Session 6: Fibromyalgia: Dispelling Myths, Improving Management

Learning Objectives
- Dispel misinformation about fibromyalgia and rely on scientific evidence to explain its causes, recognize its manifestations, and make an accurate diagnosis.
- Analyze current pharmacologic and nonpharmacologic therapies for fibromyalgia to devise tailored, evidence-based treatment plans.

Faculty

**Martin J. Bergman, MD**
Clinical Assistant Professor of Medicine  
Division of Rheumatology  
Drexel University College of Medicine  
Philadelphia, Pennsylvania

Dr Bergman is a practicing rheumatologist with over 20 years of clinical experience. He started his practice at Sacred Heart Hospital in Chester, Pennsylvania, in 1987, and relocated to Ridley Park, Pennsylvania, in 1992. Dr Bergman has a faculty appointment at the Drexel University College of Medicine, where he is clinical assistant professor in the Department of Medicine, Division of Rheumatology. He is also chief of the Section of Rheumatology at Taylor Hospital in Ridley Park, Pennsylvania. Dr Bergman's current research interests focus mainly on the use of patient self-reported outcomes tools, recognizing the importance of quantitative measurement in the management of rheumatologic diseases and the ability of patients to know how much their disease affects them. His work has been published in major national and international journals and presented at the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) scientific meetings. He is a member of the Board of Directors and past president of the Delaware County Medical Society. He is also a past president of the Philadelphia Rheumatology Society, America's oldest rheumatology society.

**Allan Gibofsky, MD, JD**
Professor of Medicine and Public Health  
Weill Medical College of Cornell University  
New York, New York

Dr Gibofsky is professor of medicine and public health at Weill Medical College of Cornell University, professor of law at Fordham University, and adjunct faculty at the Rockefeller University, all in New York City, New York. He is an attending physician and rheumatologist at both the Hospital for Special Surgery and The New York Presbyterian Hospital. Dr Gibofsky has authored or co-authored numerous papers and text chapters, primarily on the immunogenetics of rheumatic diseases and legal aspects of medical practice. He is known for his work on mechanisms of host-microbe interactions in rheumatology and, in particular, for his basic and clinical studies on rheumatic fever. Dr Gibofsky served as president of The American College of Rheumatology in 2002. He is currently secretary-treasurer of The New York Rheumatism Association. He has participated in numerous professional and public education programs, both nationally and internationally. He serves on several committees of the New York Chapter of the American College of Physicians.

Faculty Financial Disclosure Statements
The presenting faculty reported the following:
Dr Bergman has no commercial relationships to disclose.
Dr Gibofsky receives a speaker’s honorarium from Pfizer.
Education Partner Financial Disclosure Statement
The content collaborators at MedIQ Research & Education have reported the following:
Joyce Waskelo has nothing to disclose.

Drug List

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<td>(es)zopiclone</td>
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Investigational
milnacipran

Suggested Reading List


Today's Program

A presentation of facts and evidence to dispel several common myths related to fibromyalgia...

Part 1:
• Overview of Fibromyalgia
  – Epidemiology, disease classification, pathophysiology
• Diagnosis
  – Classic symptoms, clinical workup

Part 2:
• Management of Fibromyalgia
  – Treatment of pain and other symptom domains

Question
• Have you ever given a patient the diagnosis of fibromyalgia?
  1. Yes
  2. No

Question
• How would you characterize fibromyalgia?
  1. Autoimmune disease
  2. Psychological disorder
  3. Rheumatic or inflammatory disorder
  4. Central nervous system disorder
  5. Musculoskeletal disorder

Myth 1:
Fibromyalgia is not a real illness—it is psychological
Case Study Preview: Darlene’s Story

Fibromyalgia Often Associated with Other Disorders

Rheumatic disorders
- Lupus (SLE)
- Rheumatoid arthritis
- Sjögren’s syndrome
- Osteoarthritis

Infections and inflammation
- Hepatitis C
- Crohn’s disease
- Lyme disease
- Parvovirus infections

Psychological disorders
- Depression
- Anxiety states
- Posttraumatic stress disorder (PTSD)

Other pain states
- Irritable bowel syndrome
- Pelvic pain syndromes
- Sympathetic dystrophy
- Neuropathies
- Vascular headaches

Fibromyalgia diagnosis is not based on exclusion of other disorders

What Causes Fibromyalgia?

- Genetics
- “Triggers”
- Potential mechanisms
  - Central sensitization
  - Abnormalities of descending inhibitory pain pathways
  - Neurotransmitter abnormalities
  - Neurohumoral abnormalities
  - Psychiatric comorbid conditions

Genetics of Fibromyalgia

- Strong familial predisposition
  - >8 odds ratio for first-degree relatives
- Possible genetic polymorphisms:
  - 5-HT(2A) receptor
  - Serotonin transporter
  - Dopamine D4 receptor
  - COMT (catecholamine-O-methyl transferase)

Fibromyalgia “Triggers”

- Peripheral pain syndromes
- Infections (eg, parvovirus, Epstein-Barr, Lyme disease)
- Physical trauma (eg, automobile accidents)
- Psychological stress/distress
- Hormonal alterations (eg, hypothyroidism)
- Certain catastrophic events (eg, war)

Pain Pathways

Facilitatory
- Ascending Pain Pathway
- Descending Pain Pathway

Inhibitory
- Striatum
- Hypothalamus
- Spinal Cord
- Nociceptor
- Brainstem
- Nucleus raphe
- Dorsal horn
- Primary afferent fibers (PAG)
- Descending pain pathway

[References not provided in the text]
Central Sensitization: Enhanced Processing of Pain Stimuli

• Amplified pain responses: abnormal “volume control”
  – Increased response to painful stimuli (hyperalgesia)
  – Pain from normally innocuous stimuli (allodynia)

• Scientific evidence:
  – Temporal summation of second pain (“wind-up”)
  – Increased activity on fMRI scans
    • “Left-shift” in stimulus-response function
  – Elevated cerebral spinal fluid levels of neurotransmitters (substance P, nerve growth factor)


Temporal Summation: The Concept of “Wind-Up” Pain

Functional MRI: Objective Evidence of Augmented Pain Processing

Stimulus-Response Curve Shifts When Pressure-Induced Pain Is Reduced

Fibromyalgia: Elevated CSF Levels of Pain Modulator (Substance P) in Fibromyalgia Patients

Diagnosis
Myth 2: 
*Fibromyalgia is a new and rare condition that affects only middle-aged women*

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**Fibromyalgia Prevalence**

- 2% of general population in the US; about 5 million adults ≥18 years of age
- 3.4% of female population
  - Female to male ratio 7:1
- All ages, from <10 years to elderly
  - Prevalence rises sharply in middle age, peaking at ages 70-79 years
- 5%-6% of general practice patients
- 10%-16% of rheumatology practice patients

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**Nomenclature History**

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<tr>
<th>Year</th>
<th>Term</th>
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<td>Neurasthenia</td>
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<tr>
<td>1904-1981</td>
<td>Fibrositis</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>1981-Present</td>
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</table>

- Related monikers/syndromes:
  - Functional somatic syndromes
  - Psychogenic rheumatism
  - Chronic fatigue syndrome
  - Gulf War syndrome
  - Multiple chemical sensitivity syndrome

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**Identifying Fibromyalgia: ACR Classification Criteria**

- Chronic widespread musculoskeletal pain for ≥3 months
- Tenderness at ≥11 of 18 tender points
  - Detected by digital palpation of soft tissue with approximate force of 4 kg/cm²

- Sensitive (88.4%) and specific (81.1%) tool to differentiate fibromyalgia from other rheumatologic conditions
- Criteria need further refinement as knowledge about fibromyalgia evolves

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**Location of the Tender Points**

- Anterior aspects of the C5, C7 intertransverse spaces
- Second rib space – about 3 cm lateral to the sternal border
- Medial 1/3 part of trapezius proximal to joint line

**Practical use of examination:**
- Confirms diagnostic impression
- Serves as proxy for pain sensitivity
- Provides comparison with joint tenderness

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**Fibromyalgia: Constellation of Symptoms**

- Widespread pain with tender points
- Cognitive dysfunction
- Sleep disturbance
- Numbness and tingling
- Fatigue
- Dizziness
- Irritable bowel/bladder
- Headache
- Dysmenorrhea
- Multiple chemical sensitivity syndrome
- Depression/anxiety
- Weakness
- Morning stiffness
- Widespread pain with tender points
**Recommended Diagnostic Workup for Fibromyalgia**

- History of chronic widespread pain for ≥3 months
- Absence of other conditions that may present with chronic widespread pain
- General physical exam, neurologic exam, selected laboratory testing (ESR, thyroid tests; avoid screening serologic tests)
- Confirm presence of tender points (Fibromyalgia may be present, even if <11 of 18)
- Confirm diagnosis of fibromyalgia

Adapted from Burckhardt C, et al. APS Clinical Practice Guideline Series, No. 4; 2005.

**Darlene’s Story: Diagnosis and Hope for Relief**

**Initial Steps After Diagnosis**

- Confirm diagnosis of fibromyalgia
- Identify important symptom domains and their severity (eg, pain, sleep disturbance, fatigue) and level of function
- Evaluate for comorbid medical and psychiatric disorders (eg, sleep apnea, osteoarthritis, depressive or anxiety disorders)
- Confirm diagnosis of fibromyalgia
- Assess psychosocial stressors, level of fitness, and barriers to treatment
- Provide education about fibromyalgia
- May require referral to a specialist for full evaluation
- Treatment options?


**Patient Education: Common Patient Questions**

- What is wrong with me?
- Why do I hurt all over?
- Why am I so exhausted?
- How did I get this?
- How is it treated?
- When will it go away?
- Why do people not believe me?


**Educating About Fibromyalgia: Increasing Patient Self-Efficacy**

- Consider group consultation
  - Didactic talk with patient Q&A
  - More time-saving than one-on-one education
- Include core information
  - Explain pathophysiologic mechanisms (biopsychological model)
  - Dispel notion that absence of organic disease means symptoms are psychogenic
  - Describe prognosis and clinical course
  - Reassure that fibromyalgia is not a prodrome of another disease
  - Emphasize that this condition can get better, but requires hard work and self-management by the patient
  - Warn that media and Internet are often sources of misinformation

Continuing the Stepwise Approach

- Confirm diagnosis of fibromyalgia
- Identify important symptom domains and their severity (eg, pain, sleep disturbance, fatigue and level of function)
- Evaluate for comorbid medical and psychiatric disorders (eg, sleep apnea, osteoarthritis, depressive or anxiety disorders)
- Assess psychosocial stressors, level of fitness, and barriers to treatment
- Provide education about fibromyalgia

Review treatment options
- As first-line approach for patients with moderate-to-severe pain, trial with evidence-based medications
- Adjunctive cognitive-behavioral therapy for patients with prominent psychosocial stressors and/or difficulty coping and/or functioning

Encourage exercise according to fitness level


Nonpharmacologic Strategies: Evidence of Efficacy

**Strong Evidence**
- **Exercise**
  - Physical and psychological benefits
  - May increase tender point pain pressure threshold and improve pain
- **Cognitive-behavioral therapy**
  - Improvement in pain, fatigue, mood, and physical function often sustained for months
- **Patient education/self-management**
  - Improves pain, sleep, fatigue, and quality of life
- **Combination (multidisciplinary therapy)**

**Moderate Evidence**
- **Exercise**
  - Strength training
  - Acupuncture
  - Hypnotherapy
  - EMG biofeedback
  - Balneotherapy (medicinal bathing)

**Weak Evidence**
- Chiropractic
- Manual and massage therapy
- Electrotherapy
- Ultrasound

**No Evidence**
- Tender-point injections
- Flexibility exercises


Question

- Which of the following nonpharmacologic therapies has no evidence-based support for treatment of fibromyalgia?
  1. Exercise regimen
  2. Cognitive-behavioral therapy
  3. Acupuncture
  4. Hypnosis
  5. Tender (trigger)-point injections

Myth 3:
Fibromyalgia causes unavoidable, progressive physical deterioration

Managing Deconditioning: Rationale for Aerobic Exercise

- Physical activity can increase fibromyalgia pain, leading to sedentary lifestyle
- Downward spiral of deconditioning can make symptoms worse at rest or with minimal exertion

Aerobic Exercise Guidelines

- Maximize tolerance and long-term compliance
  - Avoid high-intensity aerobic exercise (high dropout rates)
- Begin 1-2 months after start of drug therapy
  - Low-impact exercise, just below patient’s total capacity
  - Gradually increase duration to goal of 30 minutes


Improvements After Aerobic Fitness Training


Managing Psychological Distress: Cognitive-Behavioral Therapy (CBT)

- Helps patients understand that fibromyalgia is manageable and teaches adaptive skills, including:
  - Relaxation techniques
  - Goal setting
  - Problem solving
  - Self-reinforcement
  - Substituting maladaptive thoughts with positive thoughts

Managing Other Symptom Domains

Sleep disturbance
- Assess for primary sleep disorder; discuss sleep hygiene
- Minimize nocturnal pain and other sources of distress
- Recommend exercise at appropriate time of day
- Medications: TCA, short-acting hypnotic, muscle relaxant

Psychological distress
- Mood-altering medications as appropriate
- Cognitive-behavioral therapy
- Psychiatric referral for selected patients

Question

- What type of drug therapy would you initially prescribe for a patient you’ve diagnosed with fibromyalgia?
  1. Antidepressant
  2. Antiepileptic
  3. NSAID
  4. Opioid analgesic
  5. Sedative-hypnotic

Myth 4:
Fibromyalgia is best managed with NSAIDs for inflammation and opioid analgesics for pain
Pharmacologic Approaches

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<tr>
<th>Class</th>
<th>Agents</th>
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<td>Antidepressants</td>
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<td>Antiepileptic Drugs</td>
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<td>Sedative/Hypnotic</td>
<td>Tramadol, Zolpidem, Zopiclone, Sodium oxybate</td>
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* The SNRI duloxetine and the AED pregabalin are the only FDA-approved agents for the treatment of fibromyalgia.

NSAIDs in Fibromyalgia

- Nonsteroidal anti-inflammatory drugs constitute the number-one class of agents used to treat fibromyalgia.
- No evidence of effectiveness as monotherapy for fibromyalgia
  - May be modestly helpful combined with a tricyclic antidepressant.
- "Since fibromyalgia is not an inflammatory disease, it is not surprising we have a lot of treatment failures."
- Chronic analgesic use can set up cycle of rebound headaches, complicating fibromyalgia management.

Opiates in Fibromyalgia

- No adequate, randomized, controlled clinical trials.
- Opioids may heighten pain sensitivity (opioid-induced hyperalgesia).
- Neuroadaptive changes lead to enhanced nociceptive output and decreased analgesic efficacy.
- Tramadol (central-acting narcotic) has some opioid activity, combined with SNRI activity.
- May be efficacious, but is associated with nausea and dizziness.
- Better tolerated in fixed-dose combination with acetaminophen.
- Risk of seizures in patients using antidepressants, neuroleptics, or other drugs that decrease seizure threshold.
- Long-term addiction or abuse potential.

Antiepileptics (Alpha-2-Delta Ligands): Pregabalin and Gabapentin

- Mechanism:
  - Bind to α2δ subunit of voltage-gated calcium channels
  - Reduce calcium influx and inhibit release of neurotransmitters (e.g., glutamate, substance P).
- Indications:
  - Postherpetic neuralgia (both agents)
  - Adjunctive therapy for partial onset seizures (both agents)
  - Pain associated with diabetic peripheral neuropathy (pregabalin)
  - Fibromyalgia (pregabalin)

Pregabalin: Improvement in Weekly Fibromyalgia Pain Scores

- Pooled analysis of 2 similarly designed randomized clinical trials (N=1493)
- Monotherapy; 2 doses per day*
- Statistically significant improvement with all pregabalin doses vs placebo began at Week 1 and was sustained through endpoint.

<table>
<thead>
<tr>
<th>Change From Baseline in LS Mean Pain Score</th>
<th>Placebo</th>
<th>Pregabalin 300 mg/d</th>
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<td>-4.8</td>
<td>-4.9</td>
<td>-4.7</td>
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</table>

* For fibromyalgia indication. FDA-approved maximum dose is 450 mg/d.

Pregabalin: Adverse Events

- Discontinuation:
  - Peripheral edema (6.4%)
  - Fatigue (4.0%)
  - Dizziness (6.4%)
  - Somnolence (4.0%)
  - Nausea (4.0%)
  - Dry mouth (4.0%)
  - Constipation (4.0%)
  - Weight gain (4.0%)
  - Headache (4.0%)

- Due to all-cause AEs; among all pregabalin patients, dizziness (6.4%) and somnolence (4.0%) were the AEs that most commonly led to discontinuation.

Antidepressants for Fibromyalgia: Which To Choose?

- Most studies using antidepressants as analgesics for fibromyalgia demonstrate effects on pain that are distinct from effects on mood.
  - Tricyclic antidepressants: Block reuptake of serotonin and/or norepinephrine. Low doses may effectively treat pain, poor sleep, fatigue.
  - Tolerability issues; initiate therapy at very low doses, then titrate slowly.
- Selective serotonin reuptake inhibitors: Better side-effect profile than TCAs. Used at higher doses, the older, less-selective SSRIs are generally more efficacious than "highly selective" agents.
- Dual receptor inhibitors: Inhibit both serotonin and norepinephrine. Unlike TCAs, generally no significant activity at other receptors; better tolerability.
  - May have better analgesic effect than pure serotonergic drugs.
  - Two SNRIs have undergone multicenter trials in fibromyalgia: duloxetine (FDA-approved therapy) and milnacipran.

Duloxetine: Phase III Study

- Male and female patients (N=520)
- Primary end points:
  - Brief Pain Inventory (average pain severity)
  - Patient Global Impression of Improvement
- Significant responses (secondary measures):
  - FIQ total score (only at 3 months)
  - CGI-S
  - SF-36 mental component
  - Certain MFI subscales
- Safety/tolerability similar to other clinical trials

Duloxetine Adverse Events: Pooled Phase III Studies (Female Subjects)

<table>
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<th>Duloxetine (n=326)</th>
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<td>26 (12.3)</td>
<td>114 (35.0)</td>
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<td>Insomnia</td>
<td>31 (14.6)</td>
<td>79 (24.2)</td>
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<tr>
<td>Headache</td>
<td>28 (13.2)</td>
<td>70 (21.5)</td>
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<tr>
<td>Dry mouth</td>
<td>52 (24.2)</td>
<td>65 (19.6)</td>
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<tr>
<td>Fatigue</td>
<td>20 (9.4)</td>
<td>54 (16.8)</td>
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<tr>
<td>Constipation</td>
<td>4 (1.9)</td>
<td>44 (13.5)</td>
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<tr>
<td>Dizziness</td>
<td>17 (7.9)</td>
<td>41 (12.6)</td>
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<tr>
<td>Somnolence</td>
<td>5 (2.3)</td>
<td>26 (8.0)</td>
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<tr>
<td>Decreased appetite</td>
<td>2 (0.9)</td>
<td>19 (6.0)</td>
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<tr>
<td>Increased sweating</td>
<td>1 (0.5)</td>
<td>18 (5.5)</td>
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Milnacipran for Treatment of Fibromyalgia: Phase III Trials

- Two trials (N=888 and N=1196)
- Milnacipran 100 or 200 mg/d

Milnacipran Outcomes: Composite Responder (Syndrome)

- Additional, secondary end points:
  - FIO total score
  - Fatigue
  - Cognition

Milnacipran is not FDA-approved for the treatment of fibromyalgia.
Milnacipran Outcomes: Composite Responder (Pain)

- Pain End Points

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>3 Months</th>
<th>6 Months</th>
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<tbody>
<tr>
<td>Milnacipran 100 mg/d</td>
<td>45%</td>
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<tr>
<td>Milnacipran 200 mg/d</td>
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<td>28%</td>
</tr>
<tr>
<td>Placebo</td>
<td>26%</td>
<td>28%</td>
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*P<0.05 vs placebo.
†P<0.001 vs placebo.


Milnacipran Phase III Extension Study: 1-Year Maintenance of Pain Relief

- % Improvement Pain VAS

<table>
<thead>
<tr>
<th>Lead-In</th>
<th>Extension</th>
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<tr>
<td>Lead-In: Milnacipran 200 mg/day</td>
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<tr>
<td>Extension: Milnacipran 200 mg/day</td>
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Data represent continuing cohort of patients at each visit. VAS=24-hour recall of pain measured on 10-cm visual analog scale.


Milnacipran AEs: Pooled Data

<table>
<thead>
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<th>AEs reported in ≥5% of patients, and at twice the incidence of placebo:</th>
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<tbody>
<tr>
<td>Nausea</td>
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<tr>
<td>Headache</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Hot flush</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Hypersalivation</td>
</tr>
<tr>
<td>Palpitations</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Heart rate increased</td>
</tr>
<tr>
<td>Dry mouth</td>
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AEs reported in ≥5% of patients, and at twice the incidence of placebo.


Summary of Findings:

Studies in Fibromyalgia

- TCAs display efficacy but are poorly tolerated
- SNRIs improve pain, other symptom domains, function, quality of life, and global well-being
  - Effect on pain independent of effect on mood
  - Duloxetine is FDA-approved for the treatment of fibromyalgia
  - Milnacipran NDA filing under FDA review
- Alpha-2-delta ligands show similar improvements and improve slow-wave sleep
  - Pregabalin is FDA-approved for the treatment of fibromyalgia
- Combination therapy may be an option for patients with:
  - Incomplete response to single agent
  - Poor tolerance to higher doses


Darlene’s Story: Outlook on Life with Fibromyalgia

Summary: Practice Points

- Fibromyalgia is a common pain syndrome characterized by:
  - Widespread pain in peripheral tissues
  - Psychological distress
  - Central sensitization
- Pain component is consequence of disordered neurophysiology
  - Patients perceive more pain from nonpainful stimuli than do healthy controls and experience greater pain from painful stimuli
- Rationale for treatment involves 3 important strategies:
  - Reduction of peripheral nociceptive input
  - Improvement or prevention of central sensitization
  - Treatment of pain-related negative affect
Summary: Practice Points (Cont’d)

- Nonpharmacologic therapy includes:
  - Aerobic exercise
  - Improved sleep
  - Cognitive behavioral therapy

- Pharmacologic therapy includes neuromodulatory agents:
  - TCAs, NREs, dual reuptake inhibitors (SNRIs seem particularly efficacious for FM pain)
  - Anti-epileptic medications (eg, pregabalin)

- For optimal disease management, treatment should be customized to address the symptom domains of each patient: pain, global sense of well being, and physical function