Fibromyalgia: The Role of the Pharmacist in Patient Education and Therapy Management

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Learning Objectives

Upon completion of this program participants will be able to:

• Define fibromyalgia.
• Discuss signs and symptoms of a fibromyalgia patient.
• Discuss treatment options available for symptom relief.
• Discuss the level of effectiveness of available treatment options.
• Describe steps to improve patient education and medication adherence through community pharmacist interaction with fibromyalgia patients.
Self Assessment Questions

1. What are the top 4 most frequently reported symptoms of fibromyalgia?
2. What role does serotonin, dopamine and norepinephrine play in the symptoms exhibited by patients with fibromyalgia?
3. What are the most effective therapies currently available to treat fibromyalgia?
4. What are the 1 or 2 most important patient counseling points for each of these current fibromyalgia therapies?

Case Example: Ann

• 28 year-old woman
• Insidious onset of whole-body pain beginning 10 years ago
• Pain is aching, constant, and unremitting
• Poor sleep
• Significant depressive symptoms
Ann’s Subjective Comments

• “Extreme joint and muscle pain, fatigue and mental fogginess have taken away most of my life.”
• “Many days, I can’t get out of bed.”
• “I don’t make plans anymore because I never know how I will feel.”
• “I feel like I am ninety; I am so depressed.”

Ann’s Pain Description
Ann’s Clinical Findings

- Physical examination unremarkable except for tenderness
- Imaging studies negative
- All blood tests negative
- Physician diagnoses fibromyalgia, but patient is unclear what it is

What is Fibromyalgia?

- A syndrome: set of symptoms and physical findings that together characterize a particular disorder
- Fibro: fibrous tissues
- My: muscles
- Algia: pain
What is Fibromyalgia? (cont.)

A syndrome characterized by

- Widespread pain and tenderness
  - Allodynia
  - Hyperalgesia
- Fatigue
- Anxiety and depression

Additional symptoms are common and include:

- Poor sleep almost always
- Headaches
- Irritable bowel/bladder syndrome
- Cognitive and memory problems “fibro fog”
- Numbness and tingling in fingers and toes
- Dizziness, poor balance
What is Fibromyalgia? (cont.)

Additional symptoms (cont.)
- Restless leg syndrome
- Temporal Mandibular Joint (TMJ) disorder
- Dry eyes and dry mouth
- Morning stiffness
- Multiple chemical and physical sensitivities
- Tendonitis/bursitis

Symptoms including pain may wax and wane over time

Sensory Processing in Fibromyalgia a Problem With Pain “Volume Control”

Patients display:
- Normal “detection threshold” to sensory stimuli
- Decreased “noxious threshold” to pressure, heat, noise, smell, and light, etc.
The Post Exertional Flare-Up Phenomenon

• Characteristic of severe FMS
• Stamina for several hours of activity might or might not be highly limited...flare up later may be severe
• Delay may be hours to days
• Effects are cumulative.

What Causes Fibromyalgia?

• Cause is unknown
• But there are biochemical abnormalities:
  • Abnormally high levels of Substance P, cytokines, NMDA stimulators
  • Abnormally low levels of serotonin, tryptophan, dopamine, ATP, growth hormone, magnesium, cortisol
• Leads to dysfunctional sensitization of CNS
What Causes Fibromyalgia? (cont.)

Dysfunctional sensitization of CNS

- Central sensitization
  - Role of serotonin
    - Regulates delta sleep (stage 4)
    - Regulates central and peripheral pain
    - Linked to concentration and memory (fibro fog)

- Role of dopamine (precursor to norepinephrine in adrenal gland)
  - Behavior
  - Cognition, attention, learning
  - Sleep
  - Motor activity
  - Mood
What Causes Fibromyalgia? (cont.)

Dysfunctional sensitization of CNS

• Peripheral sensitization
  • Role of norepinephrine
    • Muscle hypoxia
    • Exercise intolerance
    • Reduced endurance
  • All of this results in…PAIN

How is Fibromyalgia Diagnosed?

American College of Rheumatology 1990 Classification:

• Widespread Pain in all 4 body quadrants and
• Axial pain (usually neck or low back) and
• 11/18 or more tender points by digital palpation
• Minimum of 3 months
How is Fibromyalgia Diagnosed? (cont.)

The Fibromyalgia Impact Questionnaire (FIQ)

- Evaluation of other symptoms:
  - Sleep disturbances
  - Fatigue
  - Mood
  - Cognitive disturbances

How is Fibromyalgia Diagnosed? (cont.)

- X-rays, blood tests, muscle biopsies are all normal
- Objective “markers of inflammation” are normal
- Must be distinguished from other common diffuse pain conditions such as
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Hypothyroidism
  - Polymyalgia rheumatica
  - Ankylosing spondylitis
  - Hypothyroidism
Case Example: Mary

- 45 year-old woman
- Pain all over, "from head to toe", for 10+ years
- Also complains of fatigue, weakness, sleep disturbances, and morning stiffness
- Presence of 7 out of 18 tender points
- Labs normal

Can she be diagnosed with fibromyalgia without the 11 of 18 tender point ACR criteria?
Mary’s Subjective Comments

• “I was a busy, active person, but now I’m mostly bed-bound.”
• “Simple math is difficult now; I forget words, and sometimes get confused.”
• “I wake up with pain after having pain dreams.”
• “I had to quit my career which I loved, and quit school.”

Who Gets Fibromyalgia?

• Affects as many as 1 in 50 Americans (8-12 million people)
• Most common in middle-aged women (females 7 times more likely)
• Women who have a family member with FMS are more likely
• Most cases arise spontaneously
• Some are triggered by trauma

Successful Therapy is Multifaceted

- Drug Therapy (sleep/pain)
- Education
- Muscle conditioning/stretching*
- Stress reduction
- Proper sleep hygiene
- Heat and other non-drug therapies
- Dietary changes

*Treating the sleep disorder and pain must occur before muscle conditioning can take place

Treatment Recommendations

Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children
APS Clinical Practice Guidelines Series, No. 4, 2005
Ordering of Scientific Evidence

Best or Strong Evidence
- Aerobic exercise
- Cognitive-behavioral therapy (CBT)
- Amitriptyline
- Cyclobenzaprine
- Multi-component therapy (exercise, CBT, and patient education)

Moderate evidence
- SSRIs in combination with tricyclics
- Tramadol
- Muscle-strength training
- Balneotherapy (therapeutic bath)
- Patient education alone
- Hypnotherapy
- Biofeedback
- Massage therapy
Ordering of Scientific Evidence

(cont.)

Preliminary or mixed evidence

- Anticonvulsants
- Opioids
- SSRIs alone
- SNRIs injections
- Ketamine IV
- Lidocaine IV
- Hormones (growth, melatonin)
- 5-HT receptor antagonists
- Diet modifications, supplements, herbs
- Movement and body awareness therapies

- SAMe
- Acupuncture
- Chiropractic
- Trigger point

No evidence of effectiveness

- NSAIDs
- Prednisone
- Benzodiazepines (ineffective for pain)
- Guaifenesin

APS Clinical Practice Guidelines Series, No. 4, 2005
Multidisciplinary Care

- Use multidisciplinary approaches
  - Incorporate 2 or more strategies to decrease pain, improve function

- Include both pharmacologic and non-pharmacologic treatments

Non-Pharmacologic Treatment

- Heated Pool Treatment
- Individually tailored exercise programs
- Cognitive Behavioral Therapy
  - Relaxation
  - Stress management
  - Distraction
Non-Pharmacologic Treatment

• Complementary and Alternative Therapies
  • Psychological support
  • Physical therapy
  • Acupuncture
  • Chiropractic manipulation
  • Therapeutic massage
  • Thermal wraps

Non-Pharmacologic Treatment

• Education
  • Teach integration of low impact exercise
    • Strength training (Pilates)
    • Aerobic conditioning
    • Flexibility and balance work (yoga)
  • Encourage self education on condition
  • Teach goal of balance between work, leisure and activities of daily living
    • Consider meditation based relaxation, stress reduction, hypnosis, biofeedback
Non-Pharmacologic Treatment

- **Dietary Changes**
  - Avoid alcohol, caffeine, high fructose corn syrup, highly processed foods
  - Eat more whole and/or raw foods
  - Vegetarian or vegan diet
  - Vitamin and mineral supplements
    - Chlorella (blue-green algae), malic acid, Co-Q10, magnesium, antioxidant flavonoids
  - Variable views on effectiveness

Pharmacologic Treatment

  - Dr. Frederick Wolfe, Lead author on 1990 Diagnostic Guidelines
  - Now considers FMS a “physical response to stress, depression, and economic and social anxiety”
  - Pregabalin 1st approved drug for FMS
Good News/Bad News

• **Good News**: Finally starting to see random double blind studies for a wide range of drugs, 3 have FDA approval

• **Bad News**: No one class of drugs is likely to help more than a subgroup of patients for any length of time

• **Must resort to trial and error (N-of-1 research)**

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FDA Approval?

• There are now 3 approved drugs for fibromyalgia

• 22 distinct un-approved drug classes now have data supporting use in the treatment of FMS

• Management of FMS requires complex interplay between the many pharmacologic agents for pain and associated syndromes
Pharmacologic Treatment

- FDA approved for FMS
  - Pregabalin (Lyrica®) June 21, 2007
  - Duloxetine (Cymbalta®) June 16, 2008
  - Milnacipran (Savella®) January 14, 2009

Pregabalin (Lyrica®)

- 2nd generation anticonvulsant
- Mechanism in FMS unclear, may work by inhibiting excitatory inputs to spinal cord
- 8 week DBPC trial (Crofford)
  - >50% reduction in pain
  - Sleep quality and fatigue also improved
Pregabalin (Lyrica®)

- Initial dose: 75mg BID – increase to 150mg BID over 7 days. MAX = 450 mg/week
- Consider only taking at bedtime to reduce daytime drowsiness/dizziness
- Other SE: edema, weight gain, constipation, blurred vision

Duloxetine (Cymbalta®)

- SNRI antidepressant
- Also indicated for peripheral diabetic neuropathy
- 12 week DBPC trial of 207 patients (Arnold):
  - >30% improvement in pain tenderness, cognition in >50% of patients
  - Independent of mood
  - Almost all quality of life measures improved
**Duloxetine (Cymbalta®)**

- Initial dose: 20-30mg QD or BID, increase to 60mg QD or BID over 7 days
- Side effects: nausea, insomnia, headache, dry mouth, fatigue, itching, ↑BP & HR
- Avoid using in patients with any hepatic insufficiency

**Milnacipran (Savella®)**

- SNRI antidepressant, with some NMDA inhibition (greater selectivity for norepinephrine)
- 12 week DBPC study of 125 patients (Vitton):
  - 37% improved pain scores of >50% (compared to 14% in placebo group)
  - Significant improvement in all quality of life scores
  - Well tolerated, most frequent SE; nausea
Milnacipran (Savella®)

- Initial dose 100mg/day, increasing up to 200mg/day after 7 days (BID dosing better tolerated than QD)

- Side effects: itching, nausea, vomiting, vertigo, increased anxiety, sweats, shivering, dysuria, ↑BP & HR

- Approximate availability in pharmacies – March 2009

Case Example: Julie

- 56 year-old woman
- Diagnosed with fibromyalgia about a month ago
- Started on pregabalin initially
- Presents at pharmacy counter to pick up 1st refill
Julie’s Conversation with Pharmacist

• PH: Have your fibromyalgia symptoms improved since you started on the pregabalin?
• Julie: My pain has improved to a point where I am comfortable at work every day. However I still have trouble getting a good night sleep, and I am tired all day.
• PH: When do you usually take your medications?
• Julie: I take my meds in the morning before I go to work.
• PH: Pregabalin has sedative effects, therefore it should be taken at bedtime for optimal effects. This way you can sleep better at night and feel less drowsy during the day.

Julie’s Conversation with Pharmacist

• Julie: What else can I do to sleep better at night without having to take any more drugs?
• PH: You may first consider changing some of your sleep habits:
  • Try to keep a consistent sleep schedule. Wake up and go to bed around the same time every day.
  • Avoid napping during the day and get into bed only at bedtime.
  • Exercise regularly, but at least 4-6 hours before bedtime.
  • Try to avoid alcohol, caffeine, and nicotine.
  • Do not drink large amounts of fluids right before going to sleep.
  • Remove bright clocks and other sources of light from your bedroom.
  • Keep the room temperature comfortable.
Intersecting Treatment

- Treating pain may intersect with treating sleep disturbances and depression

- By improving FMS we improve secondary syndromes:
  - Sleep disturbances
  - Chronic fatigue
  - Anxiety
  - Irritable bowel syndrome
  - Muscle pain
  - Depression
  - Cognitive impairment

Categories of Off Label Agents Used to Treat Fibromyalgia

- General Pain
- Local Pain
- Sleep Disorders
- Chronic Fatigue
- Hypothermia
- Depression
- Irritable Bladder Syndrome
- Neurally Mediated Hypotension
- Irritable Bowel Syndrome
- Hormonal Deficiencies
- Restless Leg Syndrome
- Headache, Migraine
General Pain: Tricyclic Antidepressants

Reuptake inhibition of serotonin and norepinephrine

• **Amitriptyline**: DBPC trial of 55 pts for 12 weeks (50mg HS). 74% positive response measured by 7 point clinical impression of change scale (P Hannonen)
  • 8 other studies, 6 positive

May want to start with nortriptyline (less sedating). Effect of TCAs may be large but often only modest.

SE: Sedation, dry mouth, prolonged QT interval, heart arrhythmia, and weight gain

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General Pain:

Selective Serotonin Reuptake Inhibitors

• **Fluoxetine**: DBPC trial of 60 women for 12 weeks (20-80mg/day). Better than placebo, especially when combined with TCAs.

  LM Arnold

• 3 other studies show no benefit

Worth a try, but don’t expect too much benefit for pain, despite improved mood

SE: Insomnia, anxiety, headache, decreased libido, nausea, and diarrhea
General Pain: Anti-spasmodics/Muscle Relaxants

- **Cyclobenzaprine**: DBPC trial of 40pts over 15 days showed significant improvement in tender point count, quality of sleep, anxiety, fatigue, IBS, and stiffness.  
  Santandrea et al

- **Baclofen, carisprodol, and tizanidine** all have some anecdotal evidence of effectiveness in FMS

SE: drowsiness, dizziness, dry mouth

General Pain: Dopamine Agonists

- **Pramipexole** (Mirapex®): DBPC 14 week trial of 56 pts.
  - 42% achieved at least 50% decreased pain
  - Substantial improvement in function, fatigue
  - 30% lost between 5 to 35 lbs during study
  - Dose starts at 0.125 and increase slowly over few months

May be the highest response of overall improvement of FMS symptoms of any single med tested so far
**General Pain: Non-Opioid Analgesics**

- **Tramadol** (Ultram®): Binds to mu opioid receptors in the CNS, and inhibits reuptake of NE and SE.
- Robert Bennett (OHSU Rheumatology) conducted DBPC study of 315 patients for 91 days.
  - Found tramadol/APAP to have moderate benefits.
- Anecdotally Bennett reports tramadol is used in his clinic as first line analgesic. 70% of FMS patients get >50% improvement on 100-400mg/day.

SE: nausea, drowsiness, constipation

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**General Pain: Opioids**

Bind to specific endogenous receptors (mu, kappa & delta), hyperpolarize nerve endings and interrupt nerve impulses moving up pain pathway

- Opioids should never be 1st choice for pain relief in FMS
- Bennett suggests starting with hydrocodone/APAP (up to 8/day) then oxycodone SR (40-120mg/day), and when that isn’t strong enough, methadone 5-10mg 2-3 times daily

**Rule of thumb**, if opioid treatment results in patient being less distressed and more functional, continue treatment. If dysfunction is discerned, refer to addictionologist
Trigger Point Pain

- **Topical Agents**
  - Lidoderm Patch®
  - Ketamine Topical Gel (compounded)
  - Capsaicin Topical Cream

- **Trigger Point Injections**
  - Lidocaine 0.25%
  - Dry needling
  - Botox

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Case Example: Paula

- 49 year old woman
- Diagnosed with FMS 6 years ago
- Started on duloxetine but unhappy with the side effects so stopped taking it after 1 week
- She reported nausea, insomnia, headache, fatigue, and dizziness after starting on 60mg BID
Case Example: Paula

- Encourage Paula to retry duloxetine at a lower dose once a day in the morning.
- Tell her the side effects that she may encounter, but remind her that they are mild to moderate and will lessen with time.
- She needs to understand that each drug needs an adequate therapeutic trial before stopping.
- If she takes the medication long enough to have a meaningful therapeutic trial, she will have a greater chance of experiencing some treatment benefit.

Sleep Disorders

- **Tricyclic antidepressants**: Low dose amitriptyline, trazodone, doxepine used
- **Benzodiazepine**-like sleep agents:
  - Eszopicione (Lunesta®)
  - Zolpidem (Ambien®)
  - Zaleplon (Sonata®)
- **Magnesium, melatonin, diphenhydramine**

SE: Weight gain, dry mouth, cognitive impairment, watch for sleep apnea
Chronic Fatigue

**Rule out:** Inappropriate dosing of meds (TCAs), SE of drugs, depression, sleep apnea, non-restorative sleep

- **Modafinil** (Provigil®): used intermittently
- **Sodium Oxybate** (Xyrem®): GABA-B receptor agonist

Restless Leg Syndrome

**Treatment is simple and very effective**

- LDopa/carbidopa (Sinemet®): early evening dose of 10/100
- Clonazepam: 0.5-1mg HS
- Pramipexole (Mirapex®): for restless legs, also effective for general FMS pain
Case Example: Mike

- 56 year-old male
- Having difficulty sleeping, and has diffuse aches, pains and stiffness
- Due to inability to be active, has gained 20 lbs
- Mentions that he has unpleasant sensations in his legs at night that are relieved with movement
- States “I thought that was just a part of getting old”

Case Example: Mike

- Mike tests negative for all but FMS, so his provider starts him on tramadol.
- Mike dislikes the nausea tramadol causes, so stops the med.
- Dr asks you if pramipexole would be appropriate, and how to dose.
- You suggest starting with 0.5mg PO every bedtime, and increase by one tab every 5-7 days, not to exceed 3mg nightly.
- At a follow-up visit, Mike tells you it’s working well, and he is beginning to be more active and losing weight.
**Irritable Bowel Syndrome**

- Occurs in up to 60% of FMS patients
- Use bowel regimen rules for maintaining regularity
- Constipation: stool softener, fiber supplement, gentle laxative, bisacodyl, senna
- Diarrhea: loperamide, diphenoxylate/atropine
- Antispasmodics: dicyclomine, anticholinergic/sedative (Donnatal®)

**Irritable Bladder Syndrome**

- Occurs in 40-60% of FMS patients
- Rule out other etiologies (UTI, interstitial cystitis)
- Antispasmodics: Oxybutynin (Ditrofan®), flavoxate (Urispas®), hyoscyamine (Levsin®)
- Non-pharmacologic treatment: increase water intake, decrease bladder irritants, kegel exercises
**Depression**

- Occurs 20-30% of FMS patients
- Also normal with chronic illness
- Refer to use of TCAs, SSRIs, SNRIs

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**When Starting Drug Therapy in FMS Patients**

Remember that severe, complex FMS patients tend to be unusually sensitive to SE of meds

- Start new meds at half or less of usual low end starting dose
- Titrate slowly over days or weeks
- Forewarn patients about potential SE, and that SE decrease over several weeks
- Be alert for drug interactions with multiple agent use
Fibromyalgia Treatment Overview

Pharmacologic treatment to improve “symptoms” of pain, sleep and fatigue
  • Trial of TCAs or dual reuptake inhibitors
  • If insomnia, add low-dose TCA or cyclobenzaprine
  • If intolerant to TCAs, try alternative, i.e. zolpidem, zaleplon, or trazodone
  • If persistent pain, add pregabalin, gabapentin, tramadol, or tizanidine
  • If mood disorders persist, consider SSRIs

Non-pharmacologic treatment to improve “function”
  • Exercise, low-impact and aerobic
  • Cognitive-behavioral therapy

Advice for Pharmacists Who Care for Fibromyalgia Patients

• Realize that FMS patients are going to be a chronic challenge
• Be non-judgmental and be prepared to be an advocate, show understanding and empathy
• Understand that FMS represents a bewildering array of bodily and psychological problems that will seldom be “cured”
Conclusion

• When considering medication therapy, amitriptyline and cyclobenzaprine have the most supporting evidence. New FDA approvals add pregabalin, duloxetine and milnacipran to that list.

• Non-medicinal therapy such as low impact exercise, massage therapy, cognitive behavioral therapy, eliminating nicotine, caffeine, and alcohol, and patient education also have strong evidence for efficacy.

• By becoming educated about FMS and its treatments, pharmacists will be better able to counsel their patients and develop a trusting relationship with the patients they serve.

Thank you for your participation!