2017 SASKATCHEWAN OPIOID SUBSTITUTION THERAPY CONFERENCE

DOSING: METHADONE AND BUPRENORPHINE

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DISCLOSURES: NONE

Methadone

Buprenorphine

OBJECTIVES

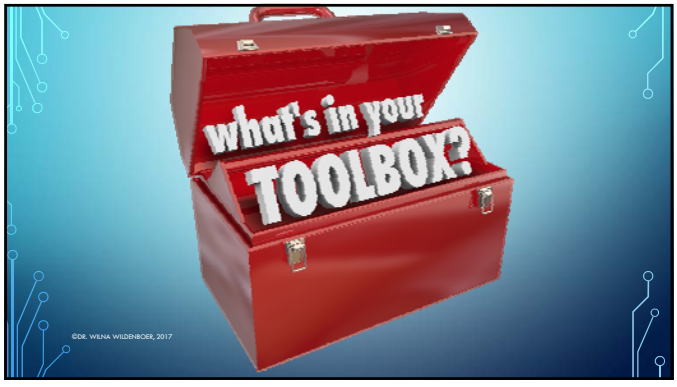
Participants will learn about:

1. The pharmacokinetics and pharmacodynamics of methadone and buprenorphine.
2. Therapeutic implications.
3. Why we dose the way we do.

METHADONE'S BACKGROUND

- 6-di methyl amine – 4, 4 d phenyl 3 heptan one
- Synthetic long-acting opioid
- Synthesized in 1938 by Bockmühl and Ehrhart (they called it Hoechst 10820.)
- Introduced in USA in 1974 as an analgesic under the trade name : Dolophine (from the Latin "dolor" (pain) and "fin"(end).
- First used for the treatment of opioid addiction in Vancouver , Canada, by Dr. Robert Holiday in 1963.
- New York City: Prof Vincent Dole and his wife , Marie Nyswander got all the glory in 1965, when they were awarded the Lasker Award for Medicine.

WITI Urban legend



PHARMACOKINETICS (What we do with methadone)

- Basic lipophilic drug
- With oral administration completely absorbed within 30 min
- Peak plasma levels: 2.5 – 3 h
- High oral bioavailability : 41 – 99%
- Long half-life: ± 24 h with wide individual variability (7-65) (8-90h)
- Large volume of distribution (brain, intestine, kidney, liver, muscle and lung)
- Protein binding: 85 – 90 %

WITI Changes in dosing takes 3 days to take full effect.

WITI Slower onset of withdrawal.

PHARMACOKINETICS

- Metabolized in the liver: Cytochrome P450 enzymes:
- CYP 3A4, CYP 2B6, CYP 2DC
- Inactive metabolites:
- 2 – ethyl – 1.5 dimethyl – 3.3 – diphenyl pyrrolidine (EDDP)
- 2 – ethyl – 5 – methyl – 3.3 – diphenyl pyrrolidine (EMDP)

SIDE – EFFECTS OF METHADONE

Common to all opioids

Some will resolve with prolonged therapy (sedation), vomiting, confusion, dizziness

Some persist: constipation (70%)

endocrinopathies

WITI
Always combine with laxative

1. Largest risk : Respiratory depression
   - Clinicians and patients underestimate methadone
     This is not a Mickey Mouse drug
   - Stick to recommended induction doses
   - Titrate slowly
   - Methadone does not have a sense of humor
   - Mostly in opioid naïve patients
   - Development of tolerance is unpredictable
     - < 2 months of methadone: patients still show a decreased ventilatory response to carbon dioxide and hypoxia
     - > 5 months: tolerance to carbon dioxide, but incomplete tolerance to hypoxia

Drug interactions due to cytochrome P450

- Inducers could potentially decrease the effectiveness of methadone – could feel like withdrawal
- Inhibitors could potentially increase the effect of methadone – dose will feel higher and the risk for toxicity is higher
- Memorize the list if Google isn't available

WITI
1) Patients learn that certain drugs will make their dose feel higher and will ask for prescriptions for those.
2) The good pharmacist will call you every time to inform you of the risk.

SIDE – EFFECTS OF METHADONE

2. Most often forgotten :
   - sex hormone abnormalities
   - Suppresses the hypothalamic – pituitary – gonadal axis

WITI
may need hormone supplementation

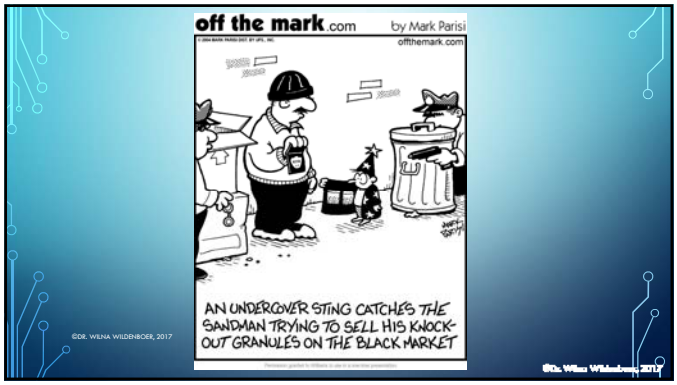
3. Cardiac :
   - Methadone is associated with Torsades de Pointes resulting from a prolonged QTc interval. Methadone blocks the hERG K channels (S-enantiomer)
   - Evidence of QTc interval prolongation: 0, 29% of patients
   - Occurrence of Torsades de Pointes: 0,78% of patients with prolonged QTc
   - Median dose where these findings were present: 345mg / day
   - 29% of TdP occurs in the typical recommended range for MMT
   - 75% of cases : female gender, interacting medication, hypokalemia, hypomagnesemia, presence of structural heart disease and other risk factors for TdP

QTc values by Age and Sex (ms)

	1-15 years (ms)	Adult males (ms)	Adult females (ms)
Normal	< 440	< 430	< 450
Borderline	440 - 460	430 - 450	450 - 470
Prolonged	> 460	> 450	> 470

Anti-infectives	Anti-emetics/ Gastric motility	Anti-psychotics	Opioid analgesics	Antidepressants	Anti-cancer
Clarithromycin	Domperidone	Haloperidol	Methadone	Escitalopram	Tamoxifen
Erythromycin	Ondansetron	Chlorpromazine		Venlafaxine	Nilotinib
Chloroquine		Risperidone			Lapatinib
Pentamidine		Quetiapine			
Azithromycin		Sertindole			
Moxifloxacin		Lithium			
		Clozapine			

WITI
Avoid combination with drugs that share the risk of QTc interval prolongation. Treat electrolyte disturbances and use diuretics that can cause with hypokalemia with care.



PHARMACOKINETICS

WITI
Safe in renal failure

WITI
Encourage breastfeeding

WITI
Encourage pregnant women to switch from IV street drugs to maintenance therapy

- Excreted in the feces and urine
- In kidney failure – completely eliminated via feces
- Found in breastmilk, but in concentrations that are harmless to the infant
- Crosses the placenta and may induce Neonatal Abstinence Syndrome
- Not associated with adverse obstetrical outcomes : Normal birth weight and Apgar scores. No congenital birth defects
- Versatile administration: Rectal, IV, IM, sub-cut, nasal, sublingual, spinal and epidural

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BUPRENORPHINE'S BACKGROUND

- Semi-synthetic long-acting opioid
- Synthesized in 1969 by researchers Reckitt & [illegible]
- Originally marketed in UK in 1978 as an analgesic
- Sublingual form launched in UK in 1982
- Approved in USA by Food and Drug Administration for the treatment of opioid addiction in 2002
- Marketed as buprenorphine alone: Subutex, Butrans, Buprenex
- In combination with naloxone: Suboxone

WITI
No stigma and therefore often a more socially acceptable Rx option

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PHARMACODYNAMICS – WHAT METHADONE DOES TO US

- Racemic mixture:
- R enantiomer (levo-methadone)
- Full MU opioid agonist. Binds to mu, delta & kappa.
  - Analgesia, miosis, euphoria.
  - Decreased GI motility
  - respiratory depression
  - dependence
  - tolerance
- S-enantiomer (dextro-methadone). No opioid activity.
- Moderate NMDA (N – methyl-D-aspartate)
  - Antagonist (against glutamate)
  - Promotes serotonin + norepinephrine uptake inhibition in CNS
- Binds to the I_{Kr} K^+ receptor

WITI
Could be the reason for decreased development of tolerance to opioids, decrease in craving for opioids and the reason for efficacy in treatment of neuropathic pain

WITI
Responsible for serious arrhythmias at higher doses (>200mg)

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PHARMACOKINETICS: WHAT WE DO WITH BUPRENORPHINE

- Fairly water soluble. Degrades in light
- Poor oral bioavailability: <10% due to [illegible]
- Fair sublingual bioavailability: 30-40%
- Rapid onset of action: 30-60min
- Protein binding: 96%
- Long half-life: 37h (20 – 70)
- Peak effects : 1 – 4h
- Durational action is dose dependent:
  - 2 – 4mg : 4 – 12h
  - 4 – 24mg : 24h
  - > 24mg : 2 – 3 days
- Metabolism : Hepatic (glucoronic conjungation) and microsomal enzyme system: CYP 3A4, CYP 2C8
- Excretion: Biliary (70%) and renal

WITI
If you swallow this drug, it loses 75% of its effect

WITI
Steady state in 3 -7 days. Dose adjustments should be made accordingly

WITI
Some patients can skip doses without feeling withdrawal

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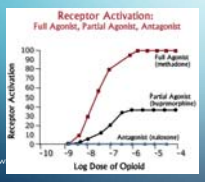
PHARMACODYNAMICS: WHAT BUPRENORPHINE DOES TO US

- Semi-synthetic opioid
  - i. Partial opioid agonist at the mu receptor – high affinity for the receptor, low intrinsic activity
  - ii. Antagonist at the kappa receptor
  - iii. Partial agonist at the nociceptin/orphanin receptor

(ii and iii of little clinical relevance as far as we know)



WITI
Decreased risk of overdose. Ceiling effect – higher dose not necessarily better

DRUG INTERACTIONS:

- Less than methadone
- Additive sedative effect with combinations for [illegible] with alcohol, benzodiazepines – respiratory depression, heavy sedation, coma, death
- Higher affinity for the receptors than antagonist
  - ∴ very high doses of naloxone needed to reverse the effect of buprenorphine
- Blocks the effect of other opioids prescribed for pain.

WITI
For patients, using other illicit opioids while on maintenance therapy with buprenorphine is a waste of money. Unfortunately could lead to poor compliance. Patients will skip doses when they want to use their drug of choice

- Side effects: Headaches - In first week of [illegible] patients
  - Constipation
  - Nausea
  - Sedation, drowsiness, lethargy
  - Sleep disturbances
  - Sweating
  - Sexual dysfunction - decreased libido, decreased performance

WITI
Induction to be done with patient in early withdrawal. COWS of 12-15

- Unique SE: Precipitated withdrawal
  - Occurs when buprenorphine "kicks off" another opioid from the mu receptors
  - 30-90 minutes after 1st dose
  - Varies in severity : sweating, abdominal cramps diarrhea, nausea, cravings anxiety

BUPRENORPHINE IN PREGNANCY:

- Not associated with adverse neonatal or [illegible]
- Birth weight and Apgar scores within normal [illegible]
- Not associated with congenital birth defects

WITI
Neonatal abstinence syndrome in ± 60% of neonates. Requires 89% less morphine to treat than methadone. 43% less time spent in hospital. 58% less time on medication while in hospital.

- Nursing infant's exposure to buprenorphine in breastmilk is low and there is no clinical or pharmacokinetic reason to discourage breastfeeding.

NALOXONE

- Pure opioid antagonist, high affinity for mu opioid receptors in the CNS, lower affinity for kappa and delta reception
- Oral bioavailability : 2% (90% absorption, but high first pass metabolism)
- IV : 100% bioavailability
- Half life 1 – 1.5 h
- Onset of action IV : 2 min
- Duration of action: 30 – 60 minutes
- Metabolized in the liver
- Excretion : Urine and biliary

WITI
- Robust and immediate precipitated withdrawal with IV administration of crushed Suboxone tablets in patients using other opioids
- Decreased street value
- Decreased risk of diversion

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COMPARISON

METHADONE	vs.	BUPRENORPHINE
• Full mu agonist		• Partial mu agonist
• Classic opioid side-effects, dose related		• Less sedating, decreased risk of overdose
• Withdrawal severe		• Withdrawal less severe
• Onset of action: 30 – 60 min		• Onset of action: 30 – 60 min
• Peak effect: 3 – 6 h		• Peak effect: 1 – 4 h
• Titration: lengthy process		• Titration: more rapid
• Oral		• Sublingual
• Affected by liver function		• Liver function has less impact
• Safe in kidney failure		• No adjustment needed in kidney failure
• Stigma		• None
• Cheap		• Expensive
• Daily dosing		• Could stretch to alternate days in higher doses
• About 50% abstinence at one year		• Lower retention in maintenance therapy
• No active metabolites		• Weak active metabolite: nor-buprenorphine

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QUESTIONS?

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