Coleman Supportive Oncology Initiative

Palliative Training Module

Topic: **Pain Management: Beyond the Basics**

Presenters: Shelly Lo, MD and Joanna Martin, MD

Version: 08072017

Learning Objectives

By the end of this module you should be able to:

1. **Explain treatment options for pain management, including opioids and adjuvant pain medications**
2. **Describe opioid pharmacology**
3. **Discuss optimal dosing of opioids**
4. **Convert from one opioid to another**

We suggest you do the Palliative Training Module #1, "Pain Assessment: The Basics", *before* this module.

Treatment Options:

Pain Medications

WHO Ladder
Around-the-clock administration of:

- Nonopioids for mild pain
- Mild opioids (codeine) for moderate pain
- Strong opioids

Adjuvant medications

- Drugs not usually thought of as analgesics
- May help relieve pain not fully responsive to opioids

Psychosocial/Behavioral coping strategies

Spiritual Intervention

Physical Activity

Massage, Music, Art Therapy

TLC Treatment

- Keep clean and dry
- Position comfortably
- Provide reassuring words
- Give human touch

Opioid Pharmacology

- **In 2013, 16,235 deaths in the US involved opioid analgesics. Most overdoses on opioids not prescribed to the person are from opioids given by friends or family.**
- **Majority of opioids are conjugated in the liver**
- **90-95% are excreted by kidneys**
- **Reach their peak analgesic effect approximately:**
  - 60 to 90 minutes after oral administration (including enteral feeding tube) or rectal administration
  - 30 minutes after subcutaneous, intramuscular
  - 6 minutes after intravenous injection
  - Steady state plasma concentrations usually attained within 1 day
- **Half Life of 3-4 hours, Reaches a steady state after 4-5 half-lives**

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain

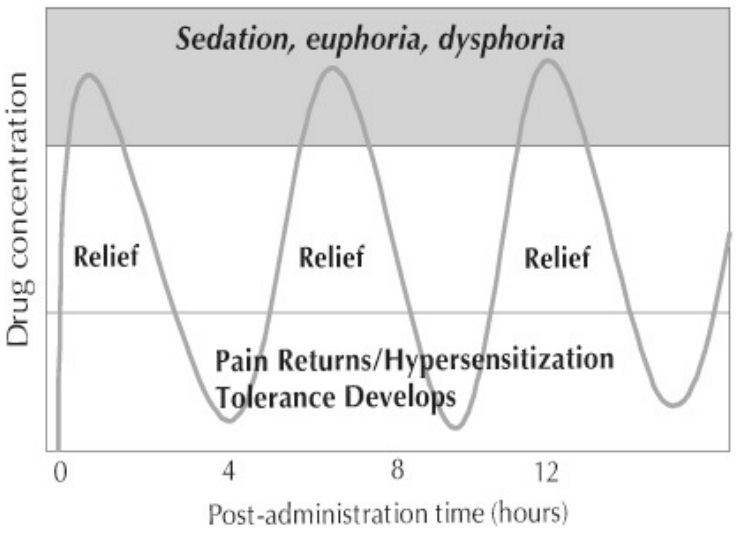
EPEC™-O, Education In Palliative And End-Of-Life Care For Oncology, Self-Study Module 2: Cancer Pain Management. Available at http://www.cancer.gov/resources-for/hp/education/epeco/self-study/module-2/module-2-pdf

Russell K Portenoy, MD, Zankhana Mehta, MD, Ebtesam Ahmed, PharmD, MS. Up To Date. Cancer pain management with opioids: Optimizing analgesia.

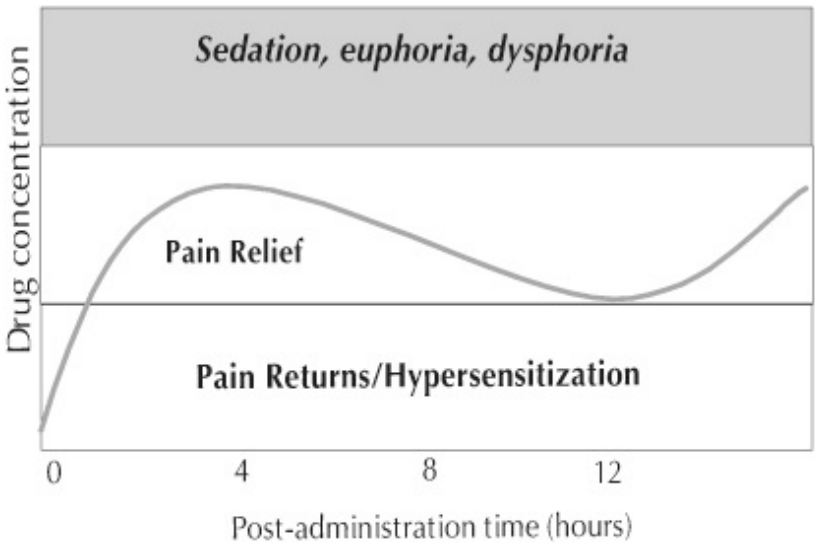
U.S. Food and Drug Administration, Full prescribing information for morphine sulfate injection USP. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202515s000lbl.pdf

Optimal Dosing of Opioids: Around-the-Clock (ATC) Dosing

PRN Dosing



ATC Dosing



Reprinted from The Permanente Journal, Fall;9(4), Whitten, Donovan, Cristobal, Treating chronic pain: new knowledge, more choices, 9-18: Figure 7 and Figure 8, (2005), with permission from ©The Permanente Press. www.thepermanentejournal.org

Short Acting Oral Opioids

- **Examples of short acting oral opioids are:**
  - Codeine
  - Hydrocodone
  - Morphine
  - Hydromorphone
  - Oxycodone
- **Peak analgesic effect occurs in 60-90 minutes, with an expected total duration of analgesia of 2-4 hours**
  - Dose every 4 hours
  - Adjust dose daily
    - Mild/moderate pain: increase by 25-50%
    - Severe/uncontrolled pain: increase by 50-100%
  - Adjust more quickly for severe, uncontrolled pain as necessary; can be dosed every 2 hours
  - After 2-3 cycles, for subsequent management and treatment

    See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Adult Cancer Pain, PAIN-6

For additional resources, see also: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain
Fast Facts and Concepts #18, Medical College of Wisconsin, Short-Acting Oral Opioid Dosing Intervals, 2nd ed

Extended-Release Opioids--Oral

- **Improve compliance and adherence**
- **Calculate total opioid dose used in 24 hours**
- **Convert to a long-acting opioid dose**
  - Morphine ER, oxycodone ER, fentanyl patch
- **Oral dosing every 8, 12, or 24 hours (product-specific)**
  - Do not crush or chew tablets
  - May flush time-release granules down feeding tubes
- **Adjust dose every 2-4 days (once steady state is reached)**

For additional resources, see also NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain

Extended Release Opioids--Transdermal Fentanyl Patch

- **Convenient, non-oral administration**
- **Replace patch every 72 hours for most patients**
- **Therapeutic blood levels reached 13-24 hours after patch application**
- **Drug will continue to be released into the blood for at least 24 hours after patch removal**
- **Place patches on non-irradiated, hairless skin**
- **Direct heat applied over the patch can increase drug absorption with increased toxic effects**
- **There are no data that cachectic patients have reduced efficacy due to loss of subcutaneous fat**

For additional resources, see also NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain

Breakthrough Pain Dosing of Opioids

- **Use Short-acting opioids for breakthrough pain:**
  - 10-20% of total 24 hour dose[1]
  - Offer after steady state plasma concentrations reached
    - Oral (PO, PR) ≈ every 1 hour
    - Subcutaneous (SC, IM) ≈ every 30 minutes
    - Intravenous (IV) ≈ every 10–15 minutes
- ***Do NOT* use extended-release opioids for breakthrough**

[1]Goroll A., Mulley, A., (2014) Primary Care Medicine: office evaluation and management of the adult patient.

For additional resources, see also NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain

Opioid Conversion

1. **Calculate total daily dose of opioid, including as-needed doses**
2. **Convert to another opioid, using equi-analgesic table:**
   See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Adult Cancer Pain, Table 1 PAIN-E (6 of 12)
   http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf
3. **If pain control is good, reduce dose by 25-50% (to allow for incomplete cross-tolerance between opioids); no dose reduction if pain control is poor**
4. **Re-assess in 1-3 days**

For additional resources, see also NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain

Opioid Conversion Case

How to convert hydromorphone 2 mg IV q3 hours given around the clock to extended-release morphine dosed q12 to short acting oral opioids for breakthrough (assuming adequate pain control)?

1. Calculate the 24 hr current dose of IV hydromorphone:
   2 mg x 8 doses = 16 mg of hydromorphone in 24 hours

2. To convert from IV hydromorphone to oral morphine:
   Equi-analgesic ratio of IV hydromorphone to oral morphine:
   16 mg hydromorphone = 320 mg oral morphine (20:1 ratio)

3. Reduce dose by 25-50% if adequate pain control:
   75% of 320 mg = 240 mg/day of oral morphine.
   Can be divided in 2 daily doses of 120 mg (MS ER 60 mg, 2 tabs BID),
   or more conservatively at MS ER 100 mg, 1 tab BID

4. Calculate PRN dose (approx. 10% of total daily opioid dose):
   10% of 240 mg morphine = 24 mg.
   Can be given as a 1 ml of a 20 mg/ml solution (20 mg),
   1 morphine sulfate immediate release 15 mg tab (15 mg),
   1.5 tabs of morphine sulfate immediate release 15 mg (22.5 mg) or
   1 morphine sulfate immediate release 30 mg tab (30 mg)

Equi-Analgesic Dosing Table Option B: NCCN Table, Pain-E, 6 of 12

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (6 of 12)

Table 1. Oral and Parenteral Opioid Equivalences and Relative Potency of Drugs as Compared with Morphine Based on Single-Dose Studies

Opioid Agonists	Parenteral Dose	Oral Dose	Factor (IV to PO)	Duration of Action[11]
Morphine[4,5]	10 mg	30 mg	3	3–4 h
Hydromorphone[4]	1.5 mg	7.5 mg	5	2–3 h
Fentanyl[6]	–	–	–	–
Methadone[7,8]	–	–	–	–
Oxycodone	–	15–20 mg	–	3–5 h
Hydrocodone[9]	–	30–45 mg	–	3–5 h
Oxymorphone	1 mg	10 mg	10	3–6 h
Codeine[4,10]	–	200 mg	–	3–4 h

NOT RECOMMENDED

Meperidine[12]

Mixed agonist-antagonists[13](pentazocine, nalbuphine, butorphanol)

See Miscellaneous Analgesics (PAIN-E 7 of 12)

[4]Codeine, morphine, hydromorphone, hydrocodone, and oxymorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites - monitor for neurologic adverse effects.

[5]Conversion factor listed for chronic dosing.

[6]6n single-dose administration, 10 mg IV morphine is equivalent to approximately 100 mcg IV fentanyl but with chronic fentanyl administration, the ratio of 10 mg IV morphine is equivalent to approximately 250 mcg IV fentanyl. For transdermal fentanyl conversions, (See PAIN-E 9 of 12).

[7]Long half-life, observe for drug accumulation and adverse effects, especially over first 4–5 days. In some individuals, steady state may not be reached for several days to 2 weeks. Methadone is typically dosed every 8–12 h.

[8]The oral conversion ratio of methadone varies. PRACTITIONERS ARE ADVISED TO CONSULT WITH A PAIN OR PALLIATIVE CARE SPECIALIST IF THEY ARE UNFAMILIAR WITH METHADONE PRESCRIBING. (See Special Notes Regarding Oral Methadone, PAIN-E 11 of 12).

[9]Equivalence data not substantiated. Clinical experience suggests use as a mild, initial use opioid but effective dose may vary. Immediate-release hydrocodone is only available commercially combined with acetaminophen (325 mg/tablet) or ibuprofen (200 mg/tablet). The FDA has limited the amount of acetaminophen in all prescription drug products to no more than 325 mg per dosage unit. Dosage must be monitored for safe limits of ASA or acetaminophen.

[10]Codeine has no analgesic effect unless it is metabolized into morphine by hepatic enzyme CYP2D6 and then to its active metabolite morphine-6-glucuronide by Phase II metabolic pathways. Individuals with low CYP2D6 activity may receive no analgesic effect from codeine, but rapid metabolizers may experience toxicity from higher morphine production. Dosage must be monitored for safe limits as it may be available in combination with acetylsalicylic acid (ASA) or acetaminophen. Dose listed refers only to opioid portion.

[11]Shorter time generally refers to parenterally administered opioids (except for controlled-release products, which have some variability); longer time generally applies to oral dosing.

[12]Not recommended for cancer pain management because of CNS toxic metabolite - normeperidine.

[13]Mixed agonists-antagonists have limited usefulness in cancer pain; however, they can be used to treat opioid-induced pruritis. They should NOT be used in combination with opioid agonist drugs. Converting from an agonist to an agonist-antagonist could precipitate a withdrawal crisis in the opioid-dependent patient.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued on next page

Adjuvant Medications for Neuropathic Pain

ANTI DEPRESSANTS

- **TCAs**
  - Amitryptyline
  - Imipramine
  - Nortriptyline
  - Desipramine
- **SSRI and SSNRIs**
  - Venlaxafine
  - Duloxetine

ANTI CONVULSANTS

- **Gabapentin**
- **Pregabalin**

McDonald & Portenoy. J Supportive Oncol Jan; 4(1) 2006:43-52.
For additional resources, see also NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain

Adjuvant Treatments for Inflammatory Bone Pain

- NSAIDs
- Lidocaine patch
- Selective COX 2 inhibitors
- Steroids
- Bisphosphonates or denosumab
- Radiation therapy
- Nerve block (example, rib pain)
- Vertebral augmentation
- Radiofrequency ablation

For additional resources, see also NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain

Opioid Poorly-Responsive Pain

- **Evaluate for:**
  - Cancer progression
  - Opioid tolerance (rapid dose escalation with no analgesic effect)
  - Dose-limiting opioid toxicity
  - Poor oral or skin absorption
  - Psychological component to pain
  - Misuse or abuse of opioid

Psychological Component to Pain

- **Total Pain Concept – coined by Dame Cicely Saunders**
  - Physical
  - Anxiety
  - Interpersonal
  - Not accepting
- **Not all pain is physical**
  - Utilize colleagues in psychiatry, social work and chaplaincy to address non-physical sources of distress
  - Consider prescribing benzodiazepines for anxiety

Saunders CM. The management of terminal malignant disease, 1st ed. London: Edward Arnold; 1978.
NCCN Guidelines for Adult Cancer Pain

Summary of Points Covered

In this training module we addressed:

- **Options for pain management including opioids and adjuvant medications**
- **Opioid pharmacology**
- **Optimal dosing of opioids**
- **Conversion from one opioid to another**

Next Steps

For more detailed training on this topic you can go to the following resources:

National Comprehensive Cancer Network® (NCCN®)

- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain Version 2.2017
  http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Palliative Care Version 2.2017. PAL-10, page 15 of 96
  http://www.nccn.org/professionals/physician_gls/PDF/palliative.pdf

Education and Training for Health Professionals, EPEC-O

- The EPEC™-O Project, Module 2 – Cancer pain Management
  http://www.cancer.gov/resources-for/hp/education #290/epeco/self-study/module-2

Fast Facts

- Palliative Care Network of Wisconsin, Fast Fact and Concepts
  http://www.mypcnow.org/#!fast-facts/c6xb
- Oral vs. Intravenous Acetaminophen #302
  - Tramadol in Palliative Care #290
  - A Comparison of Pregabalin and Gabapentin in Palliative Care #289
  - Opioid Poorly-Responsive Cancer Pain #215
  - Calculating Opioid Dose Conversions #36
  - Converting To Transdermal Fentanyl #2
  - Oral vs. Intravenous Acetaminophen #302
  - Tramadol in Palliative Care #290

Faculty Bio for Shelly Lo, MD

Shelly Lo, MD is an associate professor of medicine at Loyola University Medical Center. As a medical oncologist, she specializes in treatment of breast and GI malignancies and is director of Loyola's Cancer Risk Assessment and Prevention Clinic.

She is an associate medical director for Loyola Hospice. She is board certified in Medical Oncology and Hospice and Palliative Care.

For more Information:

https://www.loyolamedicine.org/doctor/shelly-lo

Faculty Bio for Joanna Martin, MD

Joanna Martin MD is board certified in Internal Medicine, Geriatrics, and Hospice, and Palliative Medicine. She is a palliative care physician at the Jesse Brown VA and a Health Systems Clinician at Northwestern Memorial Hospital. Dr. Martin was previously employed by Horizon Hospice and Palliative Care and Presence St. Joseph Hospital in Lincoln Park from 2006 through 2015. She was medical director of Horizon Hospice and Palliative Care and the Director of Palliative Care at Presence St. Joseph Hospital from 2007 through 2015.

As a clinician educator, Dr. Martin has experience educating all levels of learners in geriatrics and palliative care in the home and hospital setting. She is currently serving as a Design Team Leader for the Coleman Supportive Oncology Initiative, a multi-hospital initiative to improve access to supportive oncology services. Dr. Martin attended medical school at the University of Minnesota Medical School in Minneapolis and completed an Internal Medicine residency and two year Geriatrics Fellowship at the University of Chicago.

References

Goroll A., Mulley, A. Primary care medicine: office evaluation and management of the adult patient. 7th edition. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014.

McDonald & Portenoy. How to use antidepressants and anticonvulsants as adjuvant analgesics in the treatment of neuropathic cancer pain. *J Supportive Oncol.* Jan 2006; 4(1): 43-52.

National Comprehensive Cancer Network®, NCCN Guidelines® for Adult Cancer Pain. (Version 2.2017). Available at: http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf. Accessed November 18, 2015.

Russell K Portenoy, MD, Zankhana Mehta, MD, Ebtesam Ahmed, PharmD, MS. Cancer pain management with opioids: Optimizing analgesia. Up To Date. December 11, 2015.

U.S. Food and Drug Administration, Full prescribing information for morphine sulfate injection USP. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202515s000lbl.pdf

Whitten, Donovan, Cristobal. Treating chronic pain: new knowledge, more choices. *The Permanente Journal* 2005; 9(4): 9-18: Figure 7 and Figure 8. www.thepermanentejournal.org

World Health Organization, (2009). WHO's Pain Relief Ladder. http://www.who.int/cancer/palliative/painladder/en/. Accessed November 18, 2015.