Diagnosis and Management of Fibromyalgia Syndrome

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Disclosure Statement
Purpose: To advance the care of fibromyalgia syndrome patients
Investigator: NIH, Pfizer Inc.
Speakers Bureau: Pfizer Inc., Eli Lilly and Company, Forest Pharmaceuticals Inc., Takeda Pharmaceuticals
Advisory Board: Takeda Pharmaceuticals

I frequently reevaluate my corporate relationships
I welcome critique of this presentation and all its content. If you feel the material presented was inappropriate or unbalanced, please contact me at chad.boomershine@vanderbilt.edu.
Main References


Objectives

1. Understand the etiology of Fibromyalgia syndrome (FMS)
2. Diagnosis and differential diagnosis of FMS
3. Use the FIBRO mnemonic for FMS assessment
4. Use the mVASFIQ in evaluation and treatment of FMS symptoms
5. Review therapies used for management of FIBRO symptoms; Fatigue/Fibrofog, Insomnia, Blues, Rigidity and Pain
Fibromyalgia Syndrome (FMS)

• ~4% of the world population have FMS\textsuperscript{1,2}
  – True FMS prevalence likely ~50% higher
  – Prevalence increases with age

• Reported 9:1 female: male gender bias
  – True ratio likely closer to 4:1
  – Men self-medicate and do not seek medical care
  – Women more likely to meet classification criteria

Widespread pain ≥3 months:
  bilateral, above and below the waist
  including the axial skeleton

Pain with 4kg/cm\textsuperscript{2} pressure at ≥11 of 18 Tender points:

1) Occiput- at insertion of suboccipital muscles
2) Trapezius- at midpoint of upper border
3) Supraspinatus- at origins above scapula spine near medial border
4) Gluteal-in upper outer quadrants of buttocks in anterior fold of muscle
5) Greater trochanter- medial and posterior to the trochanteric prominence
6) Low cervical- anterior aspects of intertransverse spaces at C5-7
7) Second rib- second costochondral junction just lateral to the junctions on upper surfaces
8) Lateral epicondyle- 2cm distal to the epicondyles
9) Knee- At medial fat pad proximal to the joint line
FMS is more than Pain

OMERACT 9 Hierarchy of domains for fibromyalgia

FATIGUE

INSOMNIA

BLUES Depression

Anxiety

RIGIDITY (Stiffness)

Pain

Work difficulty

ACR Criteria miss 46% of FMS patients

Survey criteria:
- 8 of 19 painful areas
- ≥6 score on fatigue problem scale (FPS)
- More sensitive but less specific

Stop using the American College of Rheumatology criteria in the clinic.


3 Katz et al., A&R 2006, 54, 1, 169-76.
Proposed Fibromyalgia Clinical Diagnostic Criteria¹

1) Widespread Pain Index (WPI): Note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.

2) Symptoms Severity Score (SS):

   Fatigue
   Waking unrefreshed
   Cognitive symptoms

   For the each of the three symptoms above, indicate the level of severity over the past week:
   0 = No problem
   1 = Slight or mild problem; generally mild or intermittent
   2 = Moderate; considerable problem; often present and/or at a moderate level
   3 = Severe: pervasive, continuous, life-disturbing problem

   Considering somatic symptoms in general, indicate whether the patient has:
   0 = No symptoms, 1 = Few symptoms, 2 = A moderate number, 3 = A great deal of symptoms

   The Symptom Severity score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) and the level of somatic symptoms. The score is between 0 and 12.

   A patient satisfies clinical diagnostic criteria for fibromyalgia if the following 2 conditions are met:
   1) Widespread pain index is ≥7 and symptom severity score is ≥5 OR Widespread pain index is between 3-6 and symptom severity score scale ≥9.
   2) Symptoms have been present at a similar level for at least 3 months.

FMS Pain Etiology¹

1) Injury activates peripheral nerves

2) Excitatory signals by peripheral nerves to Inter-neurons = PAIN

3) Inhibitory signals turn off pain and reset the system to baseline

4) Dysregulation of excitatory and inhibitory signals results in FMS

BRAIN=PAIN

NMDA-glutamate
Norepinephrine (NE)
Serotonin (5-HT)
GABA and Opioids

Substance P
Nitric Oxide

FMS treatments decrease excitatory signals and increase inhibitory signals to restore balance

Presented at the 2009 ACR/ARHP Scientific Meeting Sunday October 18, 2009.
“Optimal treatment requires a multidisciplinary approach ... tailored according to pain intensity, function, associated features, such as depression, fatigue and sleep disturbance ...”

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**mVASFIQ**

**Fatigue**  
Fibrofog  
**Insomnia**  
**Blues**  
Depression  
**Anxiety**  
**Rigidity** = Stiffness  
**Ow!**  
Pain  
**Work difficulty**

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**FMS management**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>7</th>
<th>8</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>No problem</td>
<td>Very Severe Problem</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Blues</td>
<td>Not depressed</td>
<td>Very depressed</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anxiety</td>
<td>Not anxious</td>
<td>Very anxious</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pain</td>
<td>No pain</td>
<td>Very severe</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

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Patient Global Impression of Change

SINCE MY FIRST VISIT, my overall status is (Circle the number that best describes your overall status):

1. Very Much Improved
2. Much Improved
3. Minimally Improved
4. No Change
5. Minimally Worse
6. Much Worse
7. Very Much Worse

VAS Scores measure improvement well but do a poor job of indicating symptom worsening.

Fibromyalgia is Poorly Treated

- FMS misconceptions complicate care
  - FMS patients require too much time
  - FMS patients don’t get better
  - FMS is not a “real” disease
- FMS patients CAN be managed in clinic
  - Rapid evaluation and treatment approach
- Effective FMS treatments exist
  - Must manage ALL FMS symptoms
- Objective evidence for FMS
FMS Evaluation Algorithm

1. Patient evaluation
   - Does the patient have diffuse widespread pain (bilateral, above and below the waist including the axial spine)?
   - Physical examination, differential diagnosis, and laboratory evaluation
   - Does the patient have another condition that could explain their pain?

2. Consider alternative diagnosis
   - Treat fibromyalgia symptoms and individualize therapy using the mVAS/RQ
   - Administer mVAS/RQ to all patients and use answers to individualize therapy

3. Persistent symptoms
   - Treat fibromyalgia symptoms: all patients get "PAIN"
     - Prednisolone or minocycline: prednisolone (25-75 mg at night) if high insomnia score, duloxetine (20-30 mg in morning) if high depression score or minocycline (12.5 mg in morning) if high fatigue score
     - Activity: daily stretching, both low-impact aerobic and resistance exercise alternating every other day
     - Information: diseases fibromyalgia, provide information (e.g. http://www.knowfibro.com) and support group sources (e.g. http://www.thefibro.org/site/PageServer?pagename=community_supportGroupDirectory)
     - Non-narcotics: avoid naprenics, benzodiazepines and steriods

Differential Diagnosis and Work-up

1. CBC, CMP, and urinalysis (anemia, Paget’s disease ↑alk phos, liver disease, hematuria or infection)
2. TSH (Thyroid disease)
3. Vitamins and minerals: B12, Folate, Iron Studies, Vitamin D
4. HIV and Hepatitis B and C (especially if risk factors present)
5. Inflammation markers-ESR, CRP (rheumatic diseases)
6. If muscle weakness check creatinine kinase, aldolase, LDH (myositis or muscular dystrophies)
7. If history of rash and contact with ticks or kids check infectious serologies (B19, ricketsia, mononucleosis, etc.)
8. Cancer screenings as appropriate
All FMS patients get P.A.I.N.¹

- **P**rescription medications for **P**ain based on associated symptoms:
  - *P*regabalin 25-75mg qhs titrated up to 150-225bid if **I**nsomnia
  - *D*uloxetine 20/30/60 mg qam if **D**epressed
  - *M*ilnacipran 25/50/100 mg qam or bid if **F**atigue or **F**ibrofog

- **A**ctivity: Daily morning stretching along with alternating days of aerobic and resistance exercise 6 days per week.


- **N**o **N**arcotics: Avoid narcotics, benzodiazepines, and steroids
  - Use Tylenol, Cyclobenzaprine, Tramadol, NSAIDs

Education and Exercise Recommendations
Self-help + Aerobic + Resistance Combination Best¹

- Self-directed programs
  - Educational websites
    - www.knowfibro.com includes free cognitive behavioral modules
  - Morning Stretches
  - Low-impact Aerobic exercise (walking, elliptical, stationary bicycle)
  - Resistance exercise with Therabands®

- VCIH (www.VCIH.org) and Dayani (www.dayanicenter.org) programs
  - Dayani: Arthritis Foundation Exercise & Self-Help Programs
  - VCIH: YOGA, TaiChi, Quigong
  - Dayani: Water- and land-based exercise

¹ Weksa DS, Arch Intern Med 2007;167:2192–2199

Pharmacotherapy of FMS
General points:
1) Must rule out and treat disorders that can mimic FMS before symptomatic therapies are used.
2) Medications should be started individually at low dose and slowly up-titrated and/or combined since over half of FMS patients suffer from multiple medication intolerances.¹ Multiple medications or combinations may need to be tried before finding one the patient will tolerate.
3) Medications have a limited role in FMS treatment, to limit symptoms so patients can participate in non-pharmacologic modalities that provide long-term disease management (exercise, behavioral, and education).² Nonpharmacologic therapies should be used when possible.

FMS “Anchor” drugs

- **Pregabalin (Lyrica)**¹
  - α₂δ calcium channel antagonist
    - Decreases presynaptic excitatory neurotransmitter release (ascending pain pathways)
  - FDA approved for FMS, DPN, PHN, and add-on therapy for seizure disorders
  - Approved FMS doses 150 or 225mg twice daily
    - Start with 25-75mg with dinner/evening snack
    - AM dose not usually required unless patient has severe allodynia or neuropathic symptoms
      - may worsen fatigue and fibrofog


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### Pregabalin: adverse reactions¹

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>150 mg/d</th>
<th>300 mg/d</th>
<th>450 mg/d</th>
<th>600 mg/d</th>
<th>Placebo</th>
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<td>43</td>
<td>45</td>
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<tr>
<td>Somnolence</td>
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<td>18</td>
<td>22</td>
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<td>Weight gain</td>
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<td>2</td>
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<tr>
<td>Increased appetite</td>
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<td>3</td>
<td>5</td>
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<td>Peripheral Edema</td>
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<td>6</td>
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<tr>
<td>Fatigue</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>4</td>
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<tr>
<td>Attention disturbance</td>
<td>4</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Memory impairment</td>
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<td>3</td>
<td>4</td>
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<td>Euphoric Mood</td>
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<td>5</td>
<td>6</td>
<td>7</td>
<td>0</td>
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<tr>
<td>Vision blurred</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>12</td>
<td>1</td>
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<tr>
<td>Dry mouth</td>
<td>7</td>
<td>6</td>
<td>9</td>
<td>9</td>
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<td>Constipation</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>10</td>
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</table>

Pregabalin - Warnings and Precautions

- Angioedema, risk increased with ACE inhibitor use
- Hypersensitivity reactions can occur
- Theoretical seizure risk - gradually discontinue
- Antiepileptic drugs, including LYRICA, may increase the risk of suicidal thoughts or behavior.
- Peripheral edema-noncardiac, increases with dose
- Dizziness and Somnolence-avoid CNS depressants and heavy machinery
- Weight gain
- Tumorigenic potential in mice, unknown human risk
- Ophthalmological effects - blurred vision
- Creatinine Kinase Elevations
- Decreased Platelet Count
- PR Interval Prolongation

FMS “Anchor” drugs

- Duloxetine (Cymbalta)¹
  - Serotonin and Norepinephrine Reuptake Inhibitor
    - Thought to act by increasing activity of descending anti-nociceptive pathways (opposite of pregabalin)
  - FDA approved for FMS, Depression, DPN, and generalized anxiety disorder
  - Approved dose 60mg once daily
    - Start with 20-30mg with breakfast
    - Titrate up in weekly increments if needed

**Duloxetine: Warnings and Precautions**

- Black Box warning for Suicidality in children and young adults
- Hepatotoxicity risk – Monitor LFTs and avoid alcohol use
- Avoid in patients with hepatic insufficiency or CrCl <30 mL/min
- Blood pressure-hypertension, hypotension/syncope and tachycardia
- Serotonin Syndrome/Neuroleptic Malignant Syndrome
- Abnormal Bleeding Risk
- Withdrawal symptoms with discontinuation, especially when abrupt
  - dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures
- Activation of mania or hypomania-consider bipolar disease screen
- Caution in patients with history of seizure disorder
- Avoid Inhibitors of CYP1A2 or Thoridazine
- Diabetics-worsening glycemic control and slows gastric emptying
- Urinary hesitancy and retention
- Narrow angle glaucoma
- Hyponatremia especially elderly

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<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Duloxetine</th>
<th>Placebo</th>
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<tr>
<td>Nausea</td>
<td>29</td>
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<tr>
<td>Decreased appetite</td>
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<td>2</td>
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<tr>
<td>Dry mouth</td>
<td>18</td>
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<td>Constipation</td>
<td>15</td>
<td>4</td>
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<tr>
<td>Diarrhea</td>
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<td>8</td>
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<tr>
<td>Headache</td>
<td>20</td>
<td>12</td>
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<tr>
<td>Fatigue</td>
<td>15</td>
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<tr>
<td>Insomnia</td>
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<tr>
<td>Somnolence</td>
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<td>3</td>
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<tr>
<td>Agitation</td>
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<tr>
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<td>7</td>
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<td>Orgasm Abnormal</td>
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<td>Libido decreased</td>
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<td>&lt;1</td>
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<td>Ejaculation disorder</td>
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<td>Penis disorder</td>
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<tr>
<td>Hyperhidrosis</td>
<td>7</td>
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</table>
**FMS “Anchor” drugs**

- **Milnacipran** (Savella)
  - Norepinephrine and Serotonin Reuptake Inhibitor
    - Thought to act by increasing activity of descending anti-nociceptive pathways (opposite of pregabalin)
  - FDA approved for FMS management
  - Anti-depressant in Europe (1998) and Japan (1999)
  - Approved dose 50-100 mg twice daily
    - Dose-titration pack-start with 12.5 mg with breakfast
    - Some patients tolerate better only in am

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**Milnacipran: adverse reactions**

<table>
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<th>Adverse Reaction</th>
<th>100 mg/day</th>
<th>200 mg/day</th>
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<td>Headache</td>
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<td>Migraine</td>
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<td>3</td>
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<td>Dizziness</td>
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<td>Hot flush</td>
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<td>Palpitations</td>
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<td>Heart rate increased</td>
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Milnacipran: Warnings and Precautions

- Black Box warning for Suicidality in children and young adults
- Hepatotoxicity risk – Monitor LFTs and avoid alcohol use
- Blood pressure-hypertension, hypotension/syncope and tachycardia
- Serotonin Syndrome/Neuroleptic Malignant Syndrome
- Abnormal Bleeding Risk
- Withdrawal symptoms with discontinuation
- Theoretical risk for activation of mania or hypomania
- Caution in patients with history of seizure disorder
- Avoid in patients with substantial alcohol use or chronic liver disease
- Urinary hesitancy and retention
- Narrow angle glaucoma
- Hyponatremia

Use 50% dose if CrCl 5-29 mL/min

Which to choose?

- Methodological differences between treatment trials make direct efficacy comparisons impossible
  - Pregabalin if sleep problems predominate
    - Limit daytime use if fatigue or cognitive dysfunction severe
  - Duloxetine if depression or anxiety problematic
    - Avoid if renal/liver dz; caution in diabetes, migraine, insomnia, IBS
  - Milnacipran if fatigue or cognitive dysfunction primary
    - Avoid in liver disease; caution in IBS, migraine
- Combination therapy may be beneficial
  - Decreased pain with gabapentin-venlafaxine combination in DPNP patients who failed gabapentin monotherapy
  - Pregabalin with duloxetine or milnacipran
NON-FDA Approved Substitutes

• Older specific serotonin reuptake inhibitors (SSRIs) have norepinephrine activity and can improve FMS symptoms at higher doses (fluoxetine up to 80mg/d)\(^1\)
  – Combine SSRI with an agent that inhibits norepinephrine reuptake such as tricyclic antidepressant (TCA: amitriptyline) or trazadone
  – Amitriptyline 25mg qhs with fluoxetine 20mg qam particularly good
  – Risk for serotonin syndrome when combining serotonin-active drugs

• Amitriptyline provides balanced norepinephrine and serotonin re-uptake inhibition and has been shown in multiple meta-analyses to be effective in FMS patients\(^2,3\)

• Gabapentin at mean dose of 1800mg per day divided tid has demonstrated efficacy in treating FMS\(^4\)

• Tolerability can be problematic

FIBRO mnemonic for FMS\(^1\)

• Fatigue and Fibrofog

• Insomnia (Sleep Disturbance)

• Blues (Depression/Anxiety)

• Rigidity (Stiffness/Inactivity)

• Ow! (Widespread Pain and Work Difficulty)
Fatigue and Fibrofog

• Non-stimulant wakefulness promoting agents
  – Modafinil (Provigil)
    • FDA-approved for obstructive sleep apnea (OSA), narcolepsy, and shift-work-syndrome
    • 3 reports supporting use in treating FMS fatigue\(^1\),\(^2\),\(^3\)
      – Doses ranged from 50-400mg daily given as a single am dose or divided morning and noon
  – Armodafinil (Nuvigil) active enantiomer of modafinil

• Stimulants- methylphenidate (Ritalin), dexamethylphenidate (Focalin), amphetamines (dextroamphetamine)
  – Methylphenidate 5-10mg qam and noon
    • SR preparation allows once daily dosing

Stimulant Risks

• Drug abuse [U.S. Boxed Warning]: Potential for drug dependency exists; avoid abrupt discontinuation. Use caution in patients with history of ethanol or drug abuse.

• Cardiovascular events: Stimulant use has been associated with serious cardiovascular events including sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems (sudden death, stroke, and MI in adults). Stimulant use should be avoided in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could further increase their risk of sudden death. Patients should be carefully evaluated for cardiac disease prior to initiation of therapy.

• Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate.

• Psychiatric disorders: Use with caution in patients with pre-existing psychosis or bipolar disorder (may induce mixed/manic episode). May exacerbate symptoms of behavior and thought disorder in psychotic patients; new onset psychosis or mania may occur with stimulant use; observe for symptoms of aggression and/or hostility.

• Seizure disorder: Use with caution in patients with a history of seizure disorder; may lower seizure threshold leading to new onset or breakthrough seizure activity.

• Visual disturbance: Difficulty in accommodation and blurred vision has been reported with the use of stimulants.
Fatigue and Fibrofog
• Norepinephrine reuptake inhibitors
  – Atomoxetine (Strattera)
    • 80-120mg daily improved FMS symptoms\(^1\)
  – Reboxetine (Edronax, Vestra in Europe)
    • 8-10 mg daily improved FMS fatigue symptoms\(^2\)
  – Esreboxetine phase II trial in FMS\(^3\)
    • 2-8 mg daily improved pain, fatigue, global function
    • AEs included HYPERHIDROSIS, DRY MOUTH, HA, CONSTIPATION, INSOMNIA, NAUSEA, DIZZINESS

FIBRO pneumonic for FIQ VASs
• Fatigue and Fibrofog
• Insomnia (Sleep Disturbance)
• Blues (Depression/Anxiety)
• Rigidity (Stiffness/Inactivity)
• Ow! (Widespread Pain and Work Difficulty)
Insomnia Evaluation

• Identify specific sleep problem
• Restless legs syndrome (RLS), obstructive sleep apnea (OSA)
  – RLS in 1/3 of FMS patients, screen using RLS Study Group criteria\(^1\)
    • Have you ever experienced a disagreeable feeling in the legs, with aching, creeping, and motor restlessness, with an urge to move the legs? If answer YES, ask:
      – Do these symptoms appear mainly when sitting or lying down?
      – Are these symptoms worse at night?
      – Is any relief of these symptoms obtained by leg movement or walking?
    – Patient Berlin Questionnaire criteria\(^2\) should have formal sleep study
      • Persistent snoring and daytime somnolence and hypertension or obesity predicts OSA with 86% sensitivity and 77% specificity\(^2\)
      • Epworth Sleepiness Scale is very poor at identifying OSA

RLS Management

• Replete iron stores
  – Ferritin should be ≥50ug/L (100 optimal), %iron saturation ≥20%\(^1\)
    • If inflammation present, divide ferritin by 3 to get true value
    • soluble transferrin receptor (mg/L)/ferritin (mcg/L) ratio
      – If <1 likely anemia of chronic disease, if >2 likely iron deficiency anemia
  • Dopamine agonists
    – Pramipexole (Mirapex) and ropinirole (Requip) FDA approved for RLS
    – Both have also demonstrated efficacy in managing FMS\(^2,3\)
    – Start at low dose (0.125mg for pramipexole and 0.25mg for ropinirole) 2 hours before bedtime
    – Increased in weekly intervals until RLS symptoms resolve or patients become intolerant
      • Recommended maximum daily doses for RLS treatment are pramipexole 0.5mg and ropinirole 4mg
      • Higher doses are required for FMS symptoms (mean 4.5mg for pramipexole and 6mg for ropinirole)
    – Generic carbidopa/levodopa (25 and 100mg, respectively) combination tablets can be used to treat RLS off-label
**Insomnia Treatments**

- Benzodiazepines should be avoided in FMS patients
- Sedating antidepressants can benefit depressed patients
- Ramelteon (Rozerem) and eszopiclone (Lunesta) are the only nonbenzodiazepine FDA approved therapies for insomnia
  - Ramelteon is a selective melatonin receptor agonist given as 8mg tablet 90 minutes before bedtime followed by a hot shower
    - Usually well tolerated, no sedation, no “hang-over” the next day
  - Eszopiclone is a nonbenzodiazepine hypnotic given as a 1, 2 or 3mg tablet immediately before bedtime
    - Patients should be monitored for worsening depression or suicidal ideation
    - Use with other sedatives should be avoided
      - Headache and dysgeusia (unpleasant taste sensation) can limit tolerability
- Sodium Oxybate (Xyrem or GHB)
  - Shown to improve sleep and global FMS symptoms\(^1\)
  - Tightly controlled, FMS approval pending

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**FIBRO pneumonic for FIQ VASs**

- **F**atigue and **F**ibrofog
- **I**nsomnia (Sleep Disturbance)
- **B**lues (Depression/Anxiety)
- **R**igidity (Stiffness/Inactivity)
- **O**w! (Widespread Pain and Work Difficulty)
Antidepressants

- FMS patients often have major depressive disorder (30%) or an anxiety disorder (40%)
- Duloxetine is the recommended first-line treatment
- Milnacipran should have similar antidepressant effects
- Venlafaxine (Effexor) is generic SNRI shown to improve FMS symptoms at dose of 75mg once daily
  - SNRIs should be gradually tapered as rebound increases in depression and withdrawal symptoms commonly occur
- Older selective serotonin reuptake inhibitors (SSRIs): fluoxetine (Prozac) and paroxetine (Paxil)
  - Inhibit norepinephrine reuptake at 40-80mg per day
  - High doses often poorly tolerated


Sedating Antidepressants

- TCAs: amitriptyline and cyclobenzaprine
  - Low evening doses (5-10mg cyclobenzaprine, 10-50mg amitriptyline)
  - Intolerance to higher doses often makes TCA monotherapy insufficient to manage FMS or mood disorders
  - Combining low-dose TCAs with fluoxetine 20mg daily can provide synergy for treating FMS symptoms with minimal side effects
- Mirtazapine (Remeron) enhances serotonergic and noradrenergic neurotransmission via a novel mechanism
  - May allow use in patients who do not tolerate traditional SNRIs
  - 15-30mg at night improves FMS pain, insomnia, fatigue, depression
  - Somnolence inversely proportional to dose, increase if too sedating
- Trazodone is the most sedating antidepressant
  - 100mg qhs improves sleep architecture
  - Reserved for refractory insomnia

Pharmacopsychiatry (2000) 37: 166-170
Neuropsychobiol 51: 148-163
**FIBRO pneumonic for FIQ VASs**

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**Stiffness Treatments**

- **Daily morning stretching exercise**
- **Cyclobenzaprine** (Flexeril)
  - Structurally similar to TCAs
  - Significantly improves global FMS symptoms along with pain, sleep, and tender points
  - 30-50mg divided over the day can manage FMS “flares”
    - Dose typically limited by sedation
    - Nightly 15 or 30mg extended release (Amrix) is less sedating
  - Monitor for worsening fatigue and anticholinergic side effects (dry mouth, urinary retention, etc.)
  - Avoid use with other CNS depressants

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Stiffness Treatments

- Tizanidine (Zanaflex) has sedation like cyclobenzaprine
  - Start with 4mg qhs, maximum dose of 36mg divided over the day
  - Along with anticholinergic side effects, tizanidine can cause hepatotoxicity and laboratory monitoring is strongly recommended
- Methocarbamol (Robaxin) and metaxalone (Skelaxin)
  - Less sedating, limited published evidence in managing FMS
- Antispastics (baclofen and dantrolene) can be helpful especially in FMS patients with muscle cramps
- Benzodiazepines should be avoided in FMS patients due to addiction potential and worsening of nonrestorative sleep.
- Tramadol can significantly improve FMS stiffness and will be discussed in the next section.

FIBRO pneumonic for FIQ VASs

- Fatigue and Fibrofog
- Insomnia (Sleep Disturbance)
- Blues (Depression/Anxiety)
- Rigidity (Stiffness/Inactivity)
- Ow! (Widespread Pain and Work Difficulty)
Analgesics

• Acetaminophen (APAP) has proven efficacy in FMS
  – Treatment failures are common since required dosing is near 4000mg/day and usually divided 6-8 times per day
  – Compliance can be improved using extended-release formulations of 1000mg four-times daily
  – Known APAP hepatotoxicity - lab monitoring required

• Most FMS patients prefer NSAIDs over APAP
  – Evidence for efficacy of NSAIDs in FMS is lacking
  – NSAIDs are not recommended in the absence of a concomitant inflammatory condition or OA/bursitis that can serve as a pain generator in FMS

Tramadol (Ultram)

• Traditional narcotics should be avoided in FMS treatment
  – Efficacy is poor
  – Weaning can be very difficult due to the Rebound Pain Phenomenon

• Tramadol is a narcotic combining mu-opioid agonist and SNRI activities recommended for managing FMS
  – One or two tramadol/acetaminophen 37.5/325mg tablets taken 4 times daily can significantly improve pain, stiffness and work interference in FM patients
  – Side effects include nausea, pruritis and constipation
  – Risk of abuse and dependence is low
    • 97% of cases occur in patients with a prior history of substance abuse
  – Recommend screening for prior substance abuse before prescribing

• Tapentadol (Nucynta)
  – Weak mu-opioid agonist with NRI activity
  – Acute pain indication only
CARES mnemonic

• CNS pain modulators/anti-Convulsants
• Anti-depressants/Analgesics/Anti-spasmotics
• Rest (sleep aids, treat OSA and/or RLS)
• Exercise/Education (aerobics, resistance, physical therapy, support group)
• Stretching/Stimulants/Psychotherapy

Conclusions

• FMS patients can be rewarding to treat
• Identify and treat disorders that mimic FMS
• Pharmacologic therapies work best when combined with nonpharmacologic treatments
• The FIBRO mnemonic combined with the mVASFIQ provides a rapid, symptom-based method for assessment and management of FMS patients suitable for use in busy clinics
Diagnosis and Management of Fibromyalgia Syndrome

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