Understanding Fibromyalgia

Michael W. Ravotti DHSc, PA-C

This program has been supported by an educational grant from Pfizer Pharmaceuticals

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Understanding Fibromyalgia

**Speaker:** Dr. Ravotti has been a practicing Physician Assistant for over 20 years, with most of his experience being in primary care and orthopedics. He has also been involved with non-steroidal anti-inflammatory research in an industrial rehabilitative setting. Prior to becoming a PA, Dr. Ravotti earned his BS degree at Slippery Rock University in Health Education/Athletic Training and taught in the public school systems of Western Pennsylvania. Dr. Ravotti earned his Physician Assistant degree Saint Francis University and graduated in 1984. He also received his Masters degree in Human Resource Management and holds a Doctorate of Health Sciences degree from Nova Southeastern. Dr. Ravotti is currently employed by Abbot Laboratories as a cardiovascular Clinical Science Manager where he focuses most of his efforts on the management of dyslipidemia. He is also and adjunct Assistant Professor at Saint Francis University in the Department of Physician Assistant Sciences where he has taught for 22 years.2

**Speaker Disclosure:** Dr. Ravotti has no actual or potential conflicts of interest in relation to this program

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Understanding Fibromyalgia

Accreditation:  
Pharmacist –798-000-08-074-L01-P  
Technicians- 798-000-08-074-L01-T

CE Credits:  
1.0 Credit hour or 0.1 CEU for pharmacists/technicians

Target Audience:  
Pharmacists & Technicians

Expiration Date: 9/18/2011

Program Overview:  
This program will focus on the challenges faced by healthcare professionals in diagnosing and treating patients with fibromyalgia. This program will also review the most recent research findings on fibromyalgia, which will provide a better understanding of its pathophysiology and enable more efficient management of this disease.

Objectives:
1. Identify the prevalence, gender, and age demographics of fibromyalgia in the general population.
2. Outline the American College of Rheumatology criteria for the classification and diagnosis of the patient with fibromyalgia.
3. Review current therapies used in fibromyalgia, including their limitations and mechanisms of action.

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Understanding Fibromyalgia

- What is it?
- What can I do for it?

- Fibromyalgia is undoubtedly one of the most challenging Dx to make and equally challenging to manage
Fibromyalgia
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- Fibromyalgia is undoubtedly one of the most challenging Dx to make and equally challenging to manage
Fibromyalgia

Q: What is it?
A: A common pain syndrome that is extremely complex in its presentation with many nuances
Fibromyalgia: Definition

- A chronic widespread pain syndrome manifested by tenderness in all 4 quadrants of the body
- Often accompanied by stiffness, fatigue and sleep disturbance
Educational Objectives

1. Identify the prevalence, gender, and age demographics of fibromyalgia in the general population.

2. Outline the American College of Rheumatology criteria for the classification and diagnosis of the patient with fibromyalgia.

3. Review current therapies used in fibromyalgia, including their limitations and mechanisms of action.

4. Identify management strategies and complementary/alternative therapies to assist the patient, family and/or significant others in alleviating fibromyalgia pain.
Prevalence of Fibromyalgia

- 6 million Americans
- Associated Manifestations
  - Sleep disorders
  - Stress
  - Chronic-pain conditions
Age Demographics

- Diagnosis is most common in people between 20 and 55
- Women typically develop it during their childbearing years
- Prevalence increases with age
Gender Demographics

- Adult women at greater risk than men or children
- Women closely related to a sufferer are more likely to develop it themselves
- Can affect all ages and both sexes
Fibromyalgia: DDX

- Symptoms are often vague and non-specific
- Broad DDX
  1. Rheumatoid arthritis
  2. Chronic fatigue syndrome
  3. Fibromyositis
  4. Depression
  5. Anxiety/hysteria
  6. SLE
Fibro (tissue) Myo (muscle) algia (pain)

- The most common widespread pain syndrome in the US
- Affects 2% of adult population (6 million)
- Onset (ages 20-50)
- Females > Males 1.5:1
- Non inflammatory
Pain: The defining feature

- Must be present in all 4 quadrants of the body
- Joints are not involved
- No erythema or edema (non-inflammatory)
- No other objective findings
Fibromyalgia Pain Description

- Aching
- Nagging
- Stiffness or tightness
- Exhausting
- Associated with fatigue
Associated Symptoms

- Allodynia (pain from stimulus that would not normally produce pain)
- Hyperalgesia (extreme sensitivity to painful stimuli)
- Sleep disturbance (stage 4)
- Low cognitive function (short term memory)
- Fatigue (unexpected or inappropriate)
Burden of Illness

- 4X more office visits
- 4X more ED visits
- 3X more $$$
- Increased diagnostic testing
- Increased association with co-morbidities
- High absenteeism: lost productivity and wages
<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Patients With Fibromyalgia</th>
<th>Patients Without Fibromyalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulatory system diseases</td>
<td>22.0%*</td>
<td>12.1%</td>
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<tr>
<td>Diabetes</td>
<td>5.9%*</td>
<td>3.9%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.4%*</td>
<td>1.3%</td>
</tr>
<tr>
<td>Depression</td>
<td>12.3%*</td>
<td>2.8%</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>1.5%*</td>
<td>0.2%</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>5.4%*</td>
<td>1.5%</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>5.7%*</td>
<td>1.0%</td>
</tr>
<tr>
<td>Painful neuropathies</td>
<td>22.8%*</td>
<td>2.8%</td>
</tr>
<tr>
<td>Back pain</td>
<td>31.7%*</td>
<td>3.2%</td>
</tr>
<tr>
<td>Cervical pain</td>
<td>20.2%*</td>
<td>1.5%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>11.3%*</td>
<td>2.0%</td>
</tr>
<tr>
<td>Migraine</td>
<td>4.5%*</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

*P<.001
Fibromyalgia

- Genetic predisposition
- Onset associated with environmental triggers
- Perception and response to pain are altered
- Dysfunctional response to stress
- Psychological factors interact with the disease process
Environmental Triggers

- Emotional stress
- Physical trauma
- Infection/illness
- Flare-up of co-morbid conditions
Physiologic response to pain

- Sensory nerve endings (nociceptors) transmit stimuli once the activation threshold has been achieved through axons to the dorsal horn of the spinal column.
- Ascending (spinothalamic) tracts carry pain stimuli to thalamus and cerebral cortex.
- Brain interprets pain.
- Sensation of pain carried back through descending tracts.
1. Painful stimulus detected by pain receptors on peripheral nerves

2. Impulses travel along peripheral nerves toward dorsal horn

3. Peripheral nerves transmit impulses to the spinal nerves

4. Impulses ascend spinal nerves

5. Impulses travel to thalamus, brainstem, cerebral cortex, and other regions

6. Descending impulse from base of brain causes release of endogenous opioids (endorphins, enkephalins) in the spinal cord, blocks ascending transmission of pain

Adapted from Purves, 2004
Central Sensitization Theory

- Imbalanced dysfunctional pain modulation
- Enhanced **pro-nociceptive** effect
- Increased peripheral sensitization
- Reduced **modulation** of pain perception (serotonin, norepinephrine, dopamine, endorphins and enkephalins): released and carried down descending tracts to block ascending transmissions.
Pro-Nociceptive Effect

- Increased pro-nociceptive neurotransmitters (Substance-P and Glutamate)
- Increased pain transmission
- Promotes smooth muscle contraction
- Promotes vasodilation
Central Sensitization

- Pain outlasts stimulus (lasts for hours)
- Increased sensitivity in the dorsal horn neurons and peripheral nociceptors
- Reduction in nociceptor threshold
- Decreased inhibition of pain impulses
- Enhanced pain transmission
Neurotransmitters

- Activated by “Voltage-Gated Calcium Channels”
- Influx of calcium to axon terminals release transmitters to the synaptic cleft
  1. Excitatory central neuron activity +++
  2. Pro-nociceptive activity +++ (Substance-P)
  3. Modulation response – (serotonin, norepinepherine, dopamine and endorphins)
Is the Pain Real?

- Objective measurement: MRI imaging has confirmed activation of brain activity associated with pain perception with lower stimulus than controls.
- MRI confirmed reduced activity within the thalamus which modulates pain.
- Increased Substance-P in CSF.
Exaggerated Response to Stress

- Blunted hypothalamic-pituitary axis (substance-P)
- Elevated HR
- Orthostatic Hypotension
- Increased sympathetic activity (sleep disturbance, dry eyes, dry mouth and sensitivity to cold)
1990 ACR Criteria for the Classification of Fibromyalgia*

1. **History of widespread pain**
   - **Definition:** Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain.

2. **Pain in ≥11 of 18 tender point sites on digital palpation**
   - **Definition:** Pain, on digital palpation, must be present in at least 11 of the following 18 sites:
     - **Occiput:** bilateral, at the suboccipital muscle insertions.
     - **Low cervical:** bilateral, at the anterior aspects of the intertransverse spaces at C5-C7.
     - **Trapezius:** bilateral, at the midpoint of the upper border.
     - **Supraspinatus:** bilateral, at origins, above the scapula spine near the medial border.
     - **Second rib:** bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
     - **Lateral epicondyle:** bilateral, 2 cm distal to the epicondyles.
     - **Gluteal:** bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.
     - **Greater trochanter:** bilateral, posterior to the trochanteric prominence.
     - **Knee:** bilateral, at the medial fat pad proximal to the joint line.

Digital palpation should be performed with an approximate force of 4 kg.

For a tender point to be considered "positive," the subject must state that the palpation was painful. "Tender" is not to be considered "painful."

* For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.
Additional Diagnostic Criteria

- Canadian Clinical Working Case Definition (impaired concentration and short-term memory, fatigue, sleep dysfunction)
- American Pain Society
  (fatigue, sleep disturbance, cognitive disturbance)
History and Physical

- Thorough description of the pain
- Location of the pain
- Onset, duration and progress
- Triggers
- PMX
- ROS

- Musculoskeletal
- Neurological
- Cardiorespiratory
- Endocrine
- Psychological
Laboratory Values

- CBC/diff
- Sed-Rate
- CPK (Statin use?)
- LFTs
- TSH, T₃, free T₄
- *Note: All lab values will be WNL
Non-pharmacologic Management

- Patient education
- Exercise
- Stress management
- Behavioral support
- Nutritional education
- Sleep hygiene
Pharmacological Management

- Most Fibro patients require 3 meds
- 33% take 4 or more meds for Fibro
- Think (PMS)
  1. PAIN
  2. MOOD
  3. SLEEP
Pain Management

- OTC
- NSAIDS
- Tramadol
- Opioids
- Physical Therapy
- Trigger point injections
- **Alcohol counseling**
Mood Management

- **Antidepressants**
  1. SSRIs
  2. SNRIs (*Duloxetine)
  3. Ticyclics (*Amitriptyline)

- **Anxiolytics**
  1. Xanax
  2. Valium
  3. Ativan
  4. Tranxene
Tricyclic Antidepressants: Adverse Effects

- Often have unacceptable side effects in the elderly
- Most common adverse effects
  - Sedation
  - Anticholinergic effects
    - Dry mouth
    - Blurred vision
    - Increased intraocular pressure
    - Mydriasis (pupil dilation)
    - Constipation
    - Paralytic ileus
    - Urinary retention
    - Delayed micturition
    - Hyperpyrexia
    - Sinus tachycardia

Pharmacologic Options: SNRIs

- SNRIs
  - Venlafaxine
  - Duloxetine

Venlafaxine

Duloxetine

Duloxetine (Cymbalta)

- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Available in delayed release
- Brand (30mg and 60mg)
- Generic (20mg, 30mg, 40mg, 60mg)
Duloxetineine (Cymbalta)

- American College of Rheumatology research study
  - Given once or twice a day in 60mg dose reduced pain in over half of women fibromyalgia patients
  - 12 week study, subjects mostly females (11% male)
  - Improved quality of life and increased functionality among women

- Duloxetineine also used:
  - Generalized Anxiety Disorder
  - Diabetic Peripheral Neuropathy
  - Major Depressive Disorders
  - Stress Urinary Incontinence
Duloxetine

- Depression
- Fibromyalgia
  - Pregabalin can be added to treatment regimen
  - Different metabolic pathways
  - Different mechanisms of action
Duloxetine: Summary of Adverse Events

- Most common adverse events in duloxetine-treated DPN patients*
  - Nausea
  - Somnolence
  - Dizziness
  - Constipation
  - Dry mouth
  - Hyperhidrosis
  - Decreased appetite
  - Asthenia

*≥5% and at least twice the incidence in placebo-treated patients.

Opioids: Safety and Tolerability

- Associated with tolerance, dependence, and abuse liability
- Special issues in the elderly (cognitive effects, mobility, hip fractures)
- Most common adverse effects
  - Respiratory depression
  - Skeletal muscle rigidity
  - Apnea
  - Bradycardia
  - Lightheadedness
  - Dizziness
  - Sedation
  - Nausea
  - Vomiting
  - Sweating
  - Constipation

Sleep Management

- OTC (*Tylenol PM)
- Ambien (Stage 4)
- Lunesta
- Halcion
- Restoril
- Alcohol
Anticonvulsants

- Gabapentin (Neurontin) Proven beneficial, but not indicated for Fibromyalgia. Major side-effects are dizziness, somnolence and peripheral edema
- Pregabalin (Lyrica) Indicated for the Tx of Fibromyalgia and PHN. Major side-effects are dizziness and somnolence
Pregabalin (Lyrica) capsules

- MOA: Binds to voltage-gated calcium channels on the axon (specific)
- Decreases neuronal hyper-excitability and pain characteristics
- 90% bioavailable
- Peak plasma 1.5 hrs.
- Half-life 6.3 hrs.
- No-food-effect
- Renal excretion (minimal hepatic metabolism)
- Crosses BBB
- Schedule V
Pregabalin Binds to the $\alpha_2$-$\delta$ Subunit of Voltage-Gated Ca$^{2+}$ Channels in the Central Nervous System

- Schematic representation of pregabalin’s proposed mechanism of action

- Pregabalin selectively binds to $\alpha_2$-$\delta$ subunit of calcium channels
  - Modulates calcium influx in hyperexcited neurons
  - Reduces neurotransmitter release
  - Pharmacologic effect requires binding at this site
  - The clinical significance of these observations in humans is currently unknown

Pregabalin Dosage

- Appropriate dosing is the key to compliance
- Available doses: 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg and 300mg
- Appropriate titration is critical; Tx is individualized and should be titrated to minimize side-effects and optimize efficacy
- Dosed twice daily for Fibromyalgia
- Minimal effective dose 75mg twice daily
- Maximal effective dose 225mg twice daily
- Dosage adjustment for patients with renal insufficiency
- 4% D/C rate
- Proven beneficial in 2 clinical trials
Low Potential for PK Drug Interactions

- Does not inhibit major CYP450 enzymes
- No protein binding

Pregabalin has no clinically significant PK interactions, based on PK studies or population analyses, with:

<table>
<thead>
<tr>
<th>Antiepileptic Drugs</th>
<th>Other Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Hypoglycemics*</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Insulin*</td>
</tr>
<tr>
<td>Phenobarbital*</td>
<td>Diuretics*</td>
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<tr>
<td>Phenytoin</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>Topiramate*</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Tiagabine*</td>
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</tbody>
</table>

- Pregabalin may exacerbate the impairment of cognitive and gross motor function when used in conjunction with oxycodone, lorazepam, and ethanol (alcohol)

*Derived from population pharmacokinetic analyses.

Pregabalin Efficacy

- Onset of pain relief within 1 week
- 85% of patients received a pain response of at least 50% (PGIC score) patient global impression of change (validated)
- 53% of responders maintained therapeutic benefit for 6 mo.
- Improved mood vs. placebo (fatigue and functional status)
- Improved sleep vs. placebo
- Reduced need for rescue meds (pain and sleep)
Pregabalin Side-effects

- Dizziness 31% (17 days duration)
- Somnolence 22% (34 days duration)
- Mild wt. gain (9-10%)
- Blurred vision (10%)
- Dry mouth (8%)
- Peripheral edema (6%)
Living with Fibromyalgia

- Sedentary lifestyle
- Sleep disorders
- Mood disorders
- Social withdrawal
- Increased co-morbid conditions
Consequences of the Fibromyalgia Lifestyle

- Depression
- Metabolic Syndrome
- Obesity
- Atherosclerosis
- Diabetes
- Thrombo-embolic disease
- Pneumonia
Lifestyle Modification and Quality of Life

relies on

Accurate Diagnosis
Appropriate Management
Fibromyalgia Case Study
Jean – a 42 Year Old Female

- Case history
  - Always in crisis Mode
  - Hypochondriac
  - Unemployed/unskilled
  - Always tired/sleep problems
  - Marital problems
Jean – Case history

- Physical Exam
  - Weight gain
  - Mild hypertension
  - Lipids
  - Tender spots
- Lab Exam – Normal
- OTC – Pain Medication
Jean

- Diagnosed with fibromyalgia
- Elated to know what was wrong
- Treatment
  - Physical exercise
  - Sleep hygiene
- Medication