

# A Review of Unique Opioids and Their Conversions

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# DISCLOSURES

- Kaleo
- Remitigate, LLC

# OBJECTIVES

- Compare and contrast unique pharmacotherapy options for the treatment of chronic pain including: methadone, buprenorphine, tapentadol, and tramadol
- Select methadone, buprenorphine, tapentadol, or tramadol based on patient specific factors
- Apply appropriate opioid conversion strategies to unique opioids
- Understand opioid overdose risk surrounding opioid conversions and the use of unique opioids

# UNIQUE OPIOIDS

METHADONE, BUPRENORPHINE, TRAMADOL, TAPENTADOL

# IS METHADONE AN OPIATE OR AN OPIOID?

*While opiates are still classified as natural opioid drugs, opioids include all opioid drugs. Opioids, like methadone, are narcotic drugs.*



## METHADONE

My favorite drug because....?

# METHADONE- INDICATIONS

- FDA labeled indications – (1) chronic pain (2) detoxification
  - Oral soluble tablets for suspension NOT indicated for chronic pain treatment
- Initial inpatient detoxification of opioids by a licensed trained provider with methadone and supportive care is appropriate
- Methadone maintenance provider must have special credentialing and training as required by state
  - Outpatient prescription must be for pain ONLY and say “for pain” on RX
- Continuation of methadone maintenance from outside provider while patient is inpatient for another condition is appropriate

# MECHANISM OF ACTION

- Potent  $\mu$ -opioid agonist
- NMDA receptor antagonist
- Norepinephrine reuptake inhibitor
- Serotonin reuptake inhibitor

# ADVERSE EVENTS

- Constipation, N/V, sedation, itching, edema, sweating, dizziness, confusion, endocrine dysfunction, urinary retention, fall risk in elderly
- QTC prolongation
  - Dose dependent
  - QTC correction strategies, population variations
  - Other QTC prolonging drugs?  
(ex: TCAs, fluoroquinolones, antipsychotics)
- Serotonin syndrome



# PHARMACOKINETIC PROFILE

- Extensively protein bound (85-90%)
- High and variable volume of distribution
- Long half-life
- Prolonged time to reach steady state
- Elimination half-life significantly longer than analgesic effect
  - Frequent dosing escalations → toxic drug accumulation

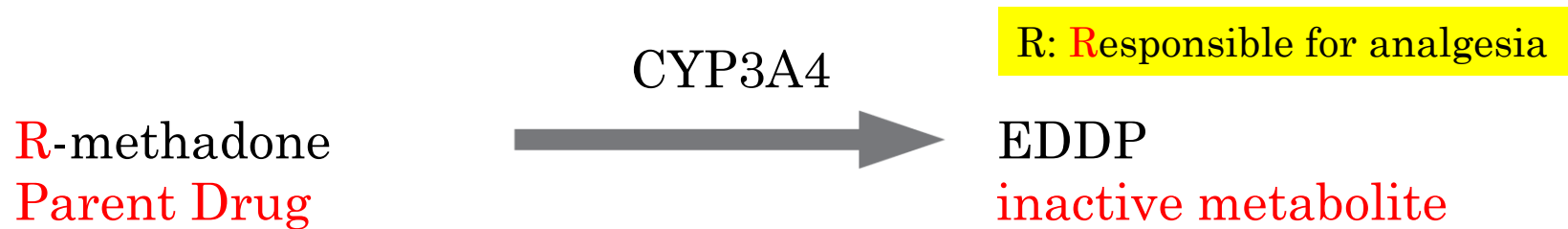
## START LOW, GO SLOW!

# OPIOID ANALGESIC P-KINETICS

Agent	Time to Peak (hr)	Half-life (hr)	Analgesic Onset (min)	Analgesic Duration (hr)
Morphine (IM)	0.5-1	2	10-20	3-5
Hydromorphone (IM)	0.5-1	2-3	10-20	3-5
Levorphanol (IM)	0.5-1	<b>12-17</b>	10-20	5-8
Hydrocodone (PO)	1	4	30-60	4-6
Codeine (IM)	0.5-1	3	10-20	4-6
Oxycodone (PO)	0.5-1	2-3	30-60	4-6
Meperidine (IM)	0.5-1	3-4	10-20	2-5
Fentanyl (IM)	10-20	3-4	7-15	1-2
Methadone (IM)	0.5-1	<b>15-300</b>	10-20	<b>&gt;8 (chronic)</b>

Combined data from: Reisine T, Paternak G 1995 and Pasero C, Portenoy RK, McCaffery M. 1999

# SUB-POP, PHARMACOGENETIC



S: Cardiotoxic effects, QT prolongation with potential of Torsade de pointes



**CYP2B6 demonstrates selectively metabolizes S-enantiomer  
Potential risk?**

# DOSE EQUIVALENCE CONVERSIONS

- Conversion to and from methadone is NOT bidirectional
- Genetic polymorphisms = inter-patient variability
- 3 proposed conversions
  - Ripamonti et al 1998: cancer related pain and heroin maintenance, 38 patients
    - 3 breakpoints: 3.7:1, 7.75:1, 12.25:1
  - Ayonrinde and Bridge 2000: 6-month conversion period, 14 neuropathic pain patients
    - 6 breakpoints: 3:1, 5:1, 10:1, 12:1, 15:1, 20:1
  - Mercadante et al 2001: 52 palliative care patients in Italy
    - 3 breakpoints: 4:1, 8:1, 12:1

Ripamonti C, Groff L, Brunelli C, Polastri D, Stravakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *J Clin Oncol.* 1998;16(10):3216-3221.

Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. *Med J Aust.* 2000;173(10):536-540.

Mercadante S, Casuccio A, Fulfaro F, et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. *J Clin Oncol.* 2001;19(11):2898-2904.

# DOSE EQUIVALENCE CONVERSIONS

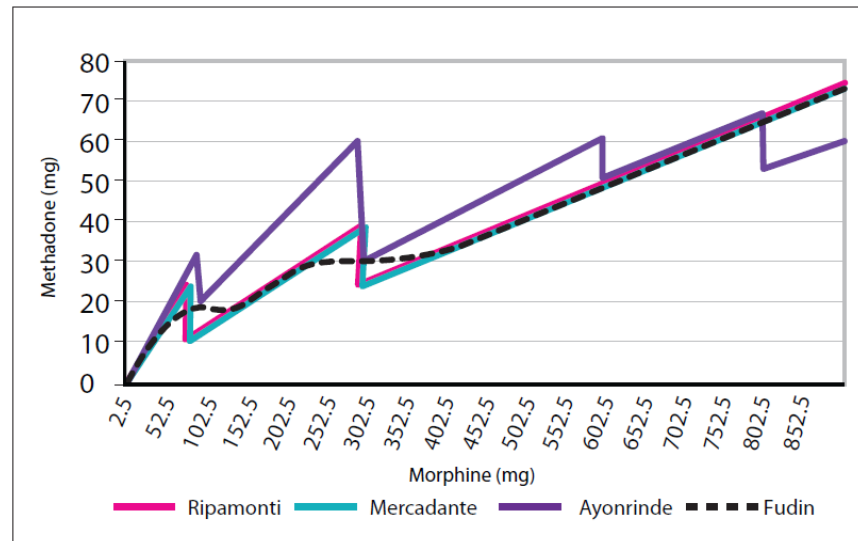


Figure 3. Morphine to methadone equianalgesic dosing ratios including Fudin equation.

- Fudin et al 2012 developed a mathematical model to eliminate breaks and peaks
- Useful if >300mg of morphine equivalents per day
- Based on previous publications
- Available for use in *Practical Pain Management's* opioid calculator

# MY FAVORITE DRUG BECAUSE...

# BENEFITS OF USE

- Inexpensive
- Good oral bioavailability
- No maximum recommended dose
- Utilization in dialysis patients
- No known active metabolites
- Unique receptor activity profile

# Is Buprenorphine An **OPIATE?**



*While buprenorphine is considered an opioid, its effects are present in a decreased capacity in comparison to drugs that are full antagonists, such as methadone or heroin.*

## BUPRENORPHINE

Pharmacologically scintillating...

# BUPRENORPHINE

- FDA approved for treating opioid abuse disorder AND for the treatment of moderate to severe pain
- Dehydroxylated phenanthrene
- Partial agonist at the mu-opioid receptor (analgesia) and antagonist at kappa receptor (ceiling effect for respiratory depression)



# WHAT IS BUPRENORPHINE

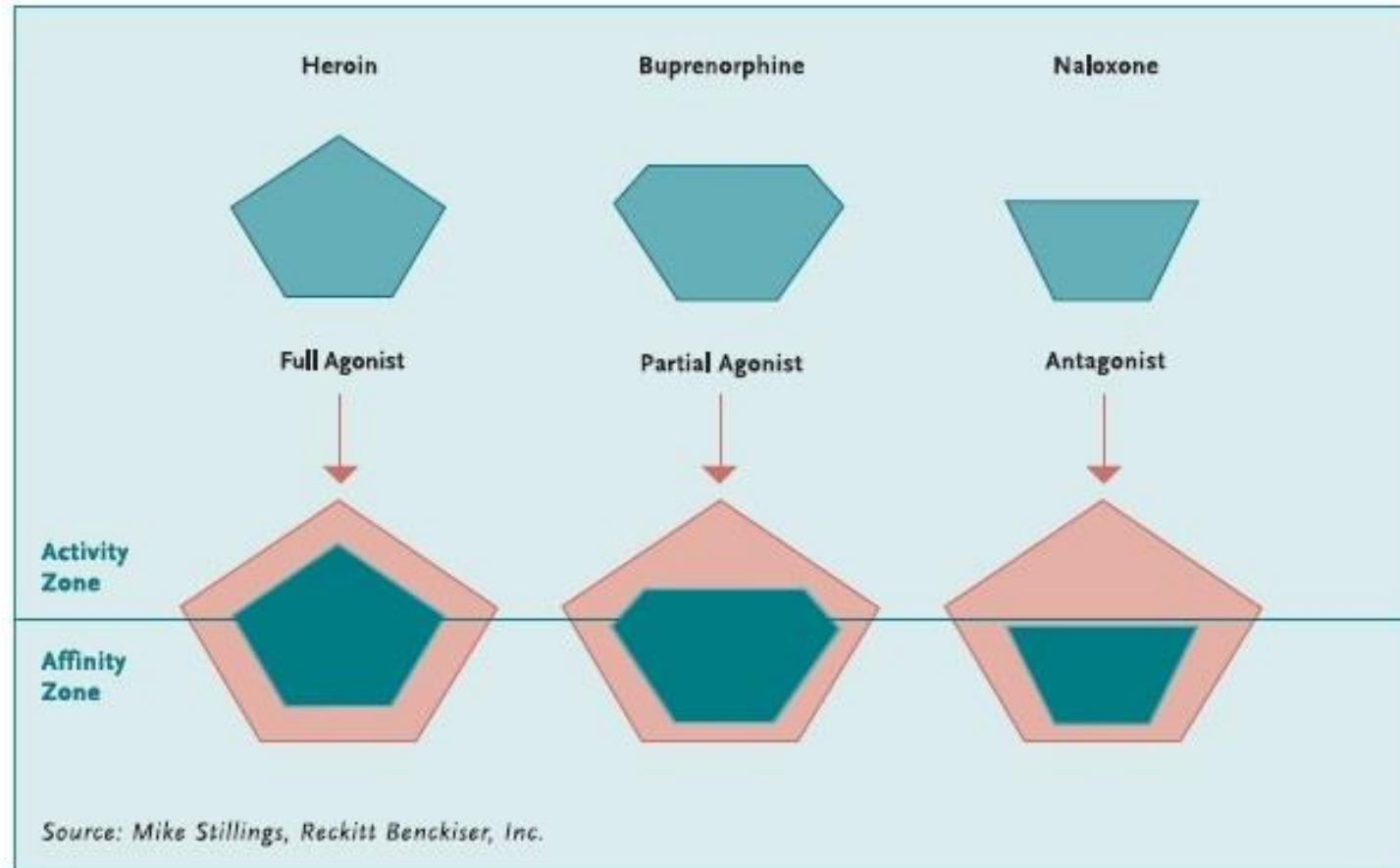
## FDA Labeled Indication

- For induction and maintenance treatment of opioid dependence
  - Prescribing requires DATA 2000 waiver to obtain DEA X license number

## Therapeutic Role

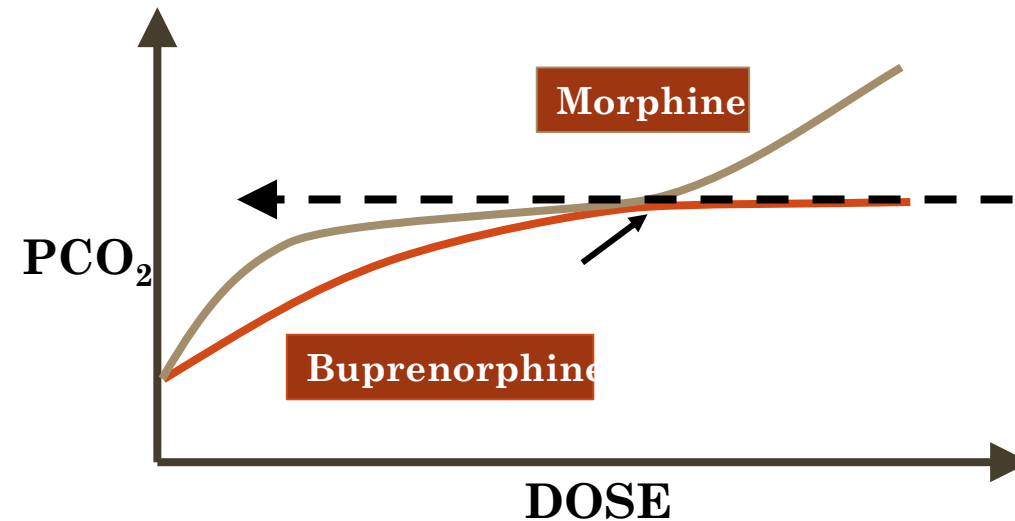
- Lower the potential for misuse of heroin and other opioids
- Diminish the effects of physical dependency to opioids, such as withdrawal symptoms and cravings
- Increase safety in cases of overdose

# UNIQUE MECHANISM OF ACTION

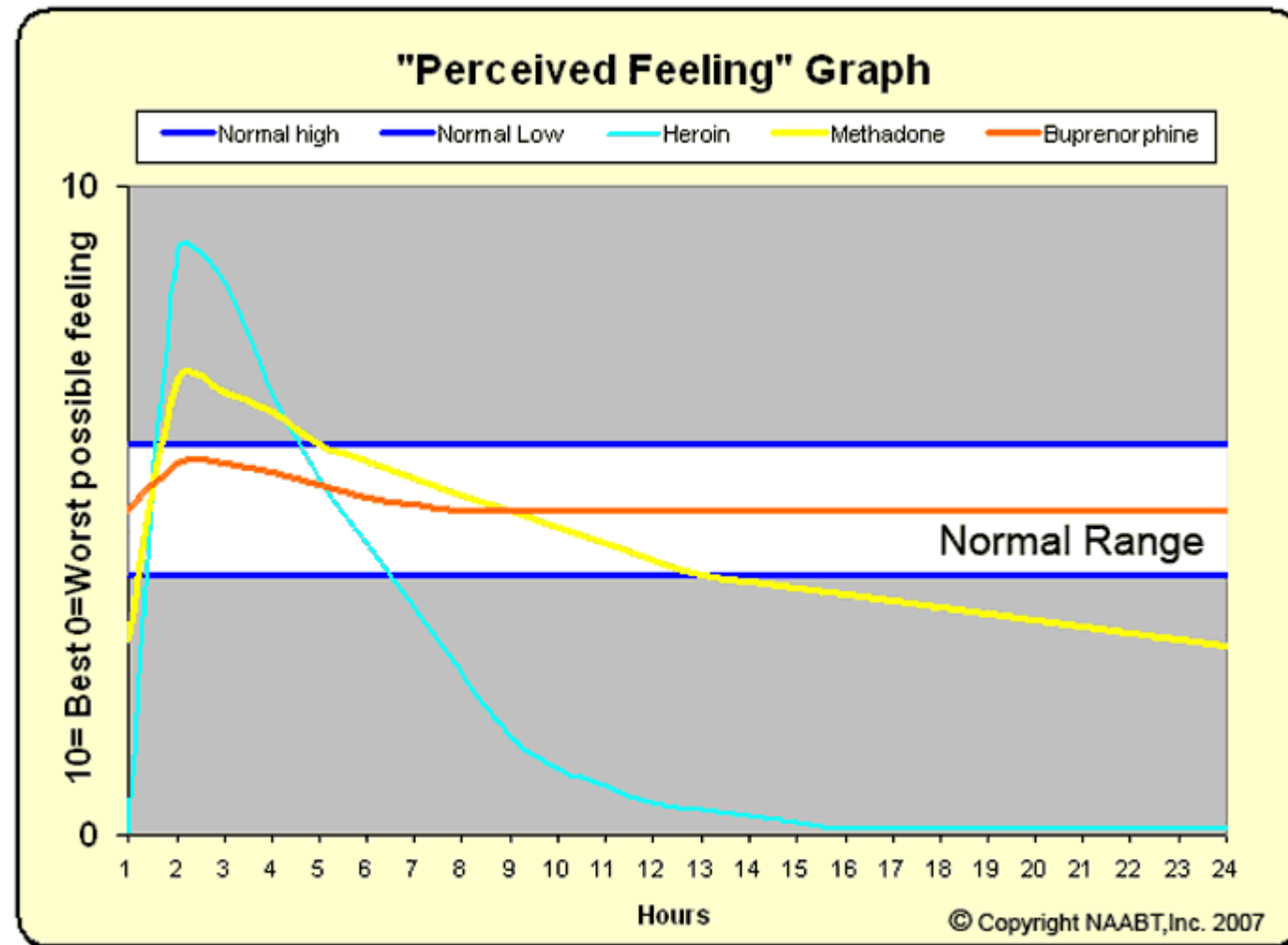


# DOSE-CEILING EFFECT

Buprenorphine reduces sensitivity of the brainstem to increases in carbon dioxide tension, achieving a ceiling effect on respiratory depression



# BUPRENORPHINE



# PHARMACOKINETIC PROFILE

- Substrate: CYP2C9 (major), CYP3A4 (minor)
- Inhibition: CYP2C8 (moderate), CYP2D6 (moderate)
- Patient case example
  - 56 YO M on Butrans 20mcg/hour transdermal patch and carbamazepine 200mg PO BID
  - Patient suffers from chronic low back pain and OA, and also has a history of COPD, DM, CHD, fluctuating kidney function
  - Patient continues to complain of increased pain

# FORMULATIONS

- Five formulations
  1. Buprenex (IV or IM)
  2. Suboxone (transmucosal film)
  3. Subutex (sublingual tablet)
  4. Butrans (transdermal patch)
  5. Belbuca (buccal film)



# SUBOXONE (BUPRENORPHINE)

- Indicated for the treatment of opioid dependence
- Formulated with naloxone
- 3 products available: Bunavil, Zubsolv, Suboxone (NOT bioequivalent)
- Requires specific DEA number for prescribing (X)
- 2mg SL ~39-50% receptor saturation
- 16mg SL ~ 79-95% receptor saturation

# SUBUTEX (BUPRENORPHINE)

- Indicated for treatment of opioid dependence
- Off-label use in the treatment of chronic pain when long-term full opioid agonists are not an option
- Dosage forms: 2mg and 8mg tablets SL
- Swallowing reduces bioavailability
- Documented deaths in opioid naive patients



# BUTRANS (BUPRENORPHINE)

- Indicated for the treatment of moderate to severe pain
- Dosage forms: 5, 7.5, 10, 15, 20mcg/hour transdermal patch
- Two patches can be worn at once in two separate adjacent sites
- Rotate sites every 7 days
- IR opioids indicated in the first 72 hours of titration (time to steady state)
- Patient using >80mg of morphine equivalents NOT a candidate for Butrans
- HOLD patch for at least 72 hours when switching therapies

# BELBUCA (BUPRENORPHINE)

- Indicated for management of “pain requiring around-the-clock, long-term opioid treatment not adequately controlled by alternatives”
- Dosage forms: 75, 150, 300, 450, 600, 750, 900mcg
- Butrans 20mcg/hour can be replaced by 150mcg q12 Belbuca (not 100% equivalent)
- Patient using >160mg of morphine equivalents NOT a candidate for Belbuca
- 30 minute dissolve time

# ACUTE PAIN MANAGEMENT

## Planned Procedure

- Hold high dose buprenorphine for 1 week (min 72 hours)
- Monitor closely- concern for relapse
- Buprenorphine's half-life for dissociation from the mu receptor is 166 min as opposed to 7 min for fentanyl

## Unplanned Procedure

- Augment therapy with NON opioid medications:
  - NSAIDs
  - IV acetaminophen
  - Anticonvulsants
  - NMDA antagonists
- High dose opioids- hydromorphone, fentanyl

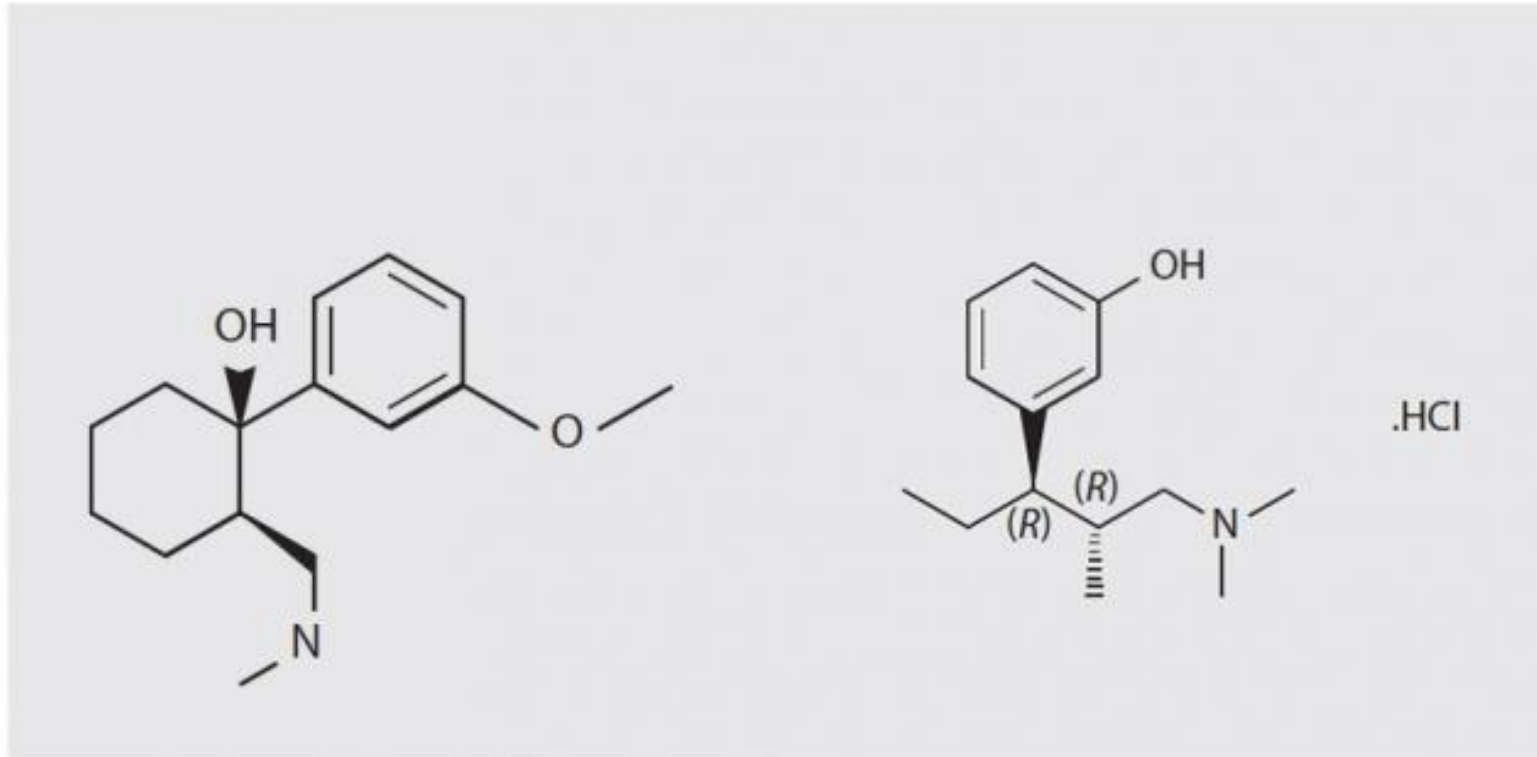


Figure 1. Chemical formulas of Tramadol (left) Tapentadol (right).

# TRAMADOL VS. TAPENTADOL

What's the difference?

# TRAMADOL

- Mu-opioid agonist (ascending pathway)
  - Binding affinity 6000X less than that of morphine
  - Considered a partial agonist
- Norepinephrine reuptake inhibitor (descending pathway)
- Serotonin reuptake inhibitor (descending pathway)

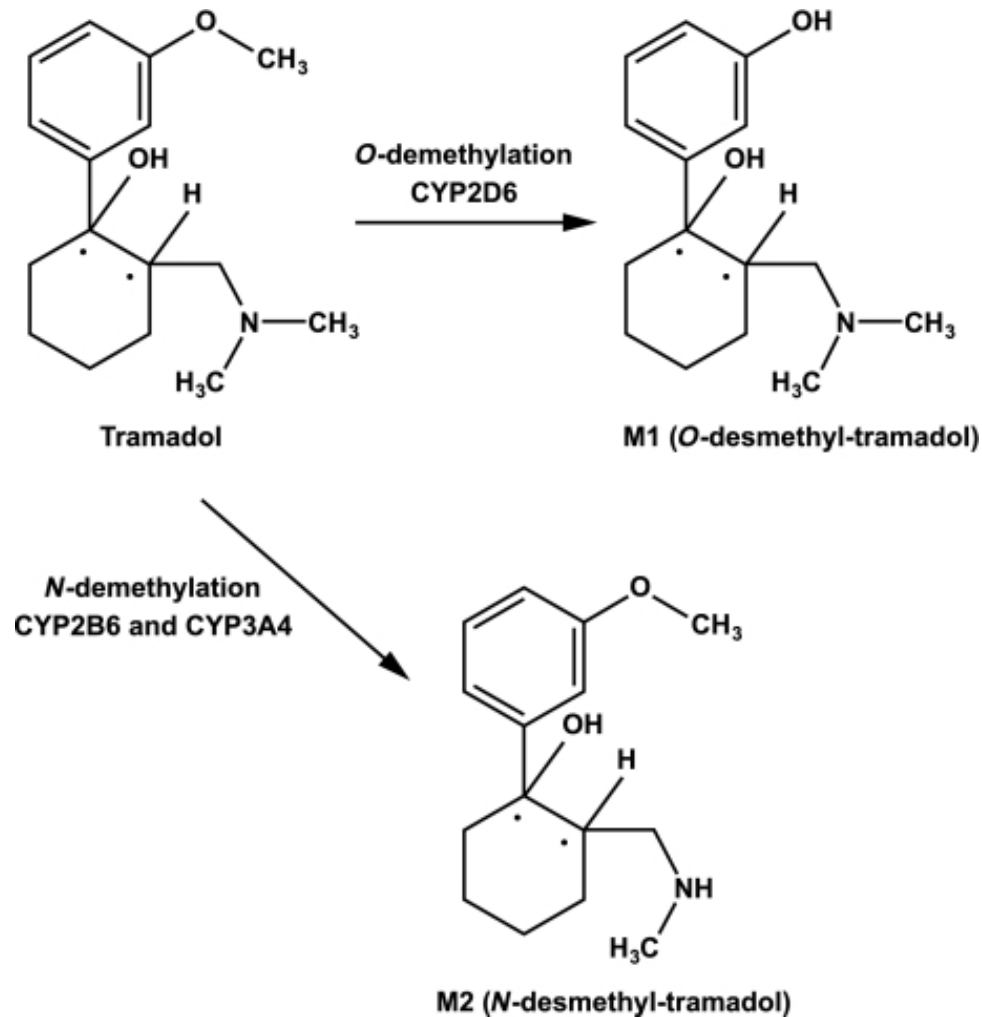
Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet.* 2004;43(13):879-923.

Raffa RB, Buschmann H, Christoph T, et al. Mechanistic and functional differentiation of tapentadol and tramadol. *Expert Opin Pharmacother.* 2012;13(10):1437-1449.

# ADVERSE EVENTS

- Constipation, N/V, sedation, itching, edema, sweating, dizziness, confusion, endocrine dysfunction, urinary retention , xerostomia, fall risk in elderly
- Headache
- Central nervous system stimulation
- Insomnia
- Serotonin syndrome
- Seizures- most commonly, tramadol-induced seizures appear to be generalized tonic-clonic seizures that occur within 24 hours of medication ingestion

# TRAMADOL METABOLISM



M1: more potent analgesic than tramadol, however LESS pain relief observed

Difficulty penetrating into CNS

# CYP2D6 PHENOTYPE BY ETHNICITY

CYP2D6 Phenotype	African (%)	African American (%)	Americas (%)	Caucasian (Europe & North America) (%)	East Asian (%)	Middle Eastern (%)	Oceanian (%)	South/Central Asian (%)
UM	4.5	3.4	4.8	3.2	1.2	11.5	20.5	2.8
EM	71.9	77.7	81.2	76.8	85.5	74.4	76.7	88.5
IM	12.6	13.2	4.5	6.9	8.8	5.6	0.5	6.9
PM	1.9	3.1	3.7	6.1	0.9	1.2	0.5	1.5

% rounded to nearest tenth



# TRAMADOL VS. TAPENTADOL

## Tramadol

- Norepinephrine, serotonin, and u-opioid activity
- IR and ER formulations
- Max dose 300mg/day
- Dosage adjustment in renal impairment
- Common AEs: dizziness, headache, drowsiness, constipation, vomiting
- 3A4, 2B6 activity and 2D6 required for active metabolite formation

## Tapentadol

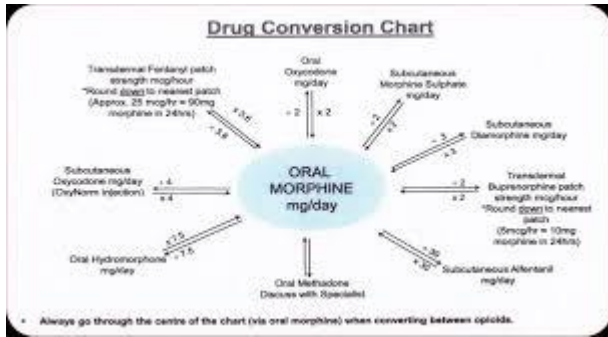
- FDA indication for chronic diabetic neuropathic pain
- Norepinephrine and u-opioid activity
- IR and ER formulations
- Max dose 500mg/day
- No data in renal patients (CrCl <30ml/min)
- Common AEs: dizziness, drowsiness, N/V, constipation
- 2C9 and 2D6 substrate

# IS TAPENTADOL (NUCYNTA®) A GLORIFIED TRAMADOL?

Properties	Tramadol	Tapentadol
Mu Binding Affinity	6000x less than morphine	18x less than morphine
Metabolism	Significant CYP 450	Conjugation, O-Glucuronide
Drug Interactions	See previous	See previous
Neuroamine Activity	5-HT / NE	NE

# UNIQUE OPIOID CONCLUSIONS

- Methadone is an EXCEPTIONAL opioid when used appropriately
  - Buprenorphine has a ceiling effect that can be VERY useful
  - Tramadol does have ABUSE potential and is not foolproof
  - Tapentadol has NE activity and no 5-HT activity but is expensive
- 
- DO YOU HAVE A PATIENT THAT WOULD BENEFIT FROM ONE OF THE ABOVE?



# Equianalgesic Opioid Dosing

Drug	Equianalgesic Doses (mg)	
	Parenteral	Oral
Morphine	10	30
Buprenorphine	0.3	0.4 (sl)
Codeine	100	200
Fentanyl	0.1	NA
Hydrocodone	NA	30
Hydromorphone	1.5	7.5
Meperidine	100	300
Oxycodone	10*	20
Oxymorphone	1	10
Tramadol	100*	120

### OPIOID CONVERSION GUIDE

These conversions are a guide only. Patients may vary in their response to different opioids. After changing opioid, dose assessment should follow and the dose altered as necessary.

#### Equianalgesic doses of oral opioids

Oral opioid	Conversion factor (opioid dose $\times$ factor = morphine dose)	Parenteral equianalgesic dose
Morphine	1	10 mg
Hydromorphone	$\times 1.5$	2 mg
Oxycodone	$\times 1.5$	5-7.5 mg
Codeine	$\times 10$	75-90 mg
Tapentadol	$\times 5$	30 mg
Tramadol	$\times 5$	30 mg

**METHADONE** conversions also published and prescribing should be restricted to medical specialists with experience of methadone prescribing for pain management.

#### Subcutaneous route conversions

Opioid	Oral dose	Equianalgesic subcutaneous dose	Conversion factor (oral dose $\times$ factor = subcut dose)
Morphine	30 mg	10 mg	$\times 3$
Hydromorphone	6 mg	2 mg	$\times 3$

#### Transdermal preparation conversions

Opioid	Patch strength	Equianalgesic oral morphine dose
Oxycodone patch	5 mcg/cm <sup>2</sup> /hr	12 mg/24 hrs
Fentanyl	12 mcg/cm <sup>2</sup> /hr	30-45 mg/24 hrs

#### Sublingual preparation conversions

Opioid	Dose	Equianalgesic oral morphine dose (up to 6mg)
Oxycodone sublingual	200 microgram	6-12 mg
Fentanyl buccal	200 microgram	no direct conversion initiate 200 microgram buccal and titrate to effect

## OPIOID CONVERSION CHART

There are differences in the literature regarding opioid conversion ratios. The conversion ratios listed below are the conversion ratios commonly used in practice at Our Lady's Hospice and Care Services (OLH&CS). The information outlined below is intended as a guide only. All medication doses derived using the information below should be checked and prescribed by an experienced practitioner. The dosage of a new opioid is based on several factors including the available equi-analgesic dose data, the clinical condition of the patient, concurrent medications and patient safety. It is recommended that the new dose should be reduced by 30-50% to allow for incomplete cross-tolerance. The patient should be monitored closely until stable when switching opioid medications.

#### GOLDEN RULE: WHEN CHANGING FROM ONE OPIOID TO ANOTHER ALWAYS CONVERT TO MORPHINE FIRST.

ORAL MORPHINE TO ORAL OPIOIDS	ORAL OPIOIDS TO PARENTERAL OPIOIDS	PARENTERAL MORPHINE TO OTHER OPIOIDS	TRANSDERMAL OPIOID TO ORAL MORPHINE
PO $\rightarrow$ PO	RATIO	PO $\rightarrow$ IV/SC	RATIO
Morphine $\rightarrow$ Oxycodone	1.5:1	Morphine $\rightarrow$ Morphine	1:1
Morphine $\rightarrow$ Hydromorphone	5:1	Oxycodone $\rightarrow$ Oxycodone	2:1
		Morphine $\rightarrow$ Hydromorphone	5:1
		Hydromorphone $\rightarrow$ Hydromorphone	2:1
		Morphine $\rightarrow$ Alfentanil	15:1
		Morphine $\rightarrow$ Oxycodone	1.5:1
		Buprenorphine $\rightarrow$ Morphine	1:175
		Fentanyl $\rightarrow$ Morphine	1:100

MORPHINE	OXYCODONE	HYDROMORPHONE	FENTANYL	ALFENTANIL	BUPRENORPHINE
24 hour dose	24 hour dose	24 hour dose	24 hour dose	24 hour dose	24 hour dose
ORAL	ORAL	ORAL	TRANSDERMAL*	IV/SC	TRANSDERMAL*
IV/SC	IV/SC	IV/SC	IV/SC	IV/SC	IV/SC
5mg	2.5mg	3.33mg	1.66mg	1mg	0.5mg
10mg	5mg	6.66mg	3.33mg	2mg	1mg
14.4mg	7.2mg	9.6mg	4.8mg	2.88mg	1.44mg
20mg	10mg	13.33mg	6.66mg	4mg	2mg
28.8mg	14.4mg	19.2mg	9.6mg	5.76mg	2.88mg
30mg	15mg	20mg	10mg	6mg	3mg
50mg	25mg	33.33mg	16.66mg	10mg	5mg
60mg	30mg	40mg	20mg	12mg	6mg
100mg	50mg	66.66mg	33.33mg	20mg	10mg
120mg	60mg	80mg	40mg	24mg	12mg
150mg	75mg	100mg	50mg	30mg	15mg
180mg	90mg	120mg	60mg	36mg	18mg
200mg	100mg	133.33mg	66.66mg	40mg	20mg
240mg	120mg	160mg	80mg	48mg	24mg
					100 micrograms/hour
					8mg

\* Transdermal fentanyl and buprenorphine patches are prescribed in micrograms (mcg)/hour. Equivalent doses are based on the 24-hour dose of fentanyl or buprenorphine received from a patch. Based on buprenorphine to morphine ratio of 1:175.

\*Not available in the US

McPherson ML. *Demystifying Opioid Conversion Calculations: A Guide For Effective Dosing*. Amer Soc of Health-Systems Pharm, Bethesda, MD, 2010. Copyright ASHP, 2010. Used with permission. NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.

# How do you do opioid conversions?

DON'T BE SHY!

# AVAILABLE ONLINE OPIOID CONVERSION CALCULATORS

WA State Agency

Med Calc

Pain Research

Pain Physicians

Hopkins

Palliative Care

Global RPh

• **Practical Pain Management (PPM)**

OTHERS...?

# ISSUES WITH MEDD & OPIOID CONVERSIONS

- Pharmacogenetic variability
- Drug interactions
- Lack of universal morphine equivalence
- Specific opioids that should never have an MEDD
  - Methadone, Buprenorphine, Tapentadol, Tramadol

Fudin J, Marcoux MD, Fudin JA. Mathematical Model For Methadone Conversion Examined. Practical Pain Management. Sept. 2012. 46-51.

Donner B, et al. Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. Pain. 1996;64:527–534.

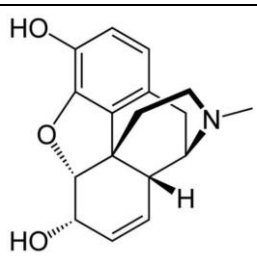
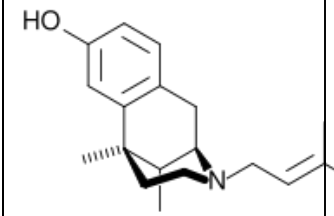
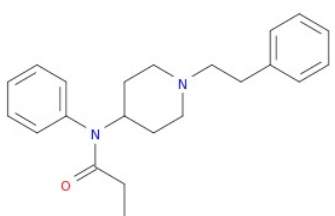
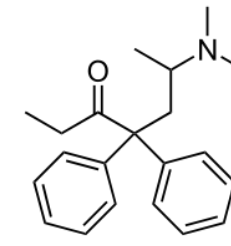
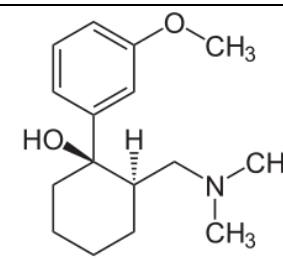
Breitbart W, Chandler S, Egel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Oncology. 2000;14:695–705.

Shaw K, Fudin J. Evaluation and Comparison of Online Equianalgesic Opioid Dose Conversion Calculators. Practical Pain Management. 2013 August; 13(7):61-66.

# OPIOID CONVERSION POINTERS...

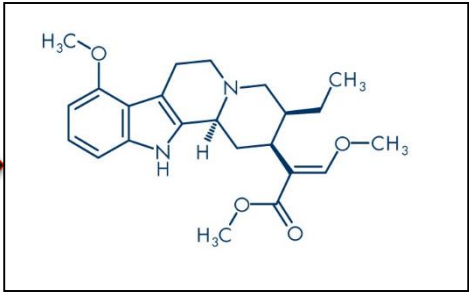
- Use more than one calculator
- What is the patients current pain level?
- What is the patients current PRN use?
- How does the drug come?
- Cross-sensitivity -> similarities of opioid structures

# Comparative Opioid Chemistry

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
<b>MORPHINE</b>	<b>PENTAZOCINE</b>	<b>FENTANYL</b>	<b>METHADONE</b>	<b>TRAMADOL</b>
Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	Diphenoxylate Loperamide Pentazocine	Alfentanil Fentanyl Meperidine Remifentanyl Sufentanyl	Methadone Propoxyphene	Tapentadol Tramadol
		<b>Illicit Fentanyl</b>		
		Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanyl		
<b>CROSS-SENSITIVITY RISK</b>				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK

Not All Opioids are Created Equal!

**Mitragynine (Kratom)**



\*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group

\*\*6-position is substituted with a ketone group and tolerability is similar to hydroxylation

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[http://paindr.com/wp-content/uploads/2018/02/Opioid-Structural-Classes-Figure\\_-updated-2018-02.pdf](http://paindr.com/wp-content/uploads/2018/02/Opioid-Structural-Classes-Figure_-updated-2018-02.pdf)



# OPIOID CONVERSION EXAMPLE

- Patient O.A. is a 58 y.o. AA male who is currently taking oxycontin 20mg PO TID with oxycodone 5mg PO q6 prn
- His provider would like to switch him to a fentanyl patch. Which of the following is an appropriate starting dose?
  - A. Fentanyl 12.5mcg/hr with NO PRN oxycodone
  - B. Fentanyl 12.5mcg/hr with PRN oxycodone 5mg PO q6 prn
  - C. Fentanyl 25mcg/hr with NO PRN oxycodone
  - D. Fentanyl 25mcg/hr with PRN oxycodone 5mg PO q6 prn
  - E. Fentanyl 37.5mcg/hr with NO PRN oxycodone

# OPIOID CONVERSION EXAMPLE

- Fentanyl and oxycodone in two different opioid classes (consider cross-tolerance)
- Patient could be taking 80mg of oxycodone total (20mg X3 + 5mg X4 = 80mg)
- PPM w/o cross tolerance = 33.3mcg patch (**HOURLY DOSE**)
  - 50% cross tolerance = 16.7 mcg patch
  - 25% cross tolerance = 25mcg patch
- How does fentanyl come?
  - 12.5, 25, 50, 75, 100 mcg/hour patches
- 12.5mg w/o PRN too little
- 37.5 (25 + 12.5) w/o PRN too little

# CONVERSION CONCLUSIONS

- Assess patients pain level prior to conversion
- Assess PRN use prior to conversion
- Determine long term goal (ex: no PRN use, etc.)
- Consider cross-tolerance
- How does the opioid come?
- USE MORE THAN ONE CALCULATOR-> phone a friend!
- Follow up with you patient
- Do they have naloxone?

# QUESTIONS?

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