OPIOID USE & ABUSE: WHAT EVERY PHARMACIST SHOULD KNOW

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Learning Objectives

 Apply principles of opioid pharmacology in pain management
 Discuss pharmacist role in optimization of opioid therapy while ensuring safe prescribing
 Become familiar with tools available to combat opioid abuse & overdose

Opioids are classified as a High-Alert Medication by Institute of Safe Medication Practices (ISMP)

Statistics from the CDC

 Health care providers wrote 259 million prescriptions for opioids in 2012, enough for every American adult to have a bottle of pills
 46 people die each day from overdose of prescription opioids in the US
 Overdose deaths now exceed automobile accidents as a preventable cause of death in the United States

Why are they Dying??

 Mixing with other CNS depressants
 Unfamiliarity with pharmacokinetic profile
 Inappropriate prescribing to opioid naïve patients
 Too rapid dose titration
 Lack of follow-up after initial prescribing
 Opioid diversion

http://www.cdc.gov/vitalsigns/opioid-prescribing/index.html

“High Risk” Populations for Overdose

- “Doctor-shoppers”
- Those on high daily doses of opioids
  > >100 mg morphine equivalent/day = 9X risk of overdose
- Poly-drug abusers
- Low-income people & those living in rural areas
- Medicaid populations
- H/o mental illness &/or substance abuse

“High Risk” Populations for Overdose

- Dual Public Health Crisis

Diagnosis

Determine Biological Mechanism of Pain

- Neuropathic pain
  - peripheral
  - central
- Muscle pain
  - fibromyalgia
  - myofascial pain syndrome
  - trauma
- Inflammatory Pain
  - inflammatory arthropathies (rheumatoid arthritis)
  - infection
  - post-operative pain
  - tissue injury
- Mechanical/Compressive Pain
  - low back pain
  - neck pain
  - musculoskeletal pain
  - visceral pain

“Match pathophysiologic mechanism of pain syndrome to most appropriate treatment regimen aimed at specific mechanism”

Adaptation of WHO Analgesic Ladder

- Vargas-Schafer MD. Is the WHO analgesic ladder still valid? Twenty-four years experience. Canadian Family Physician. June 2010 vol. 56 no. 6 514-517

Opioid Patient-Related Variables

- Individual patients differ in their response to specific opioid analgesics
- Trials of several opioids may be required before finding an agent that provides effective analgesia with acceptable tolerability

Opioid Use in Hepatic Impairment

- Avoid pro-drugs that must be metabolized for analgesic effects (e.g. morphine, tramadol, codeine)
- Prescribe lower doses with extended dosing intervals

- 2011 ASHP Foundation Pain Management and Palliative Care Traineeship – Level 1-2
**Opioid Use in Renal Impairment**

- Consider stability of renal dysfunction
- Caution with opioids that have active metabolites which can accumulate (i.e. morphine, meperidine, codeine)
- Better choices are oxycodone and hydromorphone
- **Best choices** are those that lack active metabolites e.g. methadone, fentanyl

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**History of Opioid Exposure**

**Opioid naïve vs. Opioid-tolerant**

Patient is considered opioid-tolerant if receiving the following:

- 60 mg of oral morphine daily
- 25 mcg of transdermal fentanyl per hour
- 30 mg of oral oxycodone daily
- 8 mg of oral hydromorphone daily
- 25 mg oral oxymorphone daily

or an equivalent dose of another opioid for at least 1 week

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**Immediate Release Oral Opioids**

<table>
<thead>
<tr>
<th>Solubility</th>
<th>Agent</th>
<th>Onset of analgesia</th>
<th>Half-Life (t½)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophilic</td>
<td>Morphine (PO)</td>
<td>30-40 min</td>
<td>2-4 hours</td>
</tr>
<tr>
<td></td>
<td>Oxycodone (PO)</td>
<td>30 min</td>
<td>2-4 hours</td>
</tr>
<tr>
<td></td>
<td>Oxymorphone (PO)</td>
<td>30 min</td>
<td>7-9 hours</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone (PO)</td>
<td>30 min</td>
<td>2-3 hours</td>
</tr>
<tr>
<td></td>
<td>Methadone (PO)</td>
<td>10-15 min</td>
<td>8-59 hours</td>
</tr>
<tr>
<td>Lipophilic</td>
<td>Fentanyl (transmucosal)</td>
<td>5-10 min</td>
<td>3-14 hours</td>
</tr>
</tbody>
</table>

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**Usual Starting Doses (Adult >50kg) in Opioid-Naïve Patient**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Parenteral</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>5-10mg IV/SQ q3-4 hours (<strong>2.5-5mg</strong>)</td>
<td>15-30mg every 3-4 hours (<strong>5-15mg</strong>)</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>Not available</td>
<td>10mg every 4-6 hours (<strong>5mg</strong>)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1-2mg IV/SC q3-4 hours (<strong>0.5-1mg</strong>)</td>
<td>4-8mg q3-4 hours (<strong>2-4mg</strong>)</td>
</tr>
<tr>
<td>Methadone</td>
<td>5-10mg/24 hours (By continuous infusion or intermittent dosing q4xday)</td>
<td>5-10mg every 12 hours (<strong>2.5mg</strong>)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50-100mcg IV q1-2 hours</td>
<td>Indicated for opioid-tolerant patients ONLY; dosing is product-specific</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Not available</td>
<td>5-10mg q4-6 hours</td>
</tr>
</tbody>
</table>

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**Initiation in Opioid-Naïve Patient**

If pain is continuous/persistent →

- Initiate baseline medication around the clock (ATC)
  - Start with appropriate dose of an immediate-release opioid routinely every 4 hours ATC
  - Initiate PRN “rescue” dose that is 5-15% of total 24 hour baseline dose for pain that is not controlled by baseline medication
  - Scheduled frequency should be equal to Cmax for chosen route
    - PO/PR = q1 hour PRN
    - SC/IM = q 30 min
    - IV = 10-15 min

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If pain remains uncontrolled after 24 hours

- Baseline dose by amount at least equal to total dose of rescue medication used during previous 24 hours
- Based upon pain status:
  - Mild-moderate pain: 25-50% ↑
  - Severe-uncontrolled pain: 50-100% ↑

Ensure opioid titrations are clinically significant
Once pain is controlled → Switch to an extended release preparation

**Opioid Titration**

- Module 2: Cancer Pain Management - EPIC: Education in Palliative & End of Life Care - Oncology 2005

**Opioid Therapy – Titrate to Effect**

- No standardized dosage in treatment of pain

**Non-Analgesic Effects of Opioids**

Common
- Constipation
- Dry mouth
- Nausea/vomiting
- Sedation
- Sweats

Uncommon
- Bad dreams/hallucinations
- Dysphoria/delirium
- Myoclonus/urticaria
- Respiratory depression
- Urinary retention

**Outcomes of Long Term Opioid Use**

- It is suggested that there is an increased risk of serious harms with long term opioid use that appear to be dose-dependent
- Lack of trials relevant to long term opioid use (>6 months)
- No RCTs comparing long term use of opioids vs. placebo
- Lack of studies evaluating effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse or misuse

**Equianalgesic Opioid Dosing**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parenteral (mg)</th>
<th>Oral (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<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><strong>See package insert for desired transmucosal agent</strong></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>Meperidine</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Tramadol</td>
<td>NA</td>
<td>120</td>
</tr>
</tbody>
</table>

*Portenoy et al. Cancer Management with Opioids: Optimizing Analgesia. UpToDate. 2010
*2011 ASHP Foundation Pain Management and Palliative Care Traineeship - Level 1-2
Equianalgesic Dosing Caveats

- Information provided is an approximation
- Many conversion ratios may NOT be bidirectional
- Ensure medication is taken as prescribed prior to converting
- Account for incomplete cross tolerance = increased opioid sensitivity seen when rotating opioids
- Account for current pain status, situation & amount of residual drug in patient’s system
- When switching from parenteral to non-parenteral route, the dose will ALWAYS be higher

Unique Dosage Forms – Fentanyl Patch

- For chronic, persistent pain → NOT appropriate for acute pain
- Can NOT chase increasing pain with transdermal delivery system
  - Minimally effective blood concentrations in ~ 12 hours
  - Time to max concentration is ~36 hours
- For opioid-tolerant patients ONLY (despite whether palliative care/hospice)

Converting TO Transdermal Fentanyl (TDF): Equianalgesic Dosing

- Convert 24 hr opioid requirement to morphine equivalents
  - Do NOT reduce the morphine equivalent amount to account for lack of complete cross tolerance
  - Manufacturer guidance
  - Fentanyl is approximately 75-100x more potent than morphine - Approximately 100:1 (oral morphine: TDF)
  - e.g. 100mg oral morphine per day = 1mg (1000mcg) fentanyl per day (transdermal or IV)
  - Use 2:1 ratio = every 2mg oral morphine per day = 1mcg/hr TDF
  - e.g. 50mg per day of oral morphine ~ 25mcg/hr TDF

Converting FROM TDF: Equianalgesic Dosing

- Calculate your new opioid regimen
  - (if you are working with a home based patient, make sure the new opioid is IN the home before removing the patch)

- Remove TDF Patch
  - For the first 12 hrs. after patch removal, use ONLY previously prescribed rescue opioid therapy
  - 12 hrs. after patch removal, begin with 50% of the calculated scheduled opioid regimen & continue to offer the rescue opioid as needed
  - Upon removal, >17 hrs. required for 50% ↓ in serum concentrations
  - 24 hrs. after patch removal, increase to 100% of the calculated scheduled opioid regimen, and continue to offer the rescue opioid as needed

Unique Pharmacokinetics - Methadone

- 80% oral bioavailability
- Long, variable half-life (especially with higher doses)
  - Rapid titration guidelines used for other opioids do NOT apply
  - Elimination half-life is considerably longer than half-life of analgesia (5-130 hrs. vs. 4-8hrs)
- ONLY long-acting opioid available in solution
- 3 concentrations available: 5mg/5mL, 10mg/5mL, 10mg/mL

Converting TO Methadone: Equianalgesic Dosing

- NOT a linear conversion
  - The higher the dose of the original opioid, the more potent the methadone
  - May reverse/lessen opioid tolerance
    - Molecular structure & chemical characteristics may alter receptor binding
    - NMDA receptor antagonism
  - If patient is not already taking oral morphine, convert to oral morphine 1st

Initial Methadone Dose Based on Oral Morphine Equivalent Daily Dose (MEDD)

<table>
<thead>
<tr>
<th>Oral MEDD (mg/d)</th>
<th>Initial Dose Ratio (morphine:methadone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>3:1</td>
</tr>
<tr>
<td>101-300</td>
<td>5:1</td>
</tr>
<tr>
<td>301-600</td>
<td>10:1</td>
</tr>
<tr>
<td>601-800</td>
<td>12:1</td>
</tr>
<tr>
<td>801-1000</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1001</td>
<td>20:1 or greater</td>
</tr>
</tbody>
</table>

- Opioid Reference Table. Methadone Dosing and Safety Information Paper. VA National Pain Management Strategy Coordinating Committee Pharmacy Workgroup

Methadone - Initiation

**Opioid Naive**

- 2.5mg every 8hrs, ↑5mg/d q5-7 days
- In elderly/organ dysfunction: 2.5mg q12-24h

**Opioid Tolerant**

- <40-60mg/d MEDD: Similar to opioid naive
- Higher MEDD: 75-90% of equianalgesic dose (No >30-40mg/d), ↑10mg/d q5-7 days

Methadone - Monitoring

**Baseline**

- If QTc 450-500ms, consider alternative
- If QTc >500ms, avoid

**Follow-Up**

- 2-4 wks post-initiation (if h/o RFs)
- At 30-40mg/d & 100mg/d
- With new RFs for prolonged QTc

- As approach steady state with chronic dosing, ↑ duration of analgesia
- Respiratory depression is the chief hazard – peak effects occur later & persist longer vs. peak analgesic effects
- Monitor for sx toxicity over a 5-7 day period after initiation or dosage change

**Concentrated Oral Liquids**

For those with modest opioid requirements (30-60mg/day PO MEDD)

**Dosing Strategies**

- Can administer via sublingual/buccal route for those unable to swallow
- Can be scheduled ATC for baseline pain
- Absorption dependent upon lipophilicity of agent
- Limit each dose to 1ml volume
- If larger volume is needed:
  - Change to a more potent product
  - Compound as a more highly concentrated product
  - Administer smaller doses more often

**Patient Controlled Analgesia (PCA)**

- *Ensure patient is able to administer own PCA dose***

**PCA, bolus dose**

- First line in titrating patients to comfort
- Bolus tends to be half of the hourly rate (i.e. 1mg bolus, 2mg/hr CI with lockout)
- Lockout time in minutes (or delay interval)
- Can be as long as desired but should NOT be shorter than the onset of the opioid (i.e. 5min) to prevent overdose
- Basal (continuous infusion)
  - Do NOT titrate more frequently than every 10-12 hours
  - Ensure steady state is achieved
  - i.e. 1/2 of morphine is 2 hrs & it requires 5 half-lives to achieve SS (hence the 10-12hr guideline)
- One hour max limit – the total amount of opioid that can be received in 1 hour (PCA bolus + basal infusion)
**Patient Controlled Analgesia (PCA)**

- Can be administered subcutaneously
- Commonly used agents: morphine, hydromorphone & fentanyl
- SQ & IV infusion rates are considered equivalent (1mg IV = 1mg SQ)
- Issues with volume limitation – avoid exceeding ~3ml/hr
- Use a 25- or 27-gauge butterfly SQ needle
- Placed on the upper arm, shoulder, abdomen or thigh
- Can change site every 7 days unless a high volume is infused, or local skin irritation, itching, site bleeding or infection occurs

**Topical vs. Transdermal**

**Topical Compounds**
- Targets peripheral sites of pain
- Applied directly over painful site
- Achieving high bioavailability is a challenge
- Serum levels are insignificant, thus systemic side effects are unlikely
- Expensive

**Transdermal Patch**
- Has systemic activity
- Can be applied in location away from painful site
- Avoid in fever → ↑ absorption → ↑ blood levels
- Use with caution in cachectic, low body weight patients
- May report little or no improvement in pain with ↑ patch strength
- Consider using the last EFFECTIVE patch strength to base conversion calculations

**Universal Precautions**

10 step approach to assessment & management of pain

1. Diagnosis
2. Psychological Assessment including risk of addiction disorders
   - Utilize a validated screening tool, such as SOAPP-R or Opioid Risk Tool (ORT) to determine patient's level of risk
   - Urine drug screen (monitor for "Red Flag" results), PHQ-9, CAGE-AID, etc.
3. Discuss proposed treatment plan & obtain informed consent
4. Written provider-patient opioid treatment agreement
5. Pre- and Post- Intervention assessment of pain level & function
6. Opioid Trial, with or without adjunctive medications
7. Perform regular assessments of pain & function
8. Regularly evaluate the five A’s of pain: analgesia, ADLs, adverse effects, aberrant behaviors, affect
9. Periodic review of disease status, as well as comorbid medical and psychiatric conditions
10. Documentation

**Tools to combat opioid abuse & overdose**

**Urine Drug Screen Interpretation**

- Test types:
  - Immunassay/point of care → presence or absence of drug (qualitative)
  - Lab GC-MS or LC-MS/MS → definitive identification of specific drugs/metabolites (quantitative)
- How long are drugs detected in the urine?
  - In general, most drug detection times are 1-3 days
  - Long term use of lipid soluble drugs may extend window of detection
- Interpatient differences in drug metabolism
- Limitations:
  - Cannot determine exposure time, dose or frequency of drug use
  - Opportunity for false positives & false negatives (most common with immunocassays)
  - Intermittent differences in drug metabolism

**Opioid Metabolism**

- Codeine → Hydrocodone
- Morphine → Hydromorphone
- 6-MAM
- Heroin

Important to be knowledgeable to ensure appropriate test result interpretation!
Virginia Prescription Monitoring Program (PMP)

- Database for controlled substance prescription fills
- Data collected to promote the appropriate use of controlled substances for legitimate medical purposes
- Pharmacy data on controlled substance filled-submitted within 7-10 days for all schedule II-IV medications (opioids, sedatives, anxiolytics, stimulants, testosterone)
- Consider integrate use into workflow & evaluate prior to verifying/filling EVERY new prescription or prescription renewal for an opioid

Virginia PMP – 2015 Legislation

- Prescriber requirements to register with the PMP in the state of Virginia, & to request information for those patients which:
  - The course of treatment with opioids or benzodiazepines is anticipated to last more than 90 consecutive days to ensure the prescriber is aware of all other substances prescribed to a patient prior to initiating therapy

Opioid Treatment Agreement

For those who will be prescribed opioids on a chronic basis > than 3 months

- Expectations of patient:
  - Safeguard/avoid diversion
  - Appropriate use
  - Urine drug screen
  - Refills (1 pharmacy)

- Side effects/risks of improper use

- Goals of therapy

- Criteria for discontinuation

Other Tools/Strategies

- Abuse-deterrent Formulations
  - e.g. Embeda (morphine/naltrexone)
  - Quantity limits – encourage providers to avoid prescribing >100 pills/month
  - May decrease diversion from patients to others

- Proper storage & disposal
  - DEA website - www.deadiversion.usdoj.gov

- Chronic Pain Safety insurance programs

- Referral to a specialist

Naloxone – “Take Home Access”

- WHO recommends expansion of community access
- MOA: Competitive antagonist to opioids in the central nervous system
- Routes: FDA approved: IV, IM, SQ; off-label: IN (via mucosal atomizer), INH, IO
- Role in therapy:
  - Prescribe to those at risk for overdose & to those likely to witness an overdose
  - Intended to move the continuum of care forward before arrival of EMS at the scene
- New products on the horizon:
  - e.g. Evzio (naloxone auto-injector), AntiOp nasal spray
- Cost – lack of outpatient billing and reimbursement programs

Discontinuation of Opioid Therapy

- Reasons:
  - Resolution of underlying painful condition
  - Emergence of intolerable side effects
  - Inadequate analgesic effect
  - Failure to improve quality of life despite reasonable titration
  - Deteriorating function
  - Significant aberrant medication use

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- Wermeling, Daniel. Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. Therapeutic Advances in Drug Safety. 2015, Vol. 6(1) 20–31
Summary of Strategies

BEFORE Opioids are Prescribed
- Check state PMP
- Perform/document baseline risk assessment
- Obtain urine drug screen
- Sign provider-patient agreement
- Provide patient education regarding benefits & risks of therapy (based upon duration)
- Determine h/o opioid use (naive vs. tolerant)

AFTER Opioids are Prescribed
- Develop treatment goals & f/u plan
- Evaluate response to therapy
- Opioid dose titration or discontinuation
- Alternative/add-on therapy
- Adverse effects
- Patient Education/Adherence
- Perform routine UDS (based upon risk)
- Reassess for presence of co-morbidities that may affect treatment
- Evaluate need for specialist consult

Pharmacist Role in Opioid Management
- Provide continuity of care for patients
- Treatment plan development based upon biological mechanism of pain
- Facilitate opioid conversions & appropriate dose adjustments based upon pharmacokinetic profile of medication while avoiding impeding on improved pain control
- Reduce medication errors & ensure safe prescribing
- Patient/provider/colleague education
- Protocol/treatment algorithm development
- Medication reconciliation/medication therapy management
- Risk management tool interpretation

Question 1

The Virginia Prescription Monitoring Program is a beneficial tool that can facilitate management of controlled substances (Schedule II-IV) by allowing for which of the following:

a) Ensuring patient compliance with expectations & obligations set forth in the opioid treatment agreement
b) Monitoring medication compliance
c) Deterring abuse, misuse & diversion
d) All of the above

Question 2

Which of the following is True?

a) The maximum morphine daily dose of 120mg/day should not be exceeded
b) Fentanyl patches can be titrated every 24 hours
c) Morphine is the drug of choice in the presence of renal dysfunction
d) The estimated half-life is 2-4 hours for commonly used immediate release opioids

Question 3

Which of the following should NOT be performed when initiating an opioid trial in a patient who is opioid naïve?

a) Initiate a long-acting opioid formulation
b) Ensure consideration for non-opioid & non-pharmacological therapies have been optimized
c) Write the opioid prescription for a defined period of time with a limited supply
d) Work with the patient to define specified goals that will help determine if opioid therapy is beneficial & effective

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