Opioid Agonist Therapy 101:
An Introduction to Clinical Practice Workshop

Pharmacology:

METHADONE AND BUPRENORPHINE/NALOXONE AND PRESCRIBER-PHARMACIST COLLABORATIVE CARE

(Developed by: Nicole Nakatsu)

Disclosure of Commercial Support

- This program has received financial support from ***The College of Physicians and Surgeons of Manitoba*** in the form of ***funding for payment of presenters and organizers.***
- This program has received in-kind support from ***The College of Physicians and Surgeons of Manitoba*** in the form of ***logistical support.***

- **<u>Potential for conflict(s) of interest</u>:**
  - None identified

Declaration of off-label medication recommendations

- **During this presentation, I will make therapeutic recommendations for medications that have not received regulatory approval (i.e. off-label use of medication). I will verbally identify each off-label recommendations prior to discussing it.**

Faculty/Presenter Disclosure

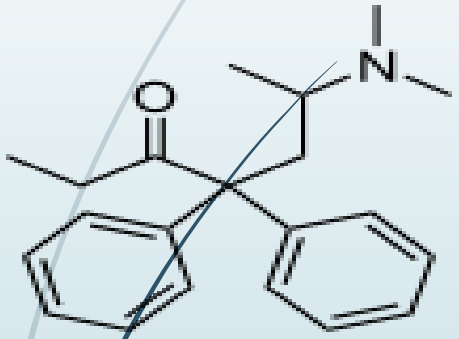
- **Faculty: Mike Sloan**
- **Relationships with commercial interests: (list None if no disclosures)**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria: None**
  - **Consulting Fees:** None
  - **Other:** None

Learning Objectives

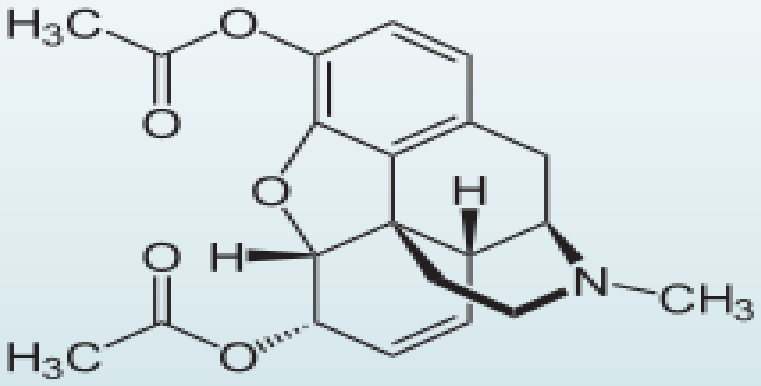
- To understand the unique pharmacology of methadone and buprenorphine/naloxone
- To identify potential and actual drug interactions.
- To review the importance and benefits of active participation in prescriber - pharmacist collaborative care.

Methadone Pharmacology

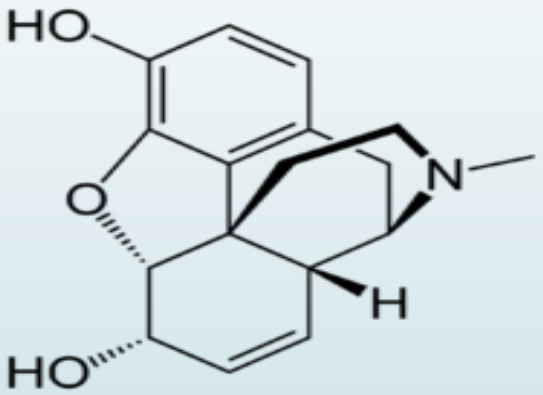
- Synthetic opioid
- Structurally unrelated to opiates



methadone



heroin



morphine

Methadone Pharmacology

- Agonist at the μ-opioid receptor
- No rush/euphoria in stabilized patients
- Blocks euphoria from heroin and other opioids
- Long duration of action allows once daily dosing in methadone maintenance therapy (MMT)
- Diversion-street value, low lethal dose

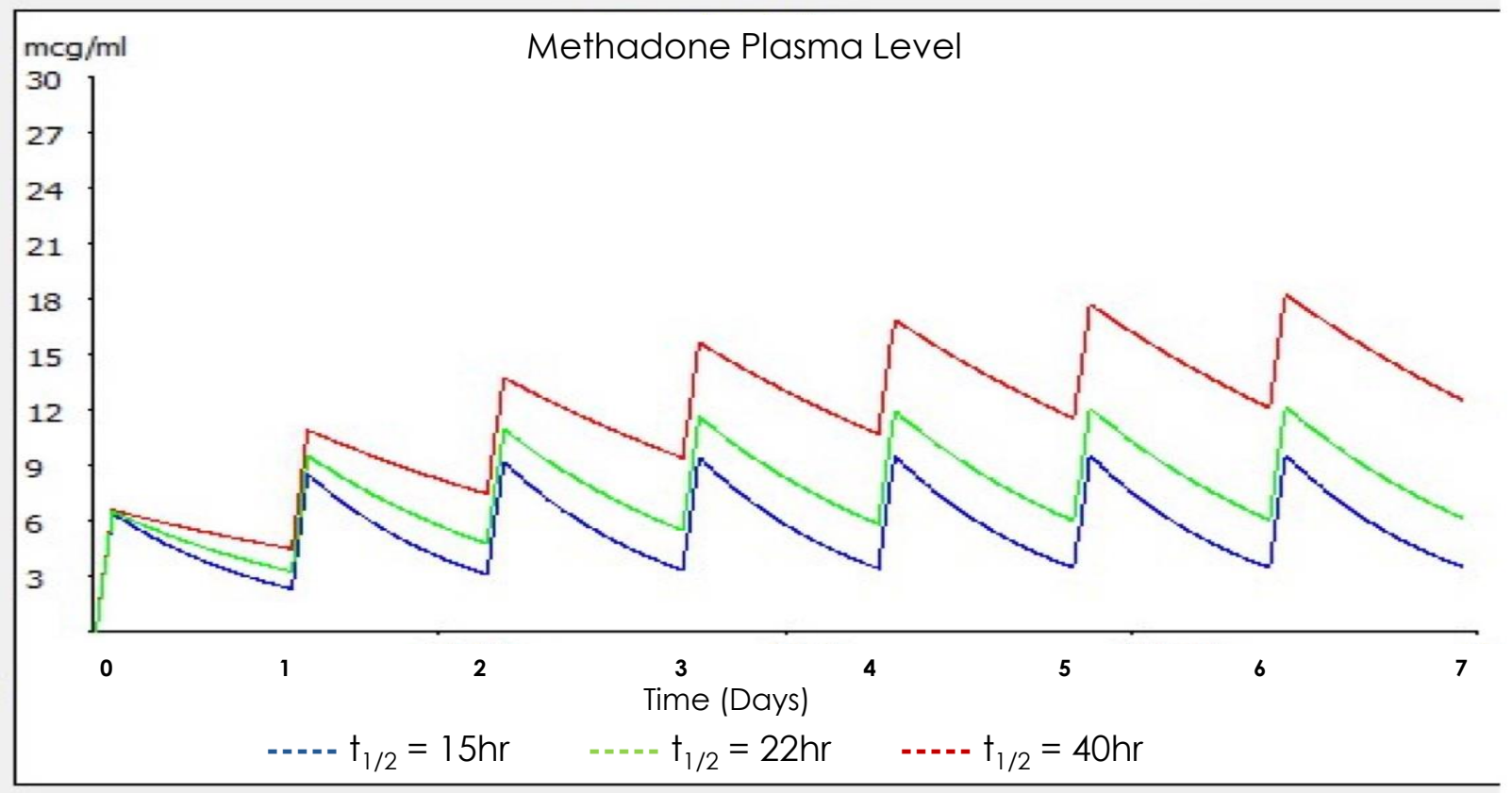
Absorption - Methadone

- Following oral dosing methadone is detected in the plasma within about 30 minutes
- Peak plasma levels 2-4 hours after ingestion
- PO bioavailability is ~90 % (range 41-100%)

Distribution - Methadone

- Highly lipid-soluble, and highly protein bound to both plasma proteins and tissue proteins
- V_D = 4-5L/kg
- $t_{½}$ = avg 22 hours (15-40 hours)
- 5 to 7 days to reach steady state with repeated dosing
- Withdrawal typically suppressed for 24-36 hours with therapeutic doses

Distribution (15hr vs 22hr vs 40hr)



Metabolism & Excretion - Methadone

- Primarily metabolized by cytochrome P450 3A4 to the inactive metabolite EDDP
  - 2-Ethylidene-1,5-Dimethyl-3,3-Diphenylpyrolidine
- Also metabolized to a lesser extent by CYP 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6
- Weak inhibitor of 2D6
- Methadone is excreted both as unchanged drug and as metabolites in urine and feces.

Adverse Effects - Methadone

- Generally well tolerated
- Common (***persistent***): constipation, dental, insomnia, neuroendocrine, sexual changes, sweating
- Common (***develop tolerance***): drowsiness, nausea, psychoactive effects, weight gain
- QT interval- QT interval prolongation with high doses.

Adverse Effects con't…

- **Sweating** – up to 45% of individuals may experience excessive sweating. May be due to dose being too high or too low. Off label: Clonidine *(use with caution, and small quantities. Misuse reported)*, Oxybutynin?, Desloratadine?
- **Sedation** - tolerance develops to this side effect but caution is advised during induction and with dose increases
- **Constipation** - inhibits propulsive contractions of the intestines while increasing non-propulsive segmental contractions. Increases tone of anal sphincter. Can start with osmotic laxative (PEG 3350) but may need to treat with stimulant laxative that works at the myenteric plexus (ie. senna, bisacodyl)

Adverse Effects

- **Weight gain** - reported by many patients. Can cause water retention and decreased metabolism.
- **Sexual problems** - may decrease desire and/or performance. Once stabilized some patients may experience an increase in desire

Adverse Effects

- **Neuroendocrine** - increased prolactin --> galactorrhea (rare). Most women will report normal periods once stabilized. Men may experience a decline in testosterone. Gynecomastia is rare.
- **Dental** - may inhibit saliva production which causes dry mouth and increased plaque production. Good oral hygiene practices should be encouraged.
- **Urinary** - some people report difficulty voiding but tolerance usually develops quickly

Adverse Effects

- **QT interval** - QT interval prolongation with high doses.
- ECG recommended for patients on high doses (100 to 120mg)
- Caution with other medications that can prolong the QT interval and in patients with a congenitally long QT interval

Tisdale Tool (Calculation of risk score for QTc interval prolongation)

Risk Factor	Points	
Age ≥ 68 years	1	
Female sex	1	
Loop diuretic	1	
Serum K+ ≤ 3.5 mEq/L	2	
Admission QTc ≥ 450 ms	2	
Acute MI	2	
≥ 2 QTc-prolonging drugs	3	**i.e. methadone + quetiapine**
Sepsis	3	
Heart failure	3	
One QTc-prolonging drug	3	**i.e. methadone**
Maximum Risk Score	**21**	

K+ = potassium; MI = Myocardial infarction

*Risk Score Category	
Low	< 7
Moderate	7–10
High	>11

Drug Interactions

PHARMACOKINETIC INTERACTIONS

- P450 3A4
- Drugs that inhibit CYP 3A4 – decrease methadone metabolism. Interaction occurs *quickly* (1-2 days). Watch for signs of toxicity (sedation, respiratory depression)
- Drugs that induce CYP 3A4 – increase methadone metabolism. Interaction is *slow* to occur with peak effect after 1-2 weeks. Watch for signs of withdrawal.

Drug Interactions – Common Examples

Decrease plasma levels

- Barbiturates
- Carbamazepine
- Ethanol (*chronic*)
- St. John's Wort
- Nelfinavir
- Phenytoin
- rifampin

Increase plasma levels

- Amitriptyline
- Ciprofloxacin
- Clarithromycin
- Erythromycin
- Ethanol (acute use)
- Fluconazole/itraconazole
- Fluvoxamine

Drug Interactions

PHARMACODYNAMIC INTERACTIONS

- Additive effects of drugs with similar side effect profile
- Be very careful with other CNS depressants and methadone-increased risk of respiratory depression and sedation

Split Dosing - Methadone

- Rapid metabolizers
  - Drowsy in afternoon but withdrawal by evening
  - Measure methadone peak and trough
  - Peak:trough ratio should be ≤ 2
  - If > 2 then may be rapid metabolizer
  - Consider splitting into BID dosing

Overdose

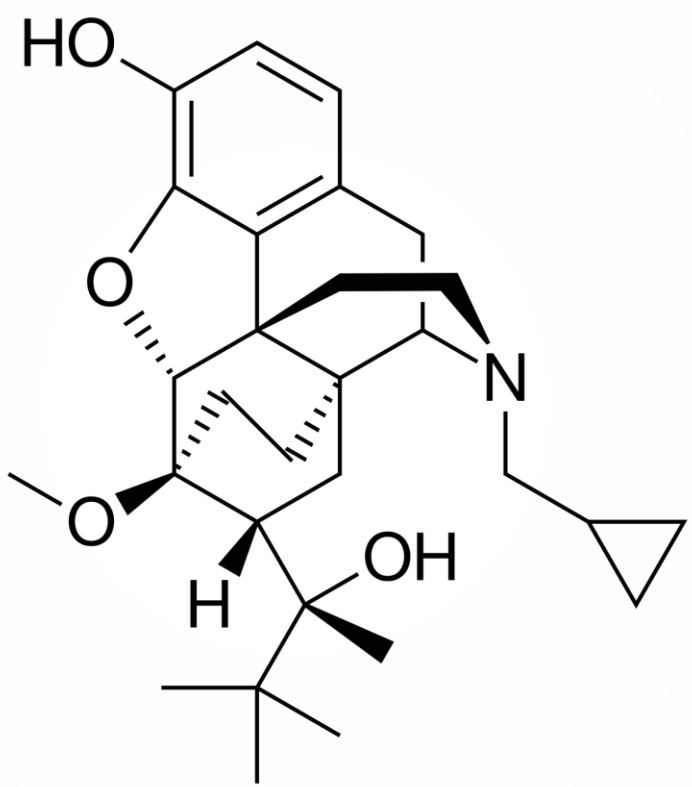
- Most often occurs when patients are using in combination with other sedating drugs
- CNS and respiratory depression
- Treat with naloxone for a minimum of 24 hours with an additional 12 hours of monitoring
- Can run as an infusion or give small bolus doses hourly

Methadone: Renal and Hepatic Failure

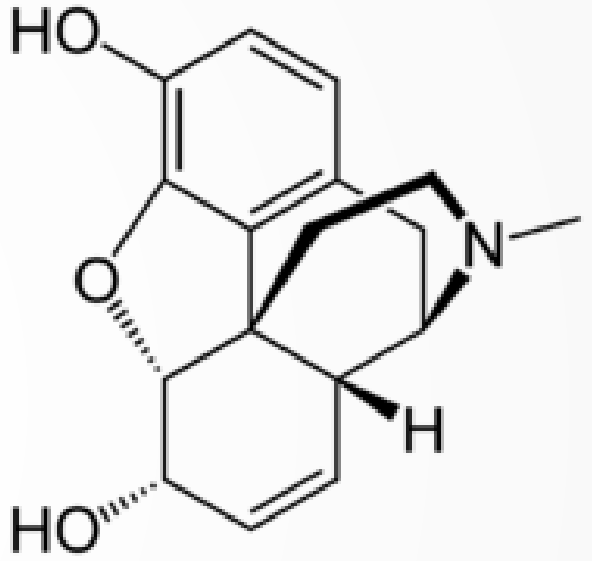
- Plasma levels remain relatively stable in renal failure
  - No active metabolites and primarily excreted in feces.
  - Generally considered safe, with caution in severe disease.
- Acute changes in liver status may require dose adjustment
  - Risk of accumulation especially in severe disease
  - Adjust according to patients' signs and symptoms.

What is Buprenorphine?

- Semi-synthetic opioid
- Partial agonist at mu opioid receptor
  - Considered safer in overdose when compared to full opioid agonists

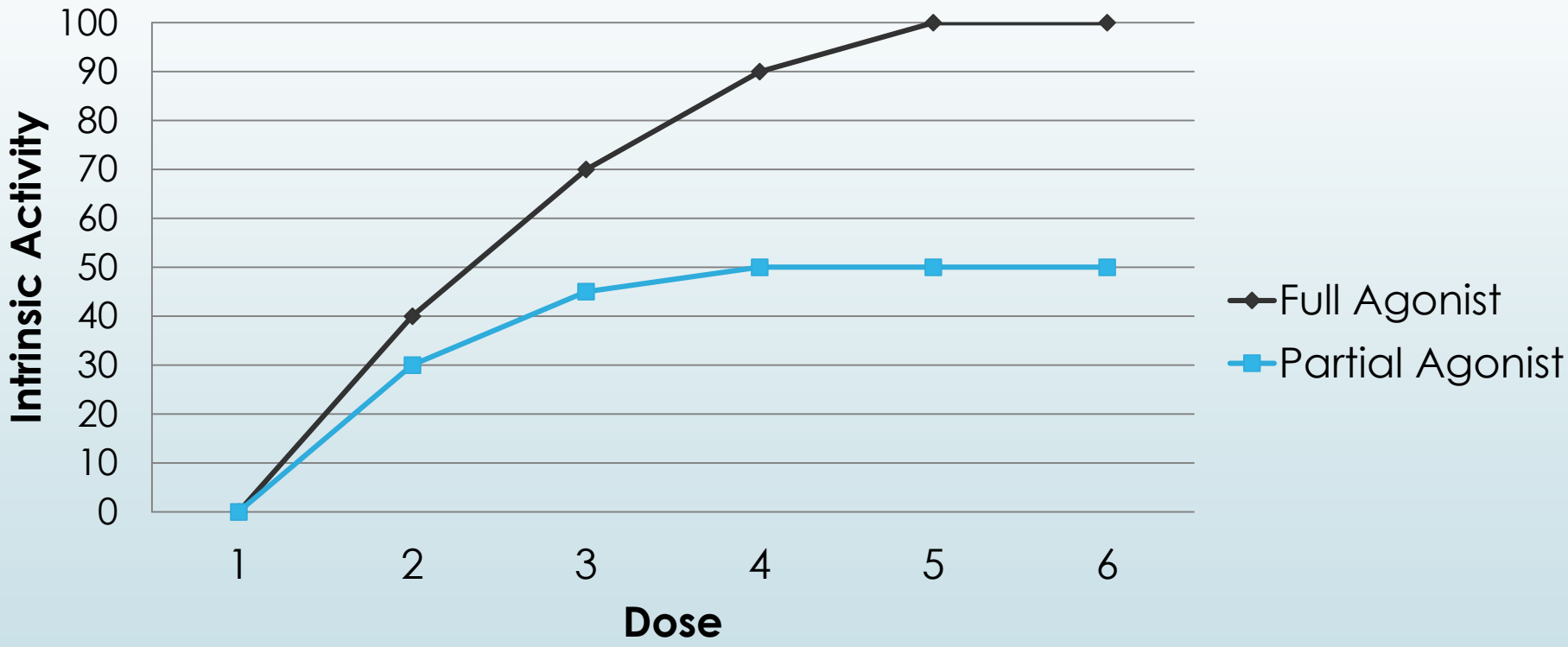


Buprenorphine



Morphine

Full Agonist vs Partial Agonist



How is Buprenorphine available?

- Buprenorphine alone (Subutex®) is available in Canada through special access only
- Buprenorphine in combination with naloxone is available both as the brand name Suboxone® and as generic versions.
- Extended-release buprenorphine (i.e. Sublocade, Probuphine)

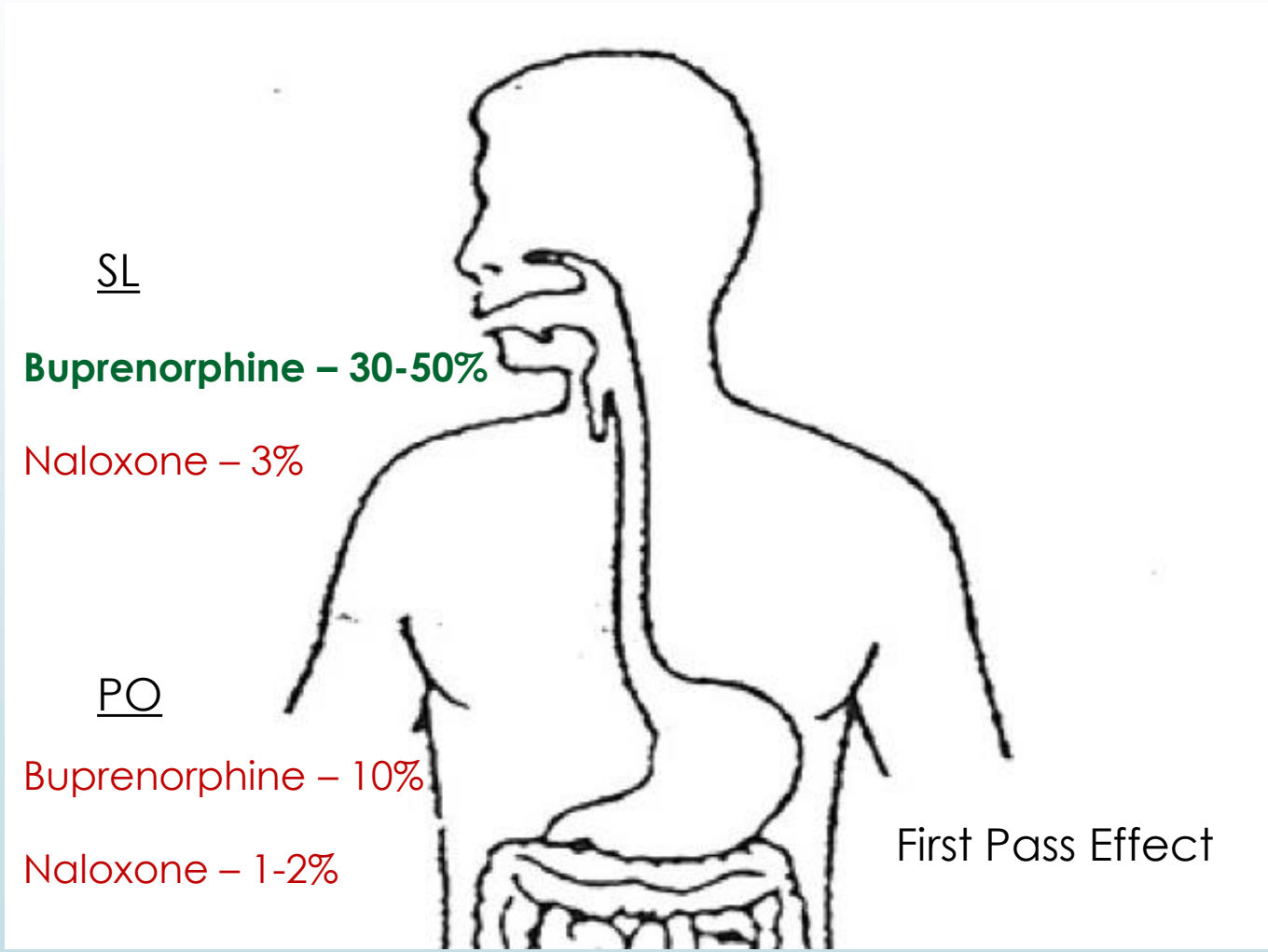
Why does Precipitated Withdrawal occur?

- Buprenorphine is a partial agonist with *stronger binding* to *μ* opioid receptors than most other opioids
- Effects from full opioid agonist are replaced by lesser effects of partial agonists
- Clinicians need to determine the **correct timing and dosage** of buprenorphine according to the patient's **last dose of opioid**

Buprenorphine/Naloxone SL

- Sublingual Tablet
- Available dosages (bup/nlx)
  - 2 mg/0.5mg
  - 8 mg/2 mg
- Dissolution time: 2-10 minutes
  - Becomes a pulpy mass
- Usual daily dose: 4 to 16 mg
- Maximum dose: **24 mg/day** (Canadian monograph)

Bioavailability – Buprenorphine/Naloxone



Naloxone

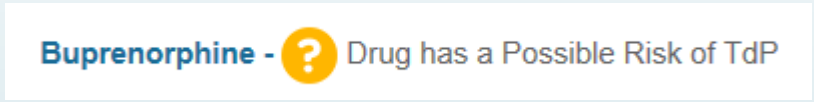
- Naloxone is a pure antagonist to *μ* (mu) opioid receptors
- The purpose of associating buprenorphine with naloxone is to reduce IV usage
  - Rapid binding **precipitates a rapid opioid-withdrawal syndrome** when naloxone injected

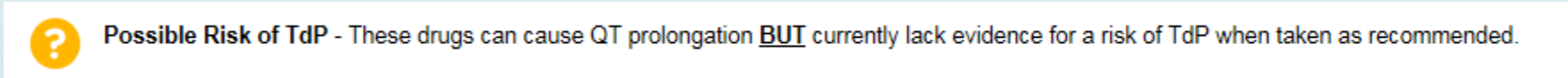
Buprenorphine - Pharmacokinetics

- Rapid onset of action : 30 to 60 minutes
- Maximum effects : 1 to 4 hrs
- Elimination half life: ~ 24 to 36 hrs
- Reaches steady state in 3 to 7 days
  - Ceiling effect at higher plasma levels, so accumulation less risky than with methadone

QT Prolongation

- CredibleMeds.org recently added buprenorphine to the list of drugs that are a possible risk for Torsades de Pointes.





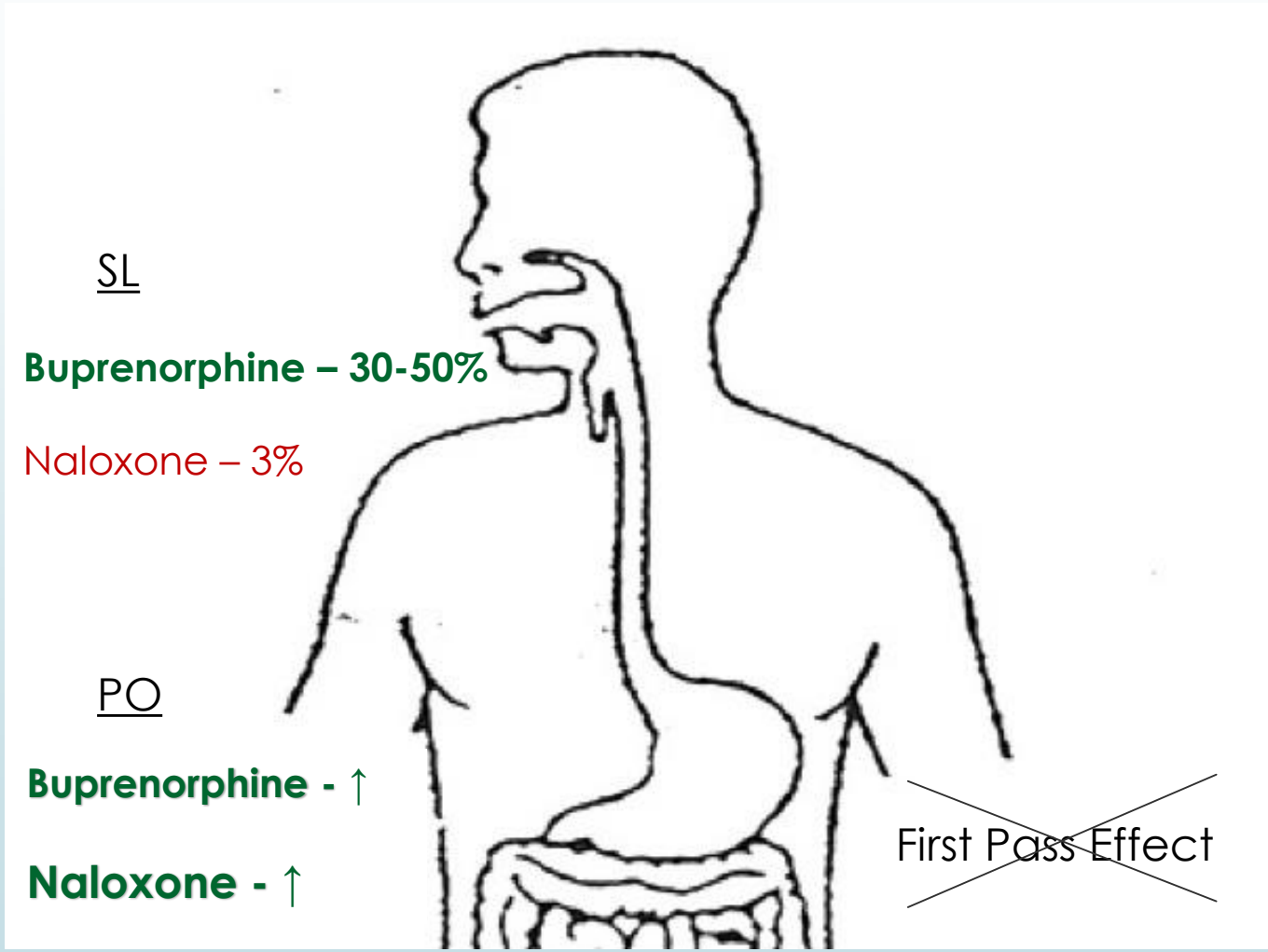
Buprenorphine - Adverse Effects

- Similar to other opioids
- In general, well tolerated and side effects are attenuated because buprenorphine is a partial agonist.

Buprenorphine/Naloxone: Renal and Hepatic Failure

- Buprenorphine/naloxone appears to be safe in renal failure
  - Not removed by hemodialysis
- Caution in patients with hepatic failure

Buprenorphine/Naloxone – Hepatic Failure



Drug-Drug interactions

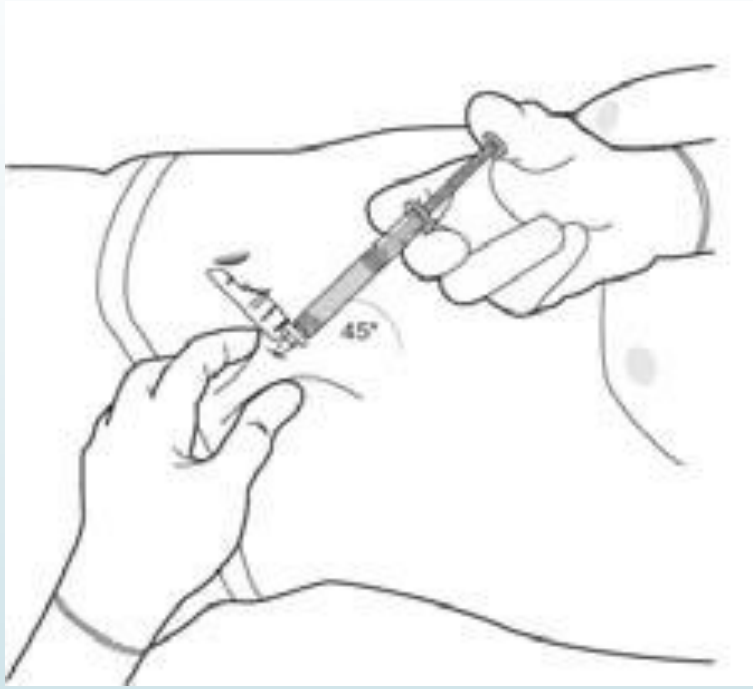
- Benzodiazepines
  - Co-administration with other sedatives can cause respiratory depression, excessive sedation, coma, or death
- Buprenorphine blocks the effects of full agonist opioids
  - Complicates the use of opioids for analgesic purposes

Interactions continued…

- Inhibitors of cytochrome P450 3A4 including but not limited to:
  - Some drugs in the drug classes of azole antimycotics, protease inhibitors, calcium channel blockers and macrolide antibiotics
  - Ritonavir, indinavir, ketoconazole, itraconazole, erythromycin, diltiazem, fluoxetine - may significantly increase levels of buprenorphine
- Inducers of CYP P450 3A4:
  - Phenytoin, carbamazepine, rifampin

Buprenorphine Extended-Release Injection

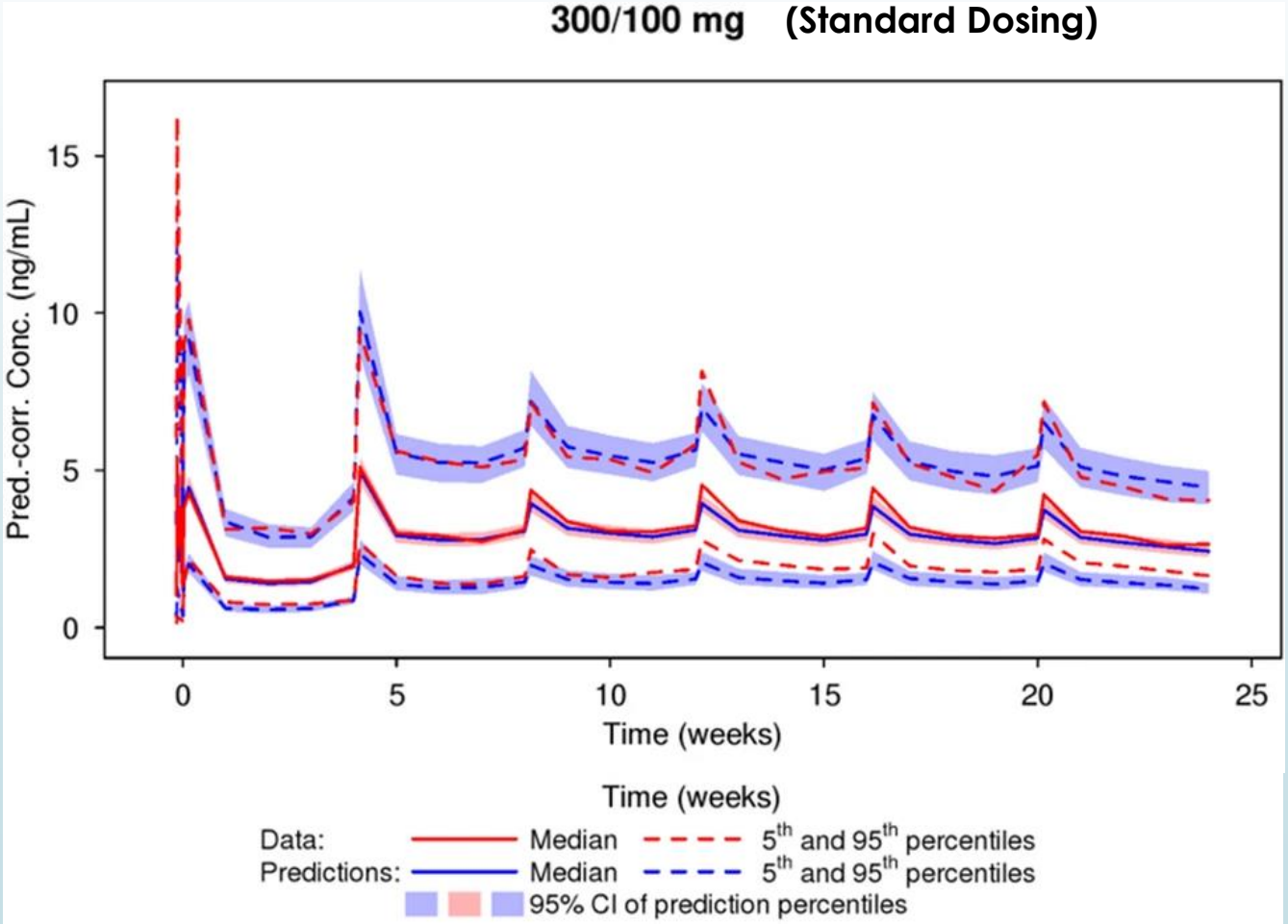
- Buprenorphine Extended-Release Injection (i.e. **Sublocade®**)
  - Monthly subcutaneous depot injection into abdomen
  - Standard dosing:
    - 300mg for 2 mths, then 100mg monthly
    - May keep at 300mg monthly if response is not sufficient



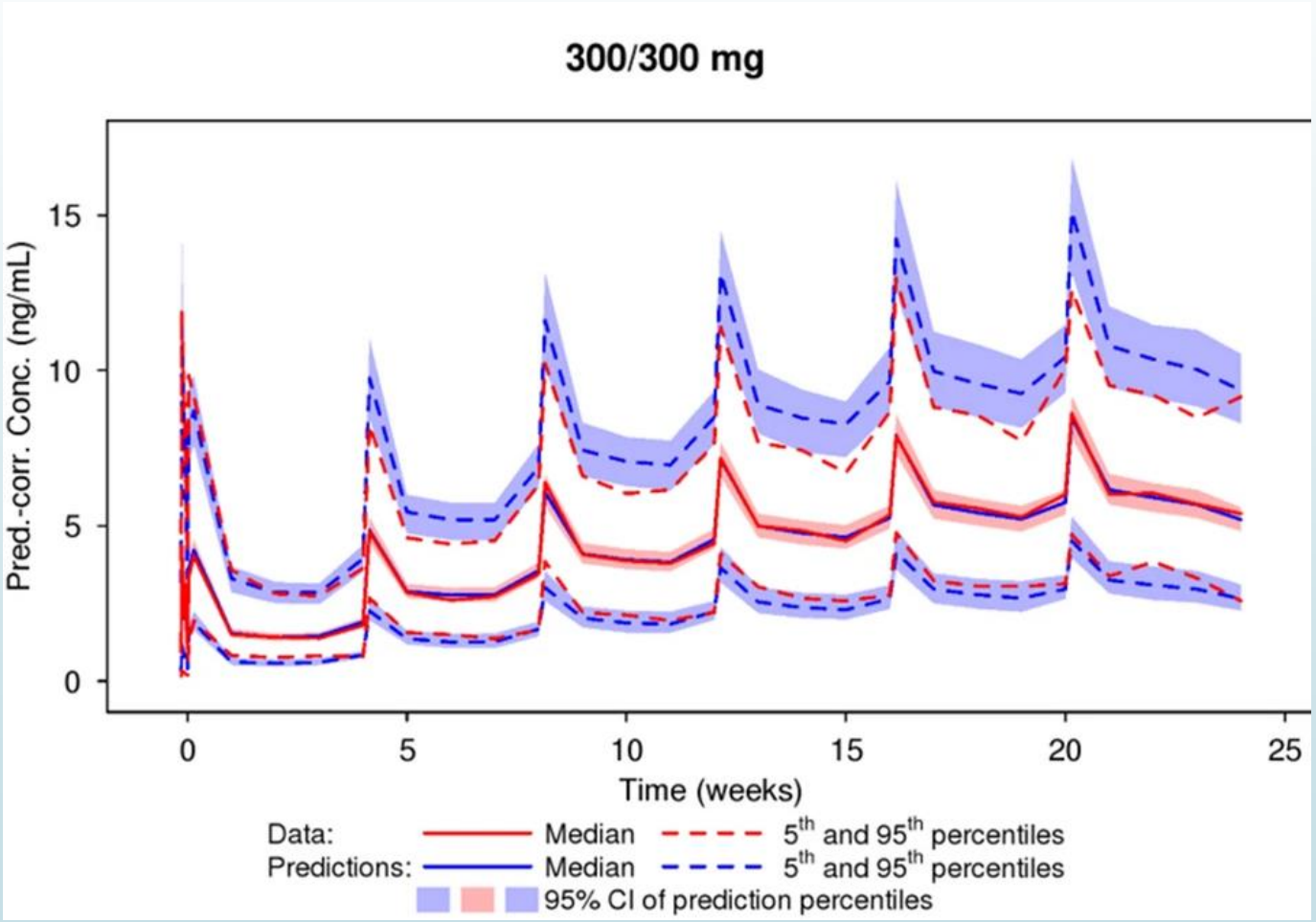
Buprenorphine Extended-Release Injection (Con't)

- Pharmacokinetics
  - Median T_{max} occurs at 24hr after injection
  - Steady-state in 4 to 6 mths

Buprenorphine Extended-Release Injection (Con't)

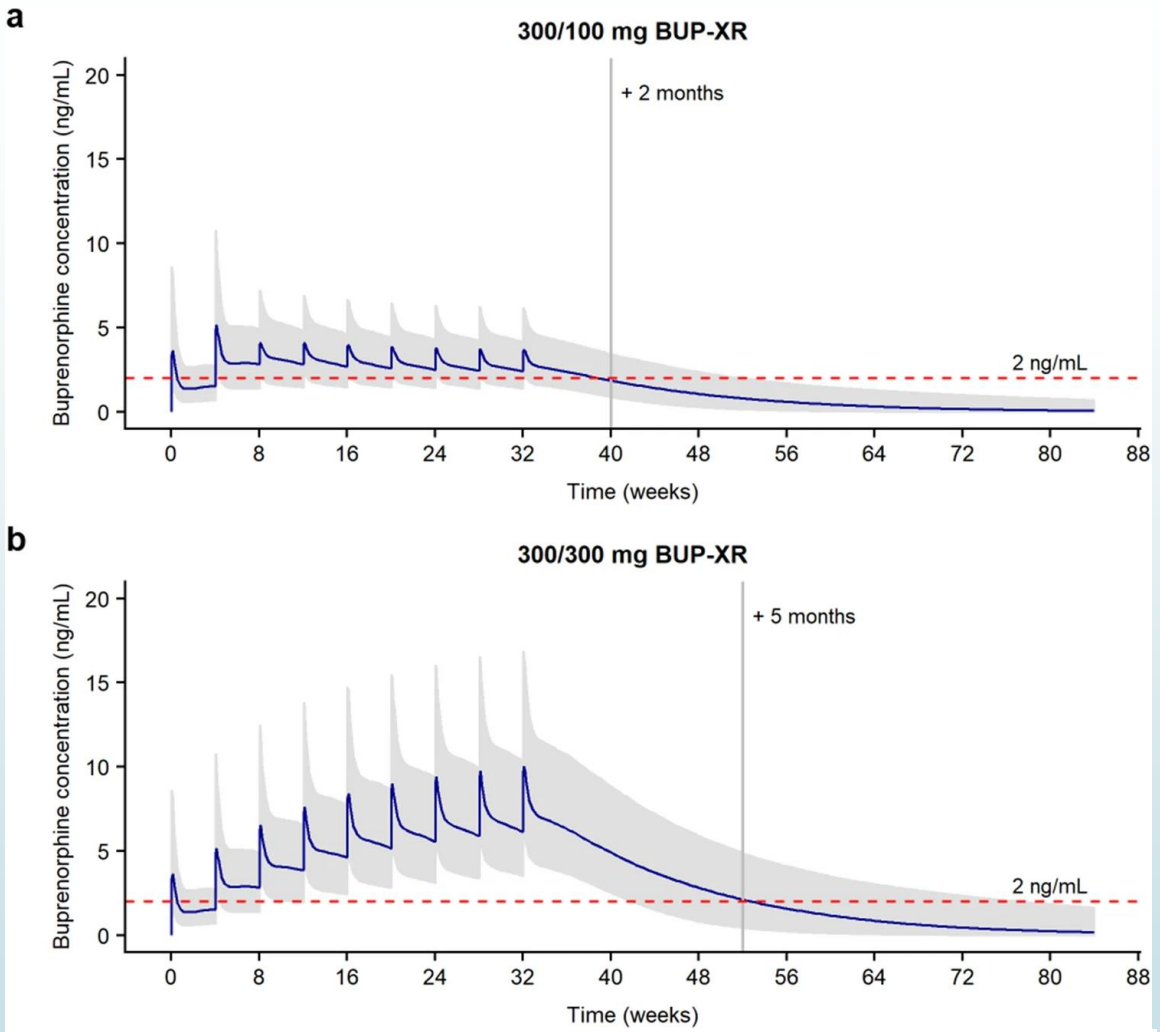


Buprenorphine Extended-Release Injection (Con't)



Buprenorphine Extended-Release Injection (Con't)

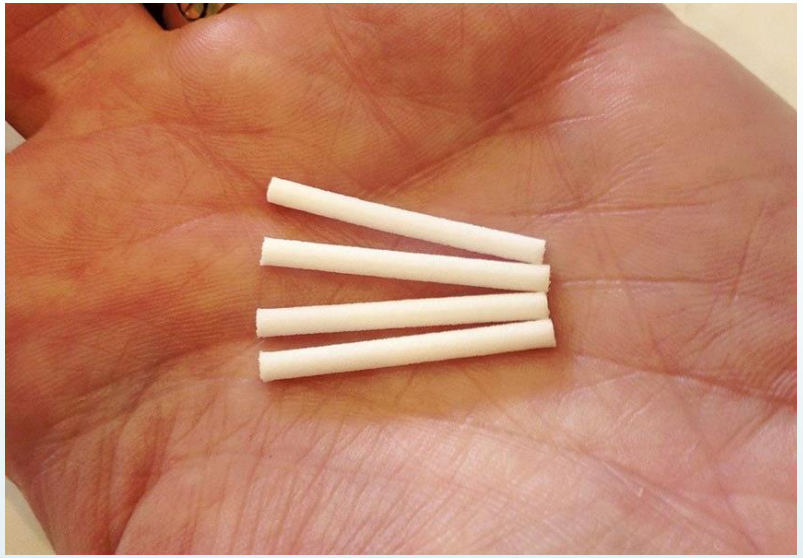
- Pharmacokinetics (con't)
  - Terminal plasma half-life is 43 to 60 *days*
  - Opioid blockade will persist for several months after discontinuation

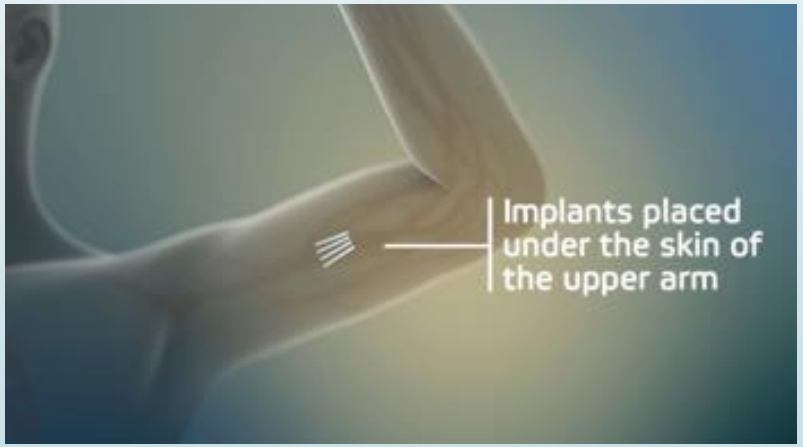


Red line = Concentration req'd for opioid blockade

Buprenorphine HCl Implant

- Probuphine®
  - Subdermal implant (4 flexible rods) inserted for 6 months and then removed
  - Data-supported use for up to 2 years using different implant sites
- Pharmacokinetics
  - T_{max} at 12 hrs, then reaches steady state at 4 weeks
  - At steady state, plasma concentrations comparable to those of a stable patient on 8mg SL





Pharmacist Role

- Pharmacist is often the healthcare provider that the patient has the most contact with. Will see OAT patients a minimum of 1/week.
- Pharmacists must develop a professional relationship with their OAT patients so they are able to assess their condition when they come in for their dose.
- Pharmacists are in an excellent position to identify when patients may need extra support or referral to other healthcare professionals.

Pharmacist-Prescriber Collaboration

- Extremely important for OAT patient population

Examples of situations that should be reported to prescriber:

- ❑ Patient does not pick up dose
- ❑ Patient refuses part or all of dose
- ❑ Patient appears intoxicated/impaired
- ❑ Patient vomits dose
- ❑ Patient receives psychoactive medications not approved by the OAT prescriber

A good working relationship between the pharmacist and prescriber is not only professionally satisfying, it is also best for patient care.

References and Resources

- Yaffe GJ, Strelinger RW, Parwatikar S. Proc Natl Conf Methadone Treat. 1973;1:507-14.Physical symptom complaints of patients on methadone maintenance.
- Tisdale,J et al. Circ Cardiovasc Qual Outcomes. 2013 Jul; 6(4): 479–487.Published online 2013 May 28. doi: 10.1161/CIRCOUTCOMES.113.000152

References

- Al-Adwani A, Basu N. Addiction. 2004 Feb;99(2):259.Methadone and excessive sweating.
- Alberta College of Pharmacists, ODT Guidelines: Medication-Assisted Treatment for Opioid Dependence: Guidelines for Pharmacists and Pharmacy Technicians, 2013
- *Bruneau J et al. Management of opioid use disorders: a national clinical practice guideline. CMAJ Mar 05, 2018 190(9) E247-E257*
- "Buprenorphine." *Wikipedia, the Free Encyclopedia*. Web. Mar 2021. <http://en.wikipedia.org/wiki/Buprenorphine>.
- Centre for Addiction and Mental Health. "A New Treatment For Opioid Dependence." *Ontario College of Pharmacists Pharmacy Connection* (Jan-Feb 2008): 32-37. Print.
- Centre for Addiction and Mental Health. "Opioid Dependence Treatment Core Course." Oct/Nov. 2010.

References Continued…

- Canadian Pharmacists Association. "Suboxone Drug Monograph." *CPS: Compendium of Pharmaceuticals and*. Ottawa: Canadian Pharmacists Assn, 2002.
- CredibleMed.org accessed Mar 29th, 2021
- *Dispensing Methadone for the Treatment of Opioid Dependence = L'execution D'ordonnances De Methadone Dans Le Traitement De La Dependance Aux Opioides.* Ottawa: Drugs Directorate, Health Protection Branch, Health Canada, 1994. Print.
- Goodman, Louis S., Joel G. Hardman, Lee E. Limbird, and Alfred Goodman Gilman. *Goodman & Gilman's the Pharmacological Basis of Therapeutics.* New York: McGraw-Hill, 2001. Print. Chapter 23.

References Continued…

- "Heroin." *Wikipedia, the Free Encyclopedia*. Web. May 2010. <http://en.wikipedia.org/wiki/Heroin>.
- Isaac, Pearl. *Methadone Maintenance: a Pharmacist's Guide to Treatment*. Toronto: Centre for Addiction and Mental Health, 2004. Print.
- Jamieson, Beals, Lalonde and Associates, Inc., comp. *Best Practices: Methadone Maintenance Treatment*. Ottawa: Health Canada, 2002. Print.
- Jones, Aksana K., et al. Population Pharmacokinetics of a Monthly Buprenorphine Depot Injection for the Treatment of Opioid Use Disorder: A Combined Analysis of Phase II and Phase III Trials. *Clinical Pharmacokinetics*, 2020. Nov 2nd, 2020. Web. https://link.springer.com/article/10.1007/s40262-020-00957-0
- Lee, Lindy, Adrian Hynes, and Morag Fisher. *Manitoba Methadone Maintenance: Recommended Practice*. Winnipeg: Addictions Foundation of Manitoba, 2008. Print.

References Continued…

- *Literature Review: Methadone Maintenance Treatment*. Ottawa: Health Canada, 2002. Print.
- *Methadone Maintenance Treatment: Client Handbook*. [Toronto]: Centre for Addiction and Mental Health, 2008. Print.
- "Methadone." *Wikipedia, the Free Encyclopedia*. Web. May 2010. <http://en.wikipedia.org/wiki/Methadone>.
- "Morphine." *Wikipedia, the Free Encyclopedia*. Web. May 2010. <http://en.wikipedia.org/wiki/Morphine>.

References Continued…

- "NIDA - Publications - Teaching Packets - The Neurobiology of Drug Addiction - Section III: The Action of Heroin (Morphine)." *National Institutes of Health - National Institute on Drug Abuse*. U.S. Department of Health and Human Services. Web. 13 Oct. 2011. http://www.nida.nih.gov/pubs/teaching/Teaching2/Teaching4.html.
- Office of Continuing Medical Education, University of Manitoba, comp. DVD - *Methadone: An Introduction to Clinical Practice*. Winnipeg, MB.
- Ordre des Pharmaciens du Quebec "Programme de formation relié au traitement de substitution à la méthadone pour les personnes dépendantes des opioïdes."
- Probuphine™ Product Monograph. Knight Therapeutics Inc. Montreal, QC. Web. https://pdf.hres.ca/dpd_pm/00044828.PDF

References Continued…

- Schering-Plough Canada Inc. "Suboxonecme.ca Opioid Dependence Education." 2007. Web. Dec. 2010. <http://www.suboxonecme.ca/en/home/.ssx>.
- Selby, Peter, and Meldon Kahan. *Methadone Maintenance Treatment: a Physician's Guide*. Toronto: Centre for Addiction and Mental Health, 2008. Print.
- Srivastava, A. "Buprenorphine: a Potential New Treatment Option for Opioid Dependence." *Canadian Medical Association Journal* 174.13 (2006): 1835. Print.
- Sublocade™ Product Monograph. Indivior UK Limited, imported and distributed by Pharma Importing Inc. Toronto, ON. 2018. Web. https://pdf.hres.ca/dpd_pm/00048406.PDF
- Yaffe GJ, Strelinger RW, Parwatikar S. Proc Natl Conf Methadone Treat. 1973;1:507-14.Physical symptom complaints of patients on methadone maintenance.