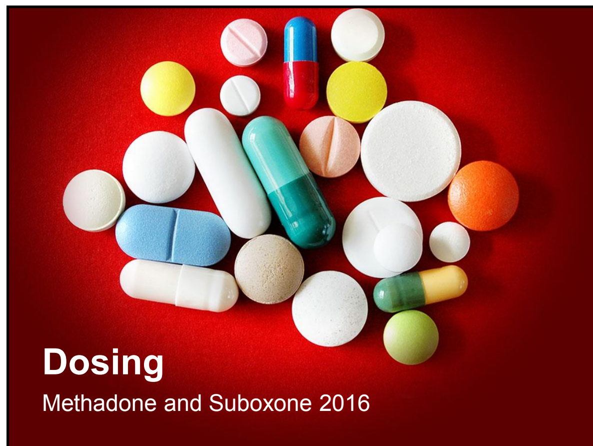


Objectives

- The Pharmacokinetics and Pharmacodynamics of methadone and buprenorphine
- Therapeutic implications
- Why we dose the way we do

Methadone

“Methadone Does Not Have a Sense of Humor”

Methadone

- A long acting, synthetic opioid
- Good oral bioavailability, slow onset of action and a long half life
- Binds strongly to the mu receptor, rendering the receptor inaccessible to most other opioids
- Prevents withdrawal, decreases craving and blocks euphoria produced by short acting opiates

Pharmacodynamics

- Methadone is a racemic mixture:
- D enantiomer (D [l] methadone) has almost all of the opioid agonist activity. It binds strongly to the:
  - μ receptor (major effect)
- Affinity (for μ receptor): morphine <methadone <buprenorphine < fentanyl < naloxone
- Half life
- Steady state – The state at which there will be no increase in blood concentration of the drug if the dose remains – 4-5 half lives.

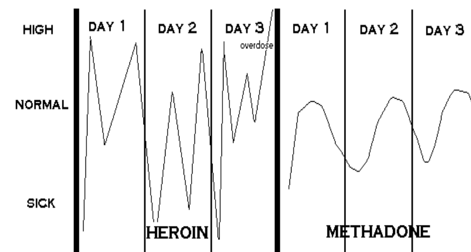
Pharmacodynamics

- A flare in liver decreases might decrease methadone metabolism leading to toxicity.
- Methadone’s elimination metabolism is biphasic.

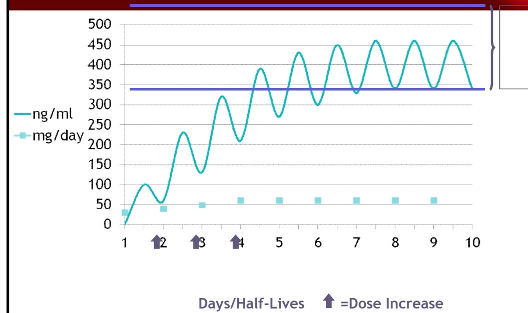
METHADONE METABOLISM

- Excretion of methadone and its metabolites is 60% renal.
- In renal failure 95% methadone is excreted by the gut - safe to give in renal failure.
- Metabolism not affected by mild to moderate hepatic failure. In severe failure methadone bypasses the liver and dosage has to be modified upwards or downwards as clinically indicated.

METHADONE METABOLISM RATE



Methadone Induction Simulation



Methadone

- Initiation
  - Low Risk
  - Days 1 to 3 30 mg daily
  - Days 4 to 6 40 mg daily
  - Days 7 to 9 50 mg daily
  - Then increase by 10 mg every 7 days until stability

Methadone

- Moderate risk – start at 20 mg or less
- High risk – start at 10 mg or less
  - Increase no more than 5 mg increments

Methadone

- Typical methadone dose to reduce cravings and withdrawal symptoms is between 60 – 120 mg

Case 1

- 34 y.o male presents requesting methadone recovery
- Has already been through the intake process
- Initial urine drug screen
  - Positive for hydromorphone

Case 1 cont'd

- IVDU 5 years
- Detox 3 times
- Rehab 1 time – was abstinent for 3 months
- Using hydromorphone 5 6's per day
- Costing 120 dollars a day
- Works construction – dry waller
- Is not getting much work lately

Case 1 cont'd

- Had money saved up but now has used it all
- Would like to go on methadone

Case 1 cont'd

- Methadone induction
- Rx
- Methadone 30 mg po od x 3/7
- Then 40 mg po od x 3/7
- Daily witness
- Plus or minus Kadian

Case 1 cont'd

- Next appointment day 7
- Assess patient's response
- Increase dose to 50 mg for 7 days
- See patient in 7 days
- Adjust dose as needed according to patient complaints of withdrawal and cravings

Case 1 cont'd

- Stable dose at 90 mg po od by week 6
- Patient feels well – no withdrawal or cravings.
- Week 10 – uds methadone and EDDP
- Week 14 – uds methadone and EDDP
- Week 18 – uds methadone and EDDP

Case 1 cont'd

- Patient states having increased cravings
- Triggered by attending a party and drugs were in site
- No withdrawal symptoms
- Increased cravings
- No slips

Case 1 cont'd

- Options
- 1. Speak with counsellor – no dose increase
- 2. Speak with counsellor – dose increase by 5 or 10 mg

Case 1 cont'd

- What if patient came to appointment and said they slipped – used a dilaudid 6 IV?
- Change previous answer?
- What if they slipped on cocaine of crystal meth?

Case 2

- 32 y.o on methadone for 6 months
- Current dose 120 mg po od
- Urine screens every other one contains hydromorphone
- Patient complaining of withdrawal – leg pain and sweating and cravings
- Patient requesting dose increase
- What next?

Case 2 cont'd

- Initial QTc – 435
- Current medications
  - Quetiapine 50 mg hs for insomnia
  - Citalopram 20 mg po od for depression

Case 2 cont'd

- ECG
- QTc 540
- What next ?

QT Interval Prolongation

- Increase in QT interval – usually more prominent above 130 mg daily
- Need baseline ECG if adding other medications that prolong the QT interval
- QTc 450 to 500 – monitor closely
- QTc > 500 consider reducing dose or discontinuing
- Consider decreasing other QTc medications

Later: • Stop the offending agent • Maintain normal K+, Mg++ and HCO_3- • Keep out of trouble as above

Table 2: Drugs which can prolong QT Interval [1,3,6,9,12,13,14] -see www.torsades.org

Cardiovascular	CNS / Psychotropic	Anti Infective	Miscellaneous	Cytochrome P450 Inhibitors (DIs: Column 5)
Anti-arrhythmics Amiodarone (low risk of TdP compared to other class III agents such as sotalol; however potential for DIs) **Bepridil** Bretylium **Disopyramide** **Dofetilide** **Dronedarone** **Flecainide** **Ibutilide** **Mexiletine** **Procainamide** **Propafenone** **Quinidine** less at ↑ dose **Sotalol** Dobutamine Dopamine Isradipine Moexipril/HCTZ Nicardipine Norepinephrine Ranolazine **ADHD agents** Amphetamine Atomoxetine Dextroamphetamine Lisdexamfetamine Methylphenidate&Dex **Antiemetics** **Dolasetron** esp IV **Domperidone** esp IV, >30mg orally/day or with ketoconazole **Droperidol**	**Anticonvulsants** Felbamate, Fosphenytoin, Lithium **Antipsychotics** Amisulpride Asenapine Aripiprazole Butyrophenones **Haloperidol** esp with ↑ dose or IV Clozapine Phenothiazines (PZs) **Chlorpromazine** **Mesoridazine** Perphenazine **Thioridazine** **Iloperidone** **Paliperidone** **Pimozide** **Quetiapine** *Risperidone* Thioxanthines **Ziprasidone** Chloral Hydrate **SSRIs** Citalopram (if >40mg/day) **Escitalopram** (in overdose) Fluoxetine Paroxetine (esp ↑ cimozine) Sertraline Trazodone **SNRI** Des & -venlafaxine **Mirtazapine** **TCAs** **Amitriptyline** Amoxapine **Clomipramine** **Desipramine** **Doxepin** **Imipramine**	**Antibiotics** Cotrimoxazole Fluoroquinolones Ciprofloxacin - only if DI, not a direct QT effect Gatifloxacin Gemifloxacin Levofloxacin **Moxifloxacin** Norfloxacin Ofloxacin **Sparfloxacin** Macrolides Azithromycin Clarithromycin **Erythromycin** IV Roxithromycin Telavancin Telithromycin **Azole Antifungals** *Fluconazole* Itraconazole Ketoconazole Posaconazole Voriconazole **Antimalarials** Artemether-lumefantrine **Chloroquine** **Halofantrine** Hydroxychloroquine Mefloquine Quinine **Pentamidine**	Alfuzosin, Amantadine, **Arsenic** trioxide, Atazanavir, Buprenorphine, **Cisapride**(Special Access) Cocaine, Crizotinib, Cyclosporin, Dasatinib, Degarelix, Donepezil, Eribulin, Fingolimod, Foscarnet, Galantamine, Ginseng, Hydroxyzine, Indapamide, Kaletra, Lapatinib, Levomethadyl, Lopinavir, **Methadone**, Midodrine, Mifepristone, Nilotinib, Octreotide, Orphenadrine, Oxytocin, Oxycodone, Pazopanib, Phenylephrine **Probucol, Propoxyphene** Pseudoephedrine, Rilpivirine Ritodrine, Ritonavir Romidepsin **Saquinavir**, Sibutramine Solifenacin, Sunitinib Tacrolimus, Tamoxifen Tizanidine, Tolterodine, Triptans (recently off QT list) **Vandetanib**, Vardenafil, **Vemurafenib** **Antihistamines** *Diphenhydramine* *Clemastine* *Loratadine*(but no reports) Withdrawn: Astemizole & Terfenadine **Appetite suppressant** Ephedrine, Fenfluramine Phentermine, Sibutramine	**CYP3A4** Amiodarone **Azole antifungals:** *Fluconazole* Itraconazole Ketoconazole **Calcium channel blocker:** Diltiazem Verapamil Cimetidine **Ciprofloxacin** Grapefruit juice **HIV**: protease inhibitors **Macrolides:** **Erythromycin** Clarithromycin Troleandomycin (not with Azithromycin) Methadone Telithromycin **SSRI's:** Fluvoxamine Norfluoxetine Nefazodone Paroxetine Trazodone **CYP2D6** Beta Blockers (BBs) Haloperidol Phenothiazines Quinidine SSRIs (not interact with citalopram) Terbinafine TCAs ------------------------- *less significant* **CYP1A2** Fluoroquinolones

Swedish ADR Registry 2008: n = 61,788 ADRs, n = 86 torsades 0.14%. Top 3 suspected drugs

Dose increases

- Watch for patients who state they have become immune to methadone
- Watch for those who state they cannot "feel it"
- Some patients will continue to push the dose

Taper

- Voluntary tapering is usually tailored to each individual patient
- Decrease by 10mg , 5 mg , 2.5 mg or even 1 mg
- Weekly, q2weekly or other

Taper

- If dose is over 100 mg – usually taper by 10 mg until 80 mg – or depends on how the patient is tolerating the decreases
- Then decrease by 5 mg each time until 50 mg
- Then 2.5 mg each time until 10 or 20 mg
- Then by 1 mg until done

Taper

- Involuntary taper – see guidelines – page 29
- Aggressive schedule 10% reduction of the daily dose per day or 1mg whichever is greater
- Decrease no more than 10 mg every 3 to 4 days

Taper

- Case
- Patient has ongoing poor behavior at both the pharmacy and the clinic – threatened staff
- Dose 120 mg po daily
- Daily witness
- Decrease by 10 mg every 5 days until off
- Could decrease faster or slower

Buprenorphine

- Long acting partial opiate agonist
- Ceiling effect
- Safer in overdose than methadone
- May be less effective than methadone at retaining patients in treatment
- Max dose 24 mg

Buprenorphine

- Why chose it?
- Patients with prolonged QTc
- Patients at higher risk for methadone toxicity – elderly, concurrent benzodiazepiine use, COPD,
- Lack of access to methadone dispensing pharmacy
- Carry restrictions for methadone

Buprenorphine

- Need to start with patient in opiate withdrawal
- Sublingual tablet – start 4 mg in am – have patient return in the afternoon- if signs of opiate withdrawal then repeat 4 mg
- Day 2 – 8 mg po od
- Then increase to 12 or 16 mg by day 3 or 4

Buprenorphine

- If BID dosing an issue then dose 4 mg first day, 8 mg second day and 16 mg third day
- A third option is 8 mg Day 1 and 16 mg day 2
- Dose range is between 16 mg and 32 mg daily dose

Buprenorphine Taper

- Once patient ready for taper – can taper by 2 mg or 4 mg at a time until down to 2 mg.
- Decrease at a rate comfortable for the patient – weekly, monthly tailoered individually

Case 1

- 24 y.o. female
- Using fake 'oxy's
- Snorting 10 to 12 tablets daily
- Tried detox – lasted 36 hours
- Would like a trial of suboxone – has a drug plan

Case 1

- Initial assessment
- Rx given – patient to pick up single tablet 8 mg and bring to clinic
- Patient arrives – agitated, diaphoretic
- Dose witnessed in office
- Follows up next day complaining of mild withdrawal
- Increased to 16 mg sl – daily witness at pharmacy

Case 2

- Patient presents but no methadone pharmacy in town.
- No drivers license
- No transportation
- Pharmacy willing to dispense suboxone
- Start patient in withdrawal – either bring in for detox or hospital
- Ensure in opiate withdrawal prior to 1st dose