Back to Basics:
The Role of Chronic Opioids for Chronic Pain

Thomas B. Gregory, PharmD, BCPS, FASPE, CPE

Disclosures

- Nothing to disclose
Objectives

- Explain the role of opioids in chronic pain
- Describe universal precautions and risk mitigation strategies for opioids in chronic pain
- Calculate opioid dose conversion and tapers
- Discuss reasons to discontinue opioid therapy

Opioid Overdose – Startling Statistics

- Leading cause of accidental deaths in the US with 55,403 overdose deaths in 2015
  - 20,101 related to prescription pain relievers
  - 12,990 related to heroin
- Parallel increase in sale of prescription pain relievers with overdose deaths and substance use disorder treatment
- 4/5 heroin users started with prescription opioids

**Initial Evaluation and Assessment**

- Review medical and psychiatric history
- Physical exam
- Nonopioid and nonpharm trials
- Assess risk for medication abuse
- Determine factors that increase risk for adverse outcomes


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**Universal Precautions**

- Make a diagnosis with appropriate differential
- Psychological assessment
- Informed consent
- Treatment agreement
- Pre- and posttreatment assessment of FUNCTION and pain
- Appropriate trial of opioid
- Reassess the 4 A’s
- Periodically review pain diagnosis, comorbid disorders (including addiction)
- Document

## Opioid Risk Stratification Tools

<table>
<thead>
<tr>
<th>Tool</th>
<th>Indication</th>
<th>Question Format</th>
<th>Scoring</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **DIRE** | Risk of opioid abuse and suitability of candidate for long-term opioid therapy | 7 via patient interview | Numeric, simple to interpret | • 2 minutes to complete  
• Correlates well with patient's compliance and efficacy of long-term opioid therapy | Prospective validation needed |
| **ORT** | Categorizes patients as low, medium, high risk | 5 | Numeric, simple to interpret | • <1 minute to complete  
• Simple scoring  
• High sensitivity and specificity for stratifying patients  
• Validated | 1 question based on patient's knowledge of family history of substance abuse |
| **PDUQ** | Assess for presence of addiction in chronic pain patients | 42 items via patient interview | Numeric, simple to interpret | • 3 items correctly predicted addiction or no addiction in 92% of patients | |
| **SOAPP-R** | Primary Care | 36 | Numeric, simple to interpret | • 5 minutes to complete  
• Cross-validated  
• Easy to interpret results | |

DIRE, Diagnosis, Intractability, Risk, Efficacy Score; ORT, Opioid Risk Tool; PDUQ, Prescription Drug Use Questionnaire; SOAPP-R, Screener and Opioid Assessment for Patients with Pain-Revised


## Opioid Misuse Assessment Tools

<table>
<thead>
<tr>
<th>Tool</th>
<th>Indication</th>
<th>Question Format</th>
<th>Scoring</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **ABC** | Ongoing assessment of patients on COT | 20 | ≥3 indicates possible inappropriate opioid | • Concise  
• Easy to score  
• Studied at VA | Need validation outside VA |
| **COMM** | Assess aberrant medications related behaviors in chronic pain | 17 | Numeric | • 10 minutes to complete  
• Useful for adherence assessment | Unknown reliability long-term |
| **PADT** | Streamline assessment of chronic pain outcomes using the 4 A's | N/A | N/A | • 5 minutes to complete  
• Documents progress  
• Complements | Not intended to predict drug-seeking behavior or positive/negative outcomes |

ABC, Addiction Behaviors Checklist; COMM, Current Opioid Misuses Measure; PADT, Pain Assessment and Documentation Tool

Risk Factors for Opioid Overdose or Addiction

**Overdose**
- Daily dose >100 MEDD
- Long-acting (LA) or extended-release (ER) formulation
- Combination with benzodiazepines
- Long-term use (>3 months)
- Period shortly after initiation of LA/ER formulation
- Age >65 years
- Sleep-disordered breathing
- Renal/hepatic impairment
- Depression
- Substance use disorder
- History of overdose

**Addiction**
- Daily dose >100 MEDD
- Long-term opioid use (>3 months)
- Depression
- Substance use depression
- Adolescence


Setting of Care

**Primary care**
- Lowest risk
- No past/current history of substance abuse
- No major medical/psychiatric comorbidities

**Primary care with specialist support**
- Moderate risk
- Past or remote history of substance use or family history but not active

**Specialty pain management**
- Highest risk
- Active substance abuse
- Major psychiatric comorbidities

Adverse Effects and Risks With Opioids: Common

- Confusion
- Constipation
- Dizziness
- Dry mouth
- Dyspepsia
- Endocrine dysfunction
- Headache
- Hyperalgesia
- Nausea and vomiting
- Pruritus
- Sexual dysfunction
- Sedation
- Sweating
- Tiredness
- Tolerance


Adverse Effects and Risks With Opioids: Severe

- Respiratory depression
- Sleep-disordered breathing
- Addiction/dependence
- Fatal drug interactions
- Death

### Adverse Effects and Risks With Opioids: Others

<table>
<thead>
<tr>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk for myocardial infarction</td>
</tr>
<tr>
<td>Falls and fractures</td>
</tr>
<tr>
<td>Neonatal abstinence syndromes</td>
</tr>
<tr>
<td>Increased motor vehicle accidents</td>
</tr>
</tbody>
</table>


### Contraindications to Opioids

<table>
<thead>
<tr>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory instability</td>
</tr>
<tr>
<td>Acute psychiatric instability</td>
</tr>
<tr>
<td>Uncontrolled suicide risk</td>
</tr>
<tr>
<td>Active, untreated alcohol or substance use disorder</td>
</tr>
<tr>
<td>True opioid allergy</td>
</tr>
<tr>
<td>Concomitant medications with life-limiting drug interactions</td>
</tr>
<tr>
<td>Prolonged QTc (≥ 500 msec) with methadone</td>
</tr>
<tr>
<td>Active diversion</td>
</tr>
<tr>
<td>Condition not likely to improve with opioids</td>
</tr>
</tbody>
</table>


Chemical Classes of Opioids

Opioids + Benzodiazepines

- ~ 4-fold increase in overdose risk
- Avoid using opioids + benzodiazepines
- Gradually taper benzodiazepines to prevent seizures
- Tapering strategies
  - Decrease by 25% q1-2 weeks

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**Place in Therapy**

- Preferred: nonpharm and nonopioid therapy
- Opioids not considered first-line
- Don’t have to fail nonpharm and nonopioids before opioid trial

**Opioid Trial**

- Moderate to severe pain
- Benefits likely to outweigh risks
- Combine with nonopioid and nonpharm options
- Establish treatment goals related to FUNCTION and pain
- Develop exit strategy

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Informed Consent and Treatment Agreements

- **Informed consent**
  - Allow patient to have all information to make a decision in line with goals and preferences
  - Benefits, risks, and alternatives are components

- **Opioid treatment agreement**
  - Aim to help exchange information, improve adherence, and develop goals
  - Outline responsibilities of patient and provider

- **CDC guidelines: discuss risks, benefits, and patient/provider responsibilities**
  

Opioid Selection

- **Patient preference**
- **Cost**
- **Health status**
- **Neuropathic pain**
- **Renal/hepatic**
- **Dosing schedule**
- **Route of administration**
- **Prior experience**
- **Tolerance level**

Opioid Selection (cont’d)

- Recommend initiating opioids with immediate release (IR) formulations
- No recommendation regarding abuse deterrent formulations
  — Still can be abused


Opioid Selection:
Extended Release/Long-acting (ER/LA) Opioids

- Higher risk of overdose at initiation
  — Use after 1 week of short-acting opioids
- Preferred by some to lesser potential for abuse, better adherence, and consistent pain relief but NOT evidence-based
- FDA labeling
  — Pain severe enough to warrant around-the-clock, long-term opioids
  — Alternatives not effective, inadequate, not tolerated
  — Not for PRN use
- Some require opioid tolerance (morphine 60 mg/day or oxycodone 30 mg/day)
- May lead to greater average daily opioid dose

Opioid Selection: ER/LA Opioids

**Methadone***
- Disproportionate number of overdoses deaths relative to amount prescribed
- QTc prolongation
- Long, variable half-life
- Respiratory effects peak later and last longer than analgesic effects

**Fentanyl***
- Variable absorption
- Increased absorption with external heat sources
- Dosed in mcg/hr

*Use if experienced with prescribing these medications

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Opioid Dose

- Use lowest effective dose
- Avoid dose adjustment before steady state is reached (5 half-lives)
- Higher doses increase risk of
  - Motor vehicle injury
  - Opioid use disorder
  - Overdose
- ≥ 50 MEDD → reassess risks vs benefits
- ≥ 90 MEDD → avoid increasing beyond 90 MEDD or carefully justify
- Limitations with MEDD
  - Pharmacogenetics
  - Drug-drug interactions
  - Other individualized patient factors

CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. Recommendations and Reports. 2016;65(1);149
**ER/LA + IR**

- Avoid the use of immediate release (IR) and ER/LA formulations in combination
  - Increased risk
  - Diminished returns
  - Lack of safety outside of cancer/hospice
- If used 10%-15% of total daily dose is typically used

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**Opioid Rotation**

<table>
<thead>
<tr>
<th>Investigate potential causes for lack of benefit with increasing doses</th>
<th>Consider opioid rotation (useful in 50%-80% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug-drug interactions</td>
<td>• Lack of benefit</td>
</tr>
<tr>
<td>• Genetics</td>
<td>• Adverse events</td>
</tr>
<tr>
<td>• Worsening of condition</td>
<td>• Changes in patient status</td>
</tr>
</tbody>
</table>

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# Opioid Rotation Steps

- Pain assessment – worsening vs new pain
- Calculate total daily dose of current opioid
- Determine equianalgesic dose
- Reduce new dose by 25%-50% due to incomplete cross-tolerance
- Further individualize dose based on patient characteristics
- Reassessment and follow-up


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# Opioid Rotation Methods

- **Single-step method**
  - Old opioid discontinued
  - Replaced with new opioid

- **Step-wise method**
  - Use when switching large doses of opioids
  - Reduce current opioid by 25%-50%
  - Initiate 25%-50% of equianalgesic dose of new opioid

**Opioid Rotation: Equianalgesic Doses**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Parenteral (mg)</th>
<th>Oral (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>0.3</td>
<td>0.4 (SL)</td>
</tr>
<tr>
<td>Codeine</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>NA</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Methadone</td>
<td>*Multiple strategies</td>
<td>N/A</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>


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**Opioid Rotation: Fentanyl**

- **Morphine → Fentanyl**

<table>
<thead>
<tr>
<th>Oral 24-hour Morphine Dose (mg/day)</th>
<th>Fentanyl Transdermal Dose (mcg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-134</td>
<td>25</td>
</tr>
<tr>
<td>135-224</td>
<td>50</td>
</tr>
<tr>
<td>225-314</td>
<td>75</td>
</tr>
<tr>
<td>315-404</td>
<td>100</td>
</tr>
</tbody>
</table>

Opioid Rotation: Fentanyl (cont’d)

- Fentanyl → Morphine
  - Manufacturer: remove fentanyl patch and titrate dose of new analgesic based on patient’s pain. Levels decrease by 50% at ≥ 17 hr
  - Fentanyl dose in mcg x 2 = morphine dose in mg
  - Remove fentanyl patch
  - For first 12h, use short-acting opioids
  - At 12h, start 50% of calculated new opioid dose
  - At 24h, start 100% of calculated new opioid dose


Opioid Rotation: Methadone

- Morphine → Methadone
  - (see figure)

- Methadone → Morphine
  - 3:1 oral morphine to oral methadone

Reassessment and Follow-up

- 4 A’s
  - Analgesia
  - Activity
  - Adverse effects
  - Adherence/aberrant behavior

- Follow-up
  - 1-4 weeks after initiation or dose change
  - Closer follow-up for fentanyl or methadone
  - Depends on level of risk
  - 3 months for stable low risk patients

- Monitoring: Methadone

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Recommendations</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Prior to initiation of methadone:</td>
<td>• Any patient with no known risk factors for QTc interval prolongation</td>
</tr>
<tr>
<td></td>
<td>• *Risk factors for QTc interval prolongation</td>
<td>• An ECG within the past year with QTc &lt; 450 ms with no new risk factors for</td>
</tr>
<tr>
<td></td>
<td>• Any record of previous ECG with QTc &gt; 450 ms</td>
<td>QTc interval prolongation</td>
</tr>
<tr>
<td></td>
<td>• Past medical history of ventricular arrhythmia</td>
<td>• Any prior ECG demonstrating a QTc &gt; 450 ms</td>
</tr>
<tr>
<td></td>
<td>• An ECG with a QTc &lt; 450 ms within the past 3 months with no new risk factors</td>
<td>For all patients:</td>
</tr>
<tr>
<td></td>
<td>is acceptable</td>
<td>• Methadone doses titrated up to 20-40 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Methadone doses titrated up to 100 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• New risk factors for QTc interval prolongation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Signs or symptoms signifying arrhythmia</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>Pending baseline ECG results, methadone dose changes, and risk factors for QTc</td>
<td></td>
</tr>
<tr>
<td></td>
<td>interval prolongation:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Performed 2 to 4 weeks after initiation of methadone therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Following significant dose increases in patients with risk factors for QTc</td>
<td></td>
</tr>
<tr>
<td></td>
<td>interval prolongation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Any prior ECG demonstrating a QTc &gt; 450 ms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Have a history of syncope</td>
<td></td>
</tr>
</tbody>
</table>

*Risk factors for QTc interval prolongation: electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia), impaired liver function, structural heart disease (e.g., congenital heart disease, history of endocarditis, congestive heart failure), genetic predisposition, QTc-prolonging drugs.

Monitoring: Urine Drug Testing (UDT)

- Obtain UDT baseline and at least yearly
- Additional testing at provider discretion or based on risk
- Subject to provider misinterpretation
- Immunoassay
  - Low cost
  - Noninvasive
  - Subject to false positive, false negatives
  - Primarily detects morphine, codeine, heroin
  - Additional testing needed for synthetic opioids and possibly semi-synthetic opioids

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Monitoring: UDT

- Develop plan for unexpected UDT results
- Discuss unexpected results with patient
- Use confirmatory testing when needed
- Do NOT dismiss patient from practice

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**Monitoring: UDT**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Detection Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine TM</td>
<td>9-76 hours</td>
</tr>
<tr>
<td>Codeine</td>
<td>48 hours</td>
</tr>
<tr>
<td>Heroin (diacetyl morphine)</td>
<td>24-72 hours</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>20-25 hours</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>48-96 hours</td>
</tr>
<tr>
<td>Meperidine</td>
<td>15-20 hours</td>
</tr>
<tr>
<td>Methadone</td>
<td>72 hours</td>
</tr>
<tr>
<td>Morphine</td>
<td>48-72 hours</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>48-96 hours</td>
</tr>
</tbody>
</table>

*TM, transmucosal; TD, transdermal*


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**Monitoring: Prescription Drug Monitoring Program (PDMP)**

- Limited evidence for benefit on overdose, addiction, abuse, or misuse
- Most fatal overdoses associated with patient getting opioids from multiple prescribers or high daily dose
- Review before prescribing opioids
- Periodically review at least q3 months
- Consider state requirements for checking PDMP

**Monitoring: PDMP (cont’d)**

- Review results with patient
- Discuss safety concerns
- Coordinate care with other providers
  - eg, opioids + benzodiazepines
- Consider substance use disorder and refer for appropriate treatment
- Do NOT dismiss patients from your practice based on results

(CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. Recommendations and Reports. 2016;65(1);149)

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**Naloxone**

- Many medical groups recommend coprescribing
- Evidence for naloxone reversal mostly in substance use disorder
- Also includes patient education about overdose prevention
- Offer to those at increased risk for overdose
  - History of overdose
  - Concomitant benzodiazepine
  - Recent change in tolerance
  - > 50 MEDD
  - Comorbid condition
  - LA/ER opioid

(CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. Recommendations and Reports. 2016;65(1);149)
## Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSORD)

<table>
<thead>
<tr>
<th>Question</th>
<th>Points for a Yes Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the past 6 months, has the patient had a healthcare visit (outpatient, inpatient, or ED) involving any of the following health conditions?</td>
<td></td>
</tr>
<tr>
<td>Opioid dependence?</td>
<td>15</td>
</tr>
<tr>
<td>Chronic hepatitis or cirrhosis?</td>
<td>9</td>
</tr>
<tr>
<td>Bipolar disorder or schizophrenia?</td>
<td>7</td>
</tr>
<tr>
<td>Chronic pulmonary disease (eg, emphysema, chronic bronchitis, asthma, pneumoconiosis, asbestosis)?</td>
<td>5</td>
</tr>
<tr>
<td>Chronic kidney disease with clinically significant renal impairment?</td>
<td>5</td>
</tr>
<tr>
<td>An active traumatic brain injury, excluding burns (eg, fracture, dislocation, contusion, laceration, wound)?</td>
<td>4</td>
</tr>
<tr>
<td>Sleep apnea?</td>
<td>3</td>
</tr>
</tbody>
</table>


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## RIOSORD (cont’d)

<table>
<thead>
<tr>
<th>Does the patient consume:</th>
<th>Points for a Yes Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>An extended-release or long-acting opioid (ER/LA) formulation of any prescribed opioid?</td>
<td>9</td>
</tr>
<tr>
<td>Methadone? (also check ER/LA- 9 points)</td>
<td>9</td>
</tr>
<tr>
<td>Oxycodone? (if ER/LA formulation also check ER/LA- 9 points)</td>
<td>3</td>
</tr>
<tr>
<td>A prescription antidepressant?</td>
<td>7</td>
</tr>
<tr>
<td>A prescription benzodiazepine?</td>
<td>4</td>
</tr>
</tbody>
</table>

| Is the patient’s current maximum prescribed opioid dose:                                    |                           |
| ≥ 100 mg morphine equivalents per day?                                                    | 16                        |
| 50 ≤ 100 mg morphine equivalents per day?                                                 | 9                         |
| 20 ≤ 50 mg morphine equivalents per day?                                                  | 5                         |

| In the past 6 months, has the patient:                                                     |                           |
| Had one or more emergency department (ED) visits?                                          | 11                        |
| Been hospitalized for one or more days?                                                   | 8                         |

Total point score (maximum 115)

**Discontinuation of Opioid Therapy**

- Risks outweigh benefits
- Fail to achieve treatment goals
- Unmanageable or serious adverse effects
- Misuse or abuse
- Nonadherence
- Patient preference
- REFER for treatment of opioid use disorder if appropriate

Opioid Tapering

- No established protocol
- Individualize to patient needs
- Need approximately 25% of previous day’s dose to prevent withdrawal
- Speed of taper
  - Discontinuation: diversion or illegal activity
  - Rapid taper (over 2-3 weeks): significant coexisting medical or psychiatric illness
  - Slow taper: 10% of original dose per week


Conclusion

<table>
<thead>
<tr>
<th>Role for opioids in chronic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate opioids if benefits likely to outweigh risks</td>
</tr>
<tr>
<td>Establish goals of treatment and exit strategy prior to trial</td>
</tr>
<tr>
<td>Incorporate universal precautions and risk mitigation strategies before and during opioid therapy</td>
</tr>
<tr>
<td>Periodically reassess the 4 A’s</td>
</tr>
<tr>
<td>Taper or discontinue opioids when risks outweigh benefits</td>
</tr>
<tr>
<td>Refer for treatment of opioid use disorder if appropriate</td>
</tr>
</tbody>
</table>
Patient Case #1

- BT is a 55 yo man with failed back surgery syndrome. He is prescribed morphine SA 30 mg BID, duloxetine 60 mg daily, and naproxen 500 mg PO BID. He has signed informed consent and an opiate treatment agreement. His UDS and PDMP reports are up-to-date and appropriate. Opioids help him maintain employment as a janitor and reduce his pain; however, lately he’s had some difficulties finishing the day’s work. The provider wishes to convert him to oxycodone CR. What does of oxycodone CR would you recommend?

A. oxycodone CR 10 mg BID
B. oxycodone CR 15 mg TID
C. oxycodone CR 30 mg BID
D. oxycodone CR 30 mg TID

Patient Case #2

- MB is a 62 yo man with MS related neuropathic pain managed with methadone 7.5 mg PO BID (45 MED). He no longer wishes to continue taking methadone or chronic opioids for his pain. What’s the first step in tapering him from methadone?

A. Discontinue methadone, a taper is not needed
B. Reduce methadone to 7.5 mg PO daily x 1 week then stop
C. Decrease methadone to 5 mg PO QAM, 7.5 mg QHS x 1-4 weeks
D. Decrease methadone to 2.5 mg PO BID x 1 month
Back to Basics:
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Presented by:
Thomas B. Gregory, PharmD, BCPS, FASPE, CPE

Developed by: Abigail Brooks, PharmD, BCPS, Courtney Kominek, PharmD, BCPS, CPE