



A Teaching Affiliate  
of Harvard Medical School

# Cancer Pain Management and Managing End of Life

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## Case Part 1

Sandy is a 57 yo F with hx of metastatic NSCLC (mets to bone, liver, brain). She reports sharp pain in R upper chest and R shoulder, corresponding with known RUL mass and R humeral met. She is currently taking tylenol without effect.



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# Cancer Pain

- 75% from direct tumor effects
- 25% from cancer therapies
  - Chemotherapy (chemo-induced neuropathy)
  - Surgery (post-thoracotomy/mastectomy)
  - Radiation (mucositis, dermatitis, proctitis)
- Non-malignant pain
  - People with chronic pains also get cancer!



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# Taxonomy of Pain

- Nociceptive Somatic Pain
  - Injury/inflammation to bones and soft tissue
  - Sharp, aching, stabbing, throbbing
  - Focal
- Nociceptive Visceral Pain
  - Organ damage, distention from tumor
  - Difficult to describe, aching/pressure
  - Poorly localized



# Taxonomy of Pain

- **Neuropathic Pain**

- Injury to PNS or CNS
- Abnormal somatosensory processing in PNS/dorsal horn
- Burning, electric, pins/needles
- Parasthesias: unusual sensations
- Dysesthesias: unusual sensations that are painful
- Allodynia: pain induced by nonpainful stimuli
- Hyperalgesia: increased perception of painful stimuli



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# Neuropathic Cancer Pain

- Chemo or radiation induced neuropathy
- Brachial/lumbosacral plexopathies (tumor invasion)
- Post-thoracotomy/tumor involvement of chest wall
- Post-herpetic neuralgia



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# Diagnosing Pain

- Do not just treat the symptom! Must have a diagnosis!
- Diagnosis leads to more effective/targeted therapy
- Goals:
  - Optimize analgesia (pain relief)
  - Optimize ADLs (psychosocial functioning)
  - Minimize adverse events
  - Avoid aberrant drug taking



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# Diagnosing Pain

- Diagnostic history
  - Imaging
  - Labs
  - Other studies
- Past therapy history
  - Medications: dose, adverse effects, efficacy
  - “Oxycodone did not work for me”
    - Were there dose-limiting side effects?
    - Was it ineffective for pain? (not correct dose?)



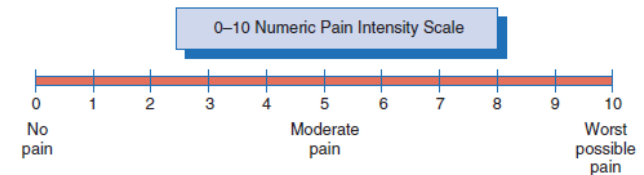
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# Characterizing Pain

- Quality: stabbing, cramping, burning, etc
- Timing: constant, intermittent, incident, post-prandial
- Intensity: VAS scores, FACES scale
  - Best, worst, average
  - Change with pain medications
- Location/radiation
- Exacerbating/alleviating factors
- Functional assessment of pain
- Existential/other nonphysical pain



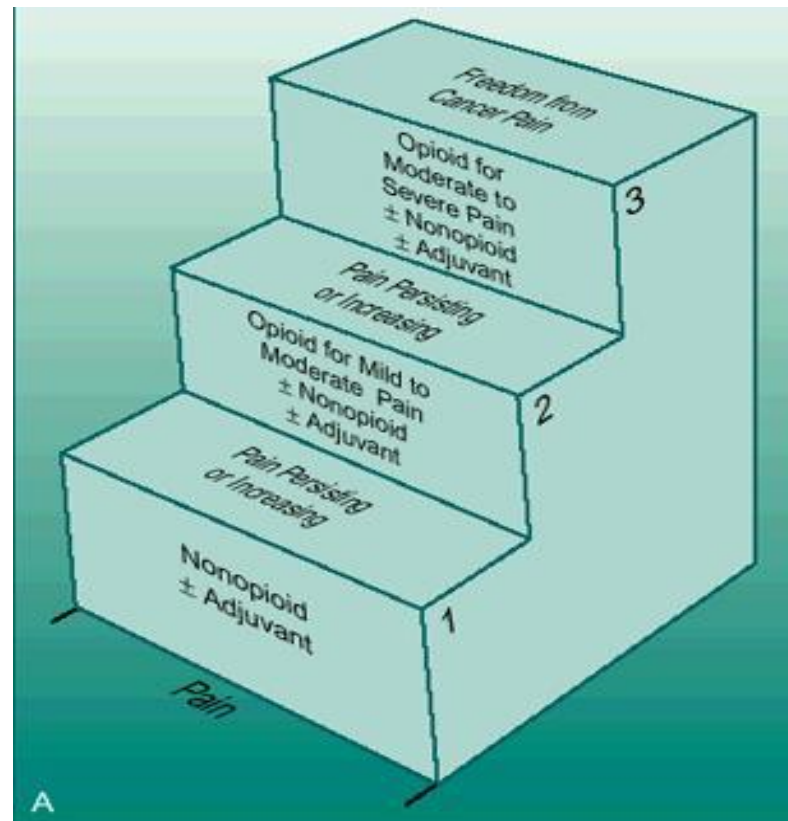
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# The WHO Cancer Pain Ladder



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# Non-opioid Analgesics

- “Adjuvants” or “co-analgesics”
  - Drugs with other indications that may be used as analgesic
  - Can be used as “opioid-sparing”
- Acetaminophen
- NSAIDS – ibuprofen, naproxen, ketorolac
- Local anesthetics – lidocaine patch, diclofenac gel
- Neuropathic agents/anticonvulsants – gabapentin
- Anti-spasmodics – tizanidine, cyclobenzaprine
- Corticosteroids – dexamethasone
- Anti-depressants – velafaxine, duloxetine



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# Neuropathic Cancer Pain

- Anti-depressants
  - TCAs (nortriptyline, amitriptyline)
  - Duloxetine (Cymbalta)
  - Venlafaxine (Effexor)
- Anti-convulsants
  - Gabapentin (Neurontin)
  - Pregabalin (Lyrica)



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# Bone Pain

- Inflammatory pain related to periosteum stretch
  - Nociceptors in periosteum, not in osseous tissue
- NSAIDs
- Corticosteroids
- Bisphosphonates
  - Caution in renal failure



# Corticosteroids

- Pain from:
  - Bony metastases
  - Spinal cord compression
  - Visceral innervation inflammation
    - Hepatic capsule stretch
    - RP lymphadenopathy
- High doses (>16mg/day decadron) are needed for spinal cord compression
- Lower doses (2 to 16mg/day decadron) for other types of pain
- Risk/benefit ratio: increased infection risk, GI bleed, delirium, candida, insomnia



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# “Short-acting” Immediate Release Opioids

- Morphine (MS IR)
- Oxycodone
- Hydromorphone (dilaudid)
- Fentanyl (IV or transmucosal/buccal)
- Combination products (such as Percocet)



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# “Long-acting” Extended Release Opioids

- Extended Release
  - Morphine: MS Contin, Kadian, Avinza
  - Oxycodone: Oxycontin
  - Hydromorphone: none (Exalgo discontinued)
  - Fentanyl: transdermal patch
- Inherently long-acting
  - Methadone



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# Opioid Dosing Guidelines



- Start with short-acting opioid in opioid-naïve patient
  - Usually oxycodone 5-10mg PO q3h PRN, or morphine IR 5-10mg PO q3h PRN
- Also, use short-acting opioids for pre-medication for “incident” pain
  - Prior to working with PT, prior to activity that predictably will cause pain



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# Opioid Dosing Guidelines



- If pt requires frequent (>3-4 doses/day) PRN short-acting doses, consider starting long-acting opioid
- Calculate total 24 hour usage of PRN opioid, and use 50-100% of this to calculate appropriate long-acting dose
  - Consider whether pain stimulus will get better or worse
  - Consider how much PRNs used for incident pain



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# Opioid Dosing Guidelines



- Must continue short-acting PRN opioid for breakthrough pain, at 10-20% of total 24 hour long-acting opioid dose
- Titrate long-acting opioid based on PRN usage
- Continue titrating until pain relief is adequate OR intolerable/unmanageable side effects occur



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## Case Part 1

Sandy is a 57 yo F with hx of metastatic NSCLC (mets to bone, liver, brain). She reports sharp pain in R upper chest and R shoulder, corresponding with known RUL mass and R humeral met. She is currently taking tylenol without effect.



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## Case Part 1

- Opioid naïve, so start oxycodone 5-10mg PO q3h PRN
- 24 hours later: used total 60mg/24hrs, with effect, but not sustained relief
- Convert 50-100% into long-acting
  - $66\% \text{ of } 60\text{mg}/24\text{hrs} = 40\text{mg oxycodone}/24\text{hrs} = \text{Oxycontin } 20\text{mg PO q12h}$
- Continue breakthrough PRN oxycodone at 10-20% of total 24hr long-acting dose
  - Oxycodone 5-10mg PO q3h PRN



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# Case Part 1

- What adjuvants can we add to be opioid-sparing?
  - NSAIDs for bony pain

# End-dose Failure



- As serum levels of long-acting opioid decrease, may correspond to increased pain
  - If q12h dose is due at 8pm, pt may experience worse pain around 5-6pm
- Commonly seen when managing cancer pain
- Change dosing from q12h to q8h



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## Case Part 2

- Now titrated to Oxycontin 30mg PO q12h, but noticing increased pain consistently in morning upon awakening, and in evening.
- She is experiencing end-dose failure
- Change to q8h dosing:
  - 30mg q12h = 60mg/24hrs
  - 60mg/3 (q8h dosing) = Oxycontin to 20mg PO q8h
- Continue PRNs



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# Opioid Side Effects

- If dose escalation leads to side effects:
  - Treat the side effect
  - Pharmacologic approach to lower opioid requirement
    - Add adjuvant analgesic
  - Opioid rotation



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# Opioid Side Effects

- Constipation: start bowel regimen when starting opioid, and titrate as needed
  - No pain, no strain!
  - Will not get better with increased opioid tolerance
- Nausea: Tolerance develops after few days, can consider dopamine antagonist (haldol, zyprexa)
- Pruritus: Tolerance develops. Usually central process; histamine blockers often ineffective
- Sedation: Tolerance may develop, consider CNS stimulant (methylphenidate, modafinil)



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# Opioid Side Effects

- Delirium: Dose-reduction or opioid rotation; consider other causes
- Allergy: True IgE reaction rare; more commonly nonspecific histamine release



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# Opioid Rotation/Equianalgesic Conversions



Opioid	PO (mg)	IV/SC (mg)
Morphine	30mg	10mg
Oxycodone	20mg	n/a
Hydromorphone	7.5mg	1.5mg
Methadone	Unique opioid...	

Fentanyl 25mcg/hr TD = oral morphine 50mg/24hrs



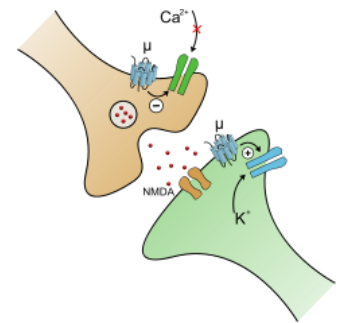
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# Incomplete Cross-Tolerance



- Variations in relative tolerance between opioids at mu receptor, which is function of:
  - Molecular structure and binding affinity of each opioid
  - Patient's individual mu receptor(s)
- When rotating opioids:
  - Reduce calculated equianalgesic dose by 25-50% to account for incomplete cross-tolerance
- Reduce LESS if pain is not adequately controlled
- Reduce MORE if medically frail



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## Case Part 3

- Now titrated to Oxycontin 30mg PO q8h, but with significant sedation and confusion
- After workup, suspicion for opioid-related sedation is high
- You decide to rotate to MS Contin (long-acting morphine)



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# Opioid Rotation/Equianalgesic Conversions

Opioid	PO (mg)	IV/SC (mg)
Morphine	30mg	10mg
Oxycodone	20mg	n/a
Hydromorphone	7.5mg	1.5mg
Methadone	Unique opioid...	

Fentanyl 25mcg/hr TD = oral morphine 50mg/24hrs



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## Case Part 3

- Oxycontin 30mg PO q8h = 90mg oxycodone/24hrs
  - For purposes of this example, we are not incorporating PRN usage
- Ratio of PO oxycodone to PO morphine is:
  - 20:30
- 90mg oxycodone = 135mg PO morphine



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## Case Part 3

- Dose-reduce for incomplete cross tolerance, by 25-50%
  - 135mg PO morphine reduced by 30% = 94.5mg PO morphine / 24hrs
- Divide dose by 3 to obtain q8h dosing
  - $94.5\text{mg} / 3 = 31.5\text{mg}$
  - MS Contin 30mg PO q8h
- PRN dose:
  - 10-20% of total 24 hour long-acting opioid
  - MS IR 10-20mg PO q3h PRN



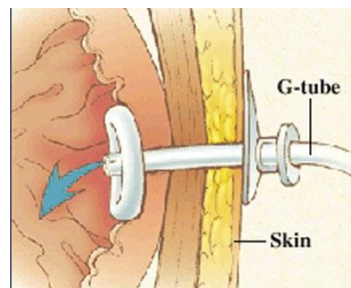
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# Opioids and Special Populations



- Renal insufficiency
  - Avoid morphine – accumulation of neurotoxic metabolites
  - Oxycodone use with caution
  - Dilaudid is generally OK
  - Fentanyl & methadone are OK
- G-tubes
  - Cannot crush extended-release tablets
  - Alternatively, can use methadone, Fentanyl TD patch, Kadian, Avinza



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# Methadone

- Unique opioid with unique properties
- NMDA, norepinephrine, 5HT3 effects
- Unique pharmacokinetics
  - Early alpha, late beta elimination
- Variable and unpredictable half-life
  - 16-150 hours
- When used for pain: Usually TID dosing
  - Steady state in 3-5 days



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# Methadone

- Close monitoring needed until steady-state achieved to reduce risk of sedation, respiratory depression
- QTc prolongation risk
- Med-med interaction risk
- Ask for help!!



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# BWH/DFCI Methadone Conversion

Oral Morphine Equivalent	Mg of oral Methadone	Mg of oral Morphine
< 100 mg/day	1	4
101-300 mg/day	1	8
301-600 mg/day	1	10
601-800 mg/day	1	12
801-1000 mg/day	1	15
>1000 mg/day	1	20
IV methadone is twice as potent as oral methadone		

USE CAUTION PRESCRIBING METHADONE FOR PAIN UNLESS YOU HAVE TRAINING, EXPERIENCE, SUPERVISION



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## Case Part 4

Sandy is now having severe n/v and unable to take any PO meds. She has been taking MS Contin 40mg PO q8h, and MS IR 15-30mg PO q3h PRN with good control of her cancer pain. Her overall pain level is unchanged.



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# Initiating a PCA



- When rotating from PO to IV, must ensure equianalgesic dosing
- Replace long-acting opioid with equivalent “basal rate”
  - MS Contin 40mg PO q8h = 120mg morphine/24hrs
  - PO morphine 30mg = IV/SC morphine 10mg
  - 120mg PO morphine = 40mg IV morphine
  - 40mg / 24 hours = 1.6mg/hr basal rate
- Do you need to dose-reduce (for incomplete cross tolerance)?



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# Initiating a PCA



- PCA bolus dose should be 50-150% of hourly rate
  - Morphine 1.6mg/hr basal rate
  - PCA bolus dose should be range of 1-2mg
- Lockout should be 10-20 minutes
  - Peak effect of bolus will be around 15 minutes
- Hourly maximum – based on clinical judgment
  - Will pt use PCA for anxiety? Concern for AMS?
  - Beware the green light!



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# Managing Pain Crises

Sandy is now on morphine PCA with previously stated settings, now in a pain crisis – reporting 12/10 pain in R shoulder/arm. Pt has been pressing PCA button without adequate relief.



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# Pain Crisis Definition

- Palliative care emergency or “code”
- Severe, uncontrolled pain that causes patient and/or family severe distress
- May be acute in onset, or progressed gradually to intolerable level, but requires immediate intervention

(Moryl, Coyle, & Foley, 2008)

# Pain Crisis Management

- Treat the pain crisis while working up etiology
- Make a pain diagnosis
  - Differentiate reversible vs intractable causes
  - Further workup
- Common etiologies:
  - Fracture/impending fracture
  - Obstructed/perforated viscus
  - Rapidly progressing disease



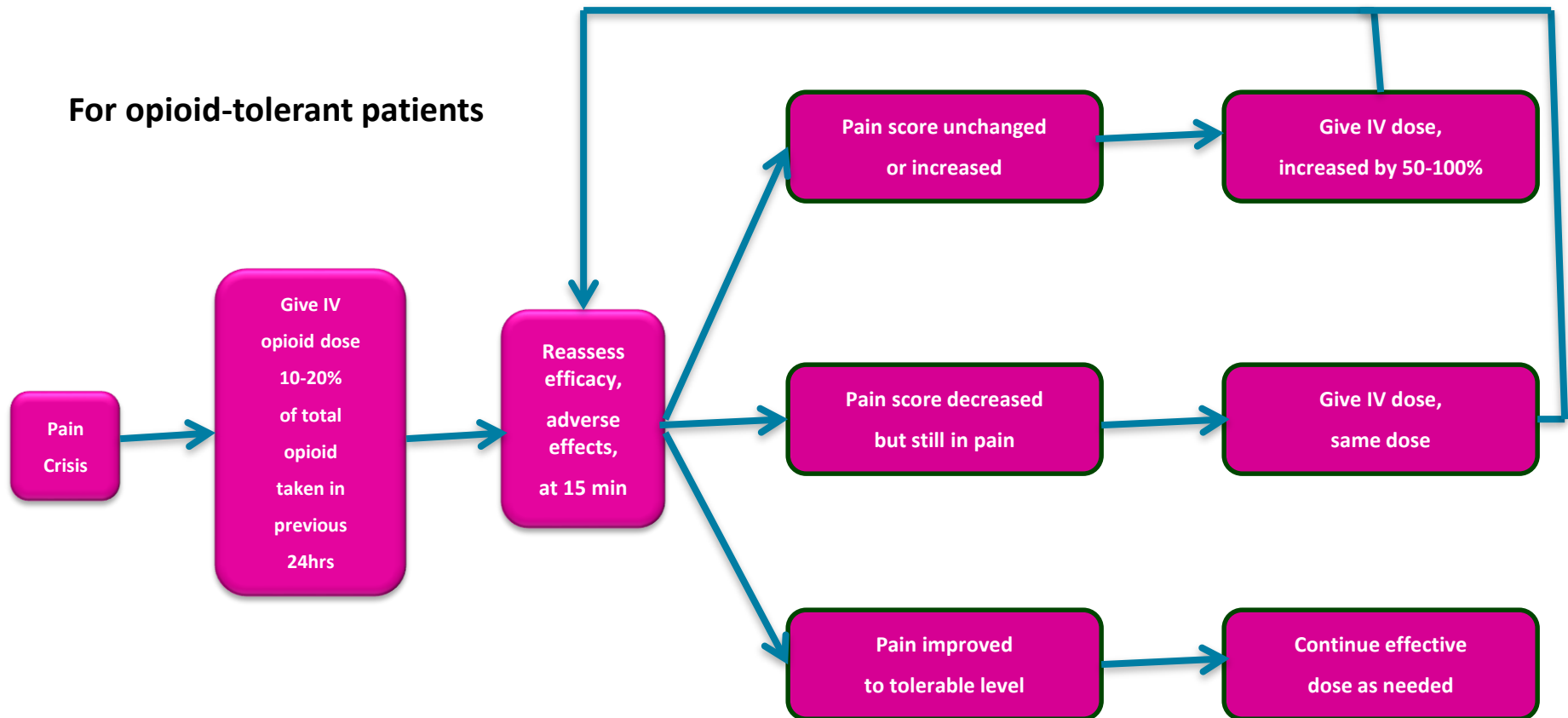
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# NCCN Cancer Pain Guidelines



**For opioid-tolerant patients**



# Titrate Continuous vs Give Bolus



- If worsening pain, would you first titrate continuous infusion, or would you bolus?

Med Order Review

MORPHINE 1 MG/ML (STANDARD CONCENTRATION)  
1-100 Mg/Hr  
IV CONTINUOUS INFUSION in Premixed continuous  
Titrate to comfort

MORPHINE SULFATE  
4-6 MG  
IV PUSH  
Q2H  
PRN: Pain-Moderate, Pain-Severe



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# Titrate Continuous vs Give Bolus



- Steady state will be reached in approximately 8-12 hours after increasing basal rate
  - Would not address acute pain
- Rely on boluses to treat breakthrough pain or crises
- Titrate continuous based on PRN requirements, no sooner than q8h titration



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# Adjuvants in Pain Crisis



- NSAIDs
  - Ketorolac (Toradol)
- Corticosteroids
  - Dexamethasone (Decadron)
- Benzodiazepines – for associated anxiety, does not treat pain
  - Lorazepam (Ativan)
  - *Caution in delirium, older adults*
- Anesthetics
  - Ketamine

(Moryl, Coyle, & Foley, 2008)



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# Opioid-Induced Hyperalgesia



- “Can’t miss” diagnosis
- Paradoxical response – pain worsens as more opioids administered
- May be worsening of underlying pain, or new pain
  - Allodynia: pain from nonpainful stimuli
- Myoclonus frequently seen
  - Often in setting of renal failure, accumulation of neurotoxic opioid metabolites
- Neuroplastic changes in PNS and CNS
  - Sensitization of specific pathways, upregulation of specific receptors

(Lee, Silverman, Hansen, et al, 2011)



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# Opioid-Induced Hyperalgesia

- Treatment
  - Reduce opioid dosage
  - Opioid rotate (renally safe: fentanyl, methadone)
  - Supplement with NMDA receptor modulators/antagonists (ketamine)
  - Benzodiazepines to treat myoclonus
  - Adjuvants

(Lee, Silverman, Hansen, et al, 2011)



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## Case Part 5

- Now Sandy is in new renal failure
- Rotate to renally-safe opioid



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# Naloxone in Cancer Pain

- Cannot treat cancer pain cases as we would narcotic overdose cases
- Goal: reverse clinically significant respiratory depression without significantly reversing analgesia

# Naloxone in Cancer Pain



- Consider when O2 sat <90%, RR<8, unresponsive, pupils constricted
- Consider non-pharmacologic stimuli
- Avoid full 0.4mg naloxone push if not in extremis
- Dilute 0.4mg naloxone (1mL) in 9mL normal saline
- Administer 1-2mL q2-3 min until arousal
- Half-life short; may need naloxone drip, especially if long-acting opioid on board



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## Case Part 6

Sandy presented to your unit in a pain crisis, which is now under control, but unfortunately imaging shows her disease has rapidly progressed. After a family meeting, her care has now shifted to intensive comfort measures. Her prognosis is measured in days.



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# Diagnosing “Dying” in Cancer Patients

- Sometimes, precipitous decline, such as hemorrhage
- More often, gradual deterioration in functional status
  - Bedbound
  - Semi-comatose
  - Only able to take sips of fluid
  - No longer able to take PO meds

# “CMO” vs Intensive Comfort Measures

- “CMO” = comfort measures only
  - Trying to move away from this language
- Intensive Comfort Measures
- Aggressively treat for comfort
- “We will only do things to you and for you that will add/contribute to your comfort.”



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# What does this mean?

- Discontinue “unnecessary” meds
- Discontinue “unnecessary” tests, procedures
  - Lab tests
  - Some vital signs
  - Parenteral fluids, artificial nutrition

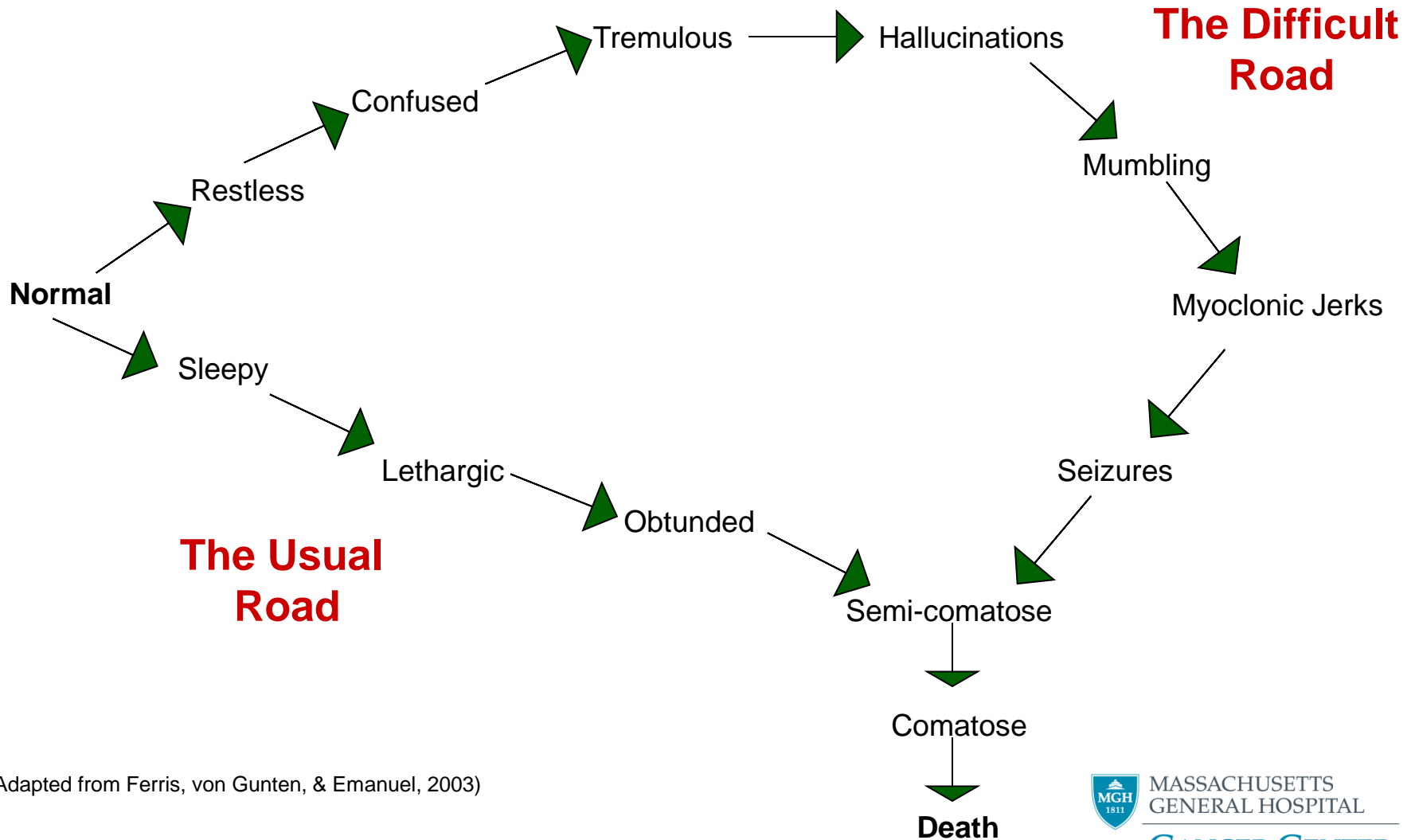


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# Two roads to death



(Adapted from Ferris, von Gunten, & Emanuel, 2003)



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# Common Symptoms at EOL

- Pain
- Shortness of breath/tachypnea
- Secretions
- Delirium



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# Pain

- Assessment
  - Objective signs of pain: moan, grimace, eyebrow furrow, guarding
  - Sometimes difficult to distinguish from other sources of distress

# Pain

- Convert from PO to IV/SC route
- Calculate carefully and deliberately

Opioid	Oral dosing	Parenteral dosing
Morphine	30 mg	10 mg
Oxycodone	20 mg	n/a
Hydromorphone	7.5 mg	1.5 mg

Fentanyl 25 mcg/hr patch = 50 mg oral morphine/24 hours

# Shortness of Breath/Tachypnea

- Opioids often first line for treatment
  - Decrease *perception* of air hunger
  - NO significant respiratory depression, but can decrease RR
  - NO effect on ventilatory parameters (SaO<sub>2</sub>, PCO<sub>2</sub>)
- Benzodiazepines are second line
  - Especially if anxiety component
  - Carefully weigh risk of worse mental status



# Shortness of Breath

- Supplemental oxygen
  - Only beneficial if hypoxemic
  - Should we be measuring O2 sat?
- Other potentially helpful interventions, depending on etiology
  - Steroids
  - Bronchodilators

# Secretions

- Ability to swallow and gag reflex diminished
- “Death rattle” – saliva & other fluids accumulate in posterior oropharynx/upper airway
- Often more distressing for family and us, than it is for patient
- Poor prognostic indicator

# Secretions

- Anticholinergic agents
  - Atropine, levsin, scopolamine all equally effective
    - Risk of altered mental status
  - Glycopyrrolate is less likely to cross blood brain barrier, so less CNS effects
    - IV or nebulizer
  - Scopolamine patch is “long-acting” and may take 12-24 hours to peak
- Avoid deep suctioning
- Reposition, elevate HOB

(Wildiers et al., 2009)



# Delirium

- “Terminal” delirium
- At end-of-life, looks like restlessness, agitation, confusion
- Moaning, groaning, grimacing with delirium might look like pain
- May be reversible causes
  - Infection, medications, constipation, metabolic derangements, undertreated pain
  - Consider workup of reversible causes in light of prognosis, goals of care

# Delirium

- Non-pharmacologic treatment
  - Avoid restraints
  - Avoid unnecessary lines, catheters
  - Family presence, familiar objects from home

(Centeno, Sanz, & Bruera, 2004)



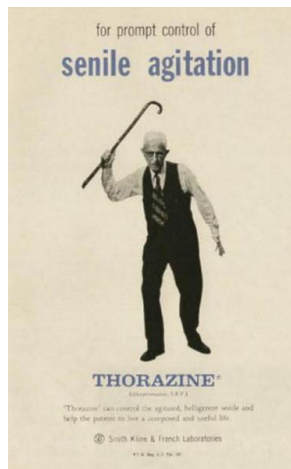
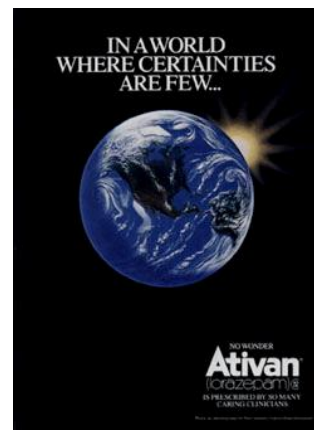
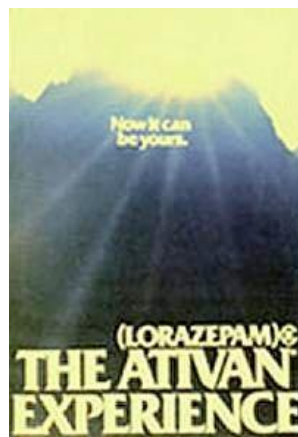
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# Delirium

- Pharmacologic treatment
  - Typical antipsychotics
    - Haloperidol – preferred, fewer anticholinergic effects, many routes of administration
  - Atypical antipsychotics
    - Olanzapine – available in SL wafer, less likely to have extrapyramidal side effects
  - AVOID benzodiazepines

(Centeno, Sanz, & Bruera, 2004)



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# Delirium

- Distinguish delirium as a distressing symptom, from auditory/visual hallucinations that may be comforting
- Family education and reassurance is key
  - Delirium can be especially distressing to caregivers

## Case Part 7

Sandy is in the active stages of dying and is somnolent but still minimally able to communicate. Despite titration of pain medications over the past few days, she is still reporting 10/10 pain and is showing nonverbal signs of pain (grimacing, wincing, eyebrow furrowing, restlessness).

Her family is severely distressed, saying “you wouldn’t treat a dog like this... she is suffering.”



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# Ethical Considerations

- Principle of Double Effect

- A bioethical concept that provides moral justification for an action that has two foreseen effects: one good and one bad.
- The key factor is the intent of the person performing the act. If the **intent** is good (*e.g., relief of pain and suffering*) then the act is **morally justifiable** even if it causes a foreseeable but **unintended result** (*e.g., hastening of death*).



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# Palliative Sedation

- For refractory suffering at end-of-life, despite all other efforts to alleviate the suffering
- Administration of sedating meds in doses to relieve awareness of suffering that may induce unconsciousness
- Intent is to relieve suffering in dying patients, but not to deliberately hasten death
- Distinct from euthanasia, physician-assisted death in that the INTENT differs
- 1997- U.S. Supreme Court decisions



# You Can Control the Narrative



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