Pharmacotherapy of Chronic Pain Syndromes: 
A Focus on Fibromyalgia and Migraine Headaches

Jose A. Rey, M.S., Pharm.D., BCPP 
Associate Professor of Pharmaceutical Sciences 
Nova Southeastern University – College of Pharmacy

Learning Objectives

• Discuss the FDA-approved treatment options for the analgesic management of the chronic pain syndromes focusing on maintenance treatment.

• Recommend both FDA-approved and alternative treatments that are historically effective for the management of Fibromyalgia and Migraine Headache, even if not FDA-approved for such use.

• Compare and contrast the benefits and risks of the various medications used for these specific and chronic pain syndromes and make recommendations for use given patient-specific information.

Definition of Pain

• “Whatever the person experiencing the pain says it is”

• “All Pain is Real”
Background

• Prevalence of Chronic Pain in USA: 31%
  – females (34.3%) than males (26.7%)
  – 100 million Americans with Chronic Pain
  – 40 million with Headaches
  – 15 million with Lower Back Pain
  – 20 million with Arthritis
  – 10 million with Fibromyalgia

• ~$600 billion per year

Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education: Relieving Pain in America, A Blueprint for Transforming Prevention, Care, Education and Research. The National Academies Press, 2011.

Types of Chronic Non-Malignant Pain

• Fibromyalgia
• Headaches
• Neuropathies and Neuralgias
• Back Pain
• Arthritis (Osteo- & Rheumatoid)
• Depression-Related Pain
• Pain of Mixed Etiologies & Others

Nonspecific Signs of Chronic Pain

• Frowning, grimacing, fearful expressions, grinding of teeth
• Bracing, guarding, rubbing
• Fidgeting; increasing or recurring restlessness
• Striking out; increasing or recurring agitation
• Eating or sleeping poorly

• Sighing, groaning, crying, breathing heavily
• Decreasing activity levels
• Resisting certain movements during care
• Change in gait or behavior
• Loss of function

(AMDA, 1999)
Chronic Pain in Long-term Care

- 25% of nursing home residents have arthritis
- Cancer pain, neuropathies, post-herpetic neuralgias, are also common
- Pain is often under-treated
- Frequently associated with depression, anxiety, sleep disorders
- Gait disturbances, falls, and slow rehabilitation due to pain

Control Over Chronic Pain

- More than half of respondents (51%) felt they had little or no control over their pain.
- Six out of ten patients (60%) said they experience breakthrough pain one or more times daily, severely impacting their quality of life and overall well-being.

- Impact on Quality of Life
  - Almost two-thirds (59%) reported an impact on their overall enjoyment of life.
  - More than ¾ of patients (77%) reported feeling depressed.
  - 70% said they have trouble concentrating.
  - 74% said their energy level is impacted by their pain.
  - 86% reported an inability to sleep well.

2006 Voices of Chronic Pain Survey (American Pain Foundation)
Assessment of Pain

• Detailed Patient History
• Pain Intensity & Characteristics
• All Medication Use
  – Current and Past Use with Outcomes
  – OTC, Alternative / Natural, and Prescription Rxs
• Physical and Neurological Exam

Assessment of Pain (cont.)

• Psychosocial Assessment
  – quality of life issues
  – attitudes and beliefs about pain
• Appropriate Work-Up for the Etiology of the Pain
• Documentation of Outcome Measurements

Assessment & Management of Pain (ABCDE)

• Ask about pain regularly & assess systematically.

• Believe the patient & family in their reports of pain and what relieves it.

• Choose pain control options appropriate for the patient/family/setting.
Assessment & Management of Pain (ABCDE) (cont.)

- **D**eliver interventions in a timely fashion.
- **E**mpower patients & their caregivers to control their course of treatment to the greatest extent possible.

Four A’s for Pain Treatment Outcome Assessment

- Analgesia (pain relief)
- Activities of daily living (psychosocial functioning)
- Adverse events (side effects)
- Aberrant drug-taking behavior (addiction-related outcomes)

Pain Assessment Tools

- Patient’s self-report
- Simple verbal descriptors for distress
- (0-10) Numerical Pain Rating Scale
- Visual Analogue Scale (0-10 cm/mm)
- Pictures / Drawings representing pain or location
- Pain Diary
  - Time / Pain Rating / Outcomes of analgesia
Figure 6. Emotional and painful physical symptoms: a shared neurochemical link in depression?

- Serotonin and norepinephrine are strongly associated with depression
- Serotonin and norepinephrine also modulate pain sensitivity via the descending pain pathway

Adapted from Gallagher RR, Vorneo & Sero in Cite Neurochemistry. 1995:4:201-205.

Serotonin and Norepinephrine in Depression and Pain

Prefrontal Cortex

Limbic System

Norepinephrine Pathways


Pain: A Conceptual Approach to Treatment

- Cognitive therapies
- Physical therapy
- Opioids
- Antidepressants
- NSAIDS
- Tylecet
- Neural augmentation
- Adjunct surgery
- Antidepressants/psychological
- Nutrition
- Relaxation
- Exercise
- Local blockade
- N-AIDS
- Dissolution
- Surgery
- Physical modulation

TREATMENT OF FIBROMYALGIA

Background

• Fibromyalgia is a diverse and chronic disease
  – Disseminated musculoskeletal pain
  – 1990 Criteria:
    – Tenderness at 11 of 18 specific tender points
    – 10 million people in the United States are believed to be affected
    – Estimated cost of FM: $12-14 billion/year

Diagnosis of Fibromyalgia

• The original diagnostic criteria, established by the ACR in 1990, required the patient to have:

  1) A history of widespread pain in all four quadrants of the body for a minimum duration of three months, and

  2) Pain in at least 11 of 18 designated tender points when four kilograms (about 10 pounds) of pressure are applied.

• Pain is not better explained by other medical condition
2010 Diagnostic Criteria
A history of widespread pain in all four quadrants of the body for a minimum duration of three months –
− A widespread pain index (WPI) score which will be determined by counting the number of areas on the body where the patient has felt pain in the last week. The checklist includes 19 specified areas.
• A symptom severity (SS) score which will be determined by rating on a scale of zero to three (three being the most pervasive) for the severity of three common symptoms: fatigue, waking unrefreshed and cognitive symptoms. An additional three points can be added to account for the extent of additional symptoms such as numbness, dizziness, nausea, or depression.

The final score is between 0 and 12.
• \( \geq 7 \) WPI pain areas and an SS score of five or more, or
• 3-6 (WPI) pain areas and an SS score of nine or more.
Treatment of Fibromyalgia

• Symptoms:
  – Fatigue, sleep disturbances, cognitive impairment, and mood disorders
  – Pain

• Current FDA-approved treatments:
  – Duloxetine (Cymbalta®): 60mg po QD
  – Milnacipran (Sevella®): 50-100mg po BID
  – Pregabalin (Lyrica®): 150-225mg po BID

Antidepressant Dosing

• “Start Low & Go Slow”
  – especially in the elderly

• TCA’s: 10-25 mg/d to 300 mg/d (~50 to 100 mg/d)
• Duloxetine: 20 mg to 60 mg/d (~60 mg/d) (FDA approved)
• Venlafaxine: 37.5 mg/d to 375 mg/d (~150 mg/d)
• Doses at less than usual antidepressant dosing may be effective
Duloxetine

• **Brand:** CYMBALTA
• **Pharmacokinetics:**
  - T1/2=12 hrs, >90% PB
• **Dosing**
  - Initial: 20mg QD
  - Therapeutic Range: 30mg - 60mg/day (for pain syndromes)
    (QD or divided BID)
• **Adverse effects**
  - Nausea, dry mouth, constipation, dec. appetite, fatigue, tremor, insomnia,
    somnolence, dizziness, inc. sweating, blurred vision, sexual dysfunction
  - Hepatotoxicity / inc. LFTs, inc. BP, discontinuation syndrome
• **Drug interactions**
  - P450: CYP2D6, and CYP1A2 substrate
  - Moderate inhibitor of CYP2D6 (caution with other 2D6 substrates)

Milnacipran

• **Brand:** SAVELLA
• **Pharmacokinetics:**
  - T1/2=6-8 hrs, 13% PB, renally eliminated (55%)
• **Dosing**
  - Initial: 12.5mg QD, 12.5mg BID...
  - Therapeutic Range: 50 - 100 mg/day (divided BID)
    (max = 100mg BID)
• **Adverse effects**
  - Nausea, dry mouth, constipation, fatigue, tremor, insomnia, HA,
    dizziness, inc. sweating, blurred vision, sexual dysfunction
  - Hepatotoxicity / inc. LFTs, inc. BP/HR, discontinuation syndrome
• **Drug interactions**
  - P450: Minimal (minor CYP3A4 = 8%)
  - Glucuronidation is principle pathway for metabolism
Anticonvulsants

• Mechanisms of Action:
  – stabilize nerve membrane firing
    (eg. Na+ channels; Ca++ channels;
    GABA?; Glutamate?; NE/5-HT?)

• AGENTS:
  – Pregabalin (FDA approved)
  – Carbamazepine, Valproic acid?
  – Phenytoin? Oxcarbazepine
  – Topiramate Lamotrigine
  – Gabapentin

Pregabalin

• MoA: Binding to alpha-2 delta site of the auxiliary subunit of voltage-gated calcium channels

• ADRs: dizziness, somnolence, weight gain and peripheral edema.

• Dosing: 150-300 mg/day
  – 50-100 mg po TID (max: 300 mg/d for DPN)
  – Up to 450 mg/d for fibromyalgia
  – Up to 600 mg/d for post-herpetic neuralgia
A 14-week, Randomized, Double-Blinded, Placebo-Controlled Monotherapy Trial of Pregabalin in Patients With Fibromyalgia

![Graph showing pain reduction over time with different doses of pregabalin compared to placebo.](image1)

**Graph Legend:**
- Placebo (n=184)
- Pregabalin 200 mg/day (n=182)
- Pregabalin 450 mg/day (n=180)
- Pregabalin 600 mg/day (n=182)

*P<.05 vs. all 3 pregabalin doses vs. placebo except 300 mg/day at Week 11

**Weeks:** 0, 4, 8, 12, 16, 20, 24, 28, 32

![Graph showing changes in pain scores at baseline and endpoint.](image2)

**Graph Title:**
A 14-week, Randomized, Double-Blinded, Placebo-Controlled Monotherapy Trial of Pregabalin in Patients With Fibromyalgia
**Mechanisms of Action**

- ** Amitriptyline ** TCA, balanced monoamine reuptake inhibition (SNRI)
- **Capsaicin (topical)** Depolarizes the nervous membrane via vanilloid receptor type 1, initially stimulates then blocks skin nerve fibers
- **Carbamazepine** Voltage-gated sodium-channel blockade
- **Desipramine** TCAs, predominantly noradrenaline reuptake inhibition
- **Duloxetine / Milnacipran** SNRIs, serotonin-noradrenaline reuptake inhibition
- **Gabapentin / Pregabalin** Binding to the 2δ subunit of presynaptic voltage-dependent calcium channels with reduced release of presynaptic transmitters
- **Lidocaine (topical)** Block of peripheral sodium channels and thus of ectopic discharges
- **Lamotrigine** Presynaptic voltage-gated sodium-channel inhibition and thus reduced release of presynaptic transmitters
- **Memantine / DM** NMDA-receptor antagonist
- **Oxcarbazepine** Voltage-gated sodium- and calcium-channel blockade
- **Tetrahydrocannabinol** Agonist to the CB1 / CB2 subtype of cannabinoid receptors
- **Topiramate** Voltage-gated sodium-channel block and inhibition of glutamate release by an action on AMPA/kainate receptors
- **Tramadol** μ-opioid-receptor agonist and monoamine reuptake inhibitor
- **Valproate** Increase of GABA levels in brain and potentiation of GABA-mediated responses

**Fibromyalgia Impact Questionnaire (FIQ)**

- Self-administered instrument
- Higher score indicates a greater impact on QOL
- FIQ demonstrates sensitivity to therapeutic change
- 10 items:
  - Physical impairment, feel good, work missed, pain, fatigue, rested, morning stiffness, morning tiredness, anxiety, and depression


**Off-Label Treatments for fibromyalgia:**

- Amitriptyline
- Gabapentin

- Since fibromyalgia is considered a chronic disease, the efficacy of these agents (approved and non-approved) needs to be evaluated with longer term trials

Table 1: Reduction in FIQ compared to placebo

<table>
<thead>
<tr>
<th>Medication</th>
<th>Placebo</th>
<th>Duloxetine 60mg/day</th>
<th>Duloxetine 120mg/day</th>
<th>Amitriptyline 25mg/day</th>
<th>Milnacipran 100mg/day</th>
<th>Milnacipran 200mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>150</td>
<td>147</td>
<td>37</td>
<td>224</td>
<td>441</td>
<td></td>
</tr>
<tr>
<td>Pre FIQ</td>
<td>51.7</td>
<td>51.7</td>
<td>63.2</td>
<td>65.1</td>
<td>64.3</td>
<td></td>
</tr>
<tr>
<td>Post FIQ</td>
<td>36.3</td>
<td>37.2</td>
<td>40.0</td>
<td>47.4</td>
<td>47.0</td>
<td></td>
</tr>
</tbody>
</table>


Table 2: Reduction in FIQ compared to placebo

<table>
<thead>
<tr>
<th>Medication</th>
<th>Placebo</th>
<th>Gabapentin 1800mg/day</th>
<th>Gabapentin 3000mg/day</th>
<th>Gabapentin 4500mg/day</th>
<th>Gabapentin 6000mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>57</td>
<td>183</td>
<td>190</td>
<td>188</td>
<td></td>
</tr>
<tr>
<td>Pre FIQ</td>
<td>46.3</td>
<td>61.1</td>
<td>59.6</td>
<td>59.5</td>
<td></td>
</tr>
<tr>
<td>Post FIQ</td>
<td>26.2</td>
<td>49.0</td>
<td>46.7</td>
<td>46.6</td>
<td></td>
</tr>
</tbody>
</table>


**LITERATURE REVIEW RESULTS**

- % Reduction in FIQ:
  - FDA-approved medications
    - Duloxetine 30%
    - Milnacipran 27%
    - Pregabalin 22%
  - Off-label treatments selected for comparison
    - Gabapentin 43%
    - Amitriptyline 37%
    - Tramadol 19%
**LITERATURE REVIEW : % REDUCTION IN FIQ**

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>45%</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>30%</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>25%</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>20%</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>15%</td>
</tr>
<tr>
<td>Tramadol/3AP</td>
<td>10%</td>
</tr>
</tbody>
</table>

Case

- 50 yo female with new dx. of Fibromyalgia
  - prior dx was “nerve pinch”/sciatica tx. with Vicodin
- Labs: WNL & BDI: 20 = moderate depression
- VAS: 8/10 cm
- Past Meds: PRN Vicodin
  - 3-4/day provided relief of VAS: to a 5/10
- CC: continued pain despite narcotic opiate use and feelings of depression and low QOL
- Meds:
  - Propranolol 20 mg BID for HTN;
  - Simvastatin 20 mg HS for Hyperlipidemia;
  - Vicodin 1 tab QID prn pain

Medication Therapy Management

- What Medication-Related Problems exist?
  - Non-Adherence?
  - Unnecessary Medication?
  - Need for a Medication?
  - Ineffective Medication?
  - Dosage too Low?
  - Dosage too High?
  - Adverse Drug Event?

- What is your Recommended Intervention?
- What are the potential MRPs associated with your recommendation?
PROPHYLACTIC TREATMENT OF CHRONIC MIGRAINE HEADACHE

Goals of Treatment

- Provide daily preventative therapy when necessary for patients suffering from frequent migraine attacks
  - Decrease the frequency and severity of the migraine attacks
- Improve QOL and disability associated with migraine attacks
- Improve pharmacoeconomic outcomes

Diagnosis of Acute Migraine

Mild to moderate Symptoms

- Simple analgesics: APAP, NSAIDS, Combo OTC

Failed Response

Severe Symptoms

- Combo analgesics: Midrin, Fiorcet

Failed Response

Triptans or Ergotamine (Preferably Triptans)

Failed Response

Last Line…

- Opioid analgesics: Stadol, meperidine, etc.
Prophylactic Therapy

- Therapy that is administered daily to prevent the recurrence of migraine attacks and to increase response to acute therapies
  - ↓ Frequency
  - ↓ Severity
  - ↓ Length of Attack
- Indicated for patients with...
  - Multiple Severe Attacks (Prolonged)
  - Extensive medication overuse (>2 week)
  - Acute therapies are ineffective or contraindicated

Prophylactic Therapy Algorithm

Beta Blockers

- Treatment of choice and first-line for prophylaxis w/out co-morbid conditions
  - MOA: Antagonize Beta Adrenergic receptors
  - Increase Migraine Threshold??
  - Effective in ↓ frequency of migraine attacks
- Two approved agents
  - **Propranolol (Inderal LA®)**
    - FDA approved
    - Highly lipid soluble
    - 80-260 mg/day in divided doses
  - **Timolol (Blocadren®)**
    - FDA approved
    - Less lipid soluble
    - 20-60 mg/day in divided doses
    - Start low and go slow to effective dose
Beta Blockers

- Other beta blockers are commonly used
  - Atenolol (β₁ selective)
  - Metoprolol (β₁ selective)
  - Nadolol (Non-selective)
- ISA Beta-blockers are ineffective for treating migraines
  - Acebutolol
  - Penbutolol
  - Pindolol

Beta Blocker ADRs/CIs

- **Side Effects**
  - Fatigue/Drowsiness
  - Bradycardia
  - Hypotension
  - Depression
  - Dizziness
  - Vivid dreams
  - Impotence
  - Insomnia
- **Relative Contraindications**
  - Asthma
  - DM
  - Depression
  - Peripheral Vascular Disease
  - Cardiac insufficiency
  - Reynaud’s Disease

Antidepressants

- **TCAs**
  - Modulates 5-HT/NE transport 5-HT/NE receptor activation (and down regulation?)
  - Amitriptyline is effective but lacks FDA approval
    - Evidence-Based
    - Ideal for patients that have co-morbid depression
    - Others are commonly used
      - Nortriptyline
      - Imipramine
      - Desipramine; Doxepin
- SSRIs (Not beneficial); Newer SNRIs may be beneficial

US Headache Consortium: Evidence-Based Guidelines for Migraine Headaches in the Primary Care Setting
Divalproex Sodium

- Enhance central GABA
  - Inhibit GABA transaminase?
  - Increases migraine threshold?
- Excellent with co-morbid
epileptic condition/or mood
disorder
- Significant reductions in
migraine frequency, duration,
and severity
- Dosing: 500-1500 mg/day
  - Target Level=50-100 mcg/mL.

Divalproex Sodium

Monitoring & ADEs

- Hepatotoxicity
  - Liver Function Tests @ baseline, every 6 months
- Metabolic Test
  - Fasting Blood Glucose, Triglycerides,
    Weight @ baseline, every 6 months
  - Pancreatitis, Weight Gain
- CBC
  - Platelets @ baseline, every 6 months
      (Thrombocytopenia)
- Pregnancy test on as needed basis (Category D)
- Ammonia level on as needed basis
  - Hyperammonemic encephalopathy
- Other ADEs: Alopecia, N/V, Tremor

Topiramate

- Anticonvulsant with
  preventive actions for
  migraines
  - Increase migraine threshold
  - Migraine frequency by 50%
  - Comparable to other
    approved treatments
  - Can take up to 1 month for
effective results
- Dosing: Titrate up to 100mg
  BID or to effective dose
Topiramate ADEs

• Parasthesia / tingling
• Memory loss
• Anorexia / Weight loss
• N/V/D
• Nephrolithiasis
• Myopia

Other Migraine Prophylactic Agents

• Ca\(^{++}\) Channel Blockers
  – Verapamil is commonly used
    • (-) chromotropic, (-) inotropic, (-) dromotropic effects
• Methysergide
  – Last line agent (5-HT\(_2\) antagonist)
    • Rare pulmonary fibrosis

Prophylactic Pearls

• Prophylactic therapy is only indicated for specific individuals
• Titrate the medication upwards slowly to an effective dose to prevent ADRs
• A normal trial is 2-3 months
  – Begin tapering down after 6 months if drug is effective
  – Many patients can remain on low dose therapy effectively
• Co-morbidities determine agent selection
• Approved and studied agents are preferred
Case 1

- JP is a 41 y/o single, underweight, white, female who has presented to her ER complaining of severe, unilateral pain in her head for the past 24 hours. She rates her pain as a 7/10 on a VAS with a 10 being labor pain. She has a prescription for Ibuprofen 800 mg and has taken up to 2400 mg/day to treat her pain. Her symptoms during the HA include nausea, sensitivity to light and sound, and visual disturbances. JP’s PMH includes a history of anorexia nervosa w/refractory depression that she is successfully being treating on Nardil® 60mg/day. She reports suffering from these types of migraine attacks twice a week.

Case 1

- JP’s PCP now considers her eligible for prophylactic therapy. According to JP’s history, which of the following would be the best choice for prophylactic therapy for JP?
  - #1-Propranolol
  - #2-Topiramate
  - #3-Amitriptyline
  - #4-Divalproex Sodium

Case 1

- JP was placed on Inderal 240 mg/day for her prophylactic therapy. Which monitoring parameters and monitoring tools should we follow and use with JP?
  - #1-Heart Rate
  - #2-Exercise Tolerance
  - #3-EKG
  - #4-Blood Pressure
Conclusions & Discussion