COMMUNITY PRESCRIBING FOR OPIATE DEPENDENCY

A major overall objective in the on-going management of the illicit substance misuser is to promote **stabilisation** of lifestyle. Illicit dependent substance misuse leads to a daily pattern of behaviour revolving around obtaining money for drugs, purchasing drugs and using drugs. Such a lifestyle precludes any involvement in more productive and socially responsible activity, and traps the user in a cycle of behaviour that may seem impossible to break. The more damaging substances are also those with relatively short durations of action (heroin and cocaine/crack cocaine), this short duration of action leading to a more frequent repetition of the behaviour.

The prescription of opiate substitute medication may offer a means of escape from this cycle by both removing the need to engage in acquisitive crime and reducing contact with the illicit drug using community. Additionally, prescription of a relatively long-acting substitute such as methadone, reduces the frequency of substance use and reduces the intensity of peaks and troughs (intoxication and withdrawal) regularly experienced by the illicit heroin user. The overall effect should be to provide biological stability, thus providing a foundation for implementing changes in the user's social and personal situation which will be necessary to achieve long-term change.

Commencement of prescribing should only take place after a referral to and assessment by specialist services. Opiate drug withdrawal is not life-threatening and requests for immediate prescribing of methadone should always be resisted. There is a theoretical risk of cardiovascular complications supervening in the elderly patient with pre-existing cardiac disease, and a potential risk of premature labour or spontaneous abortion being precipitated in the pregnant addict in withdrawal. An acute referral to the appropriate medical/obstetric team may sometimes be indicated in such cases.

There are two licenced alternatives for opiate substitution – methadone and Subutex (a formulation of buprenorphine). There are various advantages and disadvantages associated with both drugs, knowledge of which should lead to the appropriate choice being made for an individual patient.

INDUCTION ONTO METHADONE

All clients should have been assessed by the local specialist service prior to commencement of methadone prescribing. This assessment should have established the presence of a physical dependency supported by laboratory urinalysis evidence of at least one opiate positive urine sample.

For the non-tolerant adult a dose of 40mg methadone may be fatal. In most cases the starting dose will be 30mg methadone daily or less. Patients will often complain that this dose is too low to 'hold' them; reassurance should be given that the dose will be reviewed and increased as necessary, but that current guidelines prevent any larger dose being dispensed initially. The prescribing physician should remain aware that whatever the patient's claims, there is no objective evidence available as to the amount or purity of street heroin used by the client.

The immediate aim in the first week of treatment is to control withdrawal symptoms. If time allows, the client may be seen daily for the first several days of treatment, and the daily dose increased in increments of 5 to 10mg. Additional doses in the first several days should be titrated against the severity of withdrawal (*see appendix 3*, page 117 for opiate withdrawal syndrome). In any event, a total weekly increase should not usually exceed 30mg above the starting day's dose. Steady state plasma levels should be reached five to seven days after the last dose increase. In busier surgeries it will be acceptable to increase in increments of 10mg per week following prescription of the starting day's dose.

- Regular opiate use and physical dependence must be confirmed through history, examination and urinalysis before commencing methadone.
- The usual starting dose will be 30mg daily or less.
- Dosage may then be increased at a rate of 10mg weekly to reach a final stabilising dose of between 60mg and 120mg. (A minority of patients will require less than 60mg daily).
- Methadone mixture (1mg/ml) is the formulation of choice – tablets are not licensed for the treatment of addiction and injectables should usually be avoided.

Following the first week of treatment, dosage may be increased in increments of up to 10mg per week to reach a final stabilisation dose of between 60 and 120mg, although some users will stabilise on less. (Drug Misuse and Dependence – Guidelines on Clinical Management; DoH 1999). Stabilisation is usually complete by the end of the sixth week of methadone treatment, but this may take longer in some individuals.

PRESCRIPTIONS

For the first months of treatment, all prescriptions for methadone should be dispensed on a 'daily pick-up' basis. The majority of patients should also be placed on a supervised consumption regime in conjunction with a local pharmacy for the first three months of treatment. The formulation should be methadone mixture 1mg/ml. Methadone tablets and injectable formulations should never be prescribed unless directed by specialist advice (tablets may be crushed and injected).

ADVICE

All patients and carers (with consent) should be provided with basic advice on the dangers of overdose with methadone and its recognition. Medication should always be stored out of the reach of children in a locked cupboard.

ON-GOING STABILISATION WITH METHADONE

The medium to long-term plan, following induction onto a stabilisation dose will depend on an assessment of the client's motivation to engage in the various options for further management, and how realistic their expectations of treatment are. It is vital to avoid imposing a plan for reduction or detoxification on a patient who is not ready for this.

Following the initial induction period (weeks to 2 months), some patients will wish to detoxify immediately. The client should be prepared for this and a realistic after-care plan formulated. A protracted opiate withdrawal syndrome characterised by agitation, malaise, craving and insomnia may persist for many months following detoxification; if no thought is given to the difficulties which will be faced following detoxification, relapse to heroin misuse is highly likely to occur.

For clients who are not immediately motivated to undergo detoxification, or in those that are unrealistic in their plan for abstinence, an objective of on-going stabilisation should be set. A period of maintenance on methadone will allow an opportunity to develop the psychological and social tools which may maintain abstinence in the future. Additionally, there is a wealth of evidence that the benefits of methadone stabilisation outweigh the risks in terms of reduced illicit drug use, reduced injecting drug use, reduced crime and reduced spread of viral illnesses such as HIV (Newman & Whitehill 1979, Gunne & Gronbladh, 1981). The rationale for such prescribing is one of 'harm-minimisation' and is widely held to be responsible for the very low rates of HIV infection in the UK as compared to other European countries.

In contrast to the early induction period of prescribing where the immediate aim was to control withdrawal symptoms, **the dosage should now be directed towards reducing and stopping illicit opiate misuse**. The compulsion to use heroin is not directed merely by a need to prevent withdrawal (negative reinforcement) but also by a need to experience the positive effects such as euphoria (positive reinforcement). The desire to experience positive effects in the dependent user should not be understood in terms of a willful and consciously motivated act; rather it is directed by primitive components of the central nervous system such as the nucleus accumbens, which operate at the unconscious level. **This desire may be reduced, if not eliminated, by the prescription of larger doses of methadone than those required to eliminate physical withdrawal** (Effectiveness Review, 1996). There is a substantial body of evidence demonstrating a direct correlation between methadone dosage and reduced heroin misuse (Ball & Ross, 1991, Caplehorn & Bell, 1991, Ling et al, 1996).

During this phase of treatment, the patient should be seen ideally fortnightly and at least monthly. Dosage should be maintained at a level which 'holds' the patient, and prevents heroin misuse. Thus the response to a patient who is complying with appointment attendance but who is continuing to report regular heroin misuse, will often be to increase the methadone dosage. The usual maintenance dose will often be between 60 and 120mg daily (Drug Misuse and Dependence – Guidelines on Clinical Management, 1999), although some will require smaller doses. Doses over 100mg daily should usually only be prescribed following specific advice from specialist services.

PRESCRIPTIONS

It will usually be appropriate to continue on a daily dispensing regime for the first year of such prescribing. Where a trusting relationship has developed between the patient and prescriber, and there is evidence that successful stabilisation has been achieved, this rule may be relaxed in increments. It is inadvisable to dispense more than one week's worth of methadone at any one time, whatever the eventuality. Other exceptions to this rule may occur in order to support a client in remaining in employment, where a daily collection may interfere with working responsibilities, and the benefits are judged to outweigh the risks.

URINALYSIS

Urine 'drugs of abuse' screens should be performed on an occasional 'random' basis throughout this period. Detection of substances other than those reported should be discussed with the client, but should not automatically lead to discontinuation of treatment. Many clients will be mistrustful of their doctor's response in the case of their continued illicit drug use, and fear losing their prescription if they admit to this. One major aim of urinalysis is to confront mis-reporting in a positive and non-punitive way, thus demonstrating to the client that they will not automatically lose their prescription by engaging in an honest and trusting relationship with their doctor. As discussed above, the appropriate response to an opiate positive urine screen may be to increase rather than to decrease the methadone dosage.

POOR COMPLIANCE

This is discussed in detail below (Section E10, page 104).

CONCLUSIONS

1. Before commencing a methadone prescription always:
   - confirm opiate misuse with a urine drugs of abuse screen.
   - record a history of physical withdrawal symptoms and regular (usually daily) opiate use.
2. The formulation prescribed should be methadone mixture 1mg/ml.
3. The starting dose should never be more than 30mg daily. For the initial period of prescribing, dispensing should be on a supervised and daily basis.
4. As a routine, the dosage may then be increased at a rate of 10mg weekly, although this process may be more rapid if the patient can be seen more frequently than once weekly.
5. A **rough** guide to the **final** stabilisation dose can be calculated by multiplying the daily heroin use in grams by 0.07; thus a 1g/day heroin habit equates to approximately 70mg methadone.

However:

6. There is significant inter and intra-individual variation in metabolism of methadone, with half-lives varying between 10 and 150 hours in different individuals. It is thus vital that dosage is tailored to the individual. When the aim is stabilisation of illicit opiate misuse, then the dosage should be increased so as to ameliorate the positive (euphoric) effects of heroin use, rather than merely to prevent withdrawal. This should be judged mainly from the patient's self-report of how well the prescription is 'holding' them, but also from the detection (or non-detection) of morphine (heroin metabolite) in the urine. If the client is presenting as drowsy then the dosage is probably too high. It should also be noted that significant intra-individual changes in metabolism occur over the first several months of treatment, and the dose may need to altered in response to this. Physiological changes in the third trimester of **pregnancy** also often lead to reduced plasma methadone concentration and increased dosage requirements.
7. Whatever the calculation in (5) reveals, the majority of addicts will require at least 60mg of methadone daily to prevent the continued misuse of heroin on-top of their prescribed methadone.
8. It will be unusual to increase the daily dose above 100mg methadone, and the dosage should never be increased above 120mg daily without specialist advice.
9. If there is concern regarding the possible diversion of prescribed methadone to the grey market, then place the client on a supervised consumption regime or seek specialist advice.
10. There is usually little point in commencing a detoxification or reduction regime following stabilisation, if the patient is not motivated to comply with this. Physician-imposed reduction or detoxification regime is likely to result only in relapse to heroin misuse and a loss of the advantages of methadone stabilisation leading to increased crime, spread of HIV and hepatitis, and failure to retain the patient in treatment.

SLOW METHADONE REDUCTION REGIMES

The historical medical response to opiate dependency was to prescribe the drug of dependency and then slowly reduce the prescription to zero over a period of time (typically months). This practice remains commonplace but is probably a relatively ineffective route to abstinence for the majority of patients. The difficulty with such regimes usually becomes apparent when the daily methadone dose is reduced below 20mg, following which the illicit use of heroin tends to become increasingly more frequent. The medical response at this point will either be to accept failure and continue the reduction or to increase the methadone dosage in an attempt to re-stabilise before re-commencement of reduction. The National Treatment Outcome Research Study (NTORS (Gossop M et al, 1999)), demonstrated that there was no significant difference in methadone dosage between groups on methadone reduction regimes and on methadone maintenance regimes. The implication of this finding is that most doctors prescribing reduction regimes are increasing methadone doses in response to street heroin use, and that abstinence is only achieved by a minority of patients who are prescribed reduction regimes.

When considering the numbers of patients achieving abstinence (at least for 1 day), detoxification (see section C4) rather than slow reduction appears to be superior. Approximately 13% of patients prescribed a slow methadone reduction regime will complete the reduction without relapse to heroin use, whilst the number completing community detoxification is in the region of 50% and in-patient detoxification 80%. Whilst there is no direct evidence that long-term outcomes differ significantly between these treatments, it would seem likely that patients who have experienced a period of abstinence at some point would have a better long-term prognosis than patients who have failed to achieve abstinence. Despite these findings, slow methadone reduction regimes remain a valid route to abstinence for some patients. If such a regime is to be prescribed then the following phases of treatment should be considered:

- **Phase 1: stabilisation (see above).**
- **Phase 2: reduction from stabilisation dose down to 20mg methadone daily.**
- **Phase 3: completion of the reduction from 20mg methadone daily to zero.**

- Slow dosage reduction to zero over a period of months is an ineffective route to abstinence for many patients – detoxification (managed withdrawal over a period of days or weeks) is to be preferred in most cases.
- If slow reduction is chosen, then this should be preceded by a stabilisation phase, and the rate of reduction reduced when doses reach less than 20mg daily.

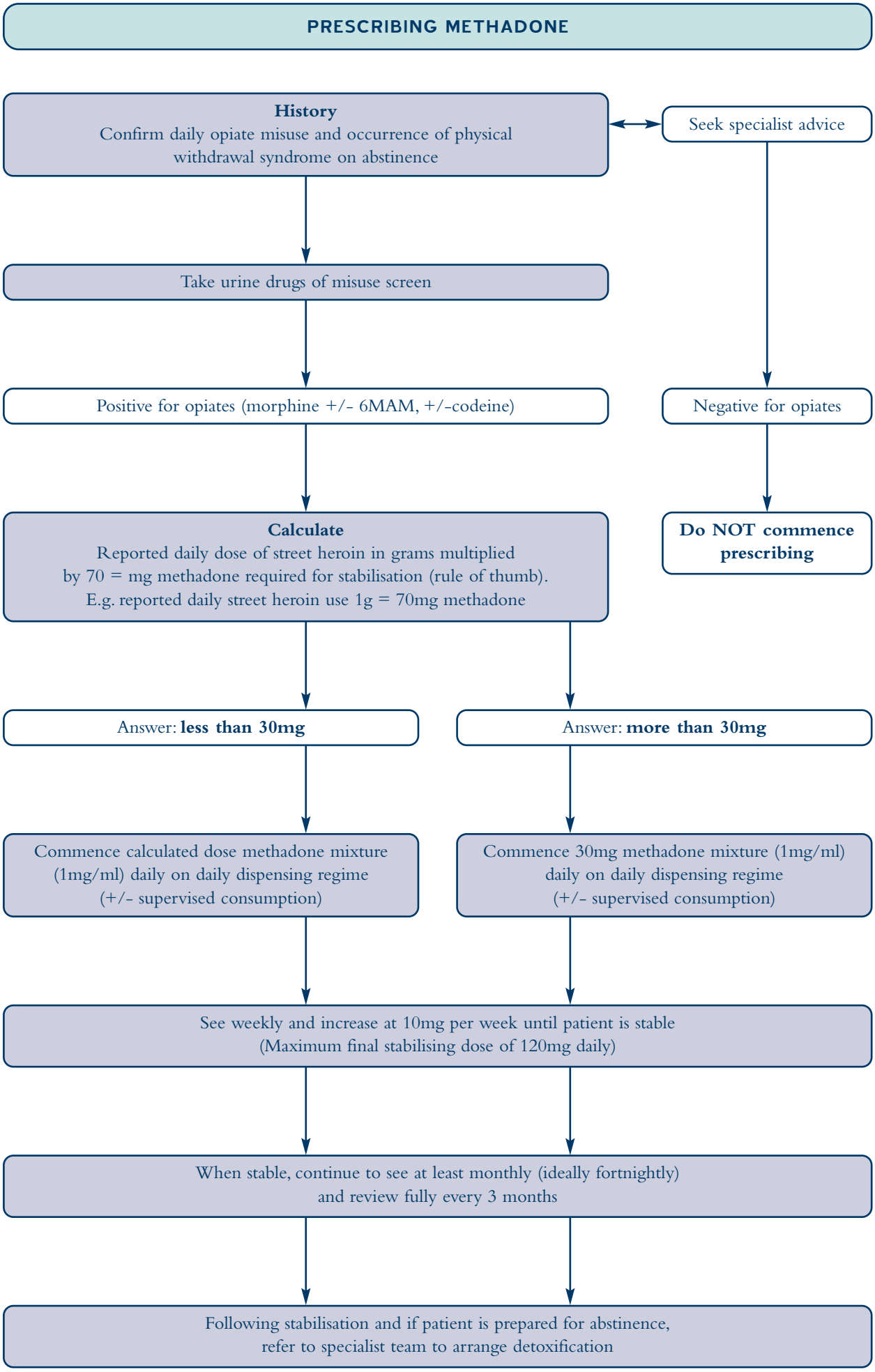
PHASE 2

Plan the total duration of the reduction (often up to 6 months in total). Agree the initial rate of reduction of methadone – usually between 5 and 10mg per fortnight.

PHASE 3

Reduce the rate of reduction as agreed with the patient; as smaller doses are achieved, the rate of reduction can be as little as 1mg per fortnight. Consider the use of 'blinding' where the pharmacist is asked to keep the volume of dispensed methadone the same while the concentration is altered (i.e. the patient is 'blind' to the prescribed dose).

If the patient has occasional lapses to heroin use (once weekly or less), it may be appropriate to continue with the reduction. If lapses occur more frequently than once weekly, it will usually be necessary to increase the methadone dosage and review the overall management plan; it may become clear at this point that detoxification rather than slow reduction is the preferred route to abstinence.


PRESCRIBING METHADONE
History
Confirm daily opiate misuse and occurrence of physical withdrawal syndrome on abstinence
Seek specialist advice
Take urine drugs of misuse screen
Positive for opiates (morphine +/- 6MAM, +/-codeine)
Negative for opiates
Calculate
Reported daily dose of street heroin in grams multiplied by 70 = mg methadone required for stabilisation (rule of thumb).
E.g. reported daily street heroin use 1g = 70mg methadone
Do NOT commence prescribing
Answer: less than 30mg
Answer: more than 30mg
Commence calculated dose methadone mixture (1mg/ml) daily on daily dispensing regime (+/- supervised consumption)
Commence 30mg methadone mixture (1mg/ml) daily on daily dispensing regime (+/- supervised consumption)
See weekly and increase at 10mg per week until patient is stable (Maximum final stabilising dose of 120mg daily)
When stable, continue to see at least monthly (ideally fortnightly) and review fully every 3 months
Following stabilisation and if patient is prepared for abstinence, refer to specialist team to arrange detoxification

OTHER DRUGS FOR OPIATE SUBSTITUTION THERAPY

BUPRENORPHINE (SUBUTEX)

Buprenorphine is a partial agonist at opioid μ receptors. Simplistically speaking this means that at lower doses it has an agonist effect at the μ receptor, whilst at higher doses it has an antagonist effect. Together with its high binding affinity for the μ receptor, this translates into various theoretical benefits for its use in the treatment of opiate drug dependency.

POTENTIAL ADVANTAGES

- One prominent risk of opiate drug use (whether illicit or prescribed) is the potential for respiratory depression and death in overdose. Due to its antagonist effect at higher doses, buprenorphine is thought to be safer in overdose than other opiates such as heroin or methadone.

- One common problem with opiate substitution therapy is the continued use of illicit opiates 'on-top' of prescribed opioids in some patients. Due to its high affinity for the opioid μ receptor, buprenorphine should not be displaced by most abused opiates, theoretically leading to ineffectiveness of illicit drug use and thus to a reduction in illicit drug use by the patient. Equally, due to its partial agonist activity, the use of buprenorphine in doses greater than those prescribed should have little euphorigenic effect, decreasing its abuse potential.

- One advantage of methadone treatment is its ability to stabilise the drug-using pattern of the individual due to its long half-life and once a day dosing schedule. Buprenorphine's high affinity for and prolonged binding to the μ receptor results in a similar effect through a pharmacodynamic rather than pharmacokinetic action. In fact, buprenorphine may be dispensed on a thrice-weekly schedule, which potentially has advantages over methadone in terms of improved compliance, greater normalisation of the patient's daily routine and reduced costs associated with dispensing.

Despite the pharmacological differences between buprenorphine and most other opioids, it should be regarded as posing the same risks as the opioid group in general. These include the risk of overdose leading to respiratory depression and death, the risk of dependency, and the risk of personal misuse of or diversion of prescribed medication.

- Subutex has advantages over methadone in some patients, particularly those using smaller amounts of illicit opiates (<1/4g heroin daily).
- The major advantage is in the reduced risk of accidental overdose and death, as compared with methadone.
- Induction should only commence at least 6 hours after last heroin use or 30 hours after last methadone use – an opiate withdrawal syndrome may be precipitated if this rule is not observed. Patients converted to Subutex from methadone must be on a maximum of 30mg methadone daily preceding conversion.
- Prescribe 4mg on day 1 and 8mg from day 2 onwards. Increase further to 16mg daily if the patient is not 'held' at 8mg daily. Subutex is administered sublingually.
- A blue FP10 for daily dispensing should be used, and the formulation specified as 'Subutex'.
- Subutex should not be routinely prescribed during pregnancy. There is no evidence of its foetotoxicity, but further research is required before its use in this context may be considered routine.

POTENTIAL DISADVANTAGES

- Due to its antagonism of μ receptors at higher doses, buprenorphine may induce an opiate withdrawal syndrome in patients who are dependent on and concurrently using other opioid drugs. The first dose of buprenorphine should thus be administered at a period after the last use of opioids which is dependent on the duration of action of the particular opioid. In general this will be at about six hours after the last dose of heroin, or 36 hours after the last dose of methadone. An alternative approach is to wait for the onset of opioid withdrawal symptoms before administering the first dose of buprenorphine. Additionally, it is not recommended to commence buprenorphine in subjects on doses of methadone greater than 30mg.

- Whilst buprenorphine is theoretically safer than other opioids in overdose due to its partial agonist activity, it has still been associated with drug-related deaths (usually when taken together with other CNS depressant drugs such as benzodiazepines). Opioid overdose is usually fully reversible by administration of parenteral naloxone, which may be effective for as long as four hours following overdose. However, due to its high affinity for the μ receptor, a buprenorphine associated respiratory depression may be only partially reversible with naloxone.
- Liver function tests should be performed three-monthly due to a theoretical risk of inducing liver disease.

DOSAGE AND PRESCRIBING

Buprenorphine may now be prescribed on a blue FP10 for daily dispensing, (as commonly used for methadone dispensing). If it is to be used in this way, it must always be prescribed as Subutex, as this is the only formulation licensed for the treatment of opiate addiction.

Various dosage regimes have been published. The first dose will be 2mg to 4mg sublingually, following which dosage should be titrated against continuing withdrawal symptoms. The majority of patients are stabilised on a maximum of 8mg daily, although buprenorphine is licensed for use at doses of up to 32mg daily. The above mentioned precautions should be taken when initiating prescribing. One commonly used regime is 2mg on day 1, 4mg on day 2 and 8mg from day 3 onwards.

SLOW REDUCTION REGIMES

There is some evidence to indicate that the use of Subutex in slow community reduction regimes may be significantly more effective than similar methadone regimes. It is too early to make a clear statement regarding this, but it may be considered good practice to institute a slow reduction of Subutex over a period of weeks or months if the patient wishes to follow this route to abstinence.

CONCLUSION

Potential advantages of Subutex over methadone.

- **Less likely to be associated with accidental opiate overdose.**
- **More rapid and safer induction onto 'holding dose'.**
- **Potential for thrice weekly dosage schedule (as compared to daily).**
- **Less likely to cause gastric irritation.**
- **Less associated with stigma of drug addiction.**

Theoretically Subutex is also:

- **Less likely to be associated with use of illicit opiates 'on-top' of prescribed buprenorphine.**
- **Less likely to be diverted onto the black market due to its potential to induce withdrawal symptoms in opiate users with heavier usage.**

However, while this is theoretically the case, it has as yet to be demonstrated in clinical trials. Additionally, buprenorphine has itself been associated with local epidemics (in Scotland) and is widely available on the black market in France (where it is frequently prescribed).

Potential disadvantages of Subutex as compared to methadone.

- **If serious overdose with cardio-respiratory depression does occur, then it may be more difficult to reverse this with naloxone.**
- **High cost in maintenance as compared to methadone.**
- **May be less suitable for opiate addicts with heavier opiate use (greater than 1/4 g heroin daily).**

Despite its excellent theoretical profile, Subutex has yet to prove itself in the clinical situation. Similar to methadone it has been associated with misuse, dependency, continued use of illicit opioids 'on-top' of prescribed buprenorphine and risk of overdose. It also poses a special risk of potentially reduced reversibility of overdose with naloxone. Furthermore, as it is not a generic drug, it remains much more expensive than methadone which greatly reduces its potential cost-effectiveness as a valid alternative to methadone in maintenance therapy. Cost is not such a significant factor in detoxification; however the use of lofexidine for opioid detoxification may be preferred, due to the ability to commence naltrexone during the lofexidine detoxification process, which may lead to lower relapse rates.

DIHYDROCODEINE, LAAM, CODEINE, DIAMORPHINE

None of these drugs are licensed for the treatment of opiate dependency. They should only be prescribed by or following documented advice from a specialist.