Decoding Opioids: Indications for Best Practice

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Opioid Myths & Misconceptions...

- Opioids always lead to addiction
- Opioids always cause heavy sedation
- Morphine hastens death in a terminally ill pt.
- Effective pain management can be achieved with the PRN use of opioids

Addiction

- When sufficient doses are used for pain management, there are no indications that opioids lead to addiction (Hospice Foundation of America 2007)
- Under-treatment of pain leads to more chronic pain w/ patients requesting more or stronger drugs (pseudo-addiction)

Excessive Sedation w/ Opioids?

- Severe pain results in exhaustion & insomnia
- Once pain is controlled w/ opioids the patient can finally rest and sleep
- Once caught up on rest: - often may resume a more normal level of mental alertness & orientation while continuing opioids
- Excessive sedation may often be the result of other drugs in the regimen (anxiolytics, sedative-hypnotics)

Do Opioids Hasten Death in Terminally ill?

Opioids are often temporally related to death but not causative in hospice patients
- Used at end of life for both pain and dyspnea
- Often used in the final hours for severe discomfort
- Allowing for death with minimal suffering is the objective with hospice

Effective Pain Management Can be Achieved w/ PRN Opioids

- “Around-the-clock” analgesic therapy better than PRN for chronic pain
  - improved overall pain management
  - better to blunt or prevent pain episodes
  - do not want to be “chasing” pain with PRNs
  - fewer side effects
- Objective is to titrate opioid to individual’s need and continue with fixed routine dosage “around the clock” …
- Long-acting opioids help achieve this objective
Opioid Selection: Classification by potency (1)

**Moderate strength opioids**
(for moderate to severe pain)

- **Codeine** (codeine only, Tylenol w/ Codeine)  C-III
- **Hydrocodone** (only in combo w/ acetaminophen or ibuprofen) (Lortab, Norco, Vicodin, Vicoprofen)  C-III
- **Tramadol** (Ultram, Ultram ER, Ultracet)  Not controlled
- **Tapentadol** (Nucynta, Nucynta ER)  **C-II**
- **Buprenorphine** (Butrans patch)  C-III

*Long-acting opioid

Opioid Selection: Classification by potency (2)

**Strong opioids**
(for severe pain only)

- **Morphine** (MSIR, Roxanol, MS-Contin, Avinza, Kadian)
- **Oxycodone** (OxyIR, Oxyfast, Oxycontin)
- **Methadone** (Dolophine)
- **Hydromorphone** (Dilaudid, Exalgo)
- **Oxymorphone** (Opana, Opana ER, Numorphan)
- **Fentanyl** (Duragesic patch, Fentora, Actiq, Otsol, others)
- **Meperidine** (Demerol)

*Long-acting opioid

Initiating Opioid Therapy in Opioid Naive Patient

- Start with **short-acting** opioids in the opioid naïve
  - titrate to effective dose
- Avoid Extended Release/Long acting drugs initially because…
  - difficult to rapidly titrate dose for adequate pain control
  - may easily over-shoot the therapeutic window
  - impact of excessive dosage may be profound and long-lasting...difficult to reverse
  - may start L-A opioids after pt. is no longer opioid naïve
  (Conservative R.O.T. - OME of 60mg/day or more for 5 days)

Examples of starting doses: Opioid Naive

- **Moderate strength opioids:**
  - Hydrocodone 5-10mg Q4h prn (Vicodin, Norco, Lortab)
  - Codeine 30 – 60mg Q4h prn (Tylenol w/ Codeine)
  - Tramadol 50 -100mg Q6h prn (Ultracet)
- **Strong opioids:**
  - Morphine 5 -10mg (MSIR, Roxanol) PO Q 2 - 4h pm
  - Oxycodone 5mg (OxyIR, Oxyfast) PO Q 2 - 4h pm
  - Hydromorphone 2mg (Dilaudid) PO Q 2 - 4h pm
- **Titrate dose to control pain / minimize side effects**

Is there a maximum ceiling dose for opioids ??

For most opioids in general: **No.**
- Titrates dose gradually based upon pain control & emergence of side effects.
- LD-50 increases as therapeutic dose requirement increases

Specific Drug Limitations:
Combination drugs w/ Acetaminophen: max of 4,000mg/day)
- liver toxicity
Tramadol (Ultram) max: 400mg/day (300mg/day for patients 75 yr and up)
- increased seizure risk
Tapentadol (Nucynta) max: 500mg/day
- increased seizure risk
Buprenorphine (Butrans patch) max: 20mcg/hr patch
- cardiac toxicity (prolonged QTc interval)
Methadone oral max: 200mg/day , 300mg/day ??
- cardiac toxicity (prolonged QTc interval)

When, how, & why start a Long-Acting opioid ?

When: After pt is opioid tolerant (no longer opioid naïve)

How: - Determine average total daily S-A opioid dose
  - Initiate the equivalent daily dose of L-A opioid
  - Continue w/ S-A opioid for PRN needs only

Why: - prevention of persistent pain
  (instead of “chasing” pain with “prn” doses)
  - provide steady baseline level of analgesic drug
  - reduced side-effects associated w/ “peak” levels
  - reduce total number of doses per day
  - enhance patient compliance and convenience
### Long-acting Strong Opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dosage Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine ER oral</td>
<td>12-24h</td>
</tr>
<tr>
<td>(Avinza, Kadian, MS-Contin)</td>
<td></td>
</tr>
<tr>
<td>Oxycodone ER oral</td>
<td>12h</td>
</tr>
<tr>
<td>(OxyContin)</td>
<td></td>
</tr>
<tr>
<td>Oxyxymorphone ER oral</td>
<td>12h</td>
</tr>
<tr>
<td>(Dolophine)</td>
<td></td>
</tr>
<tr>
<td>Methadone oral</td>
<td>24h</td>
</tr>
<tr>
<td>(Lomtheamine)</td>
<td></td>
</tr>
<tr>
<td>Fentanyl transdermal</td>
<td>72h</td>
</tr>
<tr>
<td>(Doragexic patch)</td>
<td></td>
</tr>
</tbody>
</table>

### How Soon Can the LA Opioid Dose Be Increased?

Minimum interval to reach steady-state level:

- **Fentanyl patch**: initial increase in 3 days, then every 6 days
- **Methadone**: every 5 days
- **Morphine ER**: every 2 days
- **Oxycodone ER**: every 2 days

Dose should not be increased more frequently than above time frames.

### Cost Comparison: Long-acting Opioids

Cost of a 15 day supply of equivalent doses (based on AWP):

<table>
<thead>
<tr>
<th>Dosage:</th>
<th>Cost:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycontin 80mg Q12h</td>
<td>$420.00</td>
</tr>
<tr>
<td>Opana ER 40mg Q12h</td>
<td>$400.00</td>
</tr>
<tr>
<td>Fentanyl Patch 100mcg Q72h</td>
<td>$185.00</td>
</tr>
<tr>
<td>Morphine ER tablet 100mg Q12h</td>
<td>$110.00</td>
</tr>
<tr>
<td>- Avinza capsule 240mg Q24h</td>
<td>$210.00</td>
</tr>
<tr>
<td>Methadone 10mg Q12h</td>
<td>$12.00</td>
</tr>
</tbody>
</table>

### When to Increase the LA Opioid Dose and by How Much?

- When 3 or more PRN doses are required in 24hr for BTP?
- Goal is prevention of pain vs “chasing” pain with PRNs
- Increase by equivalent amount of prn opioid used in prior 24hr
- Always have a short-acting opioid order for BTP
- Think in percentages not just mg:
  - Dose increases < 25% are often NOT noticed by the patient
  - Example: Patient on Morphine ER 100mg Q12h is still c/o significant pain
    - an increase of 30 to 40mg/day may not have a significant impact
    - appropriate minimum increase would be 60mg (130mg Q12h)
- Don’t forget to increase the PRN opioid dose accordingly

### How Do We Determine the Appropriate PRN Dose?

- **PRN dose = 10% - 15% of total daily routine opioid dose**

  - Ex: MSER (MS-Contin) 100mg Q12h (total daily dose: 200mg)
  - PRN dose: MSIR or Roxanol 20mg

- **PRN Morphine oral interval?**:
  - for initial titration (orally) in severe pain or in pain crisis:
    - Q1-2hr prn
  - for other breakthrough pain (BTP) in stable patient: Q4hr prn
  - above interval appropriate for: morphine, oxycodone, hydromorphone
    (not applicable to fentanyl transmucosal products)

### Fentanyl Transmucosal Products for BTP

Rapid onset short-acting opioids (onset w/in minutes; peak at 20 min; duration 4h)

- Only for opioid tolerant patients also taking regular routine opioid therapy
- Absorbed through oral or nasal mucosa – ability to swallow not required
- Cost prohibitive for most hospices

- **Fentanyl buccal lozenge**: Fentora
- **Fentanyl lollipop**: Actiq
- **Fentanyl buccal soluble film**: Onsolis
- **Fentanyl sublingual tablets**: Abstral
- **Fentanyl sublingual oral spray**: Subsys
- **Fentanyl nasal spray**: Lazanda

Each product has strict guidelines for initiating therapy; per manufacturer

Effective dose must be determined by titration (not predictable from usage of other opioids)

Products are NOT interchangeable on a mg per mcg equivalency.
Transmucosal Immediate Release Fentanyl REMS

REMS: Risk Evaluation and Mitigation Strategy (FDA mandate)

TIRF REMS Access Program (www.TIRFREMSaccess.com)

Goal of program: Reduce risks for misuse, abuse, over-dosage. Ensure safe use & access to these drugs for patients who need them

Physicians & Pharmacies/Pharmacists: Must enroll in the TIRF access program, review an education program, and complete a test.

Patients: Must sign a Patient-Prescriber Agreement

Avoid Meperidine in Chronic Pain Management

Meperidine (Demerol)

• Not recommended for chronic pain management in palliative care
• Weak analgesic by the oral route: (Meperidine oral 300mg = Morphine oral 30mg)
• IV/IM meperidine is 4X more potent than meperidine po
• Only appropriate for short-term use (i.e. immediate post-op)
• Toxic metabolite (nor-meperidine)
  - accumulates in renal impairment or repetitive high doses
  - associated with seizures

Morphine – notes

• Gold standard: all opioids are measured against morphine
• Wide range of dosage forms (suppository, oral IR, oral ER, oral soln, injection)
• Renal excretion (active metabolites) - use caution in renal failure patients
• Kadian, Avinza - once-a-day oral dosage forms
  - expensive (brand only)
  - capsules can be opened for patients who cannot swallow pills (sprinkle over applesauce, or place in 10ml water for G-tube)
• Morphine ER tabs (MS Contin) can be effectively administered rectally*
  * J. Pain & Symptom Manag. 1992; 7:408
• Has active metabolites that contribute to both potency and adverse effects

Morphine Active Metabolites:

Morphine-6-glucuronide & Morphine-3-glucuronide

• Two active metabolites of Morphine
• Both accumulate with renal impairment or with relatively high doses
• Morphine-6-glucuronide: Twice the analgesic potency of Morphine
• Morphine -3-glucuronide: Cause of neurotoxicity
  - myoclonus
  - mental status changes
  - allodynia
  - hyperalgesia


Alternative: Methadone

Hydromorphone - notes

• Oral dosage form 4X more potent than oral morphine; IV dosage-form 20X more potent than oral morphine
• Variety of dosage forms (oral IR, oral ER, suppository, injection)
• Generics available for Dilaudid PO short acting - inexpensive
• Long acting form: Exalgo sustained release (Q24h) -very expensive
• Renal excretion & drug metabolites - use caution in renal patients (same issues as w/ morphine)
• Use for continuous IV infusion when high potency opioid is required

Oxycodone - notes

• Oral dosage form 1.5 x more potent than oral morphine
• Only oral dosage forms available
  - oral solution - Oxyfast
  - immediate release tablets (short acting) - OxyIR, Percocet (w/ APAP)
  - extended release tablets (long acting) - OxyContin
• Possible advantages over morphine?
  - Less itching than morphine – less histamine release
  - Less nausea?
• Single source brand: Oxycontin (generics are phased out - very expensive)
### Oxymorphone - notes

- Available as:
  - oral tablets: Opana (immediate release) or Opana-ER
  - suppositories or injection: Numorphan
- Oral form is 3X more potent than oral morphine
- No clear advantage over morphine?
- Expensive - brand only

### Fentanyl Patch – notes

- Fentanyl patch 50mcg/hr approx. equivalent to oral morphine 100mg/day
- May be over-used in patients who can take oral medication
- Usually dosed Q 72 hr (some may need Q48h)
- Drug reservoir is in the skin, not just the patch
  - drug continues to be absorbed 12 hr after patch removed
- Conversely: if converting to the patch, continue previous opioid dose for 12hr after application of initial patch (slow onset)
- Drug absorption & release into systemic circulation will vary with:
  - amount of subcutaneous fat (problematic in cachexia)
  - skin condition (i.e. aging changes, atrophy)
  - body temperature (problematic in febrile pts)
  - non-intact skin (cuts, abrasions, dermatitis)

### Tramadol (Ultram, Ultracet) - notes

- Moderate potency: Tramadol 100mg = Morphine oral 10mg
- Dual action: - Mild inhibitor of serotonin, & norepinephrine reuptake (CNS)
  - mu opioid agonist
- Beneficial for moderate neuropathic pain (due to SSR/NSRI activity)
- Seizure risk when exceeding maximum dosage
  (400mg/day adults; 300mg/day geriatrics)
- Often tolerated better than Tylenol w/ Codeine and Vicodin
- Inexpensive
- Interaction with SSR/NSRI antidepressants - Serotonin Syndrome
  (Prozac, Paxil, Celeria, Lexapro, Zoloft, Effexor, Cymbalta)

### Tapentadol (Nucynta) - notes

- Moderate potency: Tapentadol 50mg = 10mg oral morphine
- Dual mechanism of action (similar to Tramadol, but more potent)
  - mu opioid agonist similar to other opioids
  - significant norepinephrine re-uptake inhibition (SNRI)
- May have a role in moderate to severe neuropathic pain
- Dose range:
  - IR: 50-100mg Q4-6h prn
  - ER: 100mg - 250mg Q12h
- Expensive
- Interaction potential: Same as listed for Tramadol

### Butrans Patch – notes

- Buprenorphine patch 20mcg/hr = 50mg oral morphine/day
- Indicated for moderate to severe pain
- Patch is changed every 7 days
- Available as 5mcg/hr, 10mcg/hr, & 20mcg/hr strengths
- Max dose: 20mcg/hr patch (risk for cardiac toxicity w/ higher dose)
- Expensive

### Methadone - notes

- Oral methadone is 5 – 20X more potent than oral morphine depending upon dosage
- Dosage forms:
  - oral solution, oral tablets, injection
- Onset of action orally = 30min
- Duration of action (bi-phasic nature)
  - with initial therapy 4 hours
  - upon continuous chronic therapy 8 – 12hr
- Very cheap!
Methadone Advantages

• Long-acting opioid w/ unique characteristics:
  - a naturally long acting opioid, not sustained release tab – tabs can be crushed
  - oral solution is long-acting as well
  - good L-A opioid for patients that can’t swallow
• Effectively absorbed via sublingual route
• NMDA receptor antagonist (effective for neuropathic pain)
  - only opioid with this activity
• No active metabolites & no renal excretion
  - good alternative to morphine or hydromorphone for opioid neurotoxicity
• Very inexpensive

Methadone dosage forms

• Tablets: 5mg or 10mg
  (40mg tablets are restricted to hospitals or detox clinics)
• Oral solutions:
  5mg/5ml, 10mg/5ml, 10mg/ml (oral concentrate)
• Solution for injection
• May be compounded into suppository form

Opioid Conversion / Rotation?

• Why do it: lack of adequate pain control on current opioid
  - intolerable adverse effects or allergy
  - loss of swallowing ability
  - renal impairment
  - acetaminophen limitation
  - formulary or cost control issues
• Use equi-analgesic conversion chart as a guide (next slide)
• Temper results from the guide based upon pt. variables
  - current level of pain control
  - how aggressive the pain-control intervention should be
  - patient history of susceptibility of to side effects

Equi-analgesic Opioid Conversion Chart

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Dose</th>
<th>Parenteral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30mg</td>
<td>10mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5mg</td>
<td>1.5mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20mg</td>
<td>n/a</td>
</tr>
<tr>
<td>Methadone</td>
<td>See methadone guidelines</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30mg</td>
<td>n/a</td>
</tr>
<tr>
<td>Codeine</td>
<td>200mg</td>
<td>n/a</td>
</tr>
<tr>
<td>Tramadol</td>
<td>150mg</td>
<td>n/a</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300mg</td>
<td>75mg</td>
</tr>
<tr>
<td>Fentanyl Patch</td>
<td>25mcg/hr patch is equivalent to 50mg Oral Morphine/day</td>
<td></td>
</tr>
</tbody>
</table>

Equi-analgesic Oral Morphine Equivalent (OME) Chart

<table>
<thead>
<tr>
<th>Opioid drug</th>
<th>Multiply current opioid dose by this factor to equal Oral Morphine Equivalent dose (OME)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone oral</td>
<td>4</td>
</tr>
<tr>
<td>Hydromorphone IV, IM, SC</td>
<td>20</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5</td>
</tr>
<tr>
<td>Morphine IV, IM, SC</td>
<td>3</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Tramadol</td>
<td>0.1</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>10mcg/hr patch is equivalent to 25mg oral morphine/day</td>
</tr>
<tr>
<td>Fentanyl Patch</td>
<td>25mcg/hr patch is equivalent to 50mg oral morphine/day</td>
</tr>
<tr>
<td>Methadone</td>
<td>See morphine to methadone guidelines (next slide)</td>
</tr>
</tbody>
</table>

Adjustments to Opioid Conversion Chart Results?

• Opioid tolerance develops with chronic therapy
• There are differences in the level of cross-tolerance among opioids
• Equi-analgesic charts may not account for differences in tolerance
• Should adjustments be made to results from equi-analgesic chart ??
• Numerous schools of thought & expert opinion
• Many experts follow this guidance . . .
  1) If pain is well controlled on current opioid: reduce new by 50%
  2) If pain somewhat controlled: reduce new by 25%
  3) If pain not controlled: no adjustment to result from the chart
<table>
<thead>
<tr>
<th>Total Daily Oral Morphine Dose</th>
<th>Morphine to Methadone Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100mg</td>
<td>5:1</td>
</tr>
<tr>
<td>101-750mg</td>
<td>10:1</td>
</tr>
<tr>
<td>751-1500mg</td>
<td>12:1</td>
</tr>
<tr>
<td>&gt;1500mg</td>
<td>15:1</td>
</tr>
</tbody>
</table>

Adapted from MD Anderson Cancer Center guidelines; Aronstam and Bridge (Med J Aust 2000), and Ripamonti (Cancer Pain & Palliative Care 1999)

Questions

Contact me for a copy of these slides:

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