SAFE Opioid Prescribing | Strategies. Assessment. Fundamentals. Education
2–2:30pm

Best Practices for How to Start Therapy with ER/LA Opioids, How to Stop, and What to Do in Between

SPEAKERS
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Presenter Disclosure Information
The following relationships exist related to this presentation:

► Dr Argoff receives advisor/consultant honoraria from Endo, Collegium Pharmaceutical, Depomed, Lilly, AmeriBox, OXRx Pharma, Pfizer, Daiichi-Sankyo, Teva Pharmaceutical expert investigator honoraria from Endo, Allergan, Janssen, Mullen Labs, Lilly and receives grants from Endo/Lilly and Forest Laboratories.

► Dr McCarberg receives advisor honorarium from Iroko, NeurogesX, Pfizer, Salt, Sucampo, Teva and Zogenix.

► Dr Stanos receives advisory board/consultant honorarium from Endo Pharmaceuticals, Pfizer, MyMatrixx and GlaxoSmithKline.

Off-Label/Investigational Discussion
► In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

SAFE Opioid Prescribing Strategies. Assessment. Fundamentals. Education

Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS)

Session II

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Learning Objectives for Session II

Upon completion of this module, the participants will be better able to:

✦ Convert patients from immediate-release to ER/LA opioids as well as from one ER/LA opioid to another

✦ Identify predisposing risk factors for significant respiratory depression

Session II

Best Practices for How to Start Therapy with ER/LA Opioids, How to Stop, and What to Do in Between

1
Opioid Therapy in Chronic Pain Management

- Opioids ARE commonly prescribed for chronic pain:
  - Efficacious for many types of pain
  - Appropriate use is KEY to safety and success
- Goals of chronic opioid therapy:
  - Improve and/or stabilize pain intensity
  - Improve function
  - Improve quality of life (QOL)
- However, significant gaps exist between guideline recommendations for safe prescribing practices of ER/LA opioids and how they are being used in practice:
  - Highlights need for further education

Key Principles of Safe Prescribing

- Know how to:
  - Identify the ER/LA opioid and dosage to use in the appropriate patient
  - Supplement pain management with immediate-release opioids and non-opioids
  - Convert patients from immediate-release to ER/LA opioids and from one ER/LA opioid to another
  - Identify the warning signs and symptoms AND PREDISPOSING RISK FACTORS for significant respiratory depression
  - Safely taper an opioid dose when therapy is no longer needed
- Keep current with regulations for opioid prescribing, both federal and those in your own state

Benefits and Limitations of ER/LA Opioids

Potential Benefits
- Provide more consistent plasma concentrations of drug compared with short-acting agents
  - This minimizes fluctuations that could contribute to end-of-dose breakthrough pain
- More consistent nighttime pain control
- Less clock-watching by patients
- Possible improved compliance/adherence to a lower pill volume

Not for
- Not for as needed or "prn" use
- Not for mild pain
- Not for pain that is not expected to persist for an extended duration
- Not for acute pain
- Not for routine use in headaches or post-operative pain

ER/LA Opioids – Contraindications

- Significant respiratory depression
- Acute or severe asthma in an unmonitored setting or in absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity

Clinical Impact of Opioid Tolerance

- Tolerance is a function of both time and dose:
  - Patients who have not taken an opioid recently are considered opioid naïve
  - THESE patients are at greater risk for respiratory depression and sedation

Know The Risk Factors for Respiratory Depression

- Generally preceded by sedation and decreased respiratory rate
- Risk factors for respiratory depression include:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep apnea or a sleep disorder diagnosis</td>
<td>Morbid obesity with a high risk of sleep apnea</td>
</tr>
<tr>
<td>Risk increases with age (&gt;60)</td>
<td>No recent opioid use</td>
</tr>
<tr>
<td>Post-surgery (particularly upper abdominal or thoracic)</td>
<td></td>
</tr>
<tr>
<td>Use of other sedating drugs (CNS depressants)</td>
<td>Preexisting pulmonary or cardiac disease or dysfunction or major organ failure</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
</tbody>
</table>
The FDA Definition of Opioid Tolerance

- Opioid naïve vs opioid tolerant
- Patients are considered opioid tolerant if they are taking, for 1 week or longer, at least:
  - Oral morphine – 60 mg daily
  - Transdermal fentanyl – 25 mcg/h
  - Oral oxycodone – 30 mg daily
  - Oral hydromorphone – 8 mg daily
  - Oral oxymorphone – 25 mg daily
  - Equianalgesic daily dose of another opioid

Be Aware

- Certain ER/LA-opioid medications should ONLY be initiated in patients who have become opioid tolerant as a result of ongoing therapy

Opioid Tolerance—Agents and Dosing
(Refer to full prescribing information)

<table>
<thead>
<tr>
<th>Agent (Oral)</th>
<th>Selected Doses for Use in Opioid-Tolerant Patients Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avana (morphine sulfate ER capsules)</td>
<td>50 mg and 120 mg capsules for use in opioid-tolerant patients only</td>
</tr>
<tr>
<td>Embeda (morphine sulfate ER-naltrexone capsules)</td>
<td>100 mg/4 mg capsule for use in opioid-tolerant patients only</td>
</tr>
<tr>
<td>Kadian (morphine sulfate ER capsules)</td>
<td>100 mg and 200 mg capsules for use in opioid-tolerant patients only</td>
</tr>
<tr>
<td>Oxycontin (oxycodone hydrochloride CR tablets)</td>
<td>Single dose greater than 40 mg or total daily dose greater than 80 mg for use in opioid-tolerant patients only</td>
</tr>
<tr>
<td>Dolophine (methadone hydrochloride tablets)</td>
<td>When used as first opioid analgesic, initiate therapy with small doses, no more than 2.5 mg to 10 mg every 8 to 12 hours</td>
</tr>
</tbody>
</table>

Opioid Tolerance—Agents and Dosing
(Refer to full prescribing information)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dosing</th>
</tr>
</thead>
</table>
| Avana (morphine sulfate ER capsules) | Once daily
- Initial dose as first analgesic (opioid-naive patients) is 30 mg once daily
- Titrate using a minimum of 3-day intervals (4-day intervals for opioid-naive patients)
- Maximum daily dose 1600 mg (due to risk of renal toxicity)
| Butrans (buprenorphine transdermal system) | One transdermal system applied every 7 days
- Initial dose for initial analgesic (opioid-naive patients) is 5 mg/8 hr
- Maximum daily dose 1600 mg (due to risk of QTc prolongation)
Initiating Therapy: Dose Selection and Titration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolophine (methadone HCl tablets)</td>
<td>Every 6 to 12 hours&lt;br&gt;Initial dose as first opioid analgesic (opioid-naive patients) is 2.5 mg to 10 mg&lt;br&gt;Conversion of opioid-tolerant patients using equivalent doses can result in overdose and death. Use low doses according to the table in the full prescribing information&lt;br&gt;Special considerations: Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics and should be initiated and titrated cautiously by clinicians familiar with its use and risks (Refer to Module VI)</td>
</tr>
<tr>
<td>Duragesic (fentanyl transdermal system)</td>
<td>Every 12 hours (3 days)&lt;br&gt;Duragesic is contraindicated in opioid non-tolerant patients&lt;br&gt;Use product-specific information for dose conversion from prior opioid&lt;br&gt;Use 50% usual dosage in mild or moderate hepatic or renal impairment&lt;br&gt;Titrate using no less than 72-hour intervals.</td>
</tr>
<tr>
<td>Embeda (morphine sulfate and ER)</td>
<td>Once a day or every 12 hours&lt;br&gt;Initial dose as first opioid is 20 mg/0.8mg&lt;br&gt;Dosage adjustments may be done every 1 to 2 days</td>
</tr>
</tbody>
</table>

Drug Initial Dosing.

Initiating Therapy: Dose Selection and Titration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exalgo (oxymorphone HCl ER tablets)</td>
<td>Once a day&lt;br&gt;Not for use in opioid non-tolerant patients. Do not begin any patient on Exalgo as the first opioid&lt;br&gt;Use the conversion tables in the full prescribing information&lt;br&gt;Start patients with moderate hepatic impairment on 25% usual dosage&lt;br&gt;Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% usual dosage&lt;br&gt;Titrate using a minimum of 3- to 4-day intervals</td>
</tr>
<tr>
<td>Nucynta ER tablets)</td>
<td>Once a day or every 12 hours&lt;br&gt;Not recommended as a first opioid&lt;br&gt;Titrate using a minimum of 2-day intervals</td>
</tr>
<tr>
<td>MS Contin (morphine sulfate CR tablets)</td>
<td>Every 8 hours or every 12 hours&lt;br&gt;Not recommended as a first opioid&lt;br&gt;Titrate using a minimum of 2-day intervals</td>
</tr>
</tbody>
</table>

Dose Selection and Titration.

Supplementing ER/LA Opioids

- Patients who are on ER/LA opioids for chronic pain may need supplemental analgesia
- Increase dose of ER/LA opioid
- Treat with non-opioid analgesics
- Treat with short-acting opioids

Rationale for Opioid Rotation

- Opioid rotation is switching from one opioid to another
- Rationale for opioid rotation:<br>Adverse effects or toxicity of initial opioid<br>Lack of efficacy of initial opioid<br>Lowering the dose
- Rotation may work because of:<br>Incomplete cross-tolerance among opioids<br>Inter-patient variability of response based on opioid receptor genetic polymorphisms

Note: Conservative dose-conversion ratios are advised


Peter

- S/p lumbar fusion with chronic back and leg pain
- Returns to your primary care office for ongoing pain management
- Current medications:<br>Oxycodeone CR tablets 100 mg every 12 hours<br>Hydrocodone/acetaminophen 5/500, 8/day for breakthrough pain<br>Gabapentin 300 mg/2 tabs TID<br>Zolpidem 10 mgHS
- Goals of therapy:<br>Work a full day<br>Sleep through the night<br>Improve daytime somnolence
- Opioid rotation may be considered if goals of therapy are not met, adverse effects are intolerable, or to lower opioid dose
Equianalgesic Dose Table – An Example

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Equianalgesic (mg) Dose Oral</th>
<th>Equianalgesic (mg) Dose Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>60 PO 10 IM/IV/SQ</td>
<td>7.5 PO 1.5 IM/IV/SQ</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>20-35 PO</td>
<td>No information available</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15 PO 1 IM/IV/SQ 10 PR</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>20 PO 3 IM/IV/SQ</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.5-2.5 mcg/hour 10-30 mcg IV/SQ</td>
<td></td>
</tr>
</tbody>
</table>

- Hydrocodone potency ranges 1:1 to 1:2 with morphine, but safest approach is 1:1
- Be aware that individual responses may vary
- Refer to individual full prescribing information (PI) for complete information


Another Example: Duragesic (fentanyl transdermal system)

- Recommended Initial Duragesic Dose Based Upon Daily Oral Morphine Dose

<table>
<thead>
<tr>
<th>Oral (mg/day)</th>
<th>Duragesic Dose (mcg/hour)</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>
<tr>
<td>405-494</td>
<td>125</td>
</tr>
<tr>
<td>495-584</td>
<td>150</td>
</tr>
<tr>
<td>585-674</td>
<td>175</td>
</tr>
<tr>
<td>675-764</td>
<td>200</td>
</tr>
<tr>
<td>765-854</td>
<td>225</td>
</tr>
<tr>
<td>855-944</td>
<td>250</td>
</tr>
<tr>
<td>945-1034</td>
<td>275</td>
</tr>
<tr>
<td>1035-1124</td>
<td>300</td>
</tr>
</tbody>
</table>

Duragesic Full Prescribing Information. Available at www.fda.gov

Incomplete Cross-Tolerance

- Pharmacologic phenomenon whereby tolerance developed to the effects of one drug translates into tolerance to other drugs from the same class
- Incomplete cross-tolerance: Failure to develop complete cross-tolerance, increasing the likelihood of therapeutic effects as well as adverse effects
- It is known to occur among opioids
  - Mechanism behind opioid rotation
  - Also reason for caution in converting from one opioid to another


Converting Patients From Immediate-Release to ER/LA Opioids or to Another ER/LA Agent

- Guidelines for select agents
  - Butrans (buprenorphine transdermal system)
    - Converting from 30-mg to 80-mg morphine equivalents:
      - First taper to 30-mg morphine equivalent per day
      - Then initiate with 10-mcg/hr dose
  - Dolophine (methadone HCl tablets)
    - Converting opioid-tolerant patients using equianalgesic tables can result in overdose and death.
    - To minimize risk, use low doses according to table in full PI
    - Note: Relative potency to oral morphine varies, depending on patient’s prior opioid experience
  - Exalgo (hydromorphone HCl ER tablets)
    - Use conversion ratios in individual product-specific PI
    - Relative potency to oral morphine approximately 5:1 oral morphine to hydromorphone oral dose ratio
  - Nucynta ER (lapentadol HCl ER tablets)
    - Equipotency to oral morphine not established
  - Opana ER (oxymorphone HCl ER tablets)
    - Relative potency to oral morphine approximately 3:1 oral morphine to oxymorphone oral dose ratio
  - OxyContin (oxycodone HCl ER tablets)
    - Relative potency to oral morphine approximately 2:1 oral morphine to oxycodone oral dose ratio
  - OxyContin (oxycodone HCl CR tablets)
    - Relative potency to oral morphine approximately 1:1 oral morphine to oxycodone oral dose ratio

- Always refer to full prescribing information (PI)

Converting Patients From Immediate-Release to ER/LA Opioids or to Another ER/LA Agent

- Duragesic (fentanyl transdermal system)
  - For relative potency to oral morphine, see individual product-specific PI for conversion recommendations from prior opioid
  - Exalgo (hydromorphone HCl ER tablets)
    - Use conversion ratios in individual product-specific PI
    - Relative potency to oral morphine approximately 5:1 oral morphine to hydromorphone oral dose ratio
  - Nucynta ER (lapentadol HCl ER tablets)
    - Equipotency to oral morphine not established
  - Opana ER (oxymorphone HCl ER tablets)
    - Relative potency to oral morphine approximately 3:1 oral morphine to oxymorphone oral dose ratio
  - OxyContin (oxycodone HCl CR tablets)
    - Relative potency to oral morphine approximately 2:1 oral morphine to oxycodone oral dose ratio

- Always refer to full prescribing information (PI)

Tapering and Discontinuing ER/LA Opioid Analgesics

- When ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically dependent patient
- Do not abruptly discontinue these products
  - Decrease original dose by 10% per week
  - Abrupt discontinuation of chronic opioids may cause withdrawal characterized by:
    - Stomach cramps, diarrhea, rhinorrhea, sweating, elevated heart rate, increased blood pressure, irritability, dysphoria, hyperalgesia, and insomnia

Federal DEA Controlled Substance Schedules:
ER/LA-Opioids are Schedule II

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No currently accepted medical use in the U.S.; high potential for abuse</td>
<td>Heroin, LSD, marijuana, peyote, methaqualone, Ecstasy</td>
</tr>
<tr>
<td>II</td>
<td>High potential for abuse, which may lead to severe psychological or physical dependence</td>
<td>Hydromorphone, methadone, meperidine, oxycodone, fentanyl, morphine, opium, and codeine, amphetamine, methamphetamine, methylphenidate</td>
</tr>
<tr>
<td>III</td>
<td>Potential for abuse, which may lead to moderate or low physical dependence or high psychological dependence</td>
<td>Products containing &lt; 15 mg hydrocodone per dose, or ≤ 30 mg codeine per dose, buprenorphine, benzphetamine, phenmetrazine, ketamine, anabolic steroids</td>
</tr>
<tr>
<td>IV</td>
<td>Low potential for abuse</td>
<td>Alprazolam, carisoprodol, clonazepam, clorazepate, diazepam, lorazepam, midazolam, temazepam, triazolam</td>
</tr>
<tr>
<td>V</td>
<td>Low potential for abuse</td>
<td>Cough preparations containing ≤ 200 mg codeine per 100 ml or per 100 g, esogabine</td>
</tr>
</tbody>
</table>

State Laws/Regulations Vary. KNOW YOUR OWN STATE Rx REQUIREMENTS


Summary Module II

✧ Be knowledgeable of both federal and state regulations regarding opioid prescribing, including those for ER/LA opioids
✧ When initiating therapy, individualize ER/LA opioid dosages in all patients
✧ Some ER/LA opioid analgesics are appropriate ONLY in patients who are opioid tolerant
✧ Supplemental pain management with immediate-release analgesics may involve opioids or non-opioids
✧ Pearls for Practice:
  • Recognize the phenomenon of incomplete cross tolerance
  • Use conservative dose ratios when rotating opioids
  • Know warning signs of opioid-related respiratory depression
  • When discontinuing opioid therapy, gradually taper dose to avoid withdrawal symptoms