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# Pharmacotherapy in the treatment of drug dependence: options to strengthen effectiveness

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Treatment of people with drug problems requires a consideration of those inviduals in their personal and social context, while being mindful of the complex interaction of genetic and developmental influences. Approaches to treatment should reflect this often complex aetiology and phenomenology, and the totality of treatment will typically include social, psychological, educational and pharmacological therapies. Treatment should result in a health benefit; consequently the goals of treatment should be tailored to the health care needs of the individual. Thus, with many patients, treatment will include abstinence as an explicit objective, whereas with other patients, intermediate goals, such as reduction of harmful injecting, may be more realistic and achievable.

Enthusiasm for new pharmacotherapies must be tempered with caution. The field of substance misuse stands as an example *par excellence* of an area in which careless use of pharmacotherapy may compound problems for the individual patient (e.g. iatrogenic benzodiazepine dependence after failure to review repeat prescriptions) as well as possibly for others (e.g. danger of overdose or of human immunodeficiency virus (HIV) infection from intravenous misuse of diverted pharmaceutical opiates or benzodiazepines).

In this paper, we will first discuss the dependence syndrome, which the clinician crucially needs to understand and examine, since several of the treatments described in the remainder of this paper may be inappropriate or even contraindicated in the absence of dependence. Thereafter, five main areas of potential action of pharmacotherapies are considered separately.

## Dependence

Identifying the presence or absence of the dependence syndrome is important in planning treatment. Dependence is a spectrum, and the therapist needs to develop experience in recognising degrees of severity. The dependence syndrome is a cluster of physiological, behavioural and cognitive phenomena (ICD–10; World Health Organization, 1992; see Box 1).

Apart from the management of overdose, which may, of course, affect those who misuse drugs only once, the majority of pharmacotherapies are designed for use by those who have, or have had, some or all of the features of the dependence syndrome. These include drugs used for the management of withdrawal; substitute pharmacotherapies used as part of a harm-reduction programme; drugs used to help maintenance of abstinence from alcohol or other substances; and drugs used to prevent specific complications of substance misuse.

## Pharmacotherapies in the management of drug overdose

### *Benzodiazepines*

Mortality from overdose with benzodiazepines alone is rare, although overdose in conjunction with

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Box 1. Dependence syndrome – a cluster of physiological, behavioural and cognitive phenomena (ICD–10; World Health Organization, 1992)

A strong desire or compulsion to take the substance
Difficulties in controlling substance-taking behaviour in terms of its onset, termination or levels of use
A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms
Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses
Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain the substance or to recover from its effects
Persisting with substance use despite clear evidence of overtly harmful consequences

other drugs, such as opiates or tricyclic antidepressants, carries a higher risk. As for alcohol poisoning, management is generally supportive. However, the benzodiazepine antagonist flumazenil may be useful in both the diagnosis and the treatment of overdoses in which benzodiazepines are involved. Flumazenil binds central nervous system benzodiazepine receptors and competitively blocks the action of benzodiazepines at inhibitory GABAergic synapses. A single injection of 0.1–0.3 mg may be given, with further increments if needed until the patient is responsive (Weinbroum *et al*, 1997). Higher doses may be needed in overdoses of benzodiazepines with other drugs. Adverse effects are uncommon but may include benzodiazepine withdrawal symptoms with transient anxiety. Care should be taken with patients with cardiovascular disease. Rarely, seizures may occur and may be more likely in patients who are benzodiazepine-dependent and in those with concurrent tricyclic antidepressant poisoning.

## Opiates

Opiate overdose produces pinpoint pupils and varying degrees of impairment of consciousness and respiratory depression. The opiate antagonist naloxone, which is available in pre-loaded syringes for use in emergency settings, should be administered intravenously if there is coma or bradypnoea. The dosage is 0.8–2 mg, and this may need to be repeated at intervals of 2–3 minutes to a maximum of 10 mg if respiratory function does not improve. If there are problems with establishing venous access, naloxone may be administered intramuscularly or subcutaneously. Naloxone has a short duration of action, and particular care needs to be taken if the patient has taken a long-acting opioid such as methadone (Hendra *et al*, 1996). In such cases it may be necessary to set up a naloxone infusion which can be adjusted according to response. In severe cases, mechanical ventilation may be necessary. After the administration of naloxone, opiate-dependent patients will experience acute withdrawal. This can be a difficult period as it is important to continue to observe the patient for at least 24 hours, but discomfort may cause the patient to leave early to seek more drugs. If it is considered that the patient may be at risk of return to overdose as the naloxone wears off, it may be appropriate to give an additional dose intramuscularly. If the patient has taken an overdose of oral opioids but does not yet show signs of impaired consciousness or respiratory depression, activated charcoal can be given and the patient observed closely, with readiness to treat with naloxone if needed.

## Stimulant and hallucinogenic drugs

Cocaine and other stimulants such as ecstasy (MDMA) and amphetamines can induce euphoria or anxiety which may proceed to more severe symptoms such as paranoid ideation, aggressive behaviour and hallucinations. Management involves calming and reassuring the patient until the effects wear off. Occasionally, oral diazepam (10–20 mg) may be needed to help calm the patient, and in severe cases where symptoms persist, antipsychotic medication may be needed. Rarely, cocaine overdose can result in cardiovascular complications including arrhythmia, hypertension and cardiac ischaemia. Seizures and hyperpyrexia can also occur. In such cases, treatment is supportive (Lobl & Carbone, 1992) – there are no specific drugs used to reverse the effect of cocaine.

Some people experience severe distress during or after use of hallucinogenic drugs and may need symptomatic treatment (such as a brief course of a benzodiazepine to reduce anxiety) as well as a safe place to be while the experience passes.

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## Overdose prevention

Certain factors are thought to put drug and alcohol users at higher risk of overdose. Among these are polydrug use (including combining alcohol with other drugs); use of unfamiliar supplies of drugs where purity is unknown; the intravenous route of administration (presumably by reducing the chance of titrating dose against effect); and use of drugs after a period of abstinence or reduced use (such as after leaving residential treatment facilities or leaving prison) (Gossop *et al*, 1996; Darke *et al*, 1996). Opportunities for preventive work in terms of advice and education for drug users can, therefore, be identified. This could extend to teaching basic resuscitation techniques. The possibility of issuing injectable naloxone to drug users for use in emergencies (Strang *et al*, 1996*a*; Darke & Hall, 1997), an idea which drug users regard as acceptable and feasible, has been proposed as a harm-reduction measure (Strang *et al*, 1999).

# Pharmacotherapies for drug withdrawal syndromes (detoxification)

## Benzodiazepines

Benzodiazepine withdrawal symptoms are due to unopposed activity of the γ-aminobutyric acid (GABA) complex. They include anxiety, tremor, tachycardia, tachypnoea, nausea, abdominal cramp, skeletal muscle cramp and diarrhoea. In more severe cases, perceptual disturbances and seizures may occur. The different benzodiazepines have a wide range of half-lives which affect the pattern and severity of the withdrawal syndrome. Temazepam is a short-acting benzodiazepine, oxazepam and nitrazepam have intermediate half-lives, and diazepam is longer-acting. Onset of withdrawal symptoms from short-acting benzodiazepines is rapid, whereas the onset of withdrawal from diazepam is more insidious, sometimes beginning days after the last dose of diazepam. Management of withdrawal involves gradual tapering of the dose – in out-patients this is usually planned over the course of several weeks (Lader & Morton, 1991). For individuals using short-acting benzodiazepines, it is usual to change over to an equivalent dose of diazepam for the purpose of withdrawal, as its longer action allows a smoother reduction. For patients with an established history of seizures, concomitant treatment with an anticonvulsant drug is advisable during and shortly after detoxification.

## Opiates

Traditionally, withdrawal from opiates has been managed by prescribing tapering doses of either the opiate of dependence or, alternatively, another opiate agonist. The choice of opiate for management of the withdrawal state is determined partly by the clinician's judgement on the most suitable drug for providing even cover, partly by the expressed wishes of the patient, and partly by the social and political context within which the treatment is provided. For example, diamorphine (heroin) is never prescribed as the drug for management of the withdrawal syndrome – largely because of the sense of public outrage that would be engendered (indeed, prescribing of the drug is entirely prohibited for any purpose whatsoever in many countries, such as the USA; its use in the UK is restricted to clinical indications other than the management of addiction, except when prescribed by one of the 100 doctors with a special heroin licence). The most commonly selected opiate, methadone, is considered more appropriate because it is effectively and reliably absorbed after oral administration, and gives an extended duration of cover so that twice-daily dosing gives good cover against the more extreme aspects of the withdrawal syndrome. It has now been demonstrated that the withdrawal syndrome can be managed as effectively, and with similar compliance rates, with a shorter 10-day withdrawal regime compared with the previously widely used 21-day withdrawal regimen (Gossop *et al*, 1989). However, the extensive reliance on the out-patient setting for the management of such withdrawal is probably ill-considered in view of the much higher failure rate of this approach compared with in-patient detoxification (Gossop *et al*, 1986). Furthermore, the setting in which the treatment is provided appears to have a profound effect, with much greater compliance and completion rates being seen when detoxification is provided within specialist in-patient services compared with general psychiatric ward settings (Strang *et al*, 1997*a*).

Since the 1980s, increased attention has been paid to non-opiate alternatives to management of detoxification. Clonidine, a centrally-acting α-adrenergic agonist, was extensively investigated (Kleber *et al*, 1985) and shown to be effective, although the marked postural hypotensive effects of the drug are usually considered to limit its application to in-patient settings. More recently, successful outcomes have been reported with lofexidine, a clonidine analogue which is not associated with hypotension to the same extent as clonidine (Bearn *et al*, 1996; Kahn *et al*, 1997), and which has been found to be acceptable for out-patient detoxification under supervision (Carnwarth & Hardman, 1998) (see Box 2). Other, more extreme treatment approaches are being explored

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in an attempt to shorten further the duration of the withdrawal syndrome; these approaches include combination pharmacotherapies such as clonidine/naloxone (Vining *et al*, 1988), and delivery of high doses of antagonists (naloxone, naltrexone) in combination with general anaesthesia or heavy sedation. However, the effectiveness of these approaches has not been investigated in rigorously designed trials and their use should be considered only in the context of carefully designed treatment trials (Strang *et al*, 1997*b*).

### *Stimulant and hallucinogenic drugs*

Stimulant drugs such as amphetamines, cocaine and ecstasy do not produce a major physiological withdrawal syndrome and can be stopped abruptly. However, people who have used stimulant drugs regularly may experience insomnia and depressed mood when the drug is stopped. Antidepressant drugs are sometimes used, but many stimulant users just need advice regarding the likely symptoms, and reassurance that they will pass. Occasionally, patients may become acutely suicidal and will require hospital admission and close observation. Hallucinogenic drugs such as lysergic acid diethylamide (LSD) do not produce a physical withdrawal syndrome and can be stopped abruptly. There is no recognised role for substitute prescribing in the management of withdrawal.

## Substitution agonist therapies

### *Benzodiazepines*

Cross-tolerance has been demonstrated between the barbiturates, alcohol, the benzodiazepines and the newer non-benzodiazepine sedative hypnotic drugs which have recently been more widely used, such as zopiclone. Long-term benzodiazepine dependence might be reduced if drugs with shorter half-lives were prescribed for night sedation, which allows clearance of the drug before the next dose. However, it is not established whether this would have any effect at the population level. For those who have become dependent on prescribed benzodiazepines, initiation of a long, slow dose reduction (see section on withdrawal) is probably the best course of action, rather than continuing 'maintenance' prescribing. However, in practice, some patients who have been prescribed benzodiazepines for many years find this prospect very distressing and maintenance prescribing is continued. Such patients are at risk if their supply is abruptly unavailable, since the withdrawal syndrome can be severe and may involve seizures. Benzodiazepines are widely available through illegal outlets and can be bought cheaply by drug misusers. Many will use these drugs in an intermittent, non-dependent fashion and there is no role for substitute prescribing. For those individuals who are using 'street' benzodiazepines in a dependent fashion, prescribing of benzodiazepines may be appropriate, although again this will usually be with the aim of dose reduction and withdrawal. In contrast to methadone prescribing, there is little evidence that continuous substitute prescribing is helpful as the harm-reduction gains are less clear than for methadone. Nevertheless, such regimes may sometimes be agreed with certain patients if there are demonstrable benefits.

**Box 2. A typical lofexidine regime for treatment of opiate withdrawal**

Number of 200 µg tablets

| | am | pm |
|---|---|---|
| Day 1 | 1 | 2 |
| Day 2 | 2 | 3 |
| Day 3 | 3 | 4 |
| Day 4 | 5 | 5 |
| Day 5 | 5 | 5 |
| Day 6 | 5 | 5 |
| Day 7 | 4 | 4 |
| Day 8 | 3 | 3 |
| Day 9 | 2 | 2 |
| Day 10 | 1 | 1 |

Monitor pulse and blood pressure regularly

### *Opiates*

The most extensively studied and applied agonist therapy is oral methadone maintenance as treatment for heroin addiction (see Boxes 3 and 4). At any one time, there are of the order of a quarter of a million opiate addicts being treated with oral methadone worldwide. Even though there has been a surprising shortage of randomised controlled trials of the treatment (Ward *et al*, 1992), there is robust evidence of major benefits across a variety of outcome domains – reduced illicit drug use, reduced injecting, reduced involvement in crime, and improved physical and social well-being (Marsch, 1998) – with these major benefits being seen even within the first month of treatment (Strang *et al*, 1997*c*). The recognition of the particular importance of reduced injecting and

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sharing as an HIV prevention strategy have prompted the development and further expansion of structured oral methadone maintenance programmes in many countries.

Although methadone gives good 24-hour cover for the majority of patients, there has been interest in developing similar agonist drugs which would provide a longer duration of cover. The most promising candidate has been LAAM which, as a pro-drug, does not have a sudden intoxicating effect and yet provides good cover over a period of 2–3 days, thereby making possible supervised dosing schedules on a Monday/Wednesday/Friday basis (Ling *et al*, 1994). Similarly, exploratory work is currently underway with high-dose buprenorphine, although it remains to be seen whether it will be possible to avoid the problem of extensive intravenous misuse of buprenorphine as encountered and reported from several UK cities (Hammersley *et al*, 1990).

Injectable agonist substitutes have been prescribed in the UK for some time (Strang & Sheridan, 1997*a*). The value of this practice was recently explored in a study in Switzerland (Perneger *et al*, 1998). While attention mostly focuses on the feasibility and possible benefits of injectable heroin prescribing (Bammer, 1993), it is injectable methadone which is the most commonly prescribed injectable agonist in the UK (Strang *et al*, 1996*b*). Such injectable prescribing remains the subject of continued heated debate, and should only be considered as a more complicated treatment for carefully selected patients under the care of specialist centres.

## *Stimulants*

There is no substantial body of evidence or experience on the prescribing of substitute stimulant drugs as treatment for cocaine or amphetamine addiction. Reports of such practice in the UK from the late 1960s (Hawks *et al*, 1969; Mitcheson *et al*, 1976) were generally accounts of management complications and lack of therapeutic benefit. Nevertheless, more recent clinical reports in the UK (Fleming & Roberts, 1994) have described clinical experiments with this approach, which had been found to be more widespread in practice than previously recognised (Strang & Sheridan, 1997*b*).

**Box 3. Substitute prescribing of methadone**

Before beginning prescribing of methadone, the doctor should establish the following:

- that the patient is using opiates (history, examination, urine drug screen)
- that opiates are being used daily or almost daily
- that there is convincing evidence of dependence (including evidence of withdrawal symptoms where possible)
- that the assessment substantiates the need for treatment
- that the patient is willing to cooperate with a prescribing regime

**Box 4. Prescribing methadone safely**

Initial dose titration and consumption should usually be supervised by a doctor, nurse or pharmacist

The dose can be titrated against continuing observed withdrawal symptoms, to determine a safe and comfortable dose

Methadone should usually be prescribed in a liquid form, as tablets can be crushed and injected

For most patients, methadone should be dispensed on a daily basis

A clear prescribing and dispensing record must be kept

Treatment should be reviewed regularly

# Relapse prevention and the maintenance of abstinence

Psychological and social interventions are the mainstays of relapse prevention in the management of patients with drug problems. Relapse prevention work, carried out on an individual or group basis, takes a cognitive–behavioural approach towards identifying vulnerability to lapses (intrapersonal states such as loneliness or anger; interpersonal states such as conflicts or fear of social situations; and peer pressures) and looking at alternative strategies for coping with these situations (Marlatt & George, 1984). Social interventions may include changes in occupation, and housing. Couple therapy or family therapy may be helpful. Although mostly designed to help patients to maintain abstinence, these approaches may be also be adapted to help patients with other goals such as reduced or safer drug use.

A number of pharmacotherapies are used in conjunction with these techniques. The pharmacotherapies are generally aimed at those patients intending to maintain abstinence.

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## Maintaining abstinence from opiates

### Naltrexone

Naltrexone is a long-acting competitive antagonist at opioid receptors. It is suitable for oral administration, and as it blocks the effects of opiates (both subjective and objective) it can be used as an adjunct to the management of opioid dependence, for patients who aim to maintain abstinence. It is well-tolerated by most patients, with a minority experiencing headache or nausea. Patients will only take naltrexone regularly if they are committed to abstinence and have an incentive to stay abstinent. It should be combined with individual or group counselling, and the best results are seen when it is provided in conjunction with family involvement and contingent rewards as in the 'community reinforcement approach' currently under study. The search for a depot form of naltrexone has not yet produced a product with acceptable safety and reliability – furthermore, it may lead to a failure to recognise the importance of the psychosocial context in which such a pharmacotherapeutic approach might be delivered.

## Maintaining abstinence from stimulant drugs

No pharmacotherapies have been clearly shown to reduce the rate of relapse among users of stimulant drugs. A variety of antidepressant drugs have been used, but their sustained effectiveness in preventing relapse is not strongly supported by research evidence. Psychological and social approaches remain the mainstay of treatment for stimulant misusers.

# Prevention of complication of drug misuse

## The scope of harm reduction

The principles of harm reduction have come to exert a powerful influence upon the development of drug policy following the recognition of the risk posed by HIV infection and transmission (Strang, 1992). The harm reduction approach is essentially a public health approach which proposes that public policy and treatments should be based on an analysis of optimal reduction of harm for the population in treatment (or the population with health need, even if not currently in treatment). Hence, abstinence is not the essential objective of treatment; rather, it is more appropriately considered as one of the ways in which the health gain may be maximised. In situations where the exclusive pursuit of abstinence may merely lead to high rates of treatment failure and drop-out (possibly with even more catastrophic consequences due to the abstinence violation effect (Marlatt & George, 1984)), there will be circumstances in which the identification of more realistic intermediate goals may lead to greater individual and public health gain (Advisory Council on the Misuse of Drugs, 1988; Strang 1990). This acceptance of the seemingly imperfect has undoubtedly led to greater health gain, with the establishment of advertising and peer network schemes for the dissemination of information about syringe cleaning, needle and syringe exchange schemes, as well as the substitute agonist programme described in the preceding section. These remain areas of dispute and debate among practitioners themselves and between practitioners and policy-makers. Harm reduction areas of continued debate also include proposals for the prevention of overdose deaths through the teaching of resuscitation techniques to known drug misusers, possibly supplemented by the provision of take-home supplies of the opiate antagonist naloxone (Strang *et al*, 1996*a*).

## Hepatitis B testing and vaccination

Markers of past hepatitis B infection are found in most injecting drug misusers, prevalence rates varying between half and three-quarters, depending on the sample. Around 10% will have chronic infection with hepatitis B, a large proportion of whom will die prematurely from either liver cirrhosis or hepatocellular carcinoma in their later lives. Furthermore, in the intervening years, they may transmit the virus either by sharing injecting equipment or by sexual transmission to their partners and thence to their children. Since the development of safe and effective vaccines, the condition is now entirely preventable for those who are not yet infected, and the World Health Organization has identified as a priority the eradication of hepatitis B through universal vaccination. The injecting drug misuser should be offered testing for hepatitis B and, if negative, hepatitis B vaccination: the manufacturers recommend a dosing schedule of 0, 1 and 6 months for the three vaccine injections, but a dosing schedule of 0, 1 and 2 months may be more realistic so as to capture the drug user during an episode of treatment, especially since the benefit conferred by this quicker vaccination protocol is almost as full as with the recommended schedule.

## Antiretroviral therapies for HIV – post-exposure therapy

The advent of new antiraetroviral therapies for treatment of HIV infection has increased the possibility

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of treatment of individuals thought to have been at risk of very recent infection. For example, this could include the treatment of medical or nursing staff following a needle-stick injury from an infected patient. It increases the possibility of use of such therapies for injecting drug misusers who have, for example, recently shared a needle with an infected person. The recurrent treatment of drug misusers who are at constant risk is impractical, but there may be arguments for its use under certain circumstances.

Caution must, however, be exercised with combination pharmacotherapies in this and other areas, since interactions may occur. For example, with patients already stabilised on methadone maintenance, the commencement of antitubercular therapy with rifampicin (Raistrick *et al*, 1996), or HIV treatment with zidovudine, can alter the breakdown of methadone. Patients on the anti-coagulant phenytoin or rifampicin and some anti-HIV treatments may need higher doses of methadone. Other anti-HIV treatments may lead to potentially dangerously high levels (certainly higher than anticipated) of either the methadone or the antimicrobial drug treatment, as is also seen with isoniazid.

## Conclusion

New applications of existing drugs and the development of new products have transformed the substance misuse field. Previously, the interest in drug treatment was restricted to a few areas where the clinician wished to be assured about the competence and safety of management. Today it has become clear that, alongside cognitive–behavioural and social components of treatment and rehabilitation, the drug therapies of the future expand greatly the armamentarium of the clinician. The challenge is to harness the power of pharmacotherapies in care plans appropriate to the needs of individual patients.

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## Multiple choice questions

1. In overdose:
   a the appropriate treatment for methadone overdose is a single dose of intravenous naloxone
   b intramuscular naloxone can be given in opiate overdose if the intravenous route is difficult to access
   c flumazenil competitively blocks the action of benzodiazepines and can be used in the management of benzodiazepine overdose
   d the risk of accidental overdose is increased when a dug user resumes use following a period of abstinence.

2. In withdrawal:
   a benzodiazepine withdrawal is best managed by prescribing a reducing regime of a short-acting benzodiazepine
   b depressed mood and suicidal ideation are recognised features of amphetamine withdrawal
   c lofexidine is a synthetic opiate used for the management of opiate withdrawal
   d management of opiate withdrawal using a reducing dose of methadone can be planned over a period as short as 10 days.

3. Regarding substitution agonist therapies:
   a reduction in risk of transmission of HIV is one of the aims of methadone maintenance treatment
   b injectable methadone has been shown to be more effective than oral methadone in reducing illicit drug use
   c substitute prescribing of benzopdiazepines is appropriate for patients who misuse benzodiazepines in an intermittent 'binge' pattern
   d buprenorphine is a possible alternative to methadone for maintenance treatment of opiate dependence, and may be advantageous as it cannot be injected.

4. In maintenance of abstinence:
   a naltrexone is effective in preventing relapse to cocaine use
   b naltrexone can be used to help patients to maintain abstinence from heroin use
   c psychological approaches such as relapse prevention work can help patients abstain from some risk-taking behaviour even if they are not completely drug-free
   d lofexidine is designed to help maintaining abstinence in patients who have completed opiate detoxification

5. Regarding harm reduction/prevention of complications:
   a injecting drug users should be advised about facilities for exchanging used needles and syringes for clean injecting equipment
   b hepatitis B vaccination is rarely appropriate for injecting drug users as most have already acquired immunity by the time they present for treatment
   c patients on methadone will need their dose reassessed on commencing treatment with rifampicin
   d patients on methadone will need their dose reassessed on stopping a course of treatment with rifampicin.

MCQ answers

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| a F | a F | a T | a F | a T |
| b T | b T | b F | b T | b F |
| c T | c F | c F | c T | c T |
| d T | d T | d F | d F | d T |

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