Treating Pain in Psychiatric Practice

(page 199 in syllabus)

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Individual Disclosure Statement

Faculty Editor / Presenter

Thomas L. Schwartz, MD, is an associate professor in the department of psychiatry at SUNY Upstate Medical University in Syracuse, NY.
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Learning Objectives

• Explain the neurobiology and underlying mechanisms of chronic widespread pain

• Implement evidence-based treatment strategies for patients with comorbid chronic pain and psychiatric illness
Pretest Question 1

A 46-year-old man presents with pain and fatigue that is so debilitating that it has caused him many days of lost work. After physical exam, laboratory tests, and psychiatric interview, he is diagnosed with chronic widespread pain. Which of the following is the most likely mechanism for this condition?

1. Degrading myelin in the peripheral nerves
2. Chronic inflammation of several joints and/or discs
3. Central sensitization in the thalamus and cortex
4. Trigeminal nerve sensitization and ephaptic cross talk
Pretest Question 2

A 28-year-old patient with a long history of painful somatic symptoms has just been diagnosed with a major depressive episode and is being prescribed an escitalopram. Due to her history of chronic pain, she is currently taking an opioid. Which of the following opioids would be of greatest concern for this patient?

1. Codeine
2. Hydrocodone
3. Oxycodone
4. Meperidine
Pretest Question 3

26-year-old woman is diagnosed with comorbid fibromyalgia and generalized anxiety disorder. Ideally, she would receive the simplest treatment regimen to address both disorders. Which of the following monotherapies has evidence of efficacy in both chronic pain and anxiety disorders?

1. Serotonin-norepinephrine reuptake inhibitor (SNRI)
2. Benzodiazepine
3. Alpha 2 delta ligand
4. SNRI or benzodiazepine
5. SNRI or alpha 2 delta ligand
6. Benzodiazepine or alpha 2 delta ligand
7. SNRI, benzodiazepine, or alpha 2 delta ligand
PHYSIOLOGY OF PAIN
Nociception: The Nerve Fibers

- **periphery**
  - non-noxious mechanical stimulus
  - noxious mechanical stimulus
  - noxious heat and chemical stimulus

- **primary afferent neurons**
  - Aβ-fiber
  - Aδ-fiber
  - C-fiber

- **dorsal root ganglion**
  - dorsal root projection neurons

- **spinal cord**
  - grey matter
  - white matter
  - to higher centers

Nociception: Transduction (The Afferents)

stimulus and
transduction →
gegenerator potential → action potential

mechanoreceptors

VSSC

Na+

Aβ-fiber

Aδ-fiber

histamine

potassium channel

BK

C-fiber

Ca^{2+}

VR1

Na+

tissue
damage

H1 = histamine 1 receptor

B2 = bradykinin 2 receptors

BK = bradykinin

V1 = vanillloid 1 receptor

VSSC: voltage-sensitive sodium channel

From Nociception to Pain: Transmission (The Neurotransmitters)

From Nociception to Pain: Perception (The Pathways)

Subjective experience of pain

ouch!

Limbic Pathway: The “Emotional” Component of Pain

- Anterior cingulate cortex
- Hypothalamus
- Thalamus
- Hippocampus
- Orbital prefrontal cortex
- Brainstem sites, e.g., periaqueductal grey, raphe nucleus, locus coeruleus, parabrachial nucleus

Nociceptive Pain Is “Normal” Pain

OUCH!

cortical projection (thalamo-cortical tract)
dorsal horn projection neuron (spino-thalamic tract)

primary afferent neuron

Neuropathic Pain Is “Abnormal” Pain?

Peripheral (somatic, autonomic, or enteric) nervous system

Nervous system abnormality

spinothalamic tract

spinobulbar tract

brainstem

spinothalamic tract

limbic structures

thalamus

somatosensory cortex

OUCH!

subjective experience of pain

Chronic Pain With Supra-Segmental Central Sensitization

OUCH!

supra-segmental central sensitization

PAIN AND PSYCHIATRIC ILLNESSES
When Pain Patients Present in Psychiatric Practice

• Multifocal pain that cannot be explained based on damage or inflammation

• Unremarkable physical exam (with exception of tenderness)

• Pain may wax and wane and be migratory

• Associated symptoms
  – Fatigue
  – Sleep difficulties
  – Weakness
  – Problems with attention or memory
  – Unexplained weight fluctuations
  – Heat and cold intolerance
  – Morning stiffness

Unexplained Physical Symptoms Predict Mood/Anxiety Disorders


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Lifetime Prevalence of Mood and Anxiety Disorders in Fibromyalgia

n=108. MDD: major depressive disorder; GAD: generalized anxiety disorder; OCD: obsessive compulsive disorder; PTSD: posttraumatic stress disorder

Do Mood, Anxiety, and Chronic Pain Disorders Fall Along a Spectrum?

Depressed Mood Disrupts Brain Deactivation and Enhances Pain Unpleasantness

- 20 healthy volunteers
- Red/green: activation vs rest
- Blue: deactivation vs rest
- Significant lack of deactivation during pain in the depressed mood state
- Patients reporting greatest increase in pain unpleasantness after sad mood induction showed greater inferior frontal gyrus and amygdala activation

Plotted on the average MNI 152 brain. Z coordinates are on the MNI system.


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Pain and PTSD

TREATMENT FOR COMORBID PAIN
Pain in Depression and Anxiety: The Role of Norepinephrine

Pain in Depression and Anxiety: The Role of Serotonin

SNRI Action Boosts NE Inhibition of Pain

SNRI Action Boosts 5-HT Inhibition of Pain

SNRI boosts 5-HT projections

descending 5-HT projections

back posture

digestion

SNRI boosts 5-HT


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SNRIs for Chronic Pain

**duloxetine** (approved)

- 60 mg once daily; higher doses increase SEs without increasing efficacy in pain disorders
- Approved for multiple neuropathic pain disorders
- SEs include nausea, dry mouth; can cause urinary retention, rare activation of suicidality, rare hepatotoxicity
- Metabolized by CYP450 1A2 and 2D6
- Inhibits CYP450 2D6
- Not for use with thioridazine, MAOIs, or in patients with uncontrolled narrow-angle closure glaucoma or hepatic impairment

**milnacipran** (approved)

- 30–200 mg/day in 2 doses
- SEs include nausea, constipation, sweating, urologic complaints, urinary hesitancy, dose-dependent increase in blood pressure; can cause rare activation of suicidality
- Few known adverse pharmacokinetic drug interactions
- Not for use with MAOIs or in patients with uncontrolled narrow-angle closure glaucoma, substantial alcohol use, or chronic liver disease
SNRIs for Chronic Pain

Venlafaxine
- 75–225 mg once daily
- Clinical efficacy in reduction of chronic pain
- SEs include headache, insomnia, nausea, sweating, dose-dependent increase in blood pressure, rare activation of suicidality
- Can cause withdrawal reactions
- Few known adverse PK drug interactions
- Use with caution in patients with cardiac impairment
- Not for use with MAOIs or in patients with uncontrolled narrow-angle closure glaucoma

Desvenlafaxine
- 50 mg once daily
- SEs include insomnia, nausea, constipation, sweating, increase in blood pressure; can cause rare activation of suicidality
- Can cause withdrawal reactions
- Few known adverse PK drug interactions
- Use with caution in patients with cardiac impairment
- Not for use with MAOIs or in patients with uncontrolled narrow-angle closure glaucoma
Tricyclics for Chronic Pain

**amitriptyline**
- 25–50 mg once daily
- Used for multiple pain disorders
- SEs include sedation, weight gain, anticholinergic effects, dizziness, hypotension, rare activation of suicidality
- Metabolized to nortriptyline by CYP450 1A2
- Significant drug-drug interactions
- Use with caution in patients with renal or hepatic impairment
- Can have cardiovascular effects and should not be used in some patients
- Multiple contraindications

**cyclobenzaprine**
- 15 mg/day in 3 doses
- 15–30 mg/day in 1 dose (ER)
- Muscle relaxant
- Not recommended for long-term use
- SEs include sedation, dry mouth, fatigue, headache
- Use with caution in patients with urinary retention, angle-closure glaucoma, hepatic impairment
- Can have cardiovascular effects and should not be used in some patients
- Not for use with MAOIs
Relief of Painful Excessive Nociceptive Activity in Central Augmentation

Alpha 2 Delta Ligands for Fibromyalgia

**pregabalin (approved)**

- 150–600 mg/day in 2–3 doses
- Approved in multiple neuropathic pain disorders
- Enhances slow-wave sleep
- Generally well tolerated
- Most common SEs: sedation, dizziness
- Unlikely to have significant PK drug interactions
- Renally excreted
- Not for use in patients with galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption

**gabapentin**

- 900–1800 mg/day in 3 doses
- Approved in postherpetic neuralgia
- Enhances slow-wave sleep
- Generally well tolerated
- SEs include sedation, dizziness, fatigue, ataxia, nystagmus, tremor
- Antacids can decrease its bioavailability
- Naproxen can increase its absorption
- Morphine and hydrocodone can increase plasma AUC values
- Renally excreted
Anticonvulsants for Chronic Pain


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Carbamazepine and Oxcarbazepine for Chronic Pain

**carbamazepine**
- ~1200 mg/day; start low
- Approved for trigeminal neuralgia; may have efficacy in other neuropathic pain disorders
- Induces P450 enzymes, so may lower levels of some other drugs

**oxcarbazepine**
- 1200–1400 mg/day; start low
- Clinical efficacy in neuropathic pain (adjunct)
- Slow titration may delay onset of action but reduces side effects
Topiramate, Lamotrigine, Zonisamide for Chronic Pain

**Topiramate**
- 50–300 mg/day
- FDA-approved for migraine prophylaxis
- May have efficacy in other neuropathic pain disorders

**Lamotrigine**
- 100–300 mg/day (more with enzyme-inducing drugs)
- Clinical efficacy in neuropathic pain
- Efficacy can wane after several weeks of use

**Zonisamide**
- 100–600 mg/day
- Some clinical efficacy in neuropathic pain and migraines
- Little documentation for off-label use
## Other Pain Agents

### NSAIDs
- Better for acute pain or for chronic inflammatory pain
- Warning for GI bleeding with SSRIs
- Combination with lithium can cause lithium toxicity

### Acetaminophen
- Mild to moderate pain
- Less effect on bleeding and renal function compared to NSAIDs
- Can cause hepatotoxicity at high doses
- Many psychotropics are metabolized by/inhibit liver enzymes

### Baclofen
- Muscle relaxant and antispastic
- Used for trigeminal neuralgia and some other neuropathic pain conditions
- Some drug-drug interactions
- Use with caution in patients with renal impairment
Opioids

• Effective for osteoarthritis, rheumatoid arthritis, musculoskeletal pain, postherpetic neuralgia, phantom limb pain, diabetic neuropathy, and chronic low back pain
  – No studies of effectiveness beyond 8 weeks

• Not effective for fibromyalgia

• Risks
  – Dependence
  – Tolerance
  – Pain worsening, hyperalgesia
  – Reduced effects of SNRIs?

29% of the opioid-dependent sample was introduced to opioids by a physician.
If a Patient is Taking an Opioid

• Avoid meperidine in patients with psychiatric illness
  – Interactions, CNS toxicity, Serotonin Syndrome

• Longer-acting formulations are preferable
  – Methadone
    • QTc prolongation at higher doses and with antipsychotics
    • p4503A4 inhibitors can raise methadone levels
  – Transdermal fentanyl patch—Serotonin Syndrome
  – Tramadol
    • SNRI with weak μ-opioid agonist activity
    • Has shown efficacy for pain in fibromyalgia
    • Serotonin Syndrome, seizure risks
  – Buprenorphine

• Avoid prn dosing, especially if history of substance abuse

Nonpharmacological Treatments for Chronic Pain

- Cognitive behavioral therapy
  - May work best if targeted to a specific outcome
  - Adherence can be an issue

- Hypnosis, relaxation, guided imagery
  - May reduce pain, distress

- Education
  - Should be combined with other treatment approaches
  - Education groups can be useful, but adherence may be low

- Aerobic exercise
Exercise for Chronic Pain (Fibromyalgia)

- Aerobic exercise
- Strength training
- Muscle flexibility

Global well-being
Physical function

Pharmacological and Nonpharmacological Treatments for Chronic Pain

1st-line
- tramadol
- SSRI
- NSAID/acetaminophen
- baclofen
- TCA
- some AEDs
- cyclobenzaprine
- SNRI
- α2δ

2nd-line
- some evidence
- strength training
- hypnotherapy
- biofeedback
- balneotherapy
- aerobic exercise
- CBT
- education

Some evidence

Fibromyalgia
- pharmacy

Fibromyalgia
- nonpharmacy

Treating PTSD and Chronic Pain

pregabalin/gabapentin  TCA  SNRI  opiate

strength training/exercise  acceptance & commitment therapy  exposure therapy

pharmacological  nonpharmacological

Stahl SM, Grady MM. Stahl’s Illustrated Anxiety, Stress, and PTSD 2010.
In Case Your Patient Asks…

Weak evidence

- Growth hormone
- 5-hydroxytryptamine
- Tropisetron
- S-adenosyl-L-methionine
- Acupuncture
- Chiropractic, manual, and massage therapy
- Electrotherapy
- Ultrasound

No evidence

- Corticosteroids
- Benzodiazepines
- Non-benzo hypnotics
- Melatonin
- Guaifenesin
- Dehydroepiandrosterone
- Tender point injections
- Flexibility exercise

Stress Sensitization: Can Pain Be Preemptively Treated?

<table>
<thead>
<tr>
<th>Biological Endophenotype</th>
<th>Symptom Endophenotype or Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprovoked - irreversible stress sensitization</td>
<td>No symptoms - vulnerable but presymptomatic</td>
</tr>
<tr>
<td>Provoked - lack of compensation</td>
<td>Prodromal symptoms begin</td>
</tr>
<tr>
<td>Provoked - decompensation with either overactivation or circuit breakdown</td>
<td>Definite but subtle/subsyndromal symptoms</td>
</tr>
<tr>
<td>Unprovoked but decompensation is sustained</td>
<td>Psychiatric symptom of a full syndrome/psychiatric disorder</td>
</tr>
</tbody>
</table>

- Emotional trauma continues
- Emotional trauma withdrawn

- Overactivation or circuit breakdown

- Depression: emotional trauma withdrawn

- Withdrawn

- Emotional trauma continues

- Emotional trauma withdrawn
Stress Sensitization: Can Pain Be Preemptively Treated?

- **Presymptomatic treatment**
  - Unprovoked - irreversible stress sensitization
  - No symptoms - vulnerable but presymptomatic

- **Prodromal treatment**
  - Provoked - lack of compensation
  - Prodromal symptoms begin

- **Subsyndromal treatment**
  - Provoked - decompensation with either overactivation or circuit breakdown
  - Definite but subtle/subsyndromal symptoms

- **Unprovoked but decompensation is sustained**
  - Psychiatric symptom of a full syndrome/psychiatric disorder

- **Biological endophenotype**
- **Symptom endophenotype or phenotype**
Diabolical Learning: Can Pain Be Unlearned?

**biological endophenotype**

- unprovoked - decompensation with either overactivation or circuit breakdown
- decompensation and circuit breakdown worsening
- further plastic changes in circuitry that facilitate maladaptive information processing, which is difficult to reverse

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**symptom endophenotype or phenotype**

- psychiatric symptom of a psychiatric disorder (e.g., drug abuse, pain, panic, depressed mood, insomnia)
- symptoms worsen or relapse
- new symptoms or treatment resistance
Summary

• For patients with comorbidity, choosing an agent that is efficacious for both disorders is ideal

• A variety of psychotropic drugs are effective for treating neuropathic pain
  – Depression: SNRI, TCA
  – Anxiety: SNRI, alpha 2 delta ligand, TCA

• Typically, treatment has to be more complex; there are several augmenting options

• It can be beneficial to integrate nonpharmacological treatment into care

• Avoid opioids if you can, especially for fibromyalgia (not effective)
Poll Question

On average, how many patients with chronic pain do you see each week?

1. None
2. 1-2
3. 3-4
4. 5-6
5. 7-8
6. 9-10
7. 11-12
8. 13-15
9. More than 15