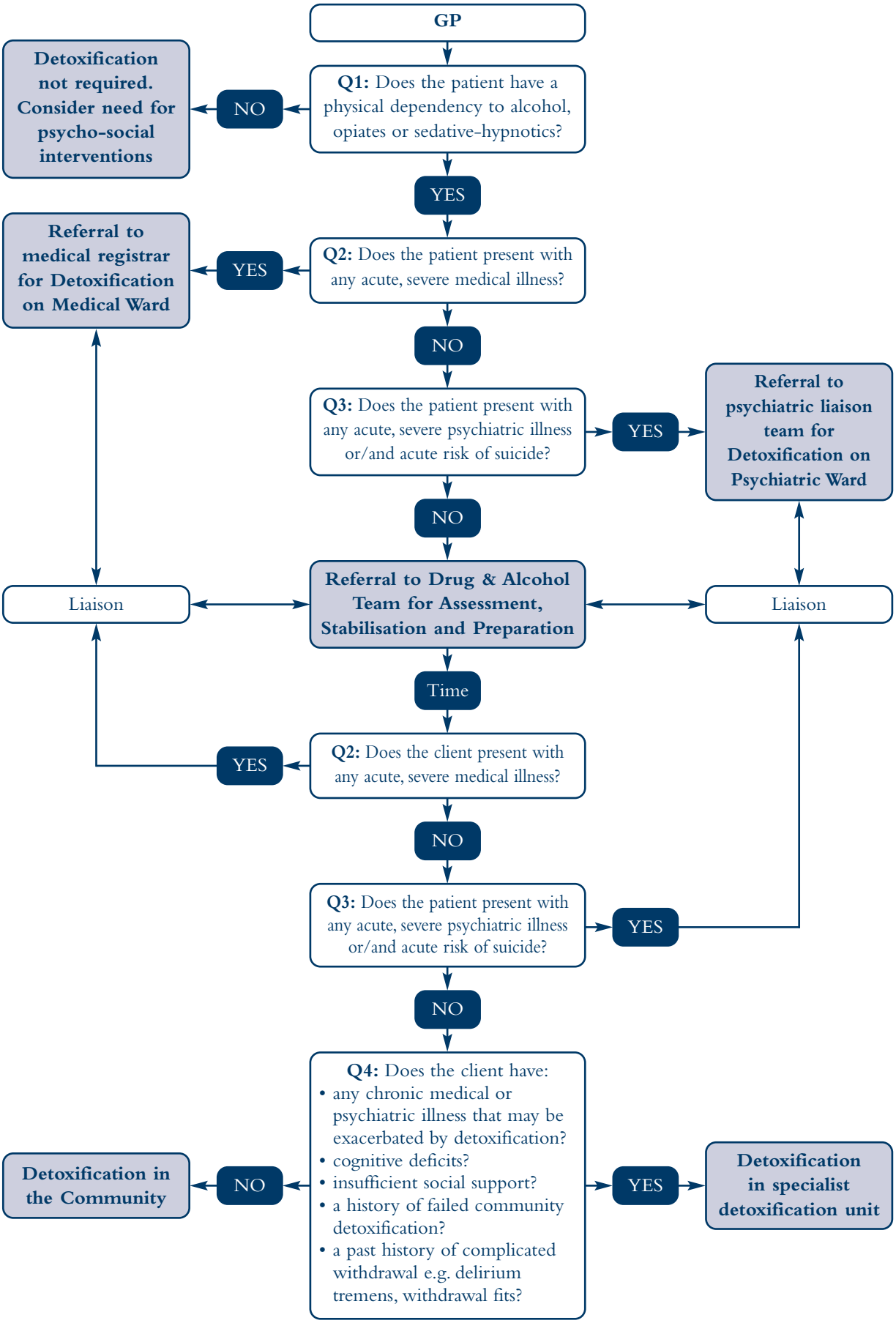
THE MANAGEMENT OF WITHDRAWAL SYNDROMES

REFERRAL CARE PATHWAY FOR DETOXIFICATION



THE MANAGEMENT OF WITHDRAWAL SYNDROMES

BASIC PRINCIPLES

In general, withdrawal syndromes are characterised by symptoms opposite to those of the main effects of the drug itself, occurring as a result of neuroadaptation which itself results from prolonged and regular exposure to the drug. Withdrawal syndromes of CNS depressant drugs are potentially life-threatening with the exception of opiate withdrawal. Withdrawal syndromes from CNS stimulant drugs are not directly life-threatening, although the associated dysphoria may acutely increase suicide risk. A description of the common withdrawal syndromes can be found in *appendix 3*, page 117. The management of withdrawal essentially involves the amelioration of withdrawal symptoms by the prescription of appropriate medication - detoxification. However, if detoxification is to be successfully completed and abstinence maintained the process must be planned and the patient psychologically prepared. A 'stand-alone' detoxification will usually end in relapse to substance misuse, either before completion of the detoxification, or soon afterwards. An aftercare plan aimed at preventing relapse should be formulated in advance of the detoxification and may include residential or community options.

Detoxification should be planned for in advance wherever possible. Urgent in-patient psychiatric admission may be indicated for the management of suicidal risk, or urgent in-patient medical admission for the management of medical complications; detoxification may then take place as a matter of course once the patient is already admitted. However, if the primary goal is to achieve and maintain abstinence, then the process should be planned. **This process can be enabled by referral to local specialist services.**

- A 'stand-alone' detoxification will usually end in relapse to substance misuse, either before completion of the detoxification, or soon afterwards.
- If the primary goal is to achieve and maintain abstinence, then the process should be planned. This can be enabled by referral to local specialist services.
- Community detoxification should only be performed with support from statutory specialist substance misuse services.
- The five stages of successful progression to abstinence are:
  Stabilisation > Decision > Preparation > Detoxification > Relapse prevention.

THE FIVE KEY THEMES OF SUCCESSFUL PROGRESSION TO ABSTINENCE

STABILISATION

The patient's social circumstances and psychological state should be as stable as possible before commencing detoxification. Stabilisation of the patient's substance misusing behaviour through a counselling process and through the prescription of substitute medication is also likely to improve the outcome of detoxification.

DECISION

The patient must be crystal clear that they are ready for detoxification and prepared for abstinence. If there is doubt, then wait.

PREPARATION

Preparation involves planning the most suitable time for the detoxification (for example to fit in with child-care or work arrangements), setting a specific date to commence detoxification (usually a Monday to avoid reduced availability of medical cover during the earlier stages of the detoxification), and most importantly agreeing the aftercare arrangements. A full physical assessment with baseline blood tests (FBC, U&E, LFT, GGT, glucose, TFT, clotting screen) and urine drugs of abuse screen should be performed as part of the planning process. **The patient should be warned that the detoxification itself is 'the easy part' and that remaining abstinent is much harder**.

Most patients who are physically dependent on a substance will experience a protracted withdrawal syndrome that can last many months after detoxification. Insomnia, agitation and craving are all common complaints during this period.

DETOXIFICATION

Decisions will need to be made regarding the setting (community or in-patient detoxification), the agent to be used, adjunctive medication to be prescribed, and the necessary degree of monitoring during detoxification. In general, in-patient as opposed to community detoxification is indicated in the following circumstances:

- **There is a past history of delirium tremens or fits during withdrawals.**
- **There is concurrent severe medical illness.**
- **There is concurrent severe psychiatric illness or suicide risk.**
- **The patient has cognitive deficits.**
- **The patient has insufficient social support available at home.**
- **There is a past history of failed community detoxification.**

Medical ward.

Patients with any of the serious medical consequences of alcohol misuse should be considered for detoxification on a medical ward. The stress of detoxification and the prescription of medication which is metabolised by the liver can precipitate a number of complications such as Wernicke's Encephalopathy or hepatic encephalopathy in the medically ill patient. For example liver failure with abnormal clotting profiles, or a recent history of bleeding from oesphageal varices, indicates the need for hospital medical supervision.

Psychiatric ward.

Patients with concurrent severe psychiatric illness, or those at acute risk of suicide should receive detoxification as an in-patient on a psychiatric ward.

Specialist in-patient detoxification unit.

Rates of completion of detoxification are typically in the region of 80 - 100% for specialist in-patient detoxification and 50% for community detoxification. However some clients will prefer the option of home (community) detoxification and the cost of in-patient detoxification precludes its automatic availability. A history of previous complicated withdrawal, insufficient social support at home, cognitive impairment or a previous failure to complete community detoxification are all indications for an in-patient as opposed to a community detoxification.

Community.

Community detoxification is appropriate for those who have sufficient social support at home and who have no serious concurrent psychiatric or medical illness. **Community detoxification should always take place with the support of staff from the local specialist substance misuse service.**

RELAPSE PREVENTION

Prevention of relapse may involve the prescription of medication (*see Section C6*, page 41), counselling interventions, attendance of self-help groups such as AA and NA, and social interventions aimed at enhancing purposeful activity and relieving stressful social circumstances.

Some patients will be suitable for an extended period of rehabilitation in a specialist unit, either on a residential or day-care basis.

DETOXIFICATION FROM ALCOHOL

Detoxification is only indicated in those who experience physical withdrawal symptoms such as shakes, sweats, panic, anxiety or withdrawal fits after a period of abstinence (e.g. overnight), or in those that drink to avoid such symptoms. As a rule of thumb, medication may not be required for women who drink less than 12 units per day, or men who drink less than 16 units per day. The final decision will be based on the elicitation of a history of alcohol withdrawal symptoms. **No patient should ever be advised to stop drinking immediately** due to the potentially life-threatening complications of Delirium Tremens, seizures and Wernicke's Encephalopathy. Patients who do not require a detoxification can be **advised to slowly reduce** their daily intake of alcohol over a period of days or weeks, as can patients who are physically dependent but cannot or will not access detoxification.

MEDICATION

The drug of choice for control of withdrawal is **chlordiazepoxide** (Librium). **Oxazepam** may be the drug of choice for alcohol detoxification in patients with hepatic insufficiency, as it is not metabolised by the liver. Diazepam should be **avoided** where possible in the treatment of addictive disorders due to its greater addictive potential as compared to chlordiazepoxide. Chlormethiazole (Heminevrin) which has been associated with a risk of death due to respiratory depression when combined with alcohol, should also be **avoided**.

A course of **parenteral thiamine (Pabrinex)** should be given over the first several days of detoxification as prophylaxis against the development of Wernicke's Encephalopathy and **chronic memory deficits**. Wernicke's-type brain damage is **highly prevalent** in alcoholics as are associated memory deficits which cause permanent disability (Ambrose et al, 2001). The process of detoxification is liable to precipitate acute loss of thiamine (vitamin B1) stores in patients who are already chronically thiamine deficient. The acute effects are often subclinical, but it is likely that many chronic memory problems in alcoholic patients are the direct result of episodes of withdrawal whether this is medically assisted or not. Oral thiamine preparations may be poorly absorbed in the alcoholic patient; **administration by the intramuscular or intravenous route is essential for effectiveness**. The administration of glucose for the treatment of hypoglycaemia may exacerbate the acute loss of thiamine even further in the detoxifying alcoholic, and **it is essential that parenteral thiamine is administered before the glucose load**. Due to the small risk of anaphylaxis associated with parenteral thiamine administration, this should only be given where medication for treatment of anaphylaxis is available on-site.

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- Patients who do not require a detoxification can be advised to slowly reduce their daily intake of alcohol over a period of days or weeks, as can patients who are physically dependent but cannot or will not access detoxification.
- The drug of choice for control of withdrawal is chlordiazepoxide (Librium).
- Chlormethiazole (Heminevrin) should be avoided due to enhanced risk of respiratory depression if used together with alcohol.
- A course of parenteral thiamine (Pabrinex) should be given over the first several days of detoxification as prophylaxis against the development of chronic memory deficits which are highly prevalent in alcoholics.
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A presumptive diagnosis of **Wernicke's Encephalopathy** should be made if any of the following supervene during detoxification: ataxia, confusion, memory disturbance, hypothermia, hypotension, opthalmoplegia or nystagmus, coma/ unconsciousness. **This represents a medical emergency** and should result in immediate transfer to hospital, and treatment with high dose Pabrinex.

DOSAGE & REGIMES

'Symptom-triggered' regimes should ideally be used for in-patient detoxification (see Section D2,page 56/ *appendix 10*, page 130), and where day-care detoxification is available. Standard symptom-triggered regimes should **not** be used for community detoxification due to the reduced availability of nursing staff for regular monitoring of the severity of alcohol withdrawal. Advice should be

sought from the local specialist team as to the regime to use in a particular patient. The following provide a 'rule of thumb' guide only for **community alcohol detoxification**.

Chlordiazepoxide - fixed-schedule regimes:

For the mildly dependent alcoholic (SADQ* 10-20): 20mg qds tapered to zero over 5 to7 days.

For the moderately dependent alcoholic (SADQ 20-30): 30mg qds tapered to zero over 7 days.

For the severely dependent alcoholic (SADQ > 30): up to 50mg qds tapered to zero over 10 days.

*Symptoms of Alcohol Dependence Questionnaire (*appendix 10*, page 130).

The effect of dosages will vary from individual to individual due to physiological variations in metabolism and the effect of liver disease and cognitive deficits on sensitivity to medication. Regular monitoring by a nurse from the specialist team will allow adjustment of dosage as necessary. Patients that appear over-sedated should be advised to omit a dose of medication. Patients whose CIWA-Ar (*see appendix 10*, page 130) (Sullivan et al, 1989) scores are consistently less than ten after the third day of detoxification should have their dosage schedule reviewed with a view to a more rapid completion of detoxification.

Pabrinex injections:

One pair IM ampoules daily for the first 3 days of treatment as prophylaxis – this should be administered in the GP's surgery or specialist team base if the detoxification is taking place in the community, due to the unlikely eventuality of anaphylaxis occurring following IM injection.

Other medication:

For fits: diazepam 10mg PR or IV followed by transfer to A&E (unless on medical ward).

For insomnia: zopiclone 7.5-15mg nocte prn for a maximum of four weeks.

General Care.

Clients undergoing detoxification require lots of fluid with sugary fluids available in case of hypoglycaemia and light regular meals despite feeling anorexic.

Caffeine intake should be cut down to 4-5 cups of tea or coffee a day.

Agitation can be reduced if there is a quiet and ordered environment.

MONITORING REQUIREMENTS

Each set of observations should include:

- **Alcometer reading.**
- **Alcohol withdrawal scale (CIWA-Ar).**
- **Observation of level of consciousness and orientation.**
- **Pulse, blood pressure and temperature**
- **Observation for nystagmus & opthalmoplegia & ataxia.**
- **Observation for dehydration & marked tremor.**

With fixed-dose regimes used in community detoxification observations should be performed:

- **Immediately before the start of the detoxification.**
- **Twice daily on days one to five.**
- **As indicated thereafter.**

In the presence of a positive alcometer reading, chlordiazepoxide should only be commenced if withdrawal symptoms are significant (i.e. CIWA-Ar of more than 15). Patients should always be requested to have their last alcoholic drink on the night before detoxification is due to commence.

If the detoxification is occurring at home, then a nurse from the local specialist substance misuse team will act as the observer, and arrange with the GP for the administration of Pabrinex in the surgery on days one to three of detoxification, and for the dispensing of chlordiazepoxide. In addition, home detoxification should only be commenced if there is a supportive spouse, family member or friend who is willing to remain continuously with the client for a minimum of 72 hours, and for the majority of the rest of the week.

An example community alcohol detoxification protocol can be found in *appendix 10*, page 130.

DETOXIFICATION FROM OPIATES

In contrast to alcohol, the opiate withdrawal syndrome (*appendix 3*, page 117) is hardly ever life-threatening. Physicians should thus resist all requests for prescription of methadone without prior assessment by the local specialist substance misuse team. The only exceptions to this rule are in the pregnant opiate addict where there is a potential for withdrawal to precipitate spontaneous abortion or premature labour, and in the elderly addict with cardiovascular disease where there is a theoretical risk of increased sympathetic tone precipitating cardio-vascular complications. In these circumstances a physical examination will usually suffice to exclude supervening complications, and if not referral to the appropriate obstetric or medical team for an opinion, rather than resorting to premature prescribing of methadone. If the client offers the name of a previous prescriber who can confirm the prescription, then medication may be continued with referral to the local specialist team.

In some cases it may be appropriate to commence detoxification without an interim period of methadone stabilisation; there is no contraindication to commence-ment of detoxification straight from heroin or any other opiate drug. However, there is evidence that the likeli-hood of completion of detoxification is greater if the patient has been first stabilised on methadone.

MEDICATION

The drug of first choice for opiate detoxification is lofexidine. Lofexidine is a central alpha-2 agonist which blocks the autonomic response to opiate withdrawal. It is a non-opiate, non-addictive and non-controlled drug and as such holds some advantages over methadone as a detoxification agent. Its potential advan-tages over methadone in this context are the possibility for a more rapid completion of detoxification, and an earlier induction onto naltrexone if the latter is to form part of the after-care plan. Both the outcome of detoxi-fication in terms of completion rates and the acceptabil-ity to the client in terms of subjective discomfort of detoxification are equivalent to methadone.

The major risk associated with administration of lofexidine is the development of postural hypotension and bradycardia. The client should be monitored on a twice-daily basis to ensure appropriate use of medica-tion and prevent the occurrence of dose-related hypotensive reactions. Over-sedation due to lofexidine usage may also occur, and the patient should be warned to avoid the use of other CNS depressant drugs throughout the course of the detoxification.

Early concerns regarding lofexidine's potential to induce a marked hypotensive response are now thought to have been largely unfounded, and it increasingly has the reputation of a safe drug. BNF guidelines regarding dosage regimes are probably excessively cautious in terms of the low starting doses recommended, which may potentially lead to early relapse. The BNF regime should nevertheless be followed in the absence of documented specialist advice to the contrary:

- **Initially 200 micrograms twice daily.**
- **Increased daily as necessary to control withdrawal, in steps of 200-400 micrograms daily to a maximum of 2.4mg daily.**
- **Withdraw gradually over 2 to 4 days (theoretical risk of rebound hypertension).**
- **Recommended duration of treatment 7 to 10 days.**

- In contrast to alcohol, the opiate withdrawal syndrome is hardly ever life-threatening. The only usual exception to this rule is that of the risk of precipitation of premature labour by opiate withdrawal. Opiate detoxification in pregnancy is a second-line treatment option, and should only be considered following specialist medical advice.
- There is evidence that the number of patients completing detoxification is greater if the patient has been first stabilised on methadone.
- The drug of first choice for opiate detoxification is lofexidine; adjunctive medication may include ibuprofen, metoclopramide, loperamide and zopiclone. Detoxification using methadone or Subutex may be appropriate in some cases.
- The use of dihydrocodeine, codeine, carbamazepine, chlorpromazine and other drugs for opiate detoxification is not licensed and is not recommended.
- Opiate detoxification under general anaesthesia is not recommended under any circumstance.

Adjunctive medication to provide symptomatic relief may be prescribed as follows:

- **Aches & pains:ibuprofen 400mg tds prn.**
- **Nausea & vomiting: metoclopramide 10mg tds prn.**
- **Diarrhoea: loperamide 2-4mg prn after loose stools – maximum 16mg in 24 hours.**
- **Insomnia: zopiclone 7.5 to 15mg nocte prn for a maximum of four weeks.**

If the patient has been first stabilized on methadone, it may be appropriate to continue the methadone for the first two days of the lofexidine detoxification. Some authorities recommend this approach as a means of protecting the patient from excessive withdrawal during the early period of detoxification when the lofexidine dose is low. Equally, this approach may also be appropriate with detoxification straight from heroin.

Methadone for detoxification.

Detoxification using methadone is an appropriate alternative for some clients who do not wish to use lofexidine, or in whom lofexidine is contraindicated. Induction onto an initial stabilisation dose should be managed as described in Section C5, *page 25*. Following this, reduction to zero in daily increments of 5 to 10mg should take place over a period of up to two weeks depending on the starting dose. Relapse is more likely towards the end of the schedule, when dosages reduce below 20mg daily, and it may be appropriate to reduce by smaller increments of 2 to 5mg for the final days of the detoxification. Adjunctive medication may be prescribed as described above for lofexidine detoxification. **Methadone should never be prescribed in the absence of prior advice from the local specialist substance misuse service.**

Subutex (buprenorphine) for detoxification.

Subutex is a valid alternative for opiate detoxification where the patient does not want detoxification with lofexidine. Care must be taken during induction onto Subutex as it may induce an opiate withdrawal syndrome in certain circumstances due to its partial agonist action. In general, Subutex may only be appropriate for opiate addicts with 'smaller' habits in the region of 1/4g heroin or less daily. If Subutex is chosen as the detoxification agent, induction onto an initial stabilisation dose should be managed as described in Section C5. A 7 to 10 day withdrawal regime can then be instituted by incremental reduction of dosage to zero. Adjunctive medication may be prescribed as described above for lofexidine detoxification.

Subutex should never be prescribed in the absence of prior advice from the local specialist substance misuse service.

Other pharmacotherapies for opiate detoxification.

The use of dihydrocodeine, codeine, carbamazepine, chlorpromazine and other drugs for opiate detoxification is not licensed and is not recommended.

MONITORING REQUIREMENTS IN OPIATE DETOXIFICATION

Each set of observations should include:

- **Opiate withdrawal scale** *(appendix 9,* page 129*).*
- **Observation of level of consciousness.**
- **Pulse and blood pressure.**

Observations should be performed:

- **Immediately before the start of the detoxification.**
- **Twice daily for the first five days.**
- **As indicated thereafter.**

Patients should usually be requested to cease opiate use by the night before detoxification is due to commence.

If the detoxification is occurring at home, then a nurse from the local specialist substance misuse team will act as the observer, and arrange with the GP for the dispensing of medication. In addition, home detoxification should only be commenced if there is a supportive spouse, family member or friend who is willing to remain with the client for a minimum of 72 hours, and for the majority of the rest of the week.

Example protocols for opiate detoxification may be found in *appendix 10*, page 130.

DETOXIFICATION FROM SEDATIVE-HYPNOTICS

A clinically significant sedative-hypnotic withdrawal syndrome is likely to occur following the discontinuation of a daily therapeutic dose (e.g. 20mg temazepam or equivalent [*see appendix* 7, page 123 for benzodiazepine equivalency doses]) after at least four months of treatment, or after as little as two months if doses more than twice the therapeutic dose have been used/prescribed. The time course and severity of the withdrawal syndrome will be dependent on the dose prescribed, the duration it was prescribed for, the duration of action and potency of the particular drug and individual factors. The withdrawal syndrome is characterised by a host of symptoms and signs classically associated with anxiety, depression, and neuromuscular hyperactivity, and may in severe cases progress to seizures, psychosis and/or delirium (*see appendix 3*, page 117). Acute, severe withdrawal will usually resolve spontaneously within one month; however, as for the opiate and stimulant classes, a protracted withdrawal syndrome that is much less intense may persist for many months.

Individual factors predicting a more severe withdrawal syndrome and poor prognosis for successful discontinuation include psychiatric comorbidity (actively present in more than 50% of long-term benzodiazepine users), polydrug misuse, concurrent alcohol misuse, family history of alcoholism, older age and female sex. Polydrug misusing, concurrent alcohol misusing and comorbid patients should be referred for a specialist assessment before commencing discontinuation.

Assessment preceding detoxification must take into account the potential of the patient to experience re-emergent psychiatric symptoms or to precipitate an episode of psychotic illness in a patient with a past history of psychosis. Equally, in patients with medical conditions that are significantly influenced by adrenergic and psychological stress factors (e.g. cardiac arrythmias, asthma, SLE, inflammatory bowel disease), care must be taken to avoid precipitating complications.

The simplest means of withdrawal on an outpatient basis is to commence a tapering reduction regime. The rate of discontinuation for long-term users should be at a maximum of 5mg diazepam equivalents per week or 6% of the starting dose, whichever is smallest (*see appendix* 7, page 123 for equivalency doses). The final 20% of the taper should be slowed down considerably. If symptoms of withdrawal occur, the dose should be increased until the symptoms resolve and the taper then re-started at a slower rate.

- Sedative-hypnotic withdrawal may be life-threatening.
- The usual approach is to commence a slow tapered reduction in the community.
- This may be enhanced by the substitution of a long-acting drug such as chlordiazepoxide for a shorter-acting drug, before commencing the reduction.
- In-patient detoxification may be indicated using barbiturate medication in some cases.

Patients who are unable to tolerate such a regime may possibly respond to a substitution and tapering regime. Chlordiazepoxide (long duration of action and low abuse potential) should be used to replace the equivalent amount of other benzodiazepine (or barbiturate). Dosing should be on a four times daily regime to provide the most stable plasma levels possible. Allow one to two weeks to attain a steady state plasma concentration before commencing the taper. Commence the taper as above.

Patients who are unable to complete a community reduction or who require in-patient treatment for other reasons (e.g. comorbidity) should **be referred to specialist services for access to in-patient detoxification**. This is often best carried out using phenobarbital substitution which provides the smoothest and most effective withdrawal; completion of prescribing is also more rapid making this a more practical solution for use on an in-patient basis. Phenobarbital 30 to 60mg hourly PRN is titrated against withdrawal symptoms until a stable 24 hour dosage has been achieved; this process may take up to one week to achieve. The stabilisation dose is then administered in divided doses over the next 24 hours before commencing reduction at the rate of 30 to 60mg phenobarbital daily. The final 20% of the taper should be accomplished more slowly, possibly at a rate of reduction of 15 to 30mg every two days, depending on the patient's response.

DETOXIFICATION FROM STIMULANT DRUGS

Abrupt cessation of stimulant (amphetamine, cocaine) use is associated with depression, anergia, anhedonia, increased drug craving, increased appetite, hypersomnolence and increased REM sleep (Weiss, Greenfield & Mirin, 1994). This initial period of intense symptoms is commonly termed the 'crash', which is usually self-limiting to a period of days. There have been reports of myocardial ischaemia occurring in the first week of stimulant withdrawal (Nademanee, Gorelick et al, 1989) although this is uncommon, and other medical effects are relatively minor.

The 'dopamine deficiency' hypothesis of stimulant withdrawal has not been supported by clinical practice – controlled clinical trials of dopamine agonists have yielded inconsistent results. Similarly the use of tricyclic antidepressants to limit the effects of withdrawal on the basis that they inhibit presynaptic catecholamine neurotransmitter uptake, have failed to deliver any significant benefit. Antidepressants may however be useful in the treatment of an on-going depressive disorder associated with stimulant drug misuse.

The stimulant withdrawal syndrome is thus best treated supportively and symptomatically by allowing the patient to sleep and eat as much as necessary. A benzodiazepine such as chlordiazepoxide may be helpful in selected patients who develop agitation or sleep disturbance

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(Pearsall & Rosen, 1992); these should not be continued any longer than two weeks. Neuroleptics should be avoided because of their potential to induce dysphoric side-effects.

As for opiate drugs, the chronic stimulant misuser is likely to experience a protracted withdrawal syndrome for months or even years which is characterised by depressed mood, lethargy and anhedonia together with intense craving. There is no specific pharmacological antidote for this syndrome or to limit the likelihood of relapse, although concurrent depressive disorder may respond to antidepressants.

In conclusion, the management of stimulant drug misuse is largely psycho-social at all stages.

DETOXIFICATION FROM NICOTINE

Nicotine replacement therapies such as the nicotine patch and nicotine gum may aid smokers in withdrawal from nicotine. Such therapies have been shown to boost the rates of smoking cessation by a factor of 1.4 to 2.6 (Fiore at al, 1996) in comparison with placebo treatments, but 70 to 80 per cent of smokers who use these therapies still start to smoke again. A maximum of two weeks should be prescribed at any one time, and replacement prescriptions only given to those who attend for a follow-up appointment.

Buproprion is a non-nicotine preparation recently marketed as an aid to help stop smoking. It is available on the NHS as a prescription-only medicine. When used in a specialist setting and in conjunction with regular counselling, it is at least twice as effective as placebo in helping patients to stop smoking (Drugs and Therapuetics Bulletin, 2000). Buproprion commonly causes dry mouth and insomnia and is contraindicated in patients with epilepsy as it can cause seizures. It has the potential to interact with and prolong the action of a range of other medications including certain antidepressants (e.g. desipramine and paroxetine), type 1c anti-

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arrythmics (e.g. propafenone and flecanide) and antipsychotics (e.g. risperidone). It may also interact with medicines known to affect the CYP2B6 system.

There is some indication that dual therapy with nicotine patches and buproprion may enhance cessation rates further, although the trend did not reach statistical significance in the study that examined this (Jorenby DE et al., 1999).