Royal College of General Practitioners

Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care

RCGP Substance Misuse Unit (SMU)
RCGP Sex, Drugs and HIV Group (SDHIVG)
Substance Misuse Management in General Practice (SMMGP)
The Alliance

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b) Combined and adapted from:
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2. Guidance for the use of methadone for the treatment of opioid dependence in primary care 2005 by:
   Chris Ford, Jim Barnard, Judy Bury, Tom Carnwath, Clare Gerada, Alan Joyce, Jenny Keen, Charlie Lowe,

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to drug usage, complies with information contained in the British Formulary, or equivalent, or manufacturers’ datasheets,
and that it complies with the latest legislation and standards of practice.
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Summary

Opioid dependence is common in the UK and there are effective substitution medications, including methadone and buprenorphine, to support treatment. This guidance covers the use of substitute medication, which can be an important element in the treatment of opioid dependent patients and their medically assisted recovery (MAR).

Effectiveness

- Methadone and buprenorphine are effective evidence-based medications used in the treatment of opioid dependence.
- Both are effective support agents in detoxification.
- The 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.
- Both are more effective as part of a package of care that includes psychosocial support.
- There are other drugs, such as morphine sulphate, dihydrocodeine and diamorphine, which are also occasionally used and which have an increasing evidence base worldwide.

Maintenance or detoxification

- Choosing between maintenance and detoxification regimes can and should occur at many points during treatment, starting at the first assessment and then at various points, as appropriate.
- Methadone and buprenorphine can be used as maintenance interventions or as detoxification agents. Other medications, such as long-acting morphine sulphate, and dihydrocodeine, can also sometimes be used.

Maintenance

- Methadone is still considered the gold standard substitute medication for long-term opioid dependence. However, buprenorphine is also effective.
- Optimal daily dose for maintenance is usually between 60 and 120 mg for methadone and 12 and 32 mg for buprenorphine. Some people need larger doses, and some smaller.
- Methadone is usually prescribed in an oral liquid formulation 1 mg/ml. Buprenorphine is prescribed as sublingual tablets of 0.4 mg, 2 mg or 8 mg; or in a buprenorphine/naloxone combination as 2 mg/0.5 mg and 8 mg/2 mg tablets.

Assessment

- Before prescribing any substitute medication opioid dependence should first be confirmed by history and examination, including physical examination, and by toxicology screening using urine or oral fluid swabs.

Induction

- The initiation of methadone and buprenorphine are very different.
- For methadone:
  - Start low and titrate up slowly until optimal dose to prevent the risk of overdose.
  - The starting dose of methadone should be low: between 10 mg and 30 mg daily, depending on the amount of heroin, the length and method of use or other opioids being used, because of the cumulative effect until steady state is reached.
  - Methadone doses should then be titrated upwards to optimal levels, usually between 60 and 120 mg.
  - Methadone increases of between 5 and 10 mg a day, with a maximum of 30 mg dose increase each week for the first two weeks, are recommended. (After that the rate of increase can be slightly quicker.) In those with short history, young people or unknown tolerance, increases may be slower.
- For buprenorphine:
  - Need to get the time of the first dose of buprenorphine right after use of heroin (or methadone or other opioid) to avoid precipitated withdrawal then can increase dose quickly.
  - Start at least 8 to 12 hours post heroin or 24 to 36 hours post methadone and when withdrawals have begun, to avoid precipitated withdrawal.
  - Precipitated withdrawal only occurs on the first dose; the longer this first dose can be left post heroin or methadone use, the lower this risk.
  - Doses above 12 mg (16 mg more effective) block the effect of heroin and other opiates if used on top.
Doses should be supervised through induction and until stability is achieved.

Three months is advised as the length of supervision but this can be shortened if it is clinically unnecessary or a hindrance to the patient, e.g. due to employment.

Both should be prescribed in instalments, on FP10 (MDA) in England and Wales or GP10 (3) in Scotland, initially daily.

It is the responsibility of the prescriber to ensure safe induction on to these drugs. 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 support is often strengthened once drug use has been stabilised.

Interactions

Both methadone and buprenorphine interact, although more so methadone, with other central nervous system depressants, including benzodiazepines, antidepressants and alcohol, increasing sedation and hence the risk of overdose; patients must be informed of this.

It is important to remember that several missed doses may mean a loss of tolerance to opioids.

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-induction if there is likely to be significant loss of tolerance.

Effective opioid maintenance doses enable patients to remain tolerant to opioids and thereby provide important protection against overdose. Opioid users in effective treatment are far less likely to overdose than those not in treatment.

Ongoing care

Treatment is reviewed at every contact and needs to be re-examined more formally, about every three to four months, to measure improvements in health and well-being, and to monitor any use of alcohol or drugs on top of the prescribing.

A prescriber should also review the prescribing and the other elements of treatment as part of an overall package of care to support people on their road to recovery.

A toxicology screen (urine or oral fluid swab) needs to be taken frequently at the beginning of treatment and when the patient is stabilised regularly (usually between two and four times a year) if continuing on maintenance, to confirm use of medication and to monitor use of additional drugs.

Screens should never be used punitively, but as an aid to treatment.

Screen positive for heroin, or other drugs, require a review of treatment and dose, but should not normally lead to the cessation of treatment or dose reduction.

It is important that patients are given good information on the drugs they are being prescribed, and on their actions and effects, along with advice on safe storage of take-home doses.

Special groups

It is important to remember the needs of special groups, such as black and minority ethnic (BME) communities, polydrug users, people with dual diagnosis, problematic drug users in prison or hospital, and women who are pregnant and/or have children.

Primary care-based drug treatment

Treatment of people who use drugs is multifaceted and the patient should always be at the centre.

Managing their care normally requires a multidisciplinary response; wherever possible, this should be provided in collaboration with others such as other primary care practitioners, practice nurses, dispensing pharmacists, practitioners with a special interest and addiction specialists.

Practitioners should only prescribe and treat to the level of practice at which they feel competent and confident.

Stable patients may not need as much input as those new to treatment but they must always continue to be reviewed and supported to make changes at each appointment with a major review at least every three months.
1. Introduction

This guidance is to aid primary care clinicians and others in the use of substitute medication for opioid dependence when prescribing for maintenance or detoxification. The use of substitute medication can be an important element in the treatment of opioid dependent patients and can help support patients on their own road to recovery. It includes methadone, buprenorphine and other medications for use with opioid dependence, including codeine, heroin and slow-release oral morphine. It should be read in conjunction with Drug misuse and dependence: UK guidelines on clinical management (2007) and Guidance on methadone and buprenorphine for the management of opioid dependence (National Institute of Clinical Excellence, NICE). Drug misuse: opioid detoxification (NICE); Naltrexone for the management of opioid dependence; Drug misuse: psychological interventions (NICE); Guidance for community-based interventions guidance on how to reduce substance misuse among disadvantaged children and vulnerable young people (NICE); Guidance for the pharmacological management of substance misuse among young people (2009); and Guidance for the pharmacological management of substance misuse among young people in secure environments (2009).

Treatment of patients with drug problems in primary care has increased markedly over the last few years, and with the increase in polydrug use (use of more than one drug with or without alcohol), treatment has become more complex. The spectrum of drugs being used by young people is also changing, and the number of young people presenting with heroin problems is falling. However, heroin still remains the most common drug problem presenting for treatment (NTA Annual Report 2008–9). Therefore, there is still a need for practical evidence-based guidance about prescribing specifically aimed at primary care. The focus of this guidance is on prescribing and it does not attempt to cover the whole spectrum of treatment options for problematic drug users in primary care. It recognises that prescribing is an important but small part of the treatment of people who use drugs.

This guidance incorporates the documents RCGP Guidance for the use of buprenorphine for the treatment of opioid dependence in primary care (2004) and RCGP Guidance for the use of methadone for the treatment of opioid dependence in primary care (2005) and the bulk of this guidance will be about prescribing these two drugs. The guidance documents are part of a series which includes the RCGP Guidance for working with cocaine and crack users in primary care (currently being updated and incorporated into a new stimulant guidance) and RCGP Guidance for the prevention, testing, treatment and management of hepatitis C in primary care.

These documents are available online at www.smmgp.org.uk and www.rcgp.org.uk.

1.1 Who is the guidance for?

This guidance is aimed at all clinicians involved in the care of patients who use drugs and/or alcohol. It has been developed specifically to support the prescribing of substitute medication in primary care. It constitutes flexible guidance to help practice and should not be used as a rigid set of protocols. It is good practice to record in the patient notes the reasons for decisions taken in individual cases, especially and in particular if they depart from this guidance or the national clinical guidelines.

1.2 Evidence-based guidance

Treatment for opioid dependence can be effective in primary care and there is a substantial body of evidence to support this. This guidance draws on British and international research in the clinical use of substitute medication. The evidence base for the effectiveness of methadone and buprenorphine in the treatment of opioid dependency is extensive and continues to grow. There is more limited evidence for the effectiveness of other substitute medications, including dihydrocodeine and slow-release morphine sulphate. This guidance concentrates mainly on the prescribing of oral methadone and buprenorphine and covers practical aspects of management, drawing on the experience and recommendations of experts in the field.

The bulk of the guidance will concentrate on the areas of methadone and buprenorphine prescribing where the evidence base is most extensive.
2. Rationale for the use of substitute opioid prescribing

Methadone and buprenorphine are effective substitute medications to use in primary care in the UK for the treatment of opioid dependence.

The UK has the highest prevalence of illicit drug use in the western world, with comparatively high levels of heroin and crack cocaine use. In the last ten years there has been a rapid expansion of drug treatment in the UK, and a significant increase in the numbers of patients being treated for drug dependence in primary care, a setting which now has an established evidence base for the treatment of opioid dependence. Problematic drug users experience increased rates of morbidity and mortality due to their substance misuse, and although drug misuse exists in every sector of society, it is most prevalent in areas of social deprivation where individuals are likely to experience poorer health outcomes, independent of their substance misuse. Primary care can offer general health care to drug users, including important health interventions such as screening for hepatitis C; vaccinations against hepatitis B; smoking and alcohol interventions; and chronic disease management, where appropriate, in addition to the treatment for opioid dependence.

The broad aim of treatment of opioid dependence will vary depending on the needs of the patient. Practitioners should strive to develop an individualised plan of treatment in consultation with the patient and others involved in their care. This plan should consider the patient’s psychosocial as well as their medical needs. Patients’ aims with regard to their substance use will vary on a spectrum from a desire to reduce or stop illicit drug use, to a desire for abstinence from all drugs, including substitute medication. It is important that practitioners allow the patient to lead and that they do not have a fixed view on what a patient should be achieving in treatment. The UK Drugs Policy Commission consensus statement on recovery from substance misuse provides a useful guide for the aims of substance misuse treatment:

Recovery is a process, characterised by voluntarily maintained control over substance use, leading towards health and well-being and participation in the responsibilities and benefits of society.

Methadone and buprenorphine can play an important role in recovery from opioid dependence. Methadone and buprenorphine treatment for drug dependency is supported by NICE guidance and clinical practice. The aim of opioid substitute treatment is to improve the quality of life of opioid-dependent patients and to reduce the potential harm of using illicit drugs, both for the individual and for those affected by their drug use, especially their children.

The two main ways in which methadone, buprenorphine and other substitution medication can be used are: maintenance therapy, using the drug as an ongoing replacement to reduce and stop the use of illicit opioids; or detoxification, which again uses the drug as a replacement with the dose reducing until all opioid use is stopped. Maintenance and detoxification are parts of the same spectrum and the evidence supports maintenance as a route to abstinence for many patients. Methadone maintenance treatment (MMT) and buprenorphine maintenance treatment (BMT) greatly reduce mortality, illicit drug use and criminal activity, and attract and retain more patients in treatment than other treatments. There is evidence that MMT and BMT reduce transmission of HIV, although the evidence for effectiveness at reducing transmission of hepatitis B virus and hepatitis C virus is less convincing. There is little evidence that MMT increases the overall length of dependence. Effective treatment of the parent can also have major benefits for the children of problem drug users.

The most effective MMT and BMT programmes are those that provide optimal doses in a flexible dosing regimen as part of a comprehensive treatment programme; the latter will include quality key working, regular reviews, general medical care and psychosocial support as required, will validate maintenance as much as abstinence as a desirable treatment goal, and will ensure that patients play an important role in determining their optimum dose.

Patient-led reductions can be effective, especially with the right support, whereas enforced reductions and putting pressure on patients to become abstinent from substitution therapy are associated with poor outcomes. Both methadone and buprenorphine are approved medications for detoxification, and reduction with eventual detoxification will usually be started from the medication that the patient is already taking. Previously, patients were routinely transferred from methadone to buprenorphine, but the evidence does not suggest that this is necessary.

A number of randomised trials suggest that buprenorphine exhibits comparable efficacy to methadone as substitute maintenance medication when used in equivalent doses. Others show that buprenorphine given in flexible doses appeared to be significantly less effective statistically than methadone in retaining patients in treatment but that it may suppress heroin use better. It is likely that there will be some patients who respond better to methadone maintenance and others who respond better to buprenorphine maintenance, with each medication having potential advantages and disadvantages.
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Figure 1: Efficacy of MMT and BMT

For heroin use and treatment retention in RCTs

- High-dose MMT (> 80 mg) better than
- Medium-dose MMT (40–60 mg)
  - Medium-dose BMT (8–12 mg) better than
- Low-dose MMT (< 40 mg)
  - Low-dose BMT (< 8 mg)

N.B. There are no reported randomised controlled trials comparing high-dose buprenorphine (≥16 mg) to high-dose methadone but these are awaited.

3. Clinical pharmacology

3.1 Methadone and buprenorphine

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.

Buprenorphine is a semi-synthetic opioid derived from the morphine alkaloid thebaine. It is a mixed agonist-antagonist and its primary action is as a partial opiate agonist. It has low intrinsic agonist activity, only partially activating mu opioid receptors. Consequently, high buprenorphine doses produce less euphoria, sedation and respiratory depression than high doses of other opioids such as heroin, methadone or morphine. However, buprenorphine exerts sufficient opiate effects to prevent or alleviate opioid withdrawal, including craving. It reduces the impact of additional opioid use (when prescribed in doses greater than 8 mg) by preventing the receptors being occupied by these additional opioids. It binds to kappa opioid receptors, where it acts as an opioid antagonist. Buprenorphine therefore produces opioid responses while also reducing the effect of additional heroin, methadone or morphine.

See figure 2 below.

3.2 Relevant properties

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

![Classification of opioids](image)

Figure 2: Opioid effect v dose (Nicholas Lintzeris presentation, 2005)
3.2.1 Time to peak plasma concentration

**Methadone:**
- Four hours after regular oral administration (range two to six hours).

**Buprenorphine:**
- 90 to 150 minutes after regular sublingual administration.

3.2.2 Time to peak clinical effects

**Methadone:**
- Two to six hours post oral dose (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, finally reaching a steady state by ten days. 38, 39
- Once a steady state is reached, variations in blood concentration levels are small.

**Buprenorphine:**
- One to four hours post sublingual dose.
- It takes three to four days for buprenorphine plasma levels to stabilise.

3.2.3 Duration of action (plasma half-life)

**Methadone:**
- The length of time it lasts in the body varies.
  - Single dose: shorter half-life than maintenance dosing 12 to 18 hours, mean 15 hours.
  - First few days: between 13 and 112 hours, mean 37 hours. 40
- Because of its cumulative effect until steady state is reached, methadone induction should be a cautious and gradual process.
- Elimination half-life is normally 20 to 37 hours but can range up to 91 hours for some individuals; its rate of clearance from the body can vary by a factor of almost 100. 41
- Optimal doses are usually between 24 and 36 hours.

**Buprenorphine:**
- Related to dose.
- Low doses (e.g. 2 to 4 mg) 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 suboptimal. 42
- Higher doses, e.g. 16 to 32 mg, can exert effects up to 48 to 72 hours.
- Optimal doses are usually between 24 and 36 hours.
- Elimination half-life is between 20 and 37 hours.

3.2.4 Metabolism

**Methadone:**
- Well absorbed from the gastrointestinal tract into the bloodstream.
- Well distributed in body fats.
- Metabolised through the liver via cytochrome P450 sub-family of enzymes, thus susceptible to pharmacokinetic interactions with drugs that inhibit or induce liver enzymes.
- 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.

**Buprenorphine:**
- Principally in the liver via two hepatic pathways: glucuronide conjugation and N-dealkylation by the cytochrome P450 enzyme system.
- The tablets are administered sublingually because it has poor oral bioavailability. It is inactivated by gastric acid and has a high first-pass metabolism.

3.2.5 Excretion

**Methadone and buprenorphine:**
- The products of methadone and buprenorphine are excreted principally in the faeces and urine; therefore urinalysis is useful only in confirming they are being taken, but not in establishing the dose.
3.2.6 Maintenance doses

Methadone:
- While research evidence suggests that optimal doses for most people lie between 60 and 120 mg, some people will need more and some need less due to a range of individual factors such as size, gender, age, other health problems and metabolic clearance rates. 
- Doses between 60 and 120 mg may exert clinical effects for 24 to 36 hours; low doses exert clinical effects for only a few hours.

Buprenorphine:
- Maintenance is between 8 and 32 mg daily but the blockade dose (dose where the effects of additional opioids are markedly reduced) is maximal above 16 mg daily.

3.2.7 Equivalence

Methadone and buprenorphine:
- Direct equivalence of methadone to buprenorphine and vice versa is difficult to estimate, as the pharmacological properties of the two agents are not identical 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. 
- Direct equivalence to street heroin is difficult to estimate, as purity of street heroin can vary (between 20 and 60%). One gram of street heroin is usually very roughly equivalent to 50 to 80 mg methadone and/or 12 to 16 mg buprenorphine.
- It is difficult to compare doses above 80 mg of methadone and above 16 mg of buprenorphine because of their different effects.

When comparing the equivalence of methadone to injectable pharmaceutical diamorphine, half-lives must be taken into consideration. This is not a linear relationship, so equivalence can vary from a methadone: diamorphine 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).

3.2.8 Tolerance

- Develops at different speed in different individuals, can change in individuals over time and develops differently for different effects.
- 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 dose of substitution that will be required. Patients react differently; some will need more, and some will need less than others using the same amount of heroin.

4. Types of methadone, buprenorphine and other opioids available for substitute prescribing in the UK

4.1 Methadone

4.1.1 Oral formulations of methadone

1 mg/1 ml

N.B. The European term 'oral solution' will 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. Intolerance to the pharmacological effects of methadone oral solution is rare but, if confirmed, consider using sugar-, chloroform- or colour-free formulations of methadone or another medication, e.g. buprenorphine. Chloroform or colour-free formulations are not commercially manufactured and have to be ordered as specials by community pharmacists from specials manufacturers; this is a lengthy and expensive process. Intolerance must be confirmed before going down this route.

Methadone is currently the formulation 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 stable, thus eliminating post-dose euphoria and pre-dose withdrawal.

Generic and trade preparations are identical in terms of ingredients but vary in price and pharmaceutical excipients, and this should be explained to the patient.

All the other forms of methadone should only be used by specialists or in specific circumstances which can be clinically justified.
4.1.1.2 Methadone oral solution
(concentrated mixture) 10 mg/ml
and 20 mg/ml

Methadone oral solution also comes in more concentrated forms, such as 10 mg/1 ml and 20 mg/1 ml, which differ in strength and tend to vary in colour. These formulations are generally 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. Also, unlike 1 mg/ml formulations, the higher concentrations are not viscous and therefore are easier to inject. The use of the higher strengths can lead to inadvertent dispensing errors at the pharmacy, regardless of how thorough and conscientious the pharmacist is. It is therefore better to stick to the 1 mg/ml solution.

Methadone linctus 1 mg/2 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.

4.1.1.3 Methadone tablets 5 mg

Methadone tablets are not licensed for the treatment of drug dependence. Reducing drug related deaths: a report by the Advisory Council for the Misuse of Drugs (ACMD) and the 1999 Clinical Guidelines advised against the prescribing of methadone tablets because they can be injected and have a high street value. The 2007 Clinical Guidelines also advise against use of tablets because these are not licensed for the treatment of drug dependence, but are more balanced about their use, stating that methadone tablets “should not normally be prescribed due to the increased potential for diversion.”

Hence the prescribing of tablets in general practice can be problematic and is 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, to reduce nausea due to chemotherapy, during holidays abroad and where there is proven intolerance to the mixture. The prescriber should have an appropriate level of experience to prescribe the tablets and should undertake the necessary precautions to ensure they are being taken appropriately. Specialist advice should be sought before prescribing tablets.

4.1.2 Injectable formulations of methadone

Some forms of methadone ampoules are now licensed for opioid dependence treatment. The 2007 Clinical Guidelines 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 (GPwSIs) if they have developed the necessary expertise in the management of injectable opiate prescribing.

The following formulations are available:
- Methadone ampoules 10 mg in 1 ml
- Methadone ampoules 35 mg in 3.5 ml
- Methadone ampoules 50 mg in 5 ml, 2 ml or 1 ml

N.B. In the rest of this document references to methadone are to the oral solution 1 mg/1 ml, unless stated otherwise.

4.2 Buprenorphine

4.2.1 Sublingual formulations

4.2.1.1 Buprenorphine 0.4 mg, 2 mg and 8 mg sublingual tablets

Buprenorphine was licensed in 1999 for the treatment of opioid dependence in the UK. There are tablets of 0.4 mg, 2 mg and 8 mg that need to be taken sublingually because, if ingested, much of the effect is lost. The 2 mg and 8 mg strengths are also available in combination with naloxone, in which case they are prescribed as Suboxone® (see Section 4.2.1.2).

Buprenorphine is a useful choice for substitute opioid prescribing because its clinical effectiveness is supported by research and it alleviates opioid withdrawal symptoms.

However, as buprenorphine is easily soluble, there is a risk that it can be dissolved and injected.

Until 2008 Subutex® was the only formula available but there is now a generic version of buprenorphine in the same strengths (0.4 mg, 2 mg and 8 mg).

However, generic buprenorphine is made differently and tastes different; as it has different fillers, it may dissolve more quickly, but the amount of active ingredient is the same.

It can be useful to be aware of what your chemist is dispensing, to have a regular dialogue with them, and to be prepared to adjust dosages.
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Misuse of buprenorphine and the injecting of tablets has been recognised for a number of years. In the early 1990s low-dose tablets of buprenorphine (known as Temgesic®) were injected by drug users in a number of areas (e.g. Glasgow and Edinburgh). Since then there have been a number of reports from around the world showing often high risks of injecting these tablets, which (like all formulations of buprenorphine) are highly soluble.

One study in France on the use of higher-dose tablets of buprenorphine showed suspected intravenous use of the tablets in 10 to 15% of cases and irregular use in as many as 20 to 30% of patients. In Australia, 23.8% of clients in community pharmacies reported diverting their buprenorphine in the past 12 months (compared with just 2.2% of those on methadone). In the same study 9.1% had injected buprenorphine in the past 12 months. A further study started to explore user feedback on strategies to reduce diversion. The most common suggestions were mouth checks (31%), crushed doses (12%) and mouth rinsing (10%).

In the UK, the abuse of buprenorphine by snorting is commonly reported and there is little research exploring this potential abuse. It is worth noting that, although a small sub-population clearly abuse their medication, a large study highlighted that the majority of users have limited experience of diversion and injection, and that two-thirds expressed a preference for taking the medication as directed.

4.2.1.2 Buprenorphine/naloxone (trade name Suboxone®)

- Buprenorphine/naloxone was licensed in 2007 for the treatment of opioid dependence in the UK.
- It includes the opioid antagonist naloxone (buprenorphine/naloxone 4:1) in a combined sublingual tablet.
- Suboxone is available as sublingual tablets in buprenorphine/naloxone 2 mg/0.5 mg and 8 mg/2 mg strengths.
- The naloxone element potentially reduces the abuse potential from injecting and so may reduce diversion.
- When buprenorphine/naloxone is taken sublingually, the absorption of naloxone is negligible and the full opiate effect of buprenorphine is experienced. However, if the tablet is injected, then the user will experience the opiate antagonist effect of naloxone, which would precipitate withdrawal from opiates.
- It is not clear if the opiate antagonist effect would be felt if the user were to snort buprenorphine/naloxone but there are some anecdotal reports that it results in headaches.

Buprenorphine/naloxone may have a place where there is a risk of diversion. Typically, this is more of a risk where there is a heightened demand for opiates due to a reduced illicit supply, e.g. in prisons. However, snorting is a far more common abuse of buprenorphine in prisons and it is not clear how buprenorphine/naloxone will have any impact on this.

International research has demonstrated the good safety profile of Suboxone when prescribed in community drug treatment settings and that patients can be easily switched from Subutex to Suboxone without destabilising their treatment. A survey of Finnish drug users who attended a needle exchange programme revealed that the street price of Suboxone was less than half that of Subutex.

When taken sublingually, Suboxone dissolves more quickly than Subutex, which may be important either in the community or in a prison treatment setting. It has a lemon-citrus flavour, for which some users may express a preference.

4.3 Unwanted (or side) effects of methadone and buprenorphine

Most unwanted effects of methadone and buprenorphine are those associated with all opioids, including nausea, vomiting, constipation and drowsiness. Larger doses of methadone produce respiratory depression and hypotension. However, buprenorphine does not have these effects due to its antagonist effect at different receptors. Dry mouth, sweating, headache (common with buprenorphine) and decreased libido may also occur. In addition, with buprenorphine many patients complain of a bitter taste, although users report that this is less pronounced with Suboxone, which has a lime-lemon flavour.

Unwanted effects vary from individual to individual but are usually most prominent in the first few days of treatment. With methadone many patients report a ‘clouding’ effect in the mind, which is valued by some but not others; subjectively, many patients on buprenorphine treatment often report a ‘clear head’ response quite different to this ‘clouding’. Some patients find this ‘clarity’ uncomfortable whilst others may value it. This subjective experience may be a factor that influences patient choice.
4.3.1 Dental issues

There is evidence that opiate users have high levels of oral disease yet they have a low uptake of dental treatment. Opiate users have worse dental health, with more cavities and absent or extracted teeth. This is apparent at a relatively young age and the severity of the dental pathology shows an association in terms of both dose and duration with tobacco, methadone, morphine and alcohol.\textsuperscript{51} One study in Dublin showed that 99% of subjects required some form of dental treatment and 30% needed dentures when entering treatment. This study also demonstrated, contrary to many methadone users' beliefs, that sugar or sugar-free formulas had no significant effect on dental health.\textsuperscript{52}

Two main factors, in combination with years of neglect, cause dental caries in users. Firstly, the dry mouth caused by opiates leads to poor oral health and, secondly, there is likely to be a predominantly high sugar content in their diet. There have been a number of reasons suggested for this, including users reporting sugar cravings, opiates reducing taste sensations, and social issues where cooking is not possible, e.g. homelessness. Changes in dental health are associated with chaotic lifestyle, polydrug use and episodes of overdose, homelessness, dietary deficiency and imprisonment.\textsuperscript{53, 54} Access to care is often poor and one study in the UK in 2001 noted that fewer than 29% of drug users with dental problems had seen a dentist in the previous 12 months. The mean time since last visit to the dentist was more than two years.\textsuperscript{55}

Oral health should be considered on assessment and during treatment, particularly as dental pain is one of the common factors leading to relapse. Some users may feel their poor dentition leaves them socially excluded, and it may have an effect on self-esteem, hindering recovery. Opiate users should be treated as a group with special dental needs and they need greater access to dental care than most people.\textsuperscript{53} They should be given simple advice on dental hygiene (e.g. regular brushing, oral rinsing and the use of sugar-free gum to stimulate saliva production) and explicit advice on how to access dental services in their local area.\textsuperscript{1, 56}

4.4 Other opioid substitute treatments occasionally used by specialists in specific circumstances that can be clinically justified, and are rarely used in primary care

4.4.1 Oral formulations

4.4.1.1 Codeine and dihydrocodeine

Codeine and dihydrocodeine are not licensed for the use of treatment of drug dependency, are mostly short-acting (therefore frequent dosing is needed), are difficult to supervise and can be diverted; the 2007 Clinical Guidelines state that they should not normally be prescribed in the community.\textsuperscript{1} They are both available in tablet form and are both Class D Schedule 5 drugs in the UK (Misuse of Drugs Act 1971). Both are prescription-only drugs but can be bought without prescription from pharmacies in combination with other drugs, e.g. paracetamol or ibuprofen; they are sometimes used as self-medication by patients who have symptoms of pain or distress and this can lead to dependency problems from overuse or inappropriate use. Some individuals who have used other opiate drugs report the use of codeine or dihydrocodeine when their preferred drug is not available.

In the recent past dihydrocodeine, in particular, has been used as a prescription drug for patients with opioid dependency, either because methadone was unavailable or doctors did not want to prescribe it. This occurred extensively in police stations or prisons. There is therefore clinical experience in the use of dihydrocodeine and now there is a small evidence base.

One trial in Scotland showed dihydrocodeine to be effective but not superior to other substitute medications. The trial concluded that an equivalent dose was 2.5 mg methadone to 30 mg dihydrocodeine and the therapeutic range was 450 to 1800 mg dihydrocodeine. At the higher doses 60 mg or 120 mg tablets of dihydrocodeine were used.\textsuperscript{57} There is no such evidence base for codeine and it should not be used.

N.B. Over-the-counter and prescription-only medications cannot be covered in detail in this guidance.
4.4.1.2 Slow-release oral morphine

Morphine sulphate is not licensed for the treatment of drug dependency in the UK and should only be used by specialists and in rare circumstances. It is used elsewhere in Europe in patients who fail to tolerate or stabilise on methadone. It may also have a higher street value, hence the risk of diversion. One trial in Austria showed a high retention rate (94%) with slow-release oral morphine and concluded that there was good acceptance of it. Another study undertaken by the same group but using small numbers compared the effectiveness of slow-release morphine and methadone for opioid maintenance therapy and found that 98% of patients completed the study, with a mean methadone dose of 65 mg and a mean slow-release morphine dose of 680 mg. No significant differences in retention or use of illicit substances (opiates, benzodiazepines, cocaine) were observed, irrespective of treatment group or medication. However, patients receiving slow-release morphine had significantly lower depression and anxiety scores, and fewer physical complaints. The trial concluded that oral slow-release morphine is as effective as methadone in the treatment of opioid dependency, with comparable safety and tolerability and a greater benefit for patient well-being. Its conclusion was that ‘greater pharmaceutical diversity represents a modern development in mainstream medicine. Slow-release morphine might represent a future treatment option that will improve long-term outcomes for this target group.’

When people are transferred to slow-release morphine sulphate, clinical experience is that each patient differs regarding the amount of drug they need in order to stabilise. However, four to eight times the dose of methadone is usually required because of shorter half-life and other variables between the two drugs. It is important to titrate the dose up in the same way as for methadone. The Eder paper, discussed above, showed that users needed around eight times the oral morphine dose compared with the mean methadone dose.

4.4.2 Injectable formulations

N.B. Also see section 4.1.2 regarding injectable methadone.

4.4.2.1 Diamorphine (pharmaceutical heroin)

Diamorphine is the pharmaceutical form of heroin. It can be useful in treatment, particularly in a small sub-group of people in whom other treatment has failed, and has the advantage that its purity is known, unlike heroin. Research from Switzerland, the Netherlands and Canada has shown good results in stabilising people and reducing crack use. The use of diamorphine in the UK has been complicated as it was previously prescribed under what was described as the ‘British System’ to small numbers of people. In recent times its use has dwindled and injectable diamorphine has again been the subject of newer studies in other countries. In 2003 an NTA working party reported on the potential roles of injectables in drug treatment in the UK. The Randomised Injectable Opioid Treatment Trial (RIOTT) has undertaken an evaluation of injectable methadone and diamorphine treatment in the UK and found that ‘Treatment with supervised injectable heroin leads to significantly lower use of street heroin than does supervised injectable methadone or optimised oral methadone. UK Government proposals should be rolled out to support the positive response that can be achieved with heroin maintenance treatment for previously unresponsive chronic heroin addicts.’ In common with the Canadian NAOMI study, the subjects have received extensive psychosocial input and intensive daily supervision. The 2007 Clinical Guidelines 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 GPwSI if they have developed the necessary expertise in the management of injectable opiate prescribing.

5. Indications, contraindications and precautions for use in primary care

5.1 Indications

- Opioid dependence.
- Informed consent to treatment.

5.2 Absolute contraindications

- Non-opioid-dependence, unless using low-dose buprenorphine for people coming out of prison as a relapse prevention measure often called ‘retox’.
- Allergy or proven intolerance to methadone or buprenorphine.

5.3 Relative contraindications

- Severe liver disease, such as decompensated liver disease. However, in many cases, with careful monitoring of liver function the benefits will outweigh the risks.
- Age under 16 years, except on the advice of a specialist.
- The licence for buprenorphine does not cover breast-feeding mothers. Pregnancy is not a contraindication under the UK Medicines and Healthcare products Regulatory Agency (MHRA) licence; rather it carries a special warning.
5.4 Cautions

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

- **Concurrent use of other sedating drugs or medications:** Full agonists and especially methadone have 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 antidepressants. Monamine oxidase inhibitors (MAOIs) need to be avoided with methadone because of the potential risk of central nervous system hyperexcitation (hyperthermia, delirium etc.), which has been noted with pethidine but never, so far, with methadone. This occurs with buprenorphine, but with much less effect. However, both alcohol and benzodiazepine use is common in those requesting opioid treatment and should not be regarded as an absolute contraindication.

- **Medical conditions complicating opioid use:** People with severe mental illness: this group may have limited capacity to provide informed consent.

- **Patients suffering with chronic pain:** When opioid analgesia is indicated, patients should normally be given appropriate doses of additional opioid analgesia on top of that required for the management of dependence. The issues around managing pain are discussed further in Section 9.3.

- **People with severe mental illness:** This group may have limited capacity to provide informed consent.

- **Medications that affect methadone levels:** Some medications have a significant effect on methadone levels: for example, rifampicin may require a 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 and so may increase methadone levels. For further details, see appendix 1 in the British National Formulary (BNF).

- **Transfer of patients on more than 30 mg of methadone to buprenorphine:** This is more likely to be associated with precipitated withdrawal and should only be attempted after consultation with a specialist or experienced prescriber.

- **History of cardiac arrhythmias or abnormal ECG:** Caution is needed when using methadone (see Section 9.6).

6. Assessment in primary care

6.1 Assessment of and care-planning for a patient who uses drugs and/or alcohol

A full assessment should be undertaken for all patients who use drugs and/or alcohol. Patients who use drugs and alcohol often have a range of needs that go beyond the medical and include social, legal and psychological health aspects. With the expansion of drug treatment services over the past ten years, there has come an expansion of drug professionals who aim to meet these diverse needs. Parents who use drugs and/or alcohol may also be in contact with other professionals, including health visitors, school staff and social services. All practitioners should be aware of assessing the needs of the children of parents who use drugs and/or alcohol.

The 2007 Clinical Guidelines emphasise the importance of assessing the degree of dependence. The issues around managing pain are discussed further in Section 9.3. Keyworking helps to ensure the delivery and ongoing review of the care plan. This would normally involve regular sessions or consultations with the patient in which progress against the care plan would be discussed and, if appropriate, the goals would be revised. It is important to communicate with the pharmacist, who will see the patient more frequently: up to seven times a week.

The assessment is an ongoing process and can be completed over time, as long as the essential information is taken in the beginning. It must not be a barrier to treatment and needs to be undertaken by one person and then shared as necessary with other workers involved. It will provide essential information for the formation of the care plan – a document that is agreed between the GP or other treatment provider – and the patient.

An assessment should be carried out on all drug users seeking treatment and should include the following:

- **treatment of any emergency or acute problem.**
- **confirmation that the patient is taking drugs, including alcohol: types, how much, how taken and how often (history, examination and drug testing).**
- **assessment of the degree of dependence.**
- **identification of physical and mental health problems.**
- **identification of social problems, including housing, employment and domestic violence, and offending.**

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Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care

6.3 Choosing between methadone or buprenorphine

If, after assessment, the need for substitute medication is identified, then a choice between starting methadone or buprenorphine is usually involved. Both are useful drugs and are NICE-approved for substitute prescribing for both detoxification and maintenance to prevent opioid withdrawals. For maintenance the evidence suggests that methadone is more likely to retain patients in treatment, but the evidence for the relative effectiveness of methadone and buprenorphine at preventing illicit opioid misuse is mixed. NICE recommends that ‘if both drugs are equally suitable, methadone should be prescribed as the first choice.’

However, the 2007 Clinical Guidelines and NICE guidance do state that other factors should be considered when deciding between methadone and buprenorphine. These include:

- patient preference
- the level of opioid use
- the risks of diversion/overdose
- the prescriber’s experience with the medications
- the patient’s history of treatment
- the patient’s history of prescribed and illicit drug use.

There appears to be consensus among clinicians experienced in choosing both buprenorphine and methadone that:

- High-dose methadone or buprenorphine may be better suited to those who wish to cease using heroin completely, as the blockade effects of both interfere with the subjective effects of additional heroin use. Those patients who wish to continue to use some heroin may prefer low-dose methadone treatment.
- Methadone is better suited to people using high levels of heroin, as people using high levels of heroin don’t appear to settle as well on high dose buprenorphine as with methadone.
- Buprenorphine is less affected by interactions with hepatic enzyme inducers/inhibitors (anticonvulsants, rifampicin and ribavirin).
- Buprenorphine is less sedating than methadone. This may be a positive or negative factor depending on the patient.
- Using buprenorphine alone is safer in overdose.
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Patients who are not responding well to adequate doses of methadone or buprenorphine, or who are experiencing persistent unwanted effects or difficulties with their medication, may benefit from transfer to the other medication or referral to a specialist practitioner for review and help.

N.B. Methadone and buprenorphine can now be prescribed by qualified non-medical prescribers (NMPs) (e.g. specialist pharmacists or nurses) where this arrangement is agreed by the doctor and the patient, and detailed in the care plan. This usually involves continuing medication rather than the induction and titration period. This can only be undertaken after the patient has seen an independent prescriber and a clinical management plan (distinct from the care plan) is in place. At the time of writing, expected changes in legislation to allow NMPs to prescribe substitute medications without a medical prescriber had yet to take place.

6.4 Starting methadone or buprenorphine

Always confirm opioid dependence before starting either medication by history, examination and toxicology. The dose induction of the two medications is very different.

6.4.1 Before starting

- Confirm opioid dependence by history, examination and toxicology; do not start medication without evidence of opioid dependence.
- Check for objective signs of opioid dependence, including dilated pupils when the patient is withdrawing, and look for injection marks.
- Carry out body fluid toxicology (usually urine, sometimes oral fluid swabs) to confirm that there are opioids in the system.
- Starting medication is always important and occasionally urgent; it needs to be initiated as rapidly as it can safely be done, to avoid drop-out from treatment.
- Starting substitute medication on the first presentation is often not possible, as results, other than on-site tests, often take days to return, but keep this time to a minimum. Use this period to continue the assessment, provide harm reduction advice, support and ask the patient to keep a drugs diary.
- In some areas the comprehensive assessment is provided by the local drug agency.

6.4.2 Starting methadone

The purpose of titration on methadone is to establish the patient, in a safe manner and 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. Insufficient dosing may increase the risk of additional illicit drug use and hence diminish treatment effectiveness and increase accidental overdose risk. There is a need to start at a low dose and titrate up until an optimal dose is reached, but too high an initial dose and/or too rapid increases also add to overdose risk in this period because of the accumulative effect before steady state is reached. This titration process and the reason for being cautious must be explained to the patient. The starting dose of methadone should be between 10 and 30 mg daily, depending on the amount of heroin or other opiates being used, and titrated upwards to optimal levels, usually between 60 and 120 mg.

- 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 bearing in mind the long but variable half-life of methadone of between 13 and 112 hours in first few days.
- Deaths have occurred in non-tolerant individuals on levels as low as 40 mg.
- If tolerance is low or uncertain, then starting doses of 10 to 20 mg should be used and increased more slowly.
- Methadone increases of between 5 and 10 mg a day, with a maximum of 30 mg a week for the first two weeks, are recommended. After that the increases can be slightly quicker.
- Better to go slow and safe than rushed and risky.
- Methadone is excreted very slowly during the first few days of treatment in methadone-naive 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 reach steady state; this can increase the risk of overdose during the early stages of treatment.
- When undertaking induction in general practice, it is preferable to see the patient frequently at the outset (daily if possible), 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.
- If it is not possible for the GP to see the patient daily, then the patient should be seen as frequently as possible – at least every few days. Only increase the dose after brief re-assessment by the GP or a drugs worker for the titration period.
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- Involve the pharmacist who is providing supervised consumption in the assessment process during titration.
- If you are not confident undertaking the titration, ask the local specialist service to initiate the patient and take over the prescribing once they are stabilised.
- Patients who have a long history of use, including past and current injecting heroin use, and higher levels of drug use, those who are well known to services and those in whom there is clear evidence of high tolerance may benefit from a slightly faster induction.
- Patients who are non-injectors, have a shorter history of drug use and/or lower levels of drug use, and in whom evidence of high tolerance is lacking need a more cautious approach.
- It is recommended that starting doses in young people are between 5 to 10 mg.

6.4.2.1 Risk factors
- Deaths during methadone titration are rare and most occur in the first two to three days.
- But over 20% of all methadone deaths in treatment take place within two weeks of commencement of prescribing and most occur during sleep, hence the need for caution.
- Risk of overdose is increased by low opioid tolerance, too high an initial dose, too rapid increases and concurrent use of other drugs, particularly alcohol, benzodiazepines and antidepressants.
- Daily assessment by a pharmacist using supervised consumption is the best safeguard to prevent undetected over-sedation in a patient, and arrangements should be made to ensure sharing of this information in a secure and confidential manner.
- Methadone patients should be informed of the ‘increasing effect of a dose’ as steady state is achieved, so that they do not excessively ‘top up’ with street drugs.
- A number of factors can alter methadone plasma levels, including gastric emptying, pregnancy and liver metabolism, which can increase the risk of overdose.

6.4.2.2 Other points to consider during methadone induction
- During induction, psychological factors and psychiatric morbidity/illness need to be taken into consideration on the premise that depression may contribute to suicidal ideation.
- Clinical experience and some published data (though not randomised controlled trials) suggest that psychiatric conditions, including major depression and psychosis, sometimes respond to appropriate methadone dosing.
- In patients with co-morbidity (diagnosis – mental health and drug / alcohol problems) good control of opioid dependence leads to stability and improvements in mental health.

6.4.3 Starting buprenorphine and Suboxone®
The purpose of induction is to establish the patient as quickly as possible and in a safe manner on a dose of buprenorphine that prevents opioid withdrawal, reduces the need to take additional illicit opioids and keeps side effects to a minimum. It is usual to start on a low dose and increase rapidly over the course of a few days, until a stabilising dose (usually between 12 and 32 mg) is reached. Doses above 12 mg (above 16 mg even more effective) block the effect of heroin and other opiates if used on top.

6.4.3.1 Risk factors
- Deaths during methadone titration are rare and most occur in the first two to three days.
- But over 20% of all methadone deaths in treatment take place within two weeks of commencement of prescribing and most occur during sleep, hence the need for caution.
- Risk of overdose is increased by low opioid tolerance, too high an initial dose, too rapid increases and concurrent use of other drugs, particularly alcohol, benzodiazepines and antidepressants.
- Daily assessment by a pharmacist using supervised consumption is the best safeguard to prevent undetected over-sedation in a patient, and arrangements should be made to ensure sharing of this information in a secure and confidential manner.
- Methadone patients should be informed of the ‘increasing effect of a dose’ as steady state is achieved, so that they do not excessively ‘top up’ with street drugs.

6.4.3.2 Other points to consider during buprenorphine and Suboxone® induction
- To avoid precipitated withdrawal, delay the first dose of buprenorphine until the patient is experiencing features of opioid withdrawal (This typically means at least eight and preferably 12 hours after last heroin use, or 24 to 48 hours after last methadone use.)
- Titration on to buprenorphine from heroin or low-dose methadone (30 mg or below) can usually be accomplished with minimal complications, although restlessness, insomnia, headache, diarrhoea and other mild opioid withdrawal-like symptoms are not uncommon in the first one to three days.
- Lofexidine may be helpful with these unpleasant effects. Steady state in the blood concentration levels of buprenorphine is reached after about five to eight days. Advice about sleep hygiene should be given.
- Precipitated withdrawal occurs only on the first dose, and the longer after the last opiate use this first dose is taken, the lower this risk (see section 6.4.4).
- To achieve this, give the first dose (only) of buprenorphine to the patient as a take-home dose to be taken at an appropriate time of their choosing as the onset of withdrawal occurs.
- Commence with an initial buprenorphine dose of between 4 and 8 mg.
See the patient daily if possible and increase the buprenorphine dose on subsequent days, or later the same day, if facilities are available, according to clinical response.

- Dose increases of 2 to 4 mg per day at a time are usually adequate, although dose increases of up to 8 mg are safe and can be used.
- Ensure frequent review of the patient and supervision of doses, where available, through induction and until stability.
- Provide a full explanation to the patient and their partner/carer, if appropriate, supported by written information to include: the properties of the drug, how it works, the induction period and the possible side effects (Provide a patient information leaflet).
- Ensure that patients understand that most people take several days to stabilise on their medication, particularly if transferring from methadone (where stabilisation can take one to two weeks). Precipitated withdrawal should also be explained.

6.4.3 Precipitated withdrawal

This form of opiate withdrawal can occur in someone commencing buprenorphine who has recently used heroin or other opiates (less than eight hours previously for heroin, as much as 36 hours for methadone). It is caused by the high affinity of buprenorphine for displacing other opioids (e.g. methadone, heroin) from opioid receptors, but having less opioid activity (partial agonist). This rapid reduction in opioid effects can be experienced as precipitated withdrawal, typically occurring within one to three hours of the first buprenorphine dose, peaking in severity over the first three to six hours, and then generally subsiding. If it occurs, reassure the patient and carer, confirm that it is unpleasant but not dangerous and that it will pass, and offer symptomatic treatment, if withdrawal symptoms are severe. Do not prescribe more buprenorphine until the opiate withdrawal symptoms have settled.

6.4.4 Induction of buprenorphine

6.4.4.1 Option 1: Induction from heroin (can be undertaken in primary care if the doctor has the necessary experience)

- The first dose of buprenorphine should be administered at least eight hours and usually 12 hours after the last use of heroin and with the onset of mild withdrawals present to reduce the risk of precipitated withdrawal (see 6.4.3.1). Precipitated withdrawal is rare with transfer from heroin. 27
- A first dose of 4 mg buprenorphine (probably unsupervised) is generally recommended. Starting doses of between 4 and 8 mg can be used and are safe, subject to there being no cautions.
- The dose can be increased by 2 to 8 mg daily, usually 4 mg, until the patient is stabilised, up to a maximum of 32 mg/day. A common effective dose is between 12 and 24 mg, though lower or higher doses may be appropriate in some patients. 72

6.4.4.2 Option 2: Induction from methadone (can be undertaken in primary care if the doctor has the necessary experience)

- The dose of methadone should be reduced if necessary and the patient stabilised on 30 mg or less.
- The first dose of buprenorphine should be administered at least 24 to 36 hours after the last use of methadone and preferably with the onset of mild to moderate withdrawals.
- Increasing the time interval between the last dose of methadone and the first dose of buprenorphine reduces the incidence and severity of precipitated withdrawal.

The principles for deciding on a starting dose are shown in the table below.

<table>
<thead>
<tr>
<th>Last methadone dose</th>
<th>Buprenorphine Day 1</th>
<th>Buprenorphine Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 30 mg</td>
<td>4 mg</td>
<td>6 to 8 mg</td>
</tr>
<tr>
<td>10 to 20 mg</td>
<td>4 mg</td>
<td>4 to 6 mg</td>
</tr>
<tr>
<td>&lt;10 mg</td>
<td>2 mg</td>
<td>2 to 6 mg</td>
</tr>
</tbody>
</table>

Subsequent titration procedures are the same as for induction from heroin (see Option 1 above).
6.4.4.3 Option 3: Induction from methadone doses between 30 and 60 mg (should only be undertaken in specialist service or if the doctor has the necessary experience)

Starting buprenorphine from higher than 30 mg can be conducted as follows:

- The methadone dose should be reduced as far as possible without the patient becoming unstable or chaotic, and then abruptly stopped.
- The first buprenorphine dose should be delayed until the patient displays clear signs of withdrawal, which is generally longer than 24 to 36 hours (and may be as long as 48 to 96 hours) after the last methadone dose. Symptomatic medication, such as lofexidine, may be useful to provide the patient with some transitory relief.
- An initial dose of 4 mg of buprenorphine should be given, and following this the patient should be reviewed two to three hours later.
- If withdrawal has been precipitated (see above), further symptomatic medication can be prescribed.
- If there has been no precipitation or worsening of withdrawal, an additional 2 to 4 mg of buprenorphine can be dispensed on the same day.
- The patient should be reviewed the following day, at which point the dose should be increased to between 8 and 12 mg. Thereafter, titration should be managed as for heroin induction (see above).

N.B. If a patient is on more than 60 mg of methadone and wants to change to buprenorphine, then they should be referred to a local specialist who has experience of managing this transfer.

6.4.4.4 Frequency of dispensing

Buprenorphine should normally be prescribed on a daily regimen.

- It has the potential to be administered every two to three days, although no more than 32 mg should be dispensed in one day. The effectiveness of alternate-day dosing is somewhat unclear and this regimen is not commonly in use in the UK.
- One of the reasons for making the buprenorphine/naloxone combination (Suboxone) available was to reduce the need for ongoing supervised consumption and daily dispensing.

6.4.4.5 Post induction and stability

Achieving the optimal dose, particularly with methadone, may take several weeks. The primary aim at this stage is for street drug use to cease but sometimes a marked reduction is acceptable. Patients should not be penalised for using illicit substances, but discussion of continuing use is part of the therapeutic dialogue.

Other benefits include:

- Improvement in the individual’s health and well-being.
- Improved family relationships and/or relationships with non-drug-using friends.
- Progress in addressing issues like debt, housing, training and employment.
- Progress in addressing social network issues, e.g. no longer associating with a drug-using network.
- Reduction or cessation in offending (N.B. Not all drug users are involved in crime.)

It is important that progress is acknowledged with encouragement and rewarded by more trusting care arrangements, e.g. transfer from supervised consumption to daily dispensing or less frequent pick-up of opiate substitute etc.

7. Maintenance and detoxification

7.1 Choosing between maintenance and detoxification

Choosing between maintenance and detoxification can and must occur at any point during treatment, starting at the first assessment and at various points along the treatment spectrum. The views of the patient are central and the patient must be given choice and presented with the evidence.

Maintenance is suitable for people who want to stop using illicit opioids but are not yet able to achieve abstinence from all opioids. Prescribing can be offered long-term, at effective doses, usually between 60 and 120 mg daily for methadone and 8 and 32 mg daily for buprenorphine, individualised for each patient. The goal is harm reduction and stabilisation of lifestyle. Maintenance may also be prescribed on harm-reduction grounds to those wanting to reduce their consumption of illicit opioids. It should be emphasised that patients doing well on either methadone or buprenorphine should remain on that medication, rather than switching medications. Work should always continue on other drug use, alcohol use, psychological interventions and any health and social needs. There is a strong evidence base for maintenance and it is often an important step towards detoxification and abstinence.
Detoxification is suitable for people who are ready to become drug-free. This can occur in the community or with the person being treated as inpatient, and the speed of reduction should be governed by the patient and their clinical response. If a patient is new to treatment, they can be offered a choice between buprenorphine and methadone to reduce from; if the patient has been maintained on methadone or buprenorphine, then detoxification should usually be undertaken using the same medication. The person needs to be given the evidence about success rates and informed that detoxification is part of the process of becoming abstinent and not a stand-alone treatment. It is also important to assess whether the patient’s circumstances are conducive to maintaining abstinence and to advise on the timing accordingly.

Where circumstances are adverse, such as when patients are polydrug users, drinkers, or homeless persons, or are awaiting a court appearance, a further period of maintenance should be recommended with support to achieve appropriate stability and psychosocial change before attempting detoxification. It should never be imposed, particularly since research has shown high mortality rates among those detoxified. Detoxification is a stage and should always be followed by a package of care, which can include inpatient 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 detoxification; relapsing to heroin after a period of abstinence may be fatal.

Choosing between detoxification and maintenance treatment is not easy; there are many factors to consider and the decision should be patient-led. Patients should be able to move between these two aspects of treatment but preparation for detoxification is essential. Evidence shows that outcomes are considerably better with long-term maintenance treatment.

![Prescribing routes with methadone or buprenorphine treatment](image)
7.2 Detoxification

Detoxification should always be seen as a stage in the process of treatment with the aim of becoming drug-free, never as a stand-alone treatment; it should never be imposed and should always be supported by after-care and relapse prevention because of the high risk of relapse, the loss of tolerance and the risk of overdose and death. The patient, with support from the clinician, key worker and a care plan, needs to make an active decision to have a detoxification. Abstinence is often the patient’s main aim and detoxification can be an important stage in the achieving of abstinence. Regular discussion with patients on a maintenance prescription as to whether an opioid detoxification might be a treatment option is important.

NICE guidance suggests that, in order for a patient to give informed consent, they need to have been given information on:

- the physical and psychological aspects of opioid withdrawal (including the duration and intensity of symptoms, and how these may be managed)
- the use of non-pharmacological approaches to manage or cope with opioid withdrawal symptoms
- the loss of opioid tolerance following detoxification, and the ensuing increased risk of overdose and death from illicit drug use that may be potentiated by the use of alcohol or benzodiazepines
- the importance of continued support, as well as psychosocial and appropriate pharmacological interventions, to maintain abstinence, treat co-morbidity and mental health problems, and reduce the risk of adverse outcomes (including death).

Once the clinician and patient are clear that detoxification is the right treatment option, community detoxification should be offered to all patients as the first-line treatment unless:

- they have not benefited from previous care-planned community detoxifications
- they have significant co-morbid physical and/or mental health problems that need additional medical and/or nursing care
- they have complex polydrug use (e.g. are also dependent on benzodiazepines and/or alcohol)
- they are experiencing significant social problems that will limit the benefit of community-based detoxification (e.g. homelessness).

For this group of patients, an inpatient detoxification may be a more suitable option and a referral to specialist services would be appropriate, although the evidence for this being more effective is poor.

Advice on the timing of withdrawal should be offered. Where circumstances are adverse, a further period of maintenance should be advised, with support to achieve appropriate psychosocial change. The first-line treatment for detoxification should be methadone or buprenorphine. If the patient has been on methadone or buprenorphine, then detoxification should usually be undertaken using the same medication.

There is no evidence that detoxification for patients on methadone maintenance is more successful if patients are transferred to buprenorphine for the detoxification. However, it is important to take into account the preference of the patient, and swapping medications for detoxification purposes may be the appropriate course of action if the patient expresses a preference.

7.2.1 Dosing regimens for detoxification

7.2.1.1 Methadone

Following stabilisation on methadone, the dose can be reduced at a rate to suit the patient. A common regime is to reduce to zero in about 12 weeks. This usually involves a reduction of around 5 mg every one or two weeks. Patients often prefer a faster reduction at the beginning, although there is no research evidence to indicate the superiority of a linear or more stepped dose reduction.

A slower reduction of methadone is also possible if preferred by the patient. As with all detoxifications, it is important for a patient to stay on their optimal dose until they have stopped using heroin completely and then reduce the dose at their own pace. This can take place over many months or even years. This has been found to be effective in practice but there is little evidence to support slow detoxification regimes. It can also improve a patient’s confidence in their abilities to manage on lower opioid doses. Careful monitoring of increased drug and/or alcohol use on top of medication is advisable during slower reductions.

7.2.1.2 Buprenorphine

Following stabilisation on buprenorphine, the dose can be reduced at a rate to suit the patient. A common regime is reducing by 2 to 4 mg every two weeks. When the dose is reduced to 2 mg, it may be necessary to change to 400 mcg tablets and continue the reduction. An example of a dosing regime is shown in the following table.
Daily buprenorphine dose | Reduction rate
--- | ---
Above 16 mg | 4 mg every 1 to 2 weeks
8 to 16 mg | 2 to 4 mg every 1 to 2 weeks
2 to 8 mg | 2 mg every 1 to 2 weeks
Below 2 mg | 0.4 to 0.8 mg every 1 to 2 weeks

Patients who do not succeed with detoxification should be offered seamless access back into maintenance or other treatment. Enforced reduction in methadone dosages used to be common in the UK but is not supported by national guidance or evidence, and can lead to an increased risk of overdose due to a loss of tolerance.

Ultra-rapid detoxification with the use of general anaesthesia or heavy sedation (where the airway needs to be supported) should not be practised due to the risk of serious adverse events, including death.

7.2.2 Assessment for detoxification

- Carry out a full assessment (see Section 6).
- Testing can provide confirmation of the use of opioids and other substances.
- Clinically assess for the signs of opioid use.
- Take a history of problematic drug and alcohol use, including previous attempts at detoxification and their outcomes.
- Review physical and mental health problems, including their current treatment.
- If the patient is new to treatment, then review the reasons for detoxification and whether they fully understand all options and are prepared for abstinence.
- If the patient is moving from maintenance, confirm the reasons for detoxification at this stage and whether the patient is prepared for abstinence.
- Consider the potential risks of detoxification, including self-harm, overdose associated with loss of tolerance, and a return to drugs and alcohol as a response to opioid withdrawal symptoms.
- Consider the patient’s social situation, including employment, child-care responsibilities, family relationships, social support, financial situation, living arrangements, and involvement in criminal activity.
- Consider the impact of detoxification on family members, including children.
- Develop strategies to reduce the risk of relapse. Consideration of support networks will be an important factor, and advice about self-help groups and advocacy is particularly important at this stage.

Patients undertaking a detoxification should receive advice on:

- a balanced diet
- adequate hydration
- sleep hygiene
- regular physical exercise
- the need to continue in treatment after detoxification for support and psychosocial interventions, including relapse prevention
- local self-help groups, including Narcotics Anonymous (NA) and local user and advocacy groups.

Help should be available to patients in order to identify situations or states when they are vulnerable to drug misuse and to explore alternative coping strategies. Clinicians should ensure that maintaining the service user’s engagement with services remains a major focus of the care plan. Patients interested in detoxification should be asked if they want their family and/or carers to be involved in the assessment process.

- Family members and carers should be supported where possible by:
  - seeking their views and concerns about the effects of the detoxification upon themselves and other family members, in particular any children
  - providing advice on the impact of substance misuse on families and carers
  - providing information about local family and carers’ support groups and organisations
  - providing information about the detoxification process
  - assessing their personal, social and mental health needs.

Opioid-dependent patients considering self-detoxification should be encouraged to enter a structured detoxification programme or at least to maintain contact with drug treatment services.

7.2.2.1 Alcohol

Patients requesting detoxification who use alcohol but who are not alcohol-dependent should be encouraged to reduce their alcohol use, as this may increase as a result of opioid withdrawal symptoms; alternatively, alcohol may become a substitute for previous opioid use.

For patients who are alcohol-dependent, an alcohol detoxification should be offered prior to an opioid detoxification. In an inpatient setting, concurrent detoxification from both opioid and alcohol can be offered. Patients who are both opioid- and alcohol-dependent may need to be referred to a specialist practitioner.
7.2.2 Benzodiazepines

If the opioid-dependent patient is also dependent on benzodiazepines, then a benzodiazepine detoxification should be considered. The patient's preference, together with the severity of the dependencies, should be taken into account when deciding whether detoxification for opioids and benzodiazepines can run concurrently. Particularly in the community, they would normally be undertaken sequentially, beginning with benzodiazepines rather than together.

7.2.3 Alternatives for undertaking detoxification

7.2.3.1 Other drugs that may sometimes be helpful for symptoms in the end stages of detoxification

See table 1 below.

The advantage of general practice is that patients remain registered wherever they are in their treatment journey, providing ongoing stability. Support should be offered after detoxification for at least six months, but preferably a year, and can take many forms such as one-to-one relapse prevention counselling, community day programmes, local 12-step groups, inpatient rehabilitation, or a combination of these. Rehabilitation centres are guided by a number of different philosophies, such as 12-step or concept houses. The NTA provides a full list of residential rehabilitation services: The Residential Directory and BEDVACS. 77

Lofexidine is a non-opioid alpha-adrenergic agonist and is not a controlled drug. It is licensed for the management of symptoms of opioid withdrawal but is being used much less frequently. Lofexidine comes as a 200 mcg tablet and the effect lasts only a few hours. The treatment course is between seven and ten days, with doses starting at 800 mcg daily and rising to a maximum of 2.4 mg in divided doses. The dose is then reduced over subsequent days. Methadone or buprenorphine can be continued for the first two days of the lofexidine regime. There is a risk of bradycardia and hypotension hence the pulse and blood pressure need to be monitored. There is also a risk of rebound hypertension when treatment with lofexidine ends. It can cause drowsiness so advise patients not to drive.

It is most likely to be successful for patients who are using small amounts of opioids or have uncertain dependence, and those with shorter drug and treatment histories. It can also be used for the last stages of methadone or buprenorphine detoxification or to help reduction from high methadone doses. 76

Lofexidine can be used in patients for whom it is clinically appropriate and in those who have made a decision not to be detoxified from methadone or buprenorphine. In every case the patient needs to be carefully assessed and selected, should make an informed choice and must want to stop using opiates.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle cramps</td>
<td>Quinine sulphate 200 mg qids pm</td>
</tr>
<tr>
<td>Gastrointestinal spasm/stomach cramps</td>
<td>Hyoscine butylbromide (Buscopan) 10 to 20 mg qds pm</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Loperamide hydrochloride (Imodium) 4 mg stat, then 2 mg after each loose stool</td>
</tr>
<tr>
<td>Nausea</td>
<td>Metoclopramide hydrochloride 10 mg tds</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Propranolol 10 mg pm</td>
</tr>
<tr>
<td>Bone pain and headaches</td>
<td>Paracetamol 1 gm qds, or</td>
</tr>
<tr>
<td></td>
<td>Non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen 400 mg tds after food</td>
</tr>
<tr>
<td>Sedation or agitation</td>
<td>Trazodone 100 to 150 mg nocte, or</td>
</tr>
<tr>
<td></td>
<td>Diazepam 2 to 10 mg pm day and 10 mg nocte for 3 to 5 days</td>
</tr>
</tbody>
</table>

Table 1
7.2.3.3 Naltrexone

Naltrexone is recommended as a treatment option in detoxified, formerly opioid-dependent people who want assistance to remain opioid-free. Naltrexone is an opioid antagonist which, when taken regularly, blocks the opioid receptors so that the person does not experience the effects of opiates. It must never be prescribed without psychological support, including relapse prevention. For some patients the most common side effects, such as unease (dysphoria), poor sleep, nausea and low energy, may be a problem. There is evidence that naltrexone is hepatotoxic. Depression and insomnia can lead to relapse. In the UK, naltrexone is only licensed for use orally and is approved by NICE in England and Wales and by NHS Quality Improvement in Scotland. A depot formulation is available but it is not licensed for drug treatment.

Due to the potentially hepatotoxic nature of naltrexone, liver tests (LTs) should be conducted before and during naltrexone treatment. If the patient says that they are free from opiates and a urine test confirms this, then naltrexone can be started. If opiates have been used, then severe and prolonged withdrawal symptoms will result if naltrexone is administered.

Following a negative urine or oral fluid test for opiates, the patient should be given a single dose of naltrexone (25 mg) orally. If no withdrawal symptoms are experienced after a few hours, a 50 mg tablet of naltrexone can be given. Patients can be commenced on naltrexone within seven to ten days of finishing a methadone or buprenorphine detoxification. The usual maintenance dose is then 50 mg a day.

It is good practice to give patients a card indicating that they are maintained on naltrexone. The outcome of naltrexone treatment is improved by a programme of supervision, which can involve carers, to ensure compliance with the regimen. The effectiveness of naltrexone in preventing opioid misuse in people being treated should be reviewed regularly.

It is important for the patient to have the resources and support to be able to maintain abstinence. Relapse prevention groups or individual counselling are essential and mutual aid organisations such as NA (Narcotics Anonymous) can also be particularly important at this stage. Advice on the timing of withdrawal should be offered accordingly. Where circumstances are adverse, a further period of maintenance should be advised and support given to achieve appropriate psychosocial change.

7.3 Maintenance prescribing

7.3.1 Medically assisted recovery (MAR)

Maintenance prescribing is an important, but not only part of MAR. Many patients enter treatment requesting detoxification but may be unable to achieve it in the first instance, often because of the range of other problems that are present. This group will require longer-term prescribing for different lengths of time, varying between months and many years. Maintenance is suitable for people who want to stop using illicit opioids but are unable to achieve abstinence from all opioids. It can play an important step in a patient’s journey towards recovery and does not prevent future abstinence. Medically assisted recovery allows patients to make changes in other areas of their lives – for example, with the support of psychosocial interventions, continue to progress in their health and wellbeing and, if necessary, arrange housing or employment.

Maintenance as a treatment option must be an active decision between the patient and the clinician, must be reviewed at regular intervals and must be part of a broader programme of care. The goal is harm reduction and stabilisation of lifestyle. When these goals are achieved, patients may consider other treatment options, including detoxification and abstinence. Long-term maintenance may also be prescribed to those wanting to reduce their consumption of illicit opioids. It should be emphasised that patients doing well on either methadone or buprenorphine should remain on the medication that they are currently prescribed. Work regarding other drug or alcohol use should continue during maintenance, alongside psychological interventions and ongoing assessment of health and social needs.

7.3.2 Dosing regimes for maintenance prescribing

There is overwhelming evidence that prescribing should be at effective doses, usually between 60 and 120 mg, for methadone after induction and stabilisation. However, due to the range of individual responses, individual patients will be effectively maintained at doses below and above the optimal range. There is less consensus and evidence on the equivalent optimal dose for buprenorphine. In general, doses between 12 and 16 mg appear to be optimal, within the range of 8 to 32 mg of buprenorphine daily, individualised for each patient.
7.3.3 Instalment prescribing

Instalment prescriptions for methadone and buprenorphine should be written on blue FP10 (MDA) prescription forms in England and Wales, and on GP10 forms in Scotland. Prescriptions should initially stipulate daily supervised consumption (see Section 7.3.7) and subsequent daily pick-ups. Frequency of dispensing may be relaxed over time, although the dispensing interval will often move from daily pick-up to weekly pick-up via a period of time on three times weekly and then twice-weekly pick-up.

Prescriptions must be completed in indelible ink and can be handwritten or computer-generated. A handwriting exemption is no longer required.

7.3.4 The importance of the pharmacist

Pharmacists are key contributors to the success of drug treatment. They will see the patient much more often than the prescriber and can provide important additional support. Close liaison with pharmacists should be maintained.

Pharmacists offer dispensing of methadone and buprenorphine as an enhanced service under their contract, the Community Pharmacy Contractual Framework. They may also offer other services, e.g. needle exchange. It is important to be aware of the services available at local pharmacies and also to involve pharmacists in the care-planning process with the patient. A small but increasing number of pharmacists are becoming non-medical prescribers. Further services useful for drug users may be commissioned as enhanced services dependent on local need, such as wound management, hepatitis C screening, provision of emergency hormonal contraception, oral hygiene promotion and anticoagulant services.

Pharmacists should only dispense to the named patient. In exceptional circumstances, at the discretion of the pharmacist, a collector who has permission from the patient can pick up. In some areas the pharmacist needs to check this with the prescriber. The doctor can ask the pharmacist to report missed doses. The doctor should inform the patient that information will be shared with the pharmacist and that pharmacists may not dispense if three doses of methadone/buprenorphine are missed without discussion with the prescriber.

It should be normal practice before issuing a prescription to a new patient for the prescriber to make contact with the patient’s nominated community pharmacy to confirm dispensing arrangements. Prescribers may stipulate on the prescription which pharmacy the prescription is to be dispensed at, but this is not a legal requirement. Where it is requested by a pharmacy, it should be adhered to in order to make sure that a care agreement is present with the dispensing chemist.

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

7.3.5 Missed doses and lost prescriptions

Missed doses can be associated with the emergence of an opioid withdrawal syndrome after two or three days, and it can take up to three days for blood levels to return to normal. Patients who have missed doses should be encouraged back into treatment. The prescribing doctor should review patients who have missed more than three consecutive days and, if it is likely that tolerance has been reduced, retitrate dose levels up to an appropriate dose. If the patient has returned to using illicit heroin, then the induction may need to be started again.

- If a patient on a daily dispensing regimen misses a pick-up from the pharmacy, the patient should return the next day as usual for their next dose. The missed dose should not be replaced and is forfeited.

- If doses are missed for more than three days, then treatment should be reviewed to discover how the patient has managed without medication and to consider recommencing from a lower dose.

- If doses are missed for five days or more, a re-assessment must be undertaken and consideration given to restarting the medication.

- All instalment prescriptions should have a Home Office directive stamp, so that if a patient is picking up several days’ medication at one time and misses a pick-up, it enables the pharmacist to dispense the medication on a subsequent day, minus the missed dose. In England the following wording needs to be used:

  “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, provided no more than three days are missed.”

This wording alters slightly for supervised consumption.

- It has been endorsed by Wales but varies slightly in Scotland.

N.B. For more information see: www.psrc.org.uk/pages/controlled_drugs_information.html
Lost or stolen prescriptions should rarely be replaced and should be reported to the appropriate local body. If this occurs more than once, it may be worth considering posting or delivering prescriptions to the pharmacy. Patients who repeatedly miss doses should have their treatment reviewed. If the patient’s dispensing regime is less than daily dosing, the prescriber should consider reverting to daily dispensing, possibly supervised. See figure 4 below.

7.3.5.1 Continuing supervision

 Occasionally, patients do not keep appointments with either their doctor or their keyworker. Maintaining the patient in treatment is 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 medication with close liaison with the pharmacist who is seeing the patient every day.

7.3.6 Split doses for methadone

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 anticonvulsant phenytoin for epilepsy, may experience a drop in methadone plasma levels during the course of 24 hours once daily dosing is commenced. Patients receiving low doses of methadone may not have stable blood levels of methadone over 24 hours and may benefit from split dosing or an increase in dose. Symptoms of overdose and the action required in the event of an overdose should be explained to patients splitting their doses of methadone.

Three day recovery to steady state from missed dose at day ten

After a missed dose it can take three days for blood levels to return to normal. 

Figure 4
Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care

7.3.7 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 for about three months, unless there is a good reason not to (such as work, distance to the pharmacy, child-care 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.

It seems logical that supervised consumption should continue for at least three weeks after the final dose increase during a dose titration, after which time tolerance to the current dose will have developed.

Before taking a patient off supervision, a review should be undertaken to confirm stability and discuss future treatment. The pharmacist may 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 such as homelessness, continued risky drug taking behaviour or chaotic or excessive use of alcohol and frequently missed doses).

Safe storage of methadone must be discussed, and ensure the methadone will be kept in a locked container if small children are in the home.

The introduction of take-away doses, when appropriate, allows patients to lead 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 with the patient. Always make appropriate arrangements with the pharmacist in advance of the patient's arrival.

Supervision of methadone is quick and relatively easy to monitor. Supervision of buprenorphine, especially 8 mg tablets, is more complex, as it is taken sublingually and can take up to five minutes to dissolve. Some pharmacists may be prepared to crush buprenorphine tablets if requested by the prescribing doctor, as a means of reducing the time required for supervision and minimising risks of diversion of medication. Buprenorphine can be crushed under certain circumstances.

The National Pharmacy Association (NPA) has agreed that its Professional Indemnity Insurance policy will cover its members if they crush buprenorphine according to the joint Royal Pharmaceutical Society of Great Britain (RPSGB)/NPA protocol. Crushing is outside of the summary of product characteristics for Suboxone and so would constitute a use outside of the product licence when crushed. It is probably unnecessary to crush Suboxone, as it dissolves more quickly than Subutex, although some generic versions of buprenorphine may dissolve more quickly than branded Subutex.

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 of medication to the illicit market. Suboxone may have a role in reducing diversion, as it has lower value on the illicit market.

Once the patient is sufficiently stable, less frequent dispensing or take-home doses can be instituted. It may help to change the frequency of pick-up gradually, to three times weekly, then twice weekly and sometimes weekly, assessing stability at each stage. It is rarely appropriate to arrange for methadone to be dispensed less frequently than weekly, unless in exceptional circumstances, e.g. for travel or work.

7.3.8 Storage and safety at home

Once a patient is receiving take-home doses, there may be concerns about the amount of medication dispensed at once. There is no legal upper limit 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, and patients who have children regularly visiting their homes) by both the clinician and the dispensing pharmacist. The symptoms of overdose and the action required in the event of an overdose should be explained to the patient.

7.3.9 Screening

Screening can be carried out by (i) urine testing, (ii) oral fluid swabs and (iii) hair analysis.
7.3.9.1 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. Heroin, codeine, dihydrocodeine and morphine are detectable for about 48 hours, methadone on maintenance doses for seven to nine days and buprenorphine eight days.

Urine testing in maintenance treatment aims to confirm the use of substitute medication and to monitor illicit use of other drugs, such as cocaine and benzodiazepines. The frequency of testing depends on clinical progress and the level of stability. During induction and periods of instability, urine tests should be carried out more frequently and can help as a therapeutic tool. When a patient is stable, random urines may be helpful and should be carried out at least twice a year. However, they are not cost-effective if the patient is in treatment and has already admitted to the substance use.

Where there is not a threat to the patient’s treatment programme, research studies have shown a high rate of concordance between a patient’s report of their urine contents and the laboratory result. 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, and the existence of injecting sites. On-site urine testing is non-specific and can only indicate the type of drug in a non-quantitative way; on its own, it cannot confirm heroin dependence. Use of over-the-counter or prescribed medicines, e.g. co-codamol or codeine phosphate, can give positive results, as heroin is detected as morphine in the urine.

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 buprenorphine and even discharge from treatment. However, there is a strong consensus that it is inappropriate and ineffective for a prescriber or others to ‘punish’ a patient in this manner. Indeed, an increase in medication 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. 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 the prescribed medication should lead to further testing and a review of treatment. In most laboratories a negative result indicates that the drug was not present below a threshold level rather than not being present at all. 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 reiterate or reduce the prescribed dose and return to supervision.

Other reasons that a urine test may be requested are:

- to confirm a patient’s suitability to end supervised dispensing or their need to return to supervision
- to inform a planned discussion about a patient’s progress in treatment
- for (criminal justice) court reports (after discussion with patient)
- when requested by a patient, e.g. to create a usage history
- to confirm parents’ drug use in child protection cases, although hair analysis is more frequently used for this purpose now.

Most urinalysis procedures are carried out using gas chromatography in specialist laboratories and there is usually a delay in receiving a result. The result establishes that the drug/s is/are present but does not measure the amounts in which the drug/s has/have been taken. 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, is not confirmatory, and should always be used in conjunction with clinical signs and history. False positives and negatives can occur with on-site tests, though they are rare.

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. An observed urine test requires consent from the patient. It is sometimes needed for court cases, and specialist advice should be sought if there is an indication for one.

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 has requested a sample, then mouth swab tests should be used.

7.3.9.2 Mouth swab 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 and more convenient, and they preserve patient dignity. However, they can be more time-consuming to obtain and have a shorter detection window than urine.
7.3.9.3 Hair testing

Hair testing can provide a longer overview of drug use over a period of months, with a quantitative result. However, it can only show average drug use over each month. It is expensive, 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.

7.3.10 Addressing continued heroin and other drug use

Some patients may find it difficult to stabilise and be maintained on substitute medication and this may be evidenced by numerous phenomena including:
- Urine screens repeatedly positive (more than twice) for heroin
- Concurrent use of other drugs (such as alcohol, illicit benzodiazepines, cocaine or amphetamines
- Clinical evidence of continued opioid use, such as fresh injecting sites and constricted pupils
- Heavy alcohol usage
- Frequently intoxicated presentations
- Overdoses and/or presentations to accident and emergency departments and out-of-hours services
- Frequently missed doses
- Physical or mental health deterioration due to continued drug use.

Evidence of continued use of heroin and other drugs requires a review of treatment, revisiting 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, checking that medication is being taken correctly (especially sublingual buprenorphine) and utilising alternative pharmacotherapies. In some cases referral to a more specialised service may be needed, including mental health services when there may be unrecognised mental health problems.

Always assess thoroughly before withdrawing maintenance treatment or transferring to alternative pharmacotherapies. Withdrawal of maintenance treatment is associated with poor outcomes and should be considered as a last resort. It should only be considered if it is determined through clinical observation that the treatment is providing no benefit, that there is no likelihood of any benefit to the patient if it is continued, or that it is detrimental to the patient to continue. It may be helpful to discuss such cases with colleagues and specialists before taking such actions as terminating treatment.

The risk of overdose is greater with methadone because it is a full agonist and causes respiratory depression. The risk increases with both methadone and buprenorphine when there is concurrent use of alcohol, benzodiazepines and other sedating drugs, markedly so if this use is episodic. Binge drinkers and benzodiazepine users are at greater risk of overdose. Studies have found evidence of polydrug use in 92% of methadone-related deaths, and a report by the Ontario Coroner’s Office on methadone-related deaths found that in the context of toxicology tests, 30% of methadone-related deaths screened positive for alcohol and 60% screened positive for benzodiazepines. 41, 79
8. Drug interactions

8.1 General methadone and buprenorphine interactions

The main drug interactions of methadone and buprenorphine are due to their opioid activity. 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 being used to treat chronic diseases. The main drug interactions of methadone are associated with its CNS depressant activity and liver metabolism.

Concurrent use of some drugs may affect the plasma levels of methadone. Enzyme-inducing drugs, such as tobacco and alcohol, can lower methadone levels, whereas enzyme inhibitors, such as allopurinol, dextropropoxyphene, chloramphenicol, ciprofloxacin, disulfiram and isoniazid, can increase methadone levels. Deaths have also been reported from the interaction of methadone, which can prolong the QTc interval, with other drugs that can do this, such as the phenothiazines (see Section 9.6).

8.2 Interactions with other drugs

8.2.1 Benzodiazepines

Taking benzodiazepines with methadone (and to a lesser degree with buprenorphine) may cause additive CNS depression and result in an enhanced sedative effect. Large numbers of opioid drug users also use benzodiazepines (between 40 and 90%). Deaths involving methadone and buprenorphine are frequently associated with concomitant use of benzodiazepines and/or alcohol. While it may occasionally be advisable to prescribe benzodiazepines with methadone or buprenorphine, caution is recommended and thorough assessment and ongoing review plans should be in place.

Benzodiazepines should usually be prescribed on a short-term, reducing basis only.

8.2.2 Alcohol

Alcohol intake may alter the metabolism of methadone, increase CNS depression and result in serious respiratory depression and hypotension. Mixing buprenorphine with alcohol or other CNS depressants can also be dangerous. Alcohol is a high risk factor for toxicity, especially with bonge or high-level dependent use. In alcohol-related liver disease with impaired liver function, methadone and the buprenorphine metabolism may be reduced and may require a reduction in dose.

8.2.3 Antidepressants

Some antidepressants, including tricyclic antidepressants and monoamine-oxidase inhibitors (MAOIs), should be prescribed with caution due to possible sedation and hence increasing risk of overdose.

8.2.4 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. Cocaine is often one of several drugs that polydrug users take, which increases problems.

8.2.5 HIV medications

Patients on methadone or buprenorphine 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. It is useful to offer prescribing treatment in conjunction with an 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, to ensure patient comfort.

8.2.6 Hepatitis C (HCV) medications

HCV medications, such as pegylated interferon and ribavirin, are usually well tolerated by patients on methadone or buprenorphine. Sometimes side effects can mimic opioid withdrawal symptoms and the methadone dose is increased. Depression is a common side effect of hepatitis C combination therapy, as well as opioid dependence, so caution is required. Regular liver tests and full blood counts are advised.
8.2.7 Tuberculosis treatment
Rifampicin reduces methadone levels by stimulating the hepatic enzymes involved in methadone metabolism. Cases of severe withdrawal have been reported.

8.2.8 Anticonvulsants
Phenytoin and carbamazepine cause a sharp decrease in plasma levels of methadone due to enzyme induction but this does not affect buprenorphine.


9. Methadone, buprenorphine and other medical conditions

9.1 HIV and hepatitis (without extensive liver disease)
Methadone and buprenorphine are safe to use when the patient has active hepatitis B or C or is HIV-positive. Interactions with specific medications are mentioned above, but LTs should be monitored regularly, particularly at the start of treatment or if the patient’s clinical condition changes.

9.2 Dual diagnosis (co-morbidity of substance misuse and psychiatric illness)
Substitute medication can be used in severe, moderate and mild psychiatric illness if the patient is opioid-dependent and understands the treatment aims.

At least a third of opioid users in treatment suffer from mental health problems, including anxiety and depression.

Entry into treatment can have a significant positive effect on 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 for vulnerable patients.

Many of the patients with mental health problems will require joint working with psychiatric services and others.

A minority (about 10%) have severe enduring mental health problems that usually require joint working with psychiatric services.

Drug interactions with psychotropics should be considered.

9.3 Chronic and acute pain

Pain in people who use drugs is common, complex, often forgotten and poorly treated, and 10 to 25% of people who use opioids say they start opiates because of pain.

Prevalence of chronic pain is between 30 and 50% in treated substance users, compared with 10 to 15% of the general population.

Under-treatment is common and is often based on misconceptions including:
- Maintenance opioid agonists provide adequate analgesia. (This is not the case, as the duration of analgesic action, four to eight hours, is substantially shorter than that required for suppression of opioid withdrawal, 24 to 48 hours.)
- The use of opioids for analgesia may trigger relapse. (The reverse is true: acute pain is a well-recognized potential trigger for relapse.)
- The additive effects of opioid analgesics and maintenance opioids may increase the likelihood of respiratory and central nervous system depression. (This is not the case when pain is present.)
- The pain complaint may simply be a manifestation of drug-seeking behaviour. (Experience teaches clinicians that this is rarely the case.) Reluctance to prescribe due to prescriber concerns about side effects or diversion may result in opioid users receiving inadequate analgesia.

Pain is subjective and person-defined; it is always unpleasant. It can be acute, which is a protective warning. It can be predictable and respond well to treatment, or chronic, tending to be continuous pain of moderate to high severity for more than six months and, in contrast, unpredictable. It has a confusing relationship with tissue damage and is often resistant to treatment.

Pain can be affected by fears, age, gender, culture, previous pain experience of either self or significant others, and a wide range of psychological factors as well as education/understanding. A history of substance use, including alcohol, is commonly linked with chronic anxiety and chronic depression, which may negatively affect a patient’s experience of pain.
9.3.1 Key treatment principles for acute pain in patients on opioid substitution treatment

- Keep the treatment of drug dependency separate from the pain control, i.e. maintain the usual dose of opioid replacement.
- Be aware that non-pharmacological approaches may be useful and when prescribing use non-opioid and adjuvant analgesics, e.g. paracetamol, NSAIDs and tricyclic antidepressants at low dosage.
- If these are ineffective, try increasing the opioid dosage with dose-splitting (e.g. oral methadone four to eight-hourly) or introduce a weak opioid in high dosage or another opioid e.g. Oramorph elixir or MST.

If the patient is prescribed maintenance buprenorphine, acute pain can be treated in one of the following ways:

- Split the daily dose to six to eight-hourly. (The analgesic qualities of buprenorphine show a disparity with tolerance/dependence, though less so than with methadone.)
- Discontinue buprenorphine and introduce a full opioid agonist until the acute phase is over.
- Give high doses of a short-acting opioid agonist in addition to buprenorphine in an attempt to flood the mu receptors.
- Admit to hospital care, convert buprenorphine to methadone, titrate the opioid requirement for analgesic effect and prevention of acute withdrawal, and then re-introduce buprenorphine after the acute pain subsides.

There are two other phenomena which explain why patients derive little pain relief from maintenance opioids:

- Differential tolerance/cross-tolerance. This affects different opioid properties in different ways but with rapid tolerance to analgesic effect.
- Opioid-induced hyperalgesia (or anti-analgesia). Chronic neuropharmacological changes in the locus coeruleus/amygdala (and other NMDA and opioid receptor sites) result in an increase in pain sensitivity, especially to cold pressor and deep pain sensation. Though more important in the context of chronic pain, this may explain why much higher doses of opioid are required when treating acute pain in a patient on a long-term opioid substitute agent.

9.3.2 Key principles of treatment of chronic pain in the context of substance use

The assessment of chronic pain in the context of substance use is more complex and time-consuming than for acute pain. It should not only take account of the pain history but also provide a mental state assessment (because of the close correlation of chronic pain with chronic psychiatric morbidity); include a psychological assessment, looking especially for chronic anxiety and depression, and also coping styles; look at relevant psychosocial factors; give a past medical history (because of the co-relation of chronic pain with chronic illness); and provide other information including beliefs and attitudes to pain, to doctors and carers, and to possible referral.

Simple chronic pain strategies, e.g. treating initial pain early to minimise secondary immobility, and encouraging early return to work or activity, so reducing the effect of chronic noxious neural change, are important. The early prescription of adequate effective analgesia reduces the risk of persistent pain.

If chronic pain is increasingly difficult to treat or where substance use is escalating or becoming difficult to manage with a substitute prescription, remember to investigate the chronic pain appropriately and use TENS, acupuncture, physiotherapy, epidural and effective pharmacotherapy for sufficient duration.

Opioid hyperalgesia may be more important than previously realised. In certain situations and with careful consideration, some patients benefit from a reduction of opioid dose or even detoxification.

- The initial strategy should be to use all the non-opioid analgesic options that are available. Paracetamol (up to 1 g qds) is first-line for mild to moderate pain.
- Non-steroidal anti-inflammatory drugs (NSAIDs) should be used where not contraindicated. The choice of NSAID should be based on the assessed risk of cardiovascular disease or gastrointestinal haemorrhage. Naproxen or ibuprofen is likely to be the safest option.
- Antidepressants, carbamazepine, gabapentin, pregabalin or topical agents, e.g. capsaicin cream, can be useful.
9.4 Liver disease

Methadone and buprenorphine are metabolised by the liver and their activity may be increased and/or prolonged in individuals with impaired hepatic function.\(^1\)

Methadone appears to be safe to use in patients with chronic hepatitis C (CHC), as severe liver disease does not increase peak serum methadone levels, despite a prolongation of the apparent terminal half-life.

Buprenorphine appears to be safe to use in patients with CHC, as long as the patient has normal liver function and no evidence of cirrhosis. There have, however, been reports of deterioration in liver function in those with pre-existing liver disease who inject buprenorphine tablets or who take an overdose of buprenorphine, so caution should be exercised.\(^6\)

If possible, liver function needs to be checked at assessment, but waiting for the results should not delay the starting of methadone or buprenorphine if the patient is well. If liver tests (LTs) are normal, monitor periodically (e.g. six to nine-monthly) through treatment, as buprenorphine can cause an increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

If there is abnormal liver function (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 tests are not well correlated with the presence or absence of cirrhosis.

In patients with advanced liver disease the risks from methadone or buprenorphine are insignificant compared to the risks from street drugs and people should therefore be encouraged to use the former.

If there is evidence of liver disease, in particular if there are significant alcohol issues and/or the user has CHC, then take LTs more regularly. If there is any evidence of marked deterioration in LTs, then refer to a liver specialist for advice.

9.5 Fertility

Methadone and buprenorphine treatment may restore fertility in women who were using heroin (this is probably more to do with improved health than the effect of the medications), so contraceptive advice should be given.

9.6 High-dose methadone, torsades de pointes and the risk of sudden cardiac death

The MHRA stated in May 2006 that patients with risk factors for QTc interval prolongation should be carefully monitored whilst taking methadone.\(^6\) The 2007 Clinical Guidelines reiterated this advice.\(^1\) This is due to concern that torsades de pointes, a potentially lethal ventricular arrhythmia that is known to be associated with a prolonged QTc interval, may be leading to some deaths as a consequence of methadone treatment.

The association of torsades de pointes with very high doses of methadone was first described by Krantz in 2002 in a retrospective review of 17 patients with arrhythmias. In these cases the mean daily dose was very high at 397 mg (100 to 600 mg) a day. Fourteen patients were given a pacemaker and all 17 survived. No other patients on high-dose methadone were examined, so the relative risk was unknown.\(^6\) A review of the literature in 2006 found 40 cases of torsades de pointes in association with methadone, with none of these being fatal and 85% having a clear precipitant in addition to high-dose methadone.\(^6\)

One study in Norway estimated that the maximum attributable mortality risk was in the region of 0.06 deaths caused by methadone-induced QTc prolongation for every 100 patients on methadone for one year. There were 8 out of 173 methadone patients (4.6%) who had a prolonged QTc greater than 500 ms that placed them at risk. A review of several cohort studies in a recent set of US consensus guidelines put the proportion with QTc intervals of over 500 ms consistently at around 2%.\(^6\)

In the Norwegian study all of the eight cases were on doses greater than 120 mg daily. There seems likely to be a dose-dependent relationship between methadone and QTc prolongation but this was not shown to rise over years in treatment.\(^6\)

There are several drugs used in clinical practice that are known to cause prolongation of the QTc interval under certain conditions; these drugs include lithium, tricyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs), macrodides such as erythromycin and clarithromycin, sotalol and verapamil. A full list is available at the Arizona Center for Education and Research on Therapeutics (www.torsades.org). There are case reports of ciprofloxacin and itraconazole inducing torsades de pointes in methadone-maintained opiate users.\(^94,95\)
9.6.1 Identifying patients at risk

There are several factors that will increase the risk of QTc prolongation and these should be identified at the initial assessment and then considered at review appointments:

- all those on methadone 100 mg or above
- anyone on methadone that has any additional factors:
  - using any other medications causing QTc prolongation
  - see list above and including cytochrome P450 CYP 3A4 inhibitors
  - having any history of structural heart disease (such as ischaemic heart disease, long QT syndrome, myocarditis, left ventricular hypertrophy)
  - using prescribed injectable formulations
  - using stimulants
  - having bradycardia
  - having a history of congenital QT prolongation in the family
  - having any relevant medical factors, such as hypothyroidism, liver disease, malnourishment, HIV infection, anorexia nervosa, alcohol dependence.

If the patient is felt to be at risk, then an ECG should be offered and the discussion and whether the patient accepts should be documented. Measurement of the QTc interval can be calculated manually from the ECG, or many ECGs will produce an automated value. The US guidelines reviewed the evidence for automated interpretation and felt this offered a reasonable estimate for arrhythmia risk screening in a primary care setting. If any ECG is normal, with no evidence of QTc prolongation, consider repeating it 6 to 12-monthly if the risk of QT prolongation remains high.

9.6.2 Managing those with prolonged QTc intervals (> 500ms)

- Discuss the findings, the risks of QTc prolongation and potential treatment options with the patient. This will include giving advice on alternative medications and on stimulant and alcohol use.
- Consider further investigations and/or referral to cardiology.
- Consider reduction in the dose of methadone but take into consideration other risks of reduction of methadone dose.

If there is felt to be a substantial risk, it may be appropriate to consider a planned detoxification or a transfer to buprenorphine. There is no risk of prolonged QTc intervals with buprenorphine. However, this has to be weighed against the difficulties of transferring the patient to buprenorphine if they are on large doses of methadone and there is a risk of relapse or increased illicit drug use.

10. Special groups

10.1 Polydrug users

Polydrug use – the use of more than one drug, including alcohol – is common. Until recently, most services were opioid-focused because previously problematic heroin use was the most common reason for presenting and much of treatment provision was based on prescribing interventions. Heroin is still the most common reason for presenting for drug treatment but it is important to be aware of other drugs and alcohol use. It is not within the scope of this guidance to outline prescribing options, which are limited, for drugs other than opioids. However, it should be acknowledged when polydrug use is part of the patient’s presenting problem, and if prescribing strategies are needed for this additional drug use (see Section 7.3.10).

10.1.2 Concurrent use of other drugs and alcohol

Concurrent use of alcohol, benzodiazepines and other sedating drugs substantially increases the risk of death from methadone overdose. It is important to explore alcohol use in a patient for whom methadone or buprenorphine is being prescribed, and doses may need adjustment if the patient continues to drink heavily. Alcohol dependence is highly associated with polydrug dependence, and bingeing (acute high intake) may induce methadone withdrawal symptoms.
The risk of interaction occurring appears to be linked to the amount of alcohol ingested, i.e. higher levels in the body carry an increased risk of harmful or fatal interaction. Steady-state levels of methadone may be altered with chronic liver disease and the use and abuse of other drugs, including alcohol. The combined acute effects of alcohol and other central nervous system depressants can result in harmful interactions, especially in chronic drug users, older patients and those with lung disease. In addition, as methadone has a long duration of action and elimination half-life, when it is ingested with alcohol there is a potential for harmful interactions for a period of time after methadone has been consumed. Alcohol interactions may go unnoticed in some cases but are more likely to occur in chronic and polydrug users and in older adults.

There is increasing concern about the prevalence of harmful alcohol consumption in the drug treatment population. Overdose is known to be higher in people who inject drugs and drink alcohol at unsafe levels. There is also concern about the effects of alcohol on those with hepatitis C. The NTA states that alcohol is a major contributing factor to illness and death for clients of drug services. 92

There are no studies to date to indicate preferential outcomes with either methadone or buprenorphine in the combined management of opioid and alcohol dependence. If opioid dependence is recognised and there is no prior history of treatment, it might be helpful to consider buprenorphine because of the reduced but not absent risk in overdose. However, there may be a problem with achieving adequacy of dosage. It is sometimes difficult to attain a reasonable dose range in the presence of associated benzodiazepine and alcohol use. Patients may actually require a higher dose due to cross-tolerance, but such higher doses are also linked to toxicity. Tricyclics need to be totally avoided because of a very high risk of additive toxicity.

10.2 Pregnancy and birth

Drug use in pregnancy results in a high-risk pregnancy but high-tech obstetric care is not needed to deal with the issues. Management of pregnancy in all drug users should be multidisciplinary at all times; good communication between the professionals involved is particularly important, especially at the beginning and around the expected time of delivery, preferably involving a planning meeting early in pregnancy. It is also important to be clear about who is managing the prescribing and to offer support about the evidence for treatment both to the mother and to the other professionals involved.

10.2.1 Methadone in pregnancy

Methadone is currently the recommended substitution treatment 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 substitution therapy alone. Women attending treatment services usually have better antenatal care and better health, even if they continue to use illicit drugs. 102 The rate of stillbirth is higher in illicit heroin users (5% compared to 1% in the non-using population) 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 for debate. Methadone stability rather than dose reduction is recommended 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 with and at a sufficient level to reap the positive benefits of methadone maintenance. 103

Abrupt withdrawal of methadone is 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, with only a few isolated case studies, but none shows a good link between detoxification and fetal death. One study showed increased catecholamines in the liquor following untreated detoxification, suggesting biochemical evidence of a stress effect on the baby. However, this is not evidence that the baby was stressed to any clinically 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. 103

Limitations on management plans should not be imposed on the basis of unsubstantiated risks. Thus the key points for assessment of whether or not a woman undergoes methadone reduction or detoxification, at what stage of pregnancy, and at what speed she does this should be dictated by what is appropriate for her circumstances, her wishes and her ability to cope. It is important to continue the current dose of methadone if the woman is admitted to hospital or arrested, in order 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. 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 the largest reductions in the third trimester and other centres report similar findings. 103 It is important to check for signs of withdrawal in pregnant women, and if detected, make a small (2 to 5 mg) increase in methadone dose. Pregnant women may sometimes benefit from splitting methadone doses if signs of withdrawal occur. Close liaison between the prescriber and the pharmacist is useful during the early months of pregnancy when morning sickness may be an issue. This may cause vomiting of methadone soon after it is swallowed; if this occurs, it is essential to ensure quick replacement of prescriptions and it may be appropriate to prescribe a safe anti-emetic.

The primary aim for the treatment of pregnant women 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.

10.2.2 Buprenorphine in pregnancy

Pregnancy is not a contraindication under the UK MHRA licence; rather it is a special warning. Trials suggest that buprenorphine may be useful in pregnancy and it is being prescribed extensively. It has a similar incidence, compared to methadone, of neonatal abstinence syndrome (see Section 10.2.3), but this tends to be less severe and needs less and shorter treatment. A pregnant patient can be told that she can continue treatment while at the same time being made aware of the facts and/or referred to a specialist if appropriate or requested by the patient. 104 It is recommended that informed consent be documented in the patient’s notes. Remember that choices of analgesia and the sex of the baby. Symptoms are less likely to be severe in preterm infants, possibly due to immaturity of the neurological system, but are more severe if the baby is otherwise unwell or irritable, e.g. in association with birth asphyxia or infection. While there is not a linear relationship between severity of neonatal withdrawal symptoms and maternal methadone or buprenorphine dose, there is evidence that the higher the maternal methadone dose, the greater the likelihood and likely severity of neonatal withdrawal symptoms. Informed consent to treatment should always be documented in the patient’s notes. Clinicians should be aware that, if the baby is judged to need treatment and the mother withholds consent, this could constitute a child protection issue.

Symptoms generally begin during the first 24 hours after birth (heroin and benzodiazepines only) but can be delayed by up to five or more days. Some clinicians have reported a delay in the onset of symptoms for as long as seven to ten days. Methadone and buprenorphine tend to cause a delay in the onset of neonatal withdrawal symptoms as 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. 105 However, the proportion that needs treatment appears to be different in different populations. For example, Glasgow, an area with higher overall neonatal morbidity than other areas in the UK, experiences severe socioeconomic deprivation. Newborns exposed to methadone and buprenorphine are more likely to experience symptoms and more often require treatment than those exposed to heroin.

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

10.2.4 Breastfeeding

Breastfeeding is to be encouraged in all women who use drugs, unless they are HIV-positive, not only because of the usual advantages this confers, but also because some medication passes across the breast milk and reduces the severity of any withdrawal symptoms the baby is experiencing. Moreover, use of tobacco, opiates and benzodiazepines, common amongst heroin users, is associated with an increased risk of sudden infant death, and the latter is lower among breastfed babies.
10.2.5 Parents who use drugs

Parental drug use can have serious implications for a child's care at all stages of development and must be carefully assessed throughout the parents' care. As drug use is a chronic relapsing condition, this is an ongoing process. Hidden harm, an Advisory Council on the Misuse of Drugs (ACMD) report on responding to the needs of children of problem drug users, and a follow-up report, Hidden harm three years on, found that daily heroin use, daily alcohol use, regular stimulant use, unstable accommodation and family breakdown involving drug use is often short-term and there tends to be less tolerance. Detoxification, usually with buprenorphine, may be appropriate for acute withdrawal, but may not be sufficient as a single intervention. 20 A further report by the ACMD, Pathways to problems, found that the children of problem drug users are more susceptible to using drugs and alcohol themselves. Hidden harm concluded that effective treatment of the parent can have major benefits for the child. 20

The needs of children of drug users are paramount and parental drug use per se does not mean that children are not being well cared for. The Children Act (2004) introduced the Common Assessment Framework (CAF) as the first step to assessing the needs of children, with a view to providing support for the child to reach its full potential in variety of ways. These include increased support at school, support with parenting skills, and support with social activities. 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 multidisciplinary approach, with good communication between agencies, when looking after parents of young children where drug use is an issue.

Particular attention to safe storage needs to be paid by parents who are prescribed methadone or buprenorphine. 21

10.4 Young people (under 18 years)

Methadone is not usually first-line treatment for young heroin-users/patients (under the age of 18), as their drug use is often short-term and there tends to be less tolerance. Detoxification, usually with buprenorphine, may be considered as first-line treatment and it is important that specialist young people services should be involved. Recommendations from the NTA suggest that all areas should have young people’s services. 2 Practitioners working in primary care should not work in isolation with children under 18 years and need to involve specialist practitioners in their care. NICE has issued guidance on interventions to be used with young substance users, which involve a variety of approaches, including family- and group-based interventions. 22 Vulnerable and disadvantaged young people or their parents and carers will present to primary care on a regular basis, and as a result it is vital being aware of the local services for young people, making a referral where appropriate.

The GP should also be involved in contributing to a CAF (Department for Children, Schools and Families (DCSF), Every Child Matters) for their young drug-using patients.

10.5 Black and minority ethnic (BME) groups

Black and minority ethnic people who use drugs can be marginalised in treatment; hence it is crucial to develop services to meet the needs of diverse communities. It is important to understand how a combination of factors may characterise the lives of many BME people: in particular, the risk factors that revolve around social exclusion and deprivation. There must also be an appreciation of how these affect the context within which drug use exists, how opiate use may take different forms, and how illicit drugs may be accessed via different routes and for different reasons. For example, Iranians may use opium; Eastern Europeans and refugees may use methadone as a sedative for clandestine entry into the UK; and imported methadone may be of different colours and unknown strengths.

It is important to emphasise the need for effective translation services when appropriate (and, where necessary, using Language Line rather than trying to co-ordinate interpreters). Once effective communication is in place, the same principles of treatment apply, i.e. that dependency should be established and then substitute medication commenced, with care when there is uncertainty about the strength of the illicit opiate being used, as in the case of opium smokers.

Access to and the quality of drug treatment in primary care should be the same for any patient, but primary care services treating patients from different cultural backgrounds need to be aware of how this may impact upon the patient, the staff and the service itself. It is not an issue that can be adequately addressed unless consideration is given to service accessibility, the appropriateness of the service being provided, and potential barriers to service utilisation.

An investigation into equality and diversity in services for BME communities by the NTA 20 looking into knowledge of drugs and drug services among a range of BME groups in England provides insight into this issue. It consists of an introduction and five reports covering the following communities: South Asian, Black African, Black Caribbean, Kurdish, Turkish Cypriot, Turkish, and Chinese and Vietnamese. Some of the key messages are as follows:

- Drug services need to work locally in order to address the heterogeneity of what are described as ‘the South Asian/African etc. communities’.
In July 2006, followed by updated guidance in 2009 and 2010. IDTS features the provision of opioid substitution treatment, and the uniting of two separate treatment services in prisons: psychosocial drug treatment, known by the acronym CARAT (Counselling, Assessment, Referral, Advice, and Through Care) and clinical substance misuse management. Enhanced psychosocial interventions for the first 28 days of custody were set out in a guidance document to commissioners and providers. IDTS seeks to reduce suicide risk though active and immediate (i.e., first night) management of substance withdrawal. This guidance also included the recommendation of opioid prescribing (methadone or buprenorphine) to stabilise opioid dependence, after which the patient is given a choice of maintenance or detoxification at a rate at which they feel comfortable. Opioid maintenance offers the potential benefits of protection against fatal overdoses on release, and a reduction in the rates of re-offending (and, therefore, re-imprisonment). Naltrexone, in conjunction with psychosocial support from drug teams both in the prison and in the community, is also an option in IDTS prisons. Some prisons may offer a re-induction using buprenorphine or methadone, prior to release. This is a viable option, and a pragmatic approach to safety. It is not a feature of the IDTS document but is mentioned in the 2007 Clinical Guidelines. The need to increase methadone treatment levels, if it is felt that the prison dose is insufficient to prevent use on discharge is mentioned in the IDTS guidance. The use of FP10 prescriptions are currently being piloted in a few prisons nationally to attempt to counteract the common problem of prisoners being released (often in an unplanned way) without the community drug treatment services being given adequate notice. The 2007 Clinical Guidelines state that people in prison will commonly achieve stability on a lower dose of methadone than those in the community, though the guidance makes the point that some will require equivalent doses. Commonly, a maximum dose is 40 mg per day, the argument being that subtherapeutic doses are satisfactory in the context of low availability of illicit drugs. However, research in New South Wales prisons showed that methadone maintenance is effective in bringing hard-to-reach drug users into treatment, lowering overdose rate during and after imprisonment, reducing injecting and HIV and hepatitis virus infection, and preventing recidivism. The dose range was similar to that used in the community, because initial community-based studies indicated that benefits only occurred when daily doses were above 60 mg/day. 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 care.
IDTs has been enhanced by the transfer of responsibility for prison health care to PCTs or other local bodies, and there has been an increase in the numbers of primary care practitioners specialising in working within secure environments and providing clinical leadership in prison-based drug treatment. Primary care practitioners should work closely with prisons and criminal justice teams to ensure continuity of care between prisons and the community, and to reduce the risk of suicide and overdose for those entering and leaving the prison system. Clinicians should be aware that a lack of available clean equipment in prisons can result in risky injecting practice leading to an increased risk of acquiring HIV and/or hepatitis.

10.7 People admitted to hospital

Patients are often frightened when entering hospital and a GP can help to alleviate this difficult process by writing a letter clearly stating the dose of substitute medication and by phoning the admitting doctor to reinforce this. When the patient is admitted via emergency departments in working hours, after proper assessment by a hospital doctor including checking their dose with the drug user, confirming opioid use with an on-site urine test, asking the community pharmacist about the last dose of medication, and confirming all this with the prescriber, treatment may be continued only if the prescription is dispensed daily and preferably is 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 if the hospital cannot confirm the dose, then titration should be undertaken. Local guidelines should be in place. If there are no local guidelines, the local shared care monitoring group or equivalent may wish to assist in the drawing up of these documents.

10.8 Substitute prescribing and driving

It is the patient’s responsibility to inform the Driver and Vehicle Licensing Authority (DVLA) if they are on substitute medication, 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. Applicants or drivers complying fully with a supervised oral maintenance programme may be licensed, subject to favourable assessment and normally an annual medical review. 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 to determine whether they can be licensed whilst on a maintenance programme.

The DVLA and General Medical Council (GMC) also state that, if doctors are aware that patients continue to drive in a dangerous way, then they should impress upon such patients more forcibly that they are not to drive. If the patient continues to drive, doctors (at their discretion) should break confidentiality, informing the DVLA and warning the patient that they are doing so. This can be a difficult area of practice and the GMC has produced specific guidance on the issue. Doctors may not want to endanger their relationship with patients, but it would certainly be tragic, as well as highly problematic for any doctor, if patients hurt or killed people while driving in a manner already known to be unsafe. More information is available on the DVLA website: www.dvla.gov.uk. Also refer to the 2007 Clinical Guidelines www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_104819

10.9 Travelling in the UK or abroad

Home Office guidance was changed in 2009 for travel abroad. There is now an open general licence that covers all prescriptions lasting under three months. Patients who are travelling for three calendar months or more and who need to carry more than three months’ supply are required to apply for a personal licence. A personal licence enables individuals to take prescribed controlled medicines out of the UK and bring them back in on their return. It has no legal standing in other countries. Patients need to apply for a personal licence at least ten working days before the date they are due to travel. The patient’s GP will need to provide a letter supporting your application.

A prescriber’s letter is recommended for anyone taking medication out of the country and should outline the prescription. It should be noted, however, that this only applies to export from the UK. Patients are strongly advised to check with the relevant embassy as to the regulations regarding the import of controlled drugs into the country they are intending to visit. Patients should also be aware of new regulations governing the carrying of liquids in hand luggage. Methadone tablets may be needed for long-haul flights, unless the methadone mixture can be proved to be ‘essential medication’.

For patients travelling within the UK, it may be safer to provide their usual script for them to take to their destination. Phoning the local drug service may be helpful with arranging access to local dispensing chemists. Sometimes when patients are travelling abroad with larger instalments of methadone it may be appropriate to transfer from methadone mixture to tablets for the purpose.

www.homeoffice.gov.uk/drugs/licensing/personal 2009
11. PRIMARY CARE-BASED DRUG AND ALCOHOL TREATMENT

Treating drug users is an enhanced service under the GP Contract (2004). A range of different models of drug treatment in primary care have evolved, often driven by local circumstances. These can include Locally Enhanced Services (LES), National Enhanced Services (NES), and bespoke services that are commissioned by local PCTs. It is important for primary care clinicians to be clear about the model of primary care drug treatment that is available in their area. The local Drug and Alcohol Action Team should be able to provide information (details can be found at www.nta.nhs.uk). Due to the government change in May 2010 all of this is likely to change.

As GPs, nurses, and pharmacists have been encouraged to develop special interests, many have become specialists in drug dependency and are involved in leading local primary care and secondary care services, as well as services based in prisons and other custodial establishments. In addition, non-medical prescribing is encouraging increasing numbers of nurses and pharmacists to train and practise in the drug dependency field. With the advent of practice-based commissioning, the UK is likely to see an even more diverse range of models of treatment commissioned locally.

Patients who use drugs and/or alcohol often have a number of requirements, including health and social care needs. Treatment, therefore, involves a multidisciplinary response. 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.

11.1 CLINICAL GOVERNANCE

It is important that practitioners working in the drug misuse field develop the relevant competencies to deliver their service. The competencies for doctors involved in the treatment of drug users are outlined in detail in Roles and Responsibilities of Doctors in the Provision of Treatment for Drug and Alcohol Misusers, which is currently being updated. Many drug services now require GPs, nurses, pharmacists and other practitioners to complete the RCGP Certificate in the Management of Drug Misuse Parts 1 and 2. Clinicians may benefit from individual or peer supervision, mentoring or other forms of professional support.

In order to deliver a safe and effective service:

- Clinicians must work as a team with other providers involved in the care of patients.
- Patients must be involved in the planning of their own treatment and in the development, design and delivery of local treatment services.
- Services should be provided that are consistent with national guidance and principles, and in line with the evidence base. This should include policies and procedures on information governance. (This should take into account confidentiality and information sharing.)
- A regular audit and review cycle should be in place.
- Where appropriate, family members and carers should be involved in the planning of patients' care and in the planning and delivery of local services.

11.2 HANDWRITING EXEMPTIONS AND PRESCRIPTION PRINTING

Handwriting exemptions are no longer necessary for writing prescriptions for methadone and buprenorphine. It is preferable to print out prescriptions for controlled drugs (CD) using a computer if available; if a computer is not available, a relevant stamp should be used. CD prescriptions issued from older versions of ‘Emis’ need additions such as how and when to dispense but can be a useful halfway solution between handwriting and bespoke computer software programs. There are a number of special programs for CD prescribing that are worth purchasing if a GP prescribes for over ten people or so. Full information on the prescription issued should be recorded on the computer or in the patient notes. If a different system is used for scripts and for general medical services (GMS), it is important to record in GMS notes that a script has been given.
Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care

12. Patient education

The prescribing of methadone and buprenorphine carries risks and it is important that patients are given full information about these medications’ action and effects. This should include: effects and unwanted effects; how to start; the risk of increased effect; risks if used with other sedative substances such as alcohol and benzodiazepines; risks from loss of tolerance post detoxification or withdrawal (especially following physical illness or imprisonment); and safety in pregnancy and in childcare. It is also useful to explain why certain medications or compositions of medications cannot be prescribed and why it is important to work within the guidance.

Contraceptive advice needs to be given to all potentially sexually active drug-using patients and this should include information on the use of condoms for protection against sexually transmitted infections. Advice about the likelihood of 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 and The Alliance Handbook on Treatment.


Methadone is defined by the Misuse of Drugs Act 1971 as a Class A drug and buprenorphine as a Class C as far as their illicit use is concerned. As a medicine, methadone falls within Schedule 2 of the Misuse of Drugs regulations 2001 and buprenorphine within Schedule 3. Consequently, methadone attracts a slightly higher dispensing fee than buprenorphine, although the drug itself is cheaper. Schedule 2 drugs are subject to the full controlled drug requirements relating to prescriptions, safe custody and the need to keep registers; Schedule 3 drugs are subject to the special prescription requirements and some are exempt from the safe custody requirements. Buprenorphine (and temazepam) must be kept in a CD cabinet but there is no requirement to keep registers (although there are requirements for the retention of invoices for two years).
Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care

References


Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care

Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care
For additional copies, and for further information on issues relevant to primary care based drug and alcohol treatment, please contact

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This guidance, and other resources including an interactive discussion forum, are available on the SMMGP website at www.smmgp.org.uk