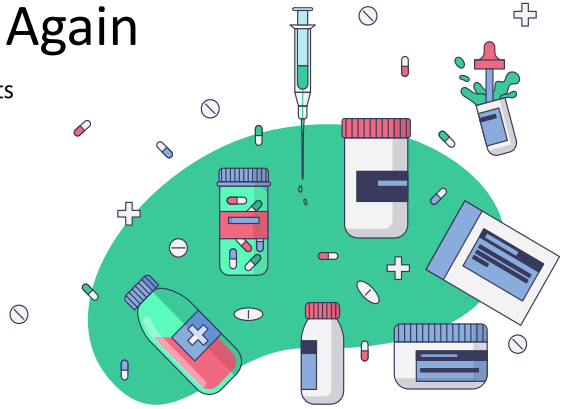
What's Old is New Again

Five Favorite Meds Pharmacists Want You To Know About

Michelle Mikus, PharmD
October 2024

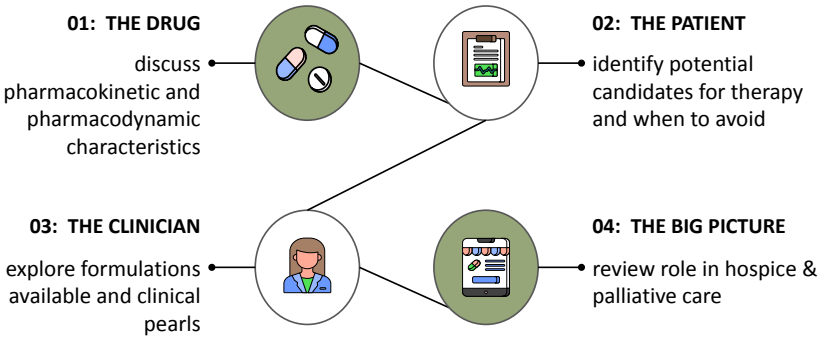


First things first

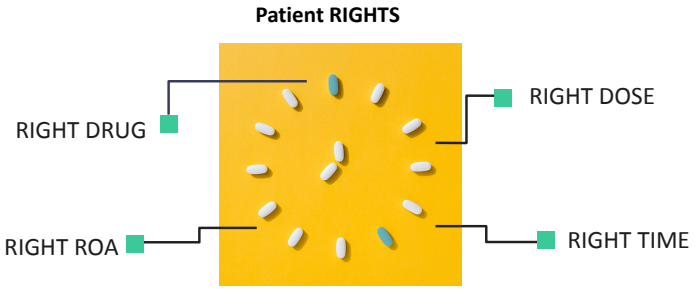
The Favorite Five:

1. Buprenorphine (1985)
2. Methadone (1947)
3. Dexmedetomidine (1999)
4. Ketamine (1970)
5. Lidocaine (1948)

For each med we will complete the following:



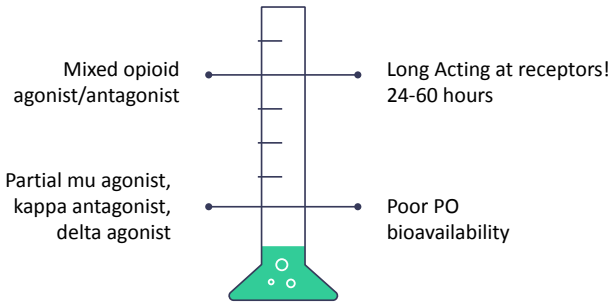
The most important slide:



BUPRENORPHINE

BUPRENORPHINE: THE DRUG

Buprenorphine Pharmacology



BUPRENORPHINE: THE DRUG

Use in Pain Management

- Partial mu-receptor agonist
  - Classic morphine-receptor type. Analgesia, resp depression, euphoria, physical dependence.
- Kappa-receptor antagonist
  - Kappa=dysphoria. Increased kappa receptor activity in patients with SUD?
- Binds tightly to mu-receptors but less active!
- Releases slowly from mu-receptors
  - Long duration of action, low level of dependence

BUPRENORPHINE: THE DRUG

Use in Pain Management

- Different types of pain
  - Nociceptive and neuropathic
- Safer in elderly & renally impaired
- Better ADR profile
  - Less respiratory depression, less constipation, less cognitive impairment (partial agonist!)
- Fewer CYP enzyme interactions than methadone
  - 3A4 substrate only

BUPRENORPHINE: THE DRUG

Use in Pain Management

- Longer analgesia than morphine
  - 6-7h vs 3-4h for morphine
- Equivalents are based on single doses!
  - Important when adjusting doses -use ratios for initial switch only, then titrate!

BUPRENORPHINE: THE PATIENT

Good vs Not Good Candidates

Good

- Mod-severe pain
- Low daily OME requirements (<30mg)
- Cannot tolerate other opioids
- History of SUD
- Potential for abuse/diversion

Reconsider

- Severe pain
- High daily opioid requirements
- Recent use of full agonist*
- Severe liver impairment
- TdP/Prolonged QT interval

BUPRENORPHINE: THE CLINICIAN

Buprenorphine Formulations

Sublingual Tablet
Subutex™

Transdermal Patch
BuTrans™

Implant
Probuphine™

Dissolving Film
Belbuca™

Solution for Inj, ER
Sublocade™

Solution for Inj
Buprenex™

Schedule III Controlled Substance

BUPRENORPHINE: THE CLINICIAN

Buprenorphine/Naloxone Formulations

Sublingual Film
Suboxone™, Bunavail™

Sublingual Tablet
Suboxone™, Zubsolv™

Schedule III Controlled Substance

BUPRENORPHINE: THE CLINICIAN

BJA

British Journal of Anaesthesia, 120 (4): 668–678 (2018)
doi: 10.1016/j.bja.2017.11.086
Advance Access Publication Date: 2 December 2017
Review Article

Efficacy and adverse effects of buprenorphine in acute pain management: systematic review and meta-analysis of randomised controlled trials

L. D. White[1,2,*], A. Hodge[2], R. Vlok[3,4], G. Hurtado[2], K. Eastern[2] and T. M. Melhuish[3,5]

BUPRENORPHINE: THE CLINICIAN

The Ceiling Effect(?)

Theoretical ceiling effect on respiratory depression (200mcg/70kg IV). There is a lower risk of death from respiratory depression.

Ceiling effect on analgesia
-controversial/unlikely.

BUPRENORPHINE: THE BIG PICTURE

Why Palliative Care/Hospice Patients?

- Effective for Pain
- "Whole Person" concept
  Both PC/H + Addiction
- Interdisciplinary Team Involved
- Increasing # of patients with SUD

Schedule III Controlled Substance

BUPRENORPHINE: THE BIG PICTURE

Open camera or QR reader and scan code to access this article and other resources online.

Top Ten Tips Palliative Care Clinicians Should Know About Buprenorphine

Kyle J. Neale, DO,[1] Melissa B. Weimer, DO, MCR,[2] Mellar P. Davis, MD,[3] Katie Fitzgerald Jones, APRN,[4] Justin G. Kullgren, PharmD,[5] Sachin S. Kale, MD,[6] Julie Childers, MD, MS,[7] Kathleen Broglio, DPN, APRN,[8] Jessica S. Merlin, MD, PhD, MBA,[9] Sarah Peck, MSW,[10] Sheria Y. Francis, MSW,[11] Jacqueline Bango, MSW,[12] Christopher A. Jones, MD, MBA,[13] Zachary Sager, MD,[14] and J. Janet Ho, MD, MPH[15]

METHADONE

Think about your experiences with methadone

Success stories?

Failures?

Preconceived notions?

Patient/caregiver opinions?

Confused about where to start?

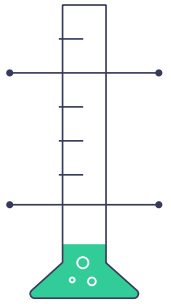
No way!

METHADONE: THE DRUG

Methadone Pharmacology

Potent synthetic opiate agonist. Also antagonizes NMDA which is why it can be particularly useful for refractory ("opioid resistant") and neuropathic pain.

No toxic metabolites = less neurotoxicity! Safe in liver and kidney impairment!



Useful for both nociceptive (somatic and visceral) and neuropathic pain (NMDA/SNRI)!

Inherently long acting! No special formulations needed. Less frequent dosing intervals may be appropriate!

Some notes on methadone metabolism

Uses the CYP450 enzymes in liver

- **Is both a substrate and inhibitor!**
- **Be aware that some drugs can induce or inhibit metabolism -dosing frequency may need adjusted to avoid either WITHDRAWAL or TOXICITY!**
- **Adjust dose by 25% (either way)**

Half-life of DISTRIBUTION is 2-3 hours, but due to slow release from binding sites in tissue, steady state is not achieved until 3-5 days after initiation (and sometimes dose changes). ELIMINATION half-life can be as long as 120 hours.

"Snowed" effect can last for 36-48 hours if dose is initiated or escalated too rapidly.

Some MORE notes on methadone metabolism

Note that even in severely impaired renal function, methadone is still a preferred agent!

Renal Function	Preferred Agents
CrCl > 40	Buprenorphine Fentanyl Hydromorphone Methadone Morphine Oxycodone Oxymorphone
CrCl = 30-40	Buprenorphine Fentanyl Hydromorphone Methadone Oxycodone
CrCl = 10-30	Methadone Oxycodone
CrCl < 10	Methadone Oxycodone

Types of Opioids

Phenanthrenes	Phenylpiperidines	Benzomorphans	Diphenylheptanes
Morphine, codeine, levorphanol, oxy-, hydro-, buprenorphine, nalbuphine, butorphanol	Fentanyl, alfentanil, sufentanil, meperidine	Pentazocine	Methadone, propoxyphene

When considering allergies, methadone is most structurally similar to propoxyphene, which is no longer on the market. Cross-sensitivity with other opioids is not likely!

Good vs Not Good Candidates

Good

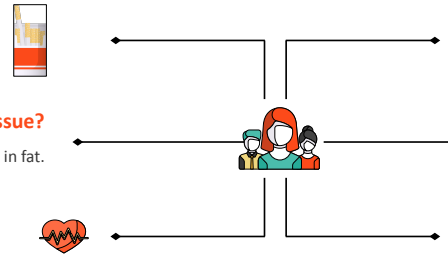
- Neuropathic pain
- TRUE morphine allergy
- Extreme opioid requirements
- Opioid induced neurotoxicity
- Kidney Impairment
- Dose-limiting ADRs with other opioids

Reconsider

- Cannot monitor for safe use
- Lack of comfort among provider team
- Cardiac risks>>potential benefits
- Hx of cardiac arrhythmias
- Rapid dose escalation necessary for pain control
- Patient/caregiver issues surround compliance/safe use

METHADONE: THE PATIENT

3 FACTORS TO CONSIDER



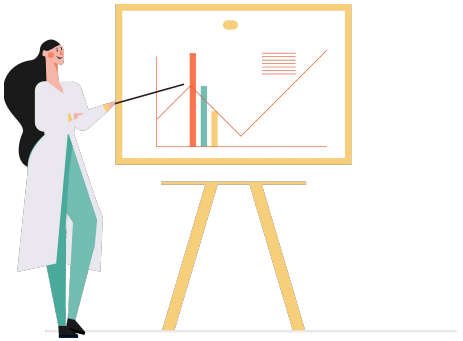
Smoker?
Smokers metabolize methadone faster than non-smokers.

Adipose tissue?
Methadone is stored in fat.

Cardiac status?
Methadone can cause QT prolongation at high doses.

METHADONE: THE PATIENT

Cardiac Status



QT Prolongation
potentially leading to TdP

Risk Factors
Doses>100mg/day!
IV Infusions
Cardiac risk factors
Other QT prolonging drugs**

To EKG or Not

Increased cardiac risk? Obtain EKG at baseline, 2-4 weeks after dose changes, and annually.

Otherwise, EKGs are appropriate if:

- Dose >100mg/day
- New episodes of syncope
- Unexplained seizures
- New cardiac risk factors

BUPRENORPHINE: THE CLINICIAN

Methadone Formulations

Oral Tablets
5mg, 10mg, 40mg*

Oral Solution
10mg/ml, 5mg/5ml

Injection Solution
$$$$

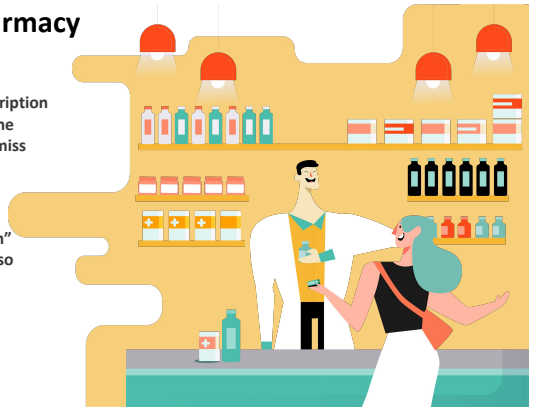
Schedule II Controlled Substance

METHADONE: THE CLINICIAN

What to expect at the pharmacy

The patient or caregiver picking up a prescription for methadone will be counseled to take the medication exactly as prescribed and not miss doses.

Make sure your prescription reads "for pain" as the indication! The prescription must also have your DEA# on it.



METHADONE: THE BIG PICTURE

A widely referenced study (Ventafridda, 1986) found that over the course of 14 days, patients on morphine required more frequent dosage escalation than patients that were receiving methadone for their pain, indicating less tolerance over time than that of morphine.

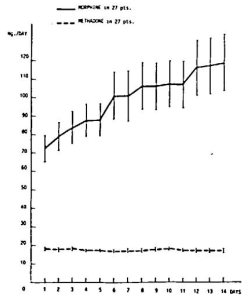


Fig 2. Variation of morphine and methadone doses during 14 days (mean ± S.D.) linear regression analysis: morphine $p < 0.001$ ($F = 21.3$), methadone $p < 0.60$ (NS.) ($F = 0.15$).

METHADONE: THE BIG PICTURE

A: Appropriate dosing

B: Be sure to check in!

C: Compliant patients

METHADONE: THE BIG PICTURE

A: Appropriate Dosing

Initiate via taper

Taper OFF of other opioids if rotation is occurring

Conversions are based on ratios!

- Numerous published methods
- The safest use of methadone requires extensive clinical experience plus a "Methadone Safe Use Protocol"

Check, check, recheck the patient and the dose/math

- Protocol will determine frequency & method
- Commonly at least every other day and via phone or in person

METHADONE: THE BIG PICTURE

A: Appropriate Dosing

Methadone Non-Linear Equianalgesic Conversion (2019)

Daily Oral Morphine Equiv. (mg)	Conversion Ratio (mg) Oral Morphine : Oral Methadone
0-60mg	Methadone 2.5mg q8h (7.5mg/day)
60-199mg AND < 65 yr. old	10:1
≥ 200mg OR > 65 yr. old	20:1

- Most often, the conversion will become 10% of the daily OME which can be administered 1-2x/day
- Initially, the daily methadone dose should not exceed 30-40/day regardless of the previous opioid dose
- For patients taking <40mg/day, dose increases should not exceed 5mg/day
- For patients taking >40mg/day, dose increases should not exceed 10mg/day

METHADONE: THE BIG PICTURE

B: Be Sure To Check In!

- **Methadone checks for the first 5 days after initiation or dose change, and as appropriate.**
- **Organization should have a methadone safe use protocol!**

METHADONE: THE BIG PICTURE

C: Compliant Patients

Patients that are educated on methadone are compliant on methadone. Do not let Google be their teacher!!

Make sure patients understand the importance of taking their methadone as prescribed.

Make sure patients understand why they are taking it, what to expect, and what common side effects may be.

Make sure patients know to track their use of PRN opioids!

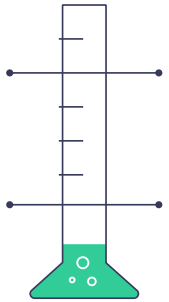
DEXMEDETOMIDINE

DEXMEDETOMIDINE: THE DRUG

Dexmedetomidine Pharmacology

Alpha-2 adrenergic receptor agonist (relatively selective!)

Centrally mediated sedative, analgesic/opioid-sparing, and sympatholytic properties



Short half-life (6 min distribution, ~3h elimination), limited respiratory depression. Onset of action 5-10 min, duration of action 1-2h

Minimal clinically significant CYP450 drug interactions

DEXMEDETOMIDINE: THE PATIENT

Good vs Not Good Candidates

Good

- Extreme agitation
- Agitation refractory to benzodiazepines

Reconsider

- AV block or ventricular dysfunction
- Significant risk for QT prolongation
- Risk of bradycardia or hypotension

DEXMEDETOMIDINE: THE CLINICIAN

Dexmedetomidine Formulations

Sublingual Film
Igalmi™

Soln for Injection
Precedex™

DEXMEDETOMIDINE: THE CLINICIAN

Dexmedetomidine Pearls

- Can be given IV, SubQ, SL, bucally, or nasally
- Typical Dosage: 0.2mcg/kg/h-1.5mcg/kg/h
- Most common side effects include hypotension and bradycardia
- Parenteral = inpatient setting

DEXMEDETOMIDINE: THE BIG PICTURE

Why Palliative Care/Hospice Patients?

- Goals of HPM: Pain management, agitation, comfort measures
- 2017: two cases of cancer patients showed improved symptom control of terminal delirium with Precedex infusion than benzodiazepine infusion
- 2022: end of life patients with terminal hyperactive delirium showed after receiving dexmedetomidine (0.3mcg/kg/h-0.6mcg/kg/h), patients showed decreased delirium or agitated
- 2002: ⅔ patients had pain, delirium, and anxiety relieved. ⅓ only had delirium relieved

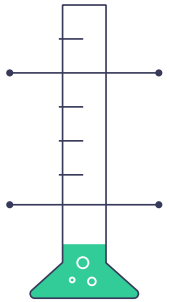
KETAMINE

KETAMINE: THE DRUG

Ketamine Pharmacology

Two optical enantiomers (S) and (R). (S) is 4x more potent!

Anesthetic, analgesic, antidepressant



Short half life of approx 1-3h & no clinically significant respiratory depression. Active metabolite has a 12h half life. DOA = 1-24h

Significant first pass metabolism = less predictable effectiveness and delayed onset when taken PO (20-30% bioavailable)

KETAMINE: THE DRUG

Use in Pain Management

NMDA receptor antagonism
specifically when these sites are open and activated

Neuropathic pain & central sensitization (mu opioid receptors)
decreases opioid requirements

Dissociation prevents higher centers from perceiving painful stimuli

Resets NMDA receptors
reduces hyperalgesia

KETAMINE: THE PATIENT

Good vs Not Good Candidates

Good

- Extreme opioid requirements
- Neuropathic pain
- Opioid induced neurotoxicity
- Dose limiting ADRs from opioids
- “Tried everything”
- Comorbid depression?

Reconsider

- Patients with memory or cognitive impairment
- Patients that cannot be monitored
- Significant cardiac comorbidities (CHF, uncontrolled hypertension)
- Head trauma, intracranial pressure
- History of stroke

KETAMINE: THE CLINICIAN

Ketamine Analgesic Dosing

Route of Administration	Ketamine Dose
Intravenous	0.15 mg/kg
Intramuscular	0.5-1 mg/kg
Intranasal	2 x 10-50 mg
Subcutaneous	0.05-0.15 mg/kg/hour for 7-days
Rectal	10 mg/kg
Oral	0.5 mg/kg

Administer an initial test dose to evaluate patient tolerability & efficacy.
Monitor vital signs & pain at 30 min and 60 min post dose.

KETAMINE: THE CLINICIAN

Adverse Drug Reactions

- Increased blood pressure
- Increased intraocular pressure
- Dissociative and psychomimetic reactions
- Memory & cognitive impairment
- Anxiety
- Delirium
- Vivid dreams
- Hallucinations
- Dizziness
- Increased salivary secretions

KETAMINE: THE CLINICIAN

Ketamine Formulations

Oral Solution*
compounded: 20mg/ml?
30mg/ml? 50mg/ml?

Injection Solution
10mg/ml, 50mg/ml, 100mg/ml

Intranasal Solution*
compounded

Schedule III Controlled Substance

KETAMINE: THE BIG PICTURE

INJECTION/INFUSION SAMPLE PROTOCOL:

1. Ketamine will be initially instituted at Hospice Inpatient Units (GIP) only.
2. Pharmacist will review all medication for drug interaction potential related to ketamine prior to infusion as well as any medication additions, deletions during drug therapy.
3. Obtain physician orders for initial dosing, titration parameters (increase by a given amount every hour as needed for pain to a maximum defined amount), adjuvant benzodiazepine or haloperidol (ordered routinely at least q12hr initially), and tapering schedule of current opioid (usually lower dose by 1/3-1/2 initially). The SubQ route is the recommended route to initiate therapy. May need to rotate SubQ site daily if local reaction occurs.
4. Adult dosing 0.5mg/kg over 6 hours. If pain improves consideration of 1.5mg/kg-2mg/kg continuously. As pain scores decrease, opioid use should decrease as stated above.
5. At start of infusion obtain baseline vital signs and pain assessment.
6. If indicated administer adjuvant benzodiazepine or haloperidol 30-60 minutes prior to start of infusion.
7. Begin ketamine infusion via ambulatory pump at prescribed rate.

KETAMINE: THE BIG PICTURE

ADDITIONAL SAMPLE PROTOCOL MENTIONING ORAL OPTION:

1. Obtain vital signs, pain assessment, and reports of any psychotomimetic side effects every 30 minutes for 2 hours, then every 60 minutes for 2 hours, then every shift thereafter or as directed by the physician. Continue for the first day after initiation of infusion and after dosage adjustments.
2. Contact the physician immediately if the patient experiences extreme agitation, bizarre behavior, hallucinations, rapid escalating BP or HR, or signs indicative of an unintended anesthetic effect (overt sedation, change in muscle tone, respiratory depression).
3. Initiation of oral ketamine or conversion from infusion (SubQ) to oral ketamine may be evaluated.
4. Ketamine HCL injection 50mg/ml can be drawn up in a syringe with a detachable needle. Once the correct dose is pulled up (e.g., 25mg [0.5ml]), the needle can be detached and the medication can be placed in a medicine cup or administered directly from the syringe. Flavoring can be added such as juice.
5. Starting dose is calculated on the past infusion dose or empirically started at 10-25mg, orally 3-4 times daily with a maximum of 50mg/24h

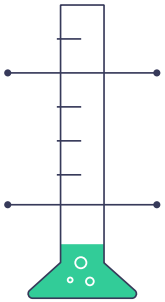
LIDOCAINE

LIDOCAINE: THE DRUG

Lidocaine Pharmacology

Reversible nerve conduction blockade & diminishes nerve membrane permeability to sodium

Decreases the rate of membrane depolarization & increases the threshold for electrical excitability



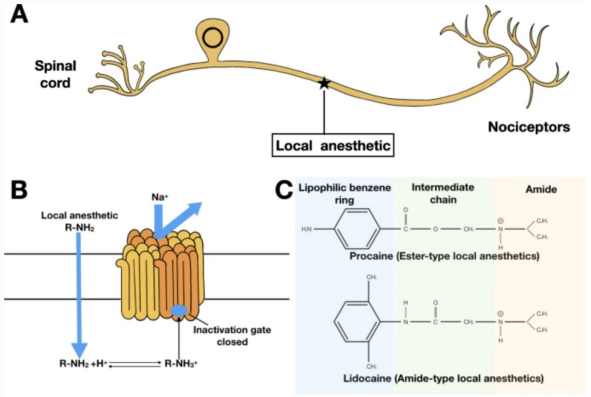
Short half life of approx 1-2h & no respiratory depression. Does have active metabolites -caution in heart failure/renal failure. Prolonged half life in these pops also

"Acts locally" = direct nerve membrane penetration is necessary.

LIDOCAINE: THE DRUG

A+B: Demonstration of how LAs interact with voltage-gated sodium channel on neuron.

C: Typical structures of ester and amide LAs



LIDOCAINE: THE PATIENT

Good vs Not Good Candidates

Good

- Severe pain refractory to other therapies (standard & adjuvant)
- Need for quick relief (<1h) compared to oral options
- Need for long acting relief (as long as 10 days after a dose)
- Severe neuropathic pain
- "Tried everything"

Reconsider

- Cognitive impairment preventing ability to accurately report pain
- Prior allergy to local anesthetics of the amide type (2 i's!)
- Hepatic/renal failure
- Severe CHF/2nd or 3rd degree heart block
- Uncontrolled seizures
- Uncontrolled hypertension

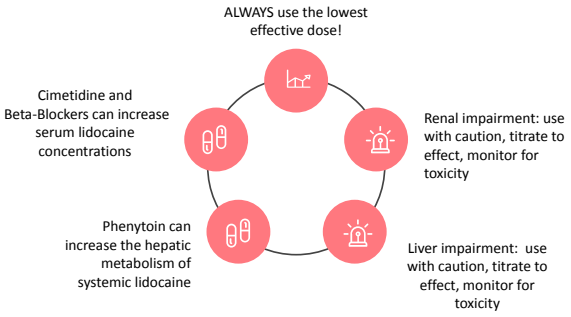
LIDOCAINE: THE PATIENT

SQ admin: no IV access required, but longer time to onset and risk of erythema/induration

PCA? If severe pain, could be an option!

Inpatient unit OR home setting possible!

LIDOCAINE: THE CLINICIAN



LIDOCAINE: THE CLINICIAN

Lidocaine Formulations

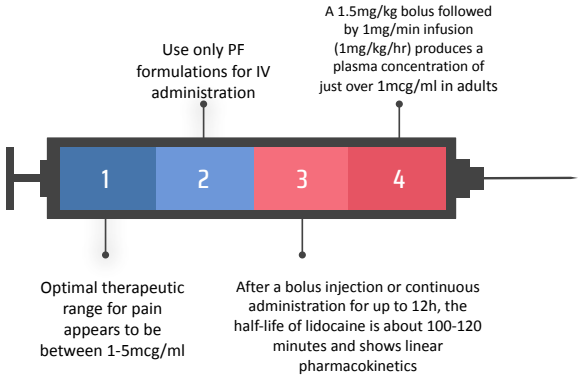
Topical Jelly, Oral Viscous Soln, Gel, Cream, etc
various strengths 0.5%-5%

Injection Solution
1%, 2% (and many more from 0.2%-20%)

Topical Patches
4% (OTC), 5% (Rx)

Non-control, numerous OTC products

LIDOCAINE: THE BIG PICTURE



LIDOCAINE: THE BIG PICTURE

Other Dosing Strategies

01 In patients that are not appropriate for continuous infusion, a 2mg/kg bolus over 20 minutes followed by 2mg/kg over 1h has shown to be promising. This can also be helpful in getting patients home from an IPU.

02 In patients that have have very good response to continuous infusion, bolus doses may be used to titrate down

03 Documented dosing strategies have included: 5mg/kg over 60 minutes, 5mg/kg in 30 minutes, 500mg over 60 minutes, 1.5mg/kg in 1 minute

04 Single doses up to 5-10mg/kg (900mg/dose max) have been used in protocols for extreme pain

LIDOCAINE: THE BIG PICTURE

Side Effects

Common: lightheadedness, perioral numbness, GI, dizziness and/or sedation

Toxic plasma lidocaine levels are considered to be in the >6 µg/ml range

LAST: perioral numbness, hypotension, metallic taste, tinnitus, visual/auditory disturbances, nausea, dizziness and drowsiness

LIDOCAINE: THE BIG PICTURE

Side Effects

Table 5. Adverse Events Associated with Intravenous Lidocaine Administration

Study design[a]	Cardiovascular[b]	Neurologic[c]	Gastrointestinal[d]	Hepatic[e]
Case series[28]	0	0	0	0
RCT[20]	0	0	0	0
Case series[26]	0	1/4 (25%)	3/4 (75%)	0
Retrospective[21]	1/82 (1%)	19/82 (23%)	5/82 (6%)	0
RCT[19]	0	10/120 (8%)	0	0
Case series[25]	0	2/9 (22%)	0	0
RCT[23]	0	0	0	0
RCT[22]	0	0	0	0
Retrospective[24]	0	3/21 (14%)	0	0

[a]Safety data were not reported in the four case reports.[27,29,30,31]
[b]Cardiovascular adverse events: new arrhythmias, cardiac arrest, or hypotension.
[c]Neurologic adverse events: dizziness, altered mental status, seizure, loss of consciousness, or slurred speech.
[d]Gastrointestinal adverse events: nausea, vomiting, or dyspepsia.
[e]Hepatic adverse events: liver dysfunction (aspartate aminotransferase and alanine aminotransferase ≥ 5 times the upper limit of normal).

LIDOCAINE: THE BIG PICTURE

Monitoring

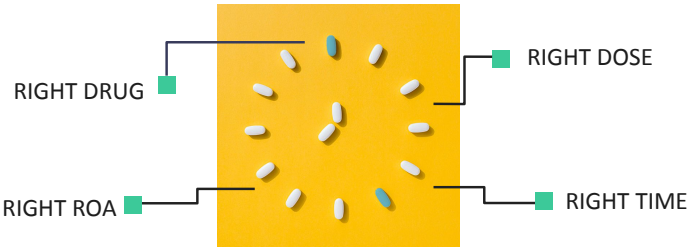
Vitals every 15 minutes

Frequent pain assessments

S/S of LAST

The most important slide again:

Patient RIGHTS



RESOURCES

- Amir R, Argoff CE, Bennett GJ, Cummins TR, Durieux ME, Gerner P, et al. The role of sodium channels in chronic inflammatory and neuropathic pain. J Pain. 2006 May;7(5 Suppl 3):S1–29.
- Berna C, Kulich RJ, Rathmell JP. Tapering long-term opioid therapy in chronic noncancer pain: Evidence and recommendations for everyday practice. Mayo Clin Proc. 2015;90(6):828-42.
- Bina B, Hersh EV, Hilario M, Alvarez K, McLaughlin B. True Allergy to Amide Local Anesthetics: A Review and Case Presentation. *Anesth Prog*. 2018;65(2):119-123. doi:10.2344/anpr-65-03-06
- Buprenorphine. Lexi-Drugs. *Lexicomp.* Accessed Aug 5, 2024.
- Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004.
- Challapalli V, Tremont-Lukats IW, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetic agents to relieve neuropathic pain. Cochrane database Syst Rev. 2005;(4):CD003345.
- Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. *Nat Rev Dis Primers*. 2017;3:17002. Published 2017 Feb 16. doi:10.1038/nrdp.2017.2
- Docherty RJ, Ginsberg L, Jadoon S, Orrell RW, Bhattacharjee A. TRPA1 insensitivity of human sural nerve axons after exposure to lidocaine. Pain. 2013;154(9):1569–77.
- Dunn KE, Finan PH, Thompkins DA, et al. Characterizing pain and associated coping strategies in methadone and buprenorphine maintained patients. Drug Alcohol Depend 2015; 157:143-149.
- Fabina J, Swindell A. Successful Use of Dexmedetomidine for the Treatment of Terminal Delirium. J Pain Symp Mgmt 2017. 53:2.
- Gaertner J, Fusi-Schmidhauser T. Dexmedetomidine: a magic bullet on its way into palliative care—a narrative review and practice recommendations. Ann Palliat Med 2022;11(4):1491-1504. doi: 10.21037/apm-21-1989
- Hawley P. B.C. *Cancer agency protocol summary for extreme pain therapy using parenteral lidocaine.* Supportive Care - Pain and Symptom Control (SCPAINLI). http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCPAINLI_Protocol.pdf. Published October 1, 2018. Accessed August 29, 2024.
- He, Y., Qin, L., Huang, Y. *et al.* Advances of Nano-Structured Extended-Release Local Anesthetics. *Nanoscale Res Lett* 15, 13 (2020). https://doi.org/10.1186/s11671-019-3241-2
- Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. J Addict Med 2015; 9(5): 358-367.
- Ketamine. Lexi-Drugs. Lexicomp Online. Lexicomp; 2022. Accessed September 8, 2024. https://online.lexi.com
- Lemus R, Jacobowski NL, Humphrey L, Tobias JD. Applications of Dexmedetomidine in Palliative and Hospice Care. J Pediatr Pharmacol Ther. 2022;27(7):587-594. doi: 10.5863/1551-6776-27.7.587. Epub 2022 Sep 26. PMID: 36186237; PMCID: PMC9514772.
- Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. Pain. 2000;87(1):7–17.
- Masic D, Liang E, Sterk E, et al. Intravenous lidocaine for acute pain: a systematic review. *Pharmacotherapy.* 2018;38(12):1250–1259
- McLean S, Twomey F. Methods of rotation from another strong opioid to methadone for the management of cancer pain: a systematic review of the available evidence. J Pain Symptom Manage. 2015;50(2): 321-337.
- McPherson ML. *Demystifying opioid conversion calculations: a guide for effective dosing.* Bethesda, MD: American Society of Health-System Pharmacists; 2019.
- McPherson ML, Walker KA, Davis MP, et al. Safe and appropriate use of methadone in hospice and palliative care: Expert consensus white paper. J Pain Symptom Manage. 2019;57(3):635-645.

RESOURCES

- Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CPN, Sessle BJ, et al. Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society. Pain Res Manag.
- Nagda J, Bajwa ZH. Definitions and classifications of pain. In: Warfield CA, Bajwa ZH, eds. Principles & Practice of Pain Medicine. 2nd ed. New York, NY: McGraw-Hill; 2004:51–4.
- Nicholson AB, Watson GR, Derry S, Wiffen PJ. Methadone for cancer pain. Cochrane Database Syst Rev. 2017;2(2):CD003971. Published 2017 Feb 8. doi:10.1002/14651858.CD003971.pub4
- Randhawa PA, Brar R, Nolan S. Buprenorphine-naloxone "microdosing": an alternative induction approach for the treatment of opioid use disorder in the wake of North America's increasingly potent illicit drug market. *CMAJ*. 2020;192(3):E73. doi:10.1503/cmaj.74018
- Sharma S, Rajagopal MR, Palat G, Singh C, Haji AG, Jain D. A phase II pilot study to evaluate use of intravenous lidocaine for opioid-refractory pain in cancer patients. J Pain Symptom Manage. 2009 Jan;37(1):85-93. doi: 10.1016/j.jpainsymman.2007.12.023. Epub 2008 Jul 2. PMID: 18599258.
- Smith HS. Opioid Metabolism. Mayo Clinic Proceedings. 2009;84(7):613-624.
- Song H, Yoo Y, Kim E, Lee C, Moon J, Kim Y. Efficacy and safety of lidocaine infusion treatment for neuropathic pain: a randomized, double-blind, and placebo controlled study. Presented at: The 17th World Congress on Pain; September 12-16, 2018; Boston, MA.
- Thomas B, Lo W-SA, Nangati Z, Barclay G. Dexmedetomidine for hyperactive delirium at the end of life: An open-label single arm pilot study with dose escalation in adult patients admitted to an inpatient palliative care unit. *Palliative Medicine*. 2021;35(4):729-737. doi:10.1177/0269216321994440
- Tsai PS, Buerkle H, Huang LT, Lee TC, Yang LC, Lee JH. Lidocaine concentrations in plasma and cerebrospinal fluid after systemic bolus administration in humans. Anesth Analg. 1998 Sep;87(3):601–4.
- van der Wal SEI, van den Heuvel SAS, Radema SA, van Berkum BFM, Vaneker M, Steegers MAH, et al. The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. Eur J Pain. 2016 May;20(5):655–74.
- Ventafridda V, Ripamonti C, Bianchi M, Sbanotto A, Conno F. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. Journal of Pain and Symptom Management 1986;1(4):203-7. [DOI: 10.1016/S0885-3924(86)80042-2]
- Walker P, Palla S, Pei B, et al. Switching from Methadone to a Different Opioid: What is the Equianalgesic Dose Ratio? J Palliat Med. 2008 Oct 11(8): 1103-1108. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2982711/
- White LD, Hodge A, Vlok R, Hurtado G, Eastern K, Melhuish TM. Efficacy and adverse effects of buprenorphine in acute pain management: systematic review and meta-analysis of randomised controlled trials. *Br J Anaesth*. 2018;120(4):668-678. doi:10.1016/j.bja.2017.11.086
- Wong E, Walker KA. A review of common methods to convert morphine to methadone. Journal of Community Hospital Internal Medicine Perspectives. 2012;2(4).
- Zanos, P., et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacological reviews*, 2018. *70*(3), 621–660. https://doi.org/10.1124/pr.117.015198

THANKS!!

Do you have any questions?

412-403-4301
michelle.mikus@dragonflyhealth.com