Fibromyalgia: The Psychiatric Faces of Pain

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Diagnostic Criteria for FibroMyalgia

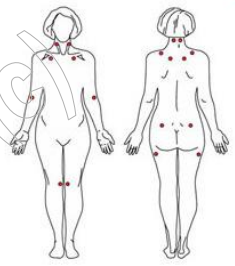
A. Generalized, chronic pain (≥ 3 months) affecting the axial, plus upper and lower segments, plus left and right sides of the body

Either "B" or "C":

B. At least 11 of 18 reproductive tender points

C. At least 4 of the following symptoms:
1. Generalized fatigue
2. Headaches
3. Sleep disturbance
4. Neuropsychiatric complaints
5. Numbness, tingling sensations
6. Irritable bowel symptoms

D. It cannot be established that the disturbance was due to another systemic condition



Wolfe F, et al. Arthritis Rheum 1990; 33(2):160-172

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Prevalence of Fibromyalgia

Country	Prevalence (%)	Year	Study
United States	2.0	1995	*Wolfe F, et al.*
US (Amish)	7.3	2003	*White KP, Thompson J*
Canada	3.3	1999	*White KP, et al.*
Pakistan	1.5	1998	*Farooqi A, Gibson T*
Spain	2.4	2001	*Carmona L, et al.*
Brazil	2.5	2004	*Senna ER, et al.*
Sweden	1.3	2000	*Lindell L, et al.*
Sweden	1.0	1989	*Jacobsson L, et al.*
Norway	10.5	1992	*Forseth KO, Gran JT*

- Almost 90% of the patients are female, and it can occur at any age although it peaks between the ages of 40 and 60
- Prevalence generally increases with age, up to 7% in women around the age of 70

Wolfe F, et al. Arthritis Rheum 1995; 38(1):19-28

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Differential Diagnosis

Illness	Tests
Rheumatic Disease	
Systemic lupus	ANA, Anti-DNA, Anti-Sm
Rheumatoid arthritis	RF/CCP, ESR/CRP
Polymyositis	CPK
Sjögren's syndrome	SSA/Ro, SSB/La, lip biopsy
Infection/Inflammation	
Tuberculosis	PPD, culture, CXR
Chronic syphilis	VDRL
Subacute bacterial endocarditis	Culture
Lyme disease	Serology
Parvovirus	Serology
Acquired immunodeficiency	Serology, CD4 count
Inflammatory bowel syndromes	Colonoscopy, EGD
Endocrine Disorders	
Hypothyroidism	T4 + TSH
Hypopituitary	Prolactin, other hormones
Vitamin D–deficient osteomalacia	25-OH vitamin D, DEXA

ANA=antinuclear antibody; ESR=erythrocyte sedimentation rate; RF=rheumatoid factor; CPK=creatine phosphokinase; PPD=purified protein derivative; DEXA=dual-energy x-ray absorptiometry

Russell IJ & Raphael KG. CNS Spectr 2008;13(suppl 5):6-11

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Fibromyalgia Comorbidities

Medical Disorder[1]	Prevalence	Psychiatric Disorder[2]	Prevalence
Chronic fatigue syndrome	21%-80%	**Major Mood Disorder**	73.1%
Irritable bowel syndrome	32%-80%	Major depressive disorder	62%
Temporomandibular disorder	75%	Bipolar disorder	11%
Tension and migraine headache	10%-80%	**Anxiety Disorders**	55.6%
Multiple chemical sensitivities	33%-35%	Panic disorder	28.7%
Interstitial cystitis	13%-21%	PTSD	21.3%
Chronic pelvic pain	18%	Social phobia	19.4%
		OCD	6.5%

1. Aaron LA et al. Best Pract Res Clin Rheumatol 2003; 17:563-574; 2. Arnold LM et al. J Clin Psychiatry 2006; 67:1219-1225

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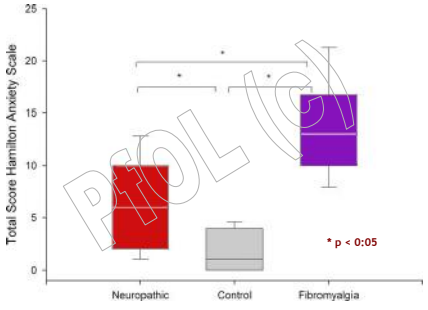
Hamilton Anxiety Scale in Patients with Fibromyalgia and Neuropathic Pain



Gormsen L, et al. Eur J Pain 2009. In press

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Fibromyalgia Is Not a Discrete Condition

- There is a strong genetic predisposition for FM, with an odds ratio of 8 in family members.[1]
- Psychiatric illnesses sometimes are present in FM but not all. Psychological factors at times can both worsen or buffer the condition.[2]
- Actual tendency: abandon looking in the peripheral muscle and started moving more centrally to look at how pain is processed centrally.[2]

1. Arnold LM, et al. Arthritis Rheum 2004;50:944-952; 2. Clauw DJ. J Clin Rheumatol 2007;13(2):102-109

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Shared Features of Fibromyalgia and Depression: Clues to Pathophysiology

- There is an increased prevalence of mood disturbances in family members of patients with FM compared to that in rheumatoid arthritis with an odds ratio of 2 (OR=8 for bipolar disorder).
- FM and MDD have strong genetic predispositions, similar comorbidity with sleep disturbances, chronic fatigue, chronic headaches, and chronic pain disorders.
- They co-aggregate in families.
- Both have similar cognitive disturbances.

Arnold LM et al. J Clin Psychiatry 2006; 67:1219-1225

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Genetics of Fibromyalgia

- Genes that may be involved
  - ◆5-HT_{2A} receptor polymorphism T/T genotype associated with higher pain severity[1]
  - ◆Serotonin transporter: 31% of patients had s/s genotype vs 16% of controls[2]
  - ◆Dopamine D_4 receptor exon III repeat tandem[3]
  - ◆↓COMT activity that ↑pain sensitivity via $\beta_{2/3}$-adrenergic mechanism[4]

1. Bondy B et al. Neurobiol Dis 1999; 6:433-439; 2. Offenbaecher M et al. Arthritis Rheum 1999; 42:2482-2488; 3. Diatchenko L et al. Trends Genet 2007; 23:605-613; 4. Nackley-Neely AG et al. Pain 2007; 128: 199-208

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Shared Features of Fibromyalgia and Depression: Endogenous Opiod Neurotransmission

- Endogenous opioid neurotransmission integrates the pain/depression response, especially that activated by stress.[1]
- In women with MDD the experimental induction of sadness is followed by a decrease in the μ-opioid receptor-binding potential in the left inferior temporal cortex versus normals.[1]
- There also was a decrease in μ-opioid receptor-binding potential during sadness in patients with MDD who did not respond to antidepressant treatment.[1]
- FM patients had reduced μ-opioid receptor binding in the nucleus accumbens, the amygdale, and the dorsal cingulate and the binding potential correlated with the relative amount of affective pain.[2]

1. Kennedy SE, et al. Arch Gen Psychiatry 2006;63:705-713; 2. Harris RE, et al. J Neurosci 2007;27:1000-1006

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Shared Features of Fibromyalgia and Depression: HPA Axis Dysfunction

- Numerous reports have correlated FM symptoms with HPA axis dysfunction.[1]
- In individuals with FM is observed an increased incidence of childhood physical, sexual, and emotional abuse.[2,3,4]
- Chronic stress may also play a role in fibromyalgia pathogenesis[5]
- But, FM patients with high depression scores, like atypical depression and PTSD, had significantly lower cortisol levels than those FM patients without depression.[6]

1. McLean SA, et al. Arthritis Rheum 2005;52:3660-3669; 2. 2. Werssbecker I et al. Psychoneuroendocrinology 2006; 31:312-324; 3. Ciccone DS et al. Clin J Pain 2005; 21:379-386; 4. Arguelles LM, et al. Pain 2006;124:155-157; 5. Gupta A et al. Arthritis Res Ther 2004; 6:98-106; 6. Heim CU et al. Psychoneuroendocrinology 2000;25(1):1-35

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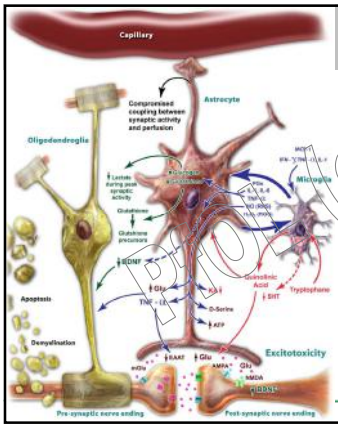
Shared Features of Fibromyalgia and Depression: Pro-Inflammatory Cytokines



RNS & ROS = reactive nitrogen and oxygen species,
IL = interleukin (IL),
TNF = tumor necrosis (TNF)-alpha,
IFN = interferon (IFN)-gamma,
IDO = indoleamine 2,3 dioxygenase,
5-HT = serotonin (5-HT),
Glu = glutamate (Glu) release,
KA = kynurenic acid,
EAAT = excitatory amino acid transporters,
BDNF = brain-derived neurotrophic factor

Maletic V & Raison CL. Frontiers in Bioscience 2009;14:5291-5338

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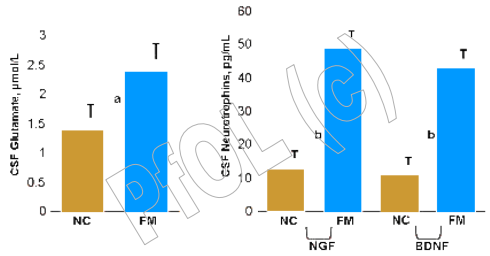
Glutamate and Neurotrophins in CSF - Fibromyalgia



a p<0.003; b p<0.001
BDNF = brain-derived neurotrophic factor; EAA = excitatory amino acid; NGF = nerve growyh factor
N=20 patients with fibromyalgia (FM) and 20 normal controls (NC)

Sarchielli et al. J Pain 2007; 8:737-745

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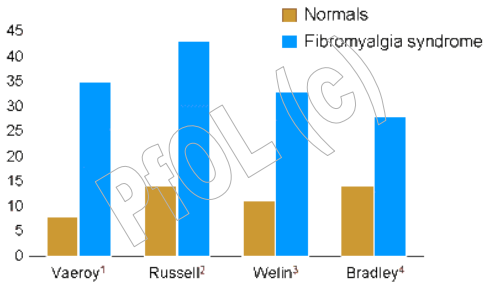
Substance P in CSF - Fibromyalgia



1. Vaeroy H et al. Pain 1988; 32:21-26; 2. Russell IJ et al. Arthritis Rheum 1994; 37:1593-1601; 3. Liu Z et al. Peptides 2000; 21:853-860; 4. Bradley LA et al. Arthritis Rheum 1999; 42: 2731-2732

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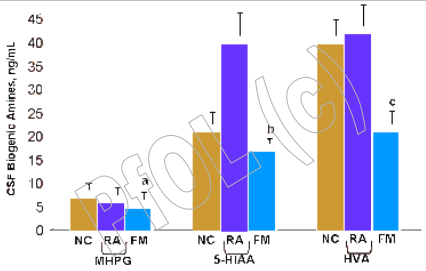
Biogenic Amines in CSF - Fibromyalgia



a p=0.026; b p=0.057; c p=0.005 versus controls
5-HIAA = 5-hydroxyindole acetic acid; HVA = homovanilic acid; MHPG = 3-methoxy-4-hydroxyphenilethylene glycol
N=17 patients with fibromyalgia (FM), 5 patients with rheumatoid arthritis (RA) and 7 normal controls (NC)

Russell J et al. Arthritis Rheum 1992; 35:550-556

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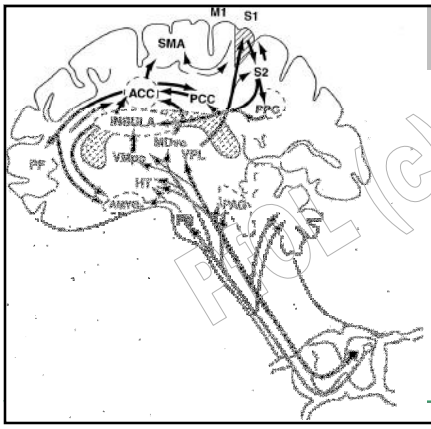
Structures Involved in Processing Pain



PAG, periaqueductal gray; PB, parabrachial nucleus of the dorsolateral pons; VMpo, ventromedial part of the posterior nuclear complex; MDvc, ventrocaudal part of the medial dorsal nucleus; VPL, ventroposterior lateral nucleus; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; HT, hypothalamus; S-1 and S-2, first and second somatosensory cortical areas; PPC, posterior parietal complex; SMA, supplementary motor area; AMYG, amygdala; PF, prefrontal cortex

Price DD. Science 2000;288:1769–1772

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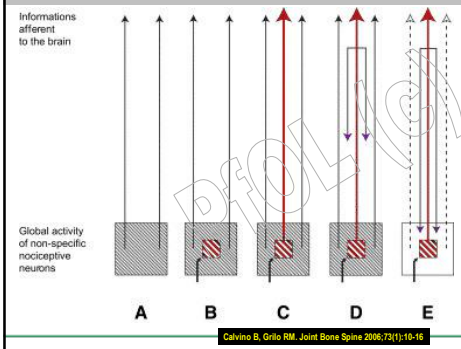
Hypothesis for Explaining the Overall Activity of Spinal Neurons in Relation to Nociception



A. Basal somatosensory activity that is transmitted to the upper central nervous system centers.
B. A nociceptive stimulus activates specific and nonspecific nociceptive neurons.
C. These neurons send an activating signal to the brain.
D. The signal secondarily triggers descendant inhibitory neurons.
E. The result is a large reduction in the activity of neurons that are not directly targeted by the initial stimulus.

Calvino B, Grilo RM. Joint Bone Spine 2006;73(1):10-16

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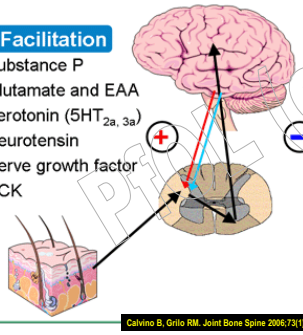
Supraspinal Influences on Nociceptive Processing



Facilitation
- Substance P
- Glutamate and EAA
- Serotonin ($5HT_{2a, 3a}$)
- Neurotensin
- Nerve growth factor
- CCK

Inhibition
- Descending antinociceptive pathways
  - Norepinephrine – serotonin ($5HT_{1a,b}$)
  - Opioids
- GABA
- Cannabinoids
- Adenosine

Calvino B, Grilo RM. Joint Bone Spine 2006;73(1):10-16

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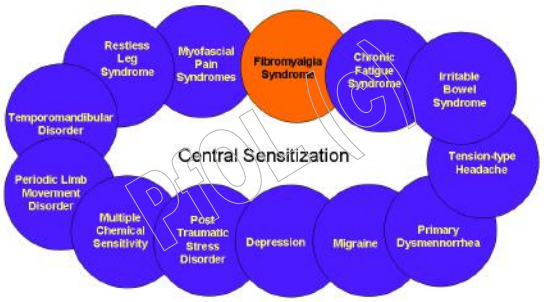
Central Sensitization[1]

- Involves abnormally sensitive pain neurons that develop pathologic spontaneous activity
- Results in greater pain perception and more prolonged pain
- Two types of hypersensitivity:
  - Hyperalgesia: increased response to painful stimulation
  - Allodynia: pain from normally non-noxious stimuli
- "Wind up": after an initial painful stimulus, subsequent stimuli perceived as more painful (through stimulation of NMDA) → ketamine useful in pain by Fibromyalgia[2]
- "Kindling": hyperexcited neurons may affect nearby neurons, spreading the abnormal pain response throughout the CNS[3]

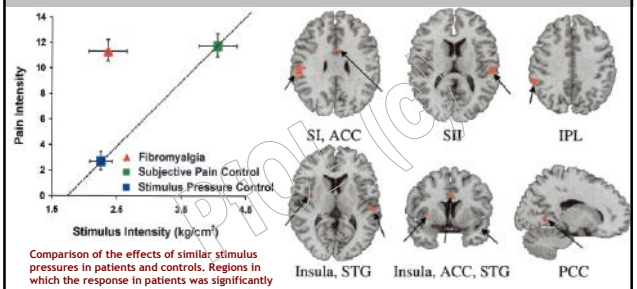
1. Staud R et al. Nat Clin Pract Rheumatol 2006; 2:90-98; 2. Gallager RM. Medscape Rheumatol 11/28/2007 (article # 566089; 3. Staud R, et al. J Pain 2005;6:323-332

Central Sensitization Syndromes



Yunus MB. The Concept of Central Sensitivity Syndromes in Fibromyalgia and Other Central Pain Syndromes. Wallace DJ and Clauw DJ, eds. 2005; 29-44

Stimuli and Responses During fMRI Scans

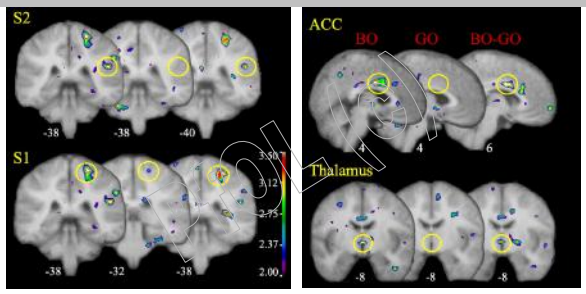


Comparison of the effects of similar stimulus pressures in patients and controls. Regions in which the response in patients was significantly greater than the response in controls are shown in red

IPL = inferior parietal lobule
STG = superior temporal gyrus

Gracely RH et al. Arthritis Rheum 2002; 46:1333-1343

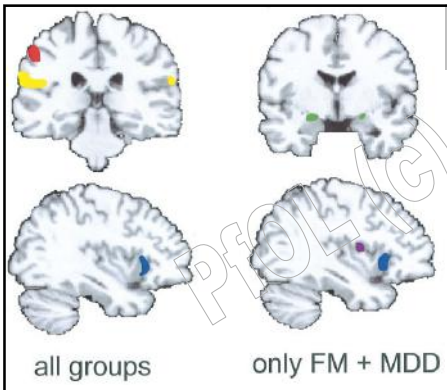
Emotional Modulation Network



Emotional effects within the previously identified pain network are observed in Anterior Cingulate Cortex, thalamus, Somatosensory cortex 2, and Somatosensory cortex 1. BO & GO - bad & good odor pared stimuli

Villemure C & Bushnell MC. J Neurosci 2009; 29(3):705-715

Pain-Evoked Neuronal Activations in Fibromyalgia



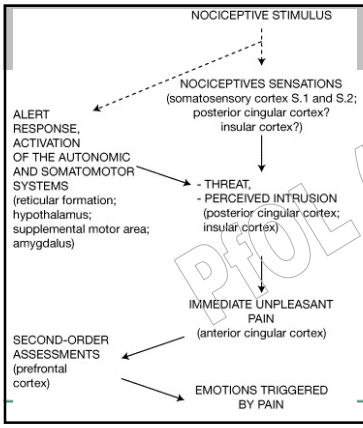
Brain regions activated by pressure-pain stimuli at the left thumb.

Neuronal activations in all groups: contralateral primary somatosensory cortex (red), secondary somatosensory cortex (yellow), and the anterior insula (blue).

Unique activations in FM patients with MDD after the same pressure stimuli: amygdalae (green) and the contralateral insula (purple).

Giesecke T et al. Arthritis Rheum 2005;52:1577-1584

Psychological and Neural Mechanisms of the Affective Dimension of Pain



Price DD. Science 2000;288:1769–1772

Brain Consequences of Fibromyalgia

- Patients with FM had significantly less total gray matter volume (3.3x) than normal controls.
- Each year with FM being equivalent to 9.5 times the loss in normal aging.
- The FM patients demonstrated significantly less gray matter density in the cingulate, the insula, the medial frontal cortex, and the para-hippocampus gyrus.

Kuchinad A, et al. J Neurosci 2007;27:4004-4007

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Fibromyalgia Management Acronym

Six Steps to ADEPT Living

- **A**ttitude – patient, healthcare professional, family, society
- **D**iagnosis – diagnosis and differential diagnosis
- **E**ducation – didactic, group, reading, psychosocial, biomedical
- **P**hysical – home (pacing, exercise, heat) and/or formal physical therapy
- **T**reatments – medications & other interventions
- **Living** – interval objective assessment, adjustment, support

Russell IJ. CNS Spectr. Vol 13, No 3 (Suppl 5). 2008

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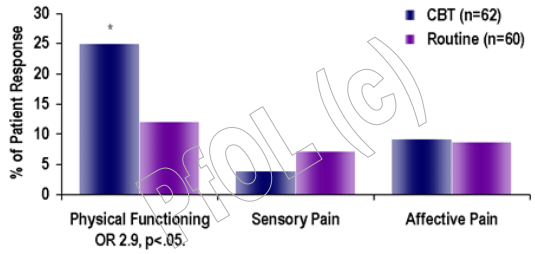
Non-Pharmacological Treatment of Fibromyalgia: CBT vs Routine Care



*Statistically significant.
OR=odds ratio.

Williams DA et al. J Rheumatol 2002; 29: 1286-1286

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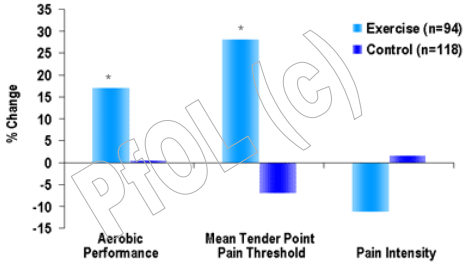
Non-Pharmacological Treatment of Fibromyalgia: Aerobic Exercise



*Statistically significant.

Busch AJ et al. Cochrane Database Syst Rev 2007(4):CD003786

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Pharmacological Agents for Fibromyalgia Syndrome

Analgesics
- Tramadol + acetaminophen (but receptors for opioid ligands are low)

Precursor
- 5-hydroxytryptophan (benefical in FMS for pain and other manifestations)

Biogenic Amine Reuptake Inhibitors
- SSRIs – many are helpful for depression but none for pain in usual dosages
- SNRIs – duloxetine, milnacipran (FMS pain and depression but not insomnia)

Serotonin Receptor Blockade
- Tropisetron, a 5-HT3 antagonist (effective dosage is narrow)

NMDA Receptor Blockade
- Ketamine (only ~50% of FMS patients respond)
- Dextromethorphan (reported marginally effective in FMS)

Anticonvulsant
- Pregabalin (FMS pain and insomnia but not depression)

Sedative
- Sodium oxybate (FMS pain and insomnia but not depression)

Russell IJ. CNS Spectr. Vol 13, No 3 (Suppl 5). 2008

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Anticonvulsants: Published Trials vs Placebo

Agent	n	Duration (weeks)	Improvement (p<0.05)
Pregabalin[1]	750	14	Yes
Pregabalin[2]	1051	32	Yes
Pregabalin[3]	529	8	Yes
Pregabalin[4]	748	13	Yes
Gabapentin[5]	150	12	Yes

Gabapentin is NOT approved by FDA in fibromyalgia

1. Arnold LM et al. J Pain 2008; 9: 792-805; 2. Crofford LJ et al. Pain 2008;136: 419–431; 3. Crofford LJ et al. Arthritis Rheum 2005; 52:1264–1273; 4.Mease PJ et al. J Rheumatol 2008;35:502–14; 5. Arnold LM et al. Arthritis Rheum 2007; 56:1336-1344

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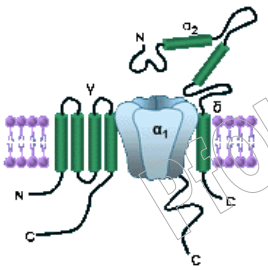
Overview of α2-δ Ligands



- Bind to α2-δ subunit of voltage-gated calcium channels of neurons
- Reduce calcium influx at nerve terminals and inhibit release of neurotransmitters (glutamate, substance P)
- Indicated for:
  - Fibromyalgia (pregabalin)
  - Adjunctive therapy in partial onset seizures (pregabalin, gabapentin)
  - Diabetic peripheral neurophatic pain (pregabalin)
  - Postherpetic neuralgia (pregabalin, gabapentin)
  - General anxiety disorder (pregabalin)

Abeles M et al. Am J Med 2008; 121:555-561

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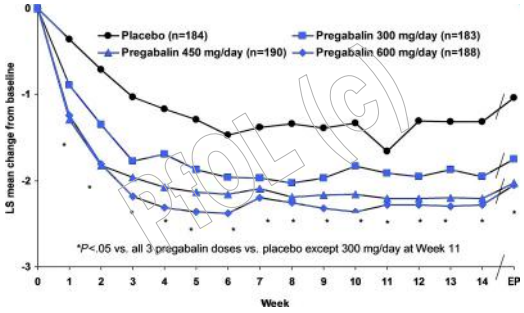
Pregabalin in Fibromyalgia (14 Wk) - Patient Global Impression of Change (PGIC)



Arnold LM et al. J Pain 2008; 9: 792-805

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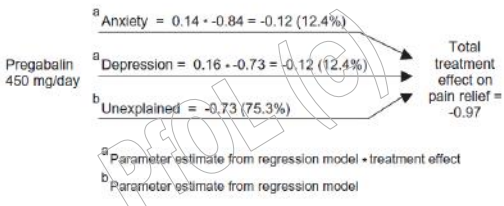
Pregabalin in Fibromyalgia - Impact of Anxiety or Depression in Efficacy (Path Analysis)



Significantly more patients reported anxiety symptoms (71%) than depressive symptoms (56%) (P<0.0001). Improvement in pain symptoms with pregabalin compared with placebo did not depend linearly on baseline anxiety or depression scores. By path analysis, 75% of the pain reduction was not explained by improvements in anxiety and depressive symptoms

Arnold LM et al. Pain Med 2007;8(8):633-638

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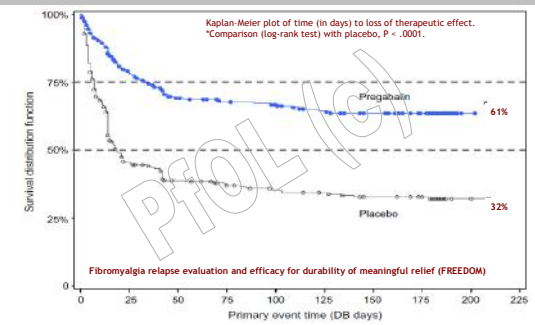
Pregabalin in Fibromyalgia (6 Months) - FREEDOM Study



Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM)

Crofford LJ et al. Pain 2008;136:419–431

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SNRIs: Published Trials vs Placebo

Agent	n	Duration (weeks)	Improvement (p<0.05)
Milnacipran[1]	125	12	Yes
Milnacipran[2]	125	12	Yes
Milnacipran[3]	888	27	Yes
Milnacipran[4]	1196	15	Yes
Duloxetine[5]	354	12	Yes
Duloxetine[6]	207	12	Yes
Duloxetine[7]	520	26	Yes
Venlafaxine[8]	15	8	Yes
Venlafaxine[9]	15	12	Yes
Venlafaxine[10]	90	6	No

Venlafaxine is NOT approved by FDA in fibromyalgia

1. Vitton O et al. Hum Psychopharmacol Clin Exp 2004; 19:S27-S35; 2. Gendreau RM et al. J Rheumatol 2005; 32:1975-1985; 3. Mease PJ et al. J Rheumatol 2009;36:398-409; 4. Clauw DJ et al. Clin Ther 2008;30:1988-2004; 5. Arnold LM et al. Pain 2005; 119:5-15; 6. Arnold LM et al. Arthritis Rheum 2004; 50:2974-2984; 7. Russell IJ et al. Pain 2008; 136:432–444; 8. Dwight MM et al. Psychosomatics 1998; 39:14-17; 9. Sayar K et al. Ann Pharmacother 2003; 37:1561-1585; 10. Zilstra TR et al. Arthritis Rheum 2002; 46:S105

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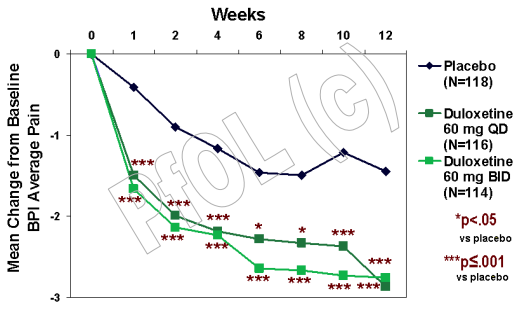
Duloxetine - BPI (Brief Pain Inventory) Average Pain Severity



Arnold LM et al. Pain 2005;119:5-15

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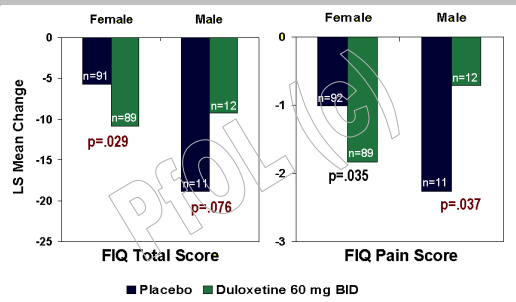
Duloxetine – FIQ (Fibromyalgia Impact Questionnaire) Results by Gender



Arnold LM et al. Arthritis Rheum 2004; 50(9):2974-2984

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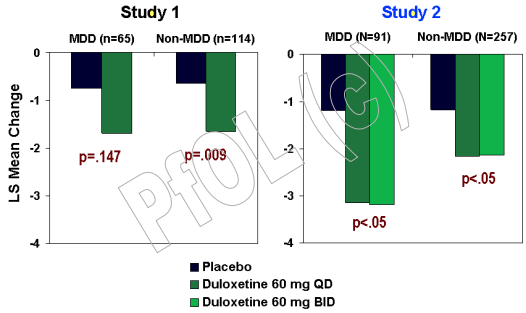
BPI Average Reduction by MDD Status in Female Patients



1. Arnold LM et al. Arthritis Rheum 2004; 50(9):2974-2984; 2. Arnold LM et al. Pain 2005;119:5-15

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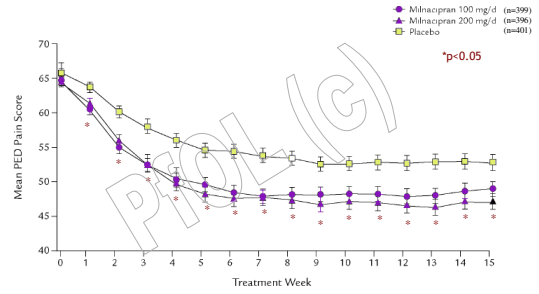
Mean (SEM) Weekly Patient Experience Diary (PED) Morning-Recall Pain Scores – Milnacipran (LOCF)



Clauw DJ et al. Clin Ther 2008;30:1988-2004

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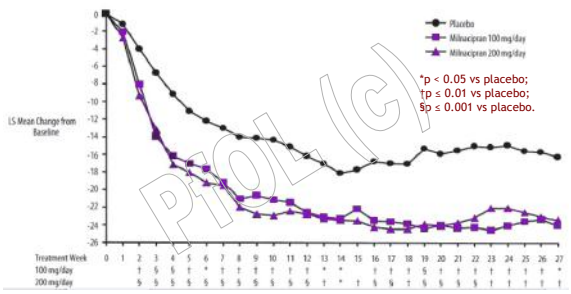
Least-squares (LS) Mean Change From Baseline In Weekly Average 24-hour Morning Recall Pain Scores



Mease PJ et al. J Rheumatol 2009;36:398–409

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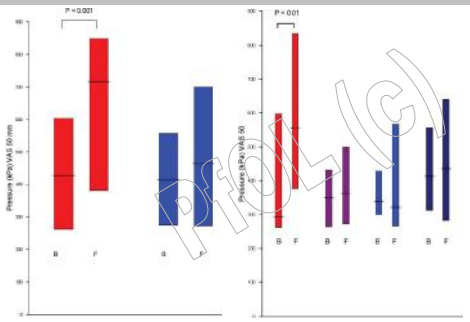
Milnacipran – Pressure Pain Sensivity in Patient Global Impression of Change



Increased (kPa) VAS 50mm values indicate a decreased sensitivity to pain.

B = before treatment,
F = following treatment.

Red bars = milnacipran PGIC responders (n=19),
Violet bars = milnacipran PGIC non-responders (n=17),
Lighter blue bars = placebo PGIC responders (n=15),
Dark blue bars = placebo PGIC non-responders (n=23).

Mainguy Y. Hum Psychopharmacol Clin Exp 2009; 24: S19–S23

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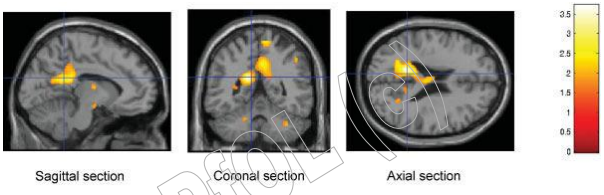
fMRI Activity Evoked by Painful Stimulation After Milnacipran Treatment Versus Placebo



The precuneus is indicated by the intersecting blue lines in the sagittal, coronal and axial sections.
Quantification of activity (increasing from dark red, through orange to yellow) is shown in the bar on the right

Mainguy Y. Hum Psychopharmacol Clin Exp 2009; 24: S19–S23

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Comparison of 6 Most Common Adverse Events in the Treatment of Fibromyalgia

Pregabalin[1] 300 mg/day (450 mg/day)	Duloxetine*[2] 60 or 120 mg/day	Milnacipran*[3] 200 mg/day
Dizziness 31% (43%)	Nausea (29%)	Nausea (40%)
Somnolence 18% (22%)	Headache (20%)	Headache (18%)
Headache 12% (14%)	Insomnia (18%)	Constipation (14%)
Weight gain 10% (10%)	Dry mouth (16%)	Hyperhydrosis (13%)
Dry mouth 6% (9%)	Constipation (15%)	Hot flush (10%)
Constipation 4% (7%)	Fatigue (15%)	Vomiting (8%)

1-3. FDA Approved drug prescription inserts

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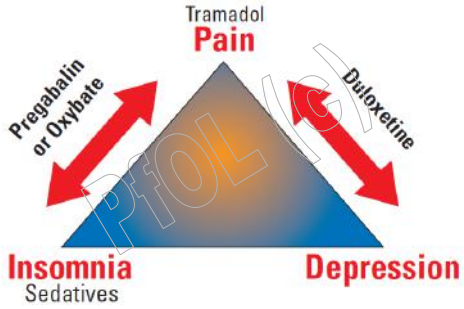
Strategic Polypharmacy in Fibromyalgia



Adapted from Russell IJ. CNS Spectr. Vol 13, No 3 (Suppl 5). 2008

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