Not Quite the Kitchen Sink

MOQC Biannual Meeting

January 2020

Michael A. Smith, PharmD, BCPS

Disclosures

- No relevant financial disclosures
- Panel member for National Comprehensive Cancer Network (NCCN) Adult Cancer Pain Guidelines

Learning Objectives

- Review current cancer pain guidelines
- Discuss cancer pain management with the following agents: buprenorphine, methadone, ketamine, and lidocaine
- Understand limitations and monitoring requirements for the use of buprenorphine, methadone, ketamine, and lidocaine

Patient Case

- WD is a 36yo M who presents with increased pain around his GJ tube and malnutrition

- Notable medical history
  - Pancreatic cancer s/p whipple 2017, gemcitabine 2018
  - Neuroblastoma s/p nephrectomy as an infant
  - Leydig cell tumor
  - Spinal Schwannomas
  - Gastroparesis s/p GJ one month ago
  - Chronic back pain and opioid dependence

Patient Case cont'd

- Major complaints
  - Pain – chronic back pain, generalized abdominal pain/cramping with concerns for recurrent pancreatic cancer, visceral pain at site of G tube
  - Gastroparesis with nausea and vomiting

- Patient is strict NPO

Cancer Pain Guidelines

- NCCN Adult Cancer Pain Guidelines
  - Updated annually with new versions each January

https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf

Current Pain Medications

- Hydromorphone PCA:
  - Settings: 0.2 mg/hr, 0.4 mg Q10min
  - 24 hour usage: 400-600 OMEs
- Pain is well controlled on the PCA with pain score of 5-7/10 consistently; patient is also sleeping well with no apparent ADEs
- Now what?

Planning for the Future

- Current goals of care are to discharge home, but patient remains strict NPO and cannot go home on an oral regimen.

Kitchen Sink Time

- Buprenorphine
- Ketamine
- Lidocaine (mexiletine)
- Methadone

How to Approach

- Safety, first and always
- Effective for patient's type of pain
- What's left and what's best (for now)

	Safety	Effective	Best
Buprenorphine			
Ketamine			
Lidocaine			
Methadone			

Safety: Buprenorphine

- No true contraindications other than allergies
- No dosage adjustments in renal disease
- May consider lower starting doses in severe hepatic disease

Safety: Ketamine

- No true contraindications other than allergies
- No dosage adjustments in renal or hepatic disease
- Caution:
  - Tachycardia, hypertension
  - Head injuries

Safety: Lidocaine

- Do not use in patients with significant cardiovascular disease
- No dosage adjustments in renal disease
- Low and slow in hepatic disease
- Large pharmacokinetic variability…

Safety: Methadone

- Do not use in patients with prolonged QTc, significant cardiovascular disease, or medication adherence issues
- No dosage adjustments in renal or hepatic impairment, but still go low and slow

Check Time

	Safety	Effective	Best
Buprenorphine	✓		
Ketamine	✓		
Lidocaine	✓		
Methadone	✓		

Effective: Buprenorphine

- Nociceptive pain
  - Effects similar to traditional opioid with lower risk of respiratory depression and side effects

- Mechanism
  - Partial mu agonist, kappa antagonist, delta agonist, ORL-1 agonist
    - Very high affinity for mu opioid receptors

Don’t Forget Your Receptors

Receptor	Agonism	Antagonism
Mu	• Supraspinal analgesia • Respiratory depression • Euphoria • Sedation • Decreased GI motility • Dependence	Mostly opposing effects
Kappa	• Spinal analgesia • Sedation • Dyspnea • Dependence • Dysphoria • Respiratory depression	• Decreased stress-induced drug seeking behavior • Antidepressant
Delta	• Pscyhomimetic • Dysphoria	Mostly opposing effects • Anxiety

Pharmacokinetics

- A: about 50% oral bioavailability
  - Naloxone – low sublingual and GI bioavailability with high first pass metabolism
- D: highly protein bound with extensive distribution
- M: liver metabolized, CYP 3A4 substrate
- E: fecal (70%) and renal (30%) elimination
  - Dissociation half-life of 5-6 hours
  - Elimination half-life of 24-42 hours
- Analgesic effect of about 6 hours
  - Formulation dependent

Buprenorphine

	Safety	Effective	Best
Buprenorphine	✓	✓	
Ketamine	✓		
Lidocaine	✓		
Methadone	✓		

Effective: Ketamine

- Nociceptive pain (via opioids) and refractory neuropathic pain

- Mechanism:
  - Non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist with SNRI activity
  - Minor opioid agonism, but likely not clinically relevant
  - Induces dissociative anesthesia
  - Functional and electrophysiological dissociation between the thalamocortical and limbic systems
  - Prevents higher centers from perceiving auditory, visual, or painful stimuli

Pharmacology

- Mechanism:
  - Non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist with SNRI activity
  - Minor opioid agonism, but likely not clinically relevant
  - Induces dissociative anesthesia
  - Functional and electrophysiological dissociation between the thalamocortical and limbic systems
  - Prevents higher centers from perceiving auditory, visual, or painful stimuli

NMDA Antagonism

- NMDA glutamate receptors are widely present in the CNS
  - Play a major role in glutaminergic system
  - Glutamine – excitatory neurotransmitter released with noxious peripheral stimuli
- Ketamine allosterically binds to NMDA receptor preventing glutamate signaling
- NMDA activity – plays a role in neuropathic pain signaling

Pharmacokinetics

- A: oral bioavailability 16%
- D: moderate protein binding and distribution
  - Brain, heart, lungs first, then redistribution
- M: liver metabolism via demethylation
- E: renal elimination of mostly changed drug (no dose changes needed)
  - Half-life of 2 to 3 hours
- Onset and Duration
  - IV within 30 seconds and full effect within 2 minutes lasting up to 60 minutes

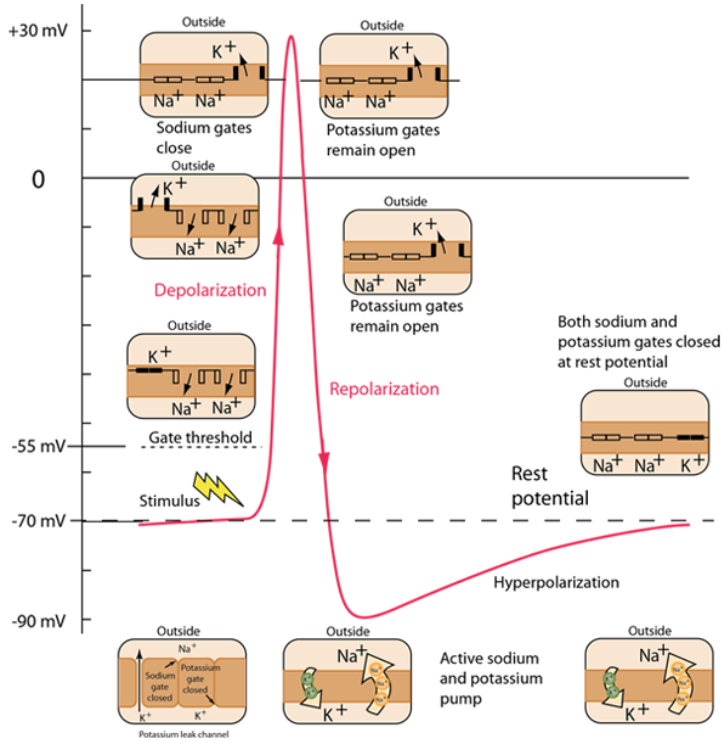
Ketamine

	Safety	Effective	Best
Buprenorphine	✓	✓	
Ketamine	✓	✓	
Lidocaine	✓		
Methadone	✓		

Effective: Lidocaine

- Nociceptive and neuropathic pain

- Mechanism:
  - Sodium channel blockade



http://hyperphysics.phy-astr.gsu.edu/hbase/Biology/actpot.html

Pharmacokinetics

- A: oral bioavailability 90% (mexiletine)
- D: moderate protein binding and distribution
- M: liver metabolism
- E: biphasic, prolonged in CHF, liver disease, shock, and severe renal disease
  - Usual half-life is 1-2 hours
- Onset and Duration
  - Effects usually seen within 4 hours of initiation

Lidocaine

	Safety	Effective	Best
Buprenorphine	✓	✓	
Ketamine	✓	✓	
Lidocaine	✓	✓	
Methadone	✓		

Effective: Methadone

- Nociceptive and neuropathic pain

- Mechanism:
  - Mu agonist
    - Kappa and delta agonism to a lesser extent
  - NMDA antagonist
  - Inhibits the re-uptake of serotonin and norepinephrine

PK: Absorption

- 80% bioavailable after oral administration
- Rapidly absorbed from the GIT
- Peak plasma concentrations reached 2.5-4 hours post-dose
- Rectal bioavailability is approximately 76%

Toombs. Am Fam Physician. 2005; 71(7):1353-8.

PK: Distribution

- Lipophilic
- 88% plasma protein bound
  - Primarily binds alfa-1 acid glycoprotein
- Vss 1.7-5.3 L/kg in chronic pain patients

Toombs. Am Fam Physician. 2005; 71(7):1353-8.

PK: Metabolism

- Extensively liver metabolized by N-demethylation to inactive drug
- 3A4 (2B6, 2C8, 2C9, 2C19, 2D6)
- Induces its own metabolism
- Empiric dose reductions survey:
  - 1 – 10%
  - 4 – 25%
  - 1 – 30%
  - 1 – 50%
  - 1 – no reduction

Toombs. Am Fam Physician. 2005; 71(7):1353-8.

Drug Interactions: Inhibitors

Drug	% Methadone Change	Dose Adjustment
Fluconazole	+35	?
Fluoxetine	?	?
Fluvoxamine	?	?
Clarithromycin	?	?
Ciprofloxacin	?	?
Amiodarone	?	?
Amitriptyline	?	?

Drug Interactions: Inducers

Drug	% Methadone Change	Dose Adjustment
Carbamazepine	?	?
Glucocorticoids	?	?
Phenytoin	-50	?
Rifampin	-30-65	?
Phenobarbital	?	?
Efavirenz	-48	?
Ritonavir	-36	?

PK: Elimination

- Long and variable elimination half-life
  - Range: 5-130 hours
  - Mean: 20-35 hours
- Low extraction ratio drug
- Fecal, renal, and minor biliary
- Changes in urinary pH affect elimination
  - pH above 6 – renal clearance ~4%
  - pH below 6 – renal clearance ~30%

Toombs. Am Fam Physician. 2005; 71(7):1353-8.

Methadone

	Safety	Effective	Best
Buprenorphine	✓	✓	
Ketamine	✓	✓	
Lidocaine	✓	✓	
Methadone	✓	✓	

Check Time

	Safety	Effective	Best
Buprenorphine	✓	✓	
Ketamine	✓	✓	
Lidocaine	✓	✓	
Methadone	✓	✓	

Best (For Now): Buprenorphine

- Sublingual and parenteral administration available for now and later
- Would help decrease his opioid related risks

Best (For Now): Ketamine

- Parenteral administration available for now
- Oral administration available for later
- Would help decrease his opioid consumption

Best (For Now): Lidocaine

- Parenteral administration available for now
- Oral (mexiletine) available for later

Best (For Now): Methadone

- Parenteral administration available for now
- Oral administration available for later
- Would help decrease his opioid consumption

So What Did We Do?

- Patient using 26 mg IV hydromorphone via PCA with pain scores not changing 9-10/10
- What do you think we did?
- What would you have done?

Buprenorphine!

- PCA stopped at 0200
- Buprenorphine 1 mg at 0800 Q30Min x 4 doses
- Then buprenorphine 2 mg Q4HRs x 4 doses

(plus some ketorolac)

Not Quite the Kitchen Sink

MOQC Biannual Meeting

January 2020

Michael A. Smith, PharmD, BCPS