Palliative Pain Management
Beyond the Basics

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Disclosures
- No financial or other conflicts of interest
- There will be off-label discussion

Objectives
- Describe basic pain management
- Identify and discuss opioid choices and routes in pain management, including conversions
- Identify and discuss non-opioid pain medication choices
- Identify and discuss interventional pain management modalities

Pain Management Menagerie
- PO to IV opioid conversions; 1:1?
- The use of very low dose methadone and haloperidol for pain control?
- Fentanyl patches and cachexia?
- What about the WHO step-ladder?
- Converting to methadone; multiple methods?
- Ketamine?
- Lidocaine?
- When should procedures be considered?

What is pain?
- Multiple definitions
  - “An unpleasant sensory and emotional experience associated with actual tissue damage, or described in terms of such damage.” - International Association for the Study of Pain
  - “Whatever the patient says it is, as bad as they say it is.”
  - Chronic persistent pain: present most days for more than several months
  - Pain is multidimensional; physical, spiritual, emotional, psychosocial
  - Pain vs. SUFFERING

Pain receptors
- Mu
  - Activation produces analgesia, sedation, slightly reduced blood pressure, slowing of heart, euphoria, decreased appetite. Morphine and related agonists bind to Mu receptors and cause analgesia.
  - Sedation, euphoria and decreased respiration tend to lessen with continued use as tolerance develops. Analgesia, miosis and reduced bowel motility tend to persist; little tolerance develops to these effects.
- Delta
  - Activation produces some analgesia, but less so than Mu
- Kappa
  - Activation can cause dissociative and deliriant effects
  - And may antagonize the effects of the mu opioid receptor
- NMDA
  - Agonists result in dissociation, hallucinations.

Types of physical pain
- Nociceptive pain
  - Pain stimulus transmitted by peripheral nociceptors
  - Somatic: musculoskeletal/dermatomal, skin
  - Articular: joint, tendon, ligament
  - Visceral: organs alerted to damage
  - Is poorly localized, diffuse, vague, hard to describe, and can be referred
  - Serves a protective function
  - Typically responds well to opioids

- Neuropathic pain
  - Injury/compression to nerve tissue, central or peripheral
  - DM, spinal stenosis, CVA, HIV (infectious), infiltration of nerve tissue
  - Pain usually exceeds observable injury
  - 40% of cancer pain is neuropathic
  - Is described as shooting, burning, tingling, lancinating, pins and needles, and can be difficult to describe
  - Altered sensory perception
  - Can be in dermatomal distribution
  - Has no protective function
  - Does not respond well to Mu agonist opioids

Types of physical pain
- Acute pain
- Chronic pain
- Breakthrough pain
- Incident pain
- Persistent pain
- Psychogenic pain (psychalgia)
  - Physical pain caused, increased or prolonged by mental, emotional, or behavioral factors

Pain definitions
How to detect pain

- **ASK**: patient, family, caregivers
- **Observe**: nonverbal findings

**Numeric Pain Intensity Scale**

- The most commonly used pain measurement tool, used in the cognitively normal patient
- The scale is from 0 (no pain) to 10 (the greatest intensity pain)
- In general, pain from 1-3 is mild pain, 4-7 is moderate pain, and 8-10 severe pain

**Numeric Pain Intensity Scale, cont.**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No pain</td>
</tr>
<tr>
<td>1-3</td>
<td>Mild pain</td>
</tr>
<tr>
<td>4-7</td>
<td>Moderate pain</td>
</tr>
<tr>
<td>8-10</td>
<td>Severe pain</td>
</tr>
</tbody>
</table>

**Pain Faces Scale**

- The patient selects the face that best represents how they feel in relation to their pain condition, from the “happiest feeling face” to the “saddest feeling face”
- The correlating number is actually the scoring card used to quantify the patient’s pain intensity

**PAINAD Scale**

- PAINAD Scale is to be utilized in evaluating non-verbal patients
- A score of 0 denotes no pain, and a score of 10 the worst possible pain
- This scale is now used in place of the FLACC scale

**PAINAD Scale**

<table>
<thead>
<tr>
<th>Items</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathing</td>
<td></td>
</tr>
<tr>
<td>Vocalization</td>
<td></td>
</tr>
<tr>
<td>Facial expression</td>
<td></td>
</tr>
<tr>
<td>Body language</td>
<td></td>
</tr>
<tr>
<td>Consolability</td>
<td></td>
</tr>
</tbody>
</table>

**General approach to pain management**

- Use a multidimensional approach: physical, psychological, spiritual, social, cultural, situational
- Collect data: history, physical exam, medication review
- Treat, reassess, adjust
How to document pain management:
The 4 A’s

- Analgesia
- ADLs
- Adverse effects
- Aberrant drug-related behavior

What to report to a physician

- History
  - Diagnoses
  - Location(s), including other related symptoms
  - Severity and desired level of comfort
  - Impact on QOL
  - Radiation
  - Duration
  - When did it start?
  - How long does it last?
  - What makes it better/worse
  - Pain timeline
  - Social, emotional, spiritual framework, last BM, urinary status...

- Medications
  - Medications ordered and medications being used for pain
  - Frequency during last 24 - 48 hours
  - Amount during last 24 - 48 hours
  - When started?
  - When dosing was changed
  - Allergies/adverse reactions
    - What has been used in the past and why no longer being used
    - Exams
      - Physical
      - Other observations, social, emotional, spiritual framework...
    - Your thoughts re the pain
      - Physical, emotional, existential, other...
    - What are we treating
      - Who are we treating?

GOALS of CARE

- Acute pain
  - Pain relief without interfering with other treatment
- Chronic pain
  - Pain improvement while allowing the greatest degree of function
- Hospice & Palliative Care
  - What are the patient’s goals of care?
  - Should we just ‘measure’ pain OR
  - Should we assess impact on ADL and QOL?

“Traditional” WHO 3-step ladder

1 mild 2 moderate 3 severe

- Analgesic
- Adjuvant

1st line / Mild pain

Opioids
- Morphine
- Fentanyl
- Oxycodone
- Hydrocodone
- Methadone
- Codeine
- Tramadol
- Oxymorphone
- Tapentadol

2nd line / Moderate-Severe Pain

- NSAIDs
- Acetaminophen
- Tri cyclic antidepressants
- Steroids
- Anti-convulsants
- SNSRIs
- other

Refractory Pain

- Opioids + NSAIDs + Adjuvants
- NK1 antagonists
- Other
- Other

From “Ladder” to “Platform”

Opioid and Non-opioid analgesics

- Opioids
  - Morphine
  - Fentanyl
  - Oxycodone
  - Hydrocodone
  - Methadone
  - Codeine
  - Tramadol
  - Oxymorphone
  - Tapentadol
  - Buprenorphine

- Non-opioids
  - NSAIDs
  - Acetaminophen
  - Cox-2 inhibitors
  - Tri cyclic antidepressants
  - Steroids
  - Anti-convulsants
  - SNSRIs
  - other
Opioids

Advantages

- Standard of pain management
- No ceiling doses, except tramadol and meperidine
- Multiple routes available
- Short and long acting formulations

Commonly Used Opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Short Acting</th>
<th>Long Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone</td>
<td>Tabs, caps, liquid concentrate</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>Tabs, caps, liquid concentrate, injectable</td>
<td>Methadone, nausea, sedation, toxicity</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Tabs, inhalation, suppository, injectable</td>
<td>Methadone, nausea, sedation, toxicity</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Transdermal: Acet, Fentora, Abstral, Onsols, Subsys*</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Injectable, tabs, dispersible tab, oral solution, liquid concentrate</td>
<td></td>
</tr>
</tbody>
</table>

Commonly Used Opioids

Other opioids

- Oxymorphone
  - Not recommended for use in moderate to severe renal and liver impairment
  - Conversion ratio morphine:oxymorphone is 3:1
- Buprenorphine Transdermal System (Butrans)
  - Every 7 day patch
  - Equipotency to oral morphine not established

Opioids with limited or no value in palliative care patients

- Hydrocode or oxycodone with acetaminophen combinations, oral only, dose ceiling due to APAP
- Meperidine: has a therapeutic ceiling due to CNS toxicity and is not indicated for chronic cancer pain.
- Codeine: weak opioid
- All three of these have narrow therapeutic to toxic ratios
- Tramadol: 400 mg limit per day. Ceiling for acetaminophen when used in combination
- Tapentadol

J.W.

J.W. is a 61 y.o. male diagnosed with pancreatic cancer 9 months ago. He has been resistant to disease-directed therapy. The cancer is now metastatic to his liver and regional lymph nodes. He c/o nagging middle upper and right upper abdominal pain, up to a 5/10 at times, but generally 2-3/10. He uses HC/APAP 10-325, one tab q4hrs prn. He uses this when his pain is a 4 or 5 and normally takes 1-2 tabs per day.

Your Thoughts?

- He should not be on a combination medication that has APAP in it
- He should be rotated to a different opioid
- If he’s good with it, I’m good with it

Opioids with limited or no value in palliative care patients-

- Tapentadol
  - Package insert states that is ½ to ⅓ as potent as morphine in producing analgesia in animal models
  - Not recommended for use in severe renal or liver disease
  - No studies on conversion from other opioids to long-acting
- Pharmacodynamics
  - Half life elimination:
    - Immediate release: ~4 hours
    - Long acting formulations: 1-6 hours, peak to diss Ol/2hrs
    - Time to peak plasma: Immediate release: 1.25 hours; Long acting formulations: 3-6 hours

Sublingual absorption of selected opioid analgesics at PH 6.5*

- Buprenorphine 55%
- Fentanyl 51%
- Methadone 34%
- Morphine 18%
- Hydromorphone and oxycodone at best no better than morphine
  - At PH 8.5 methadone absorption is 75%
- Lipophilic drugs better absorbed than hydrophilic drugs
  - Under controlled conditions
Scheduling short-acting and long-acting opioids

- Starting an opioid:
  - Schedule opioids/pain meds as immediate release every 4 hours
  - Provide rescue dose
    - Generally given as 5-15% of total daily opioid dose. May be repeated after peak effect reached.
    - Oral = q1hr
    - SC = q20 min
    - IV = q5-10 min
- Convert total daily (24 hrs) use of short-acting/breakthrough dosage to long-acting opioid
- Goal is pain rating acceptable to patient
- Do not start opioid naïve patients on long-acting opioids

The continuing saga of JW

5 weeks later, JW’s pain has worsened and he now has pain in his mid-back. He is taking the HC/APAP 10/325, 2 tabs q4hrs round the clock. This keeps his pain at around a 4, but it is periodically as high as 5-6.

Your thoughts?

- If he’s good with it, I’m good with it
- His pain control is adequate, but I’m concerned about the total daily APAP dose
- He should increase the frequency or the dose of the HC/APAP use
- Whoa pawdner, let’s use another opioid

Back to JW

You decide to convert the HC/APAP to long-acting Morphine.

We now interrupt this program for an important news flash: What is REMS?

- Really Enjoying My Snooze (until now, that is)
- The various splinter bands of the Alternative Rock band, R.E.M., who will be touring in the next few years
- Don’t know, don’t care
- Risk Evaluation and Mitigation Strategies

ER/LA Opioid REMS

- Prescriber Education
  - Approved educational programs
  - "Required by the USFDA"
- Covers
  - Assessing patients for ER/LA opioid treatment
  - Dose x Benefits
  - Misuse/abuse
  - Applying appropriate methods for initiating, modifying, and discontinuing ER/LA opioids
  - How to monitor and manage patients receiving these med
  - Methods for educating patients/companions in safe use, proper storage and disposal
  - Reviews and assesses general and product information of ER/LA opioids, including potential adverse effects

Opioid Rotation Considerations- Reason for rotation

- Adding an ER/LA opioid
- Opioid intolerance
  - Cough, dysphagia, flushing, sweating and/or mild hypertension only
  - Respiratory distress, pruritus, rash, hives, or anaphylactic reaction
  - Allergic reaction to the active ingredient or an inactive ingredient of the product
  - Seizures, severe constipation
  - Severe nausea, vomiting, or diaphoresis
  - Severe agitation, consider different opioid agent
  - Metabolism
  - Matrix (opioid, estrogens, ropinirole, HRT)
  - (Celebrex, Tramadol)
- Expectorant
- High dose
- Change in delivery route needed

More on rotating opioids- Incomplete cross tolerance

- Reduce dose of new opioid by 25-50% based on clinical judgment
  - Closer to 50% if on relatively high dose of opioid
  - Change route if possible
  - Change delivery system
  - None of the above
  - Changing route, not drug
- Methadone: reduce by 75-90%
- Titrate as needed and closely monitor during adjustment period
- Conversion tables based on single-dose potency studies, using a specific route, in patients with limited opioid exposure

And even more on opioid rotation

- Maximize dose, try to avoid the use of multiple opioids
- Simplify medication regimen
- Use the gut if it is working
- Methadone is not a linear conversion
- Morphine to Fentanyl is a more difficult conversion (long acting/fixed doses)
Titrating opioids

- If taking 3+ rescue doses/24h and pain is expected to continue — increase baseline
- No opioid should be titrated more frequently than 3-4 half-lives*
- For methadone, at steady state, half-life may be one to two (or more) days. Dose increases should not be done more frequently than every 4 days in lower doses and every 1-2 weeks in higher doses
- Titrating methadone more rapidly than every 5-7 days is potentially dangerous
- Calculate total daily dose taken
  - If pain not controlled, titrate total daily dose ↑
  - Adjust dose no more often than opioid’s t1/2 x4
- Normal-release medications (t1/2 ~4h)
- Extended-release medications (t1/2 ~12+h)
- Suggested titration depends on severity of pain:
  - If mild – moderate, then ↑ by 25% – 50%
  - If severe – uncontrolled, then ↑ by 50% – 100%

ROUTE ONSET PEAK DURATION
IV 5-10 15-30 3-4
SQ 10-20 30-60 3-4
PO 30-60 60-90 3-4

Morphine — the palliative gold standard

Opioid equivalencies

- po / pr (mg)        Analgesic             SC / IV / IM (mg)      Epi Intrathecal
  - 30, (20*)          Morphine    10 1 0.1
  - 7.5 (6*)          Hydrocodone
  - 1.5                Hydromorphone 1.6
  - 20                Oxycodone
  *REMs
  **(There is variability and drug inserts have tables of conversions with ranges)
  Fentanyl per hour IV dose = fentanyl per hour patch dose

Opioid use in renal and liver disease

- Renal Insufficiency
  - Methadone √, fentanyl √, hydromorphone ±, oxycodone ±, morphine??
- Hepatic Insufficiency
  - Use all of above with caution, except ???morphine

JW-decisions, decisions

- JW would like to continue the morphine and agrees to try the diphenhydramine.

Conversion
  - Total 24 hr morphine use = 60 mg + 60 mg = 120 mg
  - Can give as MSER 30 mg q12hrs
  - Calculate breakthrough dose: 60 mg x 10% = 6 mg
  - Can give as morphine solution 20 mg/ml at 0.25 ml (5 mg) q1hr prn or MSIR 15 mg, ½ tab (7.5 mg) q1hr prn

Now what?

- It's dry outside, so I'm not concerned about the pruritus
- Order diphenhydramine for the pruritus
- Add an oral steroid
- Rotate to another opioid
- Titrate his morphine extended release dose

Checking in on JW

JW's has been controlled for 3 weeks on the new regimen. However, his pain has worsened and he now requires MSIR 15 mg, 7.5 mg per dose, 6 doses per day, to keep his pain at a reasonable level, around a 3/10. In addition he now complains of severe left arm pruritus, without a rash. He is not jaundiced.

The saga of JW resolves, (for now)

- JW's pruritus resolves with low dose gabapentin after failing to respond to multiple medications
- JW's pain remains well-controlled for now
Can we talk about opioids?

- Fentanyl
  - The patch loads in over 12 hrs and is difficult to titrate
  - What about fentanyl patches and cachexia?

- Hydrocodone
  - Only available as a combination product
  - May be beneficial for neuropathic pain??
  - Can you give MSER or OxyContin rectally?
  - Is rehydration morphine useful for treatment of dyspepsia?
  - Can you open Kadian and Avinza capsules?

- Hydromorphone

- Tramadol and methadone
  - May be beneficial for neuropathic pain?
  - What about dose and frequency ranges??

- Can you give MSER or OxyContin rectally?

- Is nebulized morphine useful for treatment of dyspnea?

- Can you open Kadian and Avinza capsules?

Errors in prescribing opioids

- PRN dosing only for constant/chronic pain
- Scheduled dosing without prn/rescue dosing
- Scheduled long acting opioids for incident pain
- Polypharmacy complicates formulation use
- Failing to use adjuvant medications
- Insufficient rescue dose titration
- Incorrect dose
- Changing more than one drug at a time
- Incorrect equianalgesic dosing calculations
  - Incorrect conversion
  - Incorrect methodology
- Inadequate follow up

Medication cost: long-acting opioids

- Methadone < Morphine ER < Fentanyl < Oxymorphone ER** < OxyContin** < Hydromorphone

** As dose size increases, the price increase disproportionally to morphine ER

FP

- 57 y.o. female on hospice with dx of breast cancer, metastatic to bone. Is on Morphine ER 240 mg q12hrs, with BTP dose of MSIR 45 mg q1hr prn. She is taking the MSIR 4-5 times in a 24hr period. Her pain level is 5 on the average. She would like a level of 3. You recommend a conversion to methadone and she is very agreeable, in part because it also comes in a liquid form.

Methadone

- Routes of Administration
- Advantages
- Disadvantages
- EKG?-

Methadone Pharmacokinetics

- Analgesic onset 30-60 minutes
- Analgesic peak 2.5 - 4 hours
- Oral bioavailability >80%
- Highly lipophilic
- Metabolized in the liver to inactive metabolites (unlike morphine)
- Metabolites are excreted by the kidneys
- Very long and variable plasma half-life (13-120 hours)

Methadone conversion methods

- Multiple methods
  - Morely Makin
  - Toombs
  - Friedman
  - Direct
  - And others
- When converting to methadone, what is the maximum allowable dose?

One methadone equianalgesic table

<table>
<thead>
<tr>
<th>Methadone (mg)</th>
<th>Equianalgesic Morphine (mg)</th>
<th>Conversion Ratio</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>25</td>
<td>5</td>
<td>0.2</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>75</td>
<td>15</td>
<td>0.2</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Reference AAHPM Primer equianalgesic guide
MEDD stands for "Morphine Equivalent Daily Dose." There are a number of such equianalgesic charts. This one is fairly conservative.

FP

- MSER/24hrs = 480 mg
- MSIR/24hrs = 180 mg
- MEDD = 640 mg
- Conversion ratio 15:1 = 43 mg
  - 25% = 10.75 mg
  - 10% = 4.3 mg
- You start her on methadone 5 mg q12hrs
- PRN BTP dose of MSIR 60 mg q1hr prn
59 y.o. male on hospice with metastatic rectal cancer, including liver mets. C/o persistent RUQ pain, 2-4 is an acceptable pain rating for KB, but his pain goes up to a 6, hence the need for the oxycodone. Currently taking:
- OxyContin 100 mg PO q12hrs
- Oxycodone 10 mg tab, 6 to 15 tabs per 24 hrs
- Gabapentin 600 mg q12hrs

KB-What do you do?
- Nothing
- Increase his OxyContin
- Increase his gabapentin
- Rotate to methadone

KB
- You see Mr. KB one week later, after his gabapentin has been increased to 600 mg q8hrs.
- He reports
  - Improved alertness
  - Decreased pain
  - Increased ability to carry out ADLs
- He is now using 3 oxycodone tabs/24hrs on the average

Non-opioid analgesics

Advantages
- Can augment the effect of opioids
- Generally more effective for neuropathic pain
- Can treat other symptoms (depression, seizures, behavior, appetite, nausea, dyspnea)
- Minimal to no constipation or respiratory concerns

Non-opioids

Limitations
- Dose ceiling/toxicities
- Drug-disease interactions
- Drug-drug interactions
- Side effects
- Routes of delivery

The Adjuvant Game!

NSAIDS
- Acetaminophen
- Bisphosphonates
- Corticosteroids
- TCAs
- SS&NRIs
- Anticonvulsants
- Topical analgesics
- Anticholinergics

Somatic Pain
- Neuropathic Pain
- Visceral Pain
- Other Benefits
- Adverse Effects

TC
- 47 y.o. female with metastatic pancreatic cancer, with bone mets to thoracic and lumbar spine and a para-axial extrinsic mass which may be causing nerve compression. She has a hx of debilitating pain from her cancer, but has been fairly well controlled as of late. She now has intractable nausea and vomiting and she agrees to be admitted to the IPU for management. She is presently taking:
  - Oxycodone ER 200 mg q12hrs
  - Oxycodone 40 mg q4hr prn pain, 3 doses in last 24 hours

TC
- You decide to:
  - Treat the nausea with IV medication?
  - Convert to an IV opioid?
  - Try IV meds for nausea, but continue the PO oxycodone?

TC
- You start her on
  - IV haloperidol
  - Convert her to IV hydromorphone
You start her on hydromorphone
- Oxycodone ER = 400 mg
- Oxycodone IR = 120 mg
- 520 mg oxycodone = 780 mg MEDD
- 780 mg/20 = 36, reduce by 33% = 24 mg
- 24 mg/24 hrs = 1.0 mg/hr
- What is the prn breakthrough dose?
  - 0.4 mg q10 min, (10% of 24hr dose/6, given q10 min)
  - 2.4 mg q30-60 min, (10% of 24hr dose q30-60 min)
  - 1.0 mg q15 min, (dosing hourly rate q15 min)

She is started on methadone 60 mg q8hrs
- The conversion was calculated without using the BTP dosing
- This is what was used
  - 20 mg HM x 24 hours = 480 mg HM
  - 480 mg = 9600 MEDD
  - 9600 mg/20 = 480 mg methadone
  - 480 mg x 37.5% = 180 mg, 180 mg/3 =
  - 60 mg q8hrs, with HM 15 mg IV q15 min pm

Opioid side effects
- Sedation
- Nausea
- Hives/itching
- Constipation
- Respiratory depression
- Confusion/hallucinations
- Urinary retention
- Myoclonus
- Hyperalgesia

Respiratory depression
- With opioids, start low and go slow to avoid excessive rise in pCO₂
- If patient can be awakened and can hold a conversation, then the patient is not over-sedated
- Long before patients stop breathing, they develop altered mental status
- Consider writing parameters for nurses/caregivers
  - Call immediately for RR <6-8/min
- What about the actively dying patient?

Respiratory depression
- If opioid tolerant
  - Do not completely reverse!
  - Complete reversal
    - Triggers acute withdrawal syndrome
    - Completely "uncovers" all pain
  - Diluted naloxone
    - 0.4 mg diluted with NS in a 10 mL syringe
    - Administer 0.25 to 1 mL aliquots q2-3 min
    - Titrate respiratory rate to 8-10 per min
    - Awakening the patient is not necessary/desirable

Constipation
- Opioids cause colonic slowing
- Routine use of stimulant laxative plus stool softener when starting opioids (sennosides + docusate sodium), 2-6 qpm or 1 tab po bid (up to 10/day) or
  - Just a stimulant laxative
- Consider other treatment choices if constipation persists
  - For opioid-induced constipation in patients with advanced illness, receiving palliative care, with insufficient response to laxative therapy-Relistor (methylnaltrexone bromide)
    - Contraindicated in patients with mechanical bowel obstruction

Opioid-induced Neurotoxicity
- High Dose / Prolonged Use
- Renal Insufficiency
- Excitation
  - Agitation / Myoclonus / Hallucinations / Delirium / Seizures / Hyperesthesia / Bad Dreams
- Sedation / Coma
- Treatment
  - Hydration / Dose Reduction (by 20%) / Opioid Rotation

GG
- 41 y.o. male with colorectal adenocarcinoma, metastatic to lung, liver, peritoneum, s/p segmental sigmoid colon resection and multiple cycles of chemotherapy. His pain is abdominal and he has low back pain which radiates around to the abdomen. He also has anxiety. Has been on Oxycodone ER and steroids, methadone 70 mg q6hrs and Nucynta 2-3 x/day for BTP prn and scheduled at hs. He was converted to IV hydromorphone with initial good response, but ultimately complains of poorly controlled pain on what ended up being high-dose IV hydromorphone.

GG
- He is admitted to the IPU and treated with SC Ketamine per your IPU protocol
**SC ketamine**
- Is an anesthetic agent with analgesic properties
- Provides safe and, theoretically, effective analgesia as a low dose infusion
- May cause some sedation
- May be used as separate infusion alongside other opioids

**GG**
- GG has favorable response to SC ketamine initially
- In spite of following the protocol, he, ultimately, has no improvement in pain control with the ketamine
- Why?
- Largest RCT to date shows no benefit with a dose escalating regimen
  - “Ketamine does not have net clinical benefit when used as an adjunct to opioids and standard coanalgesics in cancer pain.”
  - Prior evidence for use was extrapolated from other settings
  - Primary support prior to this study comes from case series and uncontrolled studies

**GG**
- So let’s try IV Lidocaine

**IV/SC Lidocaine**
- Indications after less invasive methods have failed
  - Intractable neuropathic pain or visceral pain due to malignancy
- Pain relief is superior and reduced analgesic requirement post-infusion are better than placebo in multiple clinical settings
- Is inexpensive (24 hours supply can cost < $5)
- Other recent study found 71% positive response rate and 49% had a major positive response
- Has analgesic, anti-inflammatory, and anti-hyperalgesic properties
- Suppresses spontaneous impulses generated from injured nerve fibers and the proximal dorsal root ganglion
- Blocks neural transmission at site of tissue injury
- Interferes with the inflammatory process, suppressing peripheral and central sensitization, resulting in an anti-hyperalgesic effect

**IV/SC lidocaine**
- Many protocols require a 12 lead EKG prior to initiating infusion
  - Continuous or intermittent infusions
  - Recent study (retrospective case series between 2003 and 2013) and companion protocol only obtains EKG if:
    - Male and older than 65 years
    - Female older than 55 years
    - And/or known or suspected of having cardiac problems
  - Infusion requires close nursing supervision, as in PCU, IPU, or residential hospices, possibly in the patient’s home

**IV/SC lidocaine**
- Contraindications
  - Absolute: allergies to “caine” anesthetics
  - Relative: cardiac failure, cardiac dysrhythmias, prolonged PR interval on ECG, hepatic and renal dysfunction
- Adverse effects/Toxicity
  - Peri-oral tingling/numbness, metallic taste, light headedness, irritability/excitability, visual disturbances, mm twitching, confusion/sedation
  - Good news
    - Side-effect profile is predictable and has wide safety margin
    - Short half-life = transiently reversible side-effects

**IV/SC lidocaine**
- Thorough pre-infusion assessment
  - Medical hx, medication hx, pain hx/assessment
  - Consider a lidocaine challenge
  - Protocol sample-email
- When/how to discontinue
  - Once pain is controlled
    - Can result in significantly reduced opioid need
    - Can be tried on gabapentin or other adjuvants
  - If successful, can wean off the lidocaine
  - If not, can be maintained on lidocaine for weeks to months

**GG**
- The lidocaine is ineffective.
- What next?
  - Interventional Pain Management
  - Or??

**GG**
- MEDD ended up at 40 grams
  - Converted to methadone and ultimately went home on methadone 30 mg q8hrs and hydromorphone 30 mg q1hr pm, using up to 5 doses/24hrs, with good pain control
  - How was this accomplished?
Non-pharmacologic management of pain

- Physical modalities
  - Heat, ice, elevation
- Complementary techniques
  - Massage, acupuncture/pressure manipulation, therapeutic touch
  - Music
  - Art
  - Aromatherapy
  - Guided imagery
  - Meditation/prayer
  - Biofeedback
  - Distraction
  - Humor
  - Pet Therapy
  - Trans-epidural Nerve Stimulator Unit
  - Education about illness
  - Hypnosis
  - Cognitive and Behavioral Therapy
  - Better history

Interventional pain management and the nervous system

- Spinal chord
- Nerve roots
- Plexuses
- Ganglia

Interventional pain management in cancer patients

- 10-15% of cancer patients have intractable cancer pain poorly responsive to analgesics
  - Neurolytic techniques
    - Chemical, thermal, surgical
    - Employed for ablation of individual nerve fibers, plexuses, and peripheral nerves
    - For patients with resistant pain and short life-expectancy
  - Neuromodulation
    - Modulates or alters the pain perception
    - Neurosurgical manipulation of pain
    - Spinal cord stimulation
  - Interventional pain management in cancer patients
    - General contraindications
      - Patient refusal
      - Local or systemic infection
      - Uncontrolled coagulopathy (INR > 1.5, plt < 50,000)
      - Lack of technical expertise
      - Uncertainty regarding the dx
      - Uncooperative patient
      - Patient with opiod addiction or drug-seeking behavior
      - Allergy to the drugs to be used
    - Relative contraindications
      - Document neurological deficits prior to procedure
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Interventions

- Head and neck cancer
  - Nerve blocks
    - Trigeminal
    - Glossopharyngeal
  - Occipital
  - Vagal
  - Sphenopalatine ganglion
  - Cervical plexus

Interventions

- Intractable thoracic/chest wall cancer pain
  - Intercostal block
  - Neurolysis
  - Pulsed radiofrequency
  - Intrathecal pump implantation
- Upper abdominal cancer pain
  - Neurolotic inferior hypogastric plexus block
  - Splanchnic nerve block
- Cancer-associated pelvic and perineal visceral pain
  - Neurolotic superior hypogastric plexus block
  - Neurolotic inferior hypogastric plexus block
  - Ganglion impar block and neurolysis
  - Neurolotic of lower sacral roots (neurolotic saddle block)

Interventions

- Intraspinal techniques
  - Epidural infusions of drugs
    - 75-100% effective
    - Clinical data support intrathecal catheter use for more than 3 weeks
    - Epidural regimens greater dosages, larger volumes, and more frequent refills
    - Cost is higher as are infection rates
    - Also increased risk of side effects
    - Displacement/perforation
    - Nausea
    - Irritation
    - Catheter migration
    - Constipation
    - Opioid tolerant

Interventions

- Interventions
  - Head and neck cancer
    - Nerve blocks
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**Interventions**

**Intrathecal**
- Less complications than epidural
- Trial of intraspinal analgesia should be considered before permanent implantation to assess
- Function
- Mood
- Adverse effects
- Meds: Opioids, ziconotide, clonidine, baclofen
- Most frequently used = morphine (FDA approved), fentanyl, bupivacaine, ropivacaine, and clonidine
- Morphine oral 300 mg = 100 mg IV/SC = 10 mg epidural = 1 mg intrathecal

**Vertebroplasty and Kyphoplasty**
- Bone metastases are common in cancer
- 30-80% involve vertebrae
- Primary sources
  - Lung
  - Breast
  - Prostate
- Vertebroplasty
  - Stabilization of pathological fracture via injection of bone cement polymethylmethacrylate
- Kyphoplasty
  - Percutaneous placement of intravertebral balloon, with inflation restoring vertebral height and reducing kyphotic angulation
- Can be costly

**Role of early intervention in cancer pain**
- Neurolytic blocks can
- Provide prolonged pain relief
- Avoid or reduce distressing opioid-induced side-effects
- When to avoid
  - Multiple sites
  - Multiple types
  - Dynamic pain
  - Poor performance status

**Next steps?**
- Misuse, non-medical use
- Abuse
- Addiction
- Physical dependence
- Tolerance
- Pseudo-addiction
- Diversion
- Opioid
- Iatrogenic

**What is addiction?**
- A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations.
- Characteristics:
  - Continued use despite harm and drug craving
  - Tolerance
  - Use in socially inappropriate situations
  - Intense urges or craving
  - Disruption in interpersonal relationships and work or school performance
  - Persistent desire or unsuccessful efforts to cut down or control drug use
  - A dysfunctional emotional response
  - Much participation due to DSM-4 and earlier
  - With DSM-5 there is a new single diagnostic category of substance use disorder
- *American Society of Addiction Medicine*

**Pseudo-addiction**
- An iatrogenic condition where patients display aberrant drug-seeking behaviors mimicking opioid use disorder, but driven by intense need for pain relief.
- Resolves with adequate pain relief
- Can present as
  - Drug hoarding
  - Unsanctioned dose escalation
  - Doctor shopping aggressive demands for more drug

**Tolerance**
- A state of adaptation in which the physiologic changes from drug exposure over time lead to diminished drug effect
- Is uncommon with stable disease
- Tolerance to adverse effects, (sedation, nausea), is beneficial
- An opioid tolerant patient is someone who has been on the following for at least one week
  - 60 mg/day oral morphine
  - 25 mcg/hr transdermal fentanyl
  - 30 mg/day oral oxycodone
  - 8 mg/day oral hydromorphone
  - 25 mg/day oral oxymorphone
  - An equianalgesic dose of another opioid

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**Questions?**
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