SPECIALIST PHARMACOLOGICAL & BIOCHEMICAL INTERVENTIONS

DISPENSING SERVICES

The general model of shared-care dictates that specialist services are directly responsible for provision of prescribing services to more complex clients and for the induction of opiate substitutes for all clients, whilst GPs will prescribe for less complex and more stable clients. There are two options available to specialist services with regard to dispensing – provision of prescriptions for dispensing at community pharmacies or direct dispensing of medication to clients.

Although direct (on-site) dispensing will not be suitable for all clients, especially those in rural areas with poor transport facilities, there are potential advantages of making such a service available from the main specialist service site. There is some indication that this may improve outcomes for individual clients (Wolff et al, 1996). Potential advantages include:

- **Reduced cost to the health economy.**
- **Daily observation of the client.**
- **Direct confirmation of collection of medication.**
- **Ease of provision of supervised consumption service.**
- **Rapid induction onto holding dosage of opiate substitute medication.**
- **Daily dispensing of non-opioid controlled drugs.**
- **Community team site detoxification service provision.**
- **Improved compliance with clinic attendance leading to improved engagement with other specialist services.**
- **Reduced offending.**

REDUCED COST

Community pharmacy dispensing can be up to twice as expensive as on-site dispensing because of daily dispensing charges and the reduced cost of methadone to hospital as opposed to community pharmacy purchasers. In addition to these direct savings, further cost reductions and improved cost-effectiveness will accrue as described below.

- Specialist statutory substance misuse services should consider the need to develop on-site dispensing services from their main base.
- The potential advantages of on-site dispensing include reduced cost, daily observation of the client, direct confirmation of collection of medication, ease of provision of supervised consumption service, rapid induction onto holding dosage of opiate substitute medication, daily dispensing of non-opioid controlled drugs, day-care detoxification service provision, and improved compliance with clinic attendance leading to improved engagement with other specialist interventions.

DAILY OBSERVATION OF THE CLIENT

The dispensing nurse will have the opportunity to observe clients on a daily basis. The importance of this is clear when considering the complex and chaotic nature of the client group which will receive a prescribing service from specialist services. This may be of especial relevance to dual diagnosis cases.

DIRECT CONFIRMATION OF COLLECTION OF MEDICATION

More chaotic clients may fail to collect medication on a daily basis as prescribed. This can lead to loss of tolerance and danger of overdose when collection resumes. The methadone regime will need to be reviewed or stopped if a client fails to collect for 2 to 3 days concurrently.

EASE OF PROVISION OF SUPERVISED CONSUMPTION SERVICE

The Clinical Guidelines (DoH) state that clients should routinely be dispensed for on a supervised consumption basis for the first three months of treatment. This is easily arranged for within specialist services, but is more difficult in the community where many pharmacists have not engaged with the Supervised Consumption Scheme.

RAPID INDUCTION ONTO HOLDING DOSAGE OF OPIATE SUBSTITUTE MEDICATION

The Clinical Guidelines (DoH) require that starting doses of methadone should not usually be in excess of 30mg daily, and that the client should be monitored closely while methadone dosage is increased in small increments over a period of weeks to months. In effect, in order to comply with guidelines, a busy GP is restricted to increasing methadone at a rate of 10mg weekly. Final holding dosage of methadone will usually be between 60mg and 120mg daily (DoH Clinical Guidelines). This leaves a difficult period of weeks or months during which the client is in effect compelled to use illicit substances on-top of prescribed medication.

Through a process of 'tolerance testing' (described below), specialist services with on-site dispensing facilities can induct clients onto a holding dose within one week.

DAILY DISPENSING OF NON-OPIOID CONTROLLED DRUGS

Whilst the Law only allows for the daily dispensing in the community of methadone and Subutex by means of a single prescription, the provision of daily dispensing for other controlled medication can be just as important clinically. The commonest example of this is the prescription of benzodiazepines, but services wishing to develop dexamphetamine and injectable opioid prescribing services would also benefit from the availability of on-site dispensing facilities. Currently, individual prescriptions for benzodiazepines and dexamphetamine must be written for each day's medication which is both time-consuming and expensive in terms of community dispensing charges.

DAY-CARE DETOXIFICATION SERVICE PROVISION

All specialist services should provide a community detoxification service as part of the range of detoxification services available to clients. Alcohol detoxification protocols include the provision of Pabrinex injections on the first three days of detoxification, while opiate detoxification protocols often include the provision of a naloxone injection. Such injections can only be given where emergency medication and medical help are available. Whilst it may be possible to administer such injections in the client's GP's surgery in some instances, such an arrangement has a high cost in terms of use of nursing time. The administration of injections at a central site allows a single nurse to administer injections to a number of clients, rather than on a one-by-one basis.

In addition to the provision of injections, community detoxification protocols require twice daily home visits by nursing staff, and the support of a carer who is available at the client's home 24 hours a day. The availability of a suitable central site with dispensing facilities will enable some clients to attend this site during working hours and return home overnight. As well as decreasing the cost of community detoxification through a saving in nurse time, such an arrangement will allow some clients with working partners to receive a community rather than in-patient detoxification.

IMPROVED COMPLIANCE WITH CLINIC ATTENDANCE LEADING TO IMPROVED ENGAGEMENT WITH OTHER SPECIALIST INTERVENTIONS

Together with the provision of on-site alternative therapies, on-site dispensing services are well recognised as being a major factor in attracting clients and ensuring clinic attendance. Substance misusing clients are typically poor attenders for healthcare interventions of all kinds. Specialist services have the potential to improve up-take of a variety of interventions by offering a 'one-stop' shop which provides a range of bio-psycho-social services aimed at improving health and social outcomes. Attraction of clients into this 'one-stop shop' (through provision of on-site alternative and dispensing services) in the first place is an essential component of improving attendance of the various services provided on-site.

THE OPIATE ADDICTION TEST

RAPID DIAGNOSIS OF OPIOID DEPENDENCE WITH NALOXONE EYE-DROPS

New patients presenting for treatment of opioid misuse are routinely subjected to a lengthy assessment process to determine whether they are dependent on opiates or are casual users. If dependence is diagnosed, opioids may be prescribed on a regular basis for stabilisation prior to detoxification. However, the provision of a regular prescription to casual users may contribute to the development of dependency. Accurate diagnosis of the dependent state is therefore essential, but the current lengthy process tends to deter people from seeking help. Additionally, the use of urine screeing for opiates indicates only recent use of drugs, rather than prolonged exposure.

Instillation of eyedrops containing naloxone into one eye of an opioid-dependent subject causes, a short time later, pupil dilatation (mydriasis) in that eye only, without inducing a 'systemic' withdrawal syndrome (Bellini et al, 1982). Mydriasis is not seen if the same test is carried out in healthy, unmedicated subjects (Ghodse, 1986) or in normal subjects given an opioid prior to minor orthopaedic surgery (Creighton & Ghodse, 1989), implying that pupil dilatation indicates prolonged exposure to opiates, as opposed to isolated or intermittent use.

- Specialist services should routinely use the 'opiate addiction test' to determine opiate dependency, in order to enhance the engagement of opiate users with treatment.
- Use of binocular pupillometry can improve the identification rate at first appointments.

The opiate addiction test, using unilateral instillation of conjunctival naloxone hydrochloride and pupillometry, is a simple, reliable and accurate method of diagnosing opioid dependence. Sensitivity on the first clinic visit is enhanced by the use of binocular infrared electronic pupillometric equipment, but is not essential to institute the test as a routine component of assessment. Evaluation in the clinical situation has demonstrated a 100% specificity of the test and an 81% sensitivity (Ghodse H et al, 1999). A patient with a positive response to the opiate addiction test is thus known to be opioid-dependent; this may be determined at the initial appointment and treatment instituted immediately. However, a negative result does not provide unequivocal proof that the patient is not dependent on opiates; in this situation, the patient should be re-tested and a subsequent positive result should be taken to indicate that he or she is in fact opioid-dependent and should be treated accordingly (Ghodse H et al, 1999).

TOLERANCE TESTING

The process of tolerance testing enables clients to be inducted onto a 'holding dose' of methadone which prevents withdrawal symptoms, within a period of one week. This is in contrast to the duration of the induction period with GP prescribing, which can take weeks or even months. During this extended period, clients are likely to be using illicit opiates on-top of their prescription in order to prevent withdrawal symptoms, thereby putting themselves at risk and decreasing their GP's willingness to continue the prescription. The provision of a specialist tolerance testing service is thus likely to both directly improve clinical outcomes and the engagement of GPs with shared-care schemes.

The objective of the induction period is to prescribe a dose of methadone which prevents withdrawal symptoms, and to do this as safely and as rapidly as possible. This is in contrast to the stabilisation period (which follows the induction period and aims to ameliorate the euphoric effects of heroin through the prescription of doses larger than those merely required to prevent withdrawal).

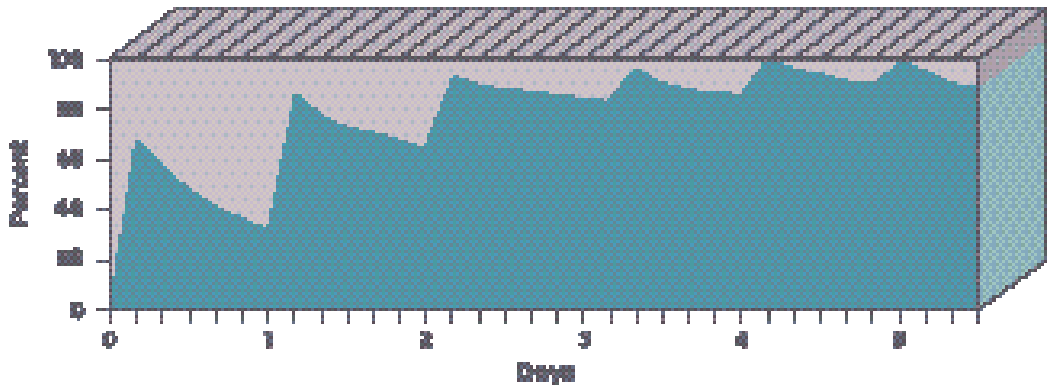
The tolerance testing procedure has evolved as a consequence of the pharmaco-kinetic profile of methadone; the variables of note are the elimination half-life of 10 to 150 hours (most commonly between 24 and 40 hours), and the time to peak plasma concentration following a single dose which is 3 to 4 hours. The long half-life means that with a daily dosing schedule, the next day's dose will add to the remnants of the previous day's dose; thus plasma methadone levels for a given daily dose, will continue to rise until steady state is reached after about one week. Awareness of the time to peak plasma concentration after a single dose (3 hours) is useful in that it enables judgments regarding the client's overall response to be made at this time, thus directing the need for dose changes. In particular, the fact that that trough levels at steady-state will nearly always be greater than plasma levels at 3 hours after the first dose, indicates that clients not withdrawing at this point should achieve a satisfactory initial stabilisation within a week or so, without further dose increases.

IN PATIENT TOLERANCE TESTING

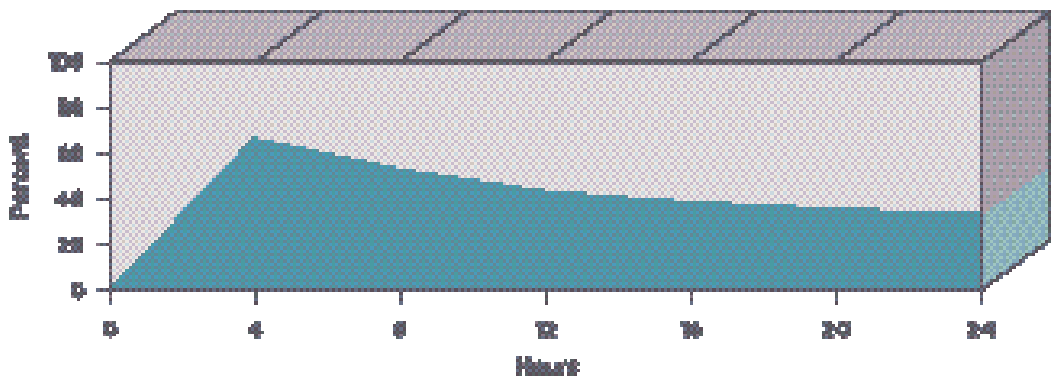
In-patients may be started on a maximum of 30mg methadone, which can then be topped up 4 hourly by increments of 10mg until they are no longer in withdrawal.

The total dose given in the first 24 hours can then be given on a once daily basis thereafter, or split to provide a twice-daily regime.

Plasma methadone level for a given daily dosage

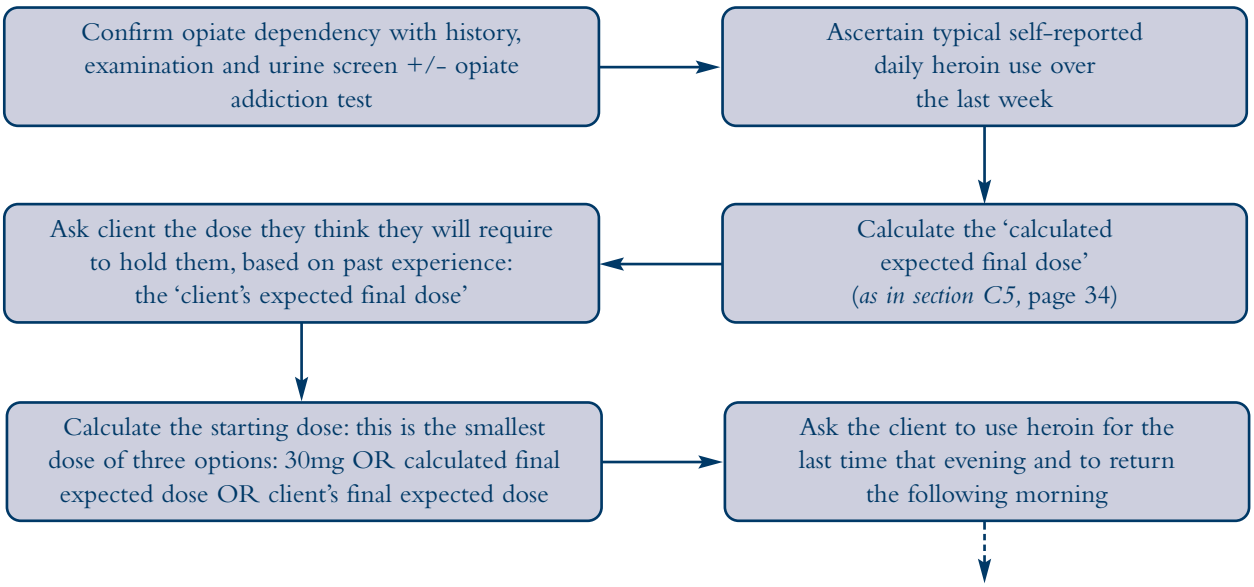


Plasma methadone level on the first day of treatment

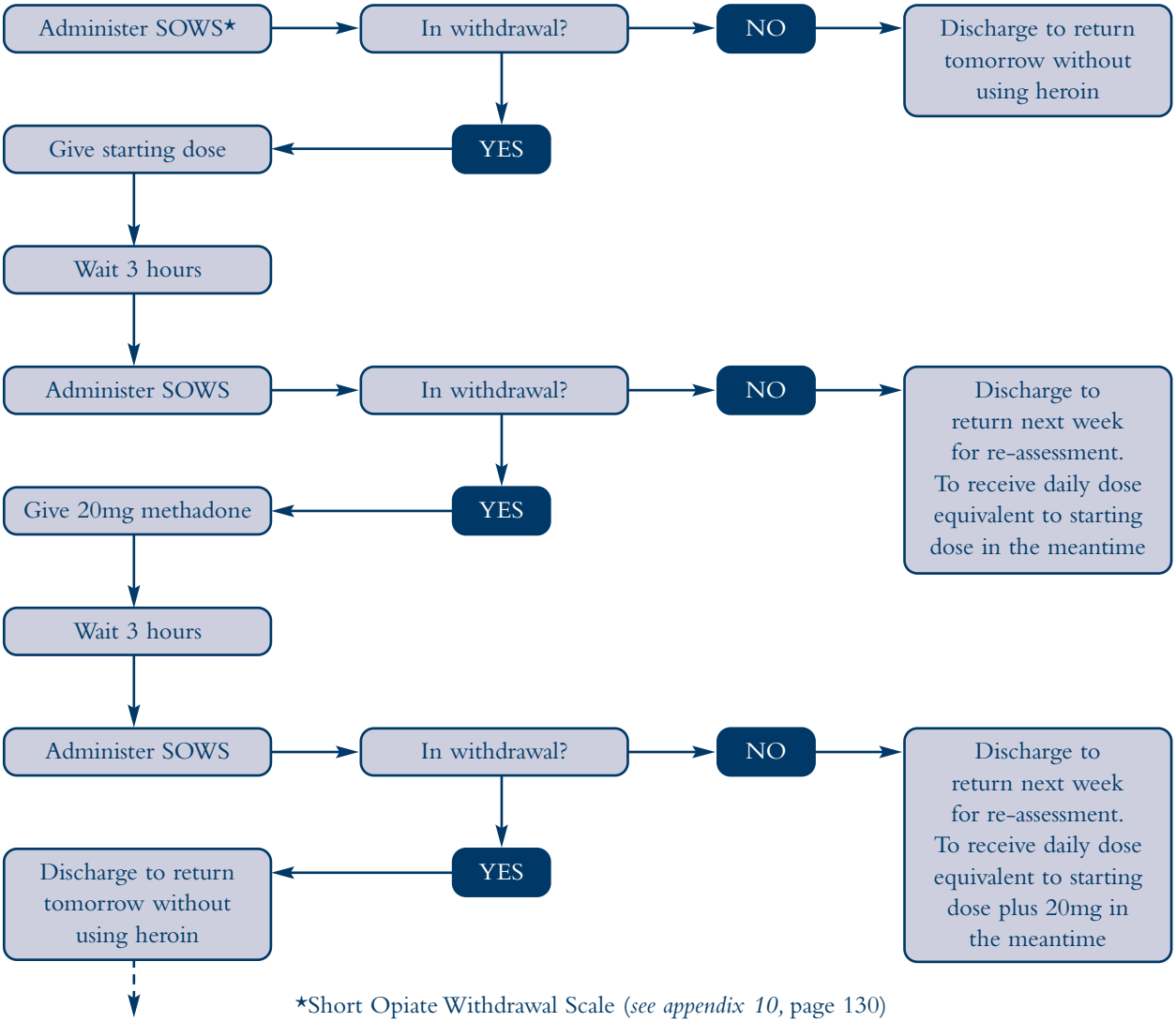


TOLERANCE TESTING: SPECIALIST COMMUNITY SERVICES

DAY 1: ASSESSMENT



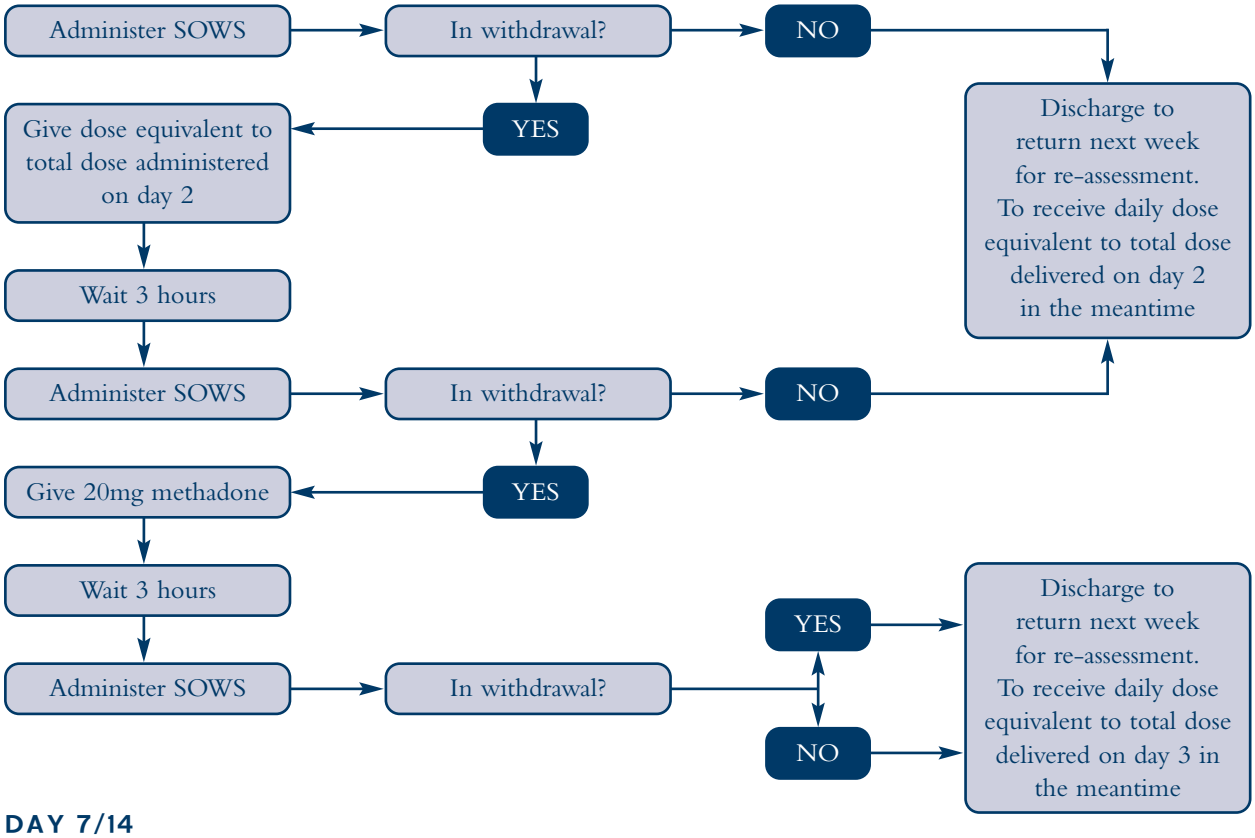
DAY 2



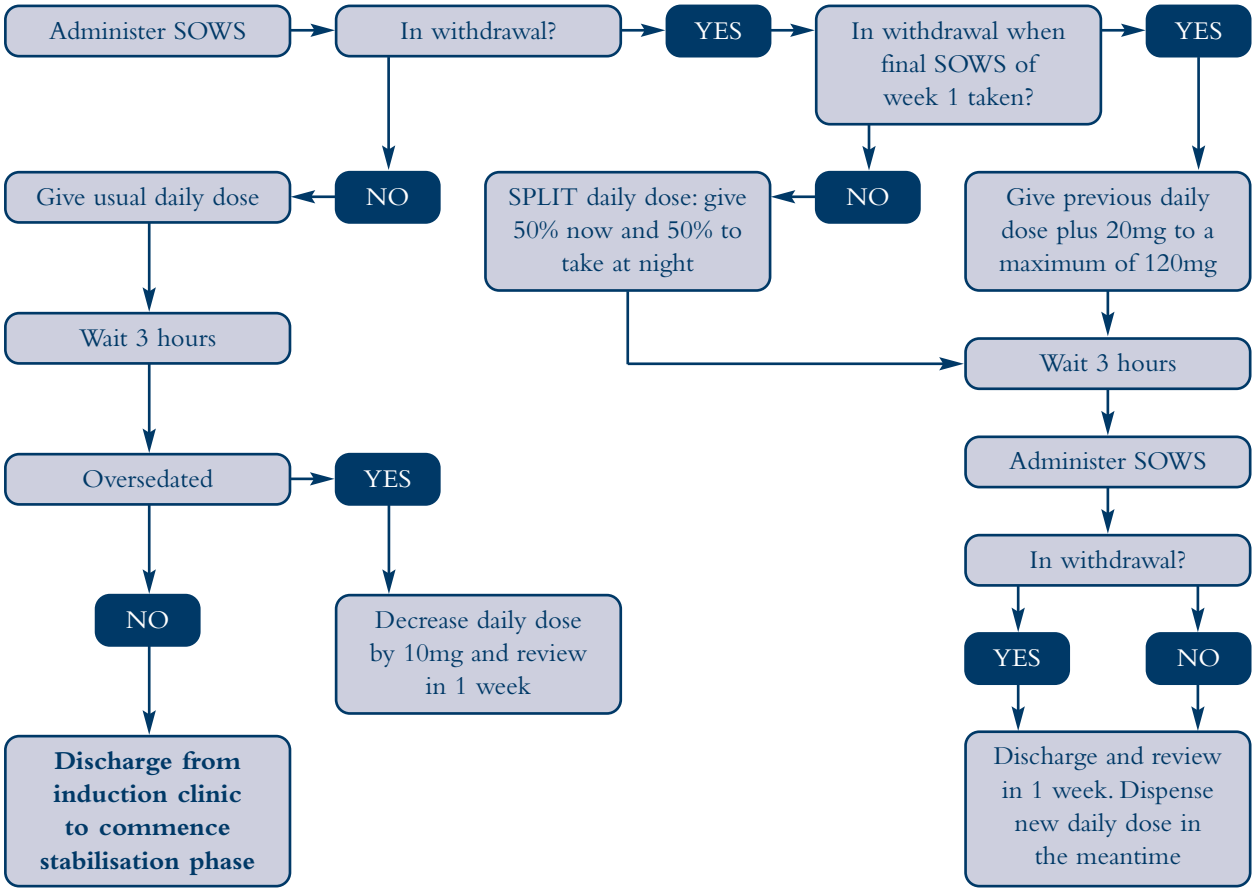
*Short Opiate Withdrawal Scale (*see appendix 10*, page 130)

TOLERANCE TESTING: SPECIALIST COMMUNITY SERVICES

DAY 3



DAY 7/14



SPECIALIST IN-PATIENT DETOXIFICATION

CLINICAL QUALITY

The setting chosen for planned in-patient detoxification should be that of a dedicated detoxification unit. Such units should provide a service which meets the following criteria:

MINIMUM STANDARDS:

- The use of up-to-date evidence to direct prescribing regimes.
- Safe practice through the minimisation of risk of morbidity and mortality occurring secondary to withdrawal and detoxification.
- A planned date for admission with high levels of achievement.
- Effective practice in terms of completion of detoxification rates.
- Effective practice in terms of minimising physical and psychological discomfort during detoxification.
- Minimisation of inconvenience to the patient caused by unnecessarily long stays in hospital.
- Provision of an illicit drug and alcohol-free environment for detoxification.

BEST PRACTICE:

- Provision of a safe, healthy and relaxing environment that is conducive to retention of the patient for the duration of the detoxification, and enhances patient satisfaction.

THE MAJOR COMPONENTS OF SAFE PRACTICE ARE:

- The availability of protocols which describe an evidence-based medication regime and the steps which should be taken when complications supervene.
- The 24 hour availability of nursing and medical staff who have been trained in the implementation of the protocols.
- Tight management standards to ensure the correct implementation of the protocols by nursing and medical staff.
- A drug and alcohol-free environment.

- Specialist services should provide access to in-patient detoxification.
- This should usually take place in a dedicated detoxification unit which has been demonstrated to meet various minimum standards.

With regard to completion rates, dedicated in-patient detoxification units tend to achieve better outcomes than general psychiatric wards (Gossop & Strang, 2000). Completion rates in some specialist units approach 100%, whereas typical completion rates in a general psychiatric ward will be in the region of 65%.

The provision of detoxification in a setting where illicit substances/alcohol are available increases the risk of non-completion, but also increases the risk of morbidity and mortality occurring during the detoxification. Frequent reports of the availability of illicit substances in a detoxification unit may also indicate the presence of generally poor management standards; poor training and supervision of nursing staff in such units is likely to lead to unsafe practice due to failure of staff to routinely follow protocols.

The availability of a guaranteed planned date for admission is an essential component of the overall package of care that is offered to the patient by a specialist drug and alcohol team. The provision of a planned date to aim for and prepare for, as part of an overall care-planning process is consistent with the use of cognitive-behavioural principles. Any member of the public who has experienced the cancellation of or uncertainty around the date of a hospital admission is likely to experience distress and frustration; however, in the case of say a hip replacement, this is unlikely to impinge directly on the final success of the operation. In the case of the addicted patient awaiting detoxification, any disruption to psychological and social stabilisation will impinge on motivation to see through what is usually a huge challenge for the individual, will decrease the adequacy of psychological preparedness, and is also likely to interfere with aftercare planning and thus long term as well as immediate outcomes.

SPECIALIST OPIATE DETOXIFICATION TECHNIQUES

There are two main objectives of specialist opiate detoxification techniques: to reduce the duration of detoxification whilst minimising discomfort to the patient and to induct the patient onto naltrexone at the earliest possible opportunity. It is hypothesised that the combination of these factors will enhance both patient up-take and the immediate and longer term outcomes of detoxification. The various techniques vary in their use of either a general anaesthetic or heavy sedation, and in the timing of opiate-antagonist administration. Specialist services should provide access to some forms of rapid opiate detoxification for selected cases.

- Specialist services should provide access to 'Naltrexone-compressed opiate detoxification' (NCOD) for selected cases.
- The major indication for NCOD is previous failure to complete in-patient detoxification due to low tolerance of discomfort.
- Ultra-rapid detoxification (using general anaesthetic) remains an experimental technique which may be associated with an unacceptably high mortality rate in its current form. Access should **NOT** be provided to ultra-rapid detoxification by specialist services.

ULTRA-RAPID OPIATE DETOXIFICATION

Ultra-rapid detoxification is an umbrella term that has come to represent a new treatment approach specifically designed to detoxify patients within hours rather than days and to almost completely eliminate the subjective discomfort of withdrawal symptoms. These factors lead directly to enhanced up-take of detoxification by clients and a more rapid induction onto naltrexone than can be achieved with traditional detoxification. The essential components of this technique are the administration of large doses of opiate antagonists (naloxone, naltrexone or nalmefene) leading to rapid reversal of opiate receptor down-regulation, together with a **general anaesthetic**. Naloxone is the most commonly used antagonist for this purpose (with or without naltrexone in addition), and naltrexone is continued orally following completion of the detoxification to prevent relapse. Adjunctive medication is used to control various withdrawal symptoms including metoclopramide for vomiting, ranitidine as a gastro-protectant and octreotide as an anti-diarrhoeal. Detoxification using such techniques may be completed within as little as 4 to 6 hours, allowing employed patients to return to work the following day, and can usually be performed on a day-patient basis.

The major risk associated with ultra-rapid detoxification is the risk associated with administration of a general anaesthetic. The risk of death having received a general anaesthetic for any purpose is in the region of 1 in 250,000 and of adverse events 1 in 10,000 (D'Ambra, 1998). However, the mortality rate may be as high as 1 in 1000 for the ultra-rapid detoxification procedures which have been carried out world-wide to date. The risk of adverse events in this client population may be increased by the increased prevalence of thyroid dysfunction in habitual opiate users. There are also two case reports indicating a possible risk of cardiovascular morbidity in patients receiving high dose naloxone under general anaesthetic (Taft R, 1983) (Andree M, 1980). All clients should be assessed by an anaesthetist before acceptance for treatment, and those with evidence of cardiovascular, thyroid or hepatic dysfunction will usually be excluded.

RAPID OPIATE DETOXIFICATION

Rapid detoxification also involves the use of naloxone and/or naltrexone to speed the withdrawal process. In contrast to ultra-rapid detoxification a general anaesthetic is not used; rather the discomfort of withdrawal is ameliorated by the use of a central adrenergic agonist (usually clonidine) and generous doses of **sedative medication** (usually benzodiazepines) rather than anaesthesia. Doses of opiate antagonist are smaller than those used in ultra-rapid detoxification, and the

duration of detoxification varies from between 2 and 12 days, depending on the particular protocol used (O'Connor & Kosten, 1998). The use of heavy sedation is usually considered to require admission to a high dependency unit (risk of accidental self-injury and aspiration of vomitus), although some regimes have been designed to limit the amount of sedation required, even to the extent of the procedure occurring on a day-patient basis (see below).

A recent Italian study (Gerra et al, 2000) compared three forms of **day-patient detoxification**. Patients were randomised to one of three groups which received either a standard methadone detoxification over 10 days, a standard adrenergic agonist detoxification for 5 days or a rapid opiate detoxification over 2 days. The rapid technique appeared to have various advantages.

- **Withdrawal symptoms were much more severe and prolonged in the methadone treated group as compared to the other two groups.**
- **Both negative and positive craving scores were much more severe and prolonged in the methadone treated group as compared to the other two groups.**
- **Mood was significantly lowered after detoxification in the methadone treated group as compared to the other two groups, although this difference resolved within weeks.**
- **Use of heroin was significantly lower during detoxification in the rapid detox group as compared to the other two groups.**
- **Acceptance and commencement of post-detoxification naltrexone therapy (75% of subjects) was significantly greater in the rapid detoxification group than in the other two groups.**
- **Relapse to heroin dependence at 6 months was significantly lower in those that initially accepted naltrexone therapy than those who refused it.**

NALTREXONE COMPRESSED OPIATE DETOXIFICATION (NCOD)

A well-known current example of this procedure in the UK is carried out in the Detox 5 group of centres. The regime differs from rapid detoxification in that adrenergic agonists are not routinely used, sedation levels are lower and naltrexone is administered for the first time on day 4 of the 5 day detoxification period. As such, naltrexone is being used only partially to speed the process of detoxification at a point when most exogenous opiates will already have cleared spontaneously from the body. Detoxification from day 1 to 5 is managed by the prescription of a moderate level of sedation (titration of sedative medication to maintain Glasgow Coma Scale at 13/15), and by the use of adjunctive medication to control vomiting, diarrhoea, and colic. Trazadone is used to aid night sedation, and continued with naltrexone for up to one year following completion of detoxification. Immediate completion rates and longer-term outcomes were all demonstrated to be impressive in a study by Beani et al (2000), with 98% of patients completing the procedure and abstinence rates of 71%, 61% and 51% at 3, 6 and 12 months respectively.

THE PLACE OF SPECIALIST DETOXIFICATION TECHNIQUES IN CURRENT PRACTICE

There appear to have been approximately 15 deaths related to the occurrence of approximately 15,000 procedures world-wide. The large majority of these have been associated with **ultra-rapid detoxification** and have probably occurred as a result of cardiac arrythmias or myocardial infarction caused by the general anaesthetic. Several deaths have followed rapid detoxification (no general anaesthetic) and two of these were probably due to gastro-intestinal complications such as acute bleeding and diarrhoea-related dehydration. There are no known deaths which have followed the naltrexone compressed detoxification technique. In conclusion, despite all the evident advantages of the technique, ultra-rapid detoxification clearly remains an experimental intervention.

With regard to **rapid detoxification**, a Cochrane Review of some of these studies (Gowing et al, 2000/2001) summarises as follows: '… it seems that compared to withdrawal managed by clonidine alone, the severity of withdrawal induced by a combination of naltrexone and clonidine is at least similar and is probably more severe for one to two days following initial administration of naltrexone. Indeed some studies found significant numbers of subjects experiencing delirium following early naltrexone administration, and vomiting and diarrhoea more common than with clonidine-only regimes. To manage such side-effects it is desirable to provide a high level of monitoring and support for several hours following administration of the first dose of opioid antagonist.' This increase in severity of the withdrawal syndrome is however at least partially offset by a probable effect on **completion rates**, with these being greater for the combination regimes than for clonidine alone. The review (Gowing et al, 2000/2001) continues: '…this can only be considered clearly the case for withdrawal from heroin, rather than from methadone. However the number of studies performed to date is small, and the magnitude of the difference uncertain. Methadone-dependent patients commenced on such a regime should be informed of the experimental nature of the regime.' A study by workers at the Institute of Psychiatry (Buntwal et al, 2000) examined a lofexidine/naltrexone combination regime with very satisfactory results for both methadone and heroin detoxification. Buntwal et al found that withdrawal symptoms were no more severe, even initially, in the naltrexone/lofexidine combination group than in a lofexidine alone group. They thought this may have been due to the ability to commence the detoxification with high doses of lofexidine, whereas the studies using clonidine started with low doses due to its propensity for hypotensive effects. The overall mean level of discomfort was less for the combination group. Additionally, the withdrawal syndrome resolved more rapidly for the combination group, dropping to low levels by day 6, whereas a similar level was only maintained after day 12 in the lofexidine only group.

Naltrexone compressed detoxification as performed at 'Detox 5' appears to be an acceptable intervention, where the potential benefits outweigh the risks, especially in selected cases where previous failure has occurred due to an inability to tolerate discomfort. Having said this, there have been no randomised controlled trials published examining the procedure, and as such it is still regarded by some as an experimental technique.

CONCLUSION

All techniques remain experimental to some extent, and there is probably an unacceptably high mortality rate with the general anaesthetic ultra-rapid techniques as they are currently practiced. The naltrexone compressed regime appears to have a low mortality rate, a limited duration of admission (5 days) and impressively high completion rates. As such it should find a place in current practice for selected clients who have failed in conventional detoxification due to low tolerance of discomfort, and those with employment commitments.

PRESCRIBING INJECTABLE FORMULATIONS

The use of injectable formulations in the management of addiction should only ever be considered for the treatment of opiate dependency. Only doctors with a special Home Office licence can prescribe diamorphine for the treatment of addiction. Currently, any registered doctor can prescribe injectable methadone, although this position may change in the near future with the introduction of new legislation.

The provision of injectable formulations of methadone and diamorphine for the treatment of opiate dependency is a contentious area. The rationale for such prescribing is that of harm-minimisation; injecting drug users (IDUs) may benefit from the provision of sterile drugs of known purity as compared to contaminated street drugs of uncertain purity. Equally, the potential to attract users into treatment by such prescribing may result in further health improvements achieved indirectly through the provision of other services such as HIV screening (for example) which would not otherwise have been accessed. Several studies examining the effectiveness of such interventions have failed to demonstrate any clear advantage for the group over treatment with non-parenteral formulations, neither in terms of health gains nor in improved engagement with services. Such studies are, however, prone to methodological difficulties and it may well be the case that certain subgroups have the potential to benefit from injectable prescribing.

Such treatments should only be prescribed after a full assessment by specialist services, and when the prescriber is in receipt of documented advice from specialist services which is supportive of the intervention. In general, consideration for the prescription of injectable methadone or diamorphine should be restricted to opiate-dependent patients who meet all the following criteria:

- The provision of injectable opioids may be appropriate in a few selected cases, but only following specialist advice.
- Only doctors with a Home Office licence can prescribe injectable diamorphine for the treatment of addiction; all registered doctors can prescribe injectable methadone, although this position may change in the near future.

- **At least a ten-year history of opiate dependency.**
- **Currently injects opiates on a daily basis, and has done so for at least the last five years.**
- **Has tried and failed to cease illicit drug use through the use of non-injectable treatments in the past.**
- **The patient and prescriber are clear that the patient will continue to inject street drugs on a regular basis in the absence of a prescription for injectable methadone or diamorphine.**
- **The patient and prescriber are clear that the patient will cease or significantly reduce the injection of street drugs if such a prescription is provided.**

The importance of instituting all the usual controls around prescribing is of especial concern in view of the greater street value and potential to cause accidental overdose of injectable opiates over oral and sublingual preparations. Prescribers should generally try to provide as few ampoules as possible for a given dose, to limit the potential for diversion of medication to the black market. The drug of choice will usually be methadone, although diamorphine may be preferred in patients who will only comply with a diamorphine prescription.

PRESCRIBING STIMULANTS

There is no indication for the prescription of cocaine or methylamphetamine in the treatment of stimulant misuse, and it is not recommended that other stimulants such as methylphenidate or phentermine, are prescribed. There may be a limited place for the prescription of **dexamphetamine sulphate (5mg tablets)** in the treatment of amphetamine misuse, but this should only ever take place following the receipt of documented advice from specialist services in support of such prescribing. In contrast to the wealth of evidence supporting the prescription of substitute medication in opiate dependency, there is no conclusive evidence to guide practice when it comes to the stimulant drug class. This represents a major deficit in treatment available for the substance misusing population, especially given the relatively high prevalence of amphetamine misuse, and the increasing prevalence of cocaine misuse. Additionally, there is thought to be a large population of injecting amphetamine misusers who are exposed to all the risks of injecting drug use, but who fail to engage with services due to absence of effective pharmacological interventions.

The rationale for prescribing will usually be one of removing the patient from their drug-using environment (including drug-dealers) in order to support a successful withdrawal from drug misuse. In this case the doses prescribed will aim to limit the effects of withdrawal (lower dose) rather than provide euphoria (higher dose). Prescribing in this context should also be time-limited according to a plan agreed with the patient, and a reduction regime should be instituted sooner rather than later. An alternative rationale may be one of harm-minimisation in that it may be safer for a patient to use non-contaminated drugs of known purity rather than street drugs, and that for injecting amphetamine misusers, the frequency of injecting may be reduced. In this case, prescribed doses may be higher, and reduction of dosage not a primary aim. As for injectable opioid prescription, there is no reliable evidence-base in support of the provision of dexamphetamine prescription, whatever the rationale.

- The provision of oral dexamphetamine for the treatment of amphetamine misuse may be appropriate in a few selected cases, but only following specialist advice.
- There is no indication for the prescription of other stimulant drugs in the treatment of addiction.

Prescription of dexamphetamine may be appropriate in the following circumstances:

- **The user is a primary amphetamine user.**
- **The user is an injecting amphetamine misuser.**
- **There is long history of heavy, dependent amphetamine misuse.**
- **There is evidence of escalating use with increasing tolerance and craving.**

Prescription would usually be considered contra-indicated in the following circumstances:

- **Polydrug misuse.**
- **History of mental illness.**
- **Hypertension or cardiovascular disease.**
- **Pregnancy.**

The potential for diversion of prescribed dexamphetamine to the black market may be particularly high, and all the usual controls should be applied. Daily dispensing may be achieved by the writing of a separate prescription for each day's dosage.

BIOCHEMICAL TECHNIQUES FOR MONITORING OF SUBSTANCE MISUSE

Testing of biological matrices such as urine, plasma and hair for substances of misuse is used largely to test for concordance with a course of treatment. It is important to avoid becoming over-reliant on such techniques in clinical practice; the emphasis must be on developing an honest and trusting relationship with the client – over-use of biochemical monitoring can act to undermine this. There is no clear evidence in support of frequent testing as an enhancer of outcomes and as a stand-alone measure without historical data, interpretation is often difficult or meaningless. Laboratory testing in particular may become extremely costly if used excessively by services; it is thus imperative that specialist services develop local protocols regarding the appropriate use of biochemical screening tests. A measured use of monitoring can however act both to test the honesty of self-reporting, as a tool for outcome monitoring and as a rewarding experience for clients who are providing clean samples.

- There is no clear evidence in support of frequent testing as an enhancer of outcomes.
- The emphasis must be on developing an honest and trusting relationship with the client.
- Services should only contract with laboratories that offer GC/MS.
- Urine drugs of misuse testing remains the mainstay of testing in specialist drug and alcohol units.
- Rapitest Multidrug (Morwell Diagnostics, GmbH, Switzerland) is the best performing on-site urine test when considering all factors.
- All services should rationalise their use of testing to contain costs whilst making the best use of the technology and body matrices available.

INTERPRETATION OF RESULTS

The interpretation of results will be dependent on 3 major factors:

- **The client's statement regarding the class, route, amount and timing of drug use.**
- **The technology used to perform the test.**
- **The body matrix used for testing (e.g. urine, saliva, hair).**

TESTING TECHNOLOGY

There are two main classes of technique – chromatography and immunoassay. Immunoassay may be an easier and cheaper alternative and is the mainstay of on-site testing techniques. Its main disadvantage is that it can usually only detect the class of drug rather than the actual drug itself. This leads to problems with interpretation, especially in the case of opiates where the same positive result may occur in response to heroin use or over-the-counter codeine use.

Chromatography techniques are able to detect the actual drug and the gold standard **laboratory test** is Gas Chromatography/Mass Spectrometry (GC/MS). If there is doubt about the validity of a test result, a confirmatory test using GC/MS should usually be performed in the laboratory. The other commonly used laboratory test is High Pressure Liquid Chromatography (HPLC), the accuracy of which approaches that of GC/MS. Some laboratories will also employ immunoassay techniques, or cheaper forms of chromatography (such as TLC) to screen samples for positives, before confirming the positive samples with GC/MS or HPLC.

Most **on-site rapid tests** use immunoassay technology, although there are paper chromatography kits available. Paper chromatography tests are inaccurate, labour-intensive and time-consuming and their use is not recommended in any setting. Most immunoassay tests operate by the binding of drug to an antibody, thus preventing the binding of a drug-conjugate (competitive immunoassay) to the antibody which in turn prevents the formation of a visible band, indicating a positive test result. (However, some tests operate in a reverse fashion where the formation of a visible band indicates a positive result: instructions must be carefully read). As a generalisation, these tests will be slightly less accurate than laboratory testing using GC/MS due to i) higher cut-off points leading to false negatives and ii) greater potential for giving false positive results. As mentioned above, they are also limited by their inability to detect a specific drug, reporting only on the class of the drug.

BODY MATRIX

The body matrix used has implications for test results in several ways:

- **Recency of drug use: typically urine will indicate drug use within the last 48 hours or so, whilst plasma indicates use within the last period of hours and hair within the last period of months.**
- **Accuracy of results: very large amounts of drug are excreted into the urine allowing for easier detection by the laboratory technology than with saliva or hair.**
- **Quantitation of results: if a quantitative level of drug is to be measured, the only suitable matrices are plasma or saliva.**

Whilst saliva (or oral fluid or oral mucosal transudate) offers many potential advantages over urine as a testing matrix, the current technology has not yet developed to the extent that saliva should routinely be used in preference to urine. In the laboratory a greater number of extraction steps are required relative to urine which increases cost. The concentrations of drugs are lower and the window of detection shorter than for urine, both of which increase the number of false negative results obtained. Currently few immunoassays exist which can detect the unique profiles of drugs in saliva, meaning that more expensive technology often has to be used for screening. Nevertheless, the many potential advantages of saliva over urine as a matrix means that this is a rapidly developing area of reseach, and in due course saliva (or oral fluid or oral mucosal transudate) will probably become the matrix of choice for drugs of misuse testing.

URINE TESTING

Urine drugs of misuse testing remains the mainstay of testing in specialist drug and alcohol units, despite its many drawbacks in terms of inconvenience, adulteration of samples, observation of sample production etc.

1. On-site (rapid) urine testing.

There are several factors to consider when selecting a rapid test:

- **The range of drugs tested for – specialist units should routinely test for opiates, methadone, cocaine, amphetamines, benzodiazepines and cannabis. An on-site urine screen is now available for detection of buprenorphine.**
- **Ease of use and interpretation of results – this is particularly important in a busy clinic – errors will be made frequently if the equipment is complex to use, if it is difficult to interpret the test and if there is a long duration required for the reaction to take place.**
- **The accuracy of the test – this will never match laboratory techniques and accuracies of below 90% should be regarded as unacceptably low.**
- **Cost.**

An on-going European study of the utility of roadside testing (ROSITA) (Gronholm & Lillsunde, 2001) has provided information regarding the accuracy and ease of use of a number of on-site urine immunoassays. Of those tested, Surescreen (Surescreen Diagnostics Ltd., UK), **Rapitest Multidrug (Morwell Diagnostics, GmbH, Switzerland)** and Status DS (Lifesign, LLC, USA) were found the easiest to use and interpret.

Taking into account all the above factors, Surescreen and Rapitest Multidrug would both appear suitable tests for use in specialist units. **The Multidrug test** offers a shorter reaction time which may be of significance in a busy unit. Status DS suffers from the major drawback of failing to detect benzodiazepine misuse. Whilst specificities are high (in the region of 98%) for all the devices, sensitivities tend to be a little lower (around 90%) apart from cocaine for which there is a high sensitivity.

2. Laboratory urine testing.

A laboratory test should always be used to confirm opiate misuse before commencing opiate substitute medication, and at any time if there is doubt as to the validity of the result given by an on-site test. Services should only contract with laboratories which offer GC/MS. Laboratory testing (in particular GC/MS) may also be used to test for the presence of almost any other substance which may be impacting on the clinical picture; e.g. confirmation of the use of an antidepressant may be sought, or a search for ingestion of substances which may be altering plasma methadone levels.

	Surescreen	Multidrug	Status DS
Drugs detected	OPI, COC, BZO, AMP, MET, THC	OPI, COC, BZO, AMP, THC	OPI, COC, AMP, THC
Time for reaction	10 min	3 min	5 min
Accuracy (mean)	97%	98%	96%

BREATH TESTING: ALCOHOL DETECTION

Breathalysers may be photoelectric or infrared based. Infrared devices with microprocessor control give the highest accuracy. Forensic grade breath analysers offer the greatest accuracy with a bias for slightly under-estimating blood alcohol levels. There is a significant initial expense, but they are cheap to use following the initial outlay. **Breathalyser** readings give an indicator of recent (several hours) alcohol consumption.

SALIVA TESTING

1. On-site salivary tests: alcohol detection.

A number of test are available with the potential advantages of smaller cost and less client cooperation needed than with breathalysers. Colorimetric strips produced by a number of companies (ALCOSCAN, Lifescan Inc., Mountain View, CA 94043 and ALCO-LEVEL, Beveridge Products Co., Knoxville, TN 37939) are particularly cheap whilst maintaining good accuracy.

2. On-site oral fluid tests: illicit substances.

Two tests have been examined in the ROSITA programme (Gronholm & Lillsunde, 2001): Cozart Rapiscan (Cozart Biosceiences Ltd., UK) and Drugwipe (Securetec GmbH, Germany). Both had basic drawbacks in their utility: Cozart Rapiscan was difficult to use, while Drugwipe results were difficult to interpret.

	Cozart Rapiscan	Drugwipe
Drugs detected	OPI, COC, BZO, AMP, THC	OPI, AMP
Accuracy	80-90%	70-80%

Cozart Rapiscan gave many more false negative results than the urine screens tested, while Drugwipe gave many more false positive results. Both these findings could be related to the difficulty of use and interpretation of results. Neither test should be considered as performing well enough for routine use in specialist services. In particular the low saliva/plasma ratio for benzodiazepines (0.3) as compared with basic drugs such as opiates (6-MAM = 6) and amphetamines (2.8) has led some authors to conclude that oral testing is currently suitable for amphetamines and opiates, but not for benzodiazepines (Gronholm & Lillsunde, 2001). There may be a place for the use of saliva testing in individuals who are regularly unable to provide urine samples, and in this case the Cozart Rapiscan test would be preferred, due to its relatively low false positive rate.

3. Laboratory oral fluid and oral mucosal transudate tests: illicit substances.

There may be a limited place for laboratory testing for clients who query an on-site oral fluid test result. This is a rapidly developing area and oral fluid or oral mucosal transudate have the potential to replace urine as the gold standard matrix in the future.

PLASMA TESTS

1. Alcohol.

Raised Mean Corpuscular Volume (**MCV**) in the absence of anaemia, and raised Gamma-Glutaryl-Transferase (**GGT**) are both indicative of although not specific for heavy use of alcohol in the medium-term (months/years). Carbohydrate-deficient transferase (**CDT**) is more highly specific for alcohol misuse and may be useful in distinguishing between raised liver enzymes associated with alcohol use and those caused by hepatitis C. Ethyl-glucuronide (**EtG**) is a metabolite of alcohol which is detectable in serum for up to 80 hours (Wurst et al, 1999), and may be useful in determining quite recent alcohol use when breathalyser readings are negative.

2. Methadone.

The future of monitoring of methadone compliance and dosage adjustment is likely to involve the use of computerised statistical models which predict trough plasma methadone levels for individuals. Plasma methadone levels will need to be taken on two occasions from an individual client – after the first dose and again after one week of dosing. This will then be sufficient to design an individualised regime for the client. Random samples during treatment thereafter may be used to assess the effectiveness of therapy, methadone compliance, dosing habits and to rationalise detoxification regimes involving opiate antagonists, by comparing predicted with measured plasma levels (Wolff et al, 2000).

Currently, plasma methadone levels may play a part in monitoring compliance and in the tailoring of dosage to an individual's needs (there is a very large variation in plasma level achieved for a particular dose, between individuals). Trough levels taken immediately before the day's dose is due (as opposed to peak levels) should be used, and compared with previous trough methadone levels taken from the same individual. There are many factors that may result in changed plasma methadone levels apart from poor compliance (Eap et al, 1999), and methadone levels cannot be used as a 'stand-alone' measure of concordance.

HAIR TESTING

Hair testing gives a long-term view of an individual's substance misuse, and at best is able to indicate whether a substance has been used within a particular month. Its main utility in specialist services may be in the monitoring of long-term outcomes amongst service users. It may also be useful where there is suspicion that a service user is abstaining from illicit substance misuse only in the several days before urine testing is due in order to provide negative results. All commonly abused substances can be detected including EtG (alcohol).

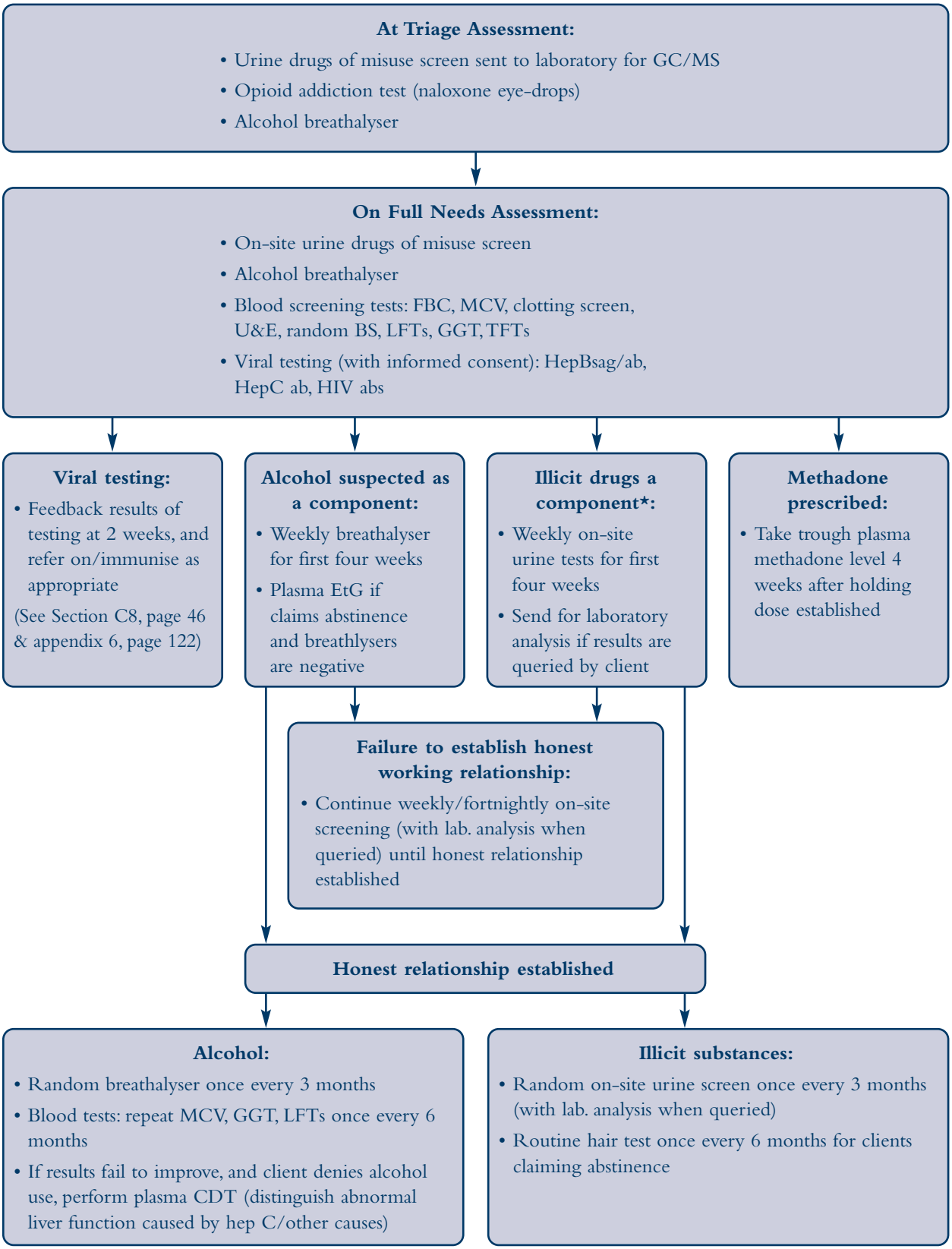
Urine testing results and detection periods.

Substance used	May be reported positive for one of or a combination of:	Typical detection period after use:
Heroin*	6-MAM,	6-24 hours
	'Opiates', morphine, codeine	48 hours
Methadone	Methadone metabolite	7-9 days
Codeine	Codeine, (rarely morphine)	48 hours
Dihydrocodeine	Dihydrocodeine	48 hours
Amphetamine	Amphetamine	48 hours
Dexamphetamine*	Amphetamine	48 hours
Cocaine	Cocaine metabolite, Benzoylecgonine (BE)	2-3 days
Benzodiazepines	**'Benzodiazepines'** The metabolic pathways of many benzodiazepines are shared, and detection of one benzodiazepine (e.g. oxazepam) may indicate use of another (e.g. chlordiazepoxide)	Detection period is dependent on the elimination half-life of the particular benzodiazepine; e.g. detection period of temazepam is 40 to 60 hours and of diazepam is up to 7 days.
Cannabis	THC/cannabinoids	After single use: 3 days With daily use: up to 27 days

* Specialist tests are available to distinguish prescribed diamorphine use from street heroin use (desmethylpapaverine (McLachlan-Troup et al, 2001)), and street amphetamine use from prescribed dexamphetamine use (stereospecific assay for the laevorotatory-isomer).

TESTING PROTOCOLS

Frequent testing at the onset of treatment can help to provide a clear picture and set a baseline for development of the treatment plan. The frequency of testing should gradually reduce thereafter at a rate determined by the development of trust between the worker and client. The worker's response to positive samples should always be motivational and never punitive.



* Consider the use of an on-site oral fluid or laboratory OMT test for clients who are frequently unable to provide a urine sample.