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Guidance for the use of buprenorphine for the treatment of opioid dependence in primary care

RCGP Drug & Alcohol Misuse Training Programme
RCGP Sex, Drugs and HIV Task Group
SMMGP

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Contents

Background	2
Who is the guidance for?	
Evidence-based guidance	
1. Rationale for use of buprenorphine	2
2. Clinical pharmacology	3
3. Indications, contraindications and precautions 	4
4. Choosing between buprenorphine and methadone	5
5. Choosing between maintenance and detoxification	6
6. Starting buprenorphine – induction	6
7. Stabilisation of buprenorphine dose	8
8. Maintenance buprenorphine prescribing	9
9. Buprenorphine and liver disease	11
10. Detoxification from buprenorphine stabilisation or maintenance	11
11. Transfer to methadone maintenance treatment	12
12. Shared care	12
13. Patient education	12
14. Training	12
15. Buprenorphine, Misuse of Drugs Act 1971	13
16. Injecting Buprenorphine and the potential for misuse	13
17. Cost	13
18. Further reading	13
References	14
Appendix 1: Patient leaflet	15
Appendix 2: Summary	17

Background

This guidance has been produced to aid medical practitioners in the use of buprenorphine as a substitute medication for opioid dependence for maintenance and detoxification. It should be read in conjunction with ‘Drug Misuse and Dependence: Guidelines on Clinical Management’ issued by the UK Departments of Health in 1999¹.

The key principles of the 1999 guidelines that pertain to this guidance are:

- The safety of the patient and of the wider community is paramount.
- Good assessment procedures and mechanisms to prevent the diversion of prescribed medication will promote safety and improve patient outcome.
- The care and treatment of drug users is a multi-disciplinary and multi-agency activity. Shared care is a rational model for service delivery within which patients prescribed buprenorphine can be managed.
- Patient involvement in their treatment is essential.
- Patient education about treatment effects is important.
- Clinicians should not undertake specific interventions beyond their level of competence and confidence. Training and professional development should underpin clinical practice.

The production of this guidance was stimulated by the needs of primary care practitioners themselves, leading to requests for such guidance at the Royal College of General Practitioners (RCGP) 6th National Conference ‘Management of Drug Users in General Practice’ in May 2001.

Since the publication of the Clinical Guidelines there has been the development of a new type of general practitioner, defined as the GP with a Special Interest (GPwSI). The GPwSI can play an important role in the implementation of this guidance as can the Practitioner with a Special Interest (PwSI), which includes nurses and pharmacists.

Who is the guidance for?

The guidance is aimed at clinicians involved in the care of drug users and has been developed specifically to support the use of buprenorphine in primary care. It is anticipated that GPs, nurse specialists and pharmacists will find the guidance particularly relevant.

Evidence-based guidance

This guidance draws on the international research literature. It is recognised that this is a developing evidence base, and that this update incorporates new evidence since the guidance was first published in 2003. Further updates will also be required as there are some areas of clinical practice with buprenorphine for which, up to now, there is limited or no direct evidence available.

To address these evidence gaps, this document draws upon the clinical experience of experts in the field from primary and secondary care, involving discussion with international² and national colleagues³. It also draws upon parallels from conventional methadone practice.

1. Rationale for use of buprenorphine

There is a growing body of evidence that treatment for opioid dependence can be effective⁴. Methadone substitute prescribing is one well-established treatment modality and is supported by a substantial body of research literature and clinical practice⁵. However, methadone is not suitable for, or popular with, all opioid users seeking treatment. The provision of a flexible menu of effective treatment options, and some degree of choice for those seeking treatment⁶, is likely to optimise the outcomes and process of treatment of opioid dependence.

Buprenorphine is an effective, safe medication for use in the treatment of opioid dependence and is a valuable addition to the formulary of medications for treating opioid dependence⁷. It was licensed for use in opioid dependency in the UK in 1999. It has been used in other parts of the world (e.g. France, Australia) for longer.

It is a partial opioid agonist, appears safer in overdose than methadone and may have an easier withdrawal phase. It can be used for maintenance or detoxification.

A number of randomised trials suggest that buprenorphine exhibits comparable efficacy to methadone as substitute maintenance medication when used in equivalent doses⁸. Others show buprenorphine given in flexible doses appeared statistically significantly less effective than methadone in retaining patients in treatment but may suppress heroin use better^{9 10}. It is likely that there will be some patients who respond better to methadone maintenance and others to buprenorphine maintenance, with each medication having potential advantages and disadvantages.

There are relatively few controlled trials of using buprenorphine as a detoxification agent¹¹. A Cochrane review of the available information, which requires updating, showed that buprenorphine is able to relieve the signs and symptoms of withdrawal from heroin and methadone, but further investigation is required¹². Evidence regarding buprenorphine efficacy compared to methadone as a detoxification agent is limited but it appears to be more effective than symptomatic medications such as alpha-adrenergic agonists (e.g. lofexidine or clonidine) in managing detoxification from heroin or methadone.

2. Clinical pharmacology

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. An understanding of its pharmacology will help guide its clinical use⁷.

Buprenorphine:

- has low intrinsic agonist activity, only partially activating mu opioid receptors, and consequently high buprenorphine doses produce a milder, less euphoric and less sedating effect than high doses of other opioids such as heroin, methadone or morphine. However, it exerts sufficient opiate effects to prevent or alleviate opioid withdrawal including craving.
- has a high affinity for mu receptors and binds more tightly than heroin, methadone or morphine. 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.
- binds strongly 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.

Box 1

Classification of opioids

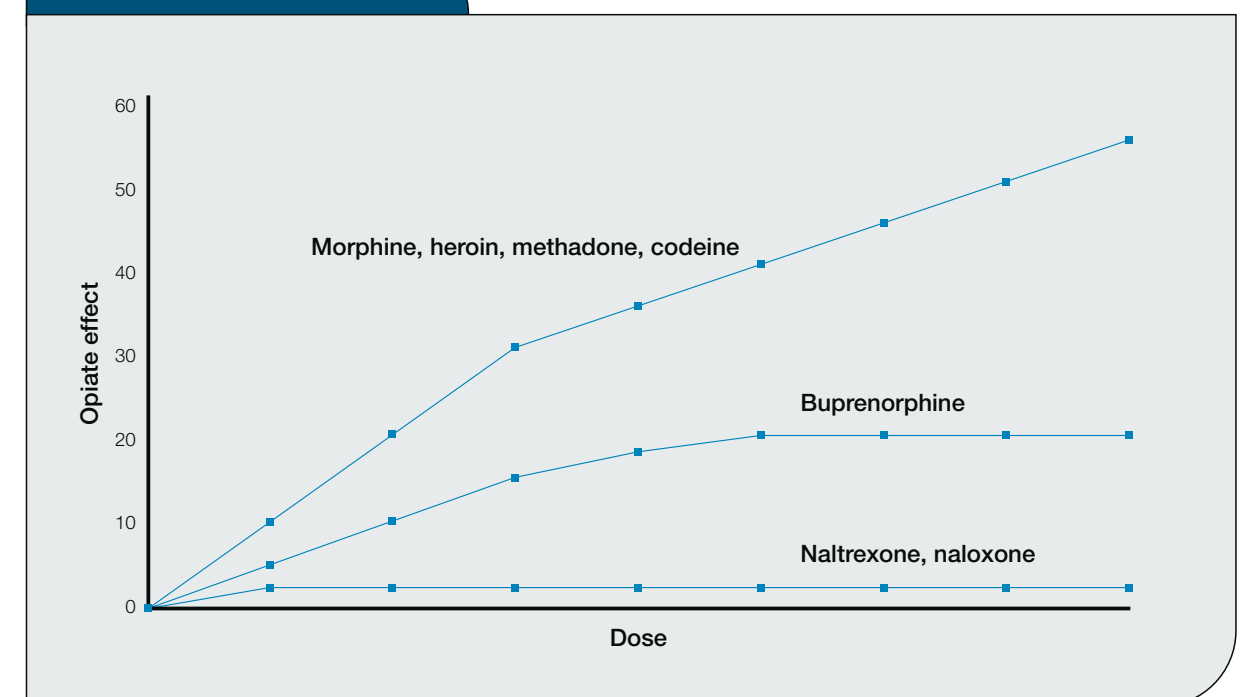


Figure 1 Opioid effect with dose of different drugs

Buprenorphine sublingual tablets are licensed for treating opioid dependence in the UK. They contain buprenorphine hydrochloride and are available in 400 micrograms (or 0.4 mg), 2 mg and 8 mg strengths. The tablets are administered sublingually because it has poor oral bioavailability (inactivated by gastric acid and a high first pass metabolism).

Relevant properties

- **Time to peak concentration**
90 to 150 minutes after sublingual administration
- **Time for peak clinical effects**
1 to 4 hours post dose
- **Duration of action**
Related to dose:
 - Low doses e.g. 2 to 4 mg exerts clinical effects for up to 12 hours
 - Higher doses e.g. 16 to 32 mg can exert effects for up to 48 to 72 hours
- **Metabolism**
Principally in the liver via two hepatic pathways: glucuronide conjugation and N-dealkylation by the CP450 enzyme system
- **Excretion**
Principally in the faeces and urine
- **Elimination half-life**
Between 20 and 37 hours
- **Blockade dose (dose where effects of additional opioids are markedly reduced)**
Maximal above 12 to 16 mg daily
- **Maintenance doses**
Between 8 to 32 mg daily
- **Equivalence**
Direct equivalence is difficult to estimate and is not a linear relationship. When comparing the efficacy of maintenance doses, 12 to 16 mg buprenorphine (sublingual tablets) is approximately as effective as 50 to 80 mg methadone in reducing heroin use and retaining patients in treatment¹². It is difficult to compare doses above 80 mg of methadone and above 16 mg of buprenorphine because of their different effects.
- **Easily soluble**
As buprenorphine is easily soluble there is a risk that it can be dissolved and injected. Consumption of the drug should be supervised to begin with to limit this risk. Injecting buprenorphine tablets can be associated with venous damage, pain on injecting, infections, risk of blood borne viruses and toxic hepatitis.

Effects and unwanted effects

Most unwanted effects of buprenorphine are similar to those associated with other opioids, including constipation, headaches (common with buprenorphine), sleeplessness, sickness and sweating. In addition many patients complain of a bitter taste. As with other opiates, side effects vary from individual to individual, but are usually most prominent in the first few days of treatment.

Subjectively, many patients on buprenorphine treatment often report a 'clear head' response quite different to the 'clouding' associated with heroin or methadone use. Some patients find this 'clarity' uncomfortable whilst others may value it. This subjective experience may be a factor that influences patient choice.

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

An assessment is essential to determine suitability for treatment. This should include urine drug testing to ascertain the presence of opioids. Patients entering treatment should have: liver function tests (LFTs) and screening for blood borne viruses (HIV and hepatitis A, B and C), although initiation of treatment should not be unnecessarily delayed whilst waiting for the results.

Its optimal use, like other medications, will depend on adequate dosing and the concurrent delivery of non-pharmacological interventions that directly and indirectly address the underlying disorder of opioid dependency⁷.

More work needs to be undertaken to ascertain which people are best suited to buprenorphine treatment. It may well be suited for treatment in primary care, outside more traditional opioid treatment delivery systems⁷.

Indications for use: Buprenorphine treatment should be considered for the following populations:

- Opioid dependent
- Informed consent to treatment with buprenorphine

Contraindications: Buprenorphine should not be used with the following populations:

- Allergic or sensitive to buprenorphine
- Under 16 years (except on the advice of a specialist)
- The licence for buprenorphine does not cover breast-feeding mothers (see Box 2 re pregnancy).

Pregnancy

Pregnancy is **not** a contraindication under the UK MHRA licence, rather it is a special warning. Trials suggest that it may be useful in pregnancy but currently there is as yet insufficient safety data to recommend its use. It has a similar incidence, compared to methadone, of neonatal abstinence syndrome but this tends to be less severe and needs less and shorter treatment. A pregnant patient on buprenorphine should be referred to a specialist and told that she can continue with the current treatment while at the same time being made aware of the facts¹³. Recommend that the patient has given informed consent and it is documented in their notes.

Box 2

Precautions:

Caution should be exercised in prescribing buprenorphine for the following patients:

1. **Concurrent use of other sedating drugs or medications.** As with methadone, buprenorphine can be associated with sedation, respiratory depression and coma when used in conjunction with central nervous system (CNS) depressants, such as alcohol, benzodiazepines, barbiturates, neuroleptics, and tricyclic anti-depressants.
2. **Patients in methadone treatment at doses of greater than 30 mg.** Transferring to buprenorphine is likely to be associated with precipitated withdrawal (see Box 4) and should only be attempted after consultation with a specialist or experienced prescriber.
3. **Medical conditions complicating opioid use.** As with other opioids (including methadone), buprenorphine should be used cautiously in individuals with recent head injury, acute abdominal conditions, or with severe respiratory, hepatic or renal disease.
4. **Patients suffering with chronic pain** – for which additional opioid analgesia is frequently required.
5. **People with severe mental illness**, with limited capacity to provide informed consent.

Box 3

4. Choosing between buprenorphine and methadone

There has been a recent Cochrane systematic review for maintenance⁹. This Cochrane review identified thirteen randomised controlled trials (RCTs) on maintenance, all but one of which were double-blind. They evaluated the effects of buprenorphine maintenance against placebo and methadone maintenance in retaining patients in treatment and in suppressing illicit drug use. Cochrane meta-analysis found the following results:

- At average / common methadone doses currently used in the UK (30 to 60 mg) buprenorphine can achieve broadly comparable outcomes. Specifically, buprenorphine given in flexible doses appeared statistically significantly less effective than methadone in retaining patients in treatment, but there was a trend (not significant) for less heroin use in buprenorphine groups compared with methadone groups.
- Optimal doses of methadone (e.g. 80 to 120 mg) are still the gold standard for maintenance.
- The efficacy of high dose buprenorphine (16 to 32 mg) compared with higher dose methadone (80 to 120 mg) had not been examined in comparative studies.

The reviewers conclude that buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is not more effective than methadone at adequate dosages. Also, buprenorphine is not significantly different from methadone in the impact on other substance use (e.g. cocaine, benzodiazepines, alcohol).

With similar outcomes, the choice between methadone and buprenorphine should be informed by other factors¹⁴. There is limited evidence of the superiority of either medication for particular subgroups, and the decision as to which medication to use should be made in consultation with each patient after consideration of the relative merits of each medication.

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

- Buprenorphine may be better suited to those who wish to cease using heroin completely, as the blockade effects of even moderate dose buprenorphine interfere with the subjective effects of additional heroin use. In contrast, whilst high dose methadone treatment is also well suited to those who wish to stop using heroin, those patients who wish to continue to use heroin may prefer low dose methadone treatment.
- Withdrawal from buprenorphine appears to be easier than from methadone, and as such may be preferred for those considering a detoxification program.
- The transition from buprenorphine to naltrexone can be accomplished much earlier than the transition from methadone to naltrexone, and consequently, those considering naltrexone treatment after detoxification may be better suited to buprenorphine.
- Buprenorphine is less affected by interactions with hepatic enzyme inducers/inhibitors (anti-convulsants, rifampicin, ribavirin).
- Buprenorphine is less sedating than methadone. This may be positive or negative for different patients.
- Using buprenorphine alone is safer in overdose.

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 transferring to the other medication or referral to a specialist practitioner for review.

It should be emphasised that patients doing well on either methadone or buprenorphine should remain on that medication.

Efficacy of BPN maintenance treatment

For heroin use and treatment retention in RCTs

High dose MMT (>80 mg)

better than

Medium dose MMT (40 to 80 mg)
= Medium dose BMT (8 to 12 mg)

better than

Low dose MMT (<40 mg)
= Low dose BMT (<8 mg)

Note: No RCTs of high dose BPN (≥16 mg) to methadone

MMT = Methadone maintenance treatment
BMT = Buprenorphine maintenance treatment

Figure 2 15

5. Choosing between maintenance and detoxification

Buprenorphine can be used as a maintenance intervention or as a detoxification agent.

Maintenance is suitable for patients who want to stop using illicit opioids but are unable to achieve abstinence from all opioids at present. Prescribing is long-term at effective doses individualised for each patient. The goal is harm reduction and stabilisation of life-style. When comparing detoxification and maintenance treatment with methadone, outcomes are considerably better with long-term maintenance treatment¹⁶. There is some evidence to suggest this is also true with buprenorphine¹⁷.

Detoxification can be attempted with patients who wish to detoxify from all opioids. There is a high relapse rate to heroin use unless detoxification is combined with psychosocial interventions. As such, detoxification should not normally be seen as a stand-alone treatment modality and should not be imposed.

6. Starting buprenorphine – induction

The purpose of induction is to safely establish the patient as quickly as possible 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 (e.g. 16 mg) is reached. Induction can be effected for patients using heroin or methadone. The key to understanding buprenorphine induction is the phenomenon of precipitated withdrawal (see Box 4).

Precipitated withdrawal

This form of opiate withdrawal can occur in someone commencing buprenorphine who has recently used heroin (less than 8 hours previously) or methadone (less than 24 hours previously). It is caused by the high affinity of buprenorphine displacing other opioids (e.g. methadone, heroin) from opioid receptors, but having less opioid activity (partial agonist). This rapid reduction in opiate effects can be experienced as precipitated withdrawal, typically occurring within 1 to 3 hours after the first buprenorphine dose, peaking in severity over the first 3 to 6 hours and then generally subsiding. If it occurs, reassure the patient and carer and offer symptomatic treatment such as lofexidine (e.g. 400 to 600 mcg 8 hourly for 1 to 2 days), as appropriate, if withdrawal symptoms are severe. Do not prescribe more buprenorphine until the opiate withdrawal symptoms have settled.

Box 4

The principles of safe induction with buprenorphine are:

- Delay the first dose of buprenorphine until the patient is experiencing features of opioid withdrawal (this typically means at least 8 hours after last heroin use, or 24 to 48 hours after last methadone use).
- Commence with an initial buprenorphine dose of between 4 and 8 mg.
- Increase the buprenorphine dose on subsequent days, or later the same day if facilities are available, according to clinical response.
- Rapidly titrate the buprenorphine dose on subsequent days according to clinical response by 2 to 4 mg (although dose increases of up to 8 mg are generally safe).
- Ensure frequent review of the patient and supervised consumption where available.
- 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 and provide patient leaflet (see Appendix 1).
- Ensure patients understand that most people take several days to stabilise on their medication, particularly if transferring from methadone (where it can take 1 to 2 weeks for patients to stabilise). Precipitated withdrawal should also be explained (see Box 4).

- Offer to see the patient yourself (or a team member) before the next appointment if required and coordinate with the pharmacist.

Transition 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 1 to 3 days. Lofexidine may be helpful with these unpleasant effects. It can be used for 1 to 2 days two tablets four times a day. Some patients transferring from methadone to buprenorphine find it difficult to stabilise and feel uncomfortable on buprenorphine for 1 or 2 weeks. Steady state in blood concentration levels is reached after about 5 to 8 days. Advice about sleep hygiene should be given.

Dispensing and supervision

The Clinical Guidelines¹ recommend that buprenorphine is dispensed daily during induction and that consumption, if possible, is supervised by the pharmacist for a period of time which may be, depending on the patient for at least the first 3 months.

Pathways into and out of buprenorphine treatment

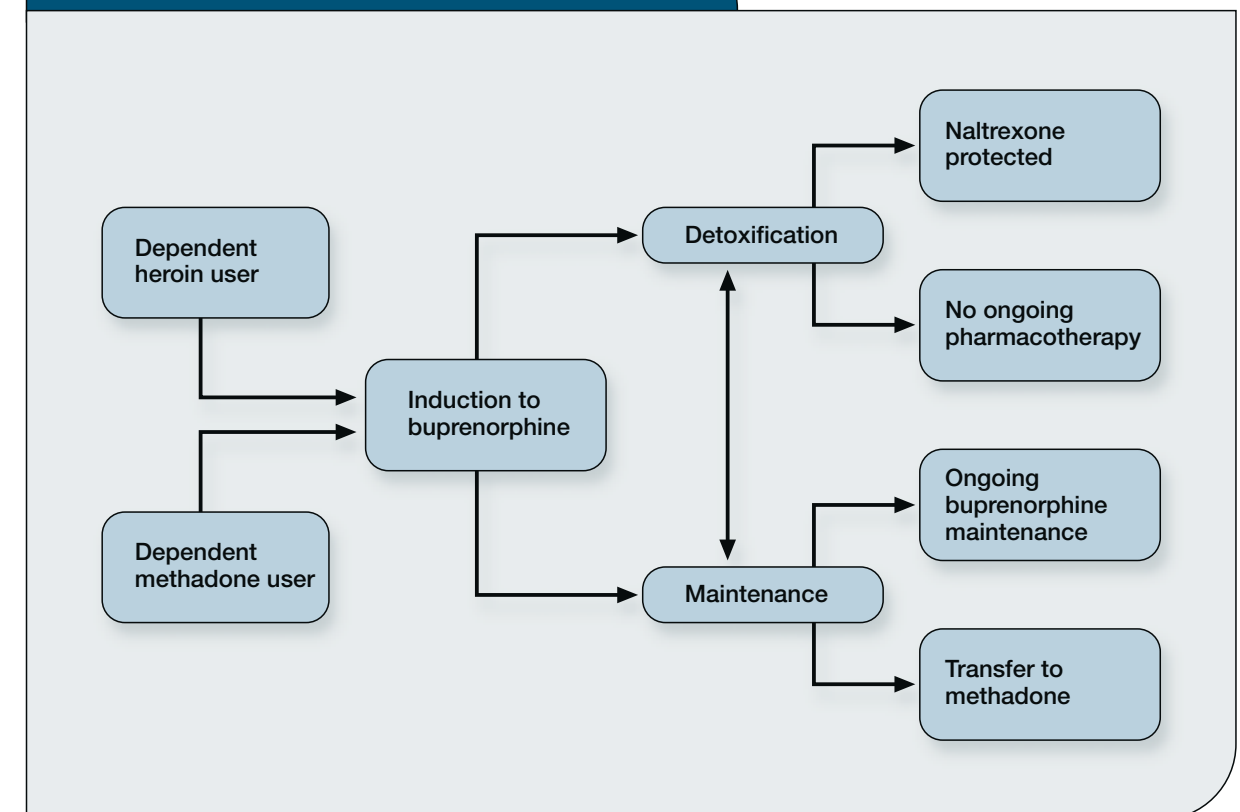


Figure 3

Option 1:**Induction from heroin (can be undertaken in primary care if doctor has necessary support and experience)**

- The first dose of buprenorphine should be administered at least 8 hours after the last use of heroin and preferably with mild withdrawals present to reduce the risk of precipitated withdrawal (see Box 4). Precipitated withdrawal is rare with transfer from heroin⁷.
- A first dose of 4 mg buprenorphine is generally recommended. Starting doses of between 4 mg to 8 mg can be used and are safe subject to there being no precautions (see Box 3).
- The dose can be increased by between 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 to 24 mg, though lower or higher doses may be appropriate in some patients¹⁸.

Option 2:**Induction from methadone (can be undertaken in primary care if doctor has necessary support and experience)**

- The dose of methadone should be reduced to and 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 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 (see Box 4).
- The principles for starting doses are shown in the table below.

Last methadone dose	Buprenorphine Day 1	Buprenorphine Day 2
20 to 30 mg	4 mg	6 to 8 mg
10 to 20 mg	4 mg	4 to 6 mg
<10 mg	2 mg	2 to 6 mg

Subsequent titration procedures are the same as for induction from heroin (see above).

Option 3:**Induction from methadone doses between 30 to 60 mg (should only be undertaken in intermediate or specialist service and/or if the doctor has 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 but 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 2 to 3 hours later.
- If withdrawal has been precipitated (see Box 4), 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 to 12 mg. Thereafter, titration should be effected as for heroin induction (see above).

Option 4:**Induction from levels of methadone greater than 60 mg daily should not be attempted in primary care.**

- If a patient is on more than 60 mg of methadone and wants to change to buprenorphine then they should be referred to the local specialist drug service.

7. Stabilisation of buprenorphine dose

Stabilisation involves finding a suitable dose that keeps the patient engaged in treatment without the need to supplement with other drugs and use heroin 'on top.'

Dose stabilisation may take several days. It is important that this is achieved as quickly as possible to prevent patient drop out. To this effect, the dose of buprenorphine should be increased daily until the dose is stable, such that the patient does not experience withdrawal symptoms. Sleep difficulties must be taken seriously and advice about sleep hygiene should be given. Consider a short-term (less than 5 days) prescription of diazepam to help the initial sleep difficulties while stabilising.

8. Maintenance buprenorphine prescribing (see also the Clinical Guidelines¹)

The value of substitute maintenance prescribing for opioid dependency is well established, in which buprenorphine has a place^{9 10}. The dose range of buprenorphine maintenance prescribing is 8 to 32 mg daily. The most usual range used to achieve abstinence from heroin use is between 12 to 24 mg daily. As a partial agonist, higher doses of buprenorphine may not produce corresponding increases in effects, so increasing the dose may not make any difference in subjective effects (e.g. increased euphoria), but may further reduce illicit opioid use by increasing the blockade effect.

There should be regular reviews of treatment, including care-plans and goals, which should be at least 3 monthly and should include checking for injecting sites. The usual General Medical Services should always be offered (including blood borne virus screening, hepatitis vaccinations [HBV and HAV if injector], smears, etc.). Patients should be made aware of, and be able to access, a range of social and psychological services within the local environment.

Optimal outcomes with buprenorphine maintenance will occur when a range of other non-pharmacological interventions, such as counselling, support the prescribing of buprenorphine¹⁹.

Frequency of dosing

- Buprenorphine should normally be prescribed on a DAILY regimen.
- It has the potential of being able to be administered every 2 to 3 days, although no more than 32 mg should be dispensed in one day.
- Alternate day dispensing will have advantages for supervised consumption (supervised self-administration), as daily attendance at the pharmacy will not be necessary.
- Patients who have been stable on buprenorphine for 3 months, who have no high-risk drug use (e.g. ongoing use of heroin, other injecting drug use, alcohol or benzodiazepines, frequent intoxicated presentations, recent history of overdose) and make this choice, may be considered for reduced-frequency dosing.
- The effectiveness of alternate day dosing is somewhat unclear and should only be considered after consultation with an experienced prescriber.

The following guide to dose levels can be recommended:

2-day dispensing regimen: 2 x daily dose (up to a maximum of 32 mg)

3-day dispensing regimen: 3 x daily dose (up to a maximum of 32 mg)



The above conversion chart is a guide only, and the dose should be titrated according to clinical need and response. There are safety concerns (e.g. liver function) about dosing clients with more than 32 mg on any given day, and a specialist should be consulted prior to attempting such high doses.

Some individuals (at least one third of patients) will not tolerate 2-day or 3-day dispensing regimes because they experience increased cravings or features of withdrawal on the non-dosing days, and it will be necessary to maintain them on a daily dispensing regime.

Instalment prescribing

Buprenorphine can be written using FP10 (MDA) prescriptions (Instalment) in England (since 1999), in Wales (since February 2003), and in Scotland using a GP10 or GP10(SS)(3) where the prescriber has a Home Office exemption from handwriting requirements.

Missed doses

Missed doses can be associated with the emergence of an opioid withdrawal syndrome after 2 or 3 days. Patients who have missed doses of buprenorphine should be encouraged back into treatment. The prescribing doctor should review patients who have missed more than 3 consecutive days of buprenorphine, and retitrate dose levels up to an appropriate maintenance dose. If they have gone back to illicit heroin then the titration needs to be started again as option 1.

Daily dispensing regimens

If a patient on a daily dispensing regimen misses a pickup from the pharmacy, the patient should return the next day as usual for their next dose. The missed dose should not be replaced.

Patients who repeatedly miss doses should have their treatment reviewed. If on less than daily dosing the first step would be to revert to daily dispensing.

Supervised consumption (supervised self-administration) and take-home doses

There are benefits and problems associated with take-home doses. Benefits include the practical and psychological advantages of greater patient control. Problems include the possibility of poor compliance, injection of tablets and diversion onto the illicit market. Supervised consumption (if available) should be continued, where possible, until the prescriber is satisfied that the patient has been stabilised on the correct dose and maintains a reasonable level of compliance. For the pharmacist to be able to provide supervision, the tablet/s should be administered sublingually and the patient supervised until the tablets have dissolved (5 minutes or more). In many areas, pharmacists are paid for providing this supervision.

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 is not currently licensed to be administered like this and there may be problems with product liability. Crushed tablets become unlicensed products for which the manufacturer is no longer liable for any damage caused to the patient. Prescribers and/or pharmacists should contact their local Primary Care Organisation or Mental Health Trust to determine the local policy and confirm with their insurer that they have the necessary professional indemnity cover.

Once the patient is sufficiently stable, less frequent dispensing or take home doses can be given. If giving take home doses, it may help to gradually change the frequency of pick up, to three times weekly, twice weekly and then weekly, assessing stability at each stage. It is not appropriate to arrange for buprenorphine to be dispensed less frequently than weekly.

Urine testing

Buprenorphine is not detected in routine tests for opioids. Some laboratories are able to test for buprenorphine by special arrangement (using microplate urine tests and/or oral fluid testing). In most circumstances, urine testing to confirm diagnosis of opiate use would be undertaken before commencement of substitute treatment with buprenorphine. The frequency of urine testing thereafter depends on clinical progress¹ but this should be no less frequently than bi-annually.

Overdose

As buprenorphine is a partial opiate antagonist it is safer in overdose than full agonists, such as methadone, causing less respiratory depression^{17,20}. There is less risk of overdose in opioid-naïve individuals. However, the phenomenon of opioid related death is complex and buprenorphine related deaths have been reported in combination with other sedative drugs such as alcohol or benzodiazepines, but less than with methadone^{21,22}.

As buprenorphine is not easily displaced by the antagonist naloxone, high doses (10 to 30 times the normal naloxone doses used to reverse opioid overdose) are needed to reverse effects of buprenorphine and may be of limited value. The initial management of overdose involves basic principles of maintaining respiration and circulation and referral to appropriate emergency services.

Drug interactions

(see also Box 3: Precautions)

The main drug interactions of buprenorphine are due to its opioid activity.

■ Benzodiazepines:

Many drug users also use benzodiazepines and deaths have been known to occur as a result of the combination of buprenorphine with benzodiazepines and/or alcohol²². As with other opiate substitute treatments, caution is advised and review procedures are recommended when prescribing benzodiazepines¹.

■ Alcohol, other sedatives, anti-depressants:

Alcohol intake may impair the metabolism of buprenorphine. Mixing buprenorphine with alcohol or other CNS depressants can be dangerous. Caution is advised, as are thorough assessment and review procedures. Some anti-depressants including tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) should be prescribed with caution due to possible sedation.

■ Cocaine:

There are no reports of a significant interaction with cocaine. This is likely to be due to cocaine being metabolised by different enzymes.

■ Other full opioid agonists (e.g. opiate analgesia):

Buprenorphine may precipitate opioid withdrawal syndrome when given to those taking full opioid agonists (e.g. morphine). Buprenorphine reduces the effects of other opioids given for analgesia.

■ Opioid antagonists:

Delayed opioid withdrawal syndrome can be precipitated by the use of naltrexone.

■ HIV medications:

There is no known interaction with HIV combination therapies. As with other opioids, patients being treated with HIV combination therapies may require buprenorphine dose levels to be adjusted. These adjustments are likely to be minor and, in keeping with titration principles, sufficient to ensure patient comfort²³. It is advisable to offer substitute prescribing treatment in conjunction with an HIV specialist.

■ Hepatitis C (HCV) medications:

There is good data on interferon / ribavirin and methadone showing that there are no problems. It is likely to be similar with anti-HCV therapy and buprenorphine but further research and experience is required.

Addressing continued heroin and other drug use

Some patients may find it difficult to stabilise and be maintained on buprenorphine. This may be evident by:

- Urine screens repeatedly positive (more than twice) for heroin or methadone
- Concurrent use of other drugs (such as alcohol, illicit benzodiazepines, cocaine or amphetamines)
- Clinical evidence of continued opioid use, such as fresh injecting sites, pin-point pupils
- Overdoses and/or presentations to A & E, out of hours, etc
- Frequent missed doses
- Physical or mental deterioration due to continued drug use

This requires a review of treatment, the first step being to determine that the patient is taking the medication properly⁷. If the patient is taking more than 2 tablets at one time and is finding this uncomfortable, advise them to take no more than 2 at any one time and allow all to dissolve in the mouth, checking the dose is sufficient and increasing as necessary. This uncomfortable feeling usually occurs early in treatment. Later in treatment it may be due to the development of tolerance, which although not common with buprenorphine, can occur. As with other treatments, it is important to check the patient is receiving appropriate psychosocial interventions. Always check all factors before withdrawing from maintenance treatment or transferring to alternative pharmacotherapies (e.g. methadone).

9. Buprenorphine and liver disease

Buprenorphine is metabolised by the liver and the activity of buprenorphine may be increased and/or extended in individuals with impaired hepatic function⁷.

- Buprenorphine appears safe in patients with hepatitis C infection (HCV) 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 (e.g. HCV or HBV) and who inject their buprenorphine tablets or take an overdose of buprenorphine, so caution should be exercised²⁴.

In practice it is recommended that:

- LFTs are checked at assessment, but waiting for the results should not delay the starting of buprenorphine if the patient is well.
- If LFTs are normal, monitor periodically (e.g. 6 monthly) through treatment as buprenorphine can cause an increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
- If there is evidence of liver disease (e.g. HCV antibody positive, alcohol misuse), take LFTs before commencing buprenorphine treatment (baseline) and monitor LFTs again after 2 to 3 months.
- If there is evidence of marked deterioration in LFTs, refer to a liver specialist for advice.

Buprenorphine and kidney disease

There is no significant difference in the kinetics of buprenorphine when patients with renal failure or renal impairment are compared to controls⁷.

10. Detoxification from buprenorphine stabilisation or maintenance

Buprenorphine is a useful detoxification agent in both primary care and specialist settings²⁵. Detoxification regimens should always be undertaken with the patient's full agreement (not forced) and be tailored to meet the needs of the patient. It is important to clarify treatment aims with the patient (e.g. expectations, concerns, and aftercare/support needs) at the outset.

Reduction can be slowed or stopped if the patient experiences difficulties or there is a resumption of heroin or other drug use, as is often seen when detoxifying from any opioid e.g. methadone.

Most patients do not experience significant withdrawal discomfort until they have reduced to low doses of buprenorphine, or even until after doses have stopped. The withdrawal syndrome is worse after buprenorphine treatment of six months or longer.

A gradual dose reduction schedule is proposed as follows:

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 may prefer to reduce more slowly than this. Alternatively, more rapid dose reductions may be considered (for example, if the patient has had a brief period of heroin use, or has a limited time period to complete withdrawal [e.g. facing a prison sentence]). Rapid dose reductions to zero have been achieved within a one-week timeframe in people withdrawing from heroin, but are not usually recommended in outpatient settings without considerable psychosocial support.

Transferring from buprenorphine to naltrexone after detoxification

Naltrexone can be useful in some patients to prevent relapse after detoxification from opioids.

The speed at which naltrexone can be initiated depends both on the final dose level of the buprenorphine, and on how tolerant of potential precipitated withdrawal the patient is prepared to be. Thus the initiation period may range between 48 hours and 7 days.

Non-pharmacotherapeutic options

It is important that the patient's needs following buprenorphine detoxification have been assessed and considered as part of the care planning process. There is a range of non-pharmacological options that may help prevent relapse. These include access to counselling and support, day care, employment and training projects, AA/NA groups, self-help and advocacy groups, and residential rehabilitation facilities. Local drug services will have information about the availability of these options and how they can be accessed.

11. Transfer to methadone maintenance treatment

Some patients may need to transfer from buprenorphine to methadone. Possible reasons include: intolerable side effects; an inadequate treatment response; the lack of availability of buprenorphine in an area into which a patient has moved; and complications around the interaction of other drugs such as opiate agonists e.g. patients requiring frequent opioid analgesia for recurrent pain.

If a patient is stable on buprenorphine, methadone can be commenced 24 hours after the last dose, at an initial daily dose of up to 40 mg. Appropriate dosage levels vary according to the dose of buprenorphine and individual factors. The following table gives guidance but dose levels of methadone should be titrated according to the response (being mindful of the residual blockading effect of buprenorphine which may last for a number of days and the long half-life of methadone):

Dose levels (guide only)

Buprenorphine dose	Methadone dose
>8 mg	40 mg
4 mg	20 mg
2 mg	10 mg

12. Shared care

Maintenance prescribing of buprenorphine and detoxification interventions should be undertaken in a planned manner in collaboration with the patient and any carers. Shared care arrangements are increasingly an important feature of local treatment arrangements and GPs should endeavour to work jointly with drug workers from local drug services or shared care schemes, where appropriate.

13. Patient education

The particular and different properties of buprenorphine compared to full opioid agonists such as methadone mean that it is important that patients are given good information about its action and effects. This should include information on the method of self-administration (sublingually and not swallowed), effects and unwanted effects, how to start, and the risk of potentiation if used with other sedative substances such as benzodiazepines and alcohol.

Consideration should be given to providing patients with written as well as verbal information about treatment issues.

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

14. Training

Practitioners should only prescribe and treat at levels of practice with which they feel competent and for which they have received adequate training. There may be local or regional training opportunities around buprenorphine that can be accessed by GPs, pharmacists, and other members of the primary health care team.

15. Buprenorphine, Misuse of Drugs Act 1971

Buprenorphine is defined by the Misuse of Drugs Act 1971 as a Class C drug and falls within Schedule 3 (as compared to methadone which falls within Schedule 2) of the Misuse of Drugs Regulations 2001.

NB: Schedule 2 drugs are subject to the full controlled drug requirements relating to prescriptions, safe custody, the need to keep registers, etc.

Schedule 3 drugs are subject to the special prescription requirements and some are exempt from the safe custody requirements. However, buprenorphine (and temazepam) must be kept in a CD cabinet and there is a requirement to keep registers (although there are requirements for the retention of invoices for 2 years).

16. Injecting buprenorphine and the potential for misuse

The misuse of buprenorphine and the injecting of tablets has been recognised for a number of years. In the early 1990's low dose tablets of buprenorphine (known as Temgesic®) were injected by drug users in a number of areas (e.g. Glasgow and Edinburgh) and 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. More recent information from 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. Similar high rates of injecting buprenorphine tablets are emerging from Australia. It is unknown how much of the drug is diverted in the UK but supervised consumption may help reduce diversion.

17. Cost

The cost of the drug buprenorphine is more expensive than methadone.

Buprenorphine:	2 mg, 7-tab pack = £6.72
	8 mg, 7-tab pack = £20.16

Methadone mixture	
1 mg / ml:	100 ml = £1.45
	500 ml = £7.59

Source: British National Formulary, 47, March 2004

As buprenorphine is a schedule 3 drug it consequently attracts a lower dispensing fee than methadone.

In a recent study, treatment with methadone was found to be less expensive and more effective than treatment with buprenorphine, but when the costs that were relevant to the provision of treatment were included (e.g. staff costs), the cost-effectiveness differences between buprenorphine and methadone were not statistically significant¹⁴.

18. Further reading

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Appendix 1: Please photocopy and give to your patient

Buprenorphine in primary care: Patient information – update 2004

Important Points

- You need to take your first dose of buprenorphine when you have no methadone or heroin in your system, or it will make you withdraw.
- Let your buprenorphine dissolve under the tongue. It doesn't work if you swallow it.
- If you want to continue using heroin then buprenorphine is not the drug for you.
- Trying to overcome the block by using increased amounts of heroin 'on top' puts you at risk of overdose.

You have been prescribed buprenorphine by your general practitioner (GP) or prescriber. This leaflet aims to give you some information about the drug and how it can help you. There are patient booklets that cover this in more detail, so ask your GP or drug worker if they can provide you with one. A booklet is no substitute for talking to your doctor, nurse, drug worker or pharmacist – so, if there is something you need more information about, just ask. They will be happy to try and answer your questions and if they can't answer your question they may know someone who can.

■ What is buprenorphine?

Buprenorphine is the general name given to the medication you have been prescribed. The manufacturer's name for buprenorphine in this country is Subutex, and you may hear your medication called this. You may have been started straight from heroin, or transferred from methadone. Either is possible. Buprenorphine is an opioid drug. It produces a depressant effect on your system, similar (though not identical) to heroin or methadone, which are also opioids. Buprenorphine can block the effect of heroin or methadone if you use 'on top', helping you to reduce your use of street drugs.

■ Why buprenorphine?

Buprenorphine is a licensed alternative to methadone, which has some possible advantages for some people. One of them is that it is probably less dangerous if you overdose and another is that it gives you a clearer head. Also, people tend to find it easier to come-off (known as reduction or detoxification). It may not be the best choice if your heroin or methadone habit is large.

■ How do I take buprenorphine?

Buprenorphine comes in tablet form and it only has an effect when it is dissolved under the tongue (also called sublingually). If you swallow or chew your tablets they will not work as the stomach juices destroy them. You may be left with a pool of saliva in your mouth but it is OK to swallow this after the tablet has all dissolved. Buprenorphine tablets take between 3 and 5 minutes to dissolve under the tongue. Allowing buprenorphine to dissolve under the tongue may feel different, especially if you are used to taking your drugs by smoking, injecting or by swallowing. You should try and take your tablets as one single dose at the same time each day. This will help stabilise your body.

■ Why do I need to wait after taking heroin or methadone before taking buprenorphine?

You will be asked to wait for at least 8 hours after last taking heroin and between 24 to 36 hours after last taking methadone (even if not prescribed) before taking your first dose of buprenorphine. It will also be necessary to lower your methadone dose (to around 30 mg / day) before starting buprenorphine. This is because you need to get most of the heroin or methadone out of your system before buprenorphine can have a positive effect. If you take buprenorphine too soon, you may put yourself into withdrawal. It is best to wait as long as you can, ideally until you start to feel the first signs of withdrawal.

■ How will buprenorphine make me feel?

The maximum effect of buprenorphine can take over an hour to feel. The high that you get while you are taking buprenorphine is not as strong as the high you felt when you were using heroin or even methadone, but you will not go into withdrawal. It can feel quite different and you might find that this can take a bit of getting used to. However, after a few days of buprenorphine, you should feel less and less craving for heroin, and feel more 'in control', more 'clear-headed' and more alert, in contrast to the 'clouding' effect of heroin or methadone. For some people this is a bonus, others don't like it. If you are going for maintenance you may want to think about this when making your choice.

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

Taking medication at the chemist in front of a pharmacist is called supervised consumption. Most people will have to undergo supervised consumption to start with as it is considered to be the best way of ensuring you are taking your buprenorphine safely and correctly. If you can show your doctor that you are stabilised on buprenorphine (i.e. you are not using heroin or other drugs bought illicitly) over a period of weeks or months (the government recommendation is 12 weeks unless there are good reasons such as working or child care for it to be less), there is no reason why you should not ask to have take-home doses of buprenorphine. Ultimately however, this is a decision that only your GP or prescriber can make.

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

Though buprenorphine is relatively safe there are dangers involved in taking any opiate-like drug in large quantities when one is not used to it. The risks are greater if buprenorphine is taken in combination with other depressant drugs. This is particularly true of drugs called benzodiazepines ('benzos' such as diazepam [Valium], temazepam, Mogadon, or Rohypnol) that are commonly prescribed for sleeping, stress or anxiety problems. However, it is also true of some other drugs that are sometimes prescribed by doctors e.g. antidepressants. Please tell your GP if you are taking any other drugs or prescribed medication.

People often forget that alcohol is a drug too. Like benzodiazepines and the other drugs mentioned, alcohol can be dangerous when taken with buprenorphine. So, if you do have a drink, be very careful not to overdo it. You should not drink more than 3 units (one and half pints of beer or 3 glasses of wine) for a man or more than 2 units for a woman per day.

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

■ What will happen if I use heroin 'on top'?

Buprenorphine reduces the effect of heroin for a long time, making it more difficult for you to get a 'buzz.' If you use a lot of heroin you are no more likely to get a buzz, but you run the risk of overdosing as the buprenorphine begins to wear off.

■ What will happen if I inject buprenorphine?

Buprenorphine should not be injected and can be painful if it is. It can also cause tissue and vein damage leading to circulation problems. Damaged tissue can allow infection in more easily and can result in abscesses and cellulitis. If you have liver problems from hepatitis C or alcohol injecting can, in some people, cause deterioration in your liver function. If you inject and share any of your injecting equipment, you run the risk of catching a blood borne virus infection like HIV or hepatitis C. Your injecting sites will be checked periodically and if you are found to be injecting buprenorphine this could lead to your script being withheld (for your own safety).

■ What happens if I get pregnant while on buprenorphine?

At the present time little is known about the safety of buprenorphine for the baby during pregnancy. This does not mean it cannot be used or is dangerous, just that the doctor needs to explain the risks and benefits to you. Talk to your GP, prescriber or primary care team member as soon as you find out that you are pregnant, and they will give you the best advice about what your options are. The best choice may be to continue. Don't stop your buprenorphine without discussing it first.

■ What happens if I am planning a pregnancy when entering treatment?

If you are planning a pregnancy you should inform your GP or prescriber as this may influence whether or not buprenorphine is the best medication for you.

■ Can I drive on buprenorphine?

You need to inform the DLVA that you are receiving a prescription of buprenorphine (as you do with methadone). You can then drive for personal reasons (not for work) while taking buprenorphine having undergone a short independent medical examination, which will include a urine screen for drugs. The licence will be issued for one year at a time and will need to be supported by a favourable medical report from your doctor. It is your responsibility to do this, not the doctor or the drug worker. If you do not notify the DVLA and drive and get stopped by the police, you will compromise your insurance and you could be heavily fined or sent to jail.

Appendix 2

Buprenorphine in primary care summary – update 2004

What is it, how to start it and how to use it

- Buprenorphine (Subutex) can be a useful addition to the formulary of medications for treating opioid dependence either for maintenance or detoxification purposes.
- Because of its safety profile, low abuse potential and clinical flexibility in use, it is well suited to use in primary care.
- It comes in 8 mg, 2 mg and 0.4 mg (400 mcg) tablets, which need to be taken sub-lingually (dissolved under tongue) as swallowing inactivates the drug properties.
- It is most suitable for use in primary care for those patients who are opioid dependent and are on either heroin or 30 mg or less of methadone (or can reduce to this level)
- Direct equivalence between buprenorphine and methadone is difficult to estimate and is not a linear relationship, 12 to 16 mg buprenorphine is approximately as effective as 50 to 80 mg methadone in reducing heroin use and retaining patients in treatment.
- Like methadone, buprenorphine interacts with other central nervous system depressants including benzodiazepines, antidepressants and alcohol.

Advantages of buprenorphine compared to methadone:

1. Less dangerous in overdose
2. With maintenance doses between 8 to 32 mg the effects of other opioids used 'on top' are markedly reduced (maximal effect between 12 to 24 mg daily)
3. Useful in maintenance and detoxification (reported as easier to withdraw from)
4. Clearer head whilst on medication, less 'clouding' effect

Disadvantages of buprenorphine:

1. Highly soluble leading to potential for injection
2. Can precipitate acute opiate withdrawal if used incorrectly
3. Less 'opiate-like' or 'clouding' effect
4. The drug itself is more expensive than methadone
5. May be less effective at retaining people in treatment

Starting buprenorphine

- Carried out by dose induction in a similar way to methadone induction, but this can, and should, be undertaken much more rapidly (i.e. over a few days) to reduce drop out.
- Generally advised to start at 4 mg a day and increase by between 2 to 8 mg (usually 4 mg) daily until stabilised, to a maximum of 32 mg per day. Commonly achieve stability between 12 to 24 mg.
- Initiate buprenorphine at least 8 hours after the last dose of heroin, and between 24 to 36 hours after the last dose of methadone (so the previously taken opiates have been metabolised) and with the first signs of withdrawal, to prevent precipitated withdrawal.

- Ask the patient to wait as long as possible, so the previously taken opiates have been metabolised before taking the first dose, to help the induction.
- Always give full explanation of the drug and its effects to the patient.
- Explain that for the first 3 days the patient may experience some unpleasant effects such as headache, restlessness, insomnia and diarrhoea. Lofexidine may be helpful with these unpleasant effects.
- Those on more than 30 mg methadone per day will need to reduce to 30 mg or be transferred to a specialist for conversion to buprenorphine.
- The value of substitute maintenance prescribing for opioid dependency is well established, in which buprenorphine has a place. The dose range of buprenorphine maintenance prescribing is 8 to 32 mg daily. The most usual range used to achieve abstinence from heroin use is between 12 to 24 mg daily.
- Buprenorphine detoxification may be carried out using rapid or gradual regimes according to the needs of the patient.
- Installment prescribing can be written on an FP10 (MDA) in England and Wales, or a GP10 in Scotland

Buprenorphine is a useful alternative substitute medication for opioid dependent people. It widens the choice for opiate users who do not want methadone or who are intolerant to it. It is a useful addition for substitute medication. It is not appropriate if the patient is stabilised and doing well on methadone. It may be considered as a first choice for people dependent on opioids who wish to become opiate free.