Module Two: Pharmacotherapies for Opioid Substitution Treatment
• Neurobiology of Addiction
• Pharmacology of Opioids
  – Methadone
  – Buprenorphine
• Pharmacokinetics of Methadone & Buprenorphine
• Opioid effects – Intoxication & Withdrawal
• Use of Methadone & Buprenorphine in OST
• Management of Side Effects & Interactions
• Properties of a substitution medication for opioid dependence (WHO 1998)
  – Oral
  – Cross tolerance
  – Longer duration of action than the drug being replaced
  – Able to be prescribed in decreasing doses for detoxification
  – Diminish effects of illicit use
  – Reduce craving
Neurobiology of Addiction

- **Mesolimbic Pathway**
  - Mediates positive emotional effect of natural rewards

- **Dopamine** – ‘master molecule’ of addiction

- **Substances of Abuse**
  - a drug-induced dopamine ‘high’ is often more intense than a natural ‘high’ & can be easily repeated on demand

- **Other areas also involved in reward** – amygdala, hippocampus, hypothalamus, frontal cortex (ie memory) emotional memory = an important aspect of addiction
Mesolimbic Pathway
(‘Pleasure’ or ‘Reward’ Pathway)

- Dopaminergic cell bodies in Ventral Tegmental Area of brainstem send axons to Nucleus Accumbens (NAc) in limbic area

Important role in emotional behaviour - also involved in psychosis

All Substances of Abuse cause increase in dopaminergic transmission in NAc acutely & chronically cause decreased baseline levels of Dopamine (tolerance) so that normal rewarding stimuli are less able to elicit an increase in Dopamine transmission
• Tolerance
  – Develops rapidly after repeated administration of opioids.
  – Larger doses required to achieve same effect.
  – Thought to be due to down-regulation of receptors.
  – Cross Tolerance within classes of drugs.
  – Does not necessarily occur for every effect of drug, but euphoric effect tends to be diminished with increased tolerance.

• Dependence (Physiological)
  – removal of the substance results in a physiological syndrome (Withdrawal).
  – the organism requires the substance in order to function normally (due to receptor down-regulation).
Pharmacology - Opioids

• Endogenous opiates – ‘brain’s own morphine’.

• Direct stimulation of opiate receptors (particularly μ) causes Dopamine release in Nucleus Accumbens.

• Inhibition of GABA-ergic neurons in Ventral Tegmental Area (VTA) disinhibits VTA Dopamine neurons → increased Dopamine release.
• Full opioid agonist, particularly at μ opiate receptor.
  – Increase in dose corresponds with direct increase in effect.
  – Overdose → respiratory depression, coma, death.
  – Treats opioid dependence because of cross tolerance (stops physiological withdrawal from other opioids).

• Lethal dose in an opioid naïve individual is 40-60mg. (in Children = 10mg)
Buprenorphine Pharmacology

- Partial opioid agonist
  - Low intrinsic activity at µ receptor
  - Maximal effect $\rightarrow$ safety in overdose (except in combination with other CNS depressants)

- High µ receptor affinity
  - Displaces other full agonists from receptor $\rightarrow$ precipitated withdrawal

- Slow dissociation from µ receptor
  - Delayed onset of withdrawal syndrome, which may be milder than that of methadone, heroin, morphine
  - Less than daily dosing possible
Opioid Dose-Effect Relationship

- **Overdose**
- **Ceiling effect**
  - Full Agonist (Methadone)
  - Partial Agonist (Buprenorphine)
  - Antagonist (Naloxone)
Opioid Effects (& Intoxication)

- Euphoria
- Analgesia
- Pinpoint Pupils
- CNS Depression (including slowed respiration)
- Increased Intestinal tone
- Slurred and Slowed Speech
- Sedation
Opioid Withdrawal

Muscle Aches

Cramps, Nausea & Vomiting and Diarrhoea

Watery eyes & runny nose

Yawning

Dilated Pupils

Gooseflesh & Chills
Methadone Pharmacokinetics
(source: The Methadone Briefing Online, Andrew Preston March 2003)

http://www.drugtext.org/library/books/methadone/intro.html

Half Life:

- 12-15 hrs for single dose (distribution)
- 13-47 hrs at steady state (average = 25hrs)
- ‘Tissue reservoirs’ in lungs, kidney, liver account for accumulation
Methadone Pharmacokinetics
(source: The Methadone Briefing Online, Andrew Preston March 2003)
http://www.drugtext.org/library/books/methadone/intro.html

- Little fluctuation in plasma levels at steady state
- Tolerance may drop within as little as 3 days of missed doses → risk of overdose if full dose given
- People most at risk of overdose = post detox & intermittent users
# Comparison of Methadone & Buprenorphine Pharmacokinetics

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<thead>
<tr>
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<th>Methadone</th>
<th>Buprenorphine</th>
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<tbody>
<tr>
<td><strong>Onset of effects</strong></td>
<td>30 – 60 min</td>
<td>30 – 60 min</td>
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<tr>
<td><strong>Peak effects</strong></td>
<td>3 – 6 hours</td>
<td>1 – 4 hours</td>
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<tr>
<td><strong>Duration of clinical effects</strong></td>
<td>16 to 30 hours</td>
<td>8-12 hours at low dose (eg 2mg)</td>
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<tr>
<td></td>
<td></td>
<td>24-72 hours at high dose (eg 16mg)</td>
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<tr>
<td><strong>Half Life</strong></td>
<td>13-47 hours at steady state</td>
<td>20-72 hours</td>
</tr>
<tr>
<td><strong>Precipitated withdrawal</strong></td>
<td>Does not occur</td>
<td>Onset 30-90 minutes, Peak 1-4 hours, Duration up to 12 hours</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic, +++ Affected by liver function</td>
<td>Hepatic, Less clinical impact of liver function</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Oral</td>
<td>Sublingual (dissolution time 2-10 minutes)</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>CNS Depressants, Opioid Antagonists, CYP 450 inducers/inhibitors</td>
<td>CNS Depressants, Opioid Agonists &amp;Antagonists, CYP 450 inducers/inhibitors</td>
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Methadone –
Side Effects & Precautions

• Side effects:
  – Sedation, Nausea / Vomiting, Respiratory depression, Constipation, Urinary retention, Itching, Sweating, dry nose & mouth, sexual dysfunction, peripheral oedema, amenorrhoea, weight gain.

• Torsade de Pointes (Prolonged Q-T interval) risk:
  – caution with other cardiac risk factors, other drugs which prolong Q-T interval (eg erythromycin, haloperidol)
Methadone

- **Breastfeeding:** considered safe - L3 (Moderately safe)
  - Milk plasma ratio 0.68 (low)
  - Amount in milk insufficient to prevent Opioid Withdrawal Syndrome in infant

- **Pregnancy:** FDA Risk factor: B (no evidence of foetal risk)
  - Substitution treatment best because of reduction in illicit use, increased antenatal care, less stressful environment for foetus, (withdrawal risky especially in 1\textsuperscript{st} and 3\textsuperscript{rd} trimester).
  - Check maternal serum levels post delivery as methadone requirement likely to decrease.
Methadone Maintenance - Stabilisation

- Stabilisation most risky time in treatment (Due to Accumulation of Methadone)
  - Australian study found ≈ 50% of deaths of people in MMT occurred in first 7 days of treatment (Due to polydrug use, increasing dose too quickly, starting dose too high)
  - Maximum starting dose 40mg, increase in increments of no more than 5-10mg, and not more often than every 3-4 days. [Practice Guidelines for Opioid Substitution Treatment in NZ (2008)]
  - Observation of client for intoxication and withdrawal especially important due to high incidence of ‘using on top’ during this period.
• Doses are usually in the range of 60-120mg daily
  – Should be individualised, and sufficient to ensure clinical stability, adequate social functioning and minimum withdrawal symptoms.
  – Doses in this range will usually provide receptor ‘blockade’, diminishing the effects of other opioids which may be used.
Methadone Maintenance – Split Doses

• Split Doses (ie AM and PM) may be prescribed for:
  – ‘fast metabolisers’ – these are clients who have been shown, by obtaining peak and trough serum methadone levels, to remove methadone from their systems more rapidly than the normal population.
  – Pregnancy – because of changes in volume of distribution, and possibly also due to increased metabolism of methadone, often the pregnant client’s dose requirements will change, sometimes necessitating a split dose.
  – Clients on very low doses. (eg those completing a withdrawal from maintenance treatment)

• At least 60% of the total daily dose should be consumed under observation.

• Never dispense split dose without authorisation of prescriber.
Buprenorphine –
Side Effects & Precautions

• Side Effects
  – Include cold or flu-like symptoms, headaches, sweating, sleeping difficulties, nausea, and mood swings.
  – Usually transient at start of treatment – may last a few weeks.

• Other CNS depressants
  – Deaths have occurred with buprenorphine in combination with benzodiazepines (IV)

• Pregnancy
  – Category C (insufficient evidence)
  – Preferred treatment option is transfer to methadone prior to/during pregnancy.
  – Breastfeeding not recommended – but should do a benefit: risk analysis.

• Liver - IV use associated with hepatotoxicity
Buprenorphine: Precipitated Withdrawal

- Occurs because of high receptor affinity but low intrinsic activity of buprenorphine → net reduction in opioid effect if it displaces another full agonist from μ receptor

- Differentiated from opioid withdrawal by time at which it occurs (begins 30 – 90 mins post dose, peaks 1 – 4 hours post dose)

- Minimise risk by:
  - Educating client
  - Administering first dose only once signs of mild objective opioid withdrawal occur, usually:
    - 12 hours after the last dose of intravenous morphine or home-bake;
    - 12–24 hours after an oral use of morphine or poppy-seed tea;
    - 24–48 hours after the last dose of oral or intravenous methadone.
  - Starting with a low dose (2-4mg)
Precipitated Withdrawal

(Courtesy of Reckitt Benckiser)
Management of Precipitated Withdrawal

- Avoid using other opioids to relieve symptoms

- Use symptomatic medications (metoclopromide, loperamide, paracetamol, ibuprofen) and/or clonidine if necessary.

- Time (duration around 12 hours)
Buprenorphine Maintenance

• Non daily dosing
  – Removes need for takeaways
  – Multiply daily dose by number of days (ie if dosing every 2nd day multiply dose x2)
  – Safe to do so because of ceiling effect on respiratory depression

• Dose range for maintenance
  – Generally 8-24mg daily
  – 4mg or less associated with reduced efficacy (c.f low dose methadone – 20mg)
  – Doses higher than 32mg not adequately studied
  – Rapid titration key to successful induction (aim for 12-16mg by day 3)

• Missed doses
  – Single missed dose unlikely to cause discomfort
  – If on non-daily regime, administer remainder of dose for period
Relative Merits of Methadone & Buprenorphine:

(NSW Opioid Treatment Program: Clinical Guidelines for Methadone and Buprenorphine treatment 2006)

- More clinical experience with methadone

- Buprenorphine is safer in overdose, may need to be taken less often.

- Buprenorphine takes longer to administer (must dissolve under the tongue).

- Buprenorphine can be more easily diverted to improper uses because it is in tablet form (the buprenorphine-naloxone combination may discourage diversion to injecting drug use).
Management of Common Side Effects

- **Constipation**
  - Give usual lifestyle advice to manage constipation. Use osmotic laxatives regularly or stimulant laxatives in a short course. Bulking laxatives are contraindicated in people who take opioids due to less movement in the gut and the risks of further impaction.

- **Excessive sweating**
  - Reducing the methadone dose may help, if this can be achieved without compromising maintenance treatment.

- **Sleep disturbance**
  - Give advice on sleep hygiene and simple relaxation techniques. Instruct client to avoid hypnotic drugs and alcohol, which may worsen sleep apnoea and which interact with opioids.

- **Teeth problems**
  - Dental problems frequently pre-date OST treatment, but opioids do reduce salivary flow. Encourage chewing to increase salivary flow and improved dental hygiene, and drinking water or other sugar-free fluid.
Management of Common Side Effects

- **Nausea and vomiting**
  - Encourage the client to eat before consuming their dose and to drink the dose slowly. Nausea is usually transient and will subside with time. In some situations anti-nausea medication may be necessary.

- **Irregular menstrual cycle/ amenorrhoea**
  - Advise female clients about the risk of pregnancy even when their menstrual cycle is irregular/they are not menstruating

- **Lethargy**
  - Look for causes other than methadone. Reducing the methadone dose may help, if this can be achieved without compromising the client’s stability.

- **Oedema**
  - Reducing the methadone dose may help, if this can be achieved without compromising the client’s stability.

- **Reduced libido, sexual dysfunction, lowered testosterone levels**
  - Reducing the methadone dose may help, if this can be achieved without compromising the client’s stability.
Interactions
[for full list, see Practice Guidelines for Opioid Substitution Treatment in NZ (2008), pages 73-74]

• Other CNS Depressants (including other opioids) → increased risk of respiratory depression

• Enzyme Inhibitors → increased serum methadone or buprenorphine levels with drugs affecting 3A4
  – eg erythromycin, fluoxetine

• Enzyme Inducers → reduced serum methadone or buprenorphine levels with drugs affecting 3A4
  – eg carbamazepine, rifampicin – often require significant increases in methadone dose
Interactions
[for full list, see Practice Guidelines for Opioid Substitution Treatment in NZ (2008), pages 73-74]

• Opioid Antagonists
  → opioid withdrawal (eg Naltrexone, Naloxone, Buprenorphine as partial agonist/antagonist)

• Drugs affecting Q-T Interval
  → increased risk of Torsade de Pointes (eg erythromycin, clarithromycin, quinidine)

• Drugs affecting Urinary pH
  → increased clearance with urinary acidifiers (eg vitamin C); decreased clearance with urinary alkalinisers (eg Ural®, Citravescent®)
Other Medications used for OST

- Occasionally other opioids may be prescribed as substitution therapy for opioid dependence, where methadone and/or buprenorphine have been trialled unsuccessfully.
  - Eg Morphine in client for whom buprenorphine is unable to be funded, but who has increased Q-T interval with methadone.

- When other opioids are prescribed for OST this is outside the indications of the medicine and the client should have given informed consent.

- Clients prescribed other opioids for substitution therapy should be managed in the same way as other OST clients, with observed consumption and pharmacist monitoring of intoxication prior to dosing, along with other treatment parameters.
End of Module Two