Overview of Noncancer Pain Treatment and 2016 Centers for Disease Control and Prevention Guidelines for Prescribing Opioids

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Pharmacist Learning Objectives

- Explain the differences between nociceptive and neuropathic pain
- Describe the role of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and other adjuvant analgesics in the outpatient management of acute and chronic pain
- Discuss the 2016 recommendations from the Centers for Disease Control and Prevention (CDC) guideline for opioid use in chronic pain management as well as opioid Food and Drug Administration (FDA) warning label changes

Pharmacy Technician Learning Objectives

- Explain the differences between nociceptive and neuropathic pain
- Recognize current treatment options and prevention strategies for the outpatient management of opioid-related side effects
- Identify two recommendations from the 2016 Centers for Disease Control and Prevention (CDC) guideline for opioid use in chronic pain management

Overview

- Define Pain
- Physiology & Pathophysiology of Pain
- Acute vs. Chronic Pain
- Assessment of Pain
- Treatment Goals & Recommendations
  - Non-opioid Analgesics
  - Adjuvant Analgesics
  - Opioid Analgesics
- Self Assessment Questions

If we know that pain and suffering can be alleviated, and do nothing about it, then we ourselves, become the tormentors.

- Primo Levi

Disclosure

The speaker has no actual or potential conflict of interest in relation to this presentation.
Definition of Pain

• An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage

Pain is whatever the person says it is, and exists whenever they say it does.

– Margo McCaffery

Two Types of Pain

• Physiologic and protective
  Nociceptive pain: Nociceptors in tissues send pain signals to the CNS

• Pathophysiologic and harmful
  Neuropathic pain: Damage to the nerve itself causes typical pain symptoms.

Physiology & Pathophysiology of Pain

Nociceptive Pain

• Pain caused by activation of nociceptors, which are sensory neurons found throughout the body in both somatic and visceral structures
  • Normal processing of stimuli (i.e., injury or trauma) that damages normal tissues or has the potential to do so if prolonged
  • Usually responds well to non-opioids (i.e., acetaminophen, NSAIDs) and/or opioid analgesics

Chronic pain is a major public health problem. It affects...

...more than one-third of people in the United States...

...and about 20 to 30% of the world's population.

The prevalence of persistent pain is expected to rise as the incidence of diseases increases in the aging U.S. population. These diseases include:

- diabetes
- cardiovascular disorders
- obesity
- arthritis
- cancer
Nociceptive Pain\textsuperscript{1,3,4}

Somatic Pain
- Arises from skin, bone, joint, muscle, or connective tissue
- Often presents as aching or throbbing and is well localized
- Examples: low back pain, inflammatory pain (osteoarthritis, rheumatoid arthritis), or muscle pain

Visceral Pain
- Arises from internal organs (i.e. gastrointestinal (GI) tract or pancreas)
- Manifests as pain feeling as if it is coming from other structures (i.e. deep, squeezing pressure) or as localized pain
- Examples: myocardial infarction, bowel obstruction, hepatic metastases

Neuropathic Pain\textsuperscript{1,3,4}

- Pain initiated or caused by a primary lesion or dysfunction of the nervous system
- Presents as burning, tingling, shooting, or shock-like pain; may be episodic or continuous pain
- Treatment usually requires adjuvant analgesics

Examples of Pathophysiologic Pain\textsuperscript{1,3,4}

- Postherpetic Neuralgia (PHN)
- Phantom Limb Pain
- Non-cardiac Chest Pain
- Nerve Root Compression
- Inflammatory Bowel Syndrome (IBS)
- Fibromyalgia

Neuropathic Pain

Characteristics of Acute and Chronic Pain\textsuperscript{1,4}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute Pain</th>
<th>Chronic Pain</th>
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</thead>
<tbody>
<tr>
<td>Relief of pain</td>
<td>Highly desirable</td>
<td>Highly desirable</td>
</tr>
<tr>
<td>Dependence and tolerance to medication</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Psychological component</td>
<td>Usually not present</td>
<td>Often a major problem</td>
</tr>
<tr>
<td>Organic cause</td>
<td>Common</td>
<td>May not be present</td>
</tr>
<tr>
<td>Environmental/family issues</td>
<td>Small</td>
<td>Significant</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Unusual</td>
<td>Common component</td>
</tr>
<tr>
<td>Treatment goal</td>
<td>Pain reduction</td>
<td>Functionality</td>
</tr>
<tr>
<td>Depression</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
</tbody>
</table>

STOP and THINK

Untreated and undertreated acute pain has been shown to increase one's risk for the development of chronic pain syndromes

ACUTE VS. CHRONIC PAIN

 Treatment Goals\textsuperscript{1,4}

| Acute pain |  |
|------------|  |
| - Rapid pain relief or reduction in pain intensity is usually the desired target |

<table>
<thead>
<tr>
<th>Chronic noncancer pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Improve or maintain the patient’s level of day-to-day functioning</td>
</tr>
<tr>
<td>- Decrease the rate of physical deterioration</td>
</tr>
<tr>
<td>- Decrease pain perception</td>
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<tr>
<td>- Improve the patient’s sense of well-being</td>
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<tr>
<td>- Improve family and social relationship</td>
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<tr>
<td>- Decrease dependency on drug therapy</td>
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</tbody>
</table>
Assessment of Pain\cite{1,3,4}

- Pain is **always** subjective
  - Patient self-report is the most reliable indicator of its existence and intensity, and is key in assessing chronic pain
- **Patient-oriented** approach is essential
  - Pain is best diagnosed based on patient description and history
  - Evaluation methods should not differ from those used in other medical conditions

TREATMENT GOALS & RECOMMENDATIONS

**Treatment Goals\cite{1-4}**

1. Identify and treat specific source(s) of pain
2. Teach self-management and measure outcome using pain rating and a function tool
3. Use cognitive-behavioral strategies
   - Encourage exercise and active participation of the patient in the plan of care

**Drug Selection\cite{1-4}**

- Define the goals of therapy before prescribing
- Tailor medications to meet the individual goals of each patient
- Select an appropriate drug based on:
  - Characteristics of the medication (i.e., onset, duration, dosing intervals, side effects)
  - Patient factors (i.e., age, comorbidities, other medications, response to previous treatments)
- Establish a pain management plan
- Strive to achieve optimal balance between analgesic benefit, side effects, and functional improvement

**The Four A’s\cite{4}**

- The goal of **opioid therapy** is to provide partial analgesia, and maintain or improve function with minimal side effects

- **Analgesia**
  - Degree of analgesia
- **Activity**
  - Functional status (physical and psychosocial)
- **Adverse drug effects**
  - Opioid-related side effects
- **Adherence**
  - Existence of aberrant drug-related behaviors
World Health Organization Step Ladder\textsuperscript{3,5}

Non-opioid Analgesics\textsuperscript{2-4}
- In most cases, treatment of pain should begin with non-opioid analgesics (i.e., acetaminophen or NSAIDs), as suggested by the WHO Step Ladder.

Acetaminophen (APAP)\textsuperscript{2-4}
- Treatment of mild chronic pain or to supplement other agents in treating \textit{mild to moderate} pain.
  - Low back pain; Osteoarthritis pain
  - Lacks anti-inflammatory effects but generally well tolerated
  - Little to no risk of GI ulcer development
  - Rarely associated with renal toxicity
- Max of 3 gm per 24 hr (4 gm per 24 hr in healthy adults).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)\textsuperscript{2-4}
- Treatment of \textit{mild to moderate inflammatory} or non-neuropathic pain.
  - Rheumatoid arthritis pain; Osteoarthritis pain
  - NSAIDs are opioid dose-sparing and may help reduce opioid-related side effects
- Generally recommended to use lowest effective dose for the shortest duration of time:
  - Ceiling effect to analgesia
  - Doses above the maximum daily dose do not offer additional therapeutic benefit and may increase risk of toxicity
- All NSAIDs are considered \textit{equally efficacious}:
  - Patients' responses may vary
  - If a trial of two consecutive NSAIDs is not effective, consider alternative therapeutic options (i.e., corticosteroid, opioid or other).

NSAIDs Warnings\textsuperscript{2-4}
- Gastrointestinal:
  - May cause ulcers and bleeding in stomach/intestines at any time during treatment
  - Use caution in those at risk for bleeding
  - Consider using with a proton pump inhibitor
- Cardiovascular:
  - Increased risk of MI, stroke, and new onset or worsening of hypertension
- Renal:
  - Use of NSAIDs may compromise renal function
  - Increased risk of renal dysfunction, especially in combination with ACE inhibitors
- Hepatic:
  - Use with caution in patients with moderate hepatic impairment and not recommended for patients with severe hepatic impairment.
Anticonvulsants

- Pregabalin (Lyrica®) and Gabapentin® (Neurontin®)
  - Indicated for treatment of diabetic neuropathy, postherpetic neuralgia, and fibromyalgia
  - Useful for constant burning pain
  - Gabapentin provides adequate pain relief in up to one third of those using it for neuropathic pain
  - Favorable side-effect profile and very few drug interactions
    - Common side effects: edema
    - Monitoring: serum creatinine
    - Adjust dose and frequency in patients with renal insufficiency

Indications
- NSC (narcotic) pain
- Neuropathic pain
- Osteoarthritis
- Low back pain
- Bone pain

Contraindications
- Active peptic ulcer disease (PUD)
- Uncontrolled hypertension
- Congestive heart failure
- Platelet dysfunction
- Liver insufficiency
- Aspirin allergy
- CACVD

Topical Analgesics

- Lidocaine (Lidoderm® patch)
  - Recommended for localized peripheral neuropathic pain after a trial of first-line therapy (TCAs, SNRIs, or gabapentin)
  - Not recommended for non-neuropathic pain

- Capsaicin cream
  - Recommended in patients who have not responded or are intolerant to other treatments for osteoarthritis, post-herpetic neuralgia, or diabetic neuropathy
  - Topical capsaicin may be applied three or four times per day

- Diclofenac (Voltaren® Gel 1%)
  - Recommended for relief of osteoarthritis pain in select joints (ankle, elbow, foot, hand, knee, and wrist)
  - Maximum dose: 3 g per day (3 g per joint per day in the upper extremity and 16 g per joint per day in the lower extremity)
  - Common adverse effects: dermatitis and pruritus

Adjuvant Analgesics

- Treatment of chronic pain with a neuropathic component usually requires adjuvant analgesics

Anticonvulsants

- Other anticonvulsants have been utilized in neuropathic pain with variable success
  - Carbamazepine: good first choice for idiopathic trigeminal neuralgia
    - Lack of evidence for success in other pain states
  - Oxcarbazepine: may have benefits in treatment of neuropathic pain
  - Newer anticonvulsants (topiramate, lamotrigine, and tiagabine) are being investigated for their neuromodulating effects on pain
Anticonvulsants Adverse Effects\(^2-4\)

- Edema
- Rash
- Sedation, dizziness
- Difficulty with balance

Cognitive effects (memory, word-finding)

- Ataxia
- Sedation, dizziness
- Rash
- Edema

Tricyclic antidepressants (TCAs)\(^2-4\)

- Amitriptyline (Elavil\(^{\circledR}\))
- Nortriptyline (Pamelor\(^{\circledR}\))
- Desipramine and Imipramine

- Continue to hold a place in the management of a broad range of pain disorders, including neuropathic pain
- Often used first-line for fibromyalgia
- Analgesia generally occurs within a few days to a week
- Antidepressant effect takes longer to occur (4-6 weeks)

Serotonin–norepinephrine reuptake inhibitors (SNRIs)\(^2-4\)

Duloxetine (Cymbalta\(^{\circledR}\))

- FDA approved for treatment of diabetic peripheral neuropathy and fibromyalgia
- Initial dose: 20-60 mg per day

Venlafaxine (Effexor\(^{\circledR}\))

- Used off-label for treatment of neuropathic pain, diabetic neuropathy, and fibromyalgia
- Initial dose: 25-75 mg per day; may increase to 75 mg BID or 150 mg per day of the ER formulation
- Maximum dose: 375 mg/day (IR) and 225 mg/day (ER)

SNRIs Adverse Effects\(^2-4\)

- Common: nausea, dizziness and fatigue
- GI symptoms are more common early in treatment
- SNRIs have a more favorable side effect profile compared to TCAs

Diabetic Neuropathy: A Position Statement by the American Diabetes Association

Diagnosis of Diabetic Neuropathy (DSPN)

- Numbness/tingling
- Paresthesia
- Weakness

Opioids are often the next step in the management of acute pain and may also be an effective option for chronic noncancer pain

OPIOID ANALGESICS
Opioid Analgesics$^{2,4,6,9}$

- Typically used to help relieve moderate to severe pain when other treatments are not enough
- May be more effective when used in combination with non-opioids (i.e., acetaminophen, NSAIDs) or adjuvant analgesics
- Opioids do not have a ceiling effect to analgesia and therefore can be most effectively titrated to pain control
- Divided into two main categories
  - Immediate-release (IR) products – intended for use every 4-6 hr
  - Extended-release/long acting (ER/LA) products – intended to be taken once or twice a day

Opioid Effectiveness$^6$

- No studies:
  - Opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for chronic pain
  - Evaluated long-term (≥1 year) with outcomes related to pain, function, or quality of life
  - How effectiveness varies according to the type/cause of pain, patient demographics, and patient comorbidities
- Most placebo-controlled randomized clinical trials
  - Less than or equal to 6 weeks in duration
- Body of evidence rated as insufficient (0 studies contributing)

Opioid Prescribing Guidelines for Chronic Pain

*Outside of Active Cancer, Palliative, & End-of-life Care*

**PRIMARY CARE**

- Determining when to initiate or continue opioids for chronic pain
- Opioid selection, dosage, duration, follow-up, and discontinuation
- Assessing risk and addressing harms of opioid use

Opioid Harms$^6$

- One cohort study found that long-term opioid therapy is associated with increased risk for an opioid abuse or dependence diagnosis (defined by ICD-9-CM codes) versus no opioid prescription
- 10 uncontrolled studies report estimates of opioid abuse, addiction, and related outcomes
  - Prevalence of opioid dependence (using DSM-IV criteria) ranges from 3-28% in primary care settings
  - Prevalence of addiction ranges from 2-4% in pain clinic settings

<table>
<thead>
<tr>
<th>Rates of opioid abuse or dependence diagnosis</th>
<th>with chronic therapy versus no opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>No opioids prescribed</td>
<td>0.004%</td>
</tr>
<tr>
<td>Lower dose (≤120 MME)</td>
<td>0.2%</td>
</tr>
<tr>
<td>Higher dose (&gt;120 MME)</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

Nonpharmacologic and Nonopioid Effectiveness$^6$

Several treatments have been shown to be effective in managing chronic pain in settings ranging from a walk to a hospital:

- **Cognitive Behavioral Therapy** helps patients modify situational factors and cognitive processes that exacerbate pain
- **Exercise Therapy** can help reduce pain and improve function
- Multiple guidelines recommend acetaminophen or NSAIDs as first-line pharmacotherapy for osteoarthritis or for low back pain
- Several guidelines agree that first- and second-line drugs for neuropathic pain include anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, and SNRIs
- Interventional approaches (i.e., epidural injection) for certain conditions (i.e., lumbar radiculopathy)
Summary of Evidence

- No evidence of long-term benefits of opioids in pain and function versus no opioids for chronic pain with outcomes examined at least 1 year later
- Most placebo-controlled randomized trials ≤ 6 weeks
- However, there is some evidence supporting short-term efficacy of opioids for reducing pain and improving function
- Extensive evidence shows the potential harms of opioids (opioid use disorder, overdose, and motor vehicle injury)
- Extensive evidence suggests some benefits of nonpharmacologic and nonopioid pharmacologic treatments compared with long-term opioid therapy, with less harm

Opioid Recommendations for Chronic Pain Conditions

Neuropathic pain
- Opioids may be considered for neuropathic pain that has not responded to first- or second-line treatment options (i.e., antidepressants, SNRIs) based on evidence-based recommendations when available

Tramadol (Ultram)
- Weak opioid analgesic with serotonin reuptake inhibition
- Dual mechanism may make it advantageous for management of neuropathic pain or mixed pain disorders

Tapentadol (Nucynta)
- Opioid analgesic with norepinephrine reuptake inhibition
- Indicated for treatment of neuropathic pain including diabetic peripheral neuropathy

Opioid Dosing
- Total daily dose of opioids should not exceed 90 mg oral morphine equivalents

<table>
<thead>
<tr>
<th>Opioid Agonist</th>
<th>Equivalent Oral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydromorphone (Halcand)</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Oxycodone (Oxycontin)</td>
<td>20-30 mg</td>
</tr>
<tr>
<td>Hydrocodone (Norco)</td>
<td>10 mg</td>
</tr>
<tr>
<td>Tramadol</td>
<td>120 mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>200 mg</td>
</tr>
</tbody>
</table>

Opioid Warnings & Precautions

- Serious risks of misuse, abuse, addiction, overdose, and death
- Serotonin Syndrome
- Adrenal Insufficiency
- Decreased Sex Hormone Levels
- Serotonin Syndrome (new recommendation)
- Health care professionals should discontinue opioid treatment and/or use of the other medication if serotonin syndrome is suspected
Opioid Warnings & Precautions

Serotonin Syndrome (new recommendation)
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Adrenal Insufficiency (new recommendation)
- Health care professionals should perform diagnostic testing if adrenal insufficiency is suspected. If diagnosed, treat with corticosteroids and wean the patient off of the opioid, if appropriate. If the opioid can be discontinued, follow-up assessment of adrenal function should be performed to determine if treatment with corticosteroids can be discontinued.

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Decreased Sex Hormone Levels (new recommendation)
- Health care professionals should conduct laboratory evaluation in patients presenting with such signs or symptoms.
- Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA’s MedWatch Safety Information and Adverse Event Reporting Program.

Opioid Warnings & Precautions

- September 2016: FDA warns of serious risks or death when combining opioid medications and benzodiazepines
- Opioid analgesics, cough products, and benzodiazepines combination may result in (signs of overdose):
  - Unusual dizziness or lightheadedness
  - Extreme sedation or sleepiness
  - Slowed or difficult breathing
  - Unresponsiveness, coma, or death
- Health professionals should avoid prescribing opioid pain or cough medications for patients taking benzodiazepines or using other CNS depressants, including alcohol

Opioid Side Effects

- Sedation
- Respiratory depression
- Physical Dependence
- Nausea
- Pruritus
- Diaphoresis
- Constipation
- All opioids cause constipation
- Little to no tolerance
- Combination stimulant-sensitizing recommended as a useful first-line option
- Discontinue all maintenance laxative therapy prior to use

Side Effects

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Constipation
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- Combination stimulant–softerner recommended as a useful first-line option
- Discontinue all maintenance laxative therapy prior to use

Hyperalgesia
- Opioids may actually increase rather than decrease sensitivity to noxious stimuli
- Note: a decrease in opioid efficacy should not always be treated by increasing the dose, but may actually require weaning

Assessing Risk and Addressing Harms of Opioid Use

Review the patient's history of controlled substance prescriptions
- Use state prescription drug monitoring program (PDMP) to determine whether the patient is receiving opioid dosages or dangerous combinations (i.e., concurrent benzodiazepine)

Evaluate risk factors for opioid-related harms
- Consider offering naloxone when factors that increase risk for opioid overdose are present
- Risk Factors: History of overdose/substance use disorder, higher opioid dosages (>50 MME/day), or concurrent benzodiazepine use

Explain in a nonjudgmental manner to patients already taking high opioid dosages (>50 MME/day)
- A new is now an established body of scientific evidence showing that overdose risk is increased at higher opioid dosages

What YOU can do to help

- Assess: Look for “Red Flags”
  - Forged prescriptions (i.e., lack of common abbreviations or overly legible handwriting)
  - Prescriptions originating from outside the immediate geographic area
  - Altered prescriptions (i.e., multiple ink colors or handwriting styles)
  - Cash payments
  - Inconsistent or early fills
  - Multiple prescribers
- Consult prescription drug monitoring programs (PDMP) as well as patient records
- Identify patients at increased risk of overdose, disperse naloxone per authority, and counsel on how to use

On the Front Lines

For more info go to: http://www.cdc.gov/nhts/overdose/nhxharms2015_brochure-a.pdf

References

2. Division of Workers’ Compensation. Chronic Pain Medical Treatment Guidelines 8-00-00. [Internet]. [cited 2016 Jan 12]
Self-Assessment Questions

Self-Assessment Question #1

- 49 year-old female presents to the clinic for pain, which she describes as burning or shock-like in her extremities for the past 2 months.
- PMH: asthma, diabetes (10 years), dyslipidemia, and anxiety
- Current medications: Advair 500/50 puff BID, atorvastatin 40mg QD, glipizide 5mg BID, lisinopril 30mg QD, budesonide 0.5mg PR, metformin 500mg BID, ProAir 1 puff Q4H pm.

Which of the following diagnoses is accurate and also correctly matched with an appropriate initial treatment option for this patient?

A. Rheumatoid arthritis – acetaminophen (Tylenol®) 650mg Q6H pm pain
B. Diabetic neuropathy – duloxetine (Cymbalta®) 30mg QD
C. Visceral pain – diclofenac (Voltaren® Gel 1%) apply 4gm to upper and lower extremities QD
D. Somatic pain – hydrocodone/APAP 5mg/325mg Q6H pm pain

Self-Assessment Question #2

- 54 year-old male returns to the clinic for follow-up of ongoing back pain from an injury suffered 12 weeks ago. Today he reports constant, aching-type pain (9/10) inadequately relieved by naproxen 550mg BID.
- PMH: anxiety, depression, hypertension
- Current medications: amlopidine 10mg QD, sertraline 100mg QD, naproxen 550mg BID

Which of the following would be the MOST appropriate next step to take in managing this patient’s pain?

A. Change naproxen to meloxicam
B. Short-term (10-day) trial with hydrocodone/APAP
C. Addition of venlafaxine to his current medications
D. Addition of tramadol to his current medications

Self-Assessment Question #3

- 38 year-old male presents to the clinic for follow-up one week after a visit to the ER because he was experiencing "seizure-like" activity, tachycardia, sweating, and vomiting.
- PMH: depression, chronic pain disorder, insomnia, narcotic abuse
- Current medications: amitriptyline 50mg HS, fluoxetine 20mg QD, hydrocodone/APAP 7.5mg/325mg BID pm, tramadol 50mg Q6H pm

Which of the following is the most appropriate recommendation for this patient to reduce the risk of serotonin syndrome?

A. Initiate oxycodeone ER 10mg BID
B. Discontinue fluoxetine and initiate duloxetine
C. Discontinue amitriptyline and initiate trazodone
D. Discontinue tramadol 50mg and hydrocodone/APAP 7.5mg/325mg
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• Current medications: amitriptyline 50mg HS, fluoxetine 20mg QD, hydrocodone/APAP 7.5mg/325mg BID prn, tramadol 50mg Q4‐6H prn
• Which of the following is the most appropriate recommendation for this patient to reduce the risk of serotonin syndrome?
  A. Initiate oxycodone ER 10mg BID
  B. Discontinue fluoxetine and initiate duloxetine
  C. Discontinue amitriptyline and initiate trazodone
  D. Discontinue tramadol 50mg and hydrocodone/APAP 7.5mg/325mg

Self-Assessment Question #4

• Despite your recommendation in the last question, the physician decides to discontinue tramadol and increase the dose of hydrocodone/APAP from 7.5mg/325mg to 10mg/325mg.
• However, after two weeks on this regimen, the patient still reports a pain score of 8/10.
• Which of the following is the MOST likely reason he has inadequate pain control?
  A. Patient is experiencing acute pain but is being treated for chronic pain
  B. Chronic pain patients never rate pain less than 8/10
  C. Patient is addicted to opioids and drug-seeking
  D. He is experiencing opioid‐induced hyperalgesia