Opioid Agonist Therapy 101:
An Introduction to Clinical Practice Workshop

Pharmacology:

METHADONE AND BUPRENORPHINE/NALOXONE AND PRESCRIBER-PHARMACIST COLLABORATIVE CARE

Disclosure of Commercial Support

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  - None identified

Faculty/Presenter Disclosure

- **Faculty:** Nicole Nakatsu

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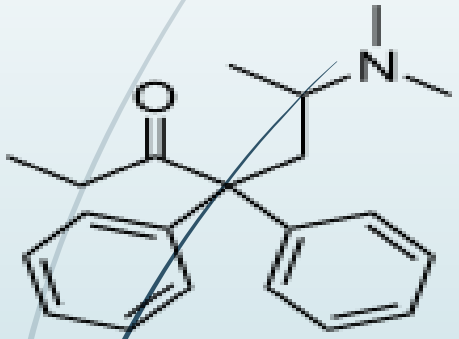
- **Mitigating potential bias: (delete this section if no disclosures above)**
  - Fresenius Kabi at the time I gave the talk sold no narcotics. The talk was on Opioid Stewardship and they had no input on the content

Learning Objectives

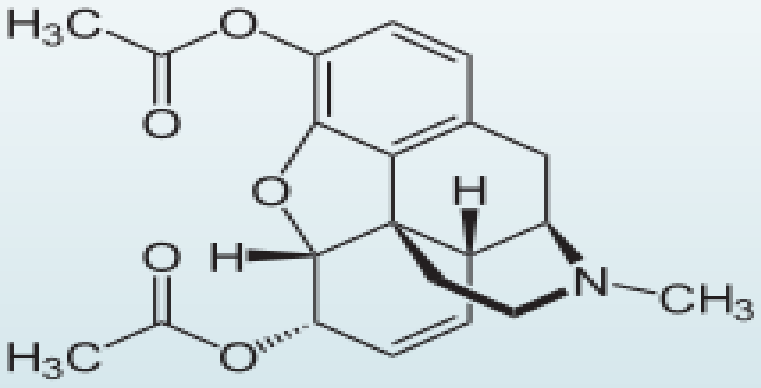
- To understand the unique pharmacology of methadone and buprenorphine/naloxone
- To identify potential and actual drug interactions.
- To review the importance and benefits of active participation in prescriber - pharmacist collaborative care.

Methadone Pharmacology

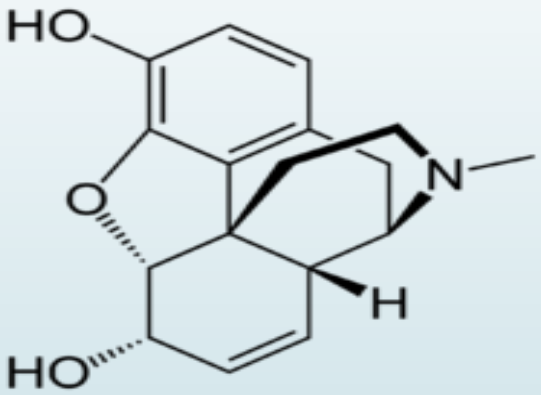
- Synthetic opioid
- Structurally unrelated to opiates



methadone



heroin



morphine

Methadone Pharmacology

- Agonist at the μ-opioid receptor
- Uses- analgesia and withdrawal management in opioid dependent individuals
- 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

- 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

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

Metabolism

- Primarily metabolized by cytochrome P450 3A4 to the inactive metabolite EDDP
- Also metabolized to a lesser extent by CYP 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6
- Weak inhibitor of 2D6

Excretion

- Methadone is excreted both as unchanged drug and as metabolites in urine and feces.
- Amount of methadone excreted in urine increases as pH decreases (acidifies).

Adverse Effects

- 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

- Sweating –up to 45% of individuals may experience excessive sweating. May be due to dose being too high or too low. Off label: ?Desloratadine, clonidine,
- Sedation- tolerance develops to this side effect but caution is advised during initiation 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.
- Psychoactive effects- patients may experience some euphoria when starting on methadone or during dose increases. When stabilized methadone will block euphoria from other opioids.

Adverse Effects

- Insomnia-generally improves as patient is stabilized. Look into other causes of insomnia such (i.e. anxiety). Instruct patient on good sleep hygiene
- Sexual problems-may decrease desire and/or performance. Once stabilized some patients may experience an increase in desire

Adverse Effects

- Neuroendocrine- increased prolactin, affects HPA and HPG axis but with chronic use tolerance develops to these affects. Most women will report normal periods once stabilized. Men may experience a decline in testosterone.
- 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.
- 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
Sepsis	3
Heart failure	3
One QTc-prolonging drug	3
Maximum Risk Score	**21**

K+ = potassium; MI = Myocardial infarction

Tisdale Tool Continued

- QTc interval risk score stratification
- ***Risk ScoreCategory**
- Low < 7
- Moderate 7–10
- High >11

- Note Mg++ not included as not enough patients had Mg++ levels done. Would consider this as well

- Tisdale, J et al. **Development and Validation of a Risk Score to Predict QT Interval Prolongation in Hospitalized Patients**
- Circ Cardiovasc Qual Outcomes. 2013 July ; 6(4): 479–487. doi:10.1161/CIRCOUTCOMES.113.000152.

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.
- Antagonist/partial-agonists-precipitate withdrawal

Drug Interactions-some common examples

Decrease plasma levels

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

Increase plasma levels

- Amitriptylline
- 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

- 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

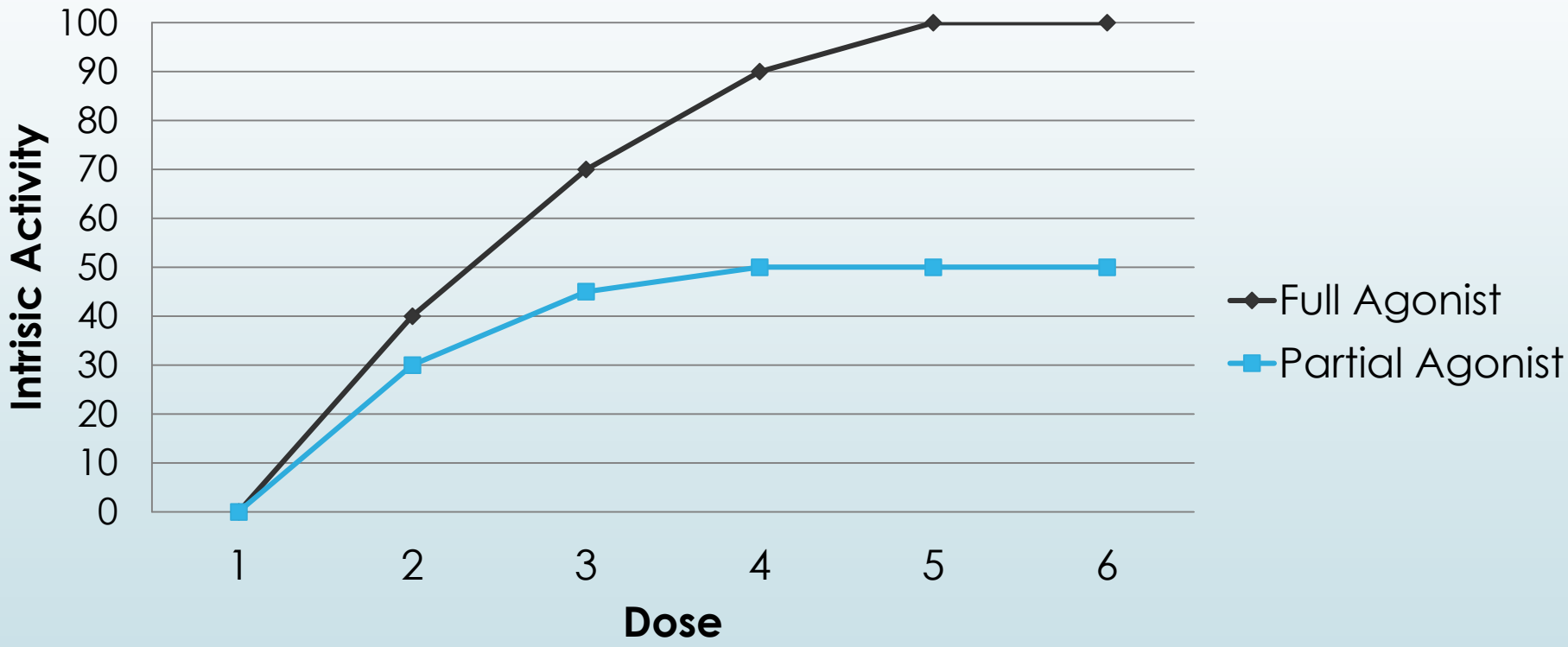
Renal and Hepatic Failure

- Plasma levels remain relatively stable in renal failure
- Very little methadone removed by peritoneal or hemodialysis
- Acute changes in liver status may require dose adjustment
  - Adjust according to patients signs and symptoms

What is Buprenorphine?

- Opioid agonist treatment option for opioid-dependent patients
  - Considered first line "Management of opioid use disorders: a national clinical practice guideline" CMAJ 2017
- Partial agonist at mu opioid receptor
  - Considered safer in overdose when compared to full opioid agonists

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.
- Buprenorphine is indicated for substitution treatment in opioid drug dependence in adults
  - Used within the framework of medical, social and psychological support
  - Pharmacare Part 1 since 2017

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 Suboxone® according to the patient's **last dose of opioid**
- Prevents other opioids from attaching to *μ* opioid receptors and displaces *μ* receptors of other opioids with weaker affinities for the receptors (morphine, methadone, heroin, oxycodone)

Buprenorphine/Naloxone

- Sublingual Tablet
- Available dosages
  - The buprenorphine/naloxone ration is 4:1
  - 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)

Naloxone

- Naloxone is a pure antagonist to *μ* (mu) and *κ* (kappa) 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
- Naloxone is has very low sublingual and oral bioavailability

Buprenorphine/Naloxone

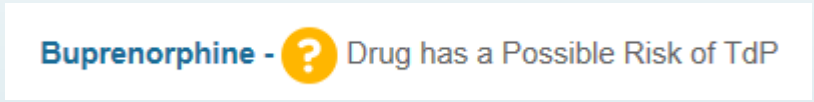
- Rapid onset of action : 30 to 60 minutes
- Maximum effects : 1 to 4 hrs
- Duration of action is proportional to the dose
  - 2 to 4 mg: 4 to 12 hrs
  - 4 to 8 mg: ~ 24 hrs
  - > 8 mg: 2 to 3 days
- Elimination half life: ~ 24 to 36 hrs
- Reaches steady state in 3 to 7 days

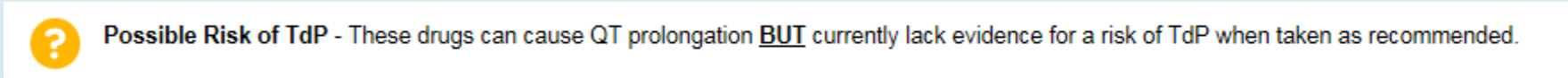
Ceiling Effect

- Partial mu-opioid receptor agonist so it has lower intrinsic activity than a full agonist
  - Ceiling effect occurs at higher doses
  - Safer in overdose (when used alone)
- Above daily doses of 16 to 32mg, there is no increased effect from increasing the dose
- Tight binding at receptor causes slow dissociation = Long duration of action
- Lower potential for overdose but only when used alone!

QT Prolongation

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





Adverse Effects

- Similar to other opioids
- In general, well tolerated and side effects are attenuated because buprenorphine is a partial agonist.
- Caution with burprenophine/naloxone in hepatic failure.

Drug-Drug interactions

- Benzodiazepines
  - Co-administration with other sedatives can cause respiratory depression, excessive sedation, coma, or death
  - Deaths due to abuse of buprenorphine with alcohol and/or benzodiazepines have been reported
- buprenorphine blocks the effects of full agonist opioids
  - Complicates the use of opioids for analgesic purposes

Interactions continued…

- Monoamine oxidase inhibitors (MAOI)
- 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

Other formulations

- Probuphine®
  - Subdermal implant into upper arm
  - For patients stabilized on 8mg or less of buprenorphine/naloxone
  - 4 flexible rods inserted for 6 months and then removed
  - not radioopaque
- Sublocade®
  - Subcutaneous depot injection into abdomen
  - For patients stabilized on 8-24mg of SL buprenorphine
  - Monthly injections
  - First 2 months 300mg dose followed by maintenance 100mg dose qmonthly that can be increased to 300mg as needed and tolerated.

Pharmacist Role

- Pharmacist is often the healthcare provider that the patient has the most contact with. Will see ORT patients a minimum of 1/week.
- Pharmacists must develop a professional relationship with their ORT patients so they are able to assess their condition when they come in for their dose.
- Phamacists 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 ORT 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 fails to provide lock box

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

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