VOLUME C
Pharmacological Treatment for Drug Use Disorders
Drug Treatment for Special Populations
Module 2

Basics of opioid dependence
Pharmacotherapy options

1. Opioids: Definition, effects and treatment implications
2. Opioid dependence treatment with Methadone
3. Opioid dependence treatment with Buprenorphine
4. Opioid antagonist treatment
Workshop 2

Opioid dependence treatment with Methadone
At the end of this workshop, you will be able to:

► Explain the rationale for opioid agonist therapy
► Understand medical withdrawal protocols using Methadone
► Explain the basic principles of maintenance treatment with Methadone
► Identify effective practices in the implementation of Methadone treatment
► Explain how to address concurrent use of other drugs and alcohol during Methadone treatment
► Determine the contraindications and medical interactions with Methadone
Let’s discuss!

- What do you know about methadone for treatment?
- What are your personal views about treatment with methadone?
<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yawning</td>
<td>Anorexia and nausea</td>
</tr>
<tr>
<td>Lacrimation, mydriasis</td>
<td>Abdominal pain or cramps</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Hot and cold flushes</td>
</tr>
<tr>
<td>Rhinorrhea, sneezing</td>
<td>Joint and muscle pain or twitching</td>
</tr>
<tr>
<td>Tremor</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Piloerection</td>
<td>Drug cravings</td>
</tr>
<tr>
<td>Diarrhoea and vomiting</td>
<td>Restlessness/anxiety</td>
</tr>
</tbody>
</table>
Progress of the acute phase of opioid withdrawal since last dose

Withdrawal from heroin
Onset: 6–24 hrs.
Duration: 4–10 days

Withdrawal from methadone
Onset: 24–48 hrs., sometimes more
Duration: 10–20 days, sometimes more
Opioid withdrawal complications

► Anxiety and agitation
► Low tolerance to discomfort and dysphoria
► Drug-seeking behaviour (requesting or seeking medication to reduce symptom severity)
► Muscle cramps
► Abdominal cramps
► Insomnia
Withdrawal management aims to:

► Reverse neuroadaptation and reduce withdrawal symptoms
► Promote the uptake of post-withdrawal treatment options
Opioid withdrawal treatment

Involves:

► Reassurance and supportive care
► Information
► Hydration and nutrition
► Opioid pharmacotherapies e.g., Methadone
► Symptomatic treatment e.g., Clonidine
Treatment of opioid dependence: Methadone
Methadone is a synthetic opioid medication developed in 1939 in Germany.

Introduced to the USA in 1947.

Widely used for treatment of opioid addiction & as analgesic.

Dole and Nyswander first used methadone in maintenance treatment for opioid addiction in 1964 & published results of clinical trial in 1965.

Numerous studies over 49 yrs consistently support clinical & cost effectiveness of methadone for opioid dependence.

Evidence also for ↓ illicit opioid use, risk of HIV, mortality, crime & ↑ social functioning.
The treatment (with Methadone) is corrective, normalizing neurological and endocrinologic processes in patients whose endogenous ligand-receptor function has been deranged by long-term use of powerful narcotic drugs. Why some persons who are more susceptible and whether long-term drug users can recover without maintenance therapy are questions for the future. At present, the most that can be said is that there seems to be a specific neurological basis for the compulsive use of heroin by drug users and that methadone taken in optimal doses can correct the disorder.

(Vincent Dole, 1988)
Methadone: clinical properties

The “Gold Standard” treatment

- Synthetic opioid with a long half-life
- μ Agonist with morphine-like properties/actions
- Action – CNS depressant
- Effects usually last about 24 hours
- Daily dosing (same time, daily) maintains constant blood levels and facilitates normal everyday activity
- Adequate dosage prevents opioid withdrawal and reduces craving without intoxication
Intrinsic activity:
full agonist, partial agonist and antagonist

Intrinsic Activity

Log Dose of Opioid

Full Agonist (Methadone)
Partial Agonist (Buprenorphine)
Antagonist (Naloxone)
Methadone: pharmacokinetics

- Good oral bioavailability
- Peak plasma concentration after 2-4 hrs.
- 96% plasma protein bound
- Mean half-life around 24 hrs.
- Steady state after 3-10 days
- Metabolism
  - Cytochrome P450 mediated
  - CYP3A4 main
  - Also CYP2D6, CYP1A2, CYP2C9 and CYP2C19
- Genetic variability
  - Risk of drug interactions
Methadone pharmacodynamics

- Full opioid agonist
- Main action on mu receptors
  - Inhibit adenylyl cyclase = \(\downarrow\) cAMP
  - \(\uparrow\) Potassium channel opening
  - \(\downarrow\) Calcium channel opening
- Inhibit serotonin reuptake
- Non-competitive antagonist NMDA receptor
Methadone: recommended formulation

- Methadone should normally be prescribed as a 1 mg in 1 ml oral solution
- Oral concentrates, containing methadone hydrochloride 10 mg/ml or 20 mg/ml, should normally be dispensed only after dilution, as appropriate
- Methadone tablets are not licensed for the treatment of drug dependence and should not normally be prescribed due to the increased potential for diversion
Methadone: safety overview

► Respiratory depression & overdose
  – ↑ Risk in low opioid tolerance and/or combination with other sedative drug use
  – ↑ Mortality in 1st fortnight of treatment, following treatment cessation, diversion to those not in treatment

► Adverse events
  – Side effects most common early in treatment: constipation, nausea, sweating
  – Less common: lowered androgens in men, sleep apnoea, osteoporosis, QTc prolongation
Methadone and prolonged QTc
Methadone and QTc prolongation

- Methadone ↓ cardiac hERG voltage-gated potassium channels (repolarization)
- ↓ Potassium channel may ↑ the QT interval
- ↑ QT interval & torsades de pointes reported
- More common with higher dose > 200 mg/day
- Most treated with large, multiple daily doses for pain
- Also at doses commonly used for OST
- In OST other medications, ↓ potassium contribute
Methadone and prolonged QTc recognised risks

- Advanced Heart Disease, IHD, Conduction defects, $\uparrow$ QT
- Liver disease
- Electrolyte abnormalities (↓K, Mg)
- Family h/o sudden death
- Treatment with medicines that $\uparrow$QT / $\uparrow$Electrolyte
- Treatment with CYP 3A4 inhibitors
- Dose >100 mg/day
Methadone and prolonged QTc management

- Patients with recognised risk factors for ↑QTc:
  - ECG before starting & at stabilisation

- No risk factors for ↑ QT:
  - ECG before dose titration > 100mg &
  - 7 days after titration
**Drug interaction – metabolism**

**Methadone**

- Metabolism Cytochrome P450 mediated
  - CYP3A4 main
  - Also CYP2D6, CYP1A2, CYP2C9 and CYP2C19, genetic variability

- CYP3A4 breaks down 50% of drugs
  - Methadone mixed inhibitor may increase other drug levels, e.g., Nifidepine, etc.
# Opioids: drug interactions

<table>
<thead>
<tr>
<th></th>
<th>Respiratory depression</th>
<th>Toxicity/risk of death</th>
<th>Hypotension</th>
<th>Coma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS depressants</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MAOIs</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>TCAs</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Betablockers</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BZDs</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Methadone: advantages of treatment

- Suppresses opioid withdrawal
- Reduces craving and blocks effects of Heroin
- Pure – no “cutting agents” present
- Oral administration (syrup or tablet forms used)
- Once-daily doses enable lifestyle changes
- Slow reduction and withdrawal can be negotiated with minimal discomfort
- Minimal reinforcing properties, relative to heroin
- Counselling and support assists long-term lifestyle changes
- Legal and affordable – reduced participation in crime
- Few long-term side effects
Methadone: disadvantages of treatment

- Initial discomfort to be expected during stabilisation phase
- Physical opioid dependence is maintained
- Slow withdrawal (preferably) negotiated and undertaken over a period of months
- Protracted withdrawal symptoms
- Can overdose, particularly with polydrug use
- Daily travel and time commitment
- Variable duration of action
- Diversion
Maximising treatment adherence

Address psychosocial issues as first priority
- Emotional stability
- “Chaotic" drug use
- Accommodation
- Income

Opioid agonist pharmacotherapy can:
- Address psychosocial instability
- Increase opportunities to directly observe the administration of various HIV therapies
Assessment objectives

► Clarify nature and severity of problems
► Establish a therapeutic relationship
► Formulate problems into a treatment plan
Key features of assessment

► History
  – Patient self-report
  – Collateral history

► Examination

► Investigations
Remember: TRAPPED

- Treatment History
- Route of administration
- Amount of drug used
- Pattern of use
- Prior abstinence
- Effects (medical, psychiatric, social)
- Duration of use

TRAPPED
## Approximate durations of detectability of selected drugs in urine

<table>
<thead>
<tr>
<th>Drug or its metabolite(s)</th>
<th>*Duration of detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines including methylamphetamine and MDMA</td>
<td>2 days</td>
</tr>
<tr>
<td>Benzodiazepines:</td>
<td></td>
</tr>
<tr>
<td>Ultra-short-acting (e.g. midazolam)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Short-acting (e.g. triazolam)</td>
<td>24 hours</td>
</tr>
<tr>
<td>Intermediate-acting (e.g. temazepam, chlordiazepoxide)</td>
<td>2–5 days</td>
</tr>
<tr>
<td>Long-acting (e.g. diazepam, nitrazepam)</td>
<td>7 days +</td>
</tr>
<tr>
<td>Buprenorphine and metabolites</td>
<td>8 days</td>
</tr>
<tr>
<td>Cocaine metabolite</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Methadone (maintenance dosing)</td>
<td>7-9 days</td>
</tr>
<tr>
<td>Codeine, dihydrocodeine, morphine, propoxyphene (heroin detected as the metabolite morphine)</td>
<td>48hrs</td>
</tr>
<tr>
<td>Cannabinoids:</td>
<td></td>
</tr>
<tr>
<td>Single use – chronic heavy use</td>
<td>3-4 days-up to 45 days</td>
</tr>
</tbody>
</table>
Where are we so far?

► What does opioid withdrawal management aim?
► What does this process involve?
► What is Methadone and why it is considered a “Gold Standard” treatment?
► What are some advantages and disadvantages of MMT?
Break
Methadone induction overview
Guidelines and procedures for Methadone maintenance treatment

1. Induction
2. Stabilization
3. Maintenance
4. Missed doses
5. Split dosing
6. Vomited dose
7. Frequency of visits
8. Take-home dose
9. Withdrawal from methadone
10. Retention in treatment
11. Detoxification using methadone
Methadone induction: aim

- Relief of withdrawal symptoms
- Relief of drug craving
- Restoration of physiological function
- Prevent relapse to use of illicit drugs
- Blocking dose
- Stability throughout the day
- Engagement in recovery
Key factors in prescribing is balancing three competing pressures:

► To prescribe an effective and appropriate dose

► To minimise the risks of overdose or precipitated withdrawal during induction

► To rapidly respond to patients’ needs for appropriate treatment to retain them in treatment and prevent harm from illicit drug misuse
The risk factors for overdose during induction are:

- Low opioid tolerance
- Use of CNS depressant drugs, including alcohol
- Too high an initial dose
- Increases in dose that are too rapid
- Slow methadone clearance
Patterns of Methadone use and overdose deaths

3 Patterns:

► **Single overdose:** accidental use by intolerant individual (e.g., child) & ↓ tolerance due to interruption in use

► **Accumulated toxicity:** Today’s dose not lethal, tomorrow’s dose not lethal, but third day’s dose combined with 1/2 of the 2nd day’s and ¼ of the 1st day’s dose accumulate to a lethal level

► **Combining with CNS depressant:** Benzodiazepines are most frequently reported. Psychiatric can ↑ risk (Fluoxetine, Amitriptyline, Quetiapine & Alprazolam)
“Start Low go Slow”

- Inappropriate dosing can result in overdosing in the first few days: as cumulative toxicity develops to methadone, this can lead to death.
- There is no uniquely fatal dose of methadone and deaths have occurred following doses as little as 20 mg.
- The commencement dose should aim to achieve an effective level of comfort, both physical and psychological, while minimising the likelihood of overdose.
Importance of achieving steady state within therapeutic window
Methadone induction: factors determining initial dose

- Degree of tolerance to opioids
- Medical illness e.g. hepatic impairment
- Time since last drug use
- Benzodiazepines/alcohol use or use of prescribed medications
- Severity of intoxication/withdrawal
- Body weight

It may be safer to start opioid-dependent polydrug users as inpatients.
Tools to aid Methadone induction: Opioid withdrawal scales

► Guide treatment
► Monitor progress (subjective and objective signs)
► Do not diagnose withdrawal but describe severity
► Guide ongoing assessment

If the withdrawal pattern is unusual or the patient is not responding, suspect other conditions.
# Opioid withdrawal scale

<table>
<thead>
<tr>
<th>Resting Pulse Rate: _______ beats/minute</th>
<th>Pupil Size</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Measured after patient is sitting or lying for one minute</em></td>
<td>0 pupils pinned or normal size for room light</td>
</tr>
<tr>
<td>0 pulse rate 80 or below</td>
<td>1 pupils possibly larger than normal for room light</td>
</tr>
<tr>
<td>1 pulse rate 83-100</td>
<td>2 pupils moderately dilated</td>
</tr>
<tr>
<td>2 pulse rate 101-120</td>
<td>5 pupils so dilated that only the rim of the iris is visible</td>
</tr>
<tr>
<td>4 pulse rate greater than 120</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sweating: over past ½ hour not accounted for by room temperature or patient activity</th>
<th>Bone or Joint aches If patient was having pain previously, only the additional component attributed to opioids withdrawal is scored</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 no report of chills or flushing</td>
<td>0 not present</td>
</tr>
<tr>
<td>1 report of chills or flushing</td>
<td>1 mild diffuse discomfort</td>
</tr>
<tr>
<td>2 flushed or observable moistness on face</td>
<td>2 patient reports severe diffuse aching of joints/muscles</td>
</tr>
<tr>
<td>3 beads of sweat on brow or face</td>
<td>4 patient is rubbing joints or muscles and is unable to sit still because of discomfort</td>
</tr>
<tr>
<td>4 sweat streaming off face</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Restlessness Observation during assessment</th>
<th>Runny nose or tearing Not accounted for by cold symptoms or allergies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 able to sit still</td>
<td>0 not present</td>
</tr>
<tr>
<td>1 reports difficulty sitting still but able to do so</td>
<td>1 nasal stuffiness or unusually moist eyes</td>
</tr>
<tr>
<td>3 frequent shifting or extraneous movements of legs/arms</td>
<td>2 nose running or tearing</td>
</tr>
<tr>
<td>5 unable to sit still for more than a few seconds</td>
<td>4 nose constantly running or tears streaming down cheeks</td>
</tr>
</tbody>
</table>
### Opioid withdrawal scale

<table>
<thead>
<tr>
<th>GL Upset: over last ½ hr.</th>
<th>Anxiety or Irritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 no GI symptoms</td>
<td>0 none</td>
</tr>
<tr>
<td>1 stomach cramps</td>
<td>1 patient reports increasing irritability or anxiousness</td>
</tr>
<tr>
<td>2 nausea or loose stool</td>
<td>2 patient obviously irritable or anxious</td>
</tr>
<tr>
<td>3 vomiting or diarrhoea</td>
<td>4 patient so irritable or anxious that participation in the assessment is difficult</td>
</tr>
<tr>
<td>5 multiple episodes of diarrhoea or vomiting</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tremor observation of outstretched hands</th>
<th>Gooseflesh skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 no tremor</td>
<td>0 skin is smooth</td>
</tr>
<tr>
<td>1 tremor can be felt but not observed</td>
<td>3 piloerection of skin can be felt or hairs standing up on arms</td>
</tr>
<tr>
<td>2 slight tremor observable</td>
<td>5 prominent piloerection</td>
</tr>
<tr>
<td>4 gross tremor or muscle twitching</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yawning Observation during assessment</th>
<th>Total Score _______</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 no yawning</td>
<td>The total score is the sum of all 11 items</td>
</tr>
<tr>
<td>1 yawning once or twice during assessment</td>
<td></td>
</tr>
<tr>
<td>2 yawning three or more times during assessment</td>
<td></td>
</tr>
<tr>
<td>4 yawning several times/minute</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initials of persons</td>
</tr>
<tr>
<td></td>
<td>Completing assessment</td>
</tr>
<tr>
<td></td>
<td>_____________________</td>
</tr>
</tbody>
</table>
Methadone induction: the titration process
Methadone tolerance testing

Day 1 of induction

Patients to attend the clinic in a state of opioid withdrawal having been abstinent from opioids for the following timescales:

- Heroin, opium, dihydrocodeine: 12 hours
- Methadone: 24 hours
- Buprenorphine: at least 24 hours
Methadone tolerance testing

Day 1 of induction

► The first dose of OST should be administered only in the presence of OWS and a positive urine screen

► Take into account the following:
  – patient’s clinical presentation
  – last use of opioids
  – subjective withdrawal symptoms reported
  – objective signs of opioid withdrawal observed
Methadone tolerance testing

Day 1 of induction

► Patients showing no signs of OWS should be requested to return to the clinic later that day or on the following day so that titration onto OST can begin, once OWS have developed

► OST should NOT be given to patients showing signs of intoxication, especially due to alcohol and other depressant drugs – risk of overdose is greatly enhanced
# Methadone tolerance testing

## Day 1: example of induction regimen

<table>
<thead>
<tr>
<th>Initial Dose</th>
<th>Suggested Dose Range of Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild OWS (COWS score 5-12)</td>
<td>No Methadone</td>
</tr>
<tr>
<td>Moderate (COWS score 13-24)</td>
<td>10mg</td>
</tr>
<tr>
<td>Moderately severe (COWS score 25-36)</td>
<td>10 - 20mg</td>
</tr>
<tr>
<td>Severe withdrawal (COWS score &gt;36)</td>
<td>20-30mg</td>
</tr>
<tr>
<td>Heavily dependent users</td>
<td>25-40mg*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2nd dose +4 hours (minimum)</th>
<th>Depending on OWS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-30mg</td>
</tr>
</tbody>
</table>

*An initial dose of 40mg must be only be prescribed by an experienced and competent clinician.
Day 2 onwards

► OST doses should be titrated against the presence of opioid withdrawal symptoms

► Increase 0-10mg Methadone per 1-3 days during the 1st week according to OWS score
Methadone induction

Day 2 onwards

► This process is repeated at each titration appointment until there is none or minimal signs of OWS

► When increasing the dose over the first week, the incremental dose for one day should be no more than 5-10 mg

► The total increase over the first week should be no more than 30 mg above the total first day dose
Day 2 onwards

- Following induction, the full effect of OST will only be achieved after 5-7 days of dose stabilisation.

- Symptomatic management is recommended for patients on OST while optimising regimes, to alleviate symptoms of opioid withdrawal.
# Opioid withdrawal management

## Symptomatic treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Usual dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyoscine Butyl bromide</td>
<td>smooth muscle spasm</td>
<td>20mg prn</td>
<td>qds</td>
</tr>
<tr>
<td>Mebeverine</td>
<td>irritable bowel</td>
<td>135mg tds</td>
<td></td>
</tr>
<tr>
<td>Loperamide Hcl</td>
<td>acute diarrhoea</td>
<td>4 mg then 2 mg/ stool</td>
<td>16mg x 5 days</td>
</tr>
<tr>
<td>Quinine Sulphate</td>
<td>leg cramps</td>
<td>200-300mg /day</td>
<td></td>
</tr>
<tr>
<td>Domperidone</td>
<td>Nausea, vomiting</td>
<td>10-20mg tds or qds</td>
<td>80mg/day</td>
</tr>
<tr>
<td>Lactulose</td>
<td>c/c constipation</td>
<td>15 ml bd</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>muscle ache, pain</td>
<td>200 - 400mg tds</td>
<td>2.4 g</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Pain, headache</td>
<td>500mg - 1000mg qds</td>
<td>4g</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>Insomnia (exceptional cases only)</td>
<td>3.75- 7.5mg nocte</td>
<td>7.5mg</td>
</tr>
</tbody>
</table>
Methadone
dose stabilisation
Optimising dose

► After 1st week, doses can continue to be increased incrementally up to a total of between 60-120 mg /day, and occasionally more

► Dose should be one at which patient feels comfortable & is no longer using illicit heroin

► Caution is to be exercised and it may take several weeks to reach the desired dose

► There should be a few days between each dose increase
Effective dose is as much as required to stop withdrawal symptoms & control craving through out day between doses of Methadone.

► Patient is alert, aware of surroundings
► Patient is able to engage in daily activities: study, work
► Patient is able to make progress in treatment goals (avoid heroin use)
► Effect of heroin is not ‘felt’ if use occurs
► Most patients would need ≥ 60mg
## Inappropriate dosing

<table>
<thead>
<tr>
<th>Dose too low – Withdrawal</th>
<th>Dose too high – Intoxicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Flu-like” symptoms</td>
<td>Drowsy, “nodding off”</td>
</tr>
<tr>
<td>Runny nose, sneezing</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Abdominal cramps, diarrhea</td>
<td>Shallow breathing</td>
</tr>
<tr>
<td>Tremor, muscle spasm, aches &amp; cramps</td>
<td>“Pinned” (pinpoint) pupils</td>
</tr>
<tr>
<td>Yawning, “teary” eyes</td>
<td>Drop in body temperature</td>
</tr>
<tr>
<td>Hot and cold sweats</td>
<td>Slow pulse, low BP, palpitations</td>
</tr>
<tr>
<td>Irritability, anxiety, aggression</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Aching bones</td>
<td></td>
</tr>
<tr>
<td>Craving</td>
<td></td>
</tr>
</tbody>
</table>
In most heroin dependent individuals
- 20-40 mg prevents withdrawal
- > 60-80 mg to block effects of additional heroin use

In non-tolerant/opioid naïve people
- 1 dose of 20 mg can be fatal for children
- doses of 40+ mg can be fatal for an adult

Dose conversions to other opioids
- difficult to estimate
- 10 mg oral Methadone ~ 30-60 mg oral morphine
Frequency of appointments

- First 5 -7 days – see every 1-2 days
- Write prescription till next appointment only
- Always see the patient before increasing the dose
- Continue the assessment process, build the therapeutic relationship
Typical reasons for dose increase

- Signs and symptoms of withdrawal
- Amount and/or frequency of opioid use not decreasing
- Persistent craving for opioids
- Failure to achieve a dose that blocks the euphoria of short acting opioids
Methadone stabilisation: Initial effects and side effects

- Relief from physical pain
- Feeling of well-being
- Constricted pupils
- Vasodilation
- Lowered sex drive
- Nausea and vomiting
- Loss of appetite
- Sweating
- Fluid retention
- Endocrine changes (loss of libido, menstrual changes)

- Intense constipation
- Lowered temperature
- Bradycardia
- Hypotensia
- Palpitations
- Shallow respirations
- Poor circulation
- Itching and skin rashes
- Recurrent dental problems
Methadone maintenance
After careful dose induction and dose stabilization, there is a consistent finding of greater benefit from maintaining individuals on a daily dose between 60-120 mg of Methadone.

In some instances, due to a patient’s high tolerance, higher doses may be required but this is exceptional.

In doses above 100mg, investigations into QTc to be carried out.
In this phase, frequency of prescription pick up may be ↓ if the treatment system/set up allows this.

Methadone prescribing to continue for the period set out in individual’s recovery care plan, which is to be reviewed regularly (3-6 months).
Supervised dosing

Supervised dosing at pharmacy/clinic/hospital

► Advantages:
   – minimises diversion to others
   – minimises misuse of medication (e.g., injecting)
   – greater medication adherence

► Disadvantages:
   – inconvenience to patients & staff
   – cost to patients/health services
   – barrier to community integration (e.g., work, study, child care)
‘Take-away’ doses

The following 3 criteria should be assessed prior to initiating take-home if treatment system/set up makes this possible:

1. **Clinical stability** – The patient demonstrates clinical stability when the dose has reached a stable level. Also he/she demonstrates this stability by stable housing, support system and activities and regular attendance at clinic appointments.

2. **Time spent in methadone treatment** – Take-home is not recommended during the first two months of treatment.

3. **Ability to safely store medication** – It is not appropriate to give take-home doses to patients with unstable living arrangements, such as those living on the street or in places without storage facilities. Ensure children don’t have access to the medicine.
Vomited dose

- Vomited Methadone doses are not replaced unless staff observes emesis.

- If the witnessed vomiting occurred in <15 minutes of consumption, dose can be replaced at no more than 50% of the regular dose.
Split dosing is commonly used during the management of pregnancy or in patients on medications that induce rapid metabolism of Methadone.
Loss of tolerance can occur within 3 days & can result in a “single-dose” overdose of Methadone.

If missed for 3 days, the dose & after tolerance to the first dose is demonstrated, it can be rapidly increased over a period of days in proportion to the previous dose for that person.

If missed ≥ 5 days, restart at 30 mg or less. After assessing response to the initial dose over 3 days, the dose may be safely increased relatively quickly toward the previous stable dose of Methadone.
# Opioid misuse on top of opioid substitute prescribing

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Risks</th>
<th>Possible Reason</th>
<th>Proposed Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid misuse on top of an opioid prescription</td>
<td>OD, BBV &amp; other infections if injecting, Continued offending &amp; involvement in drug-misusing lifestyle, impaired engagement</td>
<td>• Inadequate dose&lt;br&gt; • Medication unsuitable&lt;br&gt; • On reducing regimen&lt;br&gt; • Using heroin and/or cocaine for ‘high’ on high dose opioids</td>
<td>• Dose assessment, ↑ dose, give injecting equipment&lt;br&gt; • Change medication regimen&lt;br&gt; • Swap patient to maintenance regimen&lt;br&gt; • ↑ Psychosocial interventions, e.g., contingency management + UDS &amp; supervised consumption, provide injecting equipment, address negative social problems such as housing if applicable</td>
</tr>
</tbody>
</table>
## Cocaine misuse on top of opioid asubstitute prescribing

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Risks</th>
<th>Possible Reason</th>
<th>Proposed Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crack cocaine and cocaine misuse on top of an opioid prescription</td>
<td>Blood-borne viruses and infections if injecting More chaotic drug misuse Increased crime Psychological problems Overdose</td>
<td>• Patient using for ‘high’</td>
<td>Increase key work/ psychosocial interventions, provide injecting equipment if injecting drug misuser</td>
</tr>
</tbody>
</table>
## Alcohol / benzo misuse on top of opioid substitute prescribing

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Risks</th>
<th>Possible Reason</th>
<th>Proposed Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol or benzodiazepine misuse on top of an opioid prescription</td>
<td>Alteration of Methadone metabolism, Deterioration of hepatic functioning in those with hepatitis C, Street drinking &amp; Intoxicated presentations, Overdose or ‘near misses’, drug interactions</td>
<td>• Patient using to get intoxicated</td>
<td>Increase key work/psychosocial interventions+ supervised consumption of opioid prescriptions with breathalyser test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient dependent</td>
<td>Alcohol/benzodiazepine detoxification and/or reduction regimen plus increase key work/psychosocial interventions and supervised consumption of opioid prescriptions with breathalyser test</td>
</tr>
</tbody>
</table>
Other considerations

► Promote compassionate opioid analgesia
  – health care worker education especially at hospital
  – role of maintenance treatment in analgesia

► Encourage good vein care
  – to maintain venous access
  – important later, if applicable, in the clinical course of HIV infection
Other considerations

► Monitoring HIV progression
  – co-infection
  – cognitive state

► Mental health
  – depression
  – suicide ideation
  – ASPD
  – PTSD

► Pain management

► Drug substitution
Other considerations

► Risk exposure
  – dose
  – compliance with program rules

► Cost of medication

► Staff attitudes
Positive dose-response relationship between Methadone dose and patient retention

On doses >80 mg, better treatment adherence

In Asia MMT clinics affiliated with local health departments treat & retain more patients

Longer operating hours, incentives if compliant, facilitate treatment adherence

Psychosocial support & peer support vital for retention in treatment
Characteristics of effective programme

- Longer duration (2-4 years)
- Higher doses; > 60mg Methadone
- Accessible prescriber and dispenser
- Integrated services
- Quality of therapeutic relationship
Opioid dependence is a chronic condition which often needs long-term treatment. It is comparable to other chronic medical conditions e.g., asthma, hypertension.

Consider stopping agonist maintenance when:

► No unsanctioned drug use for > 1 – 2 years, for most patients continuing maintenance is the right choice as the risk of relapse is unacceptably high after stopping

► Stable social environment: employed, not associating with other drug users

► Stable medical/psychiatric conditions

► Patient informed consent
Reasons for terminating MMT

Few reasons for terminating MTT are:

► Violence/abuse to staff or other patients
► Diversion of Methadone from the clinic
► Confirmed drug dealing or other illegal activities around the clinic
► Continued use of dangerous quantities of other CNS depressant drugs
► Trafficking in take-away doses
The decision to withdraw and the rate of withdrawal may be determined by agreement between the patient, doctor and others in the treatment team.

Closely monitor the patient, and if he/she experience difficulties, decrease the rate of dose reduction until he/she stabilizes.
Let's think!

Case study

Discuss, how you would go with the process of establishing Methadone treatment for Chris:

*Chris, a male patient of 35 y.o., comes to your treatment centre after having failed several times with detox. He wants to start with Methadone treatment.*
Where are we so far?

► What is the main principle of Methadone safe induction?
► How to define the correct dose of Methadone after stabilization?
► What are some characteristics of an effective MMT programme?
► When and how can Methadone treatment be stopped?
Methadone for opioid detoxification
Methadone for opioid detoxification

- Methadone dose is ↓ by varying amounts over a period
- The detoxification regime to be reviewed regularly
- Be flexible in dosage adjustments
- Temporary ↑, stabilisation or ↓ may be required
- Duration is usually up to 4 weeks in inpatient setting
- It is normally up to 12 weeks in community setting
- To be supported by psychosocial interventions
- Plan 6 month aftercare at the start of detoxification
- This is to include psychosocial, mutual aid support
# Methadone withdrawal regimen

<table>
<thead>
<tr>
<th>Maintenance dose of Methadone</th>
<th>Rate of dose reduction per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 50 mg/day</td>
<td>5 mg</td>
</tr>
<tr>
<td>30-50 mg/day</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Less than 30 mg/day</td>
<td>1-2 mg</td>
</tr>
</tbody>
</table>
Rapid Methadone withdrawal
(<1 month) regimen

Reduce Methadone by 10 mg, every 3rd or 4th day until a dose of 20 mg is reached. Then follow the regimen below.

<table>
<thead>
<tr>
<th>Day</th>
<th>Methadone Dose/day</th>
<th>Day</th>
<th>Methadone Dose/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 at 20mg</td>
<td>20 mg</td>
<td>Day 8</td>
<td>10 mg</td>
</tr>
<tr>
<td>Day 2</td>
<td>20 mg</td>
<td>Day 9</td>
<td>10 mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>20 mg</td>
<td>Day 10</td>
<td>5 mg</td>
</tr>
<tr>
<td>Day 4</td>
<td>15 mg</td>
<td>Day 11</td>
<td>5 mg</td>
</tr>
<tr>
<td>Day 5</td>
<td>15 mg</td>
<td>Day 12</td>
<td>5 mg</td>
</tr>
<tr>
<td>Day 6</td>
<td>10 mg</td>
<td>Day 13</td>
<td>5 mg</td>
</tr>
<tr>
<td>Day 7</td>
<td>10 mg</td>
<td></td>
<td>stop</td>
</tr>
</tbody>
</table>
Rapid Methadone withdrawal
(< 1 month) regimen

Reduce by 10mg daily until a dose of 30 mg/day reached. Then follow regimen below.

<table>
<thead>
<tr>
<th>Day</th>
<th>Methadone Dose/day</th>
<th>Day</th>
<th>Methadone Dose/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 at 30mg</td>
<td>30 mg</td>
<td>Day 6</td>
<td>5mg</td>
</tr>
<tr>
<td>Day 2</td>
<td>25mg</td>
<td>Day 7</td>
<td>2mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>20 mg</td>
<td>Day 8</td>
<td>2mg</td>
</tr>
<tr>
<td>Day 4</td>
<td>15mg</td>
<td>Day 9</td>
<td>STOP</td>
</tr>
<tr>
<td>Day 5</td>
<td>10mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment with Methadone: evidence base
Evidence base for Methadone treatment in opioid dependence

- Methadone is among the most thoroughly studied medications in modern medicine

- First methadone study done in 1963-1964, at The Rockefeller Institute for Medical Research by Drs Vincent Dole & Nyswander

- It concluded that methadone prevented opioid withdrawal symptoms, blocked euphoria of heroin & cravings in opioid-dependent individuals

- Since then there has been numerous studies that have demonstrated across countries and populations that methadone can be effective in improving treatment retention and heroin use
The effects of opioids and Methadone on functional state

M – Methadone dose
H – Heroine injection
--- Course of mood and function
----- Course of mood and function if methadone id skipped
Methadone: Safety and side effect profile

Common side effects after 6 months to 3 years of methadone maintenance treatment

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Intermediate length treatment (6 months or more; &lt;40 to &gt;80 mg/d)</th>
<th>Long-term high-dose treatment (3 years or more; 80 to 120 mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent</td>
<td>Percent</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>Constipation</td>
<td>57</td>
<td>17</td>
</tr>
<tr>
<td>Libido abnormalities</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Orgasm abnormalities</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>Sleep abnormalities (insomnia)</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Appetite abnormalities</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>Nervousness / tension</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>Headaches</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>Body aches and pains</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Chills</td>
<td>10</td>
<td>-</td>
</tr>
</tbody>
</table>
4-5 Fold reduction in death rate
- Reduction of drug use
- Reduction of criminal activity
- Engagement in socially productive roles
- Reduced spread of HIV
- Excellent retention
Heroin use during MMT

Heroin Abuse Frequency Vs. Methadone Dose

Daily Dose In MGS.

V.P. Dole, JAMA, VOL. 282, 1989, p. 1881
Methadone dose and heroin use
Reductions in illicit opioid use during and after MMT: The DARP and TOPS studies

**TOPS Study**  
N = 4,184

- 63.5% Weekly Heroin Users
- ~18% 1st Year After Treatment
- ~19% 3–5 Years After Treatment

**DARP Study**  
N = 895

- 100% 2 Months Before Treatment
- 44% 1st Year After Treatment
- 24% 3rd Year After Treatment
MMT: Alcohol & other drug use

Methadone Treatment and Drug Use

N = 4,184

1 Year Pretreatment
1 Year Posttreatment

63% 17%
Any Opioid Use Any Cocaine Use

26% 18%
Any Cocaine Use Any Marijuana Use

55% 46%
Any Marijuana Use Alcohol Abuse

25% 24%

Source: TOPS (Hubbard et al., 1989)
Patient status before and after MMT

% of time using daily narcotics was much greater before MMT than after MMT.

% of time unemployed ↓ after MMT.
The effect of MMT duration on drug use and crime: The DARP study

**Improvements: Drugs and Crime 1 Year After DARP**

- Methadone Maintenance: 41%
  - N = 895
  - Total Improvements = 68%

- No Treatment: 27%
  - N = 152
  - Total Improvements = 41%

**Time in Treatment**

- Percent of Patients Who Are Abstinent and Not Involved in Crime in 1st Posttreatment Year
  - Under 3 Months: 14%
  - 3-12 Months: 27%
  - Over 12 Months: 41%
Death rates in treated and untreated patients addicted to heroin
## Evidence for the efficacy of MMT & death rate

### Studies published from 1943-1992

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>Treatment</th>
<th>Annual death rate</th>
<th>Age adjusted control</th>
</tr>
</thead>
<tbody>
<tr>
<td>4776</td>
<td>Untreated</td>
<td>7</td>
<td>0.6*</td>
</tr>
<tr>
<td>100</td>
<td>Treated</td>
<td>3.4</td>
<td>0.3**</td>
</tr>
<tr>
<td>109</td>
<td>Detox</td>
<td>8.3</td>
<td>***</td>
</tr>
<tr>
<td>3000</td>
<td>MM</td>
<td>0.8</td>
<td>***</td>
</tr>
<tr>
<td>368</td>
<td>MM</td>
<td>1.4</td>
<td>0.17****</td>
</tr>
</tbody>
</table>
Changes in employment during and after MTT

Changes in Employment During Treatment

- 1 Year Before Treatment: 24%
- 3 Months During Treatment: 25%
- 1st Year After Treatment: 20%
- 2nd Year After Treatment: 29%
- 3 to 5 Years After Treatment: 18%

Employment Before and After Treatment

- 1 Year Before Treatment: 33%
- 1 Year After Treatment: 57%
- 2nd Year After Treatment: 59%
- 3rd Year After Treatment: 58%

Source: TOPS (Hubbard et al., 1989)
Source: DARP (Simpson and Sells, 1982)
MMT status & HIV infection

**HIV Infection Rates by Methadone Maintenance Treatment Status**

- Baseline: 11%
- 6 Months: 18%
- 12 Months: 23%
- 18 Months: 32%
- 33%

**18-Month HIV Seroconversion by Methadone Maintenance Treatment Retention**

- In Treatment (N = 95): 3.5%
- Partial Treatment (N = 45): 4.4%
- No Treatment (N = 55): 22%
Lower rates of HIV seroconversion while in treatment

- **Metzger, 1993**
  - seroconversion 3/100 person years in substitution treatment (10/100 person years not in treatment)

- **Williams, 1992**
  - 0.7/100 person years in substitution treatment (4.3/100 person years not in treatment)

- **Moss, 1992**
  - 1.4/100 person years in substitution treatment (3.1/100 person years not in treatment)
Rapid return to IDU following premature termination of MMT

MMT associated with reductions in IDU and the risks related to HIV infection. When drug users leave MMT prematurely, they have an increased likelihood of returning to injection drug.

(Rapid Return to Injection Drug Use Following Premature Termination of Methadone Maintenance Treatment)

(N = 388 Male Patients)
MMT and IDU:
Summary of evidence base

- In IDU during OST, a consistent finding
- Reduction in number of injectors as well as frequency of injecting
- Benefits may not be sustained after treatment, particularly if treatment cessation is involuntary
WHO collaborative study on OST and HIV:
Key findings

► OST can achieve similar outcomes consistently in a culturally diverse range of settings
► Outcomes similar in low & middle-income countries, to those in high-income countries
► Associated with a substantial reduction in HIV exposure risk associated with IDU across nearly all the countries
► Results support the expansion of OST
OST: Is it cost effective?

- Investment in medication assisted treatment of opioid addiction makes good economic sense.
- For methadone, every dollar invested in treatment generates an estimated $4–5 return.
Compare the costs

Costs are for a 6 month period, per person

No treatment
- Untreated: $21,500
- Incarceration: $20,000
- Adolescent: $9,825
- Adult: $8,250
- Methadone: $1,750
- Drug free: $1,575

In treatment programme
- Residential
- Outpatient
What are the latest literature review results?
MMT: Summary of current evidence

Finding based on 31 systematic reviews and 27 RCTs:

- MMT reduces mortality
- Reduces HIV risk behaviour
- Reduces levels of crime
- Improve retention in treatment
- Lowers rate of illicit opioid use
- Higher doses more effective than lower doses
MMT: Current evidence

Cochrane review based on 11 studies, n=1969

- Effective for treating heroin dependence
- It retains patients in treatment
- Decreases heroin use
- It does not show a statistically significant superior effect on criminal activity or mortality
OST and HIV: Summary of current evidence

Cochrane review on 38 studies, with 12,400 participants

- In cases of HIV infection
- In illicit opioid use
- IDU
- Sharing Injecting Equipment
- In multiple sex partners
- In exchange of sex for drugs/money
- No significant effect on condom use
- Oral substitution treatment reduces drug-related behaviours with a high risk of HIV transmission
Methadone for opioid dependence: Summary

► Methadone is a slow-acting opioid agonist that is taken orally so that it reaches the brain slowly, dampening the “high” that occurs with other routes of administration while preventing withdrawal symptoms.

► Methadone has been used since the 1960s to treat heroin addiction and is still a good treatment option for all patients.

► Methadone is available through approved outpatient treatment programs, where it is dispensed to patients on a daily basis.
Why use opioid agonist therapy?
What evidence is there to support the use of Methadone for treating opioid dependence?
What are the basic principles of maintenance treatment with Methadone?
What contraindications and medical interactions with Methadone do you know?
Thank you for your time!
End of workshop 2