

# Guidance for the use of methadone for the treatment of opioid dependence in primary care

**RCGP Substance Misuse Unit**  
**RCGP Sex, Drugs and HIV Task Group**  
**SMMGP**  
**The Alliance**

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## Summary

### Opioid dependence is common in the UK and methadone is an effective treatment.

#### Effective:

- Methadone is an effective evidence based medication used for the treatment of opioid dependence.
- It is most effective when used as a maintenance agent at optimal dosing.
- Its primary function is to reduce (and eventually replace) illicit opioid use and in so doing, reduce harm and improve the health and psychological well-being of the patient.

#### Maintenance and detoxification:

- Choosing between maintenance and detoxification occurs at many points during treatment, starting at the first assessment and then at various points as appropriate.
- Methadone can be used as a maintenance intervention or sometimes as a detoxification agent.
- Other medications, such as buprenorphine and lofexidine, may be more effective for detoxification in some patients.

#### Methadone maintenance:

- Methadone is still considered the gold standard for long-term opioid dependence.
- Optimal dose for maintenance is usually between 60 to 120 mg daily (some people need more and some less).
- Methadone is usually prescribed in an oral formulation: methadone oral solution (mixture) 1 mg/ml.

#### Assessment:

- Before prescribing methadone, opioid dependence **must** first be confirmed by history and examination, including physical examination, and by toxicology screening using urine or oral fluid swabs.

#### Titration:

- Due to the risk of overdose, the starting dose should be between 10 and 30 mg daily.
- For patients on other sedative drugs, including benzodiazepines or alcohol, the starting dose should not be more than 20 mg daily.
- Doses should then be titrated upwards to optimal levels, usually between 60 and 120 mg.
- Increases of between 5 to 10 mg a day with a maximum of 30 mg a week for the first two weeks (after that it can be slightly quicker).
- The consumption of methadone doses should be supervised for at least the first three months and until the patient has gained stability, unless there are important other considerations (e.g. employment, child care responsibilities) and the risk of diversion has been assessed as low.
- Methadone should initially be prescribed in daily instalments, on FP10 (MDA) in England and Wales or GP10 (3) in Scotland.
- It is the responsibility of the prescriber to ensure safe induction on to methadone. This responsibility cannot be delegated. However, a close working relationship with pharmacists and drug workers can be helpful in facilitating titration to an adequate dose as quickly as possible.

#### Stabilisation:

- Stabilisation involves finding a suitable dose that keeps the patient engaged in treatment without the need to supplement with other drugs and/or heroin.
- The process of psychosocial stabilisation usually begins once drug use has begun to stabilise.

#### Interactions:

- Methadone interacts with other central nervous system depressants including benzodiazepines, antidepressants and alcohol, increasing the risk of overdose and patients must be informed of this.
- It can be particularly dangerous to use any sedative drugs, including heroin and benzodiazepines, especially by injection, while taking methadone.
- Drugs that increase metabolism such as rifampicin or phenytoin, may mean higher doses of methadone are needed to compensate.

**Loss of tolerance:**

- It is important to remember that several missed doses may mean a loss of tolerance.
- Three days missed consecutively should lead to a dose review and possible reduction in dose.
- Five days or more missed consecutively should lead to re-assessment and re-titration.
- The tolerance to opioids maintained by people on adequate methadone treatment is an important protective factor against overdose: people on adequate treatment are far less likely to overdose than opioid users not in treatment.

**Ongoing care:**

- Treatment is reviewed at every contact and needs to be reviewed formally, at least every three to four months, to measure improvements in health and well-being.
- A toxicology screen (urine or oral fluid swab) needs to be taken frequently in the beginning of treatment and, when stabilised, between two and four times a year to confirm use of medication and monitor treatment.
- Toxicology screens should never be used punitively, but as an aid to treatment.
- Screens positive for heroin, or other drugs, require a review of treatment and dose and should not normally lead to the cessation of treatment or dose reduction.
- It is important that patients are given good information on methadone's actions and effects and advice on safe storage of take-home doses.

**Shared care:**

- Treatment of drug users is multifaceted and normally requires a multidisciplinary response and, wherever possible, should be provided in collaboration with others such as other primary care workers, practice nurses, dispensing pharmacists, practitioners with a special interest and addiction specialists.
- Practitioners should only treat and prescribe to the level of practice at which they feel competent and confident.
- More stable patients may not need so much additional input.
- Shared care should be encouraged to meet the needs of the individual, not a specific drug.

# Methadone prescribing in primary care

## Background

This guidance has been produced to aid medical practitioners and others in the use of methadone as a substitute medication for opioid dependence for maintenance and detoxification. It should be read in conjunction with the Clinical Guidelines, *Drug misuse and dependence: guidelines on clinical management*, issued by the UK Departments of Health in 1999<sup>1</sup> and National Treatment Agency Research into Practice briefings: 3, 4 and 5.<sup>2, 3, 4</sup>

Methadone prescribing in primary care has increased recently and there is a need for accessible evidence-based guidance specifically aimed at primary care.<sup>5</sup> This guidance is part of a series, which also includes the use of buprenorphine in opioid dependence treatment, treatment of cocaine users and hepatitis vaccination schedules.<sup>6, 7, 8</sup>

These documents are available online at [www.smmgp.org.uk](http://www.smmgp.org.uk) and [www.rcgp.org.uk](http://www.rcgp.org.uk)

## Who is the guidance for?

This guidance is aimed at all clinicians involved in the care of drug using patients. It has been developed specifically to support the use of methadone in primary care.

## Evidence-based guidance

This guidance draws on the research literature and experience, both in the UK and internationally, in the clinical use of methadone. The evidence base for methadone as a successful treatment for opioid dependence is extensive and still growing. However, there are many technical and practical aspects to managing drug using patients in primary care. Consequently this document also draws upon recommendations from experts in the field to address the evidence gaps.

Treatment for opioid dependence can be effective in primary care and there is a substantial body of evidence to support this. There are now a number of substitution therapies supporting this treatment being used which include methadone and buprenorphine in the UK and other therapies in other parts of the world, such as morphine sulphate in Austria.<sup>2, 6, 9</sup>

## 1. Rationale for the use of methadone

**Methadone is an effective substitute medication for opioid dependence for use in UK primary care.**

There is an increasing body of evidence that the primary care setting is an effective means of delivering treatment for opioid dependence.<sup>10, 11, 12, 13</sup> Methadone maintenance treatment (MMT) is now a well-established treatment modality across a variety of treatment settings and supported by both research evidence and clinical practice.<sup>14, 15, 16, 17, 18, 19</sup>

The aim of methadone maintenance treatment is to improve the quality of life of opioid-dependent patients and to reduce the potential harm of using illicit drugs. MMT greatly reduces mortality,<sup>20</sup> illicit drug use and criminal activity, and attracts and retains more patients in treatment than other treatments.<sup>9</sup> There is good evidence that MMT reduces transmission of HIV,<sup>21, 22, 23</sup> although the evidence for effectiveness at reducing transmission of hepatitis B virus and hepatitis C virus is less convincing.<sup>24, 25, 26</sup>

There is no evidence that MMT increases the overall length of dependence.<sup>14</sup> The positive outcomes of MMT are only sustained while patients are in treatment. Effective treatment of the parent can also have major benefits for the children of problem drug users.<sup>27</sup>

Methadone is a highly effective maintenance treatment for chronic dependent opioid users that can deliver a wide range of harm reduction outcomes for large numbers of patients in a wide variety of settings. However, effectiveness may be reduced by departure from optimum methods of delivery. Enforced reductions in the methadone dose and putting pressure on patients to become abstinent from methadone are associated with poor outcomes.<sup>28</sup>

The most effective MMT programmes are those that provide optimal doses (usually between 60 to 120 mg daily) of methadone as part of a comprehensive treatment programme, which will include regular reviews, general medical care and psychosocial support as required, and which validates maintenance as much as abstinence as desirable treatment goals<sup>9, 17, 29</sup> and where patients feel they play a meaningful role in determining their optimum dose.

A summary of the evidence in 1999 concluded that given the high morbidity and mortality seen in patients with opioid dependence not in treatment, the public health challenge was to deliver safe and effective methadone treatments to as many patients as could benefit from it, while minimising the risk of diversion of prescribed medication.<sup>14</sup> Whilst methadone clearly remains the mainstay of the public health response, there has been an increase recently in the use of buprenorphine for some patients. Also with more patients now in treatment, increasing access to psychosocial and other supportive interventions in addition to the pharmacotherapy is important.

## 2. Clinical pharmacology

**The pharmacokinetics of methadone can vary considerably between individuals.**

**Methadone metabolism varies in different people and different doses of methadone are needed to create the same serum methadone level.**

**Optimal doses are usually between 60 to 120 mg and may exert clinical effects for between 24 to 36 hours; low doses exert clinical effects for only a few hours.**

**Tolerance to opioids varies between individuals and can change in individuals overtime.**

Methadone is a long acting synthetic opioid analgesic originally synthesised in 1939. It acts as a full opiate agonist and is usually used in oral mixture form as a substitute medication for the dependent use of opioids, most commonly street heroin. Methadone alleviates opioid withdrawal symptoms and at adequate doses blocks the effects of additional opioids, while at the same time alleviating craving. This can dramatically reduce and often eliminate the constant need to obtain illicit opioid drugs.

### Relevant properties

Methadone pharmacokinetics display wide variability between drug dependent individuals according to age, gender, ethnic background, body mass, prior drug and health history and is significantly different in opioid dependent people compared to non-opioid dependent people.

As a guide:

#### Time to peak plasma concentration:

- Four hours after oral administration (range two to six hours).

#### Time to peak clinical effects:

- Two to four hours for first dose.
- It takes four to five days for methadone tissue and plasma levels to stabilise, though accumulation continues beyond this to finally reach a steady state by ten days.<sup>30, 31</sup>
- Once a steady state is reached variations in blood concentration levels are small.

#### Plasma half-life:

- The length of time that methadone lasts in the body varies:
  - Single one-off dose – shorter than maintenance dosing 12 to 18 hours, mean 15 hours.
  - First few days – between 13 to 112 hours, mean 37 hours.<sup>32</sup>
  - At the onset of daily dosing half-life is very long and there is a risk of drug accumulation. For this reason, methadone induction should be a cautious and gradual process.
  - Elimination half-life normally 20 to 37 hours but can range up to 91 hours for some individuals and its rate of clearance from the body can vary by a factor of almost 100.<sup>33</sup>

#### Methadone metabolism:

- Well absorbed from the gastrointestinal tract into the blood stream.
- Well distributed in body fats.
- Binds well to plasma proteins and to lungs, liver and kidney tissues.
- Varies enormously in different people and widely different doses of methadone are needed to create the same serum methadone level.
- Metabolised through the liver via the cytochrome P450 sub-family of enzymes thus susceptible to pharmacokinetic interactions with drugs that inhibit or induce liver enzymes.

**Duration of action:**

- Low doses may exert clinical effects for only a few hours, up to a maximum of 12 hours because receptor occupancy will be minimal and plasma concentrations sub-optimal.<sup>34</sup>
- Optimal doses usually between 24 to 36 hours.

**Excretion:**

- The products are mainly excreted as non-active metabolites (and about 10% as unchanged methadone) principally in the faeces and urine, therefore urinalysis is only useful in confirming methadone being taken, but not the dose.

**Maintenance doses:**

- While research evidence suggests that optimal doses for most people lie between 60 to 120 mg, some people will need more and some need less due to a range of individual factors.<sup>1, 33</sup>

**Equivalence:**

- Direct equivalence to street heroin is difficult to estimate as the purity of street heroin can vary (between 20 to 60%, but is usually around 50%). One gramme of street heroin is usually roughly equivalent to 50 to 80 mg methadone.
- When comparing the equivalence of methadone to injectable pharmaceutical diamorphine, half-lives must be taken into consideration and it is not a linear relationship, so it can vary from a methadone: heroin ratio of 1:3 (or even 1:1 for very low doses) to around 1:5 for high doses of diamorphine (e.g. 120 mg methadone is equivalent to between 360 and 600 mg of injectable diamorphine).
- Direct equivalence to buprenorphine is difficult to estimate as the pharmacological properties of the two agents are not identical (buprenorphine is a partial agonist) and it is not a linear relationship.
- When comparing the efficacy of maintenance doses, 50 to 80 mg methadone is approximately as effective as 12 to 16 mg buprenorphine in reducing heroin use and retaining patients in treatment;<sup>35</sup> studies comparing optimal dose methadone to high dose buprenorphine have yet to be undertaken.<sup>6</sup>

**Tolerance:**

- Develops at different speeds in different individuals and can change in individuals over time.
- Develops differently for different effects e.g. quickly for vomiting and not completely developed for respiratory depression.

- With long-term use, and in response to continued exposure of the brain to opiates, neuro-adaptation occurs and involves changes in nerve and receptor function.
- Level of heroin use is not the only factor in determining the final methadone dose that will be required: patients react to methadone differently: some will need more, and some will need less than others using the same amount of heroin.
- High dose heroin use does not always equate with tolerance to methadone but there is a high degree of cross-tolerance, so broadly speaking if your patient is smoking a £10 bag of heroin a day, they won't need 120 mg of methadone, and if they are injecting 2 g of heroin they are unlikely to settle on 60 mg of methadone.
- An intolerance to the pharmacological effects of methadone oral solution (mixture) is rare but if confirmed consider using sugar, chloroform or colour-free formulations of methadone or another medication (e.g. buprenorphine).

### 3. Types of methadone (available in the UK)

**Methadone oral solution 1 mg/ml is the formulation of choice in the management of opioid substitution**

#### (a) Oral formulations

##### 1. Methadone oral solution (mixture) 1 mg/ml (green) (oral solution is the European term now to be used)

Methadone oral solution is licensed for the treatment of opioid dependence in the UK. It contains 1 mg of methadone in 1 ml of liquid and must be taken orally.

It is currently the drug of choice for substitute opioid prescribing because:

- Its clinical effectiveness is supported by extensive research.
- It alleviates opioid withdrawal symptoms.
- It is taken orally thus reducing the risk of injection.
- The dose can be carefully titrated to the optimal level.
- Blood levels can be kept very stable thus eliminating post-dose euphoria and pre-dose withdrawal.

## 2. Methadone oral solution (concentrated mixture) 10 mg/ml (blue) and 20 mg/ml (brown)

Methadone oral solution also comes in more concentrated forms, which are different strengths and vary in colour, such as 10 mg/1 ml and 20 mg/1 ml. These formulations are used in specialist settings for on-site dispensing.

Experienced practitioners working in primary care may sometimes use these strengths for patients on high dose methadone, to reduce the volume taken. However this would normally be on a supervised consumption basis as the higher concentration means there is a greater risk of overdose should it be diverted onto the illicit market and also because it is not viscous, unlike 1 mg/1ml formulations and therefore is easier to inject.

*Methadone linctus 1 mg/2.5 ml is used in palliative care for the control of distressing cough in terminal lung cancer. It is not licensed for the treatment of drug dependence.*

## 3. Methadone tablets 5 mg

Methadone tablets are not licensed for the treatment of drug dependence. The Advisory Council for the Misuse of Drugs (ACMD) and the Clinical Guidelines advise against the prescription of methadone tablets because they can be injected and have a high street value.<sup>1, 36</sup> Their prescribing in general practice is problematic and not generally advised.

However, some long-term opioid dependent patients prefer this formulation as tablets are easier to take, have no unpleasant taste and are more convenient. They may be justified for specific circumstances such as to prevent vomiting in pregnancy; nausea due to chemotherapy, during holidays abroad and where there is proven intolerance to the mixture, if the prescriber has the level of experience to prescribe them and has undertaken the necessary precautions to ensure they are being taken appropriately. Specialist advice should be taken before prescribing tablets.

### (b) Injectable formulations

Some forms of methadone ampoules are now licensed for opioid dependence treatment. The DH Clinical Guidelines, and more recent NTA expert guidance on injectable opiate prescribing, make clear that decisions concerning initiation of injectable prescribing should normally be made only after assessment by addiction specialists (or by another doctor if they have sufficient competence in this area). This could include some 'general practitioners with special interest' if they have developed the necessary expertise in the management of injectable opiate prescribing.<sup>1</sup>

Ampoules are occasionally appropriate for some severely opioid dependent patients, with a considerable injecting history, who have not benefited from optimal oral medication and for whom injecting itself has become a strongly reinforced behaviour. Such patients who have not succeeded with oral medication may obtain stability on ampoules.<sup>37, 38</sup> More research is needed and specialist prescribing advice should be sought before injectable methadone is even considered.

NB: Trials using injectable methadone and heroin under supervised conditions are about to commence in the UK (2005), which will help this discussion.<sup>39</sup>

Formulations:

- Methadone ampoules 10 mg/ml in 1 ml or 2 ml.
- Methadone ampoules 35 mg in 2 ml or 3.5 ml.
- Methadone ampoules 50 mg in 5 ml, 2 ml or 1 ml.

**NB: The rest of this document will be referring to methadone oral solution 1 mg/ml unless stated otherwise.**

### Unwanted (or side) effects

Most unwanted effects of methadone are those associated with all opioids, including nausea, vomiting, constipation and drowsiness. Larger doses produce respiratory depression and hypotension. Dry mouth, sweating, headache and decreased libido may also occur.

Unwanted effects vary from individual to individual. Many patients report a 'clouding' effect in the mind, which is valued by some but not others. The common complaint of sore leg muscles, which is sometimes described as 'getting in your bones', particularly in the 18 to 24 hour period after dosing could indicate 'breakthrough' withdrawal effect from low plasma levels of methadone. Such protracted withdrawal symptoms are commonly experienced during suboptimal maintenance dosing or when insufficient opioids are prescribed when a user is undergoing detoxification from methadone.

Poor dental health is mainly related to poor dental hygiene early in the patients using career, rather than the sugar in the solution. A sugar-free formulation is no better for the teeth and can cause abdominal symptoms, such as flatulence, but less constipation.

## 4. Indications, contraindications and precautions for use in primary care

### Indications

- Opioid dependence.

### Absolute contraindications

- Non-opioid dependent.
- Allergy or proven intolerance to methadone.

### Relative contraindications

- Severe liver disease, such as decompensated liver disease. However, in many cases the benefits will outweigh the risks with careful monitoring of liver function.
- Under 16 years except on the advice of a specialist.

### Cautions

**Extra caution should be exercised and benefits and risks assessed when prescribing methadone in the following situations:**

- 1. Concurrent use of other sedating drugs or medications.** Methadone has been associated with sedation, respiratory depression and coma when used in conjunction with central nervous system depressants such as alcohol, benzodiazepines, barbiturates, neuroleptics and tricyclic anti-depressants. Monoamine oxidase inhibitors (MAOIs) need to be avoided with methadone because of the potential risk of CNS hyperexcitation (hyperthermia, delirium etc.) which has been noted with pethidine, but never, so far, with methadone. However both alcohol and benzodiazepine use are common in those requesting methadone maintenance and should not be regarded as absolute contraindications.
- 2. Medical conditions complicating opioid use.** As with other opioids, methadone should be used cautiously in individuals with recent head injury, acute abdominal conditions, or with severe respiratory, hepatic or renal disease.
- 3. Patients suffering with chronic pain where opioid analgesia is indicated** must be given appropriate doses of additional opioid analgesia on top of that required for the management of dependence and so may need increased doses of other opioid analgesics or methadone to get pain relief. Methadone 1 mg/ml is a weak analgesic (also see section 9).
- 4. People with severe mental illness,** with limited capacity to provide informed consent.
- 5. Medications that affect methadone levels.** Some medications have a significant effect on methadone levels e.g. rifampicin may require doubling or trebling of methadone dose and can precipitate severe withdrawal. Methadone is excreted more rapidly by urine acidifiers e.g. ascorbic acid so can significantly reduce methadone levels. Urine alkalinisers, such as sodium bicarbonate, reduce excretion so can increase methadone levels.

### Assessment in primary care

A full assessment should be undertaken for all patients in the usual way (see Clinical Guidelines<sup>1</sup>). It is important to decide who is going to undertake the full assessment and with whom that assessment will be shared in order to avoid delay and unnecessary duplication. This needs to include a full drug and alcohol history and planning how to manage other drugs, alcohol and other health needs such as hepatitis C.

Assessment should be an ongoing process and not a barrier to treatment. Primary care is ideally suited to carry out assessment as a patient can be seen and much information gathered in several ten minute slots. This is a difficult period for the patient in which they can easily become distressed at unreasonable delays in providing treatment. It is important to try to convey to the patient that you are interested and willing to provide them with medical care and treatment, and to explain to them

that you will try to make the assessment process as easy and fast as possible while remaining safe and individually appropriate. The information that is vital to obtain early in the assessment is current and past drug use, previous treatment and confirmation of opioid dependence.

- Data sent by data transfer or spreadsheets is collected by the National Drug Treatment Monitoring System (NDTMS), now run in England by the NTA, or by a Drug Misuse Database form in Scotland (SMR24 form) or Wales. The required data should always be completed at assessment. These systems provide valuable information on trends in the misuse of drugs. Because the data is attributable through partial identifiers, informed consent is required.

## 5. Choosing between maintenance and detoxification

Choosing between maintenance and detoxification occurs at many points during treatment, starting at the first assessment and then at various points as appropriate. Methadone can be used as a maintenance intervention or as a detoxification agent, but is primarily now used as a maintenance drug. Methadone is probably no longer seen as the automatic first-line treatment for all patients wishing to detoxify from heroin. Many find that buprenorphine and lofexidine enable easier assisted withdrawal, although the evidence is not overwhelming.<sup>35</sup> It is important to consider the views of the patient if they express a particular preference for any of these medications.

**Maintenance** is suitable for patients who want to stop using illicit opioids but are unable to achieve abstinence from all opioids at present. Prescribing is offered long-term, at effective doses (usually between 60 to 120 mg daily) individualised for each patient. The goal is harm reduction and stabilisation of life-style. It may also be prescribed on harm reduction grounds to those wanting to reduce their consumption of illicit opioids. The most powerful evidence base for methadone is for long-term maintenance, with retention in treatment being an indicator for better outcomes.<sup>9, 14</sup> Enforced detoxification or enforced dosage reduction has been shown to be ineffective.<sup>28, 40</sup>

**Detoxification** can be attempted with highly motivated, willing patients who wish to detoxify from all opioids. However, the likelihood of success with methadone will be reduced if the process is too rapid because of the long-acting nature of the drug and its prolonged withdrawal profile. It is important to assess whether the patient's circumstances are conducive to maintaining abstinence and to advise on the timing of withdrawal accordingly. Where circumstances are adverse, such as patients who are homeless or awaiting court, a further period of maintenance should be advised with support to achieve appropriate stability and psychosocial change before attempting detoxification.

There is a high relapse rate to heroin use and as such detoxification should always be seen as a stage in the process and not normally be seen as a stand-alone treatment modality. It should never be imposed, particularly since recent research has shown high mortality rates among those detoxified.<sup>41</sup> Detoxification should be followed by a package of care, which can include: in and outpatient rehabilitation, relapse prevention, support, self-help groups and counselling. It is crucial to warn of the potential loss of tolerance to opioids after a detoxification – relapsing to heroin after a period of abstinence may be fatal. If patients are moving from maintenance to detoxification they may need to reduce their dose of methadone before transferring to another drug such as buprenorphine. Lofexidine is still sometimes used but the evidence for its effectiveness is poor, especially used as a single agent. If in doubt seek specialist advice.

## 6. Starting and titration of methadone

**Always confirm opioid dependence before starting methadone.**

**The risk of death from methadone is highest during dose induction and after detoxification or a period of abstinence.**

**Dose induction – ‘start low, go slow.’**

**Explain to the patient why you are being cautious during dose induction.**

**Methadone saves lives but can also kill.**

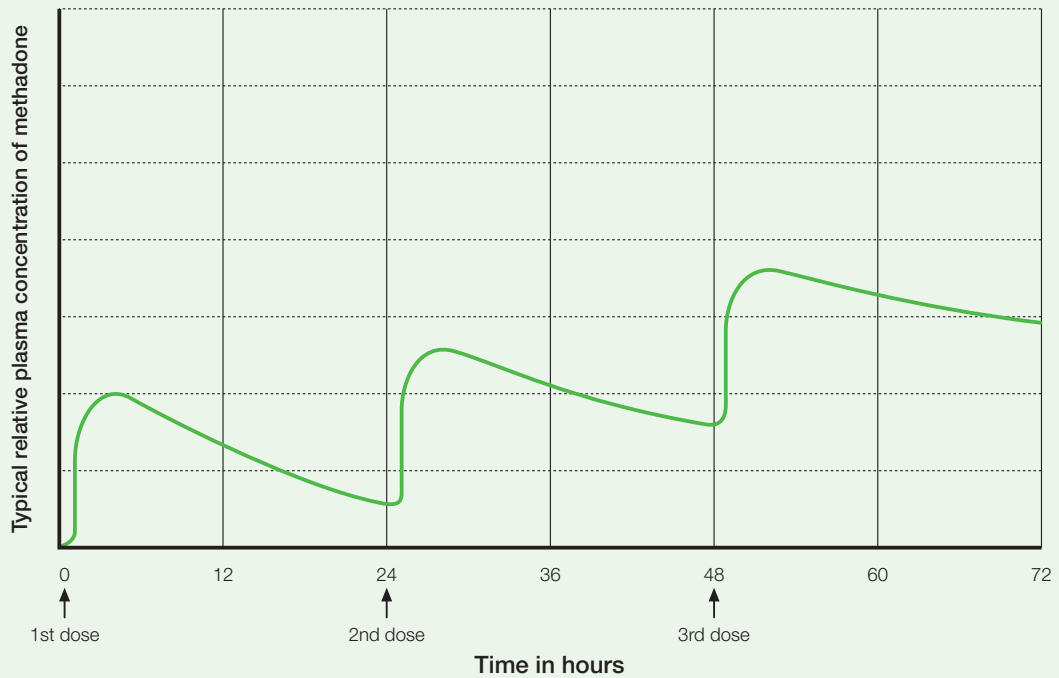
The purpose of titration is, in a safe manner, to establish the patient as quickly as possible on a dose of methadone that prevents opioid withdrawal, reduces the need to take additional illicit opioids and keeps side-effects to a minimum. Methadone dispensing and dosing should aim to avoid the dangers of overdose and diversion. Insufficient dosing may increase the risk of additional illicit drug use and hence diminish treatment effectiveness and increase accidental overdose risk.

If you are just beginning to care for opioid dependent patients, a decision to start methadone for the first time should be taken with advice from a specialist service or from a colleague with a special interest.

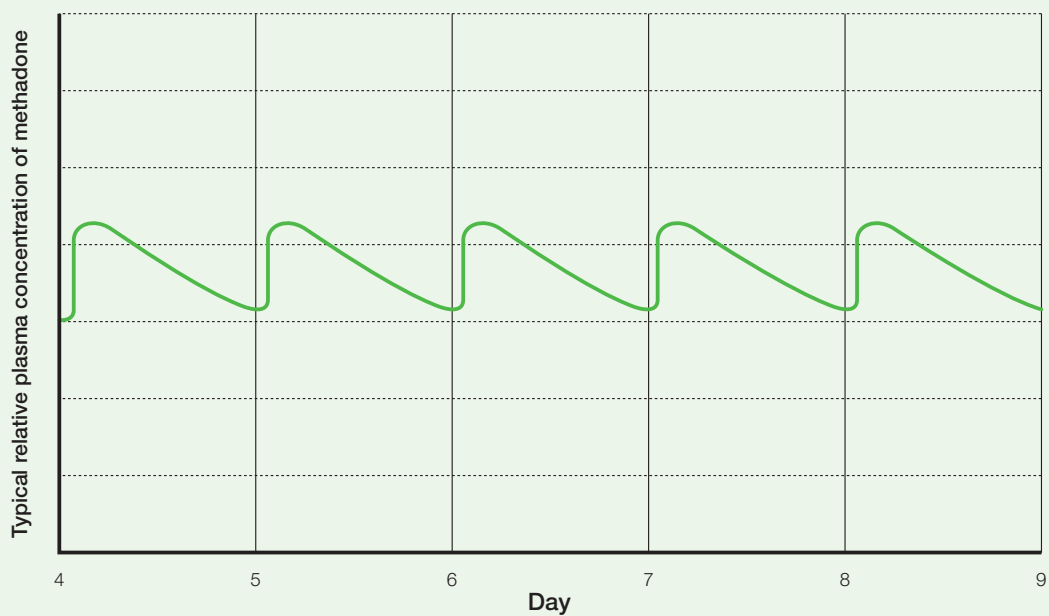
If you want to start a patient on methadone it is not difficult if done with care and remembering a few basic principles:

- Methadone is excreted very slowly during the first few days of treatment in methadone naïve individuals.
- It normally takes four to five days for plasma levels of methadone to stabilise after dose commencement, but it may take up to ten days to finally reach steady state, which can increase the risk of overdose during the early stages of treatment.
- Methadone should always be started on a low dose, on supervised consumption and increased under regular review until the correct stabilising dose for each patient is reached.
- Don't increase the dose without a practitioner seeing the patient, which needs to be frequently, up to daily, in the beginning.
- Risk of overdose is increased by using other drugs, such as heroin, benzodiazepines and alcohol on top of the methadone, with particular risk from injecting drugs.
- A number of factors can alter methadone plasma levels including gastric emptying, pregnancy and liver metabolism, which can increase the risk of overdose.

### First three days of dispensing, for oral methadone, with once-daily dosing (doses at 0, 24, 48 hours)



### Once-daily dosing of oral methadone at steady state



Once steady state is reached blood levels vary little but the patient may be aware that levels are lower just before taking the next dose.

Figure 1: Steady-state methadone concentration reached in four to five days.<sup>42</sup>

Illustrations adapted from 'The Methadone Briefing' (1996) – [www.exchangesupplies.org](http://www.exchangesupplies.org)

**Before starting methadone oral solution for the first time:**

- Confirm opioid dependence by history, examination and toxicology.
- Check for objective signs of opioid dependence including dilated pupils when the patient is withdrawing and check for injection marks.
- Carry out body fluid toxicology (usually urine, sometimes using oral fluid swabs) to confirm that there are opioids in the system.
- Starting methadone on the first presentation is usually not possible as results, other than on-site tests, often take days to return. Use this time to continue the assessment, provide harm reduction advice and ask the patient to keep a drugs diary.
- Starting methadone is always important, occasionally urgent and needs to be done as rapidly as it can safely be done to avoid drop out from treatment.
- Supervised consumption should be used for the titration period and at least the first three months.
- **Never** start methadone without evidence of opioid dependence.

**If opioid dependence is confirmed and a substitute prescription of methadone oral solution is appropriate, there are a number of different methods of initiating methadone treatment. The ideal is as follows:**

- Start with 10 to 30 mg methadone daily, based on the assessment of the person's opioid tolerance, the frequency of use, the route of administration and the use of other drugs such as benzodiazepines and alcohol whilst remembering the long half-life of methadone.
- If tolerance is low, or uncertain then starting doses of 10 to 20 mg should be used.
- Deaths have occurred in individuals on levels as low as 40 mg.
- When undertaking the induction in general practice, it is preferable to see the patient frequently at the outset, often daily, so that a series of further assessments can be made to judge the cumulative dosing effects. However this may be difficult to arrange in many general practices and there are alternatives.

They are:

1. See the patient as frequently as possible, which may be every few days and only increase the dose then.
2. Ask for a drugs worker to come into the surgery daily for the titration period.
3. Ask the local specialist service to undertake the titration and take over the prescribing only once the patient has been stabilised.

- A total increase for the first week in treatment should not usually exceed 30 mg.
- Methadone can now be prescribed by qualified 'supplementary prescribers' (e.g. specialist pharmacists or nurses) where this arrangement is agreed by the doctor and the patient and detailed in the care plan.

At any dose, but particularly in the titration period, use of alcohol, sedatives, particularly benzodiazepines, and/or short-acting opioids (e.g., heroin, morphine, dihydrocodeine, oxycodone) during induction significantly increases the risk of overdose death.<sup>43</sup> The patient must be informed of these risks. Written patient information leaflets on overdose risks are available. Commence dose induction at the start of the week and see the patient frequently during the dose induction period. The patient should also be advised that it can take a few days to feel comfortable on methadone, but this point will be reached.

It is quite common for illicit drug use to continue during the early stages of treatment and patients should be encouraged to refrain, as far as possible, from other illicit drugs. During dose induction ensure that the patient realises that they will get higher doses as necessary.

In one Australian study, 90% of those who died during stabilisation were also using other drugs. The Australian guidelines for induction of methadone suggest that it is possible that being overcautious may paradoxically increase the risk of a fatal overdose.<sup>44</sup>

**Measures to reduce risks:**

- Make sure the patient understands the long acting nature of methadone and that it interacts with other sedating drugs and alcohol.
- Arrange for the patient to receive methadone oral solution by supervised consumption during the titration and continue this for at least the first three months, unless there is a valid reason to change.
- In view of the difficulty in calculating opioid tolerance, the prudent methadone-dosing advice is to see the patient frequently in the initial stages and to 'start low and go slow'<sup>45</sup> and this can include observation one hour after the first dose, where there are concerns and this is feasible.
- Ask the patient what they have been using on top, including alcohol and benzodiazepines, respond accordingly by cautious gradual increase. When given good information about safety many patients may be able to reduce their other drug use when starting a methadone prescription.
- Remember that alcohol use may not subside automatically when methadone is prescribed in alcohol dependent patients. Alcohol use should be assessed specifically and help with alcohol withdrawal offered to those who need it.

- If people are drinking heavily then methadone may not be appropriate but if started, regular monitoring is required.
- Sleep difficulties must be taken seriously and advice about sleep hygiene should be given but avoid the prescribing of sedatives. Insomnia associated with heroin use often resolves when adequate doses of methadone have been established.
- Advice about the risks of injecting should also be given.

## 7. Stabilisation of methadone dose

**After stabilisation, the patient should feel comfortable throughout 24 hours with no subjective or objective withdrawal before doses and no sedation or euphoria after doses.**

Stabilisation involves finding a suitable dose that keeps the patient engaged in treatment without the need to supplement with heroin and other drugs. After stabilisation, the patient should feel comfortable throughout 24 hours with no subjective or objective withdrawal before doses and no sedation or euphoria after doses. The aim is to enable the patient to put their dependence into the background while tackling any associated health or social goals. Attempts to keep the dose minimal, leaving the patient with daily morning craving or disturbed sleep due to falling serum levels, are counter-productive.

The large part of titration can be undertaken in two weeks. Final dose stabilisation may take several weeks, but it is important that this is achieved as quickly but as safely as possible to prevent patient drop-out. After the first two weeks, the patient should be seen every few days to allow a steady state to be reached after a dose change. The dose should increase by between 5 to 10 mg each time, or up to a 30 mg total increase per week.<sup>1, 43</sup> It will take between four to five (and up to ten) days to reach steady state and to see the full consequences of any dose increase or decrease. After the initial induction (one to two weeks) the dose can be titrated more rapidly to the therapeutic level.

Once at a steady-state level, methadone should be present in sufficient concentration to maintain a therapeutic 'comfort range' throughout the dosing interval.<sup>46</sup> There is no clear relationship between prior 'heavy' misuse of an opioid and the methadone dose ultimately required for stabilisation.<sup>45</sup>

## 8. Maintenance methadone prescribing

**Optimal outcomes with methadone maintenance occur:**

- **When the dose is right, usually between 60 to 120 mg.**
- **Stable relationship with a key individual e.g. GP or drug worker.**
- **When a range of non-pharmacological interventions, such as counselling and lifestyle support, are also available.**
- **Together these enhance the likelihood of positive outcomes from methadone maintenance treatment.**<sup>9, 47</sup>

Methadone maintenance is an effective, evidence based treatment for opioid dependence. Outcomes for MMT have been shown to be influenced greatly by how it is delivered, and to be optimised by factors such as retaining patients in treatment and prescribing at high enough dosages.<sup>9, 14, 17, 18, 29</sup>

A recent Cochrane review confirms that doses of 60 to 100 mg daily are more effective than lower doses at retaining patients in treatment and in reducing use of heroin and cocaine while in drug treatment. The review concludes that to find the optimal dose is a clinical ability, but clinicians must consider these conclusions in treatment strategies.<sup>48</sup> The Clinical Guidelines state that on average the dose range for maintenance, which shows the greatest benefits for most patients is between 60 to 120 mg daily.<sup>1</sup>

A further Cochrane review considered the evidence of buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence.<sup>49</sup> The review considered the outcomes of retention in treatment and suppression of heroin use and concluded that methadone at optimal doses was still the gold standard for maintenance, although buprenorphine is also an effective intervention for use in maintenance. It must also be recognised that methadone is cheaper than equivalent doses of buprenorphine. With the limited evidence of the superiority of either medication for particular subgroups, there is a strong argument that under the current pricing arrangements, where there is no patient preference, or other convincing clinical reason to favour buprenorphine, methadone should be used as first line treatment for opioid maintenance therapy.

Due to individual factors some patients require significantly greater or lower doses for treatment success. If very high doses are required a specialist referral may be required which may include serum methadone level testing. In particular, patients on enzyme inducing drugs that increase methadone metabolism, such as rifampicin and phenytoin, may require higher doses of methadone while being co-prescribed with an enzyme inducing drug.

Care must be taken, with consideration of reduced methadone dose, if co-medication is discontinued. While on methadone maintenance it is important that there are regular reviews of treatment. In addition care plans and goals should be reviewed at about three monthly intervals.

#### Reviews include:

- Current drug use, including cannabis, and should include checking for injecting sites.
- Current alcohol use, including a typical day.
- Update and check hepatitis and HIV status as appropriate and complete any outstanding vaccinations or screening required.
- Patients should be asked if they would like to make any life changes and be supported to do so.
- They should be made aware of, and be able to access, a range of local social and psychological services.
- Harm reduction advice needs to be given on any other drug use, such as cocaine, alcohol and/or benzodiazepines.
- The usual general medical services should always be offered (including BP checks, smoking interventions, contraception, smears, etc).
- Assessment of progress against goals, review and renegotiation of care plan.
- Review of partner and any other family members, particularly children.

NB: People on MMT have the same and some additional health risks as any other patient and should have their hypertension, diabetes or arthritis, for example, treated and monitored in the same way against practice standards.

Methadone treatment research shows that in the UK doses are on average less than 50 mg daily and only a quarter of patients receive over 60 mg suggesting inadequate dosing is common.<sup>2</sup>

#### Frequency of dosing for maintenance

- Methadone should be prescribed on a daily regimen during the start of treatment.
- It should usually be dispensed daily under supervision for at least the first three months and until there is evidence that the patient's health and lifestyle are stabilising.
- Patients who have been stable on supervised consumption for three months, who have no high-risk drug use (e.g. ongoing use of heroin, other injecting drug use, alcohol or benzodiazepines, frequent intoxicated presentations, recent history of overdose) may be considered for a daily take-home regimen.

- When stopping supervised consumption, the methadone should normally be continued on a daily collection basis for a period of time.
- When take-home doses are given, patients should be warned of risks to children and non opioid-dependent individuals of overdose and methadone should be dispensed in child safety medicine bottles and stored safely, preferably in a lockable box or cupboard.

#### Instalment prescribing

Instalment prescriptions should be written using blue FP10 (MDA) prescription forms in England and Wales and in Scotland using a GP10 (3). Prescriptions should initially stipulate daily supervised consumption (see below) and subsequently daily pick up. Frequency of dispensing may be relaxed when patient has achieved stability, although the dispensing interval should normally be two or three times a week.

#### The importance of the pharmacist

Pharmacists are key individuals in the success of methadone treatment. They will see the patient much more often than the prescriber and can provide additional important support. Close liaison with pharmacists should be maintained. They should only dispense to the named patient or a collector who has permission from the patient. The doctor can also ask the pharmacist to report missed doses and the doctor should inform the patient that this will happen.

Ideally before issuing a prescription to a new patient, the prescriber should make contact with the patient's nominated community pharmacy to confirm dispensing arrangements.

Some pharmacists limit the number of people they are able to take on and/or supervise in a day and some shared care schemes work on the basis of available supervised spaces per pharmacy.

Methadone is a Schedule 2 controlled drug therefore clinicians are reminded that the Misuse of Drugs hand writing requirements apply. There may be changes to such requirements following consideration of the Shipman Inquiry reports.

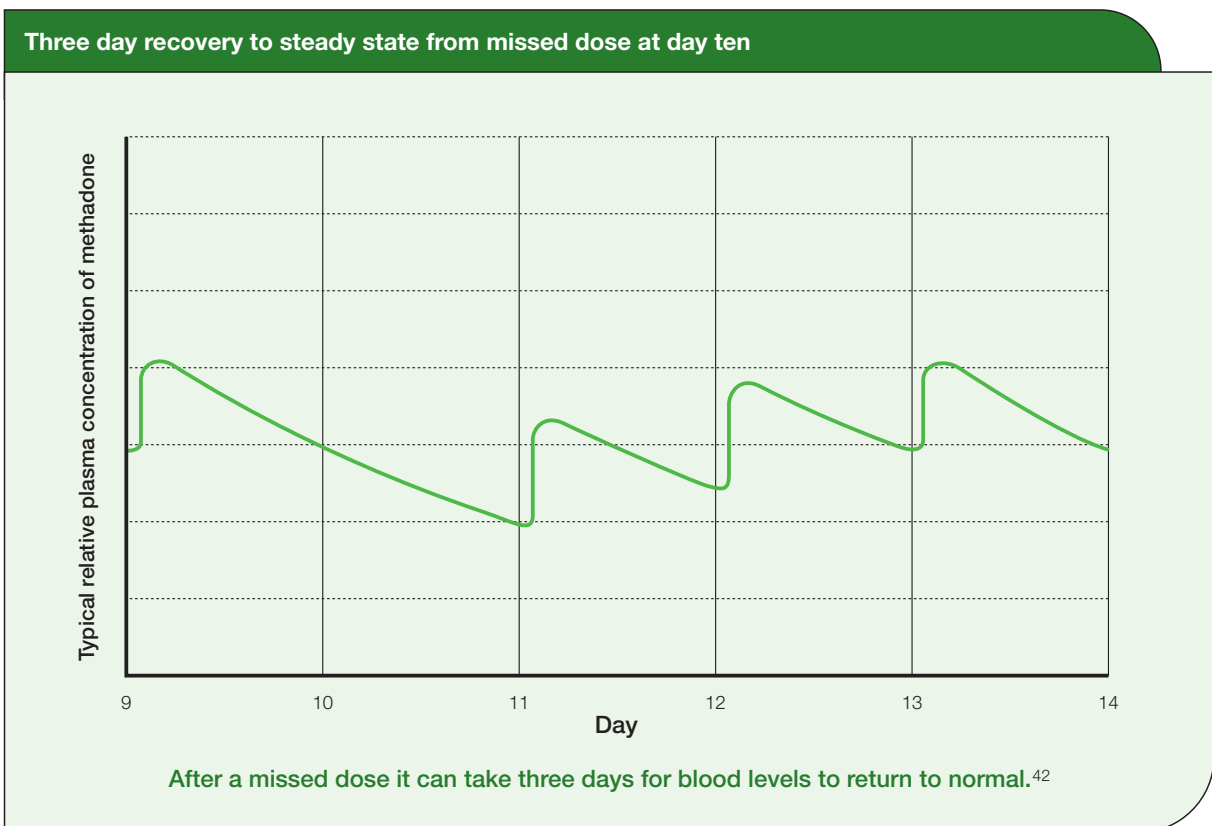


Figure 2

Illustrations adapted from 'The Methadone Briefing' (1996) – [www.exchangesupplies.org](http://www.exchangesupplies.org)

### Missed doses

Missed doses can lead to loss of tolerance and prescriber's need to be informed of any missed dose by the pharmacist. It can take up to three days for the blood levels to return to normal:

- If a patient on a daily dispensing regimen misses a pickup from the pharmacy, the patient should return the next day as usual for their next dose. The missed dose should not be replaced.
- If doses are missed for more than three days then treatment should be reviewed to discover how the patient has managed without methadone and retitration from a lower dose considered. This is due to the loss of tolerance that may have occurred.
- If missed for five days or more a reassessment must be undertaken and the titration period restarted from the beginning.
- If a patient is picking up several days methadone at one time and misses a pick-up, it is now possible to issue a directive to the pharmacist enabling them to dispense the medication on a subsequent day, minus the missed dose. If this occurs more than once, the patient should return to daily dispensing, probably supervised.

- Lost or stolen prescriptions should rarely be replaced and it may be useful to report this to the Primary Care Trust.
- If this occurs it may be worth considering posting or delivering prescriptions to the pharmacy.
- Patients who repeatedly miss doses should have their treatment reviewed. If on less than daily dosing the first step would be to revert to daily supervised dispensing.

### Continuing supervision:

- Occasionally patients do not keep appointments with either their doctor or key worker.
- Maintaining the patient in treatment may be paramount as long as some evidence of harm reduction can be demonstrated.
- This can be achieved by keeping the patient on observed consumption of their methadone and the pharmacist may become the key worker.

**Split doses**<sup>33</sup>

There is evidence that some people in maintenance treatment are more settled on split doses, particularly during the third trimester of pregnancy. Others taking enzyme-inducing medication, such as the anti-convulsant, phenytoin for epilepsy, may experience a drop in methadone plasma levels during the course of 24 hours, when once-daily dosing is used. Patients receiving low doses of methadone may not have stable blood levels of methadone over 24 hours and may benefit from split dosing.

In some people, if they are entering into withdrawal before their next dose, it may be more effective for them to split the methadone dose than have it increased. This can cause problems with supervised consumption, and if in doubt expert advice should be sought. Symptoms of overdose should be explained and the action required in the event of an overdose.

**Supervised consumption and take-home doses**

Supervised consumption should be used as a therapeutic tool at the beginning of treatment (and sometimes at other times during treatment to check dose and tolerance). It should continue where possible for a minimum of three months, unless there is a good reason (such as work, distance to the pharmacy, childcare responsibilities or risk to confidentiality) and until the prescriber is satisfied that the patient has both been stabilised on the correct dose and is maintaining a reasonable level of adherence.

Before taking a patient off supervision a review should be undertaken to confirm stability and discuss future treatment. The pharmacist should be included in this discussion. Only in rare situations is it appropriate to continue supervised consumption indefinitely (e.g. severe mental illness with risk of overdose, severe social instability, and frequently missed doses). The introduction of take-away doses, when appropriate, allows patients a more normal life, and enhances the development of trust and rapport. It also ensures that there is adequate capacity to supervise new patients in local pharmacies.

There may be cases where supervised consumption may not be appropriate and these should be resolved on an individual basis. Supervised consumption can be reinstated at any time if there are concerns. Ultimately the need for supervision is a clinical decision, taken by the doctor in conjunction with the patient, pharmacist and others working the patient. Always make appropriate arrangements with the pharmacist in advance of the patient's arrival.

There are benefits and problems with take-home doses. Benefits include the practical and psychological advantages of greater patient control. Problems include the possibility of poor compliance and diversion on to the illicit market.

Once the patient is sufficiently stable, less frequent dispensing or take-home doses can be given. If giving take-home doses, it may help to change the frequency of pick up gradually, to three times weekly and then twice weekly, assessing stability at each stage. It is rarely appropriate to arrange for methadone to be dispensed less frequently than this, unless exceptionally, for travel or work.

**Storage and safety at home**

Once a patient is receiving take-home doses, then there may be concerns about the amount of methadone that is dispensed at once. There is no legal upper limit for this, but caution and common sense should prevail. Different decisions are appropriate for different patients, based on their circumstances. Before take-home doses are considered the prescriber needs to be assured that supplies will be stored safely and away from children. Safe storage should be discussed with all patients particularly parents, by both clinician and dispensing pharmacist. Symptoms of overdose should be explained and the action required in the event of an overdose.

**Screening**

Can be done by i) urine ii) oral fluid swabs and iii) hair analysis.

**i) Urine testing**

Confirming the presence of opioids in the urine is essential at the start of treatment. Different drugs stay in the urine for different lengths of time e.g. heroin 48 hours, methadone on maintenance doses seven to nine days.

The frequency of urine testing, both to confirm the use of methadone and assess other drug use (such as cocaine and benzodiazepines) thereafter depends on clinical progress. It should be undertaken at least every three to four months and no less frequently than bi-annually.<sup>1</sup> During induction and periods of instability or other drug use, urine tests need to be done more frequently and can help as a therapeutic tool.

Research studies have shown a high rate of concordance between a patient's report of their urine contents and the lab result, where there is not a threat to the patient's treatment programme.<sup>9</sup> False positives and negatives do occur; especially with on-site urine testing and results should always be used in conjunction with clinical signs, such as signs of withdrawal, injecting sites etc. On-site testing is non-specific and can only indicate the class of drug in a non-quantitative way. Urine testing cannot alone confirm heroin dependence. Use of over the counter or prescribed medicines, e.g. cocodamol or codeine phosphate, can also give positive results.

There is a widespread fear among patients that providing a positive urine for non-prescribed drugs, including heroin, may lead to the removal or reduction of the prescription for methadone and even discharge from treatment. However there is a strong consensus that it is inappropriate and ineffective for a GP or others to 'punish' a patient in this manner. Indeed an increase in methadone may be needed if opioids are being used to treat early onset withdrawal. In discussion with the patient, the results should be used to inform decisions about the patient's response to the treatment. Even patients who continue to use illicit drugs may benefit from harm reduction in other areas. They should however be warned about the risks of overdose.

A negative result for methadone should lead to further testing and a review of treatment. In most laboratories negative means below a threshold level rather than zero. False negatives do occur in particular with low doses and in pregnancy. If it seems that a patient has not been taking their prescribed dose, then it is important to re-assess, and if appropriate re-titrate or reduce the prescribed dose and return to supervision.

#### Reasons for asking for a urine test could be:

- Initial confirmation of opioid use as part of the assessment procedure.
- To confirm a patient's suitability to end supervised dispensing or need to return to it.
- To inform a planned discussion about a patient's progress in treatment.
- For court reports (after discussion with the patient about this).
- At the request of the patient, e.g. to create a usage history.
- To confirm that methadone is being taken (in the first year every two to three months then every three to four months moving to a minimum of every six months).
- To gain more information about other drug use and to monitor this.
- To confirm parents drug use in child protection cases.
- As part of comprehensive patient record keeping.

#### On-site urine testing

Most urinalysis procedures are carried out using gas chromatography in specialist laboratories and there is a therefore a delay in receiving a result. It can therefore be very helpful to have a supply of on-site urine testing strips that provide a basic guide to the drugs being used within a couple of minutes. This is a screening tool and is not confirmatory.

#### Providing urine specimens

It is rarely necessary to watch patients while they are passing urine for analysis, as it is undignified for both patient and professional and can give rise to mistrust and suspicion. It should be done with the patient's consent. It is sometimes needed in court cases and specialist advice should be sought if there is an indication for observed urine.

There are several ways in which it is possible to be reasonably confident that a sample has been freshly passed – e.g. checking the temperature of the sample. If there are any concerns or a court order requests these then mouth swab tests should be used.

#### ii) Mouth swabs tests (oral mucosal transudate)

Mouth swab tests of oral fluid provide the same information about recent drug use as testing urine. They are less invasive, more convenient, and they preserve patient dignity. However they can be more time consuming to take and have a shorter detection window than urine (about 24 to 48 hours for heroin compared to four days for urine).

#### iii) Hair testing

Hair testing can provide a longer overview of drug use over a period of months, with a quantitative result. It can only however show an average drug use over each month. It is expensive, and takes several weeks to obtain results and tends to be used in the Criminal Justice System or in child custody cases. Interpretation of the results is complicated and may require specialist input.

#### Addressing continued heroin and other drug use

Some patients may find it difficult to stabilise and be maintained on methadone and this may be evidenced by numerous phenomena including:

- Drug positive urine screens.
- Heavy alcohol usage.
- Frequently intoxicated presentations.
- Overdoses and presentations to Accident and Emergency Departments.
- Frequently missed doses.
- Physical evidence such as fresh track marks.
- Mental deterioration, perhaps associated with increased use of other drugs.

Such a pattern of events requires a review of treatment, re-visiting the care plan and reviewing the objectives. This may involve dose level adjustment, renegotiating the short term treatment goals with the patient, altering the dispensing regime, referring for psychosocial interventions, increasing support and harm reduction advice about alcohol, other drug use (such as cocaine and benzodiazepines), utilising alternative pharmacotherapies

(e.g. buprenorphine) and the use of non-pharmacological treatment.

In some cases referral to a more specialised service may be needed. This may also be related to unrecognised mental health problems. Withdrawal of maintenance treatment is associated with poor outcomes and should be considered as a last resort. It should only happen if it is determined through clinical observation that the treatment is providing no benefit and there is not likelihood of any benefit to the patient if it is continued or that it is detrimental to the patient to continue.<sup>9</sup> It may also be helpful to discuss such cases with colleagues and specialists before taking such actions as terminating treatment.

## 9. Drug interactions

Oral methadone is generally very well tolerated with minimal drug interactions but interactions are becoming increasingly important as new drugs are developed and more complicated regimens are used to treat chronic diseases. The main drug interactions of methadone are associated with its central nervous system (CNS) depressant activity and liver metabolism. Deaths have also been reported from interaction of methadone which can prolong the QT interval and other drugs that do this such as phenothiazines.

### Benzodiazepines

Taking benzodiazepines with methadone may cause additional CNS depression and result in enhanced sedative effect. Large numbers of opioid drug users also use benzodiazepines (between 40 to 90%). Deaths involving methadone are frequently associated with concomitant use of benzodiazepines and/or alcohol.<sup>36</sup> While it may occasionally be advisable to prescribe benzodiazepines with methadone, caution is recommended, and thorough assessment and on-going review plans should be in place. Benzodiazepines should usually be prescribed on a short-term, reducing basis.

### Alcohol

Alcohol intake may alter the metabolism of methadone, increase CNS depression and result in serious respiratory depression and hypotension. Alcohol is a high risk factor for toxicity especially binge or high level dependent use. In late stage alcohol misuse there may be impaired liver function and reduced methadone metabolism, requiring reduction in methadone dose. Alcohol use should be assessed specifically and help with withdrawal offered to those who need it.<sup>50</sup>

### Other opioids

Mixing methadone with other opioid agonists or other central nervous system depressants can be dangerous. Caution is advised, as are thorough assessment and review procedures.

### Anti-depressants

Some anti-depressants, including tricyclic antidepressants, should be prescribed with caution due to possible enhanced sedation. Serotonin reuptake inhibitors (SSRIs) theoretically raise serum methadone levels but do not (except fluvoxamine) cause sedation. Monoamine oxidase inhibitors (MAOIs) are now very rarely used and should not be prescribed with methadone.

### Cocaine

There are few reports of a significant interaction with cocaine but cocaine does accelerate methadone elimination. Cocaine is also associated with cardiac rhythm disturbances and is best avoided when on methadone. Risk of accidental overdose has recently been linked to the use of these substances concomitantly. Also cocaine is often included in poly-drug use which increases problems.

### Opioid antagonists and partial agonists

Opioid withdrawal syndrome is precipitated by the use of naltrexone and naloxone and to a lesser extent buprenorphine.

### HIV medications

As with other opioids, patients on methadone being treated with HIV combination therapies may require dose levels to be adjusted but these adjustments are likely to be minor and in keeping with titration principles, sufficient to ensure patient comfort.<sup>51</sup> It may be useful to offer prescribing treatment in conjunction with a HIV specialist.

Enzyme induction by some HIV medications may necessitate a higher dose of methadone due to increased metabolism. With nevirapine, efavirenz, abacavir and nelfinavir an increase in methadone could be needed and zidovudine concentration and side-effects are increased. See further guidance in the British National Formulary and from HIV prescribing guidelines.

### HCV medications

HCV medications such as pegylated interferon and ribavirin are usually well tolerated by patients on methadone. Sometimes side-effects can mimic opioid withdrawal symptoms and methadone dose is increased.<sup>52</sup> Depression is a common side-effect of hepatitis C combination therapy, as well as opioid dependence so caution is required. Regular liver function tests and full blood count are advised.

### Tuberculosis treatment: rifampicin

Rifampicin reduces methadone levels by stimulating the hepatic enzymes involved in methadone metabolism. Cases of severe withdrawal have been reported.

### Anticonvulsants

Phenytoin and carbamazepine cause a sharp decrease in methadone due to enzyme induction.

## 10. Methadone and other medical conditions

### 1. Blood-borne viruses

- Methadone is safe to use when the patient is hepatitis B or C positive or HIV positive (for interactions with specific medications see above), but LFTs should be monitored, particularly if the patients clinical condition changes.

### 2. Dual diagnosis (co-morbidity of substance misuse and psychiatric illness)

- Methadone can be used in severe, moderate and mild psychiatric illness if the patient is opioid dependent and understands the treatment.
- About a third of opioid users suffer from mild to severe mental health problems, including anxiety and depression.
- A minority (about 10%) have severe enduring mental health problems that usually require joint working with psychiatric services.
- Entry into methadone treatment has a significant positive effect on their psychological well-being.
- A proportion of opioid users presenting at services have suicidal or self-harm risks.
- The risks of accidental or deliberate overdose, and of intimidation or exploitation should be carefully considered when deciding dispensing arrangements.
- Many of the patients with mental health problems will require joint working with psychiatric services and others.
- Drug interactions with psychotropics should be remembered.<sup>3</sup>

### 3. Chronic and acute pain

- Opioids are strong analgesics and some patients begin their use of opioids to help chronic pain.
- If pain is present when they commence methadone, a larger dose can be used to manage the addiction as well as treat the pain. If being used as analgesia it is recommended to split the dose to three or four times a day.
- A patient currently maintained on methadone requiring analgesia for the relief of pain, will need at least the usual dose and frequency of analgesia, and may require greater amounts due to opioid tolerance. Pain relief should be titrated against pain and balanced against observed toxicity signs e.g. sedation.
- Methadone 1 mg/ml is a weak analgesic but increasing the methadone can be tried as a pain relief.
- Morphine is useful for analgesia, but if the patient is on 100 mg methadone already, significant doses of morphine may be needed to ensure analgesic effect.
- NSAIDs e.g. diclofenac can be useful.
- Paracetamol is first line for mild to moderate pain.

### 4. Liver disease

- Methadone is metabolised by the liver and its activity may be increased and/or prolonged in individuals with impaired hepatic function.
- It appears safe in patients with HCV as severe liver disease does not increase peak serum methadone levels, despite a prolongation of the apparent terminal half life.<sup>52</sup>
- If there is abnormal liver function (as evidenced by lowered serum albumin or total protein) or evidence of cirrhosis, proceed with caution and seek specialist advice.
- Reduced platelet count is the best indicator of cirrhosis. Altered liver function tests are not well correlated with the presence or absence of cirrhosis.
- In patients with advanced liver disease the risks from controlled methadone are insignificant compared to the risks from street drugs and therefore we should encourage people to use it.

### 5. Fertility

- Methadone treatment may restore fertility in women who were using heroin, so contraceptive advice should also be given.

## 11. Special Groups

### Pregnancy

Methadone treatment is recommended for heroin use in pregnancy as, compared to illicit drug use, it appears to benefit fetal growth and survival and there is less risk of prematurity. These improved outcomes may however be related to improved antenatal care and improved diet and not to methadone alone.<sup>53</sup> Women attending treatment services usually have better antenatal care and better health even if they continue to use illicit drugs.<sup>54</sup>

The rate of stillbirth is higher in illicit heroin users (5% compared to 1%) but there is no increase in fetal abnormalities in opioid users compared to non-users. How best to use methadone in pregnancy is still a matter of debate. Methadone stability is recommended rather than dose reduction due to the high risk of relapse to illicit opioid use and possible loss of stability. Pregnant patients should be maintained on the dose that they are comfortable on and sufficient to get the positive benefits of MMT.

Abrupt withdrawal of methadone is probably best avoided due to the possible risks to the pregnancy such as: miscarriage, fetal distress and premature labour. The evidence that detoxification causes intrauterine death is very weak.<sup>55</sup> There are a few isolated case studies but there is not a good link between detoxification and fetal death. One study showed increased catecholamines in liquor following untreated detoxification. However there is biochemical evidence suggesting stress effect on baby but not evidence that baby was actually stressed to significant extent. There is little data to prove or disprove the effects of detoxification but results from a service in Glasgow suggest detoxification is acceptably safe at any speed at any stage of pregnancy and this is much stronger than evidence to the contrary.<sup>56</sup>

The important conclusion that should be recognised is that whether or not the woman undergoes methadone reduction or detoxification, or what stage of pregnancy, or what speed she does this at, should be dictated by what is appropriate for her circumstances/wishes/ability to cope etc and not only by any consideration about what is or isn't safe for the fetus. Also we shouldn't impose limitations on management plans that women choose on the basis of unsubstantiated risks. It is also important to continue the current dose of methadone if the woman is arrested or admitted to hospital to avoid any problems and to prevent stability being lost.

There is some suggestion that an increase in dose may be needed in the third trimester to maintain pre-pregnancy blood levels due to the increase in blood volume (haemodilution effect) in pregnancy, increased liver metabolism and increased glomerular filtration rate. But again there is little evidence to support this. There is evidence of reduced serum levels but this is not necessarily indicative of less effect.

A maternity drug service in Glasgow has found that most women manage greatest reductions in the third trimester and other centres following their advice are finding the same thing.<sup>57</sup> But always check for signs of withdrawal and if detected, make a small (2 to 5 mg) increase in methadone dose. Pregnant women may sometimes benefit from splitting their dose of methadone if signs of withdrawal occur. It is useful to have close liaison between prescriber and pharmacist during the early months of pregnancy when morning sickness may be an issue. This may cause vomiting of methadone soon after it is swallowed and it is essential to ensure quick replacement of prescriptions and it may be appropriate to prescribe a safe anti-emetic.

The primary aim should be to stabilise the patient and prevent injecting. Stabilisation helps to engage the person with antenatal care. Adequate postnatal preparation can then be planned to manage any withdrawal effects observed in the infant. No long-term consequences of opioid withdrawal have been observed in infants born to opioid using women.

### Neonates

At all doses there is a risk of neonatal abstinence syndrome (NAS), which is a generalized disorder presenting a clinical picture of CNS hyperirritability, high pitched cry, rapid breathing, gastrointestinal dysfunction, respiratory distress, hungry but ineffective sucking and excessive wakefulness. It varies with individuals and is not influenced by maternal age or the sex of the baby. Symptoms are less likely to be severe in preterm infants, possibly due to immaturity of the neurological system, and are more severe if the baby is otherwise unwell or irritable for example in association with birth asphyxia, infection etc. While there is not a linear relationship between severity of neonatal withdrawal symptoms and maternal methadone dose in the individual case there is an overall correlation with evidence that the higher the maternal methadone dose the greater the likelihood and likely severity of neonatal withdrawal symptoms.<sup>58</sup> Informed consent to treatment should always be documented in the patient's notes. (But note if the mother withheld consent and the baby is judged to need treatment this could be a child protection issue).

Symptoms generally begin during the first 24 hours (heroin and benzodiazepines only) after birth but can be delayed by up to five or more days.<sup>58</sup> Some have reported a delay in the onset of symptoms for as long as seven to ten days. Methadone tends to cause a delay in the onset of neonatal withdrawal symptoms when compared to heroin. While up to 90% of newborns exposed to opioids during fetal life have some symptoms, only 50 to 75% will require treatment. However the proportion that needs treatment is different in different populations and for example will be higher in areas with higher overall neonatal morbidity, e.g. in Glasgow where there is very severe socio-economic deprivation. Newborns exposed to methadone are more likely to experience symptoms and more often require treatment than those exposed to heroin.

Women using drugs or delivering a baby who experiences withdrawals may suffer severe guilt feelings and they will need help and counselling to address these. Caring for babies that are unwell, including babies with neonatal withdrawal symptoms, can also be more demanding and drug-using mothers whose babies develop withdrawals may need additional parenting support.

### Breast-feeding

Breast-feeding is to be encouraged in all drug-using women, unless they are HIV positive, not only because of the usual advantages but also because some methadone does pass across to the breast milk and this in turn will reduce the severity of any withdrawals the baby is experiencing. Moreover use of tobacco, opiates and benzodiazepines is associated with an increased risk of sudden infant death which is lower among breast-fed babies.

### Parents of young children

Parental drug use can have serious implications to a child at all stages and must be carefully assessed throughout care. As drug use is a chronic relapsing condition this is an on-going process. *Hidden Harm*, the report of the Advisory Council for the Misuse of Drugs on responding to the needs of children of problem drug users, found that daily heroin use, daily alcohol use, regular stimulant use, unstable accommodation and criminal justice involvement are risk indicators for children of drug-using parents.<sup>27</sup> But *Hidden Harm* also concluded that effective treatment of the parent can have major benefits for the child.<sup>27</sup>

The children's needs are paramount but drug use *per se* is not a reason to instigate child protection procedures. Parenting skills may need to be assessed and appropriate support offered where indicated. GPs and others in primary care have an important role in the assessment, monitoring and care of children in families where there is parental drug use. It is essential to use a multi-disciplinary approach with good communication between agencies when looking after parents of young children where drug use is an issue.

Particular attention on safe storage needs to be given to parents on methadone.

### Young people (under 18 years)

Methadone is not usually first line treatment for young opioid using patients (under the age of 18) as their drug use is often short-term and there is less tolerance. Detoxification, with buprenorphine, may be considered as first line plus more specialist services should be involved. Practitioners working in primary care should not work in isolation with children under 13 years and need to involve specialist practitioners in their care.

### Black and minority ethnic groups

Heroin users from BME communities can be marginalised in treatment. It is crucial to develop services to meet the needs of diverse communities.<sup>59</sup> There is also a need to understand how a combination of factors that characterise the lives of many BME people, in particular risk factors that revolve around social exclusion and deprivation, mean that the context within which drug use exists provides an environment in which it can be particularly problematic.

Methadone treatment in primary care is the same for any patient, but primary care services treating patients from different cultural backgrounds need to be aware of this issue and how it may impact upon the user, staff and the service itself. It is not an issue that can be adequately addressed unless there is understanding and services will need to give consideration to service accessibility, appropriateness of service and potential barriers to service utilisation.

### People in prison

People in prison should have access to the same treatment options as in the community, including methadone maintenance and detoxification options.<sup>43</sup> Staff need to have relevant training. A national system in the UK to accommodate universal access to substitution treatment in prisons is currently being introduced.

Methadone maintenance has recently become available at many prisons throughout the world, but usually with a maximum dose of 40 or 45 mg per day, the argument being that these doses are satisfactory in the context of low availability of illicit drugs.<sup>60</sup> However, the only serious research on the subject comes from New South Wales, where they have shown that methadone maintenance is effective in bringing hard-to-reach drug-users into treatment, reducing overdose rate during and after imprisonment, reducing injecting and blood-borne virus infection, and preventing recidivism.<sup>61</sup> The dose range was similar to that used in the community, because initial studies indicated that benefits only occurred when daily doses were above 60 mg/day.<sup>62</sup> Studies are being planned in this country, but until they take place, it is probably safest to assume that the effective dose range in prison is the same as elsewhere. Currently this issue will need to be determined locally by practitioners working in prison health.

Also staff need to remember the dangers of detoxification in prison, with increase overdose risk on release.<sup>63</sup>

### People admitted to hospital

Patients are often frightened when entering hospital and the GP can help to improve this difficult process by writing a letter with the dose of methadone clearly stated and phoning the admitting doctor to reinforce this.

If the patient is admitted via Emergency Departments in working hours and after proper assessment, checking their dose with the drug user, confirming opioid use via on-site urine test, checking with the community pharmacist and confirmation with the prescriber methadone treatment may be continued only if the prescription is daily dispensed and preferably supervised. Out of hours, if the prescription cannot be verified, if there is any doubt that the person is taking the total prescribed dose or the hospital cannot confirm the dose then titration should be undertaken. Local guidelines should be in place. If not then the local shared care monitoring group may wish to assist in the drawing up of local guidelines.

## 12. Detoxification from methadone maintenance

**Detoxification should always be seen as a stage in the process, never as a stand alone treatment and never imposed. It should always be supported by after-care because of the high risk of relapse, the loss of tolerance and the risk of overdose and death.<sup>41</sup>**

The patient needs to make an active decision to transfer from maintenance to detoxification. The clinician and patient should be clear about the distinction and together they should ensure the patient is actively choosing to undergo detoxification. It is important that the patient has the resources and support to be able to maintain abstinence. Advice on the timing of withdrawal should be offered accordingly. Where circumstances are adverse, a further period of maintenance should be advised with support to achieve appropriate psychosocial change. Detoxification is more likely to be completed in a residential setting and should always be part of a package which will include relapse prevention, counselling, rehabilitation and support.

If the patient wishes, methadone can be prescribed in reducing doses as agreed between doctor and patient until final detoxification is achieved. This slow reduction of methadone is not necessarily the first-line method of opioid detoxification, but some patients may prefer it. If this is the patients preferred method then it is preferable to remain on an optimal dose until the patient has stopped using heroin completely and then reduce the dose at their own pace. Reductions of no more than 5 mg weekly are recommended. It is also possible to reduce the methadone dose to 30 mg and then transfer to buprenorphine which is reportedly easier to withdraw from.<sup>6</sup> Specialist advice can also assist in the timing and choice of method of detoxification.

Enforced reduction in doses of methadone is still a common treatment modality in the UK despite having no supporting evidence base and mounting evidence against its effectiveness.<sup>28</sup>

## 13. Shared care

Treatment of drug-using patients is multi-faceted and often requires a multidisciplinary response. Most drug-using patients now use a combination of drugs (poly-drug use). The treatment of the other drug and alcohol problems must not be forgotten in the case of this group of patients. Methadone prescribing is only a part of treatment and should be undertaken in a planned manner in collaboration with the patient and other individuals and agencies, such as a primary care drug worker and community pharmacist.

Prescribing should not be undertaken in isolation and working within a local support structure for primary care is important from both clinical and medico-legal perspectives.

There is now consensus in the field that care planning in primary care contributes to common goal setting in the treatment of the drug user. It also mitigates against professional isolation. There is a wide variety of models of care planning and indeed models of shared care working. Regardless of setting the support for both the professional and the user who takes methadone should be consistent.

Many shared care schemes are set up to manage opioid users and rarely meet the needs of poly-drug users. Schemes should be encouraged to meet the needs of the individual, not a specific drug.<sup>7</sup>

Supplementary prescribers may play an increasing role in shared care.

## 14. Methadone and driving

Applicants or drivers complying fully with a supervised oral methadone maintenance programme may be licensed, subject to favourable assessment and normally an annual medical review (DVLA, 2004). However, patients will be subject to revocation of their licence for a minimum 12 month period where it can be shown that there has been persistent use of, or dependency on, heroin; morphine; methadone and/or cocaine. Once the 12 month period is completed the applicant will be assessed as to whether they can be licensed whilst on a methadone maintenance programme.

It is the patient's responsibility to inform the DVLA, and it is the doctor's responsibility to inform the patient of this. It is important to record that this advice has been given to the patient.

The DVLA and GMC also state that if doctors are aware that patients continue to drive in a dangerous way, then they should first press such patients more forcibly not to drive. If the patient continues to drive, doctors (at their discretion) should break confidentiality, inform DVLA and inform the patient that they are doing so. This is a very difficult area of practice. Doctors may not want to endanger the relationship with patients, but it would certainly be both tragic, as well as highly problematic, for any doctor,

if patients hurt or kill people while driving in a manner already known to be unsafe.

More information is available on the DVLA website: [www.dvla.gov.uk](http://www.dvla.gov.uk)

## 15. Holiday prescribing

Larger instalments of methadone may be needed for patients going on holiday. If leaving the country a home office export license is required for total amounts over 500 mg, which is usually granted. A doctor needs to write on behalf of the patient to apply for this (see appendix 3). This does not automatically allow importation to the country being visited and some countries do not allow importation. Patients will need also to check the requirements of the country they are entering by contacting the embassy. A prescriber's note outlining the prescription is also advisable for anyone taking methadone out of the country. It is advisable to ask the pharmacist to supply measured daily doses in plastic bottles to minimise the risk of breakage and spillage.

For patients travelling in the UK it may be safer to provide their usual FP10 (MDA) to take to their destination. Phoning the local drug service may be helpful with arranging local dispensing chemists.

For more details see appendix 3.

## 16. Patient education

The properties of methadone as a full opiate agonist mean that it carries the same risks as other opiate agonists. It is therefore important that patients are given full information about its action and effects. This should include effects and unwanted effects, how to start, the risk of potentiation if used with other sedative substances such as alcohol and benzodiazepines, the risks from loss of tolerance post-detoxification or withdrawal (especially following physical illness or imprisonment), risks of using with cocaine and information regarding safety in pregnancy.

Contraceptive advice needs to be discussed with all potentially sexually active drug-using patients, including the use of condoms for protection against sexually transmitted infections.

Advice about fertility returning to normal soon after initiation of treatment, probably related to improved general health and weight gain, should be given to all women commencing treatment. Consideration should be given to providing patients with written as well as verbal information about treatment issues. Some high quality patient information booklets exist about methadone treatment e.g. *The Methadone Handbook*.<sup>64</sup>

Appendix 1 is a leaflet that can be photocopied and given to patients.

## 17. Training

The most important skills needed for managing drug-using patients in general practice are the skills doctors use every day with every patient.

Practitioners should only prescribe and treat at levels of practice with which they feel competent and for which they have received adequate training. There is a full range of national training opportunities, organised by the Royal College of General Practitioners (RCGP) that can be accessed by GPs, pharmacists and other members of the primary health care team, including Part 1 and Part 2 of the RCGP Certificate in Drug Misuse. There are also many other both national and local training opportunities. The minimum training requirement for prescribers should be the RCGP Certificate Part 1 or equivalent.

## 18. Methadone, the Misuse of Drugs Act 1971, the Misuse of Drugs Regulations 2001 and cost

Methadone is defined by the Misuse of Drugs Act 1971 as a class A drug regarding its illicit use. As a medicine it falls within Schedule 2 of the Misuse of Drugs regulations 2001 (as compared to buprenorphine which falls within schedule 3). Consequently it attracts a slightly higher dispensing fee than buprenorphine although the drug itself is cheaper. Both require compliance with the MDA handwriting regulations.

For the latest price of methadone, see the monthly drug tariff for prices. The approximate cost for 500 ml (1 mg/ml) ingredient costs is £7.59p (source British National Formulary, 49, March 2005).

## 19. Handwriting exemptions (NB likely to change post Shipman Inquiry)

If treating 'or likely to treat' 10 or more patients for drug dependence using a blue FP10 (MDA) form (in England and Wales) then a doctor can apply for an exemption from handwriting requirements from the Home Office. Forms are available from the Home Office on request. This is probably going to change because of the overall increase in the number of computer generated prescriptions.

There are a number of rubber stamps and computer packages, which can be used to help the speed and accuracy of filling in the prescriptions. Computer generated prescriptions or stamps are permissible if a doctor has a hand writing exemption but the date and signature still need to be hand written. This requirement may change following consideration of the recommendations of the Shipman Inquiry.

## 20. Further reading

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- b) *Care of drug users in general practice: a harm reduction approach*. Second edition. Edited by Berry Beaumont. Radcliffe Publishing, 2004.
- c) *Drug Misuse and Dependence: Guidelines on Clinical Management*. DoH, 1999.
- d) *RCGP Guide to The Management of Substance Misuse in Primary care*. Edited by Clare Gerada.
- e) *Methadone Guidelines*. Edited by Annette Verster and Ernst Buning Eurometh, June 2000.
- f) *Methadone Matters: evolving community methadone treatment of opiate addiction*. Edited by Gillian Tober and John Strang, Martin Dunitz Publishing, London, 2003.
- g) *Methadone treatment for opioid dependence*. Edited by EC Strain and ML Stitzer, The John Hopkins University Press, Baltimore and London, 1999.
- h) *Drug Misuse and Community Pharmacy*. Edited by Janie Sheridan and John Strang, Taylor and Francis, 2003.

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## Appendix 1

# Methadone in primary care: patient information leaflet

## Important points

- **When starting methadone, your prescriber has to weigh up a number of factors to get to the right dose for you. This process is called ‘titration’, and it means assessing the safest amount of methadone to control your withdrawal symptoms. There is a serious risk of overdose if this is not done with care. You can help by not using other drugs during this period, or telling the doctor if you are uncomfortable.**
- **This is the beginning of a process that can take a few weeks and the dose should continue to be increased until you feel comfortable and don’t need to use heroin on top. For most people, this is usually when the dose is between 60 to 120 mg of methadone.**

**You have been prescribed methadone by your general practitioner (GP) or prescriber. This leaflet aims to give you some information about the drug and how it can help you. There are patient booklets available that can give you more details. So ask your GP or drug worker if they can provide you with one. A booklet is no substitute to talking to your doctor, nurse, drug worker or pharmacist – so, if there is something you need more information about, just ask. They will be happy to try and answer your questions and if they can’t answer your question they may know someone who can. There are many places on the web where you can get more information and we mention a few at the end of this leaflet.**

### What is methadone?

Methadone is the name given to the medication you have been prescribed. Methadone is a long-acting opioid drug which acts in your body for between 24 and 36 hours. It has a depressant effect on your body and breathing, which is similar (though not identical) to heroin, which is also an opioid. It stabilises you and your body by preventing withdrawal symptoms and it ensures you can feel well without using heroin. If you are taking the right dose of methadone, you won’t feel much from heroin if you use on top, and this helps you to reduce your use of street drugs.

### Why methadone?

Methadone is licensed by the Department of Health as an effective treatment for opioid dependence. There is also a lot of medical research that says it is effective and helpful for many people.

### Why has it been difficult to get methadone?

Until recently there was a lot of confusion among doctors about providing methadone treatment. Some believed it should only be used for a short time; others believed it had no place in treatment. This led to situations where many drug users had bad experiences of methadone treatment, and this left them with a bad impression.

Fortunately in most places, this controversy has now ended. It changed because of the sheer volume of research showing that methadone can be very helpful to opiate dependent drug users. And in the last few years,

people getting methadone have been working with treatment providers, the National Treatment Agency, and others to challenge poor practices that are not friendly to patients.

For many people, methadone is very effective. It isn’t right for everyone, which is why it is important to talk about other alternative treatments with your doctor and counsellor. But if you haven’t had methadone from a doctor trained in how best to use it, and who wants to help drug users, then it might be time to give it a go and see if it can help you.

### So what does methadone do?

It stabilises the changes that happen in the brain when you become dependent on opiates. Your brain has natural opiates called endorphins. When you become dependent on heroin, this replaces the body’s endorphins. But if you stop taking heroin, it takes time for the brain to register this and bring back the natural endorphins. It is this lack of opiates (no heroin, no endorphins) which causes withdrawal symptoms.

Sometimes called clucking, or getting sick, it is an unpleasant experience, particularly without any help to reduce some of the worst symptoms.

If you are dependent and taking short acting opiates like heroin, you will get sick about six to eight hours after you last use. But as methadone is long-acting and works for between 24 and 36 hours it will take 24 hours or more without methadone before you start to get sick.

### What is the right dose of methadone for you?

The right dose depends very much on you as an individual. It is partly dependent on your size and age, and to a lesser extent, the amount of heroin or other opioid you are using. The length of time you have used for can also affect the dose you should take. Research shows that the best doses for maintenance are between 60 to 120 mg. The aim is for you to feel comfortable and well without withdrawal symptoms.

### What does methadone maintenance mean?

It means taking the same amount of medication without reducing it. Staying on a regular dose helps you reduce and often stop using heroin or other opiate drugs. It used to be that people were expected to come off methadone after a short time but this led to many people returning to injecting street drugs who had been doing well on methadone. Research suggests that some people need to keep taking methadone over a long period of time to stay well, perhaps for the foreseeable future. However, others do stop taking methadone at some point without returning to using. Keep an open mind and listen to your own feelings. No one should force you to stop methadone if it is clearly helping you to manage your condition.

### Why do people say it is more addictive and more difficult to get off than heroin?

All opiates are difficult to get off. Because methadone is an opiate that has a long duration of action, it takes longer to come out of the body than other short acting opiates. So it takes longer for the withdrawals to start to ease. This is actually why methadone is an excellent drug for maintenance treatment – it lasts a very long time. You get optimum benefit when your body enters a 'steady state' where the amount of methadone in your blood remains constant. This happens in a few days when you take the same amount of methadone regularly at around the same time.

Also, people feel less scared nowadays of staying on methadone if they need it. When people were expected to stop, sometimes without agreement, people felt vulnerable. Some refused to take methadone because they were scared of the possibility of it being cut off. Now the days when patients were forced to come off their methadone have largely ended.

### How do I take methadone?

Methadone commonly comes in a liquid form, which is called methadone mixture or more recently methadone oral solution. It should only be swallowed (taken orally).

### How will methadone make me feel?

It can take an hour for you to start to feel the effects of the methadone you have taken, especially if you took your methadone after a meal. You should feel your body start to relax from any withdrawal-related tension, and you should start to feel comfortable without feeling drowsy or confused. The opiate sensation that you get from taking methadone is unlikely to be as strong as the high you felt when you were using heroin, but as your dose is adjusted you should start to feel comfortable and well and without any feelings of withdrawal. After a few days, you should feel less and less craving for heroin. You will feel a lot healthier if you can stop using illicit heroin and try to manage with just the methadone.

The maximum effect of methadone mixture can take well over an hour to feel. The high that you get while you are taking methadone is not as strong as the high you felt when you were using heroin, but you will not go into withdrawal. It feels different from heroin, but after a few days you should feel less and less craving for heroin.

### Are there any serious side-effects to methadone treatment?

There are very few side-effects to methadone, and all of them can be managed with help and advice. Some people may find they perspire more, particularly around the face. This usually gets better with time.

Constipation is also a possible side-effect, as the medicine acts directly on the gut to slow down the passage of food through the body. Your doctor can give you more advice about this. It is important to drink adequate amounts of water during the day and to eat fruit and vegetables containing dietary fibre.

Methadone does not cause any direct damage to your bones or teeth. The stories you may have heard that methadone 'gets into the bones' are not true.

### Will I have to take my dose in front of the pharmacist?

Taking medication at the chemist in front of a pharmacist is called 'supervised consumption.' Most people will have to take it under supervised consumption to start with as it is the best way of ensuring you are taking your methadone safely and correctly. If you can show your doctor that you are stabilised on methadone (i.e. you are not using heroin or other drugs bought illicitly) there is no reason why you should not ask to have take-home doses of methadone. This should be possible after a period of months, unless there are good reasons such as working or child care for it to be less. Ultimately however, this is a decision that only your GP or prescriber can make.

### **What should I do to keep other people and myself safe?**

Methadone is dangerous to people who are not used to it. The risks are greater if methadone is taken in combination with other depressant drugs. This is particularly true of drugs called benzodiazepines ('benzos' such as diazepam [Valium], temazepam, nitrazepam [Mogadon], or Rohypnol) that are commonly prescribed for sleeping, stress, or anxiety problems. However, it is also true for some other drugs that are sometimes prescribed by doctors e.g. antidepressants like Prozac. Please tell your GP if you are taking any other drugs or prescribed medication.

People often forget that alcohol is a drug too. Like benzodiazepines and the other drugs mentioned, alcohol can be dangerous when taken with methadone. So, if you do have a drink, be very careful not to overdo it. You should not drink more than three units of alcohol (one and half pints of beer or three glasses of wine) for a man or more than two units (pint of beer or two glasses of wine) for a woman per day.

Because opiates can harm and even kill people who are not used to taking them, it is important that no one else takes or gets access to your medication. Like all medicines, but especially with these drugs, it is very important that methadone is stored safely out of the reach of children. A very small dose of methadone can kill a child.

### **What will happen if I use heroin 'on top'?**

Methadone, in adequate doses, reduces any effect from heroin so you may find yourself disappointed. However, you can still overdose, so if you do use heroin 'on top', remember to take great care, as there is a risk of overdose and always use a clean needle and syringe. Talk to your doctor – he or she wants to help you manage this.

### **What will happen if I use cocaine 'on top'?**

This can increase your risk of overdose and is best avoided. If this is not possible, use with at least one other person present and be aware how to manage overdose.

### **What happens if I get pregnant while on methadone?**

Methadone is not known to harm your baby during pregnancy. But if you are taking it at the time of the delivery the baby may experience some withdrawal symptoms. These are uncomfortable and if necessary can be treated but they are not dangerous to the baby. Talk to your GP, prescriber or primary care team member as soon as you find out that you are pregnant, and they will give you the best advice on what your options are. Don't stop your methadone as this will be the worst option for the baby.

### **Can I drive on methadone?**

You need to inform the DVLA that you are receiving a prescription of methadone. You can then drive for personal reasons (not for work) while taking oral methadone after undergoing a short independent medical examination, which will include a urine screen for drugs. The licence will be issued for one year at a time and will need to be supported by a favourable medical report from your doctor. It is your responsibility to do this, not the doctor or the drug worker. If you do not notify the DVLA, continue to drive and your doctor feels you are posing a risk to others on the road they now have to inform the DVLA. Also if you get stopped by the police or have an accident and haven't notified the DVLA, your insurance is likely to be invalid and you could be heavily fined or sent to jail.

## Appendix 2

# Writing prescriptions

All prescriptions for the use of methadone in the treatment of opiate dependence should be written on the form FP10 (MDA), in England and Wales or GP10 (3) in Scotland. This form allows the prescribing of 14 days supply of methadone to be dispensed in instalments.

Incomplete or inaccurately written prescriptions for CDs such as methadone can cause real problems for patients, prescribers and pharmacists. It is an offence for a prescriber to **issue** an incomplete prescription and a pharmacist is **not allowed** to dispense a CD unless all the information required by law is present on the prescription. Therefore, it is in the best interest of all concerned to ensure that the strict requirements of the law are complied with **before** the prescription leaves the practice.

Full details on how to write a prescription for preparations covered by Schedules 2 and 3 of the Misuse of Drugs Regulations 2001 (SI 3998) can be found on page 7 of the British National Formulary (see Controlled Drugs and Dependence).

Prescriptions for methadone must comply with the requirements of Schedules 15 and 16 of the Regulations. These cover the form and the provisions as to supply on a prescription of Schedules 2 and 3 CDs.

### How to write a prescription

Prescriptions for methadone **must** be signed and dated by the prescriber, with the date of signing, and specify the prescriber's address. At present a CD prescription is valid for 13 weeks from the date stated. This means that the prescription can be dispensed within 13 weeks after the date on which it was issued. In addition, it is good practice to write the starting date on the prescription. This will ensure that if the patient is already in receipt of a prescription there is no chance of an inadvertent 'overlap' of dates that could result in a double supply of methadone.

#### The prescription must specify:

- The name and address of the patient.
- The form of the preparation e.g. mixture; 'sugar free.'
- The strength of the methadone preparation e.g.; 1 mg/ml.
- The daily dose to be taken e.g. 80 ml daily.
- The total quantity of the preparation OR the number of dosage units in both words and figures e.g. 500 ml (Five hundred ml); 500 mg (five hundred milligrams).
- Be signed and dated by the prescriber.
- Instructions to cover when the pharmacy is closed e.g. Sundays and Bank Holidays.
- The provision for patients to receive daily supplies of methadone on form FP10 (MDA) or GP10 (3) in Scotland is an administrative arrangement made under the National Health Service and does not form part of the Misuse of Drugs Regulations.

- In the case of a prescription for a total quantity to be dispensed in instalments, the prescription must contain a **clear and unambiguous** direction specifying the amount that must be supplied on each occasion and the intervals to be observed when supplies are to be made. e.g. 80 ml to be supplied daily in instalments; 80ml daily, 160 ml to be supplied on Monday and Wednesday and 240 ml to be supplied in Fridays; 80 ml to be supplied daily in instalments Monday to Friday and 160 ml on Saturdays.

### Handwriting exemptions

Practitioners treating more than ten patients or more per week for dependence may apply to the Home Office for an 'own handwriting exemption certificate.' Application form (MD 40A) and guidance notes can be obtained via the Home Office Website <http://www.homeoffice.gov.uk/drugs/licensing/index.html>. Please note that 'own handwriting' exemptions apply to the specified prescriber at a specified address. If you practise at more than one site you will need an exemption for each site. It is expected that the own handwriting requirement will be repealed in the near future.

## Appendix 3

### Travel abroad

#### Home Office Export Licence is required for those wishing to travel abroad with amounts in excess of 500 mg of methadone.

Once proof of travel has been established a letter, giving 14 days notice, needs to be faxed or posted to:

Home Office, Drugs Branch,  
2 Marsham Street, London SW1P 4DF  
Tel: 020 7035 0472  
Fax: 020 7035 6161

#### Usual problems and solutions

A computer generated date is not acceptable, even where a prescriber has an own handwriting exemption, however a prescriber may use a date stamp or write the date in ink on the form.

#### Home Office ruling on missed collections of instalments:

- If a patient fails to collect an instalment on the due date then that dose is forfeited. The pharmacist cannot dispense or supply the dose on the following day.

However, the Home Office has provided the following, helpful advice in the case of missed days where the instalment is for more than one day.

- 'Instalment prescriptions covering more than one day should be collected on the specified day; **if this collection is missed the remainder of the instalment (i.e. the instalment less the amount prescribed for the day(s) missed) may be supplied.**'

The advice from the Home Office goes on to state that their legal advice is that regulation 15(1)(g) does not necessarily require a **regular** interval to be specified in the direction (from the prescriber). For this reason, a direction that enables the remainder of the prescription to be collected the following day conforms with that regulation and that the statement above is clear and unambiguous.

Prescribers are thus advised to use the above direction on prescriptions that are for intervals greater than one day. Without the direction the patient will forfeit the whole of the instalment.

Another useful tip is to write 'and in advance for days of closure' after the dispensing instructions on the prescription means the pharmacist can adjust for weekends and other times when the pharmacy is shut, without more specific instructions.

#### For the future

One recommendation of the Fourth Report of the Shipman Inquiry is that pharmacists should be allowed to endorse 'technical errors/omissions' on prescriptions for Schedule 2 and 3 CDs after confirming the intention of the prescriber with him/her.

It is anticipated that machine/computer generated prescriptions and controlled drugs records will become legal in the near future.

- The letter needs to clearly state the name and address of the person travelling, date of birth, the quantity of drugs to be carried, the strength and form in which the drugs will be dispensed and the dates of travel to and from the UK.

- The Licence only permits export. It does not guarantee that the country being travelled to will allow the person and their drugs into the country. This should be clearly explained to the patient and they should check with the relevant embassy whether they could import the drugs.

- Some countries will not allow the import of all controlled drugs and others only certain drugs.

- It is good practice to provide a 'to whom it may concern' letter that the patient can carry with them stating that they are engaged in treatment, this being the reason they are carrying the drugs.

- Specific requirements for different countries can change and it is always best to check with the individual embassies.

For more information visit the Home Office website on [www.homeoffice.gov.uk](http://www.homeoffice.gov.uk)

A very useful website to visit for more information about travel abroad is: <http://www.indro-online.de/travel.htm>

**For additional copies, and for further information about training on cocaine, crack and other issues relevant to primary care based drug and alcohol treatment, please contact**

Jo Betterton  
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Royal College of General Practitioners  
Office 314  
Frazer House  
32–38 Leman Street  
London  
E1 8EW  
020 7173 6091  
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or

Mark Birtwistle  
Substance Misuse Management in General Practice  
c/o Bolton, Salford & Trafford Mental Health NHS Trust  
Bury New Road  
Prestwich  
Manchester  
M25 3BL  
0161 772 3546  
mark@smmgp2.demon.co.uk

This guidance, and other resources including an interactive discussion forum, are available on the SMMGP website at **[www.smmgp.org.uk](http://www.smmgp.org.uk)**