KNOW
CENTRAL SENSITIZATION
/DYSFUNCTIONAL
PAIN
## Development Committee

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Learning Objectives

• After completing this module, participants will be able to:
  – Discuss the prevalence of various syndromes involving central sensitization/dysfunctional pain, focusing on fibromyalgia
  – Understand the impact of syndromes involving central sensitization/dysfunctional pain, such as fibromyalgia, on patient functioning and quality of life
  – Explain the pathophysiology of central sensitization/dysfunctional pain
  – Recognize core clinical features of fibromyalgia
  – Select appropriate pharmacological and non-pharmacological strategies for the management of fibromyalgia
Table of Contents

• What is central sensitization/dysfunctional pain?
• How common is central sensitization/dysfunctional pain?
• What are the clinical features of syndromes involving central sensitization/dysfunctional pain, such as fibromyalgia?
• How should syndromes involving central sensitization/dysfunctional pain, such as fibromyalgia, be treated based on their pathophysiology?
Multiple pain mechanisms may coexist (mixed pain)

Nociceptive pain
- Somatic
- Visceral

Neuropathic pain
- Peripheral
- Central

Central sensitization/dysfunctional pain

References:
Why do patients suffering from central sensitization experience dysfunctional pain?

- During central sensitization, the sensation of pain is enhanced as a result of:
  - Changes in nerve fibers and the environment
  - Modifications of the functional properties and the genetic programming of primary and secondary afferent neurons

**What is central sensitization/dysfunctional pain?**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Examples</th>
<th>Pain Quality</th>
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</table>
| • Amplification of neural signaling within the CNS that elicits pain hypersensitivity | • Fibromyalgia  
• Tension-type headache  
• Irritable bowel syndrome  
• Interstitial cystitis  
• Temporomandibular joint pain  
• May be present in many patients with chronic low back pain, osteoarthritis and rheumatoid arthritis | • Often diffuse  
• Frequently with allodynia and/or hyperalgesia  
• Rarely burning, lancinating or electric shock-like |

*CNS = central nervous system*  
Clinical Features of Central Sensitization/Dysfunctional Pain

**Pain**
- Pain all over body
- Muscles stiff/achy
- Headaches
- Pain in jaw
- Pelvic pain
- Bladder/urination pain

**Anxiety/depression**
- Sad or depressed
- Anxiety
- Stress makes symptoms worse
- Tension in neck and shoulder
- Grind/clench teeth

**Fatigue**
- Do not sleep well
- Unrefreshed in morning
- Easily tired with physical activity

**Other symptoms**
- Difficulty concentrating
- Need help with daily activities
- Sensitive to bright lights
- Skin problems
- Diarrhea/constipation

Discussion Question

HOW OFTEN DO YOU SEE PATIENTS WITH THESE CLINICAL FEATURES?
How common is central sensitization/dysfunctional pain?

~40% of adults suffer from chronic pain\(^1\)

17–35% of chronic pain patients suffer from generalized hypersensitivity and conditioned pain modulation\(^2\)

Common Diagnoses Among Patients Suffering from Central Sensitization/Dysfunctional Pain

- TH/M = tension headache/migraine
- MPS = myofascial pain syndrome
- FM = fibromyalgia
- IBS = irritable bowel syndrome
- TMJ = temporomandibular joint disorder
- PTSD = post-traumatic stress disorder

Note: some patients had more than one diagnosis; less common diagnoses included restless leg syndrome (8%); chronic fatigue syndrome (4%) interstitial cystitis (4%), complex regional pain syndrome (2%) and multiple chemical sensitivity (1%)

FM = fibromyalgia; IBS = irritable bowel syndrome; MPS = myofascial pain syndrome; PTSD = post-traumatic stress disorder; TH/M = tension headache/migraine; TMJ = temporomandibular joint disorder

What is fibromyalgia?

FIBROMYALGIA IS A COMMON CHRONIC WIDESPREAD PAIN DISORDER, CHARACTERIZED BY AN AMPLIFICATION OF PAIN SIGNALS, ANALOGOUS TO THE “VOLUME CONTROL SETTING” BEING TURNED UP TOO HIGH.
Epidemiology of Fibromyalgia

Fibromyalgia is one of the most common central sensitization/dysfunctional conditions.¹

Prevalence in USA is estimated to be 2–5% of the adult population.¹

Fibromyalgia is highly underdiagnosed:²
- Only 1 in 5 is diagnosed
- Diagnosis takes an average of 5 years³

Fibromyalgia occurs in all ages, both sexes and all cultures but occurs more frequently in:⁴
- Women
- Those between the ages of 35 and 60 years

USA = United States of America
Patient-Reported Impact of Fibromyalgia

Overall quality of life: 84
Personal relationships: 76
Ability to keep appointments: 70
Ability to participate in hobbies: 70
Ability to care for family: 67
Sex life: 63
Physical mobility: 75
Overall mood: 71
Concentration/memory: 71
Motivation/drive: 72

Percentage rating fibromyalgia as having strong/very strong impact on various aspects of life

Clark P et al. BMC Musculoskeletal Disorder 2013; 14:188.
Discussion Question

HOW DO YOU IDENTIFY PATIENTS WITH FIBROMYALGIA IN CLINICAL PRACTICE?
How to Recognize Fibromyalgia:

Pain Is the Common Piece of the Puzzle

- Pain
- Numbness/tingling
- Insomnia
- Depression
- Impaired memory/concentration
- Fatigue
- Nervousness
- Leg cramps
- Restless legs
- Depression

Symptoms of Fibromyalgia

- Pain, fatigue and sleep disturbance are present in at least **86% of patients**

*United States data
Core Clinical Features of Fibromyalgia

Widespread pain
- Chronic, widespread pain is the defining feature of fibromyalgia
- Patient descriptors of pain include:
  - Aching
  - Exhausting
  - Nagging
  - Hurting

Neurocognitive impairment ("fibro fog")

Sleep disturbance/fatigue

Mood disorders

Morning stiffness

Many Fibromyalgia Patients Have Cognitive Complaints: “Fibro Fog”

- Compared to those without the condition, patients with fibromyalgia complain more often of:¹
  - Mental confusion
  - Memory decline
  - Speech difficulty

- Performance on cognitive tests shows they have poorer performance than age-matched controls on tasks involving:²
  - Working memory
  - Recognition memory
  - Free recall
  - Verbal fluency
  - Verbal knowledge

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Sleep Disturbances and Fibromyalgia

Fibromyalgia patients may complain of:

• Non-restorative sleep
• Insomnia
• Early morning awakening
• Poor sleep quality

Mood Disorders and Fibromyalgia

At time of diagnosis

20–40% have an identifiable mood disorder

Lifetime prevalence

• Depression: 75%
• Anxiety: 60%

In many cases, depression or anxiety may be the result of chronic pain.

The Paradigm of Pain: Interrelationship Among Pain, Sleep Disturbance and Psychological Symptoms

PAIN

Sleep disturbances can directly result from and/or contribute to fibromyalgia.

Psychological symptoms are strongly associated with fibromyalgia.

Management strategy for fibromyalgia patients is to improve overall patient functionality.

Diagnosing Fibromyalgia

Overview of Diagnosis

- History of fibromyalgia or related conditions
  - Personal and family history
- Physical examination
  - Most important to identify any other possible conditions
- Differential diagnosis
  - Clinical/laboratory evaluation to identify other possible conditions

Consequences of Non-diagnosis

- Failure to diagnose fibromyalgia is associated with increased costs and increased use of medical resources

On average it takes patients >2 years to be diagnosed with fibromyalgia.
A estimated 75% of people with fibromyalgia remain undiagnosed.

Differential Diagnosis of Fibromyalgia

- Hypothyroidism
- Vitamin D deficiency
- Inflammatory rheumatic disease
- Cancer
- Inflammatory muscle diseases

Patients with Fibromyalgia Present with a Global Pain Disorder

- This is a pain drawing
  - Patient colors all areas of the body in which he or she feels pain
- The diagram shows that the pain of fibromyalgia is widespread

ACR Classification Criteria for Fibromyalgia (1990)

- **ACR criteria:**
  - History of chronic widespread pain ≥3 months
  - Patients must exhibit ≥11 of 18 tender points
- **ACR criteria are both sensitive (88.4%) and specific (81.1%)**

ACR = American College of Rheumatology
Performing a Manual Tender Point Survey

- Digital palpation with an approximate force of 4 kg
  - Estimated pressure needed to turn the examiner’s thumbnail white upon depressing
  - For a “positive” tender point, subject must state palpation was painful

- Accuracy for fibromyalgia:
  - Sensitivity: **88.4%**
  - Specificity: **81.1%**

- **Controversies** regarding tender point evaluation:
  - Subjective
  - May not be necessary for diagnostic studies
  - What about fewer than 11 of 18 tender points?

ACR Proposed Diagnostic Criteria for Fibromyalgia (2010)

• Fibromyalgia can be diagnosed if:
  – Patient experiences widespread pain and associated symptoms
  – Symptoms have been present at same level for ≥3 months
  – No other condition otherwise explains the pain

Associated symptoms include:
  • Unrefreshed sleep
  • Cognitive symptoms
  • Fatigue
  • Other somatic symptoms

ACR = American College of Rheumatology
**FiRST: Fibromyalgia Rapid Screening Tool**

- Self-administered 6-item questionnaire
- Score of \( \geq 5 \) is indicative of fibromyalgia
- Sensitivity: 90.5%
- Specificity: 85.7%

<table>
<thead>
<tr>
<th>Items</th>
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</thead>
<tbody>
<tr>
<td>1. I have pain all over my body.</td>
</tr>
<tr>
<td>2. My pain is accompanied by continuous and very unpleasant general fatigue.</td>
</tr>
<tr>
<td>3. My pain feels like burns, electric shocks or cramps.</td>
</tr>
<tr>
<td>4. My pain is accompanied by other unusual sensations throughout my body, such as pins and needles, tingling or numbness.</td>
</tr>
<tr>
<td>5. My pain is accompanied by other health problems such as digestive problems, urinary problems, headaches or restless legs.</td>
</tr>
<tr>
<td>6. My pain has a significant impact on my life, particularly on my sleep and my ability to concentrate, making me feel slower generally.</td>
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Discussion Question

What do you tell your patients you think are suffering from fibromyalgia?
Tips on Providing the Diagnosis of Fibromyalgia

• Be **specific** about the diagnosis

• Be **positive** about the diagnosis

• Promote and encourage patient self-efficacy around the disease but...
  
  – Set realistic expectations
  
  – Emphasize there is no cure but improved control of symptoms is usually possible

Diagnosis of Fibromyalgia Can Improve Patient Satisfaction

*Statistically significant vs. baseline (confidence interval -1.2 to -0.4)

WHAT NON-PHARMACOLOGICAL APPROACHES COULD YOU USE TO HELP ADDRESS FIBROMYALGIA FROM A BIOPSYCHOSOCIAL PERSPECTIVE?
Multimodal Treatment of Fibromyalgia Based on Biopsychosocial Approach

- Multimodal treatment of pain
- Sleep hygiene
- Self-management support
- Physical therapy
- Manage expectations
- Treat comorbid conditions
- Pharmacotherapy
- Education
- Cognitive behavioral therapy

Non-pharmacological Treatment of Fibromyalgia

Sleep hygiene

Physical activity

Cognitive behavioral therapy

Self-management support

Seek support from other health care professionals – nurses, social workers, occupational therapists, physiotherapists, psychologists, psychiatrists, etc.

Non-pharmacologic Interventions to Improve Sleep in Fibromyalgia

1. Avoid stimulants
2. Go to bed and rise at regular times
3. Avoid napping through day
4. Exercise regularly, particularly in the afternoon
5. Use the bed only for sleep and sex
6. Relax before bed
7. Printed information on sleep for patients

### Benefits

- Stimulates release of endorphins and enkephalins within 30 minutes
- These bind to opioid receptors, reducing pain by an action on both ascending and descending neural pathways

### Recommendations for Fibromyalgia

**Type of Exercise**
- Try to include different types in one session (e.g., aerobic, strengthening, stretching)
- Patient preference and availability should guide selection

**Intensity**
- Start low, go slow
- Gradually increase to reach moderate intensity level
Cognitive Behavioral Therapy in Fibromyalgia

Technique

Learn to identify emotions that influence cognitive and affective components of pain (anxiety, helplessness, depression)

Employ active cognitive, problem-solving and distraction/relaxation techniques to modify emotions

Develop active strategies targeting well-being and control

Discussion Question

Is fibromyalgia “all in their head”?

What are the pathophysiological mechanisms behind the pain these patients experience?
Fibromyalgia: An Amplified Pain Response

Subjective pain intensity

Stimulus intensity

Hyperalgesia
(when a pinprick causes an intense stabbing sensation)

Allodynia
(hugs that feel painful)

Pain in fibromyalgia

Normal pain response

Pathophysiological Changes in Fibromyalgia

- Gray matter atrophy
- Altered intrinsic connectivity
- Exaggerated pain perception
- Altered metabolite levels in pain-processing regions of brain
- Increased levels of pain neurotransmitter substance P (>3x)
- Deficit in endogenous pain inhibitory systems noted
- Impaired small fiber function
- Minimal stimuli → Nociceptive afferent fiber → Spinal cord → Brain
- fMRI studies show marked regional increase in cerebral blood flow following a painful stimulus in patients with fibromyalgia compared to controls

fMRI = functional magnetic resonance imaging
Central Sensitization Produces Abnormal Pain Signaling

Pain treatment options
- $\alpha_2\delta$ ligands
- Antidepressants

Increased release of pain neurotransmitters
- glutamate and substance P

Increased neuronal excitability

Minimal stimuli

Nociceptive afferent fiber

Spinal cord

Brain

Perceived pain (hyperalgesia/allodynia)

Pain amplification

Loss of Inhibitory Control: Disinhibition

Pain treatment options
- $\alpha_2\delta$ ligands
- Antidepressants

Noxious stimuli
- Transduction
- Transmission
- Nociceptive afferent fiber
- Spinal cord
- Descending modulation
- Ascending input
- Brain

Exaggerated pain perception

How $\alpha_2\delta$ Ligands Decrease Pain Sensitivity

- Increased numbers of calcium channels
- Increased calcium influx
- Increased neuronal excitability

Binding of $\alpha_2\delta$ ligands to $\alpha_2\delta$ inhibits calcium channel transport

Calcium channels transported to nerve terminals in dorsal horn

INCREASED PAIN SENSITIVITY

Note: gabapentin and pregabalin are $\alpha_2\delta$ ligands
# Adverse Effects of $\alpha_2\delta$ Ligands

$\alpha_2\delta$ ligands include gabapentin and pregabalin

CNS = central nervous system


<table>
<thead>
<tr>
<th>System</th>
<th>Adverse effects</th>
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<tbody>
<tr>
<td>Digestive system</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>CNS</td>
<td>Dizziness, somnolence</td>
</tr>
<tr>
<td>Other</td>
<td>Asthenia, headache, peripheral edema, weight gain</td>
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Inhibiting reuptake of serotonin and norepinephrine enhances descending modulation.
## Adverse Effects of Antidepressants

<table>
<thead>
<tr>
<th>System</th>
<th>TCAs</th>
<th>SNRIss</th>
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<tbody>
<tr>
<td>Digestive system</td>
<td>Constipation, dry mouth, urinary retention</td>
<td>Constipation, diarrhea, dry mouth, nausea, reduced appetite</td>
</tr>
<tr>
<td>CNS</td>
<td>Cognitive disorders, dizziness, drowsiness, sedation</td>
<td>Dizziness, somnolence</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Orthostatic hypotension, palpitations</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Other</td>
<td>Blurred vision, falls, gait disturbance, sweating</td>
<td>Elevated liver enzymes, elevated plasma glucose, sweating</td>
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CNS = central nervous system; TCA = tricyclic antidepressant; SNRI = serotonin-norepinephrine reuptake inhibitor

IASP: Pharmacological Treatment for Fibromyalgia

**Level 1**

A
- Amitriptyline
- Duloxetine
- Milnacipran
- Pregabalin

B
- Gabapentin

**Level 2**

A
- Cyclobenzapine
- Fluoxetine

B
- Paroxetine
- Tramadol

IASP = International Association for the Study of Pain
Discussion Question

HOW WOULD YOU INTEGRATE THE CONCEPTS DISCUSSED TODAY INTO A CONCRETE TREATMENT PLAN FOR A PATIENT WITH FIBROMYALGIA?
Core Treatment of Fibromyalgia

- Confirm diagnosis

- Identify important symptom domains, their severity and level of patient function

- Evaluate for comorbid medical and psychiatric disorders

- Assess psychosocial stressors, level of fitness and barriers to treatment

- May require referral to a specialist for full evaluation

- Provide education about fibromyalgia

- Review treatment options
  Initiate therapy based on patient’s presentation and evidence-based guidelines

Overview of Fibromyalgia Management

Confirm fibromyalgia diagnosis

Educate the patient

Collaborate with patient to prioritize individual treatment goals

Develop treatment plan reflecting patient’s priorities and preferences

Pharmacotherapy

Non-pharmacological therapy

Treatment of comorbid conditions

Identify other health care providers who can work with you to care for patient

Identify community resources for self-management

At follow-up visits evaluate:
- Progress towards treatment goals
- Physical activity
- Use of self-management techniques
- Medication efficacy and adverse effects
- Comorbidities
- Adjustments to treatment plan

Maintain focus on progress over time vs. daily ups and downs

Fibromyalgia: Medication Is Just One Part of the Treatment Approach

**Pharmacological treatment**
- 3 medications approved by the FDA:
  - Pregabalin
  - Duloxetine
  - Milnacipran

**Non-pharmacological treatment**
- Aerobic exercise
- Cognitive behavioral therapy
- Strength training
- Acupuncture
- Hypnotherapy
- Biofeedback
- Balneotherapy
- Massage therapy
- Behavioral therapies, such as relaxation
- Transcranial magnetic stimulation?

**NOT shown to be effective or recommended:**
- Opioids
- Benzodiazepines
- NSAIDs
- Magnesium
- Vitamin B1
- Hormonal agents (thyroxine, DHEA, melatonin, calcitonin)

DHEA = dehydroepiandrosterone; FDA = Food and Drug Administration; NSAID = non-steroidal anti-inflammatory drug

Key Messages

• Up to 15% of adults may experience central sensitization/dysfunctional pain, with 2–5% of adults suffering from fibromyalgia
• Central sensitization/dysfunctional pain is hypothesized to be a result of persistent neuronal dysregulation or dysfunction
• Many patients with central sensitization/dysfunctional pain syndromes such as fibromyalgia also suffer from poor sleep, fatigue, anxiety and mood disorders
• Multimodal therapy including both non-pharmacological and pharmacological components should be used to target symptoms of fibromyalgia