Palliative Care Pearls For the Hospitalized Patient

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Disclosures

- I have no conflicts of interest to disclose

Today's Case

Your patient, Mr. Smith, is a 70 year old man with multiple myeloma who presents to the ED in a pain crisis. He has recently received the oncologic diagnosis and is noted to have osteolytic lesions of his lumbar spine. MRI spine one week ago without evidence of cord compression. He is due to start XRT. The oncologist had started him on time-release Oxycodone 40mg BID which was recently increased to q 8hrs for escalating pain. The patient is requiring an additional 60 mg of PRN Oxycodone (in 10 mg doses) each day. Palliative care referral is pending.

Complex Severe Pain

- Mr. Smith is admitted through the ED for uncontrolled low back pain.
  - 10/10 excruciating pain of low back across midline with radiation into right leg
  - Pain is constant, unable to lay flat
  - Nothing has helped, couldn't be any worse
- Initial assessment:
  - How can I most effectively bring down his pain?
  - Will he need a PCA?

Initial dosing depends on peak and duration

- Initial Dosing - What to start with?
  - Think about peak and duration

	Onset	Peak	Duration
Oxycodone PO	15-30 min	30-60 min	4-6 hours
Morphine PO	15-60 min	90-120 min	4 hours
Morphine IV/SQ	5-10 min	10-30 min	3-5 hours
Hydromorphone PO	15-30 min	90-120 min	4-6 hours
Hydromorphone IV/SQ	5-20 min	15-30 min	3-4 hours
Fentanyl IV/SQ	1 min	5-7 min	1-2+ hours

Peak and duration are not the same

- Peak – think "Am I giving enough or too much?"
- Duration – think "Is it lasting long enough?"

For a pain crisis, think IV

- Don't forget:
  - patient characteristics, renal and hepatic function, prior adverse reactions
  - Account for incomplete cross tolerance

Opioid Equianalgesic Doses		
Drug	**PO/PR (mg)**	**Subcut/IV (mg)**
Morphine	30	10
OxyCODONE	20	n/a
HYDROcodone	20	n/a
HYDROmorphone	7.5	1.5
Methadone	See page #10 for conversion	
FentaNYL (See page #12 for transdermal conversions)	n/a	0.1 (100 mcg)

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Drug metabolism is affected in older adults

- Age dependent decline in:
  - Absorption – seems more related to diseases than aging
  - Hepatic first pass metabolism
  - Hepatic clearance, related to enzymatic changes, but not always and not consistently
  - Decreased GFR – but often no change in Cr due to muscle mass loss

Pain management in older adults

- What to start with – Dose reduction
- The big fear - Delirium and opioids in the elderly – It's real but…
  - Literature suggests that pain may be more likely than opioids to cause delirium
  - Especially if patient cognitively intact – severe pain 9x (CI 1.8-45.2) increased risk of delirium
- So, don't be afraid to try to treat pain, just do it more carefully

Morrison RS et al. J Gerontol A Biol Sci Med Sci. 2003 Jan;58(1):76-81.

Liver and renal impairment impact opioid metabolism

- Morphine
  - Hepatically generated metabolites: stronger analgesics as well as excitatory neurotoxins
  - Renal clearance of both parent and metabolites
  - Least amount of parent drug effect
  - Most likely to cause toxicity in renal failure
- Oxycodone and hydromorphone
  - Metabolized by liver – Oxycodone some active metabolites, Hydromorphone inactive metabolites
  - Renal clearance of both parent and metabolites

Liver and renal impairment impact opioid metabolism

- Fentanyl
  - Highly lipophilic – rapid onset/offset
  - Results in variable late duration due to redistribution in tissues
  - Almost completely hepatically cleared – considered safe in renal failure, we use in dialysis patients
- Methadone
  - Highly lipophilic – responsible for rapid onset/offset
  - Primarily CYP inactivation in the liver – also considered safe in renal failure

Initial dosing depends on opioid tolerance

- What to start with for pain crisis?

The opioid naïve patient …

	Initial Doses	Frequency
Oral	Morphine* 7.5-15mg Oxycodone 5mg	q2-4 hours
Parenteral	Morphine* 2-5mg Hydromorphone 0.5-1mg Fentanyl 25-50 mcg	q1-4 hours

Our patient is opioid tolerant

1. Tally up total long-acting and PRN opioid usage
2. Aim for PRN dose about 10-20% of 24 hr dose
3. Continue long acting as is for now

OXY ER 40mg x 3 + OXY IR 60mg =
180mg PO Oxy PO
10% of 180mg = 18mg PO Oxy

Use equianalgesic table for opioid conversion

$$18\text{mg PO Oxy} \times \frac{10\text{mg IV Morphine}}{20\text{mg PO Oxy}} = \textbf{9mg IV Morphine}$$

$$18\text{mg PO Oxy} \times \frac{1.5\text{mg IV Hydromorph (HM)}}{20\text{mg PO Oxy}} = \textbf{1.35mg IV HM}$$

- Dose reduce by 25-50%
- Give IV medications every 1-2 hours if nursing will allow

Reassessment is key

- Reassess after peak effect after first several doses
  - Pain responding but still moderate to severe -> consider increasing PRN dose by 50%
  - Pain not responding to current dose -> consider increasing PRN dose by 100%
    - If this trend continues despite multiple titrations, consider PCA
  - Pain responding and patient experiencing side effects (e.g. sedation) -> consider dose reduction

Once pain is controlled, assess again

- Think about the type of pain for adjuvants

Type of Pain	Mechanism	Adjuvants			
		Neuropathic agents	NSAIDS	Steroid	Acetaminophen
Nociceptive	Pain sensors		X		X
Neuropathic	Nerve damage	X			
Inflammation	COX, etc		X	X	X

Back to our case …

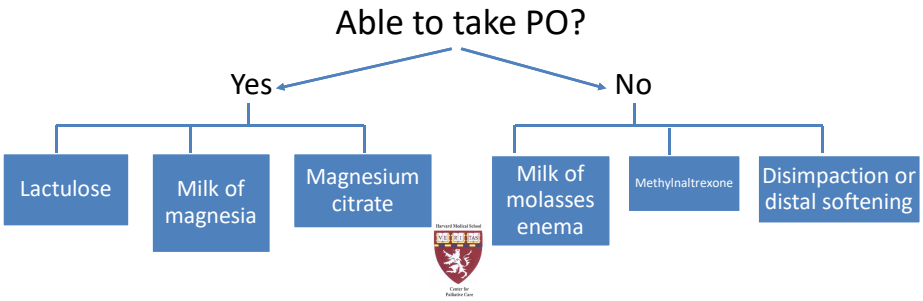
Mr. Smith's acute pain crisis has improved in response to IV hydromorphone 1mg-2mg q 2 hours prn. He is more comfortable but is unable to lay flat and cannot tolerate simulation planning for XRT. You add gabapentin and dexamethasone.

He also notes progressive nausea, anorexia, and abdominal distension. He has not had a bowel movement for two weeks prior to admission despite taking senna and miralax occasionally.

Severe constipation

Over the next two days, you schedule senna and miralax, and try bisacodyl suppository and tap water enema without relief.

- What's next in your constipation toolbox?



Severe constipation

Milk of Molasses

- 8 oz. warm water
- 3 oz. powdered milk
- 4.5 oz. molasses

Preparation:

1. Put water and powdered milk in a plastic jar. Close the jar and shake until fully mixed.
2. Add the molasses and shake the jar again until even color throughout.
3. Pour the mixture into an enema bag. Gently insert the enema tubing a few inches inside the rectum. Hold the bag high until all the liquid has been drained into the rectum.

Methylnaltrexone

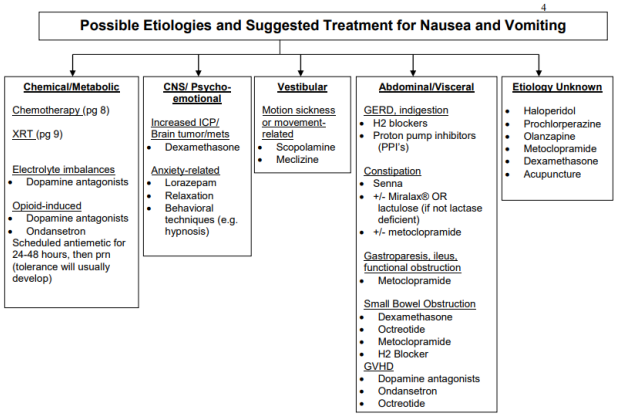
- peripherally-acting μ-opioid receptor antagonist
- Subcutaneous injection
- 50% effective, observed effect after 4 hours
- Contraindicated in bowel obstruction or impaired gut motility
- Can cause **abdominal cramping!!**

Constipation relieved, nausea persists

Mr. Smith responds nicely to a milk of molasses enema but he remains nauseous and unable to eat. His pain remains improved but he still isn't able to lie flat for radiation. The oncologist is worried about his anorexia and weight loss and whether he will be able to tolerate chemotherapy in the future. The patient senses things aren't going well and is becoming increasingly anxious.

Severe nausea

- If not constipation, what's causing nausea?



https://pinkbook.dfci.org/assets/docs/greenBook.pdf

Severe nausea

- For our patient, here are the top contenders:

Opioid-induced
- Dopamine antagonists
- Ondansetron

Scheduled antiemetic for 24-48 hours, then prn (tolerance will usually develop)

Anxiety-related
- Lorazepam
- Relaxation
- Behavioral techniques (e.g. hypnosis)

Etiology Unknown
- Haloperidol
- Prochlorperazine
- Olanzapine
- Metoclopramide
- Dexamethasone
- Acupuncture

https://pinkbook.dfci.org/assets/docs/greenBook.pdf

A few steps forward, more steps backward

Mr. Smith's nausea improves on scheduled haloperidol 0.5mg PO q 8 hrs. His appetite remains low and he is minimally getting out of bed.

One week into his hospital course, his pain continues to limit tolerance of cancer-directed interventions and again becomes the foremost concern.

Complex severe pain

- What's next?
  - Should we start methadone?
  - Could he benefit from an interventional pain consult?
  - What about ketamine?

Complex severe pain

- When should you consider methadone?
  - Escalating doses of opioids, limited by side effects
  - Severe neuropathic pain
  - Opioid-induced hyperalgesia
  - Co-morbid substance use concerns
- When should you not?
  - Lack of outpatient prescriber
  - Prolonged QTc
  - Patient preference

McPherson, Mary Lynn et al. *JPSM*. vol. 57,3 (2019): 635-645.e4.

Complex severe pain

- While we're on the topic of NMDA antagonism, escalating opioid needs, and treatment for severe neuropathic pain, shouldn't we consider ketamine?
- Consider it? Yes. Use in this case? I wouldn't. Here's why:
  - No evidence of neurotoxicity
  - Age, anxious at baseline
  - Primarily used as a bridge

Loveday BA, Sindt J. *J Adv Pract Oncol*. 2015;6(6):555-561.

Complex severe pain

When thinking about multimodal approach …

Modalities	Examples
Disease Modifying	Medical therapy, surgery Chemotherapy, XRT
Pharmacologic	Opioids, non-opioids Adjuvants, steroids
Physical Therapy	Exercise, stretching
Psychological	Psychodynamic, CBT, mindfulness
Spiritual	Prayer, meditation
Alternative	Acupuncture, healing touch, aromatherapy, massage Hot/cold, TENS, biofeedback
Relaxation	Guided imagery, music/art
Interventional	Blocks, intrathecal pump

… have a low threshold to involve interventional pain colleagues for refractory cancer pain.

Interventional strategies for severe pain

Injection therapies

- Epidural steroid injections
- Facet injections
- Trigger point injections
- Non-neurolytic block
- Neurolytic block

Intrathecal pump

- More targeted approach
- Less systemic side effects
- Allows for addition of adjuvants to opioid
- Consider prognosis

Careskey H, Narang S. *Hematol Oncol Clin North Am*. 2018;32(3):433-445.

What's next for our patient?

You request consultation with the interventional pain service and Mr. Smith undergoes a lumbar epidural steroid injection. He has significant relief in the first 24 hours and is able to tolerate XRT simulation.

The following day, he is scheduled for his first session of radiation therapy. He is appropriately pre-medicated but does not tolerate lying flat.

Complex severe pain

Over the next week, Mr. Smith experiences recurrent, severe low back pain without further improvement. He is averaging 8mg IV hydromorphone daily in PRN doses and you increase his long acting oxycodone accordingly. The patient is increasingly sleepy with mild delirium. New renal impairment is noted on lab work.

The radiation oncologist worries he will not be able to complete the recommended treatment course.

What's the next step?

- Take a step back
  - Consider discussion on goals of care
  - Identify a healthcare proxy
  - Include multidisciplinary team
- Why now?
  - The patient is moving further and further from the treatment goal
  - Multiple people have expressed "I'm worried"

Serious illness Communication

- Setup
  - Rationale, warning shot, mutual agenda
- Explore Illness Understanding & Information Preferences
  - "*what have you heard from your healthcare team about your illness?*"
  - "*what changes have you noticed throughout the illness?*"
- Deliver a Prognosis
  - Time, function, uncertainty

Bernacki JAMA Internal Medicine 2014
Back Ca Cancer J Clin 2005

Serious illness communication

- Explore what is most important to patients
  - *"if you become sicker, how much are you willing to go through in order to gain more time?"*
  - *"knowing that time may be short, what's most important to you?"*
- Summarize and make recommendations

Expect and respond to emotion **throughout**.

Bernacki JAMA Internal Medicine 2014
Back Ca Cancer J Clin 2005

Transition in goals of care

All involved clinicians are in agreement to conduct a family meeting to address goals of care. Mr. Smith asks his daughter, who he has designated to be his healthcare proxy, to be present. Hearing how challenging it may continue to be to get to the point of tolerating cancer directed treatments, Mr. Smith prioritizes quality of life and elects to transition the focus of his care to primarily comfort-measures.

Transition in goals of care

- Over the next week, Mr. Smith's renal function worsens, he stops taking in any oral medications or food, and becomes increasingly withdrawn and somnolent
- How do we treat his pain without oral access?
  - Consider a continuous infusion and bolus
  - If comfortable, account for 50% of opioid needs in continuous rate (if uncomfortable, consider more)

Let's briefly return to the math

- One week ago, he was taking 8mg IV hydromorphone/24 hrs so his long-acting regimen was adjusted

$$8\text{mg IV HM} \times \frac{20\text{ mg PO Oxy}}{1.5\text{mg IV HM}} = \textbf{106mg PO Oxy}$$

120 mg (40mg q 8 hrs) + 106mg = 226mg PO Oxy

226mg PO oxy / 3 = **75mg PO Oxy q 8 hrs**

The dying patient

He's now taking 6mg IV hydromorphone/day on top of the long-acting oxycodone. He appears comfortable on this regimen.

- Convert regimen to a continuous infusion:

225mg PO oxy = 17mg IV hydromorphone

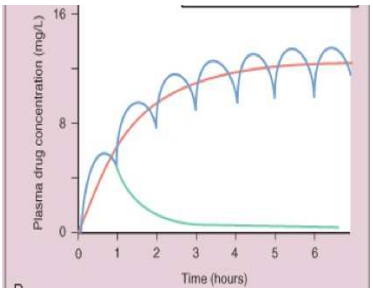
17mg IV HM + 6mg IV HM = **23mg IV hydromorphone**

50% of 23 mg IV HM = 11.5mg IV HM / 24 =

0.5mg/hr IV HM continuous gtt + 2mg IV HM q 1 hr PRN bolus dose

How often should we adjust the drip?

- Think of drips as long acting & poorly titratable
- 4 half lives to reach steady state – Morphine ½ life 2-4h
- Can take hours to take effect
- Use bolus dosing for acute symptoms
- Adjust drip rate every 6-8 hours based on PRN usage



Portenoy RK. *J Pain Symptom Manage*. 1986;1(4):223-228.

The common mistake with opioid infusions

- Start opioid infusion, titrate to patient comfort
- Nurse starts drip at prescribed rate, patient is still uncomfortable
- Drip rate is increased in response, patient still uncomfortable…
- At 4 x the initial drip rate after 3 hours, patient starting to have relief, everyone is happy
- At 8 hours patient comatose, shallow breathing, frequent myoclonic jerking, vomiting

Back to our case …

Mr. Smith is comfortable on the hydromorphone infusion and his PRN requirements decrease to several times a day, primarily before being turned. It has been three days since the last adjustment of the pain regimen.

He becomes delirious and eventually less interactive, but does not have any myoclonus or respiratory depression. The next day, Mr. Smith passes peacefully on the floor.

Palliative care pearls

- Utilize a multimodal approach to treat pain and other symptoms
- Pay attention to unique patient characteristics and preferences
- Expect questions about addiction, screen for misuse and chemical coping
- Don’t forget about cost, prior authorization, longitudinal prescriber

Palliative care pearls

- When dealing with opioid tolerant patients, always tally past meds to get your foundation
- Do dose conversion calculations and don’t forget dose reduction for cross tolerance
- Recheck your numbers but opioid tolerant patients need higher doses

Palliative care pearls

- Caution with morphine in renal failure
- Caution with everything in liver failure
- Use opioids in the elderly, just at lower dose
- Treat pain before just using restraints and haldol

Palliative care pearls

- Bolus dosing is key for achieving comfort
  - Think of drips as long acting meds, behave accordingly
- To avoid side effects – do your calculations

  Most frequent/worrisome:
  - Constipation – patients do not build tolerance it
  - Delirium
  - Respiratory depression – this is why doing the calculations is very important
  - Neurotoxicity – primarily from toxic metabolites

Tarumi J Pain and Symptom Management 2013

Chronic Pain in Palliative Care

- Ongoing severe pain at site of prior injury
- Difficult to disentangle from addiction and chemical coping – can look very much like aberrant behaviors
- Poorly opioid responsive
- Poorly responsive to hospitalization
- Chronic pain in palliative care patients is a team game + goals of care conversation

Palliative care pearls

- Evidence supports early conversations about goals and values between you and your seriously ill patients
- Focus on prognostic awareness, goals, and values – not CPR and feeding tubes – then make recommendations about medical care and use forms after discussion
- Chronic pain shows up in palliative care too
- Treat chronic pain initially as a goals of care conversation – come with compassion, humility

Useful resources

- https://www.pallicovid.app/
- https://pinkbook.dfci.org/
- https://www.mypcnow.org/
- Jain N, Bernacki RE. Goals of Care Conversations in Serious Illness: A Practical Guide. *Med Clin North Am*. 2020;104(3):375-389. doi:10.1016/j.mcna.2019.12.001

Thank you!
Questions?