9th Annual Great Lakes Palliative Care Virtual Conference
May 6, 2021 to May 7, 2021

Preconference
When the Going Gets Tough...
May 6, 2021
When the Going Gets Tough, The Tough Get Going!
Complex Pain Management in Serious Illness

Mary Lynn McPherson, PharmD, MA, MDE, BCPS; Professor, University of Maryland Baltimore
Executive Program Director, Online Master of Science and Graduate Certificate Program in Palliative Care
Graduate.umaryland.edu/palliative | mmcphers@rx.umaryland.edu | @mlmcpherson
Disclosure

Dr. McPherson has nothing to disclose.
At least relevant to THIS presentation!
Learning Objectives

• At the conclusion of this presentation the participant will be able to:
  • Differentiate between opioid-poorly responsive pain, opioid-induced hyperalgesia, tolerance, disease progression and other potential causes.
  • Describe management strategies for opioid-induced hyperalgesia.
  • Describe the pathogenesis of difficult to control pain syndromes, and suggest appropriate treatment strategies.
  • Given a simulated patient with a problematic opioid calculation, identify the error and suggest corrective action.
  • Describe best practices for dosing methadone in opioid-naïve and opioid-tolerant patients.
Patient 1

- Ms. R. is a 43 year old woman with end-stage cervical cancer. She is admitted to hospice from the hospital, on IV morphine 80 mg/hour with a 20 mg bolus every 15 minutes (uses about once an hour).
- She is experiencing myoclonus, and the hospice medical director prescribed lorazepam 2 mg po q6h scheduled.
- Two days after admission the patient went on vacation for a week to the ocean.
Patient 1

- When the patient returned from vacation, she was admitted directly back to the hospital. It was discovered that she spent most of her ocean side vacation in the local hospital complaining of increased pain and myoclonus.

- On returning home, she is now on IV morphine 130 mg/hour plus a 30 mg bolus, which she uses once or twice an hour, plus a continuous infusion of midazolam at 10 mg/hour. She continues to experience significant myoclonus.

- What the heck is going on??!
Opioid Therapy

• Cornerstone of therapy for the treatment of moderate to severe pain (cancer, non-cancer)

• Increased availability and comfort level in using opioids in recent years
  • Greater attention to pain management
  • Better education
  • Used earlier in disease process
  • Used in higher doses

• Adverse effects of opioid
  • Usual – nausea, vomiting, constipation, pruritus, sleepy, confused
It could be...

- Opioid poorly-responsive pain
- Type of pain; temporal pattern of pain (breakthrough)
- Opioid-induced tolerance / Disease progression
- Opioid-induced hyperalgesia
- Poorly managed opioid therapy
- Non-physical pain
Pain Management is NOT One-Sizes-Fits-All!

- The WHO method for cancer pain relief
  - Validated in thousands of patients
  - 1970’s and 1980’s – move away from invasive procedures to treat pain, to analgesics 80%

- Up (to 90%) of pain could be controlled with WHO ladder approach (non-opioids, opioids)

- What about the rest?
  - Opioid-non-responsive pain or opioid-resistant pain
Opioid Responsiveness

• Most pain will respond at least partially to opioid therapy

• Patients with advanced illness (particularly cancer) more often than not have more than one type of pain (with varying degrees of responsiveness to opioid therapy)

Opioid responsiveness is defined as the degree of analgesia achieved as the dose is titrated to an endpoint defined either by intolerable side effects or the occurrence of acceptable analgesia

Types of Pain

Neuropathic pain

• Reported to be unresponsive to opioids at usually effective doses
• Morphine may change affective but not sensory dimension of neuropathic pain
• Neuropathic pain has negative predictive prognostication with cancer pain therapy
• Neuropathic pain reduces the likelihood of a favorable outcome
• Not a class effect; try opioid rotation

Other Types of Pain

• Skin ulceration
• Rectal tenesmus
• Muscle pain
• Development or worsening of a non-cancer pain syndrome such as painful diabetic neuropathy
• New non-cancer pain syndrome such as a dental abscess
Symptom Analysis

Multidimensional Pain Assessment

- P (palliative / precipitating / previous therapy)
- Q (quality)
- R (region / radiating)
- S (severity)
- T (temporal)
- U (YOU – associated symptoms)
Multidimensional Pain Assessment

- P (palliative)
- P (precipitating)
- P (previous therapy)
- Q (quality)
- R (region/radiating)
- S (severity)
- T (temporal)
- U (YOU – assoc’d Sx)

1. R (region / radiation)
2. T (temporal)
3. Q (quality)
4. P (palliative)
5. P (precipitating)
6. S (severity)
7. U (YOU – assoc’d Sx)
8. P (previous therapy)
Pain

Nociceptive

Visceral
- Diffuse, deep, gnawing
- Distention, cramping, angina

Somatic
- Sharp, throbbing, aching
- Injury to skin, bones, joints, soft tissue
- Well-localized

Neuropathic

Central or peripheral
- Burning, shooting, paresthesia
- Phantom limb, diabetic neuropathy, post-herpetic neuralgia
Pain

Nociceptive

Visceral
- Diffuse, deep, aching, gnawing
- Distention, cramping, angina

Somatic
- Poorly localized
- Sharp, throbbing, aching
- Injury to skin, bones, joints, soft tissue

Neuropathic

Partially opioid-responsive Adjuvant analgesic

- Central or peripheral
  - Burning, shooting, paresthesia
  - Phantom limb, diabetic neuropathy, PHN

Traditional Analgesics: Non-opioids, Opioids

PG-mediated pain: Steroids, NSAIDs

Adjuvant analgesic

Partially opioid-responsive Adjuvant analgesic

Traditional Analgesics: Non-opioids, Opioids

PG-mediated pain: Steroids, NSAIDs

Partially opioid-responsive Adjuvant analgesic
CNS Adverse Effects of Opioids

- Adverse effects of opioids on CNS (neurotoxicity - damage to nerve cells)
  - Reduced level of consciousness (sedation, drowsiness, sleep disturbance)
  - Adverse effects on thinking process and ability to reaction (cognitive impairment, psychomotor impairment, delirium, hallucinations, dreams, nightmares)
  - Direct toxic effect on neurons (myoclonus, seizures, hyperalgesia and tolerance)

Clin J Pain 2008;24:479-496; A – OIH; B - Tolerance
Vicious Cycle of Opioid-Induced Neurotoxicity
Clinically...

**Patient reports**
- Increased sensitivity to pain stimulus (hyperalgesia)
- Worsening pain despite increasing doses of opioids
- Pain that becomes more diffuse, extending beyond the distribution of the pre-existing pain

**Provider observes**
- Any dose of an opioid, but particularly with high-dose morphine or hydromorphone, and in renal impairment/failure
- Pain elicited from ordinary nonpainful stimuli (e.g., stroking skin with cotton [allodynia])
- Presence of other manifestations of opioid-induced hyperexcitability: myoclonus, delirium, seizures
Morphine and Hydromorphone
Active Metabolite Accumulation in Renal Failure

http://palliative.info/pages/TeachingMaterial.htm
Management of OIH

Hydration if clinically appropriate

Reduce the opioid dose
- Consider use of an opioid-sparing coanalgesic
  - Acetaminophen, NSAID

Opioid rotation
- Allows comparable analgesia at a lower equianalgesic dose
  - Fentanyl
  - Methadone
  - NMDA receptor antagonist

Ketamine (NMDA receptor antagonist)
Ketamine protocol

- **Indications for use:**
  - Neuropathic pain poorly responsive to opioids and adjunctive analgesics, particularly in patients with hyperalgesia/allodynia
  - Somatic/visceral pain despite appropriately titrated opioid therapy
  - Adverse effects to increasing doses of opioids (e.g., myoclonus, uncontrolled constipation, respiratory depression)
  - Severe pain associated with wound care
  - Adjunctive for analgesia
Ketamine protocol

• **IV/SQ dosing**
  - 2.5-5 mg administered over 1 minute
  - Evaluate patient response over the next 15 minutes

• **IV/SQ Infusion**
  - Reduce total daily opioid dose by 30%; reduce BZD
  - Continue breakthrough opioid at previously prescribed dose
  - Loading dose up to 10 mg
  - Starting dose – 50 mg over 24 hours (e.g., 2 mg/hour)
  - Increase dose by an additional 50 mg per 24 hours if needed
  - Usual dosage range – 100-400 mg/24 hours
• **Oral dosing**
  • Put injectable ketamine in fruit juice
  • Reduce total daily opioid dose by 30%; reduce BZD
  • Continue breakthrough opioid at previously prescribed dose
  • Starting dose – 10-15 mg every 6 hours
  • Dose titration – increase 10 mg per dose every 2-3 days
  • Usual maximum dose – 50 mg every 6 hours

• **Oral ketamine for wound care**
  • 2.5-5 mg by mouth 30 minutes prior to wound care/procedure

• **Topical ketamine for mucositis**
  • Injectable ketamine in artificial saliva (20 mg [0.2 ml] with 5 ml saliva substitute
  • 20 mg swish and SPIT solution
• Oral dosing
  • Use ketamine 100 mg/ml (10 ml vial)
  • Dilute with 90 ml sterile water (or flavored syrup)
  • Resulting solution is ketamine 10 mg/ml (100 ml total)
  • Expires in 7 days; keep refrigerated
  • Dose may be further diluted with orange juice, cola, etc. immediately before administration to mask bitter taste
Patient 1

• Begin ketamine 10 mg po q6h, mixed in orange juice
• Empirically reduce morphine infusion by 30% to 90 mg/hour; keep bolus in place
• Empirically reduce midazolam infusion by 50% to 5 mg/hour
• Increase ketamine by 10 mg per dose every 2-3 days (while titrating morphine and midazolam down)
Managing Resistant and Difficult Pain
Lidocaine for Neuropathic Pain

- **Advantages**
  - Inexpensive, effective
  - Not associated with opioid-induced adverse effects
- **Lidocaine adverse effects**
  - Predictable
  - Wide safety margin
  - Transient and easily reversed

Lidocaine for Neuropathic Pain

- Candidates for therapy
  - Neuropathic pain states (diabetic neuropathy, post-operative pain, post-herpetic neuralgia, centrally-mediated pain, headache, malignant nerve infiltration)
  - Visceral or central pain
  - When opioids are ineffective or causing unacceptable adverse effects

Lidocaine for Neuropathic Pain

• Pre-Infusion Assessment
  • Complete pain history
  • Allergy history (to “caine” anesthetics)
  • Quantitative pain assessment
  • Physical examination
  • History of heart failure or liver disease

Lidocaine for Neuropathic Pain

- **Lidocaine Challenge**
  - To determine patient’s response and ability to tolerate medication
  - 1-3 mg/kg (100 mg is often used)
  - Administered IV in a concentration of 8 mg/ml over 20-30 minutes (or SQ over 30-60 minutes at 40 mg/ml)
  - Monitor VS and pain intensity every 15 minutes

Lidocaine for Neuropathic Pain

- Lidocaine Infusion
  - If challenge effective or partially effective, and tolerated:
  - Start continuous infusion SQ or IV:
    - 0.5-2 mg/kg per hour, using lowest possible dose to control pain
  - Gradually titrate downward to find lowest effective dose
  - Monitor for signs of toxicity, especially with dosage increases
• Lidocaine Infusion
  • Reduce opioids rapidly if patient has sx opioid toxicity (particularly sedation)
  • Pain relief generally seen at 1-2 mg/kg/hr
    • Blood levels often less than 3 mcg/ml and toxicity rare
    • At 4-6 mcg/ml patients complain of lightheadedness, numbness around tongue or mouth and/or dizziness

Patient 2

- HR is a 58-year-old man admitted to hospice with a diagnosis of lung cancer with widespread mets.
- The patient also has comorbid conditions of type 1 diabetes, hypertension and chronic kidney disease stage 4.
- His serum creatinine is 3.2 mg/dl. Patient is 5’8”, 140 pounds
- HR’s physician contacts you for advice – should he dose-adjust the patient’s analgesics?
  - MS Contin 45 mg po q12h
  - Oral morphine solution 10 mg po q2h prn
  - Gabapentin 900 mg po q8h
  - Dexamethasone 4 mg po bid (breakfast and lunch)

What is HR had end-stage liver disease?
What if he had BOTH end-stage liver and renal disease?
### Opioids in Renal Dysfunction

<table>
<thead>
<tr>
<th>Favorable Opioids</th>
<th>Unfavorable Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Codeine</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Dihydrocodeine</td>
</tr>
<tr>
<td>Methadone</td>
<td>Hydrocodone</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Tramadol</td>
</tr>
</tbody>
</table>

David M, McPherson ML. Which opioids are safest and most effective in patients with renal or hepatic failure? In press.
<table>
<thead>
<tr>
<th>Opioid</th>
<th>Recommendation in Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>No change in dosing</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Generally safe, start with low doses and go slow</td>
</tr>
<tr>
<td>Methadone</td>
<td>No changes in dosing</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>No changes in dosing</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>No changes in dosing</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Generally, start at lower doses, can give around the clock</td>
</tr>
<tr>
<td>Morphine</td>
<td>Use cautiously, dosing strategy unknown in CKD, if used prefer prn dosing</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Best to avoid</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Best to avoid</td>
</tr>
</tbody>
</table>

David M, McPherson ML. Which opioids are safest and most effective in patients with renal or hepatic failure? In press.
Hepatic Impairment: Impact on Opioid Pharmacokinetics

• **Absorption** – delayed drug absorption
  - Cirrhosis → gastritis, portal hypertensive gastropathy, GI ulcers, delayed gastric emptying
  - Consider using immediate release opioids instead of prolonged release

• **Distribution** – expanded
  - Cirrhosis → increased Vd due to third spacing
  - Increased adverse effect with hydrophilic opioids (morphine, oxycodone, hydromorphone); start with lower doses
  - Protein binding → may see less production of alpha-1-acid glycoprotein and albumin, so higher opioid free fraction of high protein-binding opioids (methadone [80-90%], buprenorphine [96%])

Gelot and Nakhla, US Pharmacist 2014
Hepatic Impairment: Impact on Opioid P’kin

• Metabolism
  • Child-Pugh classification and Model for End-Stage Liver Disease (MELD) score a not helpful for use with cirrhosis and estimating hepatic clearance
  • Hepatic Extraction Ratio may provide some insight (0 [no liver metabolism] to 10 [entire drug metabolized on first pass])
    • High extraction ratio > 0.7; intermediate is 0.3-.07; low extraction is < 0.3
    • Morphine and fentanyl are high extraction
    • Methadone is a low extraction ratio
  • CYP-450 mediated reactions are more altered by hepatic impairment (phase I); phase II less affected

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Opioid Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 (phase I)</td>
<td>Fentanyl, oxycodone, tramadol</td>
</tr>
<tr>
<td>CYP2D6 (phase I)</td>
<td>Codeine, hydrocodone</td>
</tr>
<tr>
<td>Glucuronidation (phase II)</td>
<td>Hydromorphone, oxymorphone morphine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Extraction Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>0.52</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.51</td>
</tr>
<tr>
<td>Methadone</td>
<td>&lt; 0.30</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.52</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.76</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Gelot and Nakhla, US Pharmacist 2014
## Opioids in Hepatic Dysfunction

<table>
<thead>
<tr>
<th>Preferred Opioids</th>
<th>Use with Caution</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Buprenorphine</td>
<td>Codeine Meperidine</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Hydrocodone</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
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</table>
Does liver cancer alter hepatic metabolism?
Patient 3

- 73-year-old man with CKD III and severe peripheral vascular disease (PVD) presents with left leg pain (7/10) and early gangrene left lateral foot and toes.
- The surgeon assesses the extent of disease and finds no surgical option and offers amputation.
- The patient refuses.
- You are consulted for pain and goals of care.
- How will you manage his pain?
- What is his prognosis?
Patient 3 – Epidemiology/Pathophysiology

- Critical leg ischemia develops 500-1000/10^6
- Cardiovascular events occur more frequently than those with CAD
- Conservative management-mortality is 45% at 2 years, all cause mortality 50%
- Mortality worse than advanced colorectal, breast and prostate cancer

- Pain is caused by an distal axonopathy-neuropathic
- Secondary alterations in muscle and oxidative stress
- Pain is worse at night (limb is no longer in a dependent position)
- Wakens patients from sleep
- Risk of phantom pain syndrome s/p amputation

Norgren L 2007
Patient 3 - Palliation

- Lumbar sympathectomy - inconclusive
- Spinal cord stimulation - inconclusive
- Lidocaine IV > morphine – problems with portability
- Ketamine 0.6mg/kg > placebo (NNT 5) - problems with portability and side effects
- Gabapentin- single arm, 15/17 responded (NRS 9/10 to 5/10 over 28 days)
- Buprenorphine added to epidural morphine/ local anesthetic in 2 RCT- improved pain > morphine alone, less morphine needed and better sleep

Ubbin D 2013; Vahidi E 2015; Mitchell A 2002; Aurilio B 2005 and 2009
Patient 3 - Summary

- Palliation
  - Gabapentin
  - Buprenorphine =/- spinal analgesia
  - Ketamine IV
  - Lidocaine IV
  - Lumbar sympathectomy
Patient 4

- A 57-year-old man presents with muscle invasive rectal cancer and liver metastases.
- He is given a palliative course of radiation to the pelvis with capecitabine and then is started on FOLFOX chemotherapy.
- His obstipation and bleeding resolves but after 7 months of FOLFOX he develops rectal discomfort described as “drilling” or “pressing” which intensifies with defecation.
- A repeat CT scan demonstrates persistent cancer in the rectum, improved liver metastases.
- There is stranding to the sacrum.
- A PET scan demonstrates persistent uptake in the rectum and perirectal tissues extending to but not invading his sacrum.
- He refuses a consideration of a colostomy.
- How would you manage his pain?
Patient 4 - Tenesmus

- Relatively resistant to opioid therapy
- Opioids cause sphincter dysfunction and circular muscle contraction
- Refractoriness to opioid therapy is similar to pancreatic pain, decubitus ulcers, superficial skin ulcers and pain from shear injury

Hanks G 1991
Patient 4 - Tenesmus

- “Orphan” pain syndrome - found in 9/362 home palliative care patients
- Rarity means that the evidence base for managing the symptom is low and is dependent on case reports, case series and cohort studies

Mercadante S 2013
Patient 4 - Pathophysiology of Tenesmus

- Smooth muscle contractions
- Tumor invasion of lumbar plexus
- Tumor induced inflammation which sensitizes afferents

Laoire A 2017
Patient 4 - Management of Tenesmus

- Calcium channel blockers nifedipine and diltiazem -5 of 6 responses
- Methadone - 2 case reports
- Mexiletine - 5 patient reports
- Intrathecal and intrarectal bupivacaine
- Lumbar sympathectomy -10 of 12 responses
- Endoscopic laser therapy -21 of 26 responses and 4 of 8 responses
- Phenol neurolytic saddle block - 1 case report

Laoire A 2017
Patient 4 - Traditional Therapies of Tenesmus

Possible therapies without data

- Dicyclomine - muscle spasm
- Gabapentinoids - hypersensitivity or plexopathy
- Anticholinergics - muscle spasm
- Ketamine - neuropathic (visceral)
Patient 5 - What a pain in the butt!

• Pain related to anal cancer – SO challenging to treat!
• Reports of intrathecal opioid therapy, calcium channel blockers for perineal pressure-like pain and tenesmus
• Opioids, steroids, lidocaine ointments
• Case report from Nigeria – 34 yo man with anal cancer
  • Complained of extreme, nonradiating sharp pain within anal canal
  • Morphine 20 mg q4h plus acetaminophen 500 q6h plus meloxicam 15 qd
  • Radiation did not help pain
• Rectal suppositories lidocaine 60 mg plus hydrocortisone 5 mg pr q12h

Ali SK, Abdulkarim S. JPSM 2018;56(1):e1-e2
Opioid Conversion Calculations
Reasons for Changing Opioids

- Lack of therapeutic response
- Development of adverse effects
- Change in patient status
- Other considerations
  - Opioid/formulation availability
  - Formulary issues
  - Patient/family health care beliefs
# Equianalgesic Opioid Dosing

**2010 Equianalgesic Doses (mg)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parenteral</th>
<th>Oral</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</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>Oxycodone</td>
<td>10*</td>
<td>20</td>
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**2018 Equianalgesic Doses (mg)**

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<td>25</td>
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<tr>
<td>Fentanyl</td>
<td>0.15</td>
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<td>Hydrocodone</td>
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<td>25</td>
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<tr>
<td>Hydromorphone</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
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# Equianalgesic Opioid Dosing

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</tbody>
</table>

*Not available in the US*

NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.

Parenteral to Oral Hydromorphone

- Largely determined by oral bioavailability (of oral hydromorphone)
  - Parab - 50.7 +/- 29.8%; Ritschel – 51.35 +/- 29.3%
- Do we need to evaluate conversion from oral to parenteral?
  - No, because conversion is determined primarily by BAB
  - Secondarily by pharmacogenetics
- Clinical experience in large patient populations provide average guidance
- Best data is 1:2.5 (IV:oral)

<table>
<thead>
<tr>
<th>McPherson Table</th>
<th>Equianalgesic Doses (mg)</th>
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<tbody>
<tr>
<td>Drug</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Hydromorphone</td>
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## Conversion Ratio from IV Hydromorphone to Oral Opioids in Cancer Patients

<table>
<thead>
<tr>
<th>IV Hydromorphone</th>
<th>→</th>
<th>Oral Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg IV hydromorphone (&lt; 30 mg/day)</td>
<td>→</td>
<td>Oral hydromorphone 2.5 mg</td>
</tr>
<tr>
<td>1 mg IV hydromorphone (&gt; 30 mg/day)</td>
<td>→</td>
<td>Oral hydromorphone 2.1 mg</td>
</tr>
<tr>
<td>1 mg IV hydromorphone (&lt; 30 mg/day)</td>
<td>→</td>
<td>Oral morphine 11.54 mg</td>
</tr>
<tr>
<td>1 mg IV hydromorphone (&gt; 30 mg/day)</td>
<td>→</td>
<td>Oral morphine 9.86 mg</td>
</tr>
<tr>
<td>1 mg IV hydromorphone</td>
<td>→</td>
<td>Oral oxycodone 8.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>McPherson Table</th>
<th>Equianalgesic Doses (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
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</tr>
<tr>
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<tr>
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<td>2</td>
</tr>
<tr>
<td>Oxycodone</td>
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</tr>
</tbody>
</table>

**Reddy’s bottom line:**
- 1:2.5 (IV hydromorphone to oral hydromorphone)
- 1:10 (IV hydromorphone to oral morphine)
- 1:8 (IV hydromorphone to oral oxycodone)

Morphine ↔ Hydromorphone

• Is it bidirectional? (IV HM to PO MS equal to PO MS to IV HM?)

• Study by Lawlor – SQ to SQ HM/MS and PO to PO HM/MS
  • Going from morphine to hydromorphone (same route) was 5:1 (M:HM)
  • Going from hydromorphone to morphine (same route) was 3.7:1 (M:HM)

• Limitations of Lawlor study:
  • Data highly skewed and variable, not normally distributed
  • Authors stated differences in direction were clinically insignificant and called for further research...in the meantime differences in M→HM and HM→M remain speculative

How about oral MS to parenteral hydromorphone?

<table>
<thead>
<tr>
<th>Switching from 10 mg IV HM per day to PO MS</th>
<th>IV HM:PO MS - 1.5:30</th>
<th>IV HM:PO MS – 2:25</th>
<th>Coments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Calculate 200 mg PO MS</td>
<td>B. Calculate 125 mg PO MS</td>
<td>New conversion more conservative, and it’s consistent with Reddy findings.</td>
<td></td>
</tr>
</tbody>
</table>

| Switching from 200 mg PO MS per day to IV HM | C. Calculate 10 mg IV HM | D. Calculate 16 mg IV HM | New conversion seems more aggressive than older conversion ratio. |

But wait! There’s more than one way to pluck a chicken! 200 mg oral morphine → 40 mg oral hydromorphone → 16 mg IV hydromorphone

<table>
<thead>
<tr>
<th>2018</th>
<th>Equianalgesic Doses (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>
## Equianalgesic Opioid Dosing

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>NA</td>
<td>0.15</td>
<td>NA</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
<td>30</td>
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<td>25</td>
</tr>
<tr>
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<td>1.5</td>
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<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10*</td>
<td>20</td>
<td>10*</td>
<td>20</td>
</tr>
</tbody>
</table>

*Not available in the US

Note: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.

IV to Oral Morphine – what’s the dealio?

• Equianalgesic tables range from 1:2 to 1:3
• Supported by Kalso (1990)
  • 20-30 mg of morphine by mouth ~ 10 mg IV or SQ morphine
• Starlander (2011)
  • Conversion factor of 1:2 (calls for individual adjustments)
  • 11 patients, pilot study, not definitive
• Takahashi (2003)
  • Conversion factors between 1:2 and 1:3 (based on morphine and M6G in advanced cancer patients receiving chronic morphine treatment)
• Lasheen (2010) – 1:3 IV to PO confirmed

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</table>
Which is my seat?
Don’t know – I just got you in the ball park!
Patient 6

- WP is a 62-year-old man with multiple myeloma and diffuse bony mets admitted to hospice.
- Current analgesic regimen extended-release oral morphine 30 mg po q12h plus oral morphine solution 10 mg prn (takes six times per day), plus dexamethasone.
- Admitted to inpatient to switch to IV morphine due to continued pain.

- Pain assessed
- TDD oral morphine = 30 mg po q12h = 60
- Oral morphine solution 10 mg x 6 = 60 mg
- TDD = 120 mg oral morphine
- Consult equianalgesic dosing chart for equivalency

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<td>10*</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
</tr>
</tbody>
</table>

TDD – total daily dose
Patient 6

“x” mg new opioid = equivalent mg new opioid
mg of current opioid equivalent mg current opioid

“x” mg IV morphine = 10 mg (IV morphine)
120 mg oral morphine 25 mg (oral morphine)

(x)(25) = (10)(120)
X = 48 mg IV morphine per day
25-50% increase → morphine 10 mg IV q4h (TDD 60 mg)
Patient 6 To Go Points

- You’re converting from morphine to morphine, BUT you’re converting between routes of administration (oral to IV)
  - Morphine IV dose = ~ 1/3 of morphine PO dose
  - So, morphine IV dose is ~ 1/3 morphine PO dose (work in total daily doses for ease of calculation)

- When you do a conversion calculation if you are SWITCHING from one opioid to a DIFFERENT opioid, you usually need to reduce the dose you calculated
  - This patient was going from morphine to morphine so you don’t have to do that

- BUT he is in pain, so you need to increase the dose
Switching

From one formulation or route to another of the SAME opioid
- Account for bioavailability (and genetics and contribution of M6G)
- Increase if patient in pain

From one opioid to another opioid
- Use ratios from equianalgesic chart
- If pain controlled, REDUCE calculated dose by 25-50%
- If patient in pain, use calculated dose, or a little less.
Patient 7

• PR is a 58-year-old man end stage 4 lung cancer, admitted directed to the hospice inpatient unit with a complaint of uncontrolled pain.
• He is started on an IV infusion of hydromorphone at 0.2 mg/hr which was titrated up over 4 days to 0.5 mg/hour with a bolus of 0.2 mg every 15 minutes as needed.
  • PR is using the bolus about 4 times in a 24 hour period.
• It is time to discharge the patient home with hospice care, and you would like to switch him to oral morphine to maintain his current level of pain control.
• What dosage regimen do you recommend?
Patient 7

- 0.5 mg/hr hydromorphone x 24 hours = 12 mg/day, plus four doses of the 0.2 mg IV hydromorphone bolus (0.8 mg) for a TDD of 12.8 mg IV hydromorphone

- \( \frac{\text{x mg PO morphine}}{12.8 \text{ mg IV HM}} = \frac{25 \text{ mg PO morphine}}{2 \text{ mg IV HM}} \)

- \( (2)(x) = (25)(12.8) \)
- \( X = 160 \)
- Reduce by 25% - 120 mg oral morphine a day
- LA MS – MS Contin 60 mg po q12h
- SA MS – Oral morphine 20 mg po q4h

Reddy’s bottom line:
- 1:2.5 (IV hydromorphone to oral hydromorphone)
- 1:10 (IV hydromorphone to oral morphine)
- 1:8 (IV hydromorphone to oral oxycodone)
Patient 7 To Go Points

- Going from one opioid to a different opioid
  - IV hydromorphone to oral morphine
- Reduce slightly for lack of cross tolerance (but our table for this conversion IS built on steady-state data)

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1:10 (IV hydromorphone to oral morphine)
1:8 (IV hydromorphone to oral oxycodone)
Patient 8
Patient 8 – What’s the sitch?

- Mrs. Gladson is a 78 year old woman diagnosed with end-stage hepatic cancer. She was admitted to hospice on MS Contin 15 mg po q12h with oral morphine solution 5 mg every 3 hours as needed for additional pain.
- Hospice RN reports patient is having a pain crisis; she is taking her MS Contin as directed and several doses of oral morphine solution with no relief at all.
- Patient rates pain as greater than a 10 on a 0-10 scale, family is insistent she be admitted to the hospice inpatient unit.
- She is transported to the inpatient unit, arriving at 6 pm. The attending on call is Dr. Doogie Howser (he’s so excited – this is his first position post-fellowship!).
- Dr. Howser calculates that the patient was receiving approximately 40 mg oral morphine in the past 24 hours, which he figures in about 16-mg IV morphine per day (0.6 mg/h)
- He orders a 2.5 mg IV morphine loading dose, and a continuous infusion at 1.2 mg/hour, with an order to titrate to comfort per nursing judgment.
Patient 8 – What’s the sitch?

• The family stays with the patient and keeps the nurse informed as to the patient’s response to the morphine infusion.

• The family is concerned that she’s still complaining of pain that she rates as 9/10 at 8 pm, so the nurse increases the infusion to 3 mg/hour and the clinician bolus to 5 mg.

• At 10 pm the family reports the patient is still grimacing and crying out, so the nurse repeats the 5 mg IV morphine loading dose and increases the continuous infusion to 5 mg/hour.

• The patient seems to settle down, and the family leaves around midnight.

• When the nurse checks on Mrs. Gladson at 3 am, she is nonresponsive, even to sternal rub.

• Her respiratory rate is 6 breaths/minute with periods of apnea. She has pinpoint pupils, and the nurse calls Dr. Howser in a panic.
Patient 8 – What’s wrong with this picture?

A. The family must have increased Mrs. Gladson’s infusion before they left
B. The nurse was trigger happy with the hourly clinician bolus
C. Dr. Howser incorrectly calculated the starting dose of morphine (bolus and infusion)
D. The infusion rate was titrated incorrectly (too quickly)
Patient 8 – What’s wrong with this picture?

A. The family must have increased Mrs. Gladson’s infusion before they left
B. The nurse was trigger happy with the hourly clinician bolus
C. Dr. Howser incorrectly calculated the starting dose of morphine (bolus and infusion)
D. **The infusion rate was titrated incorrectly (too quickly)**

The family didn’t do anything. The nurse gave the hourly bolus as ordered. Dr. Howser’s math was fine. That leaves us with – the order was inappropriate – “titrate to comfort??”

The infusion started at 6 pm, increased at 8 pm and again at 10 pm.

The patient is elderly and has a terminal illness, so her half-life of morphine is probably closer to 5 hours. To get to 87.5% or 93.75% of the way to steady-state it would take 15-20 hours, NOT 4 hours.

The infusion was titrated way too aggressively, too quickly.
Patient 8 – What’s wrong with this picture?

• We need to recognize the two issues at play here:
  • We need to FULLY appreciate the clinical impact of the current continuous opioid infusion dose when it achieves a steady-state serum level (both therapeutic gain and potential toxicity) BEFORE we increase the dose (and make the situation worse, and that always seems to happen at 3 am when no one is really paying close attention); and
  • We don’t want the patient to suffer with pain while we are waiting for the magical moment of steady-state to make sure we haven’t overdosed the patient.

• Doogie, Doogie, DOOGIE...this is why we never let 14 year-olds be doctors – EVER!
Answer is...

• “Why yes, I happen to look good in orange. Why do you ask?”

• “If you start an IV infusion of morphine at 2 mg/hour and order “titrate to comfort,” the consequences may beg the question how you look in orange.”
“Titrate to Comfort” is not a good look

- Half-life of morphine
  - General population 2-3 hours
  - Cancer patients 5 hours
  - Liver impairment 8 or more hours

<table>
<thead>
<tr>
<th>Number t ½</th>
<th>% of Steady State Achieved</th>
<th>2 hour t ½</th>
<th>3 hour t ½</th>
<th>5 hour t ½</th>
<th>8 hour t ½</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>2</td>
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<td>4</td>
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<tr>
<td>5</td>
<td>96.875</td>
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</table>

- More aggressive – increase continuous infusion in 8 -12 hours
“Titrate to Comfort” is not a good look

<table>
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<tr>
<th>Number $t \frac{1}{2}$</th>
<th>% of Steady State Achieved</th>
<th>2 hour $t \frac{1}{2}$</th>
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- Most aggressive – increase continuous infusion in 8 -12 hours
- More conservative – increase continuous infusion in 12-24 hours
Patient 8– Play it again Sam!

- Dr. Howser correctly calculated the patient’s home use of oral morphine (40 mg a day) and converted this to an IV infusion (0.6 mg/hour).
- Given patient’s severe pain he correctly doubled it to 1.2 mg/hour as a continuous infusion.
- He correctly ordered a clinician bolus (for the RN to give as often as hourly) (10-20% of the total opioid taken in the previous 24 hours [10% 16 mg IV morphine equivalent = 1.6 mg; 20% = 3.2 mg])
- He should NOT have ordered “titrate to comfort per nursing judgment” – should have given better guidance.
- “Administer 2.5 mg IV morphine now. Begin continuous morphine infusion at 1.2 mg/hour. Reassess pain every 30 minutes x 3 and repeat 2.5 mg IV bolus dose of morphine if pain decreased but not adequately controlled, or increase to 5 mg if pain unchanged or increased. If pain is not adequately controlled after 3-IV bolus doses, contact prescriber. Do not increase continuous infusion before 8 am (morning rounds).”
Patient 9
Patient 9 – What’s the sitch?

• Mr. Morganstern is a 58 year old man with end-stage lung cancer being discharged from the hospital to home hospice.

• He is receiving a complex opioid regimen, and Dr. Davis wants to switch the whole mess to long- and short-acting morphine.

• The patient is 5’8”, 150 pounds and can swallow tablets and capsules.

• The patient is currently receiving:
  • Transdermal fentanyl 50 mcg/h
  • LA oxycodone 20 mg po q12h
  • Hydromorphone 4 mg IV every 4 hours as needed (getting about 5 doses per day)
  • Hydrocodone/acetaminophen 5/325 mg every 4 hours as needed (not using).
Patient 9 – What’s the sitch?

• Dr. Davis decides this is a pretty complex calculation so he whips out his iPhone and uses an opioid conversion app. The app provides the following conversion information to oral morphine:
  • TDF 50 mcg/h → 180 mg oral morphine per day
  • LA oxycodone 20 mg po q12h → 60 mg oral morphine per day
  • Hydromorphone 4 mg IV q4h prn (5 doses = 20 mg) → 400 mg oral morphine per day
  • GRAND total is 640 mg oral morphine per day.

• Dr. Davis puts the patient on MS Contin 200 mg by mouth every 8 hours with MSIR 60 mg, every 2 hours as needed.

• The patient starts on this regimen, but within a day or so he is extremely lethargic and according to Mrs. Morganstern, “Nobody likes a drunk monkey, and that’s what he is right now!”

• Dr. Davis is shocked! “I used an app – the calculation is impeccable!”
Patient 9 – What’s wrong with this picture?

A. Just because there’s an app for it, doesn’t make it right!
B. Dr. Davis had no idea what assumptions the app made
C. Using an app without doing the math yourself is the lazy pants approach to calculations!
D. All of the above are TRUE TRUE TRUE!
Patient 9 – What’s wrong with this picture?

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D. All of the above are TRUE TRUE TRUE!
Patient 9 – What’s wrong with this picture?

• Dr. Davis returns to the app website. After looking forever, he finds the equianalgesic conversion ratio used by the app, and he compared it to more recent data, as follows:

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<td>TDF mcg/h ~ 50% TDD oral morphine equivalent</td>
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Patient 9 – What’s wrong with this picture?

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- Apps are “plug and chug” calculators – there’s no brain or clinical judgment in the loop!
- Some allow for dose reduction due to lack of complete cross-tolerance, but not all
- Users often lose their sense of “does that LOOK right?”
Patient 9 – Play it again Sam!

• It would have been preferable for Dr. Davis to use a better equianalgesic equivalency table.

• Check your math, ESPECIALLY if you use an app!

• Adjust for patient-specific considerations:
  • Young, old
  • Frail, robust
  • In pain or not in pain
  • Organ dysfunction or not

• Or, call a really good-looking pharmacist!

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</tr>
<tr>
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</tr>
</tbody>
</table>

TDF mcg/h ~ 50% TDD oral morphine equivalent
Variability among online opioid conversion calculators performing common palliative care conversions

Costantino RC, McPherson ML, et al.
Accepted for publication, Journal of Palliative Medicine
Methods

• This study was conducted among a cohort of students enrolled during the summer of 2018 and 2019 in an advanced pain management and opioid dosing course

• Participants were asked to identify three OOCC and complete conversions for three scenarios described in Table 1.
78 year old woman receiving transdermal fentanyl 75 mcg/h. Patient doesn’t seem to be responding despite dose increases. She is 5’4” and weighs 82 pounds. Convert to long-acting oral morphine and determine a dose of short-acting oral morphine for breakthrough pain.

58 year old man with end-stage lung cancer receiving IV hydromorphone, 6 mg/hour with 3 mg bolus every 10 minutes (uses about 3 doses/hour). The pharmacy just called and you just got the last of the IV hydromorphone they have in stock. The patient can swallow tablets and capsules. Calculate an equivalent oral morphine regimen (oral long-acting and short-acting for breakthrough pain).

42 year old man with low back pain, receiving MS Contin 45 mg po q12h, with MSIR 15 mg po q4h as needed (takes 2 doses per day on average). His pain seems to have a neuropathic component. Convert to oral methadone.
## Dosing and Reduced Tolerance Indicator for all Scenarios

<table>
<thead>
<tr>
<th>Break</th>
<th>Scenario A</th>
<th>Scenario B</th>
<th>Scenario C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Frequency</td>
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<td>Reduce Cross Tolerance</td>
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<tr>
<td>No</td>
<td>23</td>
<td>39.66</td>
<td>18</td>
</tr>
</tbody>
</table>
Five-Step Approach to Opioid Conversion

1. Globally assess the patient (i.e., PQRSTU, or another method) to determine if the uncontrolled pain is secondary to worsening of existing pain or development of a new type of pain.

2. Determine the total daily usage of the current opioid. This should include all long-acting and breakthrough opioid doses.

3. Decide which opioid analgesic will be used for the new agent and consult the established conversion tables to arrive at the proper dose of the new opioid, recognizing the limitations of the data.

4. Individualize the dosage based on assessment information gathered in Step 1 and ensure adequate access to breakthrough medication.

5. Patient follow-up and continual reassessment, especially during the first 7–14 days, to fine-tune the total daily dose (long-acting + short-acting) and increase or decrease the around the clock long-acting dosage accordingly.

Patient 10
Patient 10 – What’s the sitch?

- Mrs. Madderhorn is an 82-year-old woman with multiple comorbidities, including: uterine cancer, post-stroke pain, diabetes, heart disease, osteoarthritis (knees, hips, spine) and Alzheimer’s dementia.
- Patient lives in a LTC facility because her care is too great for her family to handle at home.
- Usual BP is 105/70 mmHg, HR 68 bpm, RR 16 bpm
- 5’0”, 86 pounds
- Her appetite is poor, and she appears to be malnourished
- She has been admitted to hospice under the uterine cancer diagnosis
- She had been receiving LA morphine 15 mg by mouth every 12 hours with oral morphine solution for breakthrough (not using) on admission, but as her dementia worsened she started to forget to take her medication
Patient 10 – What’s the sitch?

- Patient was switched to transdermal fentanyl (TDF) 12 mcg/h with oral morphine solution for breakthrough pain, 5 mg every 2 hours as needed.
  - The hospice nurse, Stephanie, observes that Mrs. Madderhorn is exhibiting signs of pain, even though the patient isn’t verbal.
    - Stephanie uses the Checklist of Nonverbal Pain Indicators and decides the patient is in moderate pain; TDF is increased to 25 mcg/h on day 3, and again to 50 mcg/h on day 5.
- Stephanie reports to the team that the patient doesn’t seem to be getting the relief from the TDF patch that you would expect.
- Based on the patient using TDF 50 mcg/h, the physician switched the patient to MS Contin 60 mg po q12h due to continued pain with oral morphine 15 mg every 2 hours as needed for pain.
- Stephanie was instructed to remove the TDF and start LA morphine 12 hours later.
- Within 24-36 hours Mrs. Madderhorn is completed zonked and very hard to wake up. The LTC nurse says she can’t awaken the patient to administer the LA morphine. Uh oh.
Patient 10 – What’s wrong with this picture?

A. The patient was never an appropriate candidate for transdermal fentanyl (TDF)
B. The patient was wasted and cachectic, making her a poor candidate for TDF
C. TDF was titrated too quickly
D. The conversion OFF TDF was incorrectly calculated
E. All of the above (duh)
Patient 10 – What’s wrong with this picture?

A. The patient was never an appropriate candidate for transdermal fentanyl (TDF)
B. The patient was wasted and cachectic, making her a poor candidate for TDF
C. TDF was titrated too quickly
D. The conversion OFF TDF was incorrectly calculated
E. **All of the above (duh)**

She was not receiving \( \geq 60 \) mg oral morphine per day for at least a week. Patient cachectic and unlikely to get full benefit from TDF. Titrated way too quickly – day 3 and day 5
Physician gave her full credit for TDF AND increased the dose of morphine – too aggressive!
Transitioned too quickly to LA morphine (should have waited 24 hours)
Transdermal Fentanyl

- Useful with patients who cannot swallow tablets or capsules
- Mu-opioid receptor agonist; 75-100x potency of morphine
- Metabolized in liver to inactive metabolites; useful in renal patients
- Fat-soluble; large volume of distribution; highly bound to albumin
- Routes of administration
  - Parenteral – IV, IM, SQ, intrathecal
  - Transmucosal – buccal, sublingual, intranasal
  - Transdermal
- Indicated for “the management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.”
Mr. Johnson

• 72-year-old man admitted to hospice with end stage liver cancer
• Lives alone, caregiver visits daily
• Experiencing pain; order for morphine 5 mg po q4h as needed
• Caregiver gives one dose; patient forgets he has it otherwise
• RN suggests TDF 12 mcg/h (lowest dose) every 3 days
• Is this appropriate?

Mr. Johnson is not appropriate for TDF. Cannot use TDF for acute pain, or in opioid-naïve patients.
Other TDF facts

- Available in two formulations
  - Gel-containing reservoir (Duragesic) and drug-in-adhesive matrix
- Drug absorbed via passive diffusion (area of higher to lower concentration)
- Produces drug depot in upper skin layers, then diffuses into systemic circulation
- TDF available as 12, 25, 50, 75, 100 mcg/h
- Usually q72h; 15-20% need q48h
- Apply to chest, back, flank or upper arm (intact skin, non-irritated, non-irradiated; do not shave hair)
- Minimum serum level 12 hours; max in 36 hours; steady state 3-6 days
Other TDF Facts

• Burn, baby, burn
  • Body temperature of 104°F – increases fentanyl concentration by 30%
  • Infectious process, heating pad, electric blanket, tanning bed, sunbathing, hot bath, hot tub, sauna

• Converting to TDF
  • Total daily dose oral morphine (mg/day) / 2 = TDF mcg/h patch strength
  • 100 mg oral morphine per day ~ TDF 50 mcg/h
Cachexia

• Cachectic patients do not get full expected benefit from TDF
• Application site – fat pad?
• Sequestered with albumin in extravascular space
• Be careful switching OFF TDF in cachectic patients
Patient 10 – Play it again Sam!

- If the family had a paid caregiver all along, the caregiver could have given the LA morphine and the breakthrough morphine, avoiding the need to consider TDF.
- Patient was NOT a candidate for TDF (not receiving 60 mg oral morphine per day for at least a week)
- TDF increased too quickly – can increase on Day 3, then every 6 days thereafter
- Converting OFF TDF 50 mcg/h ~ 100 mg oral morphine, then MD increased to 120 mg oral morphine – too high
  - Should have gone back to LA morphine15 mg po q12h (or even used short-acting morphine instead around the clock until the dust settled).
  - Safer to wait 24 hours before starting scheduled morphine; can start PRN dose as soon as the TDF was removed
Did’ja know? Methadone!

Mary Lynn McPherson, PharmD, MA, MDE, BCPS
Professor and Executive Director Advanced Post-Graduate Education in Palliative Care
Graduate.umaryland.edu/palliative
Graduate Certificate | Master of Science | PhD*
Graduate.umaryland.edu/palliative

EDUCATION is LEARNING what YOU didn’t even KNOW you didn’t KNOW

*pending MHEC approval
Case presentation...

• JH is a 52-year-old man admitted to hospice with end-stage colon cancer with mets to the spine, causing neuropathic pain.
• His prescriber has asked you to calculate an equivalent dose of methadone, hoping it may better target the neuropathic pain.
• JH’s current regimen is:
  • LA morphine 30 mg po q12h
  • SA morphine 5 mg for moderate pain, or 10 mg for severe pain q2h prn
    • Patient uses about 30 mg a day
• How do we do this conversion?
Dosing Methadone

- Evaluate patient’s risk status (e.g., QTc prolongation), prognosis, history of medication adherence, interacting medications, pain history

- Opioid naïve patients (and those receiving up to 59 mg OME per day):
  - 2-5 mg oral methadone total daily dose (or even up to 7.5 mg per day if appropriate)
  - Consider interacting medications
    - Anti-infectives, antidepressants, amiodarone

- Opioid tolerant patients

<table>
<thead>
<tr>
<th>Total Daily Dose Oral Morphine Equivalent (OME)</th>
<th>Conversion Ratio to Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-59 mg</td>
<td>Follow opioid naïve dosing</td>
</tr>
<tr>
<td>60-199 mg OME AND &lt; 65 years old</td>
<td>10 mg OME : 1 mg oral methadone</td>
</tr>
<tr>
<td>≥ 200 mg OME AND/OR ≥ 65 years old</td>
<td>20 mg OME : 1 mg oral methadone</td>
</tr>
</tbody>
</table>

McPherson ML, et al. Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper

Dosing Methadone

- Do not increase dose before 5 days
- Do not increase total daily oral methadone dose by more than 5 mg per DAY
  - Once total daily dose is ≥ 30 mg oral methadone, can increase by 10 mg per DAY
- When converting to methadone, do not exceed 30-40 mg oral methadone per day as a starting dose, regardless of previous opioid dose
- Reduce calculated oral methadone dose by 25-30% if patient receiving known enzyme inhibitor
- Assess patient daily for 5-14 days after methadone initiation and adjustment

McPherson ML, et al. Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper
Case presentation...

• JH is a 52-year-old man admitted to hospice with end-stage colon cancer with mets to the spine, causing neuropathic pain.

• JH’s current regimen is:
  • LA morphine 30 mg po q12h
  • SA morphine 5 mg for moderate pain, or 10 mg for severe pain q2h prn
    • Patient uses about 30 mg a day

• Patient’s TDD oral morphine = 90 mg

• < 65 yo, and < 200 mg OME, so 10:1 conversion (9 mg a day oral methadone)
  • No interacting medications

• Recommendation:
  • Methadone 5 mg po q12h
  • Morphine 10 mg every two hours as needed for additional pain
**DOSING METHADONE IN ADVANCED ILLNESS**

- Methadone is a very useful opioid, but requires close attention to detail in dosing and follow-up.
- Evaluate patient's risk status (e.g., QTc prolongation), prognosis, history of medication adherence, interacting medications, pain history.
- **Opioid-naïve patients**: 2-5 mg oral methadone total daily dose (or, up to 7.5 mg per day if appropriate). Consider interacting medications.
- **Opioid-tolerant patients**: Convert patient’s current opioid regimen to oral morphine equivalents (see reserve side).

**Recommended dosing is as follows:**

<table>
<thead>
<tr>
<th>Total Daily Dose Oral Morphine Equivalent (OME)</th>
<th>Conversion Ratio to Oral Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-60 mg</td>
<td>Follow opioid-naïve dosing (above)</td>
</tr>
<tr>
<td>60-199 OME and &lt; 65 years old</td>
<td>10 mg OME : 1 mg oral methadone</td>
</tr>
<tr>
<td>≥ 200 mg OME and/or ≥ 65 years old</td>
<td>20 mg OME : 1 mg oral methadone</td>
</tr>
</tbody>
</table>

**ADDITIONAL GUIDANCE:**

- Do not increase dose before 5-7 days.
- Do not increase total daily oral methadone dose by more than 5 mg/day (can increase by up to 10 mg/day once total daily oral methadone dose is 30-40 mg/day)
- When converting to oral methadone, do not exceed 30-40 mg oral methadone per day as starting dose, regardless of previous opioid dose.
- Reduce calculated oral methadone dose by 25-30% if patient receiving known enzyme inhibitor.
- Assess patient daily for 5-14 days after methadone initiation and adjustment.

**References:** palliative@umaryland.edu

*This is not a substitute for clinical judgment, particularly with complex comorbidities and high morphine equivalents.*

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**University of Maryland Graduate School**

410-706-PALL (7255) | graduate.umaryland.edu/palliative
Did’ja know?

Mary Lynn McPherson, PharmD, MA, MDE, BCPS
mmcphers@rx.umaryland.edu
Sign up for “Did’ja know?”

“EDUCATION is LEARNING what YOU didn’t even KNOW you didn’t KNOW

*pending MHEC approval
Patient 11
Patient 11 – What’s the sitch?

• Ms. Ives is a 32-year-old woman with end-stage cervical cancer, referred to hospice.

• On admission she is receiving IV morphine 30 mg/hour, with a 10-mg bolus every 15 minutes as needed (using at least once, often twice, per hour).

• Her 24-hour use of IV morphine is 1,080 mg, which is about equivalent to 2,700 mg oral morphine per day.

• Wow, that’s a lotta morphine!

• The attending physician, Dr. Rosenthal says, “This dose of morphine is ridiculous! She can swallow and she has a fair prognosis – let’s switch her to methadone.”

• Dr. Rosenthal asks you to do the conversion calculation. Oh my – where to start – so many methods recommended in the literature!
Patient 11 – What’s the sitch?

• You decide to use the Ayonrinde methadone which calls for a 20:1 (oral morphine:oral methadone) conversion for a total daily oral morphine dose over 1001 mg/day. This calculates to 135 mg oral methadone per day.

• The patient declines to be admitted as an inpatient (she’s a single mother with three small children at home), so you decide to do this as a rapid switch at home.

• You stop the morphine infusion, start methadone 45 mg by mouth every 8 hours, and you decide to use morphine 60 mg by mouth every 2 hours as needed for breakthrough pain.

• For the first couple of days things are a little rough; the patient uses the morphine breakthrough pain dose frequently.

• They by Day 2-3, things are starting to look up. The patient has achieved a reasonable level of pain control, and she’s actually happy to not be dragging the IV pump around with her.

• Day 4 she complains of being really sleepy, and Day 5 she can’t get OOB. What’s the scoop?
Patient 11 – What’s wrong with this picture?

A. Ayonrinde was all washed up
B. Research has shown there should be a MAXIMUM starting dose of methadone
C. You shouldn’t have included the breakthrough morphine doses in your calculation
D. The conversion should have been done over three days instead of a rapid switch
Patient 11 – What’s wrong with this picture?

A. Ayonrinde was all washed up
B. Research has shown there should be a MAXIMUM starting dose of methadone
C. You shouldn’t have included the breakthrough morphine doses in your calculation
D. The conversion should have been done over three days instead of a rapid switch

Ayonrinde was NOT all washed up, but Dr. Eduardo Bruera argues WHY there is a sort of proposed maximum starting dose for methadone, regardless of how much opioid you are switching FROM:

- Slight binding differences at the opioid receptor
- Methadone has multiple mechanisms of action
- High dose of current opioid may be proalgesic (causing pain – hyperalgesia)

• Chatham and colleagues reported a series of 10 patients receiving very high-dose morphine, and the vast majority were convert to, and stabilized on methadone 10 mg po q8h.

• APS guidelines on methadone use suggest starting no higher than 30-40 mg oral methadone per day
Patient 11 – Play it again Sam!

• This is a huge conversion, would be better accomplished inpatient
• Or, so a partial conversion over several weeks
• Last, the maximum starting dose of methadone should not exceed 30-40 mg a day
• Close follow-up is critically important!
## Initiating Methadone (HPM)

<table>
<thead>
<tr>
<th>OME per day</th>
<th>Recommended Methadone Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 – 60 mg</td>
<td>2-7.5 mg po qd in 2-3 divided doses</td>
</tr>
<tr>
<td>&gt; 60 – 199 mg (and &lt; 65 yo)</td>
<td>10:1 (morphine : methadone)</td>
</tr>
<tr>
<td>&gt; 200 mg (+/or ≥ 65 yo)</td>
<td>20:1 (morphine : methadone)</td>
</tr>
</tbody>
</table>

- Do not exceed 30 mg methadone per day as a starting dose
- Reduce calculated dose by 25-33% if enzyme inhibiting medication on board
- Do not adjust dose for 5-7 days (or per clinical judgement)
The road to steady-state

Figure 6-1. Steady-state methadone concentration reached in about 5 days. Source: Addiction Treatment Forum: Methadone Dosing and Safety in the Treatment of Opioid Addiction, Stewart B. Leavitt, PhD.

Used with permission Pain Topics
Maximum TDD Conversion

<table>
<thead>
<tr>
<th>Pt</th>
<th>Prior MPSS</th>
<th>Stabilized MPSS</th>
<th>Initial methadone dose</th>
<th>Stabilized methadone dose</th>
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<tbody>
<tr>
<td>1</td>
<td>9.0</td>
<td>6.0</td>
<td>5 mg po q6h</td>
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<td>2</td>
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<td>15 mg po q8h</td>
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<td>7.0</td>
<td>0</td>
<td>10 mg po q8h</td>
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Pt, patient; MPSS, median pain scale score.

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<thead>
<tr>
<th>Enzyme Inducers</th>
<th>Enzyme Inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Rifampicin / rifampin</td>
<td>Amiodarone</td>
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<tr>
<td>Rifabutin</td>
<td>Fluconazole</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Paroxetine</td>
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<tr>
<td>Spironolactone</td>
<td>Sertraline</td>
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<tr>
<td>Nevirapine</td>
<td>Ciprofloxacin</td>
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<td>Ritonavir</td>
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<tr>
<td>Ritonavir</td>
<td>Carbamazepine</td>
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<tr>
<td></td>
<td>Amiodarone</td>
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<tr>
<td></td>
<td>Fluconazole</td>
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<td>Amitriptyline</td>
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<tr>
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<td>Troleandomycin</td>
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<td>Citalopram</td>
</tr>
<tr>
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<td>Desipramine</td>
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<tr>
<td></td>
<td>Clarithromycin</td>
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<tr>
<td></td>
<td>Telithromycin</td>
</tr>
<tr>
<td></td>
<td>Itraconazole</td>
</tr>
</tbody>
</table>

http://medicine.iupui.edu/clinpharm/ddis/
Drugs that prolong QTc

- Clarithromycin, erythromycin
- Quetiapine, haloperidol
- TCA’s
  - Amitriptyline, desipramine, imipramine, nortriptyline
- Cocaine

Patient 12

• AO is a 64-year-old woman with end-stage breast cancer. She is taking extended-release morphine 60 mg by mouth q12h with morphine oral solution 20 mg by mouth q2h prn breakthrough pain (using about 2 doses qd).

• The morphine makes her itch, and diphenhydramine makes her too sleepy. Her physician would like to switch her to methadone. AO not taking any interacting medications.

• Step 1 - PQRST

• Pain is nociceptive and neuropathic; pain in chest area, numbness and tingling from axilla, down arm
Patient 12 – Step 2 (TDD Opioid)

• She is taking extended-release morphine 60 mg by mouth q12h with morphine oral solution 20 mg by mouth q2h prn breakthrough pain (using about 2 doses qd).

• TDD = 60 mg x 2 = 120 mg PLUS 20 x 2 = 40 mg for a TDD of 160 mg oral morphine

• If patient is not already taking oral morphine, convert to oral morphine
  – Refer to equianalgesic dosing chart
  – Consider LA and SA opioid use
  – Do not reduce for lack of complete cross-tolerance

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Parenteral</th>
<th>Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.15</td>
<td>NA</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
<td>25</td>
</tr>
<tr>
<td>Hydromorphone</td>
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<td>5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10 (not in US)</td>
<td>20</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>


NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.
Patient 12 – Step 3 – Conversion

• Patient’s TDD oral morphine is 160 mg; < 65 years old
• Use 10:1 conversion
  – Methadone 16 mg TDD
  – Recommendation: 8 mg po q12h (or 5 mg po q8h)
• No interacting medications
  – No need to reduce methadone dose
• What to do for rescue medication?
  – Methadone?
  – Morphine or oxycodone – 10-15% TDD
    • Morphine (MSIR) 15 mg by mouth q4h prn breakthrough pain
• Rapid switch or gradual?

TDD – total daily dose
Patient 12 – Step 5: Patient Monitoring

• Ask AO’s husband to observe AO several times a day for changes in her respirations (depth, rhythm, rate), difficulty awakening her, snoring, and other signs of opioid overdose.
• We will see or speak to AO/husband daily over the next week.
• Do not adjust therapy before 5-7 days.
Mrs. Juniper is an 84 year old woman residing in a long-term care facility, admitted to hospice with a diagnosis of Alzheimer’s dementia.

She also has a long history of chronic low back pain (spinal stenosis) and osteoarthritis of both knees and hips.

She is bedbound for much of the day, and shifts about restlessly. The nurse case manager believes this is due to physical discomfort.

The patient was admitted to hospice on OxyContin 20 mg by mouth every 12 hours, and oxycodone oral solution 5 mg every 2 hours as needed for additional pain (not receiving).

You decide to switch her to methadone. Not receiving any interacting drugs.
The patient was admitted to hospice on OxyContin 20 mg by mouth every 12 hours, and oxycodone oral solution 5 mg every 2 hours as needed for additional pain (not receiving).

Her total daily dose of oral oxycodone is 40 mg

How do you convert this to oral morphine equivalents per day?
1. Assess patient’s pain complaint thoroughly; is pain controlled (at goal?).

2. Determine average total daily dose of current opioid use (long- and short-acting).

3. Set up ratio using equianalgesic equivalence chart; calculate new dose.


5. Monitor patient closely; adjust as needed.

<table>
<thead>
<tr>
<th>Opioid Parenteral</th>
<th>Opioid Parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10 (not in US)</td>
</tr>
<tr>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>


NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.
Patient 13

• Total daily dose of oxycodone is 40 mg

• “x” mg oral morphine = 25 mg oral morphine
  40 mg oral oxycodone  20 mg oral oxycodone

• (20)(x) = (25)(40)

• X = 50 mg oral morphine

• Because you are using this number to convert to methadone, no need to adjust
Patient 13

- 84 years old (> 65 years old)
- Receiving 50 mg OME per day
- Defaults to opioid naïve dosing
- Methadone 1 mg by mouth every 8 OR 12 hours
- Methadone 2 mg by mouth every 12 hours
- Oral morphine solution 5 mg by mouth as needed for additional pain every 2 hours

OME – oral morphine equivalent
Patient 14

• Mr. J. is a 62-year-old man admitted to home-based hospice with a diagnosis of end-stage prostate cancer, with widespread metastases to the bone.

• He is 5’8” and weighs 165 pounds (normal body habitus)

• Mr. J. is on a transdermal fentanyl patch 75 mcg/h, changed every 72 hours.

• He also has an order for oral morphine solution 20 mg every 2 hours as needed for additional pain (about 5 doses/day).

• His pain is not well managed on this regimen and he wants to switch to a different opioid. Not on any interacting medications.
You decide to switch him from transdermal fentanyl to methadone, and to add dexamethasone for the metastatic bone pain (no history of diabetes or serious gastrointestinal issues)

How do you determine the oral morphine equivalent of his current regimen?

What dose of methadone do you recommend starting?

How would you time removing the transdermal fentanyl patch and starting oral methadone?

All EXCELLENT questions!
Patient 14

• How do you determine the oral morphine equivalent of his current regimen?
  • TDF in mcg/h ~ 50% of total daily dose oral morphine
  • TDF 75 mcg/h ~ 150 mg oral morphine
  • Plus five doses of morphine 20 mg a day = 100 mg
  • TDD oral morphine ~ 250 mg
What dose of methadone do you recommend starting?

- 62 years old
- > 200 mg oral morphine per day (he’s receiving 250 mg oral morphine)
- 20:1 (20 mg OME:1 mg oral methadone) → 12.5 mg oral methadone per day

Considerations

- He’s not that much > 200 mg oral morphine a day
- Is he a “young” 62 year old or an “old” 62 year old?
- But you’re adding a co-analgesic which COULD give you a significant opioid-sparing effect
- Be conservative with scheduled methadone, but generous with breakthrough
Patient 14

• Recommendation:
  • Methadone 7 mg by mouth every 12 hours (methadone 10 mg/ml)
  • Patient tells you a 20 mg dose of oral morphine brings pain down about 2 points
  • Morphine solution 20 mg by mouth every 2 hours as needed for moderate pain, OR
  • Morphine solution 30 mg by mouth every 2 hours as needed for severe pain

• How would you time removing the transdermal fentanyl patch and starting oral methadone?
Patient 14

• How would you time removing the transdermal fentanyl patch and starting oral methadone?

• Once the oral methadone solution is IN THE HOME, remove the transdermal fentanyl patch

• Start methadone 8 hours later

• Use oral morphine solution (at 20 or 30 mg q2h prn)
Patient 14

Patient’s opioid log

<table>
<thead>
<tr>
<th>Day</th>
<th>Methadone</th>
<th>Morphine</th>
<th>Avg Pain Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Removed TDF at 8 am, one dose methadone 7 mg at 8 pm</td>
<td>4 doses x 30 mg 2 doses x 20 mg = 160 mg OME</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Methadone 7 mg at 8 am and 8 pm</td>
<td>5 doses x 30 mg 2 doses x 20 mg = 190 mg OME</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>Methadone 7 mg at 8 am and 8 pm</td>
<td>3 doses x 30 mg 3 doses x 20 mg = 150 mg OME</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Methadone 7 mg at 8 am and 8 pm</td>
<td>2 doses x 30 mg 2 doses x 20 mg = 100 mg OME</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>Methadone 7 mg at 8 am and 8 pm</td>
<td>4 doses x 20 mg = 80 mg OME</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>Methadone 7 mg at 8 am and 8 pm</td>
<td>4 doses x 20 mg = 80 mg OME</td>
<td>4-5</td>
</tr>
</tbody>
</table>

What would you like to do at this time? Pain goal < 3.
Patient 14

• Do not increase methadone before 5 days
• Do not increase by more than 5 mg/day (until TDD methadone > 30 mg)
• Patient currently on methadone 7 mg by mouth every 12 hours
• Increase methadone to 9 mg (or even 10 mg) by mouth every 12 hours
• Maintain oral morphine as prescribed for breakthrough pain
Methadone as a co-analgesic

- Patients with advanced illness may experience opioid dosage escalation
  - Disease progression
  - Tolerance to opioid
  - Development of opioid-induced hyperalgesia
  - Poorly opioid-responsive pain
- May in part be due to NMDA receptor activation
- Methadone is an NMDA receptor antagonist
- Using methadone as a co-analgesic may be beneficial, especially with patients close to death
Methadone as a co-analgesic

- 146 cancer pain patients on chronic opioid therapy
- Median oral morphine dose was 120 mg/day
- Added methadone, median dose was 3 mg a day
- 72/146 patients (49.3%) had ≥30% reduction in pain
- Median time to first significant response was seven days

Methadone as a co-analgesic

- 20 cancer patients in an outpatient palliative care clinic
- Mean daily routine oral morphine:
  - 338 +/- 217.8 mg at initiation of study
  - 332 +/- 191 mg at evaluation (one month or closest available date)
- Methadone added as co-analgesic:
  - 4.4 +/- 1.4 mg/day at initiation
  - 15.5 +/- 5.9 mg at evaluation
- 15/20 patients achieved decrease in pain score by 2 points at one month or first evaluation

Wallace et al. J Pall Med 2013;16(20:305-309.)
Methadone by different routes

- Oral methadone = transmucosal methadone = rectal methadone
- Switching from oral methadone to parenteral methadone
  - TDD oral methadone → divide in half for TDD parenteral methadone
- Switching from parenteral methadone to oral methadone
  - TDD parenteral methadone → multiply by 1.3 for TDD oral methadone
Opening the Door...

- We know people diagnosed with a serious illness have a thousand thoughts running through their head
  - Physical
  - Emotional
  - Spiritual
  - Practical
  - Financial
  - Work vs. home
  - Family

Questions....

- What do you fear?
- What do you hope for?
- What’s bothering you the most?
- What helps you cope?
- What do I need to know about you to provide the best care I can?
Treating Uncontrolled Pain in an IPU: Non-parenteral opioid options

Mary Lynn McPherson, PharmD, MA, MDE, BCPS
National Consultant Pharmacist
lmcpherson@seasons.org | 443-822-6036
Patient opioid-naïve, but with pain crisis or uncontrolled pain, regardless of ability to swallow

- Use oral morphine solution 20 mg/ml
- 5 mg (0.25 ml) in the buccal cavity every 30 minutes until pain drops 30%, up to 4 doses
- If no response after 4 doses, contact prescriber or clinical pharmacist as needed
- Doses may be increased 50-100% every two hours
- Morphine is available as a 20 mg/ml oral solution (intensol)
- Enclara can compound a higher concentration (40 mg/ml)
Patient opioid-naïve and in pain, but not a crisis situation and patient can swallow tablets or capsules.

- Use oral morphine solution by mouth, 5-10 mg every 4 hours, with 5-10 mg every 1-2 hours as needed.
- Once pain is stabilized, consider switching to long-acting oral morphine, or methadone.
Patient opioid-tolerant, but can swallow tablets or capsules, with uncontrolled pain

- Evaluate pain; is the pain an opioid-responsive pain?
- Would adding a corticosteroid or other adjunctive analgesic help?
- If opioid-responsive pain, continue opioid regimen prior to admission.
- Consider switch to oral morphine, perhaps increase by 25-50%. Add oral morphine solution for breakthrough pain at 20% of total daily scheduled dose, and offer hourly.
- If patient continues to require four or more doses of breakthrough per day, consider increasing scheduled opioid dose (if opioid-responsive pain).
- Consider methadone, particularly for multi-pathology type pain (nociceptive and neuropathic)
Patient already receiving parenteral morphine or hydromorphone

• Calculate total daily dose of IV dilaudid and multiply by 10 – that’s your total daily dose of oral morphine
  • Patient can swallow – use long-acting oral morphine (e.g., MS Contin) plus oral morphine solution for breakthrough pain hourly (20% of total daily dose)
  • Patient cannot swallow tablets or capsules – switch entirely to regularly scheduled oral morphine solution every 4 hours to replace IV dilaudid, plus oral morphine solution for breakthrough pain hourly
• Consider methadone oral solution (10 mg/ml) as an alternative, with oral morphine solution (20 mg/ml) for breakthrough as needed hourly

IV Dilaudid
Patient already receiving parenteral morphine or hydromorphone

**IV Morphine**

- Calculate total daily dose of IV morphine and multiply by 3 – that’s your total daily dose of oral morphine.
  - Patient can swallow – use long-acting oral morphine (e.g., MS Contin) plus oral morphine solution for breakthrough pain hourly (20% of total daily dose)
  - Patient cannot swallow tablets or capsules – switch entirely to regularly scheduled oral morphine solution every 4 hours to replace IV dilaudid, plus oral morphine solution for breakthrough pain hourly
  - Consider methadone oral solution (10 mg/ml) as an alternative, with oral morphine solution (20 mg/ml) for breakthrough as needed hourly
Patient cannot swallow tablets or capsules, buccal route not feasible

- Sometimes patient with excess oral secretions don’t absorb medications from the buccal cavity well.
- If patient is stable (even if severe), you can insert MS Contin tablet rectally (similar bioavailability, but delayed onset of action), transdermal fentanyl (if receiving at least 60 mg a day oral morphine, and normal body habitus), or methadone.
More on intensols!

- Morphine available as 20 mg/ml (40 mg/ml compounded)
- Methadone 10 mg/ml
- Hydromorphone 4 mg/ml (compounded 10 mg/ml)
- Alprazolam 1 mg/ml
- Dexamethasone 1 mg/ml
- Diazepam 5 mg/ml
- Lorazepam 2 mg/ml
- Oxycodone 20 mg/ml (very expensive), (40 mg/ml compounded and less expensive than 20 mg/ml)
- Prednisone 5 mg/ml
Even MORE about intensols!

- Tips for administering intensols
  - Prop upper body up 30 degrees
  - Instill no more than 1-1.5 ml oral intensol in the buccal cavity
  - You can always administer a lower dose more frequently to get the volume in
    - Patient on morphine 40 mg every 4 hours = 2 ml
    - You could give morphine 20 mg every 2 hours (1 ml/dose) to get in total daily dose
  - The lipophilicity of the drug determines how much gets actually absorbed transmucosally.
  - The balance of the dose trickles slowly down the throat and gets absorbed orally.
Equianalgesic Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equianalgesic Doses (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parenteral</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
</tr>
<tr>
<td>Codeine</td>
<td>100</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.15</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2</td>
</tr>
<tr>
<td>Meperidine</td>
<td>100</td>
</tr>
<tr>
<td>Methadone</td>
<td>See Chapter 6</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10*</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>NA</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100*</td>
</tr>
</tbody>
</table>

* Not available in the U.S.

Equianalgesic data presented in this table are that which are most commonly used by healthcare practitioners, but they are approximate. The clinician is urged to read the following considerations, along with the information in this text, and use good clinical judgment at all times.

Remember—these are NOT opioid DOSES for individual patient use, this is equivalency information.

Case 1

- Mr. Smith is an opioid-naïve 74-year-old admitted to hospice with end-stage prostate cancer (widespread mets). He’s been doing fairly well, taking an occasional acetaminophen or ibuprofen for pain control. His wife calls the on-call nurse today, frantic, exclaiming “All he did was reach over to grab the TV remote control and he experienced a sudden, intense pain in his ribs on the right. He is howling in pain – what should I do? Should I call 911?” What do you advise?
  
  A. Absolutely, call 911
  
  B. No, the nurse case manager is on her way; open the comfort pak and take morphine 5 mg. The nurse should be there in 30 minutes or less.
  
  C. No, the nurse case manager is on her way; open the comfort pak and take morphine 10 mg. The nurse should be there in 30 minutes or less.
  
  D. Please jump in the car and drive Mr. Smith to our inpatient unit; our nurse will meet you there
Case 1

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  D. Please jump in the car and drive Mr. Smith to our inpatient unit; our nurse will meet you there
Mrs. Johnson is a 62-year-old woman with end-stage breast cancer receiving hospice care at home. She has been experiencing quite a bit of pain due to her widespread disease. She is currently receiving MS Contin 30 mg po q12h, oral morphine solution 5 mg po q2h prn (which she’s taking about 8-9 times a day), dexamethasone 2 mg po once daily. Her pain continues to escalate; she’s quite tearful and a decision was made to admit her to the inpatient unit. How should the physician proceed when Mrs. Johnson arrives in the IPU?

I. Perform a careful assessment to assure the patient’s pain is opioid responsive
II. Increase dexamethasone to 4 mg po bid (assuming no contraindications, and patient does have confirmed bone metastases)
III. Increase oral morphine to MS Contin 60 mg po q12h and increase oral morphine solution to 20 mg hourly as needed
IV. Begin a morphine infusion at 1.5 mg/hour with a bolus of 1 mg every 15 minutes
   A. I and II
   B. II and III
   C. I, II and III
   D. I, II, and IV
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A. I and II
B. II and III
C. I, II and III
D. I, II, and IV
Case 3

Which of the following is an important action step when administering an intensol solution (e.g., oral morphine solution 20 mg/ml):

A. Prop the patient’s upper body up 30 degrees to avoid aspiration
B. Instill up to 1.5 ml of the oral intensol in the buccal cavity
C. Make sure the patient is wide awake before administering the intensol
D. A and B are correct
E. A, B and C are correct
Case 3

Which of the following is an important action step when administering an intensol solution (e.g., oral morphine solution 20 mg/ml):

A. Prop the patient’s upper body up 30 degrees to avoid aspiration
B. Instill up to 1.5 ml of the oral intensol in the buccal cavity
C. Make sure the patient is wide awake before administering the intensol
D. A and B are correct
E. A, B and C are correct
Mr. Hunter is a 58-year-old man with end-stage colon cancer, who was admitted to hospice directly to the IPU due to uncontrolled pain. He has been titrated on a morphine infusion IV to 3 mg/hour, with a 2 mg bolus every 15 minutes as needed (he uses about 3-4 in 24 hours). His average pain rating has decreased from a 10 to a 4-5 which he finds close to acceptable. You just got the news that your supplier has run out of parenteral morphine and you only have a 24-hour supply remaining. The patient cannot easily swallow tablets or capsules. His only other medications include haloperidol 1 mg prn nausea, and lorazepam prn sleeplessness or anxiety. What do you recommend?

A. Put two MS Contin 60 mg tablets in a gelatin capsule and insert rectally every 12 hours. Order oral morphine solution 30 mg for breakthrough pain every 2 hours as needed (in buccal cavity).

B. Order methadone 8 mg po every 8 hours, and oral morphine solution 30 mg prn additional pain every 2 hours. Administer both in buccal cavity.

C. Order methadone 5 mg po every 8 hours, and oral morphine solution 20 mg prn additional pain every 2 hours. Administer both in buccal cavity.

D. Switch to IV hydromorphone 0.5 mg/hour continuous infusion, and IV hydromorphone 0.5 mg every 15 minutes as needed for additional pain.
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C. Order methadone 5 mg po every 8 hours, and oral morphine solution 20 mg prn additional pain every 2 hours. Administer both in buccal cavity.

D. Switch to IV hydromorphone 0.5 mg/hour continuous infusion, and IV hydromorphone 0.5 mg every 15 minutes as needed for additional pain.
Mrs. Chalk is a 48-year-old woman with end-stage COPD, in the IPU for poorly controlled pain. She is receiving IV hydromorphone 0.2 mg/hour continuous infusion, and a 0.1 mg bolus every 15 minutes as needed (rarely uses). Her pain is now well controlled, and she is ready for discharge home. Her husband would like to continue the IV hydromorphone at home since it’s worked so well for Mrs. Chalk. Unfortunately, you have heard about the impending parenteral hydromorphone shortage, and you and Mrs. Chalk have discussed that it would sure be nice to go home on an oral regimen. Which of the following regimens would be acceptable to switch to?

A. IV morphine 1 mg/hour continuous infusion, plus 0.5 mg every 15 minutes as needed.
B. Oral hydromorphone 2 mg po q4h, and hydromorphone 1 mg po q2h prn
C. Exalgo (once daily oral hydromorphone) 12 mg po qd with hydromorphone 1 mg po q2h prn
D. MS Contin 30 mg po q12h with oral morphine solution 10 mg po q2h prn
E. MS Contin 60 mg po q12h with oral morphine solution 15 mg po q2h prn
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A. IV morphine 1 mg/hour continuous infusion, plus 0.5 mg every 15 minutes as needed.
B. Oral hydromorphone 2 mg po q4h, and hydromorphone 1 mg po q2h prn
C. Exalgo (once daily oral hydromorphone) 12 mg po qd with hydromorphone 1 mg po q2h prn
D. MS Contin 30 mg po q12h with oral morphine solution 10 mg po q2h prn
E. MS Contin 60 mg po q12h with oral morphine solution 15 mg po q2h prn
Treating Uncontrolled Pain in an IPU: Non-parenteral opioid options

Mary Lynn McPherson, PharmD, MA, MDE, BCPS
National Consultant Pharmacist
lmcperson@seasons.org | 443-822-6036
When the Going Gets Tough, The Tough Get Going!
Complex Pain Management in Serious Illness

Mary Lynn McPherson, PharmD, MA, MDE, BCPS; Professor, University of Maryland Baltimore
Executive Program Director, Online Master of Science and Graduate Certificate Program in Palliative Care
Graduate.umaryland.edu/palliative | mmcphers@rx.umaryland.edu | @mlmcpherson