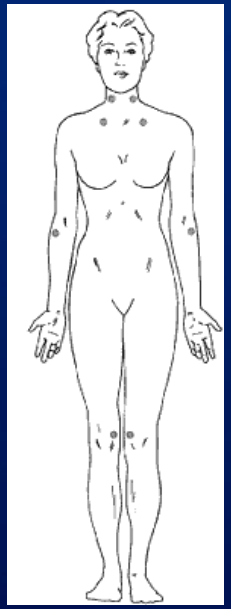
Wolfe F et al. *Seminars in Arthritis and Rheumatism* 2016; 46:319–329

Widespread Pain Index (WPI) is scored 0-19 in five regions

It accounts for pain in the last week

Right upper region (Region 2)
Jaw, right[a]
Shoulder girdle, right
Upper arm, right
Lower arm, right

Right lower region (Region 4)
Hip (buttock, trochanter), right
Upper leg, right
Lower leg, right



Left upper region (Region 1)
Jaw, left[a]
Shoulder girdle, left
Upper arm, left
Lower arm, left

Left lower region (region 3)
Hip (buttock, trochanter), left
Upper leg, left
Lower leg, left

Axial region (Region 5)
Neck
Upper back
Lower back
Chest[a]
Abdomen[a]

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Symptom Severity Scale (SSS) Score

Consider the following over the past week:

- **Fatigue**
- **Waking unrefreshed**
- **Cognitive symptoms**

Score each:
0 = No problem
1 = Slight or mild problems, mild or intermittent
2 = Moderate, considerable problems
3 = Severe: pervasive, continuous, life-disturbing

Add in (previous 6 months):
(1) Headaches (0–1)
(2) Pain or cramps in lower abdomen (0–1)
(3) Depression (0–1)

The final symptom severity score is between 0 and 12

Widespread pain index (WPI) > 7 and symptom severity scale (SSS) score > 5
OR WPI of 4–6 and SSS score > 9

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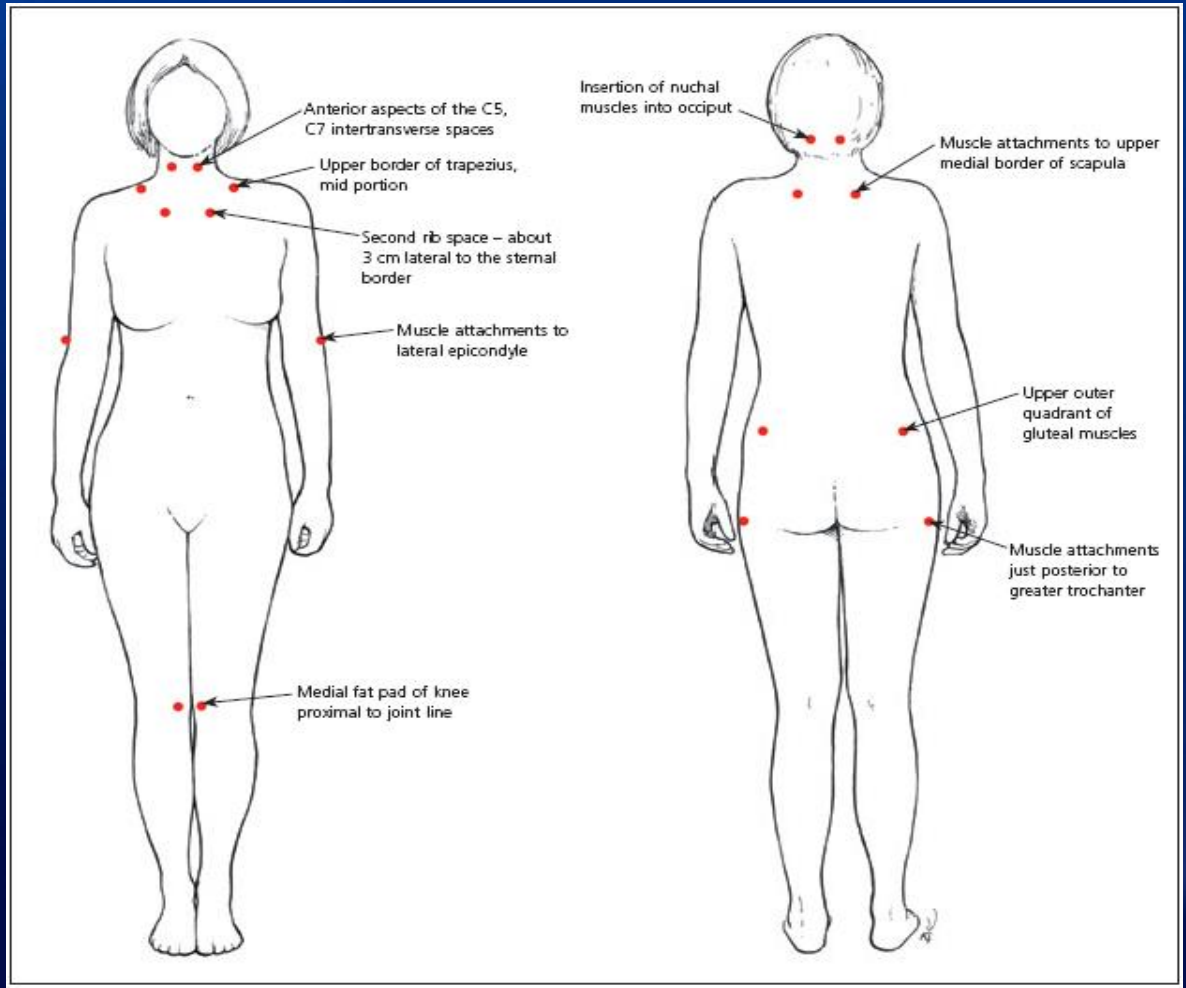
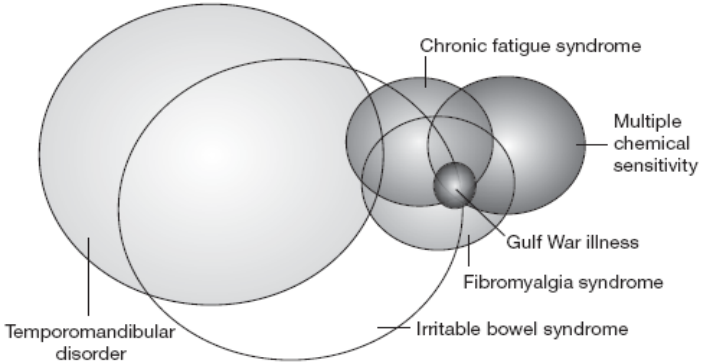

Anterior aspects of the C5, C7 intertransverse spaces
Upper border of trapezius, mid portion
Second rib space – about 3 cm lateral to the sternal border
Muscle attachments to lateral epicondyle
Medial fat pad of knee proximal to joint line
Insertion of nuchal muscles into occiput
Muscle attachments to upper medial border of scapula
Upper outer quadrant of gluteal muscles
Muscle attachments just posterior to greater trochanter

The Broader Context of Fibromyalgia



Primary diagnosis	Degree of overlap with secondary condition (%)[67,68]				
	FMS	CFS	IBS	TMD	MCS
FMS	NA	70	32–80	75	55
CFS	35–70	NA	58–92	20	41–67
IBS	32–65[a]	58–92[a]	NA	32-65[a]	ND
TMD	13–18	20	64	NA	ND
MCS	33–55	30	ND	ND	NA

Figure 1 Central pain syndromes that have symptoms overlapping with those of fibromyalgia syndrome. There is overlap of a number of prevalent systemic and regional chronic pain and abnormal sensory conditions that share common mechanisms and effective treatments.[16,65–68] Abbreviations: CFS, chronic fatigue syndrome; FMS, fibromyalgia syndrome; IBS, irritable bowel syndrome; MCS, multiple chemical sensitivity; NA, not applicable; ND, not determined; TMD, temporomandibular disorder. [a]Not numerically represented on diagram.

Dadabhoy D and Clauw D.
Nature Clin Prac Rheum 2006; 2(7):364.

Fibromyalgia and the Central Sensitization Syndromes

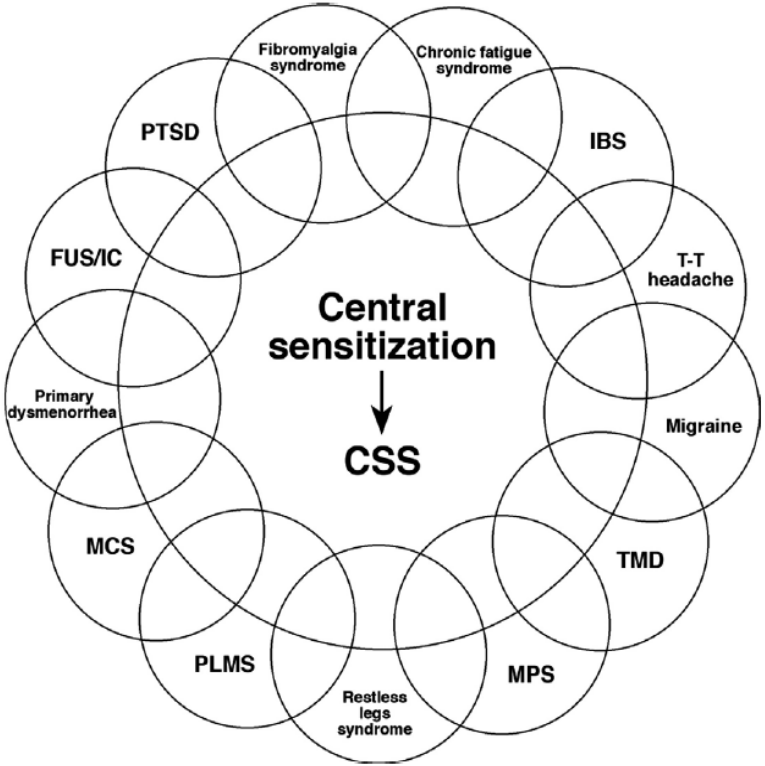


Figure 1 Currently proposed members of the CSS family with overlapping relationships and a common pathophysiological link of CS. IBS, irritable bowel syndrome; T-T headache, tension-type headache; TMD, temporomandibular disorders; MPS, myofascial pain syndrome; RSTPS, regional soft-tissue pain syndrome; PLMS, periodic limb movements in sleep; MCS, multiple chemical sensitivity; FUS, female urethral syndrome; IC, interstitial cystitis; PTSD, posttraumatic stress disorder. Depression may also be a member (see text). Modified from reference 198.

Yunus MB. *Semin Arthritis Rheum* 2007; 36:339-356

Changing Concepts

- Beginning in the 19th century: predominately muscular and connective tissue – "muscular rheumatism" (Virchow, 1852), "fibrositis" (Gowers, 1904), "nodular fibromyositis" (Kelly, 1945)
- Early 20th century: FMS as a psychological disorder - "psychogenic rheumatism" and "psychosomatic rheumatism"
- Late 20th century: evolution of specific criteria, centering on pain manifestations
- Early 21st century: neuroscience-based concepts, neuroendocrine models, genetic factors

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Recent Insights in Physiology

- Disordered pain and sensory processing: central sensitization, "myalgic encephalomyelopathy" (revival in 2015)
  - **Peripheral** neuronal dysfunction
  - **Spinal** sensitization
  - **Supraspinal** abnormalities
  - **Autonomic** dysfunction
- Neuroendocrine influences
- Genetic predisposition

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Sensory Processing in Fibromyalgia: More Facilitation, Less Inhibition

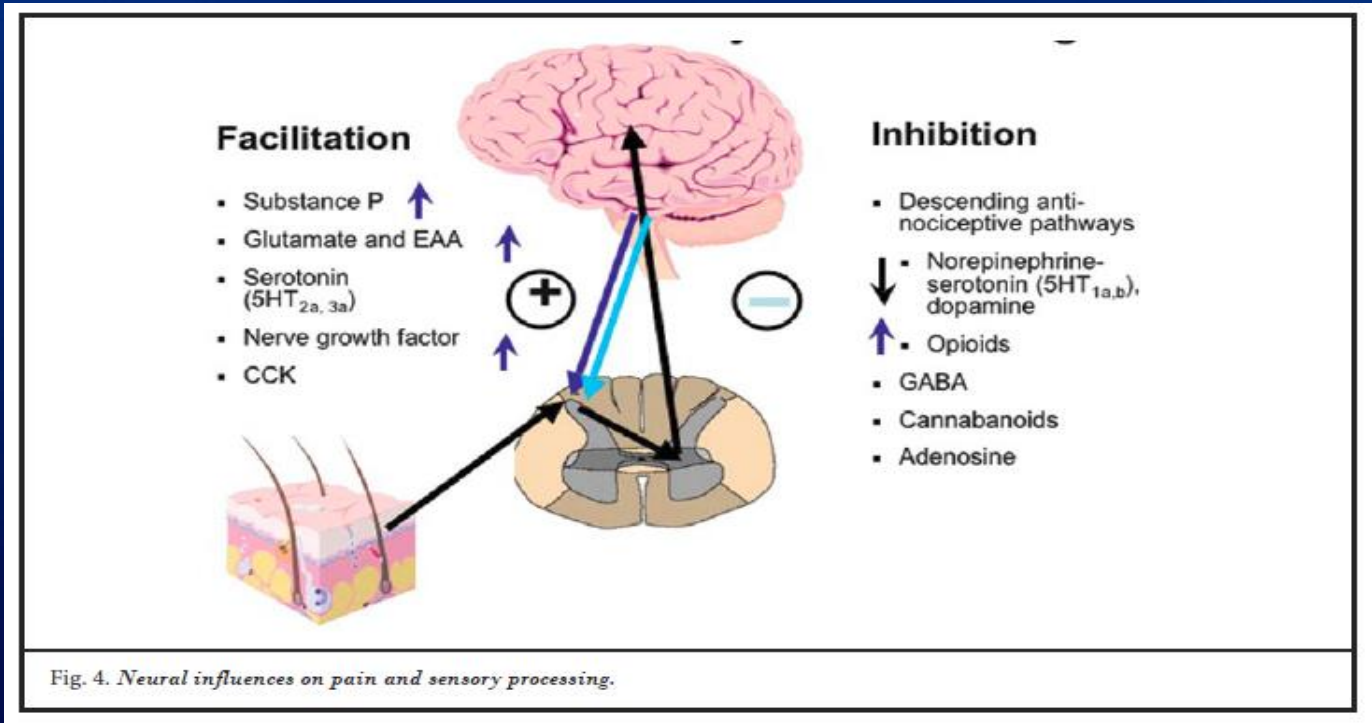

Fig. 4. *Neural influences on pain and sensory processing.*

Clauw D, et al. *Mayo Clinic Proc* 2011; 86(9): 907-911.

Where does fibromyalgia begin?

- **Chronic illnesses**
  - Inflammatory diseases including autoimmune connective tissue disorders (e.g. SLE, Sjogren's, rheumatoid arthritis)
  - Infections (Lyme, viral) – debated; recent XMRV "myth"
- **Trauma (surgical, motor vehicle accident)**
  - 7.8% incidence of widespread pain within 12 months of MVA (Wynne-Jones, 2006)
  - Risk factors: older age, post-collision physical symptoms, pre-collision health-seeking behavior, pre-collision somatization, perceived initial injury severity
- **A Teleologic explanation?** – survival advantage with hypersensitivity? (Voss, 2002)

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Peripheral Nerve Dysfunction

- Importance of acid-sensing ion channel 3 (ASIC3) in chronic pain induction
  - In ASIC3 knockout mice, secondary mechanical hyperalgesia does not develop (Benson, 2007)
  - Re-expression of ASIC3 in muscle tissue (but not skin) of ASIC3 knockout mice restores the development of hyperalgesia (Ikeuchi, 2008)
  - In parallel, central sensitization of dorsal horn neurons, measured as a bilateral spread of receptive fields and increased mechanical sensitivity, does not develop in ASIC3 knockout mice (Sluka, 2003)
- Calcium channel subunit α2-δ is abnormally upregulated
  - Binds small molecules that reduce pain (e.g. gabapentin, pregabalin)
  - Affects function of main α1 subunit of calcium channel

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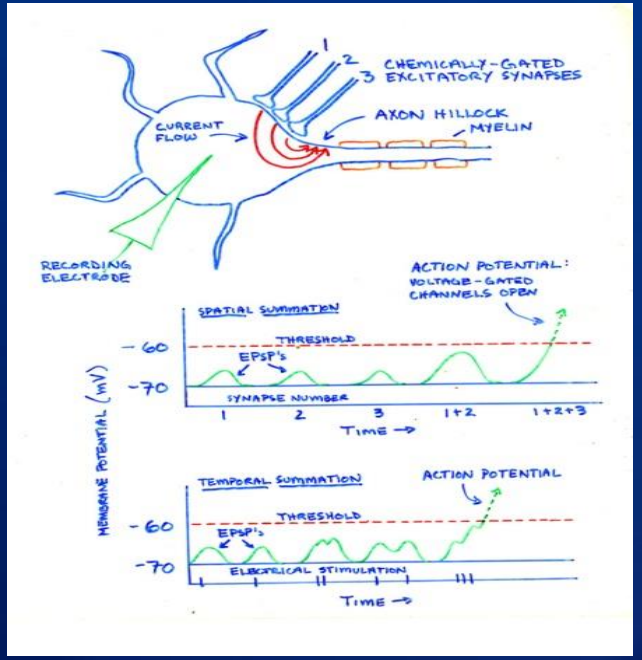
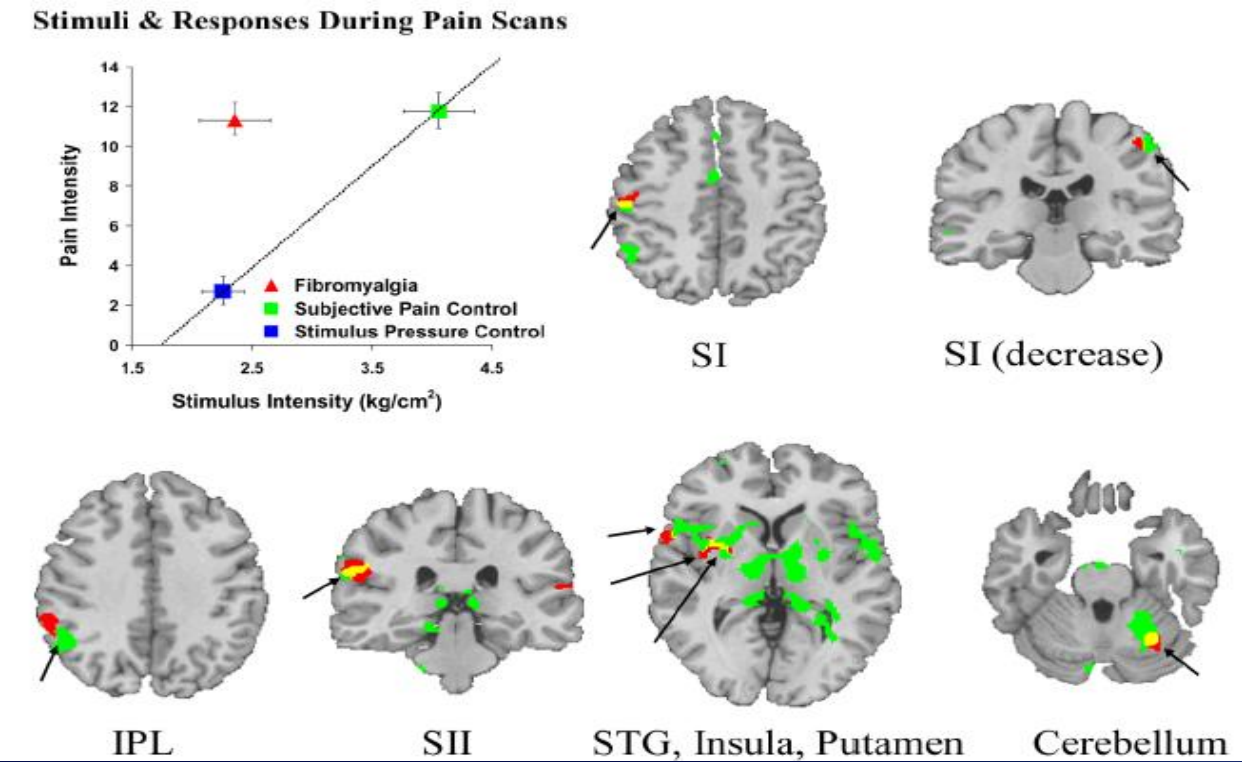
A Key Mechanism: Spinal Sensitization

- Amplification of second-order neuron sensory impulses in spinal cord
- Promoted by abnormal calcium channel activity
- Receptor to NMDA (N-methyl-D-aspartate) upregulated in spinal cord of experimental FMS
  - Normally inactive but is upregulated after repeated stimulation by glutamate and substance P
  - Generates wind-up (temporal summation) to amplify and perpetuate afferent nociceptive signals
  - Blocked by ketamine and dextromethorphan; latter has not shown clinical benefit in early trials
- Spinal activation of the cAMP pathway
  - produces mechanical hyperalgesia and increases the response of spinothalamic tract neurons to noxious but not innocuous mechanical stimuli



Functional MRI Demonstrates Abnormal Cortical Activation



Gracely RH et al. *Arthritis Rheum* 2002; 46(5): 1333-1343.

SPECT can localize and quantify areas of brain activation and inhibition in fibromyalgia

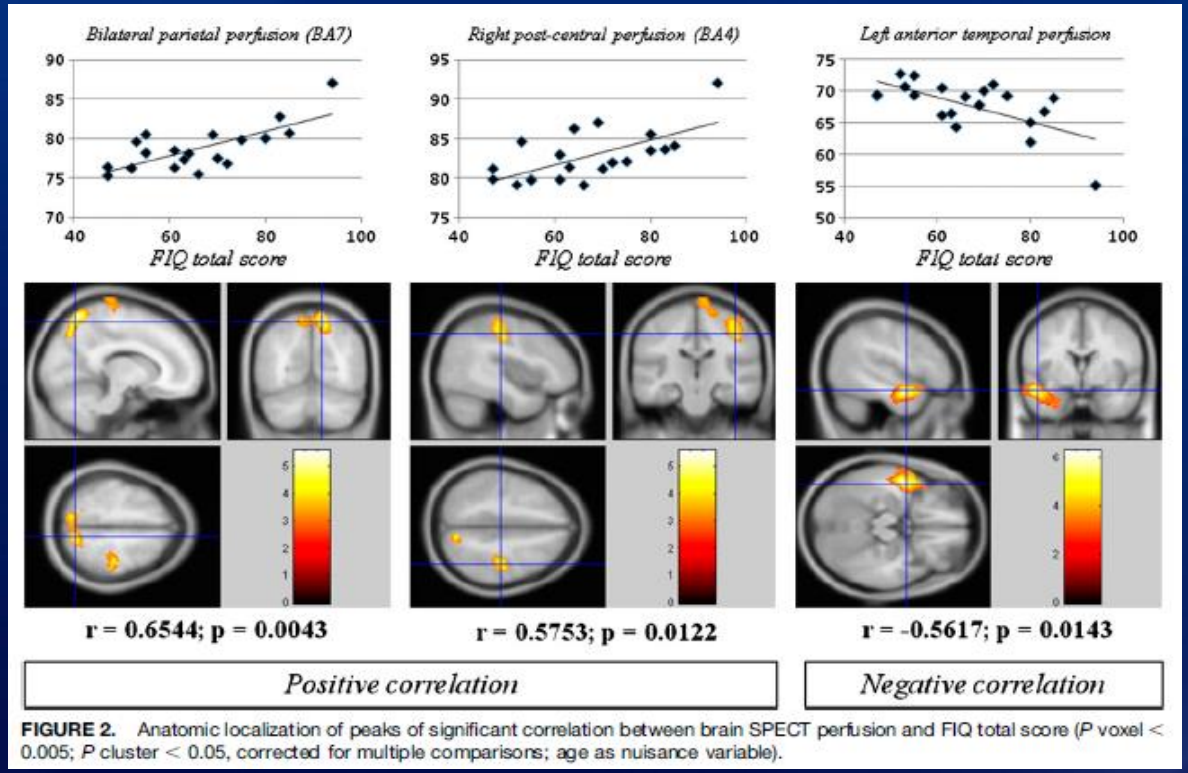
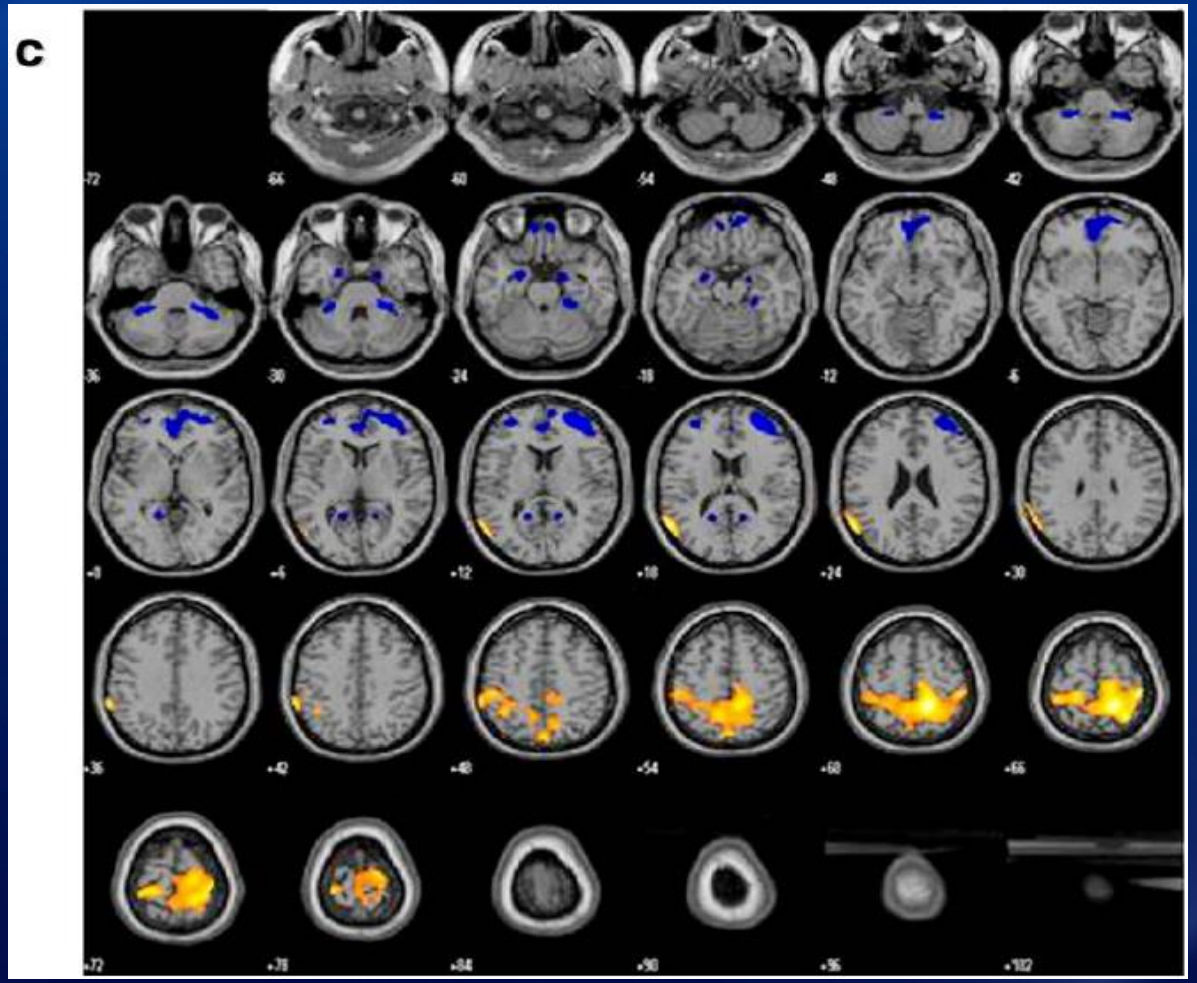


FIGURE 2. Anatomic localization of peaks of significant correlation between brain SPECT perfusion and FIQ total score (*P* voxel < 0.005; *P* cluster < 0.05, corrected for multiple comparisons; age as nuisance variable).

Guedj E et al. *J Nucl Med* 2008; 49:1798–1803



Guedj E. *Eur J Nucl Med Mol Imaging* 2007; 34:130–134

Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in Rostral Anterior Cingulate Cortex during provoked pain

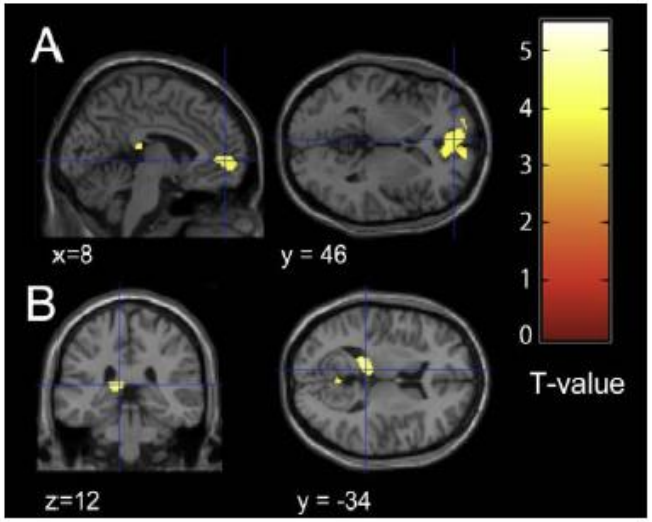


Fig. 2. Regions of the brain where healthy controls have higher activity than FMS patients during subjectively calibrated painful stimulation minus sensory stimulation. Clusters corresponding to (A) the rACC, and (B) the pulvinar nucleus of thalamus. The exact anatomical locations (x, y, z) are given in MNI coordinates.

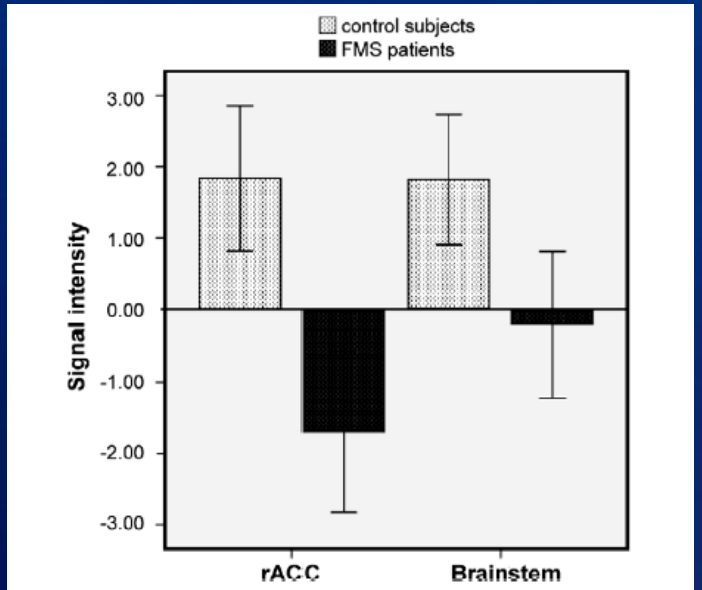


Fig. 3. Representation of neuronal activity in the rACC and the brainstem during subjectively calibrated painful stimulation minus sensory stimulation in patients and controls. The bars represent the signal intensity for the same coordinate in the rACC ($x = -8$, $y = 46$, $z = 4$) and the brainstem ($x = 4$, $y = -22$, $z = 40$). The signal intensity for the contrast pain minus sensory stimulation was recorded for every individual and bars represent the mean intensity. Error bars represent the standard error. The exact anatomical location (x, y, z) is given in MNI coordinates.

Jenson KB et al. *Pain* 144 (2009) 95–100.

Gray Matter Changes Over Time in Fibromyalgia

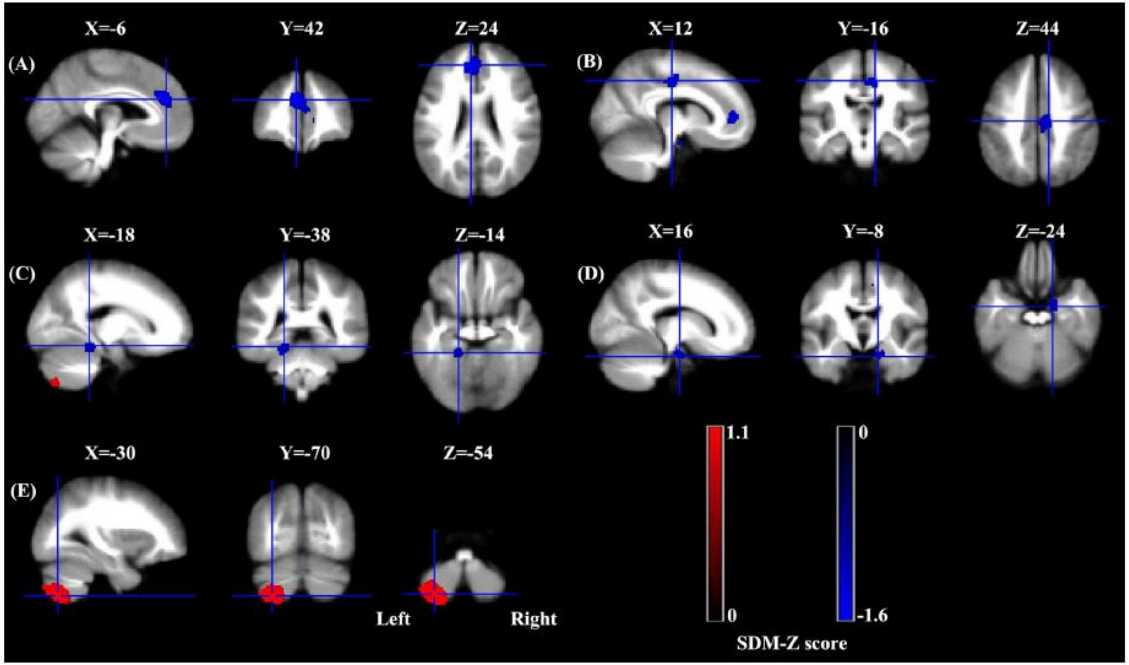


Fig. 2. Meta-analytic results for seven voxel-based morphometric studies comparing fibromyalgia patients with healthy controls. Regions of gray matter (GM) showing a decrease are seen in bilateral anterior cingulate/paracingulate cortex/medial prefrontal cortex (A), in bilateral posterior cingulate/paracingulate cortex (B), in left parahippocampal gyrus/fusiform cortex (C), and in right parahippocampal gyrus/hippocampus (D). Increases are seen in the left cerebellum (E). *Note:* Areas with decreased GM relative to controls are displayed in blue, and areas with increased GM are displayed in red. The color bar indicates the maximum and the minimum SDM-*Z* values. SDM, Seed-based *d* Mapping. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Shi HC st al. *Semin Arthritis Rheum* 2016; 46:330-337.

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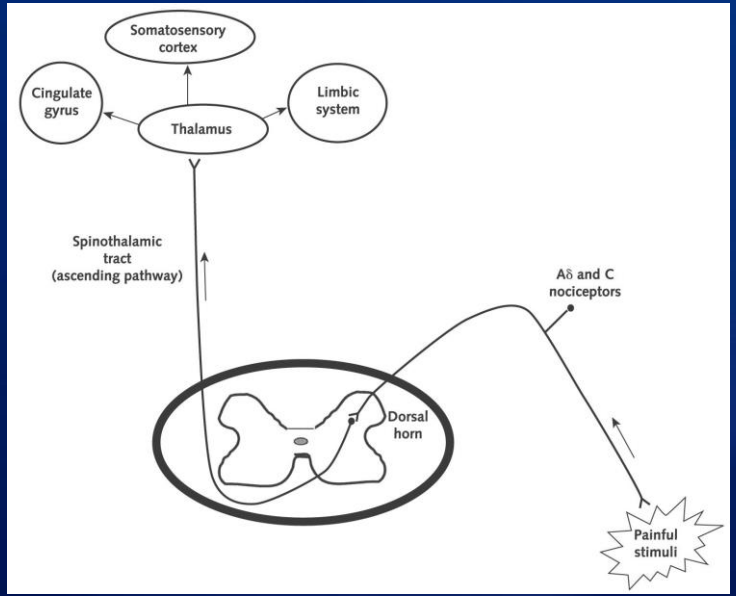
The Mind-Body Connection

- The **spinothalamic tract**, provides nociceptive information to thalamic nuclei as well as to the primary and secondary somatosensory cortices
  - Involved in **sensory discriminative aspects** of pain as well as in the anticipation of painful stimuli
- **Spinothalamic tract projections** also facilitate nociceptive input to the insular cortex which has interconnections with the amygdala, prefrontal cortex, and anterior cingulate cortex
  - Involved in **affective, cognitive, and autonomic responses** to nociception
- Chronic pain processing reflects decreased sensory processing in somatosensory regions in favor of enhanced activation of regions
  - Associated with cognitive, emotional, and introspective processing of events (Apkarian, 2005)



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The Influence of Brain and Body Hormones

- Hypothalamic-pituitary-adrenal axis abnormalities
  - Increased sympathetic outflow with decreased parasympathetic tone results in visceral hyperactivity
  - May impact sleep
  - Systemic norepinephrine release with increased sympathetic tone reduces pain inhibition
  - This may explain the responsiveness of patients to short-term conrticosteroids – not an anti-inflammatory benefit, but a hormonal one

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Genetic Factors

- Some genes have been identified that may be important as risk factors for fibromyalgia
  - Polymorphisms of gene encoding catechol-O-methyltransferase (COMT) described. Low enzymatic haplotypes more frequent in FMS patient samples and may account for some of the neuroendocrine abnormalities
- Differences in gene expression have been described in fibromyalgia patients compared to controls

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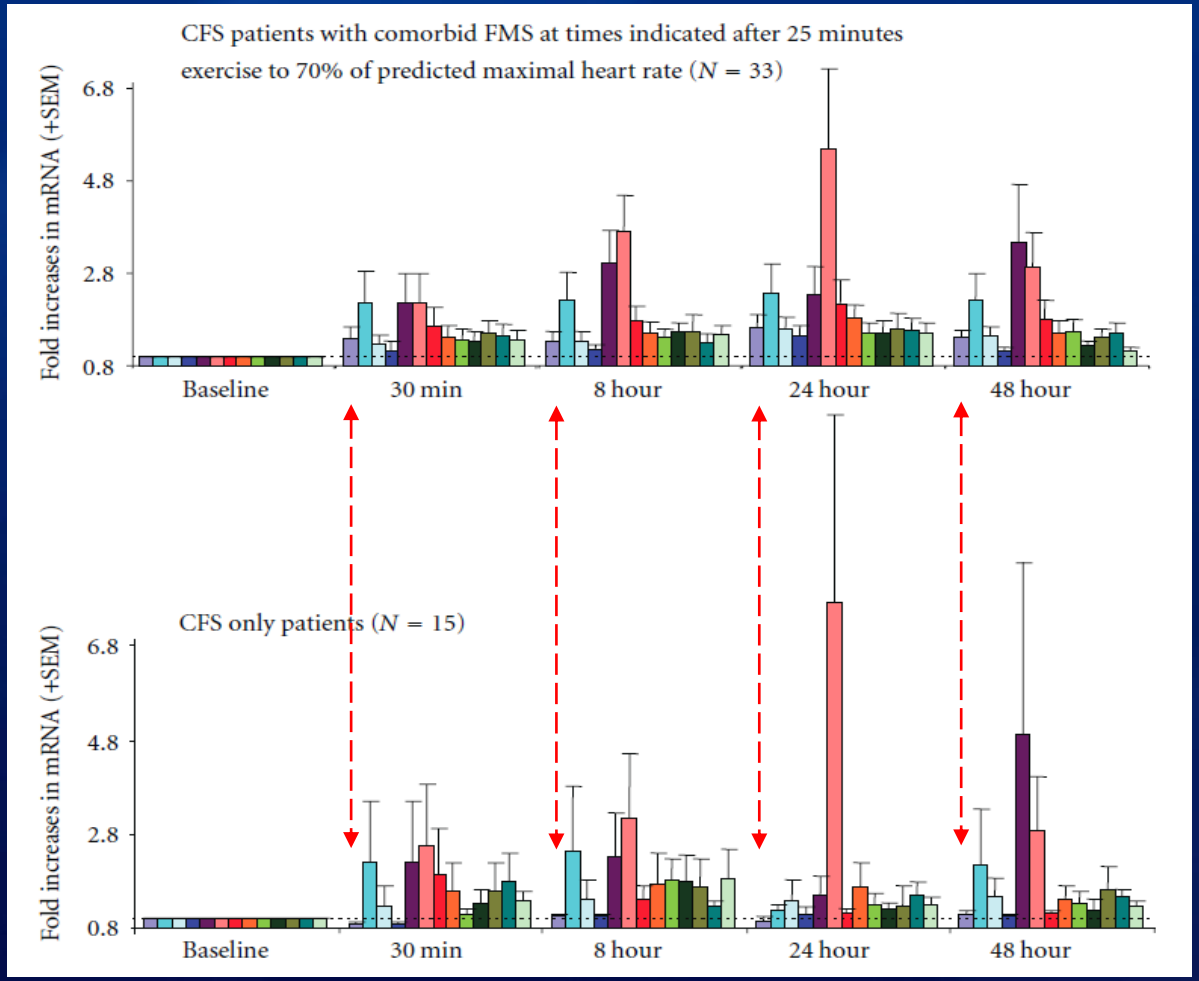
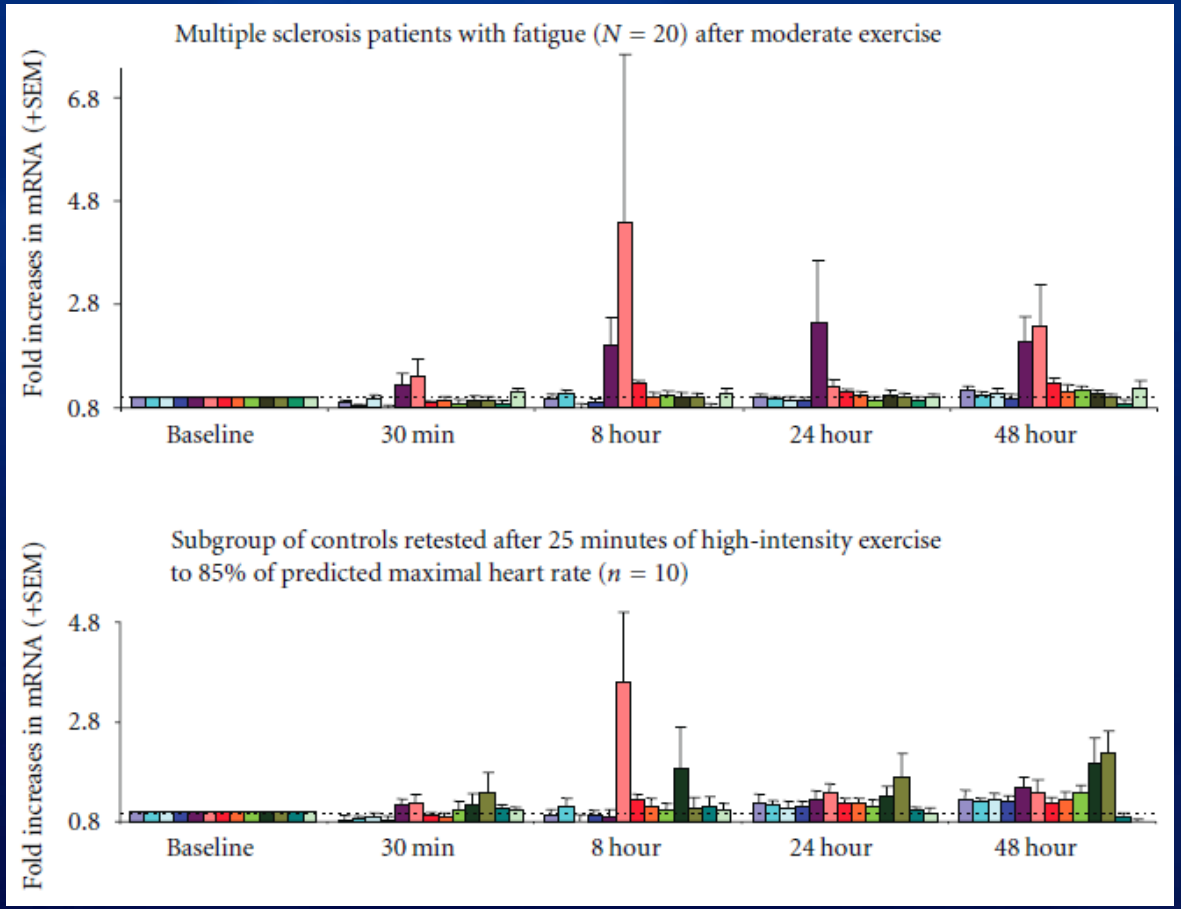


Patients with central sensitization and FM features have higher levels of expression of genes related to sensory transmission than those without FM features…

Sensory	Adrenergic	Immune
ASIC3	α2A	IL6
P2X4	β1	IL10
P2X5	β2	LTα
TRPV1	COMT	TLR4
		CD14

Light KC, White AT, et al. *Pain Res and Treatment* (2012)



…and far more expression than controls with other inflammatory conditions or healthy controls.

Sensory	Adrenergic	Immune
ASIC3	α2A	IL6
P2X4	β1	IL10
P2X5	β2	LTα
TRPV1	COMT	TLR4
		CD14

Light KC, White AT, et al. *Pain Res and Treatment* (2012)

Treatment

- Evidence supports a multimodality approach that addresses pain management, sleep quality, behavioral and psychological issues, and physical exercise and rehabilitation

Efficacy of Multicomponent Treatment in Fibromyalgia Syndrome: A Meta-Analysis of Randomized Controlled Clinical Trials

Total treatment ≥30 hours					
Pain	2	52	SMD (Fixed)	−0.36 (−0.78, −0.05)	0.09
Fatigue	1	38	WMD (Fixed)	−1.20 (−2.20, −0.20)	0.02
Sleep	ND				
Depressed mood	1	38	SMD (Fixed)	−1.07 (−2.73, 0.60)	0.26
Quality of life	1	38	SMD (Fixed)	−0.58 (−1.08, −0.07)	0.02
Self-efficacy pain	1	38	SMD (Fixed)	0.63 (0.13, 1.14)	0.01
Physical fitness	1	38	SMD (Fixed)	0.44 (−0.06, 0.94)	0.09
Total treatment <30 hours					
Pain	3	84	SMD (Fixed)	−0.38 (−0.68, −0.07)	0.02
Fatigue	2	48	WMD (Fixed)	−0.59 (−1.45, 0.27)	0.18
Sleep	ND				
Depressed mood	3	84	SMD (Fixed)	−0.84 (−1.16, −0.52)	< 0.0001
Quality of life	2	54	SMD (Fixed)	−0.60 (−1.00, −0.19)	0.004
Self-efficacy pain	3	74	SMD (Fixed)	0.50 (0.16, 0.84)	0.004
Physical fitness	3	74	SMD (Fixed)	0.24 (−0.10, 0.57)	0.16

* MT = multicomponent therapy; 95% CI = 95% confidence interval; SMD = standardized mean difference; WMD = weighted mean difference; ND = no data.

Hauser W et al. *Arthritis & Rheumatism (Arthritis Care & Research)* 2009; 61:216–224

Exercise: Effect on Pain in Fibromyalgia

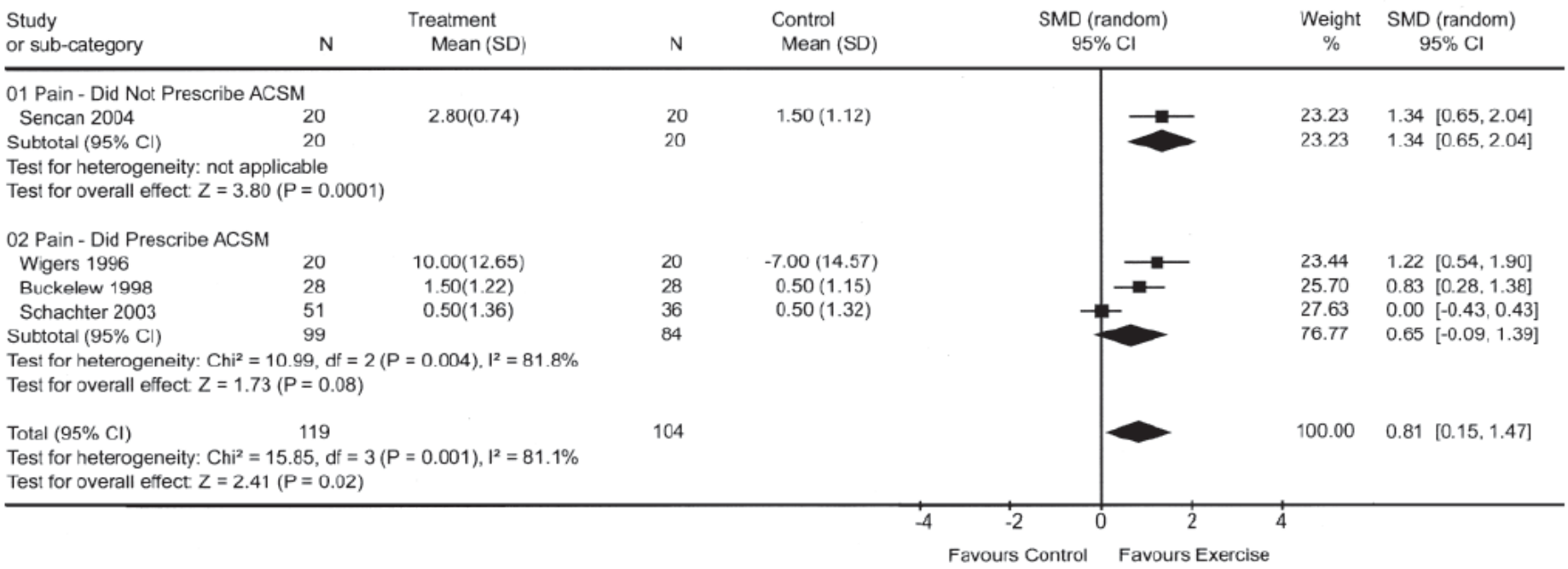


Figure 1. Metaanalysis for effect of aerobic exercise on pain (01: exercise programs did not meet ACSM standards; 02: exercise programs met ACSM standards). SMD: standardized mean difference. From The Cochrane Library 2007, Issue 4, with permission.

Busch AJ et al. *J Rheumatol* 2008; 35:1130–44.

Exercise: Effect on Depression in Fibromyalgia

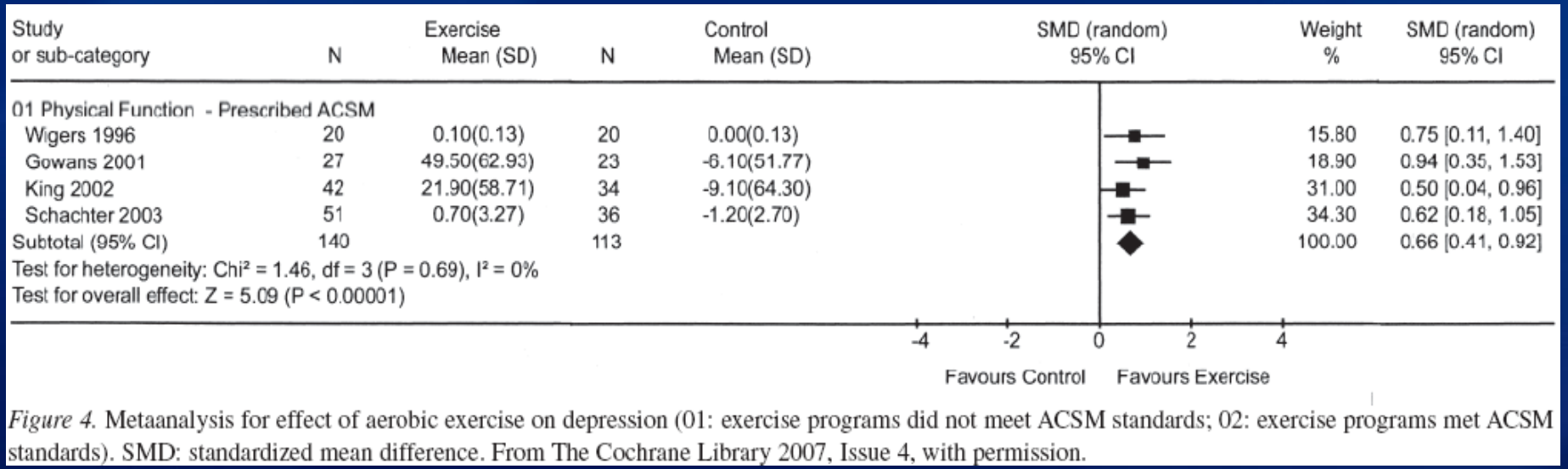


Figure 4. Metaanalysis for effect of aerobic exercise on depression (01: exercise programs did not meet ACSM standards; 02: exercise programs met ACSM standards). SMD: standardized mean difference. From The Cochrane Library 2007, Issue 4, with permission.

- Submaximal levels of exertion appear to be most sustainable
- Most common mistake: overexercise

Busch AJ et al. *J Rheumatol* 2008; 35:1130–44.

Treating Sleep

- Sleep-related problems almost universal in fibromyalgia syndrome, and are strongly predictive of pain, fatigue, and difficulty with social functioning (Theadom, 2007)
- Increased airways resistance without overt apnea is frequently observed and may respond to positive airways pressure (Gold, 2005)

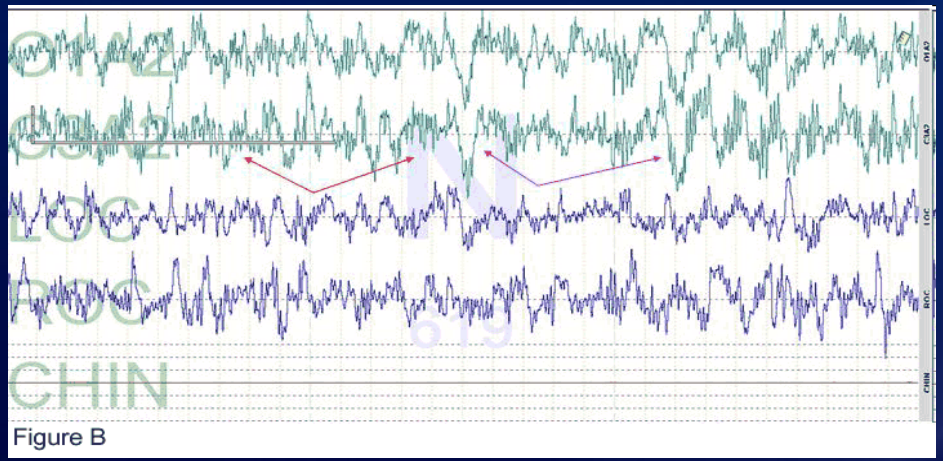


Figure B

Drug therapy does not provide significant relief of symptoms or lasting benefits

- Most evidence for efficacy
  - Amitriptyline: long-term efficacy data lacking
  - Cyclobenzaprine
  - Tramadol
- Moderate evidence for efficacy
  - SSRI: fluoxetine, buproprion, etc.
  - SNRI: **duloxetine**, **milnacipran**
  - **Pregabalin**, gabapentin, topiramate

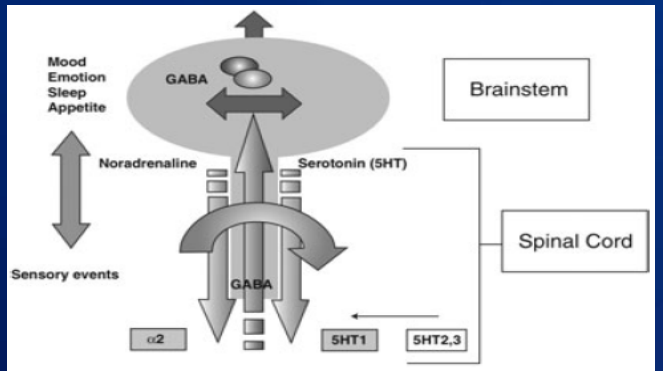


Figure 2. Neurotransmitter-modulated spinal-brain loop interference. GABA, gamma-aminobutyric acid; 5HT, serotonin.

- No evidence for efficacy: opiate analgesics, NSAIDs, corticosteroids, benzodiazepines, thyroid hormone, calcitonin, magnesium.

[Bold = FDA approved for fibromyalgia**]**

EULAR Fibromyalgia Treatment Recommendations 2016

Recommendation	Level of evidence	Grade	Strength of recommendation	Agreement (%)*
Overarching principles				
Optimal management requires prompt diagnosis. Full understanding of fibromyalgia requires comprehensive assessment of pain, function and psychosocial context. It should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features. In general, the management of FM should take the form of a graduated approach.	IV	D		100
Management of fibromyalgia should aim at improving health-related quality of life balancing benefit and risk of treatment that often requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features (such as depression), fatigue, sleep disturbance and patient preferences and comorbidities; by shared decision-making with the patient. Initial management should focus on non-pharmacological therapies.	IV	D		100

*Percentage of working group scoring at least 7 on 0–10 numerical rating scale assessing agreement.

Macfarlane GJ, et al. *Ann Rheum Dis* 2017;76:318–328.

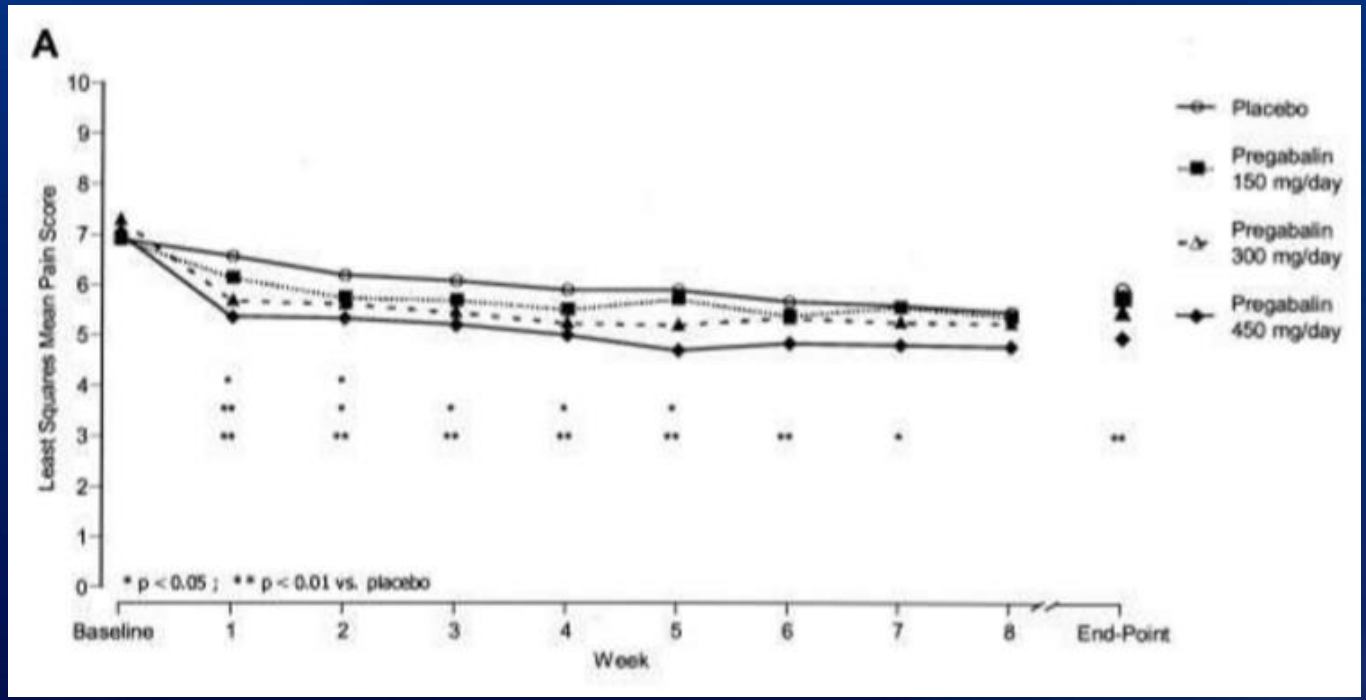
EULAR Fibromyalgia Treatment Recommendations 2016

Specific recommendations				
Non-pharmacological management				
Aerobic and strengthening exercise	Ia	A	Strong for	100
Cognitive behavioural therapies	Ia	A	Weak for	100
Multicomponent therapies	Ia	A	Weak for	93
Defined physical therapies: acupuncture or hydrotherapy	Ia	A	Weak for	93
Meditative movement therapies (qigong, yoga, tai chi) and mindfulness-based stress reduction	Ia	A	Weak for	71–73
Pharmacological management				
Amitriptyline (at low dose)	Ia	A	Weak for	100
Duloxetine or milnacipran	Ia	A	Weak for	100
Tramadol	Ib	A	Weak for	100
Pregabalin	Ia	A	Weak for	94
Cyclobenzaprine	Ia	A	Weak for	75

*Percentage of working group scoring at least 7 on 0–10 numerical rating scale assessing agreement.

Macfarlane GJ, et al. *Ann Rheum Dis* 2017;76:318–328.

Pregabalin: a modest effect only at the highest doses



Crofford L et al. *Arthritis Rheum* 2005; 52(4):1264.

Comparative efficacy: a Bayesian network meta-analysis of randomized controlled trials

RANKING PERFORMANCE OF DRUGS AT RECOMMENDED DOSES		
Pain reduced >30%	**Probability of success**	**Withdrawl**
Duloxetine 60 mg	Duloxetine 60 mg	Pregabalin 300 mg
Pregabalin 300 mg	Pregabalin 300 mg	Duloxetine 60 mg
Milnacipran 100 mg	Milnacipran 100 mg	Milnacipran 100 mg
Milnacipran 200 mg	Milnacipran 200 mg	Milnacipran 200 mg
Placebo	Pregabalin 150 mg	Placebo
	Placebo	

- Nine RCTs including 5,140 patients
- Duloxetine 60 mg, pregabalin 300 mg, milnacipran 100 mg, and milnacipran 200 mg were more efficacious than placebo
- Small differences were observed between drugs. There was no significant difference in the overall efficacy and tolerability between the medications at the recommended doses

Lee YH and Song GG. *Rheumatol Int* 2016;36(5):663-72

MAYO CLINIC

Behavioral Therapy: Key Elements

- Education
- Goal setting
- Behavioral pacing
- Relaxation training
- Identification of dysfunctional thought patterns such as catastrophizing
- Communication skills and strategies for acquisition, maintenance, and generalization of skills
- Strategies for relapse prevention and for managing flare-ups
- Use of multidisciplinary teams

Bennett R. *Nature Clin Pract Rh*eum 2006; 2:416-424.

MAYO CLINIC

Mayo Clinic Fibromyalgia Treatment Program

- Multi-disciplinary outpatient 2-day treatment program
- Now expanding capacity for outpatient referrals through the Mayo Referring Provider Office (RPO)

- Assessment – through expert nursing with consultants in Rheumatology and General Internal Medicine –symptoms, function, medications, comorbidities

MAYO CLINIC

Mayo Clinic Fibromyalgia Treatment Program

- Treatment – educational, behavioral, physical interventions
  - Teaching: symptoms, physiology, principles of interventions
  - Coaching in techniques to improve symptoms and improve function
    - Relaxation, cognitive techniques, distraction
    - Identifying and overcoming negative behaviors
    - Exercise, energy conservation
  - Integrating with **Mayo Pain Rehabilitation Clinic** for patients requiring more hands-on PT or OT intervention, poor initial treatment response, or chronic opiate use

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Summary

- Fibromyalgia is a common disorder of chronic widespread pain associated with many symptoms such as fatigue and sleep disorder
- The physiology involves abnormal sensory processing and central sensitization
- Treatment should involve multiple components to address pain, deconditioning, sleep disorders, and psychological aspects. Ideally, rehabilitative measures should form the cornerstone of treatment.

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Thank you

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