Fibromyalgia – Review of Second and Third-Line Therapies

Fibromyalgia Pathophysiology

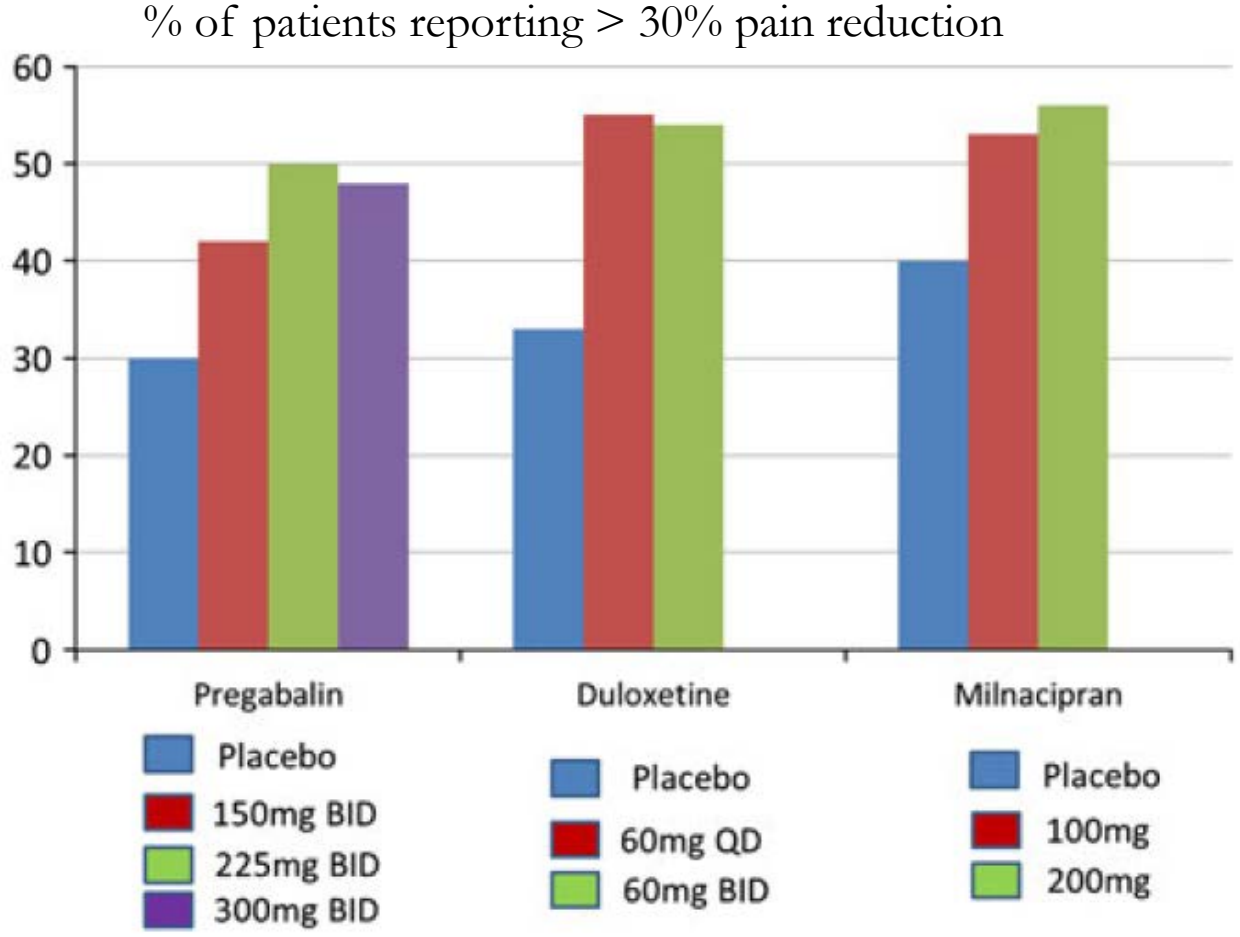
- Central pain modulation
  - Hypersensitized NMDA receptors → increased CNS pain perception
  - Elevated substance P and glutamate in CSF
- Monoamine dysregulation
  - Deficient descending NE & 5-HT projections
  - Low NE and 5-HT metabolites in CSF and serum
- Inflammation
  - Inflammatory mediators (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

Pain Ther. 2013;2:87-104.
BMC Musculoskelet Disord. 2011;12:245.

FDA-Approved Fibromyalgia Treatments

- Duloxetine – serotonin/norepinephrine reuptake inhibitor (SNRI)
- Milnacipran – SNRI
- Pregabalin – calcium channel modulator

FDA-Approved Fibromyalgia Treatments



Pain Ther. 2013;2:87-104.

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

Pain Res Manag. 2013;18(3):119-26.

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]

Ann Rheum Dis. 2017;76(12):e54.

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

Ann Rheum Dis. 2017;76(12):e54.

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

Arthritis Care Res. 2004;51(1):9-13.

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

Arthritis Care Res. 2004;51(1):9-13.

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)

Molecules. 2016;21(7):doi:10.3390.

Capsaicin – Efficacy

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

Semin Arthritis Rheum. 1994;23(Supp 3):41-7.
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

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

Pain. 2014;155:2517-25.

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

BMJ Open. 2015;5:e006681.

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