Fibromyalgia – Review of Second and Third-Line Therapies
Fibromyalgia Pathophysiology

- Central pain modulation
  - Hypersensitized NMDA receptors → increased CNS pain perception
  - Elevated substance P and glutamate in CSF

- Monoamine dysregulation
  - Deficient descending NE & 5-HT projections
  - Low NE and 5-HT metabolites in CSF and serum

- Inflammation
  - Inflammatory mediators (e.g. cytokines and interleukins) produced by glial cells

- Sympatho-adrenal & hypothalamic-pituitary-adrenal axes dysregulation
  - High basal catecholamine levels
  - Low cortisol & increased ACTH levels

FDA-Approved Fibromyalgia Treatments

• Duloxetine – serotonin/norepinephrine reuptake inhibitor (SNRI)

• Milnacipran – SNRI

• Pregabalin – calcium channel modulator
FDA-Approved Fibromyalgia Treatments

% of patients reporting > 30% pain reduction

Off-Label Fibromyalgia Options

• Gabapentin – calcium channel modulator

• Amitriptyline – tricyclic antidepressant

• Tramadol – weak opioid agonist with SNRI properties

• Cyclobenzaprine – centrally-acting muscle relaxant

• Capsaicin – topical anti-substance P compound

• Memantine – NMDA antagonist
Fibromyalgia – Canadian Guidelines

• Non-pharmacologic
  • Cognitive behavioral therapy [Level 1A]
  • Self-efficacy and coping skill development [Level 1A]
  • Graduated exercise program [Level 1A]

• Pharmacologic
  • SSRI, SNRI, TCA [Level 1A]
  • Pregabalin, gabapentin [Level 1A]
  • Weak opioid (e.g. tramadol) for moderate-severe unresponsive to other therapies [Level 2D]
  • Strong opioids discouraged

Fibromyalgia – European Guidelines

• Non-pharmacologic
  • Cognitive behavioral therapy [Level 1A]
  • Acupuncture [Level 1A]
  • Aquatherapy [Level 1A]
  • Aerobic and strength exercise [Level 1A]
  • Meditative movement therapy (e.g. yoga) [Level 1A]

• Pharmacologic
  • Amitriptyline [Level 1A]
  • Duloxetine or milnacipran [Level 1A]
  • Pregabalin [Level 1A]
  • Cyclobenzaprine [Level 1A]*
  • Tramadol [Level IB]
Cyclobenzaprine

• Centrally-acting muscle relaxant
  • Structurally similar to TCAs with different mechanism/effects

• Included in EULAR guidelines, but recommendation is limited to fibromyalgia patients with sleep disturbance

Cyclobenzaprine – Efficacy

2004 meta-analysis

• 5 RCTs (N = 312)
• Median study duration = 6 weeks (range 4 – 24)
• Studies published in years 1988 – 1994
• Dosing range = 10 – 40 mg/day in divided doses
• Subjective and objective outcomes were compared to placebo at weeks 4, 8, and 12 where possible
  • Global improvement, pain, fatigue, sleep, tender point sensitivity

Cyclobenzaprine – Efficacy

• Self-reported subjective improvement (i.e. “improved” vs. “not improved”) favored cyclobenzaprine over placebo
  • OR = 3.0 (95% CI 1.6 – 5.6)
  • NNT = 4.8

• Objective improvement was modest and placebo response very high
  • Sleep improved at all time points (moderate effect size, SMD 0.43, p < 0.05)
  • Pain was improved at week 4 (SMD 0.35, p < 0.05) but not weeks 8 & 12
  • No improvement in fatigue or tender point sensitivity at any time point
Cyclobenzaprine – Safety

• Primary side effects
  • Anticholinergic (e.g. dry mouth, sedation, blurred vision)
  • Dizziness, muscle weakness

• Avoid in elderly population where possible
  • Anticholinergic side effect sensitivity
  • Half-life significantly longer in elderly patients → drug accumulation

• Caution in hepatic dysfunction
Capsaicin

• OTC product used for musculoskeletal and neuropathic pain

• With short-term exposure, capsaicin can induce nociception
  • Transient burning sensation

• With chronic exposure, capsaicin provides analgesia via several proposed mechanisms
  • Depletion of substance P
  • Inhibition of select calcium channels
  • Desensitization of peripheral nociceptors (e.g. TRPV1 receptors)
## Capsaicin – Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCarty et al (1994)</td>
<td>Capsaicin 0.025% vs. placebo</td>
<td>Pain on 0 – 100 VAS</td>
<td>Tender point sensitivity significantly improved in capsaicin groups vs. placebo (p = 0.03)</td>
</tr>
<tr>
<td>N = 45</td>
<td>Topical application to tender points four times daily for 4 weeks</td>
<td>Sleep on 0 – 100 VAS</td>
<td>No significant difference in overall pain, sleep, or grip strength</td>
</tr>
<tr>
<td>RCT</td>
<td>Limited treatment-as-usual allowed in both groups (stabilized pre-trial)</td>
<td>Tender point sensitivity via dolorimeter</td>
<td></td>
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<tr>
<td></td>
<td>Grip strength via sphygmanometer cuff</td>
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<tr>
<td>Casanueva et al (2013)</td>
<td>Capsaicin 0.075% vs. no capsaicin</td>
<td>Global subjective improvement</td>
<td>Global subjective improvement favored capsaicin group (22.8% vs. 5%, p = 0.001)</td>
</tr>
<tr>
<td>N = 130</td>
<td>Topical application to tender points three times daily for 6 weeks</td>
<td>Myalgic score via dolorimeter</td>
<td>Myalgic score improvement favored capsaicin group (21.2% vs. 3.5%, p = 0.02)</td>
</tr>
<tr>
<td>RnCT</td>
<td>Treatment-as-usual allowed in both groups (stabilized pre-trial)</td>
<td>Battery of pain, functioning, mood, and sleep assessments</td>
<td>No significant difference in other outcomes</td>
</tr>
</tbody>
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Rheumatol Int. 2013;33:2665-70.
Capsaicin – Safety

• Primary side effects
  • Transient burning at application site
  • Site irritation, redness

• Wear gloves to apply product and wash hands after handling
  • Avoid contact with eyes, mucous membranes, broken skin
Memantine

• FDA approved for treatment of Alzheimer’s Disease

• Blocks glutamate at NMDA receptors
  • NMDA receptor hypersensitivity is one of theorized mechanisms for fibromyalgia pathophysiology
Memantine – Efficacy

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<tr>
<td>Olivan-Blazquez et al</td>
<td>Memantine 20 mg/day vs. placebo</td>
<td>Pain threshold via sphygmomanometer cuff</td>
<td>Pain threshold increase favored memantine group (30.8% vs. -2.0%, p &lt; 0.05)</td>
</tr>
<tr>
<td>(2014)</td>
<td>6 month study duration</td>
<td>Pain on 0 – 100 VAS</td>
<td>Pain reduction on VAS favored memantine group (-25.8% vs. 8.2%, p &lt; 0.05)</td>
</tr>
<tr>
<td>N = 63</td>
<td>No other treatments allowed during study</td>
<td>Battery of secondary outcome scales</td>
<td>50% pain reduction NNT = 6.2 patients</td>
</tr>
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<td>RCT</td>
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Memantine – Safety

• Primary side effects
  • Dizziness
  • GI complaints
  • Headache

• Slow titration is recommended to avoid side effects
  • Initial dose: 5 mg/day
  • Increase by 5 mg in weekly intervals
  • Target dose: 10 mg twice daily
Polypharmacy & Exit Strategies

• Mayo Clinic cross-sectional study of fibromyalgia patients in Rochester, MN (N = 1111)
  • > 50% of sample had 7 or more comorbid chronic conditions
    • Arthritis, depression, migraines, anxiety most common
  • ~40% of sample were taking at least 3 medications for fibromyalgia
    • SSRI/SNRI, sleep aids, and opioids most common
  • Conclusion: the prevalence of polypharmacy in patients with fibromyalgia is high and problematic
Polypharmacy & Exit Strategies

• Clear expectations regarding degree of benefit
  • 20-30% reduction in overall pain is reasonable goal
• Objective symptom assessments
• Identify a stopping point at onset of treatment
• Optimize medication dose prior to initiating additional agents
• Treat multiple conditions with 1 drug where possible
  • FM + MDD → SNRI or TCA
  • FM + migraines → TCA
• Avoid redundant pharmacology
  • SSRI + SNRI
  • Gabapentin + pregabalin
• Recognize side effects and remove offending agent when possible
• Encourage non-pharmacologic therapies