Clinical guidelines and procedures for the use of methadone in the maintenance treatment of opioid dependence

Abbreviated version
Clinical Guidelines and Procedures for the Use of Methadone in the Maintenance Treatment of Opioid Dependence

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August 2003
Introduction

These guidelines have been prepared to aid medical practitioners in the selection and management of patients seeking treatment with methadone for opioid dependence.

These guidelines were prepared under the auspices of the National Expert Advisory Committee on Illicit Drugs (NEACID) in collaboration with the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project, the Royal Australian College of General Practitioners (RACGP) and the Australian Professional Society on Alcohol and Other Drugs (APSAD), and are funded by the Australian Government Department of Health and Ageing.

These guidelines are based on national and international research literature and clinical experience with the use of methadone in Australia. These guidelines have undergone a rigorous process of review and have been formally endorsed by the RACGP and APSAD.

The contribution of various individuals and organisations in the drafting and review process is gratefully acknowledged.

The oral methadone preparations Methadone Syrup® and Biodone Forte® are registered only for treating heroin dependence in Australia. Methadone Syrup® contains 5 mg/ml methadone hydrochloride, sorbitol, glycerol, ethanol (4.75%), caramel, amber colouring and sodium benzoate while Biodone Forte® contains 5mg/ml methadone hydrochloride and permicol-red colouring.
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Clinical Pharmacology

Methadone is a potent synthetic opioid agonist which is well absorbed orally and has a long, although variable, plasma half life. The effects of methadone are qualitatively similar to those of morphine and other opiates.

Methadone is effective in the treatment of heroin dependence as it:
- substitutes for heroin, prevents the emergence of opioid withdrawal symptoms and reduces cravings for heroin;
- is well absorbed orally but does not produce rapid intoxication;
- has a long half life and is taken in a single daily dose;
- binds to various body tissues and is very slowly released enabling the patient to be maintained in a stable state; and
- diminishes the euphoric effects of additional opioids.

Other relevant properties:

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of effects</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Peak effects</td>
<td>Approx 3 hours</td>
</tr>
<tr>
<td>Half life (in Methadone Maintenance Treatment)</td>
<td>Approx 24 hours</td>
</tr>
<tr>
<td>Time to reach stabilisation</td>
<td>3-10 days</td>
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</tbody>
</table>

- Metabolised in the liver via the cytochrome P450 enzyme system
- Eliminated principally in the urine and faeces.

Withdrawal syndrome

The withdrawal syndrome from methadone tends to emerge later and be more prolonged than with short acting opioids (eg heroin). Signs and symptoms usually begin 36 to 48 hours after the last dose. The duration of methadone withdrawal is typically 5 to 21 days with some features lasting for a prolonged period characterised by a general feeling of reduced well-being.

Side effects

- Most dependent opioid users will experience few side effects from methadone.
- Once on a stable dose, tolerance develops until cognitive skills and attention are not impaired.
- Symptoms of constipation, sexual dysfunction and occasionally increased sweating can continue to be troubling for the duration of treatment.
Drug interactions

- **Other sedatives** (e.g., alcohol and benzodiazepines) in combination with methadone can result in respiratory depression, coma and death.

- **Cytochrome P450 inducing drugs** can increase the metabolism of methadone and cause a withdrawal syndrome if administered to patients maintained on methadone.

- **CYP 3A inhibitors** can decrease the metabolism of methadone and cause overdose.

- **Opioid antagonists** (e.g., naltrexone, naloxone) will precipitate withdrawal in opioid dependent patients.

- **SSRI, MAOI, tricyclic antidepressants and some antibiotics** may raise plasma methadone levels and increase the effects of methadone.

The full list of drugs which interact with Methadone appears at Appendix 1 of the unabridged Clinical Guidelines for the use of Methadone in the Maintenance Treatment of Opioid Dependence.

Safety

- The long term side effects of methadone taken orally in controlled doses are few.
- Overdose is the main risk.
- Overdose risk is increased:
  - In the first two weeks of induction to methadone maintenance treatment;
  - when methadone is used in combination with other sedative drugs.
- Toxic effects of overdose may become life threatening several hours after ingestion due to the slow onset of action and long half life of methadone.

Clinical Guidelines and Procedures for the use of Methadone in the
Entry into Methadone Treatment

A comprehensive assessment by a medical practitioner authorised to prescribe methadone is essential.

Indications
- opioid dependent
- 18 years or older (check jurisdictional requirements regarding age limits for MMT)
- able to provide proof of identity as is required for treatment with all S8 medications.
- capable of giving informed consent

Contraindications
- severe hepatic impairment or respiratory insufficiency.
- hypersensitivity to methadone or other ingredients in the formulation.

Precautions
Particular caution should be exercised by prescribers when assessing individuals with the following clinical conditions (seek specialist advice or assistance in such cases):
- High risk poly drug use.
- Co-occurring alcohol dependence.
- History of naltrexone use.
- Psychiatric illness.
- Chronic pain – refer to pain clinic for assessment first.
- Concomitant medical problems.

Key features of assessment for treatment with methadone

Opioid use
- Opioids used, quantity, frequency, route of administration, duration of current opioid use, use over the last 3 days
- Severity of dependence
- Age of commencement, age of regular use, age of dependence, timing and duration of periods of abstinence
- Episodes of overdose

Other drug use
- Including alcohol, illegal and prescribed drugs, current medications.
Health status
● Diseases from drug use (blood borne viruses, other)
● Intercurrent health conditions (psychiatric, general)

Psychosocial status
● Legal
● Social - employment, educational/vocational skills, housing financial, family
● Psychological – mood, affect, cognition.

Past treatment
● Where
● When
● Periods of abstinence
● Degrees of success/acceptance of treatment

Patient views regarding treatment
● Motivation for treatment
● Trigger for seeking treatment
● Patient goals for treatment episode
● Stage of change

Physical examination
● Observation of clinical signs related to drug use (needle track marks, intoxication, withdrawal)
● Evidence of medical problems (eg liver disease – jaundice, ascites, encephalopathy).

Investigations
● Urine tests may be indicated if there are concerns about the accuracy of the drug history and diagnosis and may also be useful to confirm benzodiazepine and other drug use.
● Investigations for HIV and hepatitis B and C if indicated.

Informed consent and patient information.

Obtain informed consent to methadone treatment in writing from the patient before he/she enters treatment.

For patients to make a fully informed decision provide them with written information about:
● The nature of methadone treatment
● Other treatment options
● Program policies and expectations
● Recommended duration of treatment
● Side effects and risks associated with taking methadone
● Risks of other drug use
● The potential impact of methadone on their capacity to drive or operate machinery
● Availability of further information
Methadone may affect the capacity of patients to drive or operate machinery during the early stages of treatment, after an increase in dose, or when patients are also taking other drugs. Warn patients about this effect before entry into treatment, when the dose of methadone is increased, or when the use of other drugs is suspected.

Meeting legislative requirements

Methadone is a Schedule 8 medication.

- A medical practitioner must be authorised by the relevant jurisdictional body to prescribe methadone for addiction.
- Prescribers must obtain authority to prescribe methadone for each patient.

Check your jurisdictional policy for details of authorisation procedures.

Coordinated care

- Effective methadone treatment requires ongoing regular collaboration between the prescriber and dispenser.
Induction to methadone treatment

Commencing methadone from heroin use

Deaths due to methadone toxicity in the early stages of treatment have been related to:

- Concomitant use of other drugs, particularly sedatives;
- Inadequate assessment of tolerance;
- Commencement on doses that are too high for the level of tolerance;
- Inadequate understanding of the cumulative effect of methadone;
- Inadequate supervision of ingestion of methadone;
- Individual variation in metabolism of methadone.

For most patients withdrawal symptoms will be alleviated but not eliminated by methadone doses less than 30mg.

Size of the first dose

The first dose of methadone should be determined for each patient based on the severity of dependence and level of tolerance to opioids.

- A dose of <20 mg for a 70kg patient can be presumed to be safe, even in opioid-naïve users as this is the lowest dose at which toxicity has been observed.
- Caution should be exercised for starting doses of 30mg or more.
- Extreme care should be exercised when the initial dose of methadone exceeds 40mg.

Stabilisation of methadone dose

Stabilisation is about titrating the dose against needs of individual patients.

Monitoring during the first two weeks.

- **Patients should be observed daily prior to dosing** and an assessment made of intoxication. If there are any concerns they should be seen by a doctor before the dose is administered.
- **Because of the pharmacology of methadone, to ensure safety, it is desirable that patients are reviewed at least once, and preferably twice by an experienced clinician** (doctor or nurse) in the first week with a view to assessing intoxication from methadone.
- **Dose increases should only be considered subject to assessment by the prescriber.**
Dose Titration

- Do not increase the methadone dose for at least the first 3 days of treatment unless there are clear signs of withdrawal at the time of peak effect, i.e. 3-4 hours after dose.
- Consider dose increments of 5-10mg every 3 days subject to assessment.
- Total weekly increase should not exceed 20mg.
- The maximum dose at the end of the first week should typically be no more than 40mg.

Transfer from other pharmacotherapies

Seek specialist advice when prescribing for patients who are transferring from other pharmacotherapies.

Buprenorphine

(See also “National guidelines and procedures for the use of buprenorphine in the treatment of heroin dependence”)

- Stabilise on daily doses of buprenorphine and reduce dose to 16mg or less for several days prior to transfer.
- Commence methadone 24 hours after the last dose of buprenorphine.
- The initial methadone dose should not exceed 30mg.
- For transfer from doses of 4 mg or less, commence on lower doses of methadone.
- Do not increase the dose of methadone in the first three days.

Naltrexone

- Treat patients transferring from naltrexone as if they were naïve to opioids and non tolerant to their effects unless the assessment clearly indicates a return to regular, heavy heroin use.
- Do not administer methadone until at least 72 hours after the last dose of naltrexone.
- Extreme caution should be exercised with commencing doses of methadone greater than 20mg.

Maintenance dosing

Dose Levels

Doses should be determined for individual patients. Doses for effective MMT are typically 60-100mg per day.

Changing dose level

The following must be taken into consideration when considering dose changes:

- Concurrent use of illicit opioids and continued injecting use
- Individual variation in methadone metabolism
- Use of other medications
- Pregnancy
- Polydrug use
Monitoring drug use

Urine Testing

- Urinalysis is most useful in the following circumstances:
  - Patients in the early stages of treatment.
  - Where clarity of drug use is required for diagnostic purposes
- Medicare allows for a maximum of 21 urinalysis tests per patient per year.

Adjunct treatment

Providing therapies such as motivational interviewing, relapse prevention, counselling, social skills training, vocational, financial, accommodation and family assistance contributes positively to the progress of MMT. However, participation in these should be voluntary.

Takeaway doses

- The takeaway policy for methadone is determined for each jurisdiction in line with the National Policy on Methadone Treatment. There are both benefits and problems associated with takeaway doses and particular care should be exercised when authorising this as a component of management.
- Takeaway doses for interstate or overseas travel must be organised through the jurisdictional authority responsible for controlling methadone and the Australian Government Department of Health and Ageing.

Missed doses and reintroduction of methadone

In general the following schedule can be presumed to be safe and effective. If the patient has missed:

<table>
<thead>
<tr>
<th>Number of Days</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>One day</td>
<td>No change in dose.</td>
</tr>
<tr>
<td>Two days</td>
<td>If no evidence of intoxication administer normal dose.</td>
</tr>
<tr>
<td>Three days</td>
<td>Administer half dose in discussion with the prescriber.</td>
</tr>
<tr>
<td>Four days</td>
<td>Patient must see prescriber. Recommence at 40mg or half dose whichever is the lower.</td>
</tr>
<tr>
<td>Five days or more</td>
<td>Regard as a new induction.</td>
</tr>
</tbody>
</table>
Cessation of methadone maintenance treatment

It is recommended that patients be encouraged to remain in treatment for at least 12 months to achieve enduring lifestyle changes.

Voluntary withdrawal schedule

- The recommended rate of reduction is 10mg/week to 40mg/day, then 5mg/week. Rates of reduction should be negotiated with patients, and dose changes should occur once a week.
- Abrupt cessation of methadone could be considered from 40mg/day with administration of clonidine and symptomatic medications as needed.
- Supportive care/after care:
  - Supportive care should be offered for at least 6 months following cessation of methadone.
  - For recently discharged patients fast readmission to MMT should be available.

Involuntary withdrawal

- It is sometimes necessary to discharge a patient from treatment for the safety or well being of the patient, other patients or staff.
- Patients should, where possible, be withdrawn to 40mg/day according to the above voluntary withdrawal schedule.
- Abrupt cessation of methadone or rapid dose reduction may occasionally be warranted in cases of violence, assault or threatened assault against staff or patients.

Transfer to naltrexone

- Administration of naltrexone to a patient physically dependent on opioids will precipitate a severe withdrawal syndrome.
- Patients being transferred to naltrexone should undergo detoxification followed by a 14 day drug free period to allow stored methadone to be eliminated from the body.
- Seek specialist advice from an alcohol and drug service if it is not possible to follow this regime.

Transfer to buprenorphine

See the National Buprenorphine Guidelines for further information or seek specialist advice.

- When methadone patients take a dose of buprenorphine, it may precipitate withdrawal.
- Patients on low doses of methadone (<30mg) generally tolerate this transfer with minimal discomfort.
- Very low doses of buprenorphine (eg 2 mg) are generally not adequate to substitute for methadone while high doses (8 mg or more) are more likely to precipitate withdrawal.
- Buprenorphine should not be dispensed within 24 hours of last methadone dose. Increasing the interval between the last dose of methadone and the first dose of buprenorphine reduces the incidence and severity of precipitated withdrawal.
4 Management Issues during Treatment

Overdose

Signs and Symptoms of Methadone Overdose

- Pinpoint pupils
- Sedation/coma
- Unsteady gait, slurred speech
- Hypotension
- Bradycardia
- Hypoventilation

**NOTE:** Symptoms may last for 24 hours or more. Death generally occurs from respiratory depression.

- Administration of methadone in the morning will ensure peak methadone concentrations occur when patients are normally awake and other people may be available.
- Naloxone should be given as a prolonged infusion when treating methadone overdose.
- Patients thought to have taken a methadone overdose require prolonged observation.

Intoxicated presentations

- Patients who appear intoxicated with CNS depressant drugs should not be given their usual methadone dose or a takeaway dose at that time. They can be asked to re-present later when no longer intoxicated.
- If intoxication is evident but appears mild the patient may be given a reduced dose but only after being reviewed by the prescriber.

Analgesia and anaesthesia

Analgesic requirements for patients on methadone:

- Consider non-opioid analgesics (NSAIDs) Where parenteral analgesics are required, consider ketorolac, (Toradol®) or tramadol (Tramal®).
- Management of acute pain in hospital for patients on Methadone Maintenance Treatment:
  - Patients in MMT should receive analgesia in the same way as for other patients. This includes the use of injectable and patient controlled analgesia.
  - Patients taking methadone frequently require larger doses of opioid analgesia for adequate pain relief.
  - Partial agonists such as buprenorphine should be avoided as they may precipitate withdrawal symptoms.
- Patients on methadone may require higher doses of anaesthetic agents in the event of dental or surgical procedures.
Diversion of methadone

The risk of diversion of prescribed methadone can be reduced by:

- Ensuring that, in general, methadone is consumed under supervision.
- Careful selection and monitoring of patients eligible to receive takeaway doses taking into account the patient’s stability, reliability and progress in treatment.
- Limiting the number of consecutive takeaway doses.

Pregnancy and lactation

Antenatal and postnatal care should be managed in collaboration with specialist obstetric services experienced in the management of drug dependency during pregnancy.

- Naloxone challenge should not be used in pregnant women because this may precipitate miscarriage or premature labour.
- Pregnant women should be maintained on an adequate dose of methadone, to achieve stability and prevent relapse or continued illicit drug use.
- If dose reductions of methadone or detoxification are to be undertaken during pregnancy these should occur in the second trimester only if the pregnancy is stable.
  — In most instances, dose reductions of 2.5mg-5 mg per week are considered safe.
- The bioavailability of methadone is decreased in the later stages of pregnancy. It may be necessary to divide the daily dose and possibly to increase the dose in the third trimester.
- Breast milk contains only small amounts of methadone and mothers can be encouraged to breastfeed.
- Neonatal care should be managed in collaboration with specialist obstetric or paediatric services experienced in the management of babies born to drug dependent mothers.

Polydrug use

It is recommended that specialist advice be sought when treating patients at high risk from polydrug use especially where sedatives are involved.

HIV, Hepatitis B and C

- Methadone treatment programs should ensure that HIV positive patients have access to specialist HIV medical care so that the patient’s health may be monitored and appropriate treatment provided as required.
- Patients who are acutely infected with Hepatitis B or who are chronic carriers should be referred to a gastroenterologist for specialist assessment and followup.
- Patients who are Hepatitis C antibody positive should be managed in accordance with *Hepatitis C, A Management Guide for General Practitioners* (RACGP 1999).
Psychiatric comorbidity

- Many opioid users exhibit symptoms of anxiety and depression at the time of presentation for treatment but this usually improves within weeks of commencing treatment.
- If clinical depression persists antidepressants may be prescribed. Unless there is a particular indication for tricyclic antidepressants, SSRIs should be preferred.