PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

Complicated Pain Management in Serious Illness

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Learning Objectives

1. Describe pharmacologic and interventional strategies for management of rectal tenesmus.
2. Describe pharmacologic and nonpharmacologic management strategies for painful wounds.
3. Describe the role of ketamine in the management of complicated pain, neuropathic pain, and opioid-induced hyperalgesia.
4. Describe the role of systemic lidocaine in the management of difficult neuropathic pain.

Rectal Tenesmus

What is it?

- Painful sensation of incomplete evacuation of bowel, resulting in sensation of needing to defecate many times daily

What causes it?

- Rectal carcinoma
- Pelvic malignancies
- Nonmalignant conditions (eg, inflammatory bowel disease)
- Treatment side effects (eg, radiation proctitis)

How do we treat it?

- Definitive treatment (eg, surgery, radiation, chemotherapy)
- Symptomatic management
  - Medications
  - Interventions

Laoire et al. *Palliat Med*. 2017;31(10):975-981.

Rectal Tenesmus – Pathophysiology

- Not fully understood
- Several proposed theories
  - Tumor invasion of lumbosacral plexus resulting in neuropathic pain
  - Tumor inflammation transmitting pain through somatic afferents
  - Smooth muscle contraction transmitting pain through autonomic afferents

Laoire et al. *Palliat Med*. 2017;31(10):975-981.

Rectal Tenesmus – Medications

- Diltiazem 30 mg po q6h; transition to 120 mg ER formulation after 48-72h
  - N = 2; clinically significant reduction in pain, reduction in total daily OME use
- Nifedipine 10-20 mg po BID
  - N = 4; 75% reported improvement in severity of tenesmus and defecation frequency
- Methadone 2.5 mg po q8h (max. starting dose)
  - N = 4; reduction in pain severity from severe to mild in 75% of patients at day 1, 100% of patients were pain free with subsequent dose increases
- Mexiletine 50 mg po TID
  - N = 5; resolution of tenesmus in 100% 1-2 days after intervention, reduction in desire to defecate
- Bupivacaine (rectal or intrathecal)
- Lidocaine

Laoire et al. *Palliat Med*. 2017;31(10):975-981.

Rectal Tenesmus – Interventions

- Anesthetic interventions
  - Lumbar sympathectomy
    - N = 12; 83% achieved complete relief
  - Neurolytic superior hypogastric plexus block from a posteromedian transdiscal approach
    - N = 3; reduction in pain from 9/10 to 2/10 (2/3), complete resolution (1/3)
- Endoscopic treatment
  - Nd-YAG laser
    - N = 8; 50% achieved complete relief; 37.5% partial relief
    - N = 26; 80.8% achieved complete relief

Laoire et al. *Palliat Med*. 2017;31(10):975-981.

Wound Care

Pathophysiology

- Pressure
- Malignant
- Venous/edematous
- Arterial
- Diabetic

- Wounds and surrounding tissues are susceptible to…
  - Infections
  - Inflammation

Palliative Population Is at Increased Risk

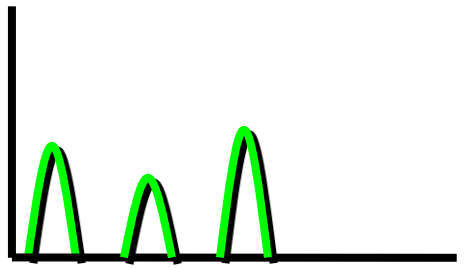
- Impaired oxygenation
  - Low hemoglobin
  - Impaired gas exchange
- Lower blood pressure
- With increased age, skin becomes drier, more fragile, and prone to injury
  - Delayed wound healing
- Decreased activity and mobility
  - Tissue ischemia from prolonged pressure
- Protein-calorie malnutrition

Wound Pain

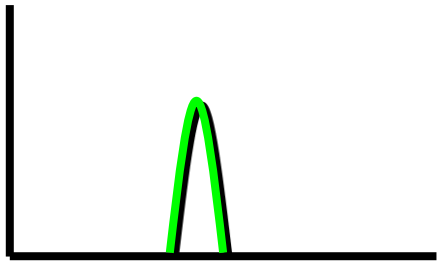
- Nociceptive pain: due to chemical, mechanical, and thermal stimuli
  - Wound edges
  - Surrounding tissues
  - Muscle sheath
  - Periosteum
- Neuropathic pain: due to nerve damage, death

Temporal Profile

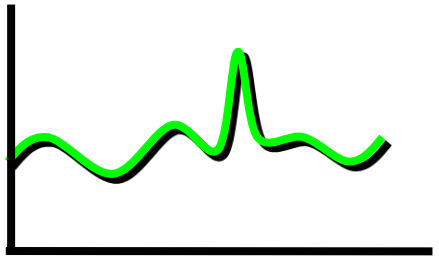
- Acute, intermittent, cyclic
  - Dressing changes
  - Wound cleansing
  - Repositioning



- Acute, intermittent, noncyclic
  - Sharp debridement

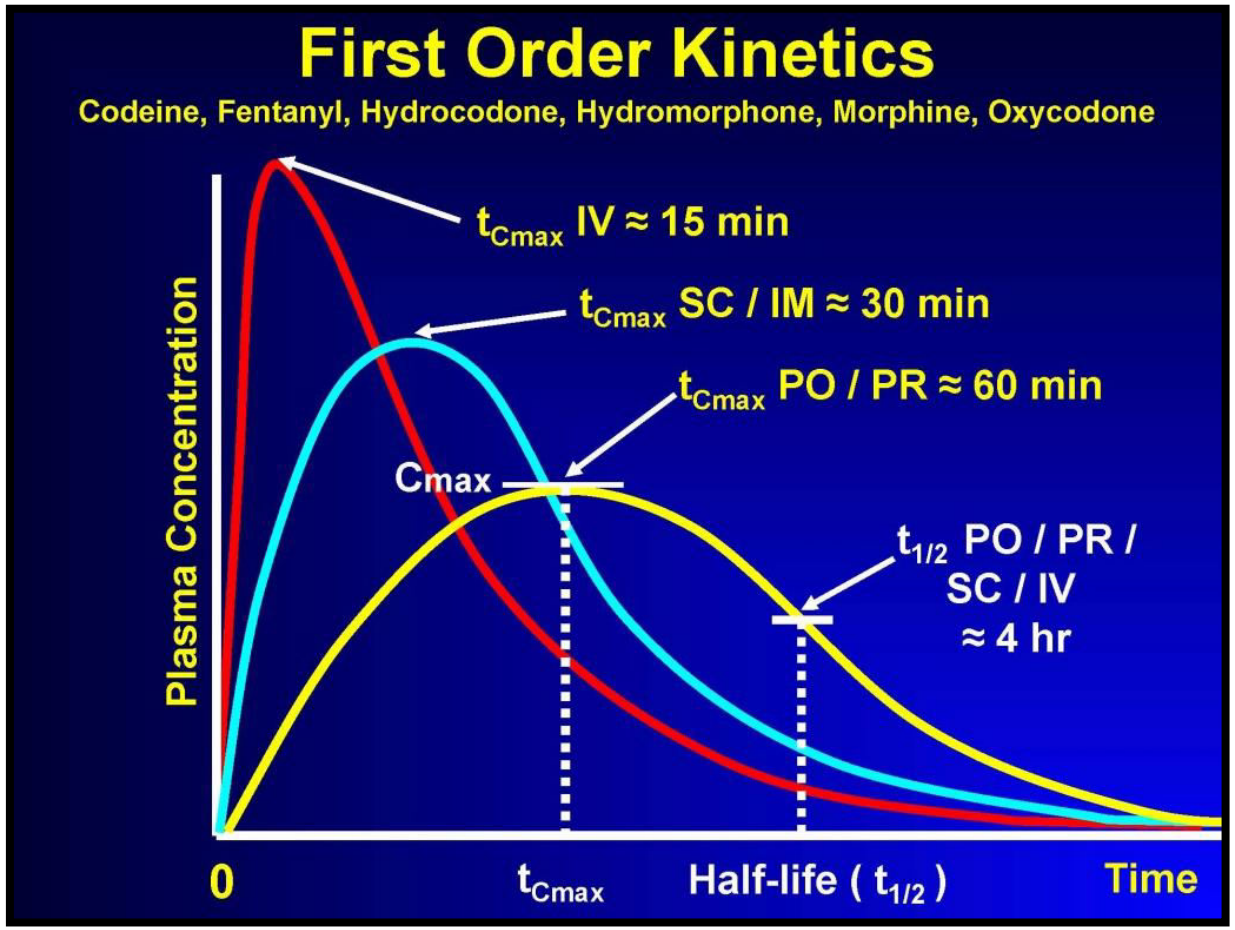


- Chronic
  - Inflammation
  - Underlying disease

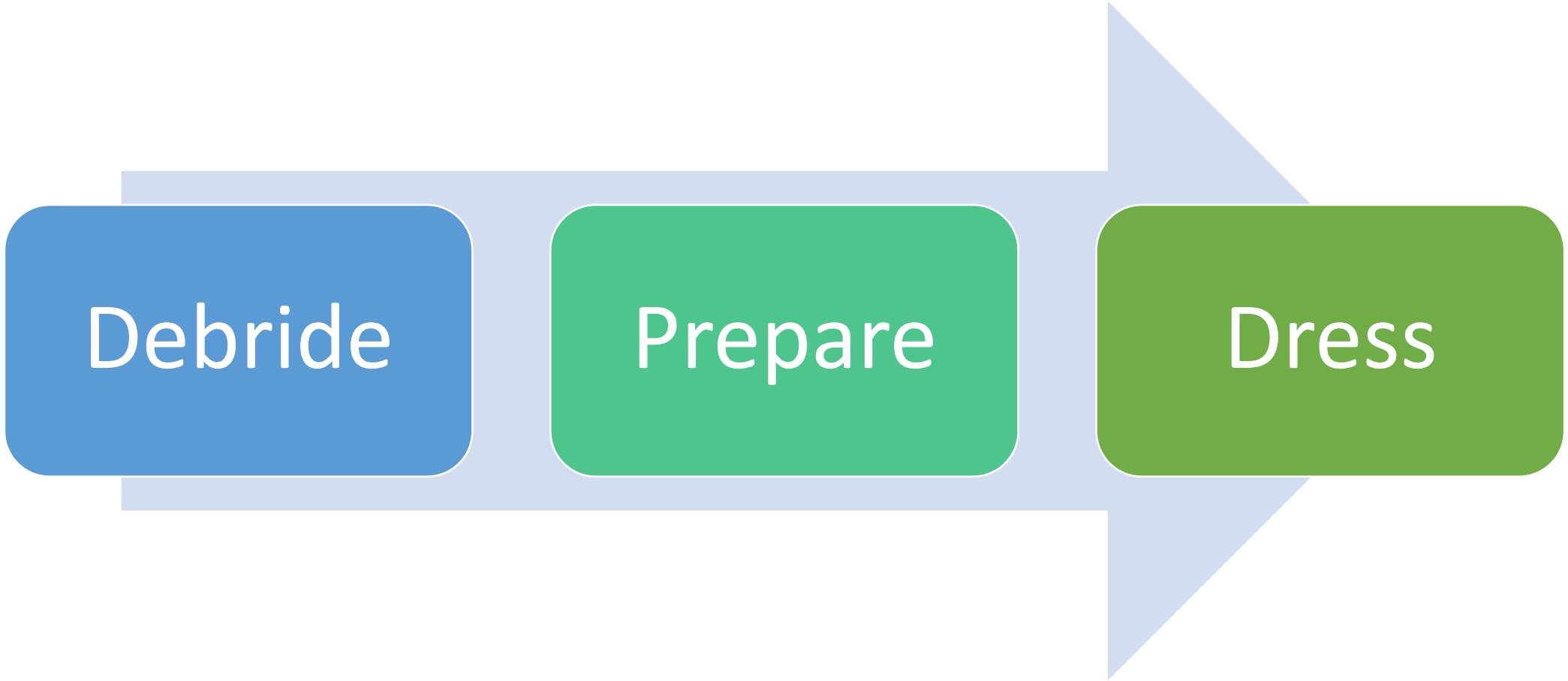


Principles of Analgesia in Wound Care

- Premedicate with analgesics and/or anesthetics for procedures
- Match analgesic to temporal profile of pain
  - Match duration of procedure to $t_{½}$
  - Wait until C_{max} has been reached before starting procedure



Management



Debridement

Surgery

- Aggressive
- Nonaggressive

Autolytic

- Dressings

Enzymes

- Collagenase

Mechanical

- Hydrotherapy

Maggot therapy

Preparation

- Cleansing the wound
  - Saline
  - Water
  - Hydrogen peroxide
  - Sodium hypochlorite (eg, Dakins)
  - Povidone iodine (eg, Betadine)
  - Aniline dyes (eg, Neutral Red, Crystal Violet)
  - Aluminum salts (eg, Burow's Solution)
- Protect skin margins and surrounding tissues
  - Barrier films and creams

Keep the wound warm and moist

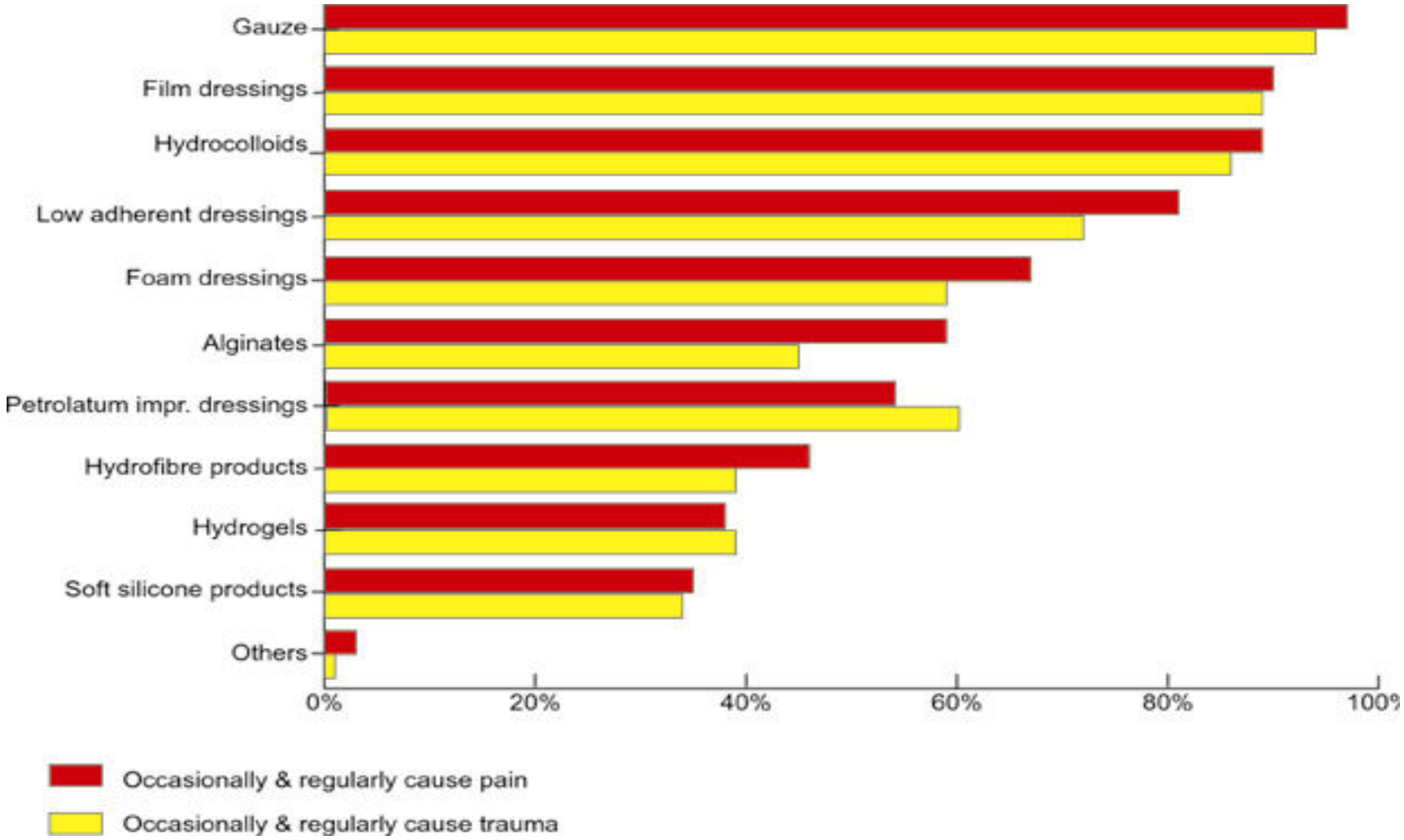
Dressing

- Ideal dressings…
  - Protect the wound from pressure
  - Insulate the wound
  - Remove drainage from the peri-wound surface
  - Adhere to healthy tissue, not to the wound

Types of Dressings

- Foams
- Calcium Alginates
- Hydrogels
- Hydrocolloids
- Transparent Films
- Gauze
- Nonadherent

Types of Dressings (continued)



Dykes. *J Wound Care*. 2001;10(2):7-10.

Local Anesthetics

- Lidocaine
  - Onset of action = 10-15 min
  - t_{Cmax} = 30-60 min
  - Dose < 200 mg/24 hrs
    - 2% solution = 2 g/100 ml; 200 mg = 10 ml
  - Ideally should mix with sodium bicarbonate (buffer) to prevent burning

± Epinephrine
  - Decrease bleeding
  - Risk of tachycardia

Topical Opioids

- Topical 0.1% morphine gel
  - Add 1 ml of 10 mg/ml morphine injection solution to 8 g hydrogel in a plastic container, thoroughly mix (final concentration 1 mg/ml)
  - After cleansing, apply the gel mixture directly to the exposed tissue of the wound or apply to clean gauze and firmly apply to the wound
  - Apply 1-3 times daily or with every dressing change
  - Onset of pain relief: 20 min to a few hours
  - Duration of effect: 2-45 hrs
- Topical 1% ketamine gel
  - 100 mg in 10 g of base
  - Can apply up to 3 times daily
  - Onset of pain relief: 15 min
  - Duration of effect: 2.5 hrs

Woo et al. *Adv Skin Wound Care*. 2015;28(3):130-140.

Neuropathic Wound Pain

- Occurs frequently in wounds due to ischemia, nerve damage
- Pharmacologic management
  - Adrenergic/serotonergic agonists
    - Amitriptyline, nortriptyline, imipramine, desipramine
  - NMDA antagonists
    - Methadone, ketamine
  - Calcium channel blockers
    - Gabapentin, pregabalin
  - Sodium channel blockers
    - Carbamazepine, lidocaine, valproic acid, mexiletine
  - Alpha-2 adrenergic agonists
    - Clonidine, prazosin
  - GABA agonists
    - Baclofen

Management of Odor

- Topical metronidazole
  - Gel, cream, powder
- Silver dressings
- Activated charcoal dressings
- Honey-coated dressings
- Povidone-iodine
- Environmental aids
  - Kitty litter
  - Coffee beans

Multidimensional Suffering

Pain

Depression

Anxiety

Fear

Embarrassment

Social isolation

Self-Assessment!

- WC is scheduled to receive twice weekly dressing changes that last 80 minutes on average. She finds this to be exquisitely painful and the primary team consults Palliative Care for pain management. Which of the following would be most appropriate?
  A. Administer inhaled nitrous oxide 15 minutes prior to initiating procedure
  B. Apply a topical anesthetic, such as lidocaine, at the start of the procedure
  C. Administer oral immediate-release morphine 60 minutes prior to initiating procedure
  D. A and B
  E. All of the above

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What the Heck?

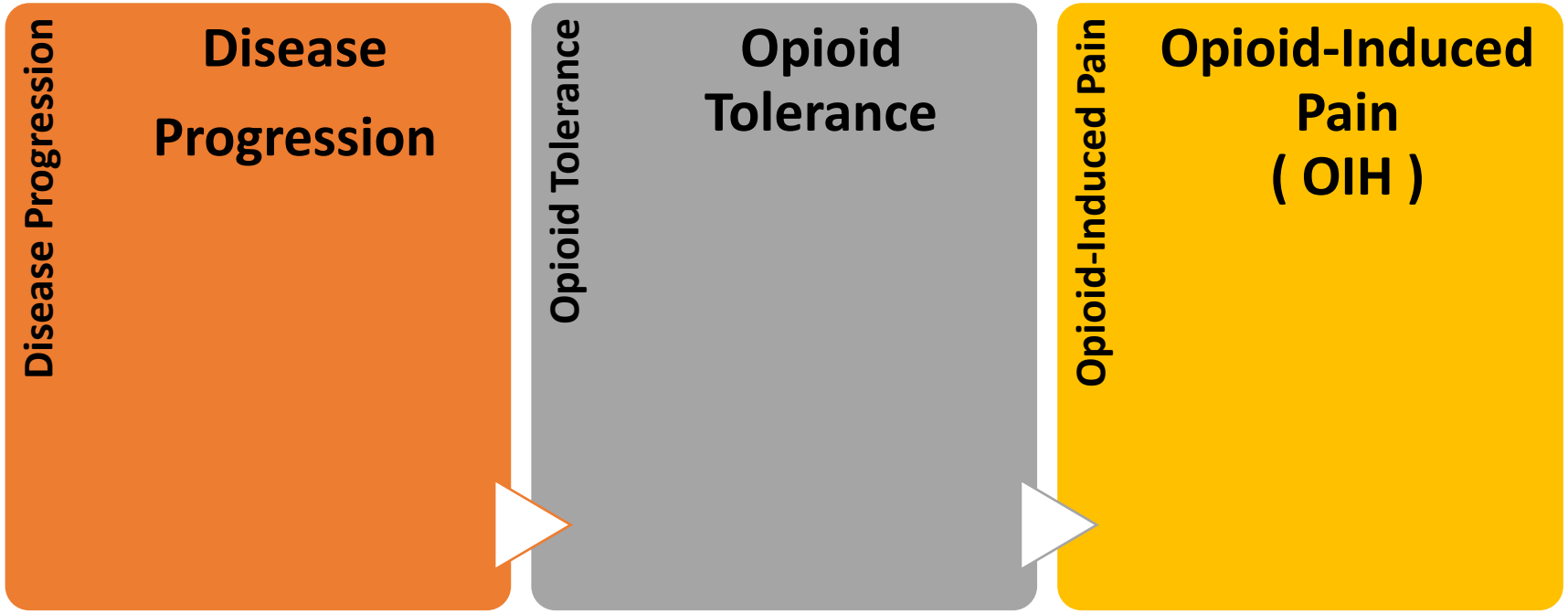
- Mrs. DA is a 68-year-old woman with end-stage breast cancer, admitted to the inpatient hospice unit with poorly controlled pain.
- Her IV hydromorphone infusion has been increased many times, now running at 10 mg/hour with a 5 mg bolus every 15 minutes as needed
  - Between patient and her son (proxy dosing) she's getting a bolus at least once or twice an hour
- The patient's pain seems to be getting worse ironically with dose increases.
- She is having periodic hallucinations, and now she is displaying myoclonus (muscle twitching and jerking).
- What the heck?


• Is it a bird?
• Is it a plane?
• Is it tolerance?
• Is it hyperalgesia?

What's Going On?

A common clinical observation:

- Opioid-requiring patients need a dosage increase to maintain adequate analgesia. Why ?



Chu, Angst, Clark. *Clin J Pain*. 2008;24(6):479-496.

CNS Adverse Effects of Opioids

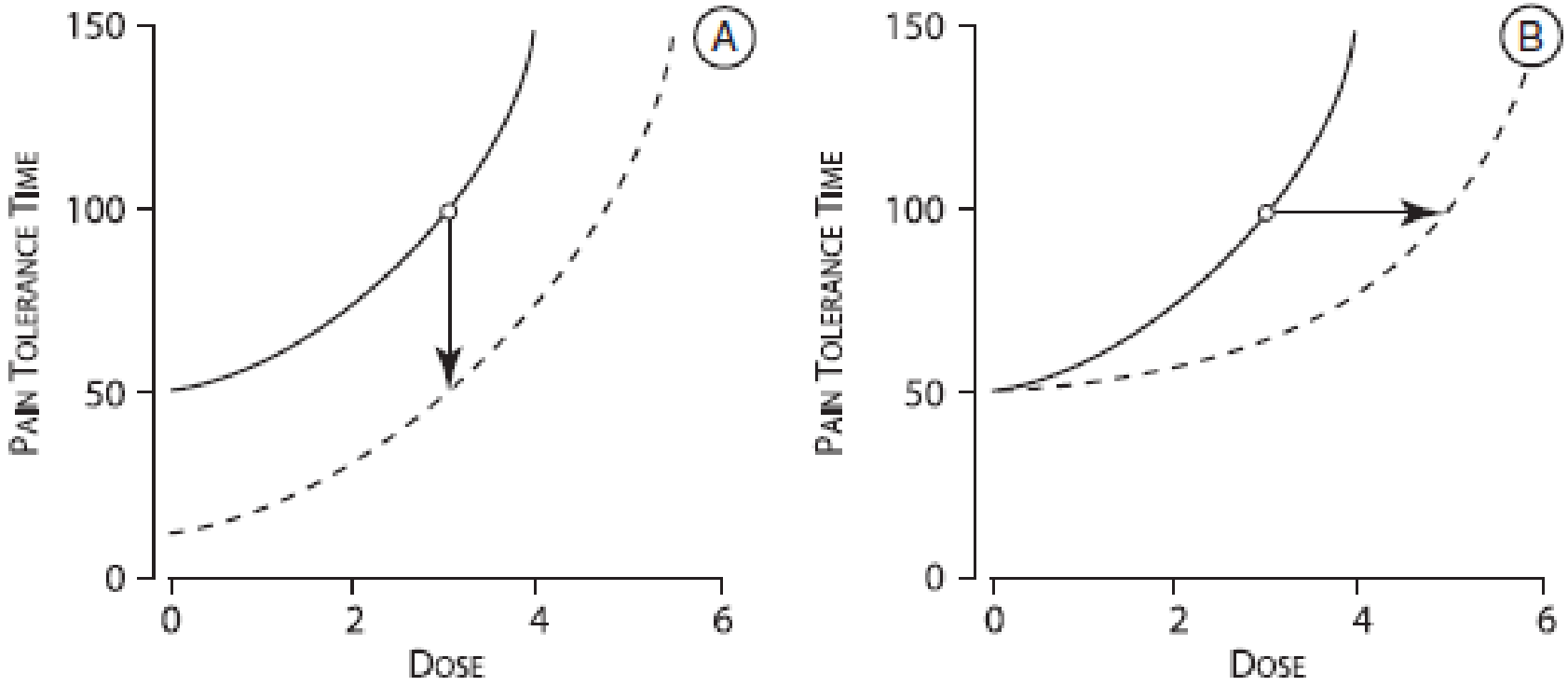
Adverse effects of opioids on CNS (neurotoxicity – damage to nerve cells)

- Reduced level of consciousness
  - Sedation, drowsiness, sleep disturbance
- Adverse effects on thinking process and ability to react
  - Cognitive impairment, psychomotor impairment, delirium, hallucinations, dreams, nightmares
- Direct toxic effect on neurons
  - Myoclonus, seizures, hyperalgesia and tolerance

Opioid-Induced Hyperalgesia and Opioid Tolerance

Two sides of the same coin?

OIH vs Tolerance



A – OIH; B – Tolerance

Chu, Angst, Clark. *Clin J Pain*. 2008;24(6):479-496.

Progression of Disease

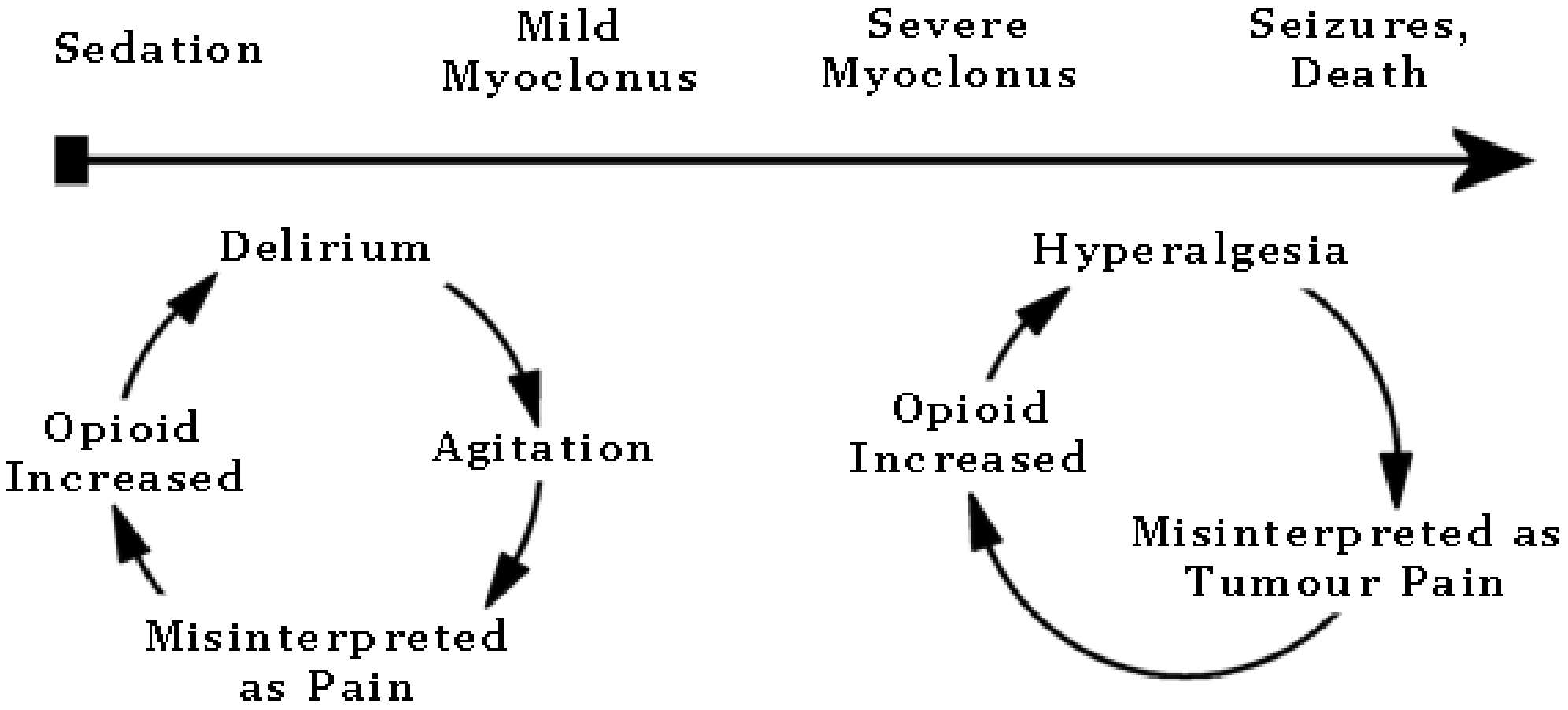
Is it tolerance, or disease progression?

- Difficult to differentiate
- Do we even need to differentiate ?

Patients given chronic opioids for pain and remain clinically stable for a substantial period of time on the same dose will experience increased pain intensity with disease progression

- Increase TDD 25-50% for moderate pain
- Increase TDD 50-100% for severe pain

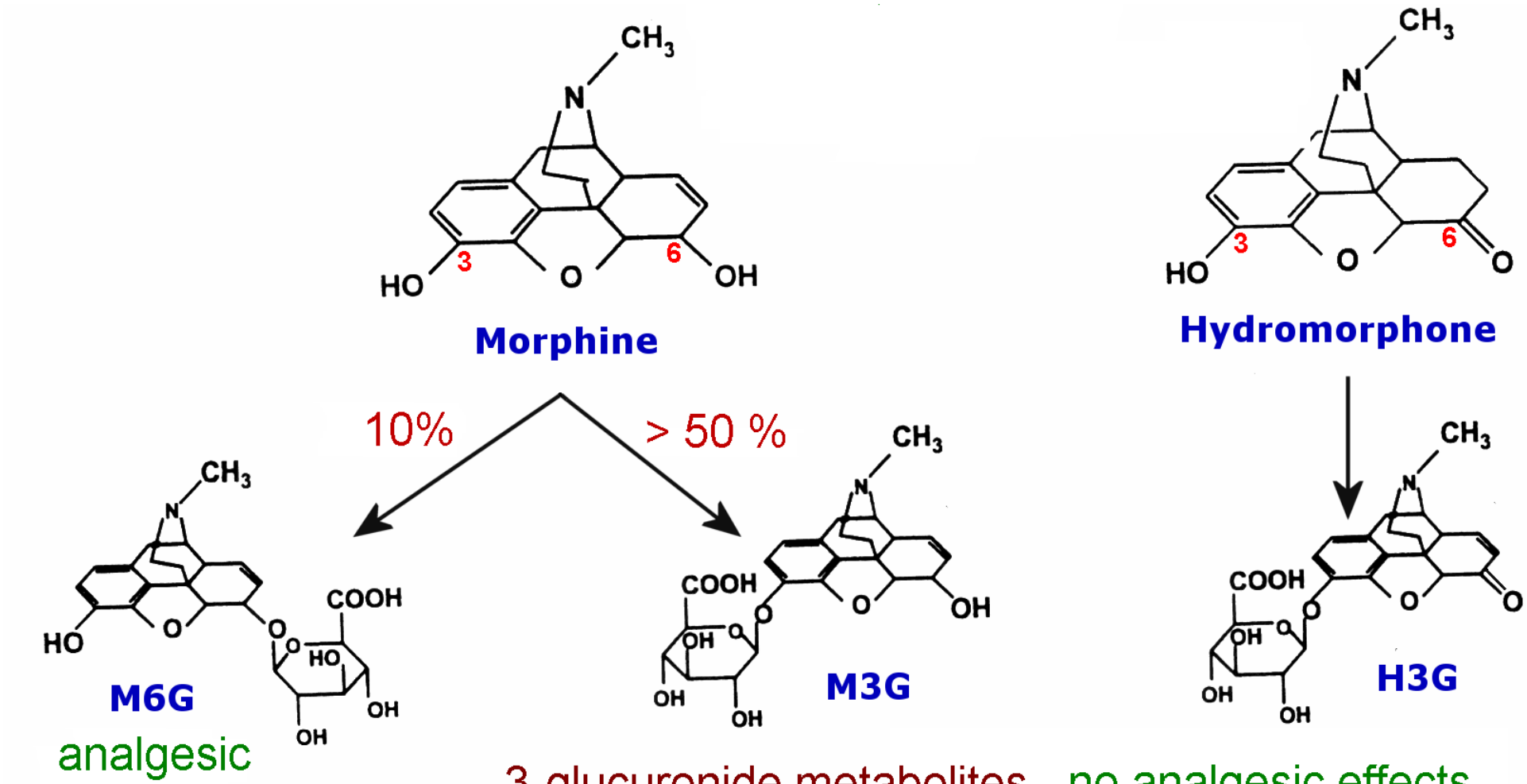
Vicious Cycle of Opioid-Induced Neurotoxicity



Patient Says – Provider Sees

What the patient says…	What the provider sees…
Increased sensitivity to pain stimulus (hyperalgesia)	Any dose of an opioid, but particularly with high-dose morphine or hydromorphone, and in renal impairment/failure
Worsening pain despite increasing doses of opioids	Pain elicited from ordinary nonpainful stimuli, eg, stroking skin with cotton (allodynia)
Pain that becomes more diffuse, extending beyond the distribution of the pre-existing pain	Presence of other manifestations of opioid-induced hyperexcitability: myoclonus, delirium, seizures

Morphine and Hydromorphone
Active Metabolite Accumulation in Renal Failure



3-glucuronide metabolites - no analgesic effects
- potent neuroexcitants
- accumulate in CSF

Management of OIH

- Hydration if clinically appropriate
- Reduce the opioid dose
  - Consider use of an opioid-sparing coanalgesic
    - Acetaminophen, NSAID
- Opioid rotation
  - Allows comparable analgesia at a lower equianalgesic dose
    - Fentanyl
    - Methadone
      - NMDA receptor antagonist
- Ketamine (NMDA receptor antagonist)

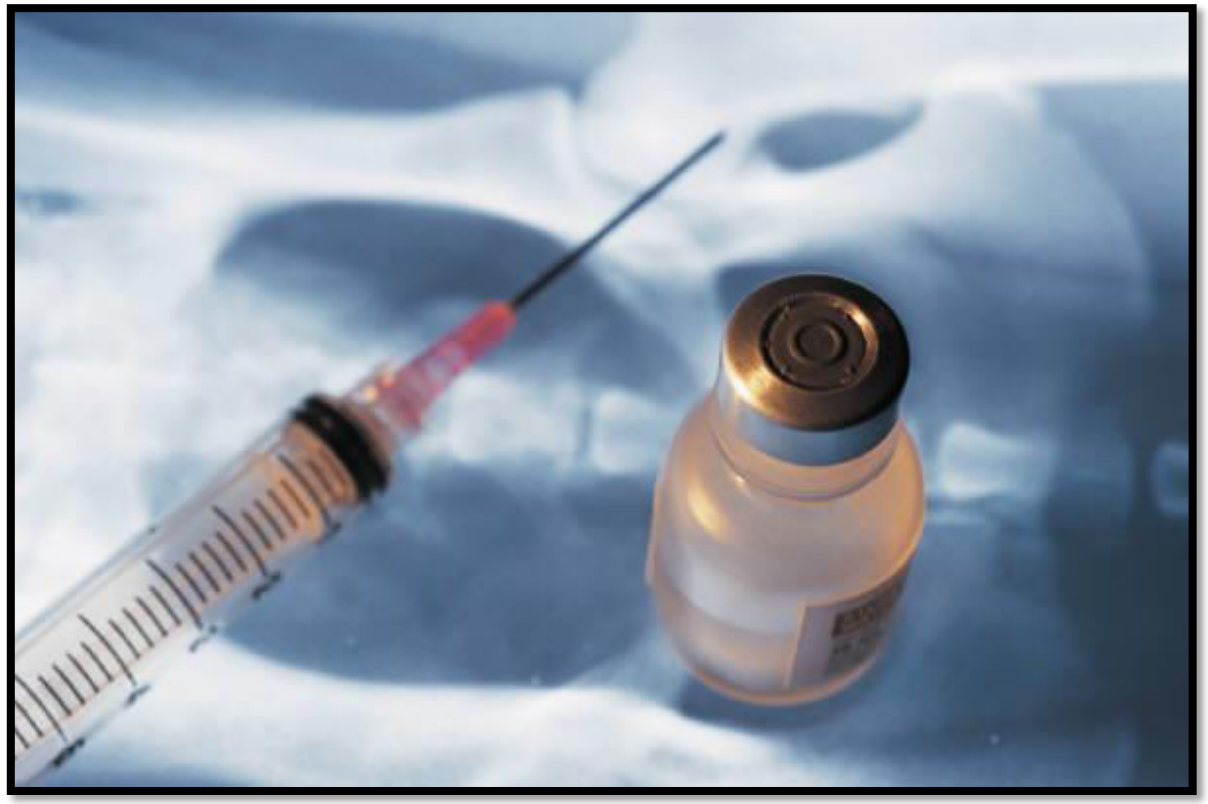
Ketamine Mechanism of Action

- N-methyl-D-aspartate (NMDA) receptor antagonist
- Interact with other sodium and calcium channels
- Weak opioid receptor agonist
- Muscarinic receptor antagonist
- Blocks reuptake of serotonin and norepinephrine

Quibell, Prommer, Mihalyo, Twycross, Wilcock. Ketamine. *J Pain Symptom Manage*. 2011;41(3):640-649.

Routes of Administration

- Intravenous
- Intramuscular
- Intrathecal
- Epidural
- Subcutaneous
- Oral
- Transdermal
- Sublingual
- Intranasal
- Rectal



Analgesic Dosage

Intravenous/subcutaneous bolus

- 2.5-5 mg as needed

Intravenous/subcutaneous infusion

- Starting dose: 0.2 mg/kg/hr or 100-200 mg/24 hrs
- Usual dose: 100-400 mg/24 hrs
- Maximum reported dose: 3.6 gm/24 hrs

Oral

- Starting dose: 10 mg every 6-8 hrs
- Maximum reported dose: 240 mg/day

Quibell, Prommer, Mihalyo, Twycross, Wilcock. Ketamine. *J Pain Symptom Manage*. 2011;41(3):640-649.

Pharmacokinetics

Onset of action: 5 minutes (SC), 30 minutes (PO)

Hepatic metabolism to active metabolite norketamine

- Extensive first pass metabolism after oral administration

Duration of action: 2 hours (IM) and 4-8 hrs (PO)

Renally excreted (< 10 % unhanged)

Quibell, Prommer, Mihalyo, Twycross, Wilcock. Ketamine. *J Pain Symptom Manage*. 2011;41(3):640-649.

Adverse Effects

- Fatigue
- Nausea
- “Emergence phenomena”
- Tachycardia
- Hypertension
- Dizziness
- Nystagmus

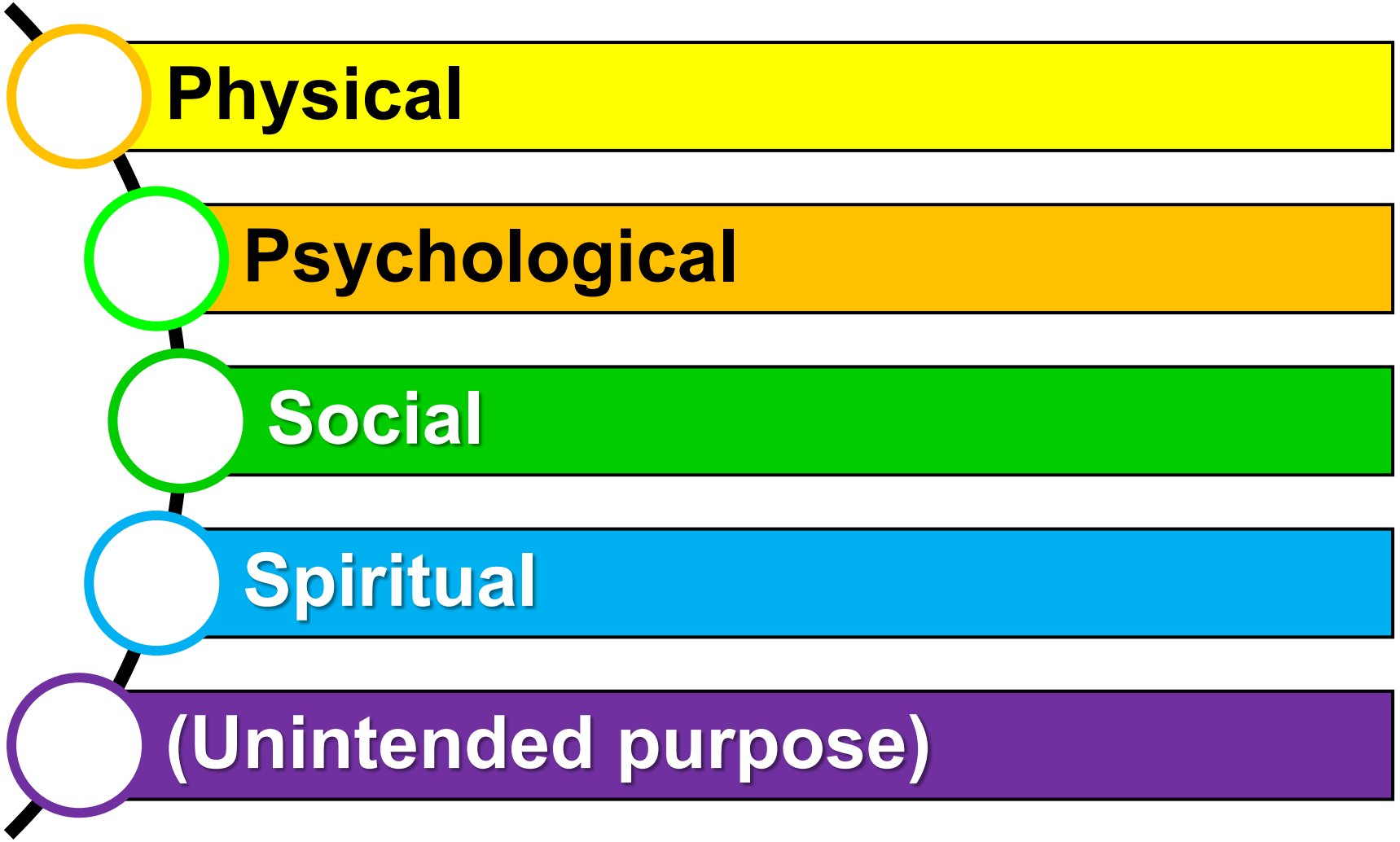
Quibell, Prommer, Mihalyo, Twycross, Wilcock. Ketamine. *J Pain Symptom Manage*. 2011;41(3):640-649.

Sure, but does it work?

- “Current evidence is insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of refractory cancer pain.
- The evidence was of very low quality, meaning that it does not provide a reliable indication of the likely effect, and the likelihood that the effect will be substantially different is high.
- Rapid dose escalation of ketamine to high dose (500 mg) does not appear to have clinical benefit and may be associated with serious adverse events.
- More randomized controlled trials (RCTs) examining specific low-dose ketamine clinical regimens in current use are needed.”

Bell, Eccleston, Kalso. *Cochrane Database Syst Rev*. 2017;6(6):CD003351. Published 2017 Jun 28.

Total Pain – Dame Cicely Saunders



What about other difficult to treat pain syndromes?

Systemic Lidocaine for Neuropathic Pain

- Neuropathic pain: pain resulting from a lesion or disease of the somatosensory system
  - Including peripheral fibers and central nervous system
- Analgesic properties of lidocaine
  - Inhibition of ectopic neuronal discharges by modulating the activation state of voltage-gated sodium channels
- Limited safety and long-term data available
- Cochrane review published in 2019

Iolascon. *Neurorehabilitation*. 2020;47:247-249.

Cochrane Systematic Review

- Lidocaine is more effective than placebo in reducing pain
  - Mean change in 0-100 VAS ranged from -17.3 to -5.22
  - Higher proportion of responders (patients reporting ≥ 30% decrease in pain intensity) reported with lidocaine or mexiletine as compared to placebo
  - No difference between intervention vs other analgesics (eg, carbamazepine, gabapentin, amantadine, or morphine) for pain relief or adverse effects
  - Patients receiving systemic lidocaine or oral analogs have a significant increased risk of adverse effects, especially somnolence and lightheadedness vs placebo

Challapalli, Tremont-Lukats, McNicol, Lau, Carr. *Cochrane Database Syst Rev*. 2019;2019(10):10.1002/14651858.CD003345.pub2.
Iolascon. *Neurorehabilitation*. 2020;47:247-249.

Lidocaine for Neuropathic Pain

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

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

Ferrini, Paice. *J Support Oncol*. 2004;2(1):90-94.

Lidocaine for Neuropathic Pain

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

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

Ferrini, Paice. *J Support Oncol*. 2004;2(1):90-94.

Lidocaine for Neuropathic Pain

- Lidocaine infusion
  - If challenge effective or partially effective, and tolerated: start continuous infusion SQ or IV:
    - 0.5-2 mg/kg per hour, using lowest possible dose to control pain
  - Gradually titrate downward to find lowest effective dose
  - Monitor for signs of toxicity, especially with dosage increases

- Adverse effects
  - Perioral numbness
  - Tinnitus
  - Sedation
  - Light-headedness
  - Headache
  - Metallic taste
  - EKG changes?
  - Seizures

Ferrini, Paice. *J Support Oncol*. 2004;2(1):90-94.

Lidocaine for Neuropathic Pain

- Lidocaine infusion
  - Reduce opioids rapidly if patient has sxs opioid toxicity (particularly sedation)
  - Pain relief generally seen at 1-2 mg/kg/hr
    - Blood levels often less than 3 mcg/ml and toxicity rare
    - At 4-6 mcg/ml patients complain of lightheadedness, numbness around tongue or mouth and/or dizziness
- Protocol for home infusion
  - Administer SQ or IV?
  - Bolus, continuous, or both?
  - Requires table caregiving situation (24/7)
  - Visiting nurse 2-7 times/week
  - Infusion should be adjusted as required
  - Patient/caregiver should be adequately educated and able to describe situation to RN

Ferrini, Paice. *J Support Oncol*. 2004;2(1):90-94.

Self-Assessment!

- Which of the following is the predominant mechanism of action of ketamine in the management of difficult pain syndromes?

A. Mu-opioid agonist
B. NMDA receptor antagonist
C. Blocks voltage-gated sodium channels
D. Kappa antagonist

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Conclusion

- Rectal tenesmus is a distressing symptom that is only partially opioid-responsive and challenging to treat
- Painful wounds are very common in the palliative care population, and managing the pain can be challenging
- Ketamine MAY be considered for difficult pain, particularly with a neuropathic component, and perhaps in opioid-induced hyperalgesia
- Lidocaine is not a first line option; use is associated with adverse effects, and systematic review shows no clear advantage over more traditional analgesics or adjuvant analgesics

Additional References

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