Management of Fibromyalgia: Applying Multimodal Therapy to a Tough Condition

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Objectives

- Upon completion of this lecture, the participant will be able to:
  - Identify diagnostic criteria for fibromyalgia
  - Discuss the various pharmacologic and non-pharmacologic treatments available for individuals with fibromyalgia

Disclosures

- Speaker Bureau:
  - Sanofi-Pasteur, Merck, Takeda, Boehringer
- Consultant:
  - Sanofi-Pasteur, Takeda, Pfizer

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Overview: What Is Fibromyalgia?

- FM is a common chronic widespread pain condition
  - FM patients often have heightened sensitivity to pain (hyperalgesia); in addition, nonnoxious stimuli may result in pain (allodynia)
  - Patients may present with a wide range of additional symptoms including tenderness, sleep disturbances, fatigue, morning stiffness, cognitive complaints, and mood disorders

FM = fibromyalgia.
Wolfe et al. *Arthritis Rheum*. 1995;38:19-28; Staud and Rodriguez. *Nat Clin Pract Rheumatol*. 2006;2:90-98; Wolfe et al. *Arthritis Rheum*. 1990;33:160-172; Henriksson. *J Rehabil Med*. 2003;(suppl 41):89-94.

Proposed Etiology of Fibromyalgia

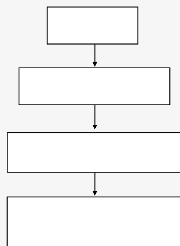
- Emerging evidence of a genetic component of FM
  - Specific gene mutations may predispose individuals to FM
  - Polymorphisms in the COMT enzyme and the serotonin transporter are potentially associated with FM and other disorders
- Environmental factors that may trigger the onset of FM
  - Physical trauma or injury
  - Infections (hepatitis C, Lyme disease, parvovirus, EBV)
  - Psychological stressors
- FM may occur concurrently with arthritis (OA), autoimmune diseases (RA, SLE), and hypothyroidism

COMT = catechol-O-methyltransferase; RA = rheumatoid arthritis; OA = osteoarthritis; SLE = systemic lupus erythematosus.
Zubieta et al. *Science*. 2003;299:1240-1243; Arnold et al. *Arthritis Rheum*. 2004;50:944-952; Clauw and Crofford. *Best Prac Res Clin Rheumatol*. 2003;17:685-701; Burckhardt et al. APS Clinical Practice Guideline Series, No.4. Glenview, IL; 2005.

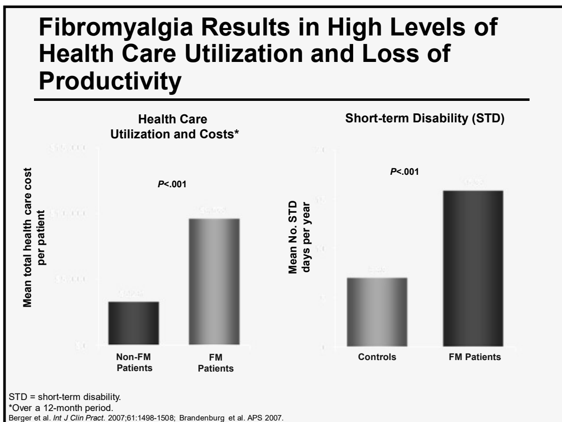
Epidemiology of Fibromyalgia

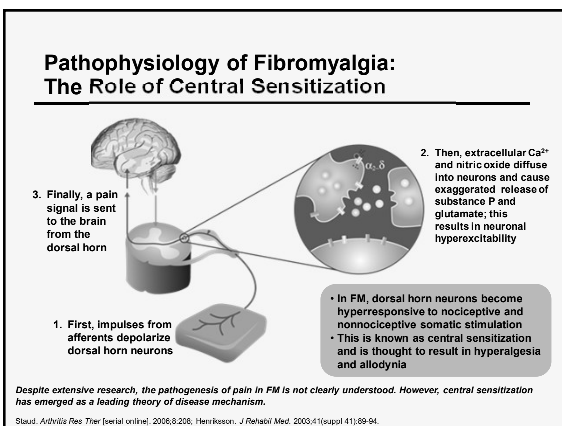
- Prevalence
  - FM is common worldwide and affects 5 million people or 2%-5% of US adult population
  - Majority of patients between the ages of 35 and 60 years
- Gender differences
  - Women are more likely to be diagnosed with FM than men (80-90%)

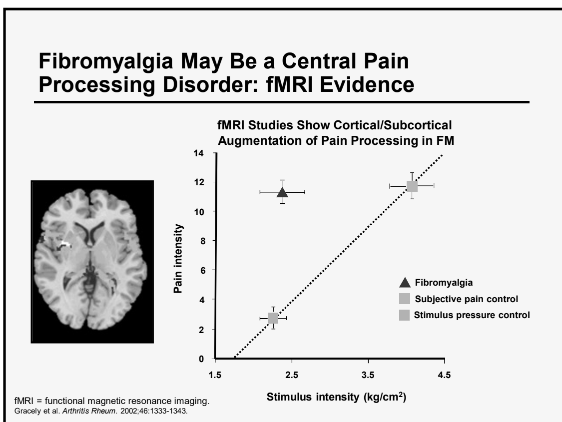
Determining FM Prevalence



Wolfe et al. *Arthritis Rheum*. 1995;38:19-28; Lawrence et al. *Arthritis Rheum*. 1998;41:778-799; Wolfe. *Am J Med*. 1986(suppl 3A);81:7-14; Weir et al. *J Clin Rheumatol*. 2006;12:124-128.


Fibromyalgia Results in High Levels of Health Care Utilization and Loss of Productivity
Health Care Utilization and Costs*
Short-term Disability (STD)
Mean total health care cost per patient
P<.001
Non-FM Patients
FM Patients
Mean No. STD days per year
P<.001
Controls
FM Patients
STD = short-term disability.
*Over a 12-month period.
Berger et al. Int J Clin Pract. 2007;61:1498-1508; Brandenburg et al. APS 2007.


Pathophysiology of Fibromyalgia: The Role of Central Sensitization
2. Then, extracellular Ca2+ and nitric oxide diffuse into neurons and cause exaggerated release of substance P and glutamate; this results in neuronal hyperexcitability
3. Finally, a pain signal is sent to the brain from the dorsal horn
1. First, impulses from afferents depolarize dorsal horn neurons
• In FM, dorsal horn neurons become hyperresponsive to nociceptive and nonnociceptive somatic stimulation
• This is known as central sensitization and is thought to result in hyperalgesia and allodynia
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.
Staud. Arthritis Res Ther [serial online]. 2006;8:208; Henriksson. J Rehabil Med. 2003;41(suppl 41):89-94.

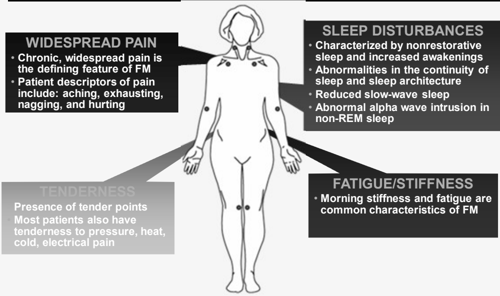

Fibromyalgia May Be a Central Pain Processing Disorder: fMRI Evidence
fMRI Studies Show Cortical/Subcortical Augmentation of Pain Processing in FM
Pain intensity
Stimulus intensity (kg/cm2)
Fibromyalgia
Subjective pain control
Stimulus pressure control
fMRI = functional magnetic resonance imaging.
Gracely et al. Arthritis Rheum. 2002;46:1333-1343.

Recent Study

- Brain imaging study reveals that patients with fibromyalgia (FM) show unique brain activity in response to pain.
- Patients had increased connectivity between the primary region of the brain that recognizes touch, the S1 somatosensory cortex, and a second region that assigns salience to stimuli, the anterior insula

Kim, J., Loggia, M. L., Cahalan, C. M., Harris, R. E., Beissner, F., Garcia, R. G., Kim, H., Barbieri, R., Wasan, A. D., Edwards, R. R. and Napadow, V. (2015), The Somatosensory Link in Fibromyalgia: Functional Connectivity of the Primary Somatosensory Cortex Is Altered by Sustained Pain and Is Associated With Clinical/Autonomic Dysfunction. Arthritis & Rheumatology, 67: 1395–1405. doi: 10.1002/art.39043

Clinical Features of Fibromyalgia

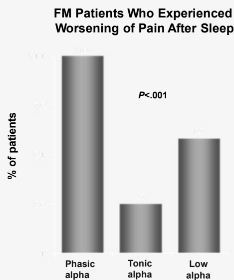


Wolfe et al. *Arthritis Rheum.* 1995;38:19-28; Leavitt et al. *Arthritis Rheum.* 1986;29:775-781; Wolfe et al. *Arthritis Rheum.* 1990:33:160-172; Roizenblatt et al. *Arthritis Rheum.* 2001;44:222-230; Harding. *Am J Med Sci.* 1998;315:367-376.

Fibromyalgia Is Often Associated With Sleep Disturbances

- Nonrestorative sleep is a prominent feature of FM
- FM patients report insomnia, early morning awakenings, and poor-quality sleep
- Alpha intrusion is a common but nonspecific EEG finding in FM patients
  - May interfere with sleep function and contribute to worsening of pain after sleep
  - Phasic, tonic, and low alpha are subtypes of alpha sleep intrusion observed in patients with FM

FM Patients Who Experienced Worsening of Pain After Sleep



EEG = electroencephalogram.

Roizenblatt et al. *Arthritis Rheum.* 2001;44:222-230; Harding. *Am J Med Sci.* 1998;315:367-376.

All of the Following Are Components of Fibromyalgia Except:

1. Non-restorative sleep
2. Widespread pain
3. Cognitive issues
4. Restless Leg Syndrome

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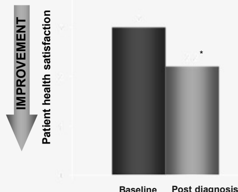
Diagnosis Is an Essential Component of Successful FM Management

- Diagnosis of FM improves health satisfaction
- ACR and Canadian criteria may be used to diagnose FM
- Broad-based differential diagnosis must be considered, including:
  - SLE, RA, OA, spondyloarthropathies, polymyalgia rheumatica

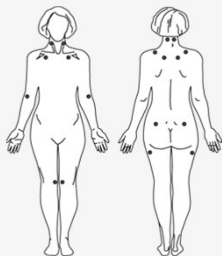


*Statistically significant versus baseline (*P* value not provided).

Goldenberg et al. *JAMA*. 2004;292:2388-2395; Wolfe et al. *Arthritis Rheum*. 1990:33:160-172; Jain et al. *J Musculoskelet Pain*. 2003;11(4):3-107; Hwang and Barkhuizen. *Curr Pain Headache Rep*. 2006;327-332; White et al. *Arthritis Rheum*. 2002;47:260-265.

American College of Rheumatology (ACR) Criteria for FM

- ACR criteria
  - History of chronic widespread pain ≥3 months
  - Patients must exhibit ≥11 of 18 tender points
- Widespread pain was found in 97% of patients with FM, compared with 70% in controls
- FM can be identified from among other rheumatologic conditions with use of ACR criteria
  - Criteria need further refinement as knowledge about FM evolves



ACR criteria are both sensitive (88.4%) and specific (81.1%)

Wolfe et al. *Arthritis Rheum*. 1990:33:160-172.

Canadian Diagnostic Criteria for FM

- Includes the ACR criteria and evaluates patients based on other symptoms commonly observed in FM (ie, sleep disturbance, fatigue)
- Chronic widespread pain and tenderness are core diagnostic features
- Clinical case definition of FM includes evaluation of additional clinical signs and symptoms commonly observed in patients with FM (neurocognitive manifestations, sleep disturbance, fatigue)
- Allows clinician to evaluate impact of entire clinical spectrum of FM and tailor treatment

Jain et al. *J Musculoskelet Pain.* 2003;11(4):3-107; Mease. *J Rheumatol Suppl.* 2005;75:6-21; Wolfe et al. *Arthritis Rheum.* 1990:33:160-172.

New Clinical Fibromyalgia Diagnostic Criteria – Part 1.

To answer the following questions, patients should take into consideration

- how you felt the **past week**,
- while taking your current therapies and treatments, and
- exclude your pain or symptoms from other known illnesses such as arthritis, Lupus, Sjogren's, etc.

Determining Your Widespread Pain Index (WPI)
The WPI Index score from Part 1 is between 0 and 19.

Criteria Needed for a Fibromyalgia Diagnosis

1. Pain and symptoms over the past week, based on the total of:
   Number of painful areas out of 18 parts of the body
   Plus level of severity of these symptoms:
   - Fatigue
   - Waking unrefreshed
   - Cognitive (memory or thought) problems

   Plus number of other general physical symptoms
2. Symptoms lasting at least three months at a similar level
3. No other health problem that would explain the pain and other symptoms

Source: American College of Rheumatology, 2010

http://neuro.memorialhermann.org/uploadedFiles/_Library_Files/MNII/NewFibroCriteriaSurvey.pdf accessed 06-07-2015

New Clinical Fibromyalgia Diagnostic Criteria

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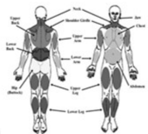
Determining Your Widespread Pain Index (WPI)
The WPI Index score from Part 1 is between 0 and 19.

Check each area you have felt pain in over the past week.

- ☐ Shoulder girdle, left
- ☐ Shoulder girdle, right
- ☐ Upper arm, left
- ☐ Upper arm, right
- ☐ Lower arm, left
- ☐ Lower arm, right
- ☐ Hip (buttock) left
- ☐ Hip (buttock) right
- ☐ Upper leg left
- ☐ Upper leg right
- ☐ Lower leg left
- ☐ Lower leg right
- ☐ Jaw left
- ☐ Jaw right
- ☐ Chest
- ☐ Abdomen
- ☐ Neck
- ☐ Upper back
- ☐ Lower back
- ☐ None of these areas



Count up the number of areas checked and enter your Widespread Pain Index or WPI score score here _____.

http://neuro.memorialhermann.org/uploadedFiles/_Library_Files/MNII/NewFibroCriteriaSurvey.pdf accessed 06-07-2015

New Criteria

- Determining Widespread Pain Index (WPI)
  - Score: 0-19
- Determine Symptom Severity Score (SS)
  - Part 2a: Score: 0-9
  - Part 2b: Score: 0-3
- Add up score
  - Total score will provide likelihood of FM or other diagnoses

http://neuro.memorialhermann.org/uploadedFiles/_Library_Files/MNII/NewFibroCriteriaSurvey.pdf accessed 06-07-2015

Example of Comprehensive Diagnostic Workup for Fibromyalgia

Confirm history of chronic, widespread pain for ≥3 months

Physical exam, patient history, laboratory testing

Rule out other conditions that may present with chronic widespread pain

Administer WPI/SS

Confirm diagnosis of fibromyalgia

Adapted from Burckhardt et al. APS Clinical Practice Guideline Series, No.4; 2005.

Most Patients With Fibromyalgia Will Require Multimodal Therapies

One of the Most Important Treatments

- Listen to patient
- Validate symptoms
- Set realistic expectations

Dr. Brian Wallit, National Institutes of Health Lecture 2016

Management of Fibromyalgia (FM)

Nonpharmacologic

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

Pharmacologic

- Antidepressants
- Analgesics
- Anticonvulsants
- Analgesics

Goldenberg et al. *JAMA*. 2004;292:2388-2395; Clauw et al. *Best Prac Res Clin Rheumatol*. 2003;17:685-701; Arnold et al. *Arthritis Rheum*. 2007;56:1336-1344.

Nonpharmacologic Therapies*

- 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.

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, VSGI	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; VSGI = 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*.

Guidance on TCA's

- Significant anticholinergic effects
- Dose mainly at bedtime
- Consider ECG prior to initiating
- Caution with SSRI's or SNRI's due to serotonin syndrome
- Dosing:
  - Amitriptyline 10 mg – 150 mg at bedtime
  - Nortriptyline 25 mg – 150 mg at bedtime

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)*: Published Trials

Study	Agent	N	Study Duration (weeks)	Primary End Point	Significant Improvement
Vitton et al† (2004)	Milnacipran vs PBO	125	12	Pain intensity (pain diary)	Yes
Gendreau et al† (2005)	Milnacipran vs PBO	125	12	Average daily pain score	Yes
Arnold et al (2005)	Duloxetine vs PBO	354	12	BPI average pain severity	Yes
Arnold et al (2004)	Duloxetine vs PBO	207	12	FIQ (total and pain)	Yes (FIQ total) No (FIQ pain)
Dwight et al (1998)	Venlafaxine vs PBO	15	8	McGill Pain Questionnaire VAS	Yes
Sayar et al (2003)	Venlafaxine vs PBO	15	12	FIQ Pain score	Yes

*.

†Both publications are based on the same trial.

BPI = Brief Pain Inventory; VAS = Visual Analog Score.

Vitton et al. *Hum Psychopharmacol Clin Exp*. 2004;19:S27-S35; Gendreau et al. *J Rheumatol*. 2005;32:1975-1985; Arnold et al. *Pain*. 2005;119:5-15; Arnold et al. *Arthritis Rheum*. 2004;50:2974-2984; Dwight et al. *Psychosom*. 1998;39:14-17; Sayar et al. *Ann Pharmacother*. 2003; 37:1561-1565.

SNRI's

- Likely all within class are beneficial
- Duloxetine:
  - 30 mg – 120 mg daily
  - Caution: short ½ life
  - Slow taper
- Milnacipran
  - 50 mg two times daily
  - Slow increase: 12.5 mg po qd x 1 day then 12.5 mg po bid x 2 days then 25 mg po bid x 4 days and then 50 mg po bid
  - Maximum: 200 mg daily
- Monitor blood pressures in individuals on these medications
- Caution in patients with hepatic disease

Analgesics*: Published Trials

Study	Agent	N	Study Duration (weeks)	Primary End Point	Significant Improvement
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†	38	200	Improvement in pain	No
Russell et al (2000)	Tramadol vs PBO	100	9	Time to discontinuation	Yes
Biasi et al‡ (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.**

†Doses of morphine equivalent per 24 hour were determined; ‡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.

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.

AE's

- Pregabalin
  - No effects on GABA
    - Thought to work on alpha2-delta subunits of the calcium channels reducing neurotransmitter release
    - Anti-nociceptive effects
  - Dosing: 150 mg – 225 mg po bid
  - Start at 75 mg bid x 1 week
  - Maximum: 450 mg/day
  - Taper slowly
  - Dosage adjustment with renal disease
  - Schedule V

AE's

- Gabapentin
  - Not FDA approved for FM
  - Does not work on GABA; exact mechanism unknown but is believed to block voltage-dependent calcium channels
  - 100 mg – 1200 mg
  - Dose in two time daily dosing
  - Not a scheduled medication like pregabalin
  - Adjust dosing in patients with renal disease

Which of the Following Medications is FDA Approved for Fibromyalgia

A. Amitriptyline
B. Gabapentin
C. Milnacipran
D. Venlafaxine

Other Treatments to Correct Sleep and Improve Pain

- Help to correct sleep issue
  - Consider sleep apnea
  - Trazodone or similar
  - Some evidence that pramipexole (Mirapex) may be beneficial; it is currently under investigation for fibromyalgia pain
- Consider treatment with muscle relaxants, particularly at bedtime (cyclobenzaprine, tizanidine)

http://emedicine.medscape.com/article/329838-medication accessed 06-07-2015

Other Treatments to Correct Sleep and Improve Pain

- NSAIDs or acetaminophen provide very little benefit
- Alpha 2 agonists (eg, clonidine)
  - May help sleep
- Dopamine agonists (eg, pramipexole)
- Consider: tiagabine (Gabitril): 2-12 mg at bedtime
- Naltrexone: 9 mg – 50mg once daily
- Tramadol 50 mg – 100 mg every 8 hours
- Consider B blockers for patients with orthostatic hypotension/tachycardia (POTS)

http://emedicine.medscape.com/article/329838-medication accessed 06-07-2015

Memantine

- Small, double-blinded placebo controlled trial
- 20 mg memantine vs. placebo
- 6 month trial
- Patients in memantine trial had:
  - Statistically significant reduction in pain
  - Other secondary benefits: improved QOL scores
- Side effects:
  - Dizziness most significant

Olivan-Blázquez, Bárbara; Herrera-Mercadal, Paola; Puebla-Guedea, Marta; More **Pain**. 155(12):2517-2525, December 2014

Additional Reported Options

- Dextromethorphan: anecdotal evidence that it is helpful
  - NMDA receptor antagonist
- Topical Capsaicin may helpful
- The selective estrogen receptor modulator raloxifene (Evista), 60 mg every other day has been shown to be effective in improving pain, improving fatigue, reducing tender-point count, and improving daily functioning in postmenopausal women with fibromyalgia
- Modafinil (Provigil), approved for narcolepsy and shift-work sleep disorder, 100-200 mg in the morning, improves fatigue and cognitive disturbances
- Beta blocker (propranolol) at bedtime – can help with pain

http://emedicine.medscape.com/article/329838-medication accessed 06-07-2015

Additional Treatments

- Synthetic cannabinoid nabilone (Cesamet) in doses escalating from 0.5 mg daily to 1 mg twice daily improves pain and anxiety in fibromyalgia
- Numerous patients with fibromyalgia are requesting medical marijuana

Summary

- Fibromyalgia is a common condition affecting millions of individuals
- Many are unhappy with current management
- Numerous options exist for treatment
  - These patients are frequently going to require multimodal therapies