CHAPTER 1

What works in drug addiction?

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Summary Treatment of illicit drug dependence typically involves a combination of pharmacotherapy and psychosocial interventions. Efficacy research supports methadone maintenance in opiate dependence. There is less evidence to support the use of buprenorphine (an opiate receptor partial agonist), lofexidine (an α_2-adrenoreceptor agonist) and naltrexone (an opiate receptor antagonist). Evidence for the effectiveness of detoxification, which is one of the most widely used treatments, is poor. Of the psychosocial interventions, reasonable evidence exists for the effectiveness of motivational interviewing. Other psychosocial treatments have rarely been compared with no or minimal contact conditions in randomised trials, and their reported effectiveness is often weak. Residential treatments are not demonstrably more effective than community programmes.

Substance dependence, or 'addiction', is diagnosed taking several factors into consideration (Box 1.1). Substance misuse refers to the non-therapeutic use of drugs in a manner that is potentially harmful, but does not meet criteria for dependence.

Many trials report significant benefits of addiction treatments (National Consensus Development Panel, 1998), and guidelines for drug addiction treatment have been published by the Department of Health (1999). However, only 20% of participants report abstinence from all illicit substances for at least 1 year, despite receiving treatment. Furthermore, drop-out rates

Box 1.1 Diagnostic features for substance dependence

Three or more of the following should have been present in the previous year:

- a compulsion to take the substance
- escalation of amount used
- a withdrawal syndrome following reduction in use
- tolerance
- neglect of other activities in favour of substance use (salience)
- persistent use despite evidence of harm

of nearly 50% are common. It is notable that only half of patients with other chronic disorders (such as hypertension or diabetes) fully adhere to medication schedules, and high drop-out rates are common with many forms of psychotherapy.

Trials of treatment for drug addiction are liable to all the common methodological flaws seen in clinical trials in psychiatry, including failure to use intention-to-treat analysis, failure to randomise results, lack of socio-demographically matched control groups and confounding due to unplanned variations in contact with treatment services. A US government report concluded that 'results derived from self-selected patients who remain in treatment optimistically skew findings in favour of effectiveness' (National Research Council, 2002).

There is no consensus on outcome measures of trials of addiction treatments. Urine (and saliva) analysis can provide objective measures of drug use. However, many trials report subjective ratings, such as scores on the Addiction Severity Index (McLellan *et al*, 1980), a 45 min semi-structured interview based on psychosocial functioning and drug use. Meta-analysis results are often expressed as an effect size: the difference in mean scores divided by the pooled standard deviation. This statistical technique allows the direct comparison of the results of trials that have used different outcome measures. A trial comparing 50–100 users and controls is usually sufficient to identify a treatment with a modest effect size (conventionally 0.25–0.5) that is likely to be clinically significant.

Pharmacotherapy for drug dependence

There are no effective medications for treating stimulant dependence, despite trials of several agents (Bruce, 2000; de Lima *et al*, 2002; see also chapter 3, this volume). Hence, most research involves treatment of opiate dependence. Commonly used agents are summarised in Table 1.1.

Prescribed maintenance treatment

Maintenance treatment involves the prolonged prescription of a drug with no intention to reduce the dose, whereas detoxification is any treatment intended to produce abstinence from use of drugs (including prescribed drugs).

Methadone and buprenorphine are both long-acting opioid agonists or partial agonists that are used to prevent withdrawal symptoms in opioid addicts. Persistent use leads to cross-tolerance and reduces the reinforcement effects of illicit opiates. Ward *et al* (1999) have produced an excellent short review of methadone treatment.

An influential meeting of experts in the USA concluded that the safety and efficacy of methadone maintenance treatment 'has been unequivocally established' (National Consensus Development Panel, 1998). Many studies

Table 1.1 Drugs used in opioid dependence

Medication	Action	Typical daily dose
Methadone	Opioid agonist	20–100 mg orally
Buprenorphine	Partial agonist	8–24 mg sublingually
Naltrexone	Opioid agonist	50 mg orally
Lofexidine	α_2-adrenergic agonist	0.8–2.4 mg orally

have shown the advantages of methadone maintenance in reducing drug use, criminality and blood-borne virus infection and improving general health and social status. The median death rate for addicted individuals maintained on methadone is 30% of that for those who are not in treatment. Urine analysis from one sample of 435 methadone maintenance clients showed that almost half were able to quit daily heroin after 12 months (Simpson *et al*, 1997). The average number of 'crime-days' fell from 11 per month to 4. Two large cohort studies suggest that the odds of HIV infection were five times greater among those who were not in methadone maintenance treatment than among those who were (Ward *et al*, 1999).

A classic double-blind study involved 100 heroin addicts in Hong Kong, who were randomised to methadone maintenance or methadone detoxification at 1 mg/day (Newman & Whitehill, 1979). Retention rates were 60% in the maintenance group and 5% in the detoxification group. Urine analysis at 2-year follow-up indicated that 70% of participants in the maintenance group had abstained from illicit opiate use in the previous month. Similar results have been obtained with buprenorphine (Kakko *et al*, 2003).

Methadone doses above 60 mg/day are often required to prevent heroin use. However, it is important to note that initial methadone doses should be less than 40 mg/day to prevent accidental overdose by individuals who have not developed a high tolerance to opiates. One study concluded that patients who receive daily doses of less than 60 mg of methadone have nearly five times the risk of dropping out of treatment than those who receive doses of 80 mg or more (Capelhorn & Bell, 1991). A double-blind trial of 193 intravenous opiate addicts revealed that 53% of the urine samples after 30 weeks were heroin-positive in those randomised to 80–100 mg methadone, compared with 62% of those on 40–50 mg (Strain *et al*, 1999).

Contingency management in methadone maintenance and cocaine treatment

Contingency management techniques make clinic privileges or even continued prescribing available pending objective evidence of abstinence from illicit drugs (see chapter 16).

McCarthy & Borders (1985) reported a controlled trial of 69 individuals in methadone maintenance programmes who were randomised so that for half of them prescribing would be discontinued after 4 consecutive months with one or more opioid-positive urine result. Intention-to-treat analysis indicated that 48% of the participants in the trial sample were drug-free at 1 year compared with 31% in the more liberal control group. Unfortunately, aversive control techniques (such as reduction of methadone) led some individuals to leave treatment. Positive control techniques are reported by Stitzer *et al* (1992) in a study of 53 individuals in methadone maintenance who were randomly assigned to contingent or non-contingent take-home privileges: up to three take-home doses per week were permitted following 2 consecutive weeks of drug-free urine samples. The contingent group produced more individuals with at least 4 consecutive weeks of abstinence (32% *v*. 8%) over the 6-month trial.

Comparable results are reported in a randomised controlled trial of opiate and cocaine addicts in which clean urine samples were rewarded with vouchers that could be exchanged for retail goods (Higgins *et al*, 1994; Preston *et al*, 2000).

Opioid detoxification

Medical detoxification relies on the use of agents, including methadone, buprenorphine, lofexidine or clonidine, in relatively short courses to suppress withdrawal symptoms. The daily dose of methadone can comfortably be reduced at rates of 1 mg/week in the community or 5 mg/day in in-patients. Detoxification is widely used, and it is perhaps surprising to find that it is one of the least effective treatments for drug addiction.

A major problem with opioid detoxification is the rate of relapse. A US follow-up study of 10 000 opiate addicts (the Drug Abuse Reporting Program; Simpson & Friend, 1988) found that individuals entering out-patient detoxification had almost half the abstinence rate at discharge of those who received other types of treatment (12% *v*. 18–21%). The results for Newman & Whitehill's (1979) randomised controlled trial of methadone maintenance described above indicated that detoxification had poor outcomes. The expert National Consensus Development Panel (1998) concluded that 'although the drug-free state represents an optimal treatment goal, research has demonstrated that the state cannot be achieved or sustained by the majority of persons dependent on opiates'.

Other agents used in the treatment of opioid dependence

Clonidine and lofexidine are α_2-adrenoreceptor agonists that reduce somatic symptoms of opioid withdrawal. Opioid detoxification with these agents can be achieved in 5–7 days. However, neither agent can suppress symptoms such as craving, lethargy, insomnia, restlessness and muscle

aches. Adverse effects include sedation and hypotension, although these are less common with lofexidine.

A systematic Cochrane review of 10 studies comparing α_2-agonists and methadone detoxification over 10 days found no difference in efficacy, although more clients remained in contact with treatment services following methadone detoxification (Gowing *et al*, 2002). Kleber *et al* (1985) reported a trial involving 49 individuals on methadone maintenance randomised to out-patient detoxification with clonidine or reducing doses of methadone over 30 days. Forty per cent completed the detoxification process, of whom one-third were abstinent at 6-month follow-up. An equivalent proportion had returned to methadone maintenance. There was no significant difference in outcome between the groups.

Buprenorphine is a partial opioid agonist and partial antagonist that is given sublingually. It might have a lower risk of overdose than methadone and produce less severe dependence, allowing a smoother withdrawal than methadone. A meta-analysis identified five randomised clinical trials, involving 540 participants over 16–26 weeks. This showed that buprenorphine was comparable with methadone in preventing illicit drug use, although it was more expensive (Barnett *et al*, 2001). Around 50% of urine tests were positive for illicit opiates. Doses of 8–12 mg/day of buprenorphine have been shown to be as effective as 60–90 mg of methadone (Schottenfeld *et al*, 1997). The risk that oral buprenorphine will be injected is greater than that for oral methadone, and to deter this a combination of buprenorphine with naloxone has recently been marketed in the UK under the trade name Suboxone (the naloxone nullifies the buprenorphine only when injected).

Naltrexone is an opioid antagonist that produces no psychoactive effects or dependence. Naltrexone completely blocks the effects of opiates and acts as an 'insurance policy' against opiate use. It can precipitate acute withdrawal and should only be used following abstinence from all opioids (including methadone). Treatment can be given daily or three times per week. Unfortunately, naltrexone has not proven effective in treatment settings (Kirchmayer *et al*, 2002), although peculiarly, some investigators appear to have viewed it as a direct alternative to methadone rather than as an approach that can enable a completely opiate-free state. For example, in one trial only 15 of 300 participants chose naltrexone instead of detoxification or methadone maintenance, and of those 15, only three continued naltrexone for more than 2 months (Fram *et al*, 1989).

L-alpha-acetylmethadol (LAAM) is a long-acting opiate agonist like methadone. It is not available in the UK, following reports of cardiotoxicity.

Ultra-rapid opiate detoxification

Ultra-rapid opiate detoxification involves administration of opiate antagonists (naloxone and naltrexone) to opiate-dependent individuals under general anaesthesia. This leads to an acute withdrawal. No large-scale

controlled trials of this procedure have been published (O'Connor & Kosten, 1998). Concerns about safety, expense and effectiveness also limit its usefulness. In the UK, ultra-rapid opiate detoxification was the subject of a General Medical Council investigation following the death of a patient during recovery, and the anaesthetist involved was struck off the medical register (Bedenoch, 2002). It seems unlikely that there will be any enthusiasm for ultra-rapid opiate detoxification among clinicians in the foreseeable future, although less drastic measures involving sedation rather than anaesthesia are not so controversial.

Injectable opioid treatment

Heroin is available to addicts in the UK from licensed specialists. Parenteral methadone is also available, with licensing not required. Hartnoll *et al* (1980) reported a 12-month follow-up trial of intravenous heroin *v.* oral methadone in 96 heroin-addicted individuals in London. Those on heroin maintenance were twice as likely to remain in treatment (74% *v.* 29%). However, the proportion remaining dependent on opiates (prescribed and illicit) at 12 months was higher in the heroin maintenance group (90% *v.* 70%). There were no differences between the groups for self-reported criminal activity, health or employment. This report led to greatly reduced enthusiasm for injectable opioid treatment. Another UK trial found no advantage between injectable methadone and oral methadone (Strang *et al*, 2000).

Injectable opioid treatment is claimed by some enthusiasts to engage users in treatment more effectively than oral alternatives. Opponents suggest that it perpetuates injecting behaviour and thereby postpones eventual abstinence from heroin and also, in effect, endorses injecting. The treatment is expensive and there is a risk of deep-vein thrombosis and infection. The prospect of being offered injectable opiates may also provide some users with a vested interest in poor adherence to methadone maintenance. Relatively few individuals are ever likely to receive the treatment, so the overall effects on crime will be small. Needle exchange programmes probably reduce health risks more than the prescription of injectables. The available evidence does not support the widespread adoption of injectable opioid treatment.

Psychosocial treatment (see also chapter 16)

Intensity of psychotherapy

Many studies have shown that the intensity and duration of involvement in drug misuse treatment programmes is one of the best predictors of outcome (National Consensus Development Panel, 1998). However, the 'more is better' idea is often based on uncontrolled follow-up studies, in which patient motivation and selection might be primarily responsible for the good outcome.

Kraft *et al* (1997) reported a trial of 100 opiate-addicted individuals, randomised to three psychosocial treatments of 6 months duration: minimum-contact methadone maintenance; methadone maintenance plus standard drug counselling three times weekly; and an enhanced programme of psychosocial treatment with daily counselling, family therapy and social work activity to improve job prospects, housing and address other social problems. However, many of the participants who were randomised to the enhanced programme actually attended only once each week, despite the offer of more-frequent sessions. All participants received 60–90 mg methadone per day. Abstinence from opiates and cocaine use at 1 year were 29%, 47% and 49% of participants in the minimum-contact, standard and enhanced groups respectively. Overall, the enhanced programme did not confer significant benefit over standard drug counselling, although it was better than minimum-contact methadone maintenance. A cost-effectiveness analysis confirmed this.

Narcotics Anonymous and its Twelve-Step Approach

Narcotics Anonymous provides support groups for problem drug users. These groups are widely available and are free to participants. Applying the disease model to substance misuse, they promote the Twelve-Step Approach. This involves recognition that addiction is a relapsing illness that requires complete abstinence (Box 1.2). Participants are required to acknowledge their addiction and the harm they are causing themselves and others. No randomised controlled trial has attempted to determine the effectiveness of Narcotics Anonymous or of 12-step approaches in opiate addiction. However, a study of 487 cocaine users, all of whom received group twelve-step drug counselling throughout the trial, involved randomisation to individual counselling (based on the Twelve-Step Approach), supportive–expressive psychotherapy or cognitive–behavioural therapy (CBT) with a 1-year follow-up (Crits-Christoph *et al*, 1999). One-third of the eligible cocaine users initially approached were recruited, of whom 28% completed the 6-month treatment programmes. Cocaine use was reduced from a mean of 10 days per month to only 3 days. However, 71% of the group receiving a combination of individual and group counselling were abstinent for at least 1 month, compared with 55–60% for combinations of group counselling with formal psychotherapy. The psychotherapy approaches were able to retain more participants in treatment (33% completed treatment *v.* 22% for drug counselling). Similarly, Wells *et al* (1994) report a controlled comparison of CBT-based relapse prevention *v.* 12-step approaches in out-patient treatment of 110 cocaine users. The two treatments were equally effective at 1 year, and the number of days of cocaine use halved. Overall, the evidence suggests that a 12-step approach is at least as effective as other structured psychotherapies.

Box 1.2 The Twelve Steps of Narcotics Anonymous

1 We admitted that we were powerless over our addiction, that our lives had become unmanageable.
2 We came to believe that a Power greater than ourselves could restore us to sanity.
3 We made a decision to turn our will and our lives over to the care of God as we understood Him.
4 We made a searching and fearless moral inventory of ourselves.
5 We admitted to God, to ourselves, and to another human being the exact nature of our wrongs.
6 We were entirely ready to have God remove all these defects of character.
7 We humbly asked Him to remove our shortcomings.
8 We made a list of all persons we had harmed, and became willing to make amends to them all.
9 We made direct amends to such people wherever possible, except when to do so would injure them or others.
10 We continued to take personal inventory and when we were wrong promptly admitted it.
11 We sought through prayer and meditation to improve our conscious contact with God as we understood Him, praying only for knowledge of His will for us and the power to carry that out.
12 Having had a spiritual awakening as a result of these steps, we tried to carry this message to addicts, and to practice these principles in all our affairs.

Relapse prevention and cognitive–behavioural therapy

Relapse prevention techniques using CBT are based on the work of Marlatt & Gordon (1985). The techniques assume that substance misuse is a means of coping with difficult situations, dysphoric mood and peer pressure. Treatment aims to help individuals recognise high-risk situations and either avoid or cope with them without drug use.

Irvin *et al* (1999) reported a meta-analysis of five randomised controlled trials of relapse prevention treatment for polydrug misuse. The overall effect was modest. For example, Carroll *et al* (1994) compared CBT-based treatment with routine clinical management over 1 year for cocaine addicts. They found that CBT was superior only for participants who were also depressed and for those with high levels of cocaine use. Wells *et al* (1994) found no difference between CBT-based relapse prevention and a 12-step approach in cocaine users (see above).

In one randomised controlled trial involving 64 amphetamine users, 2–4 CBT/motivational interviewing sessions were compared with provision

of a self-help booklet. Participants typically attended half the sessions. Twenty-four (38%) of the treatment group abstained from amphetamine use, compared with 13 (21%) of the self-help group (Baker *et al*, 2001).

Overall, CBT approaches are better researched, but are probably no more effective than the other psychological methods used in addiction treatment.

Psychodynamic psychotherapy

There is a widespread opinion that psychodynamic psychotherapy is of low acceptability to drug misusers, as illustrated by a trial of interpersonal psychodynamic psychotherapy with 72 opiate addicts in methadone maintenance (Rounsaville *et al*, 1983). Weekly individual interpersonal therapy was compared with monthly 'low-contact' control treatment. Both treatments continued for 6 months. Only 5% of eligible clients agreed to attend psychotherapy and only 38% of these completed the interpersonal therapy programme. There were no significant differences in outcome between the two groups, although both made significant gains. Woody *et al* (1995) reported a similar randomised trial of supportive–expressive psychotherapy, in which the overall effect size was small (0.26). Other investigators have failed to find advantages for psychodynamic psychotherapy in substance misuse (Crits-Christoph *et al*, 1999).

Motivational interviewing/motivational enhancement therapy

Motivational interviewing is a technique described by Miller & Rollnick (2002). It is based on theories of cognitive dissonance and attempts to promote a favourable attitude towards change. Briefly, instructing addicts on the problems of dependency and the advantages of abstinence tends to provoke them to contradiction. This might reinforce continued dependence. Motivational interviewing encourages clients to give their own reasons for attempting to change their drug use (see chapters 16 and 17).

A systematic review identified five randomised trials of motivational interviewing in drug dependence, involving 800 participants (Dunn *et al*, 2001). Typical effect sizes were 0.5–0.6 (although confidence intervals were large). One randomised trial of 122 opiate addicts found that motivational interviewing compared with health education alone increased retention in methadone programmes at 6 months from 50% to 70% (Saunders *et al*, 1995). Booth *et al* (1998) reported a trial of 4000 intravenous drug users seeking HIV testing. Individuals were randomly assigned to either standard testing alone or testing plus three sessions of motivational counselling from a health educator. At 6-month follow-up, the latter group showed half the rate of drug injection (20% *v.* 45%) and were four times more likely to be abstinent (confirmed by urine analysis). They also had significantly lower arrest rates (14% *v.* 24%).

Community reinforcement, couple and family therapies

Reinforcement treatments typically involve clients' partners or families rewarding them for abstinence using agreed strategies. Stanton & Shadish (1997) performed a meta-analysis of 15 randomised controlled trials, involving 1571 opiate addicts, that compared couple/family therapy with individual counselling, peer-group therapy and family psychoeducation. Six of the trials involved adult clients. Family therapy methods had an effect size at 1 year that was 0.46 greater than that for non-family therapy. The drop-out rate was also lower in the family therapy group (~45% *v*. ~25%).

Community reinforcement using families and couples is feasible and shows some effectiveness, although it is often overlooked. Not all clients have family members or partners who are willing to be involved in substance misuse treatment. However, where they can be recruited as co-therapists, family members can be encouraged to provide agreed rewards to clients for abstinence. The nature of the reward needs to be negotiated in advance with the client and family member. Family members also provide a degree of surveillance over the clients and can provide supervision, support, advice or comment if clients begin using drugs again, feel tempted or put themselves in risk situations.

Therapeutic communities and residential rehabilitation units

These units typically require prolonged residence (often 12–18 months). Clients are closely involved in running the programmes, including selecting and discharging residents. Abstinence is usually a prerequisite. Several large studies suggest that therapeutic communities are beneficial, although completion rates for prolonged residential programmes are often below 20%.

Bale *et al* (1980) randomly assigned 585 male heroin addicts to methadone maintenance or therapeutic communities. The outcomes between the two groups were comparable. Roughly half of the participants who completed the programmes reported heroin use during the 12th (and final) month of the study. Unfortunately, only 18% of the participants randomised to the therapeutic communities actually began the 6-month residential programmes. Overall, only 10% of participants successfully engaged in either of the programmes to which they had been assigned.

The National Treatment Outcome Research study is a follow-up of 1075 clients (most of whom were addicted to heroin) attending UK drug treatment agencies (Gossop *et al*, 2003). At 5 years, 42% of those who were attending community methadone programmes at the start of the study were regularly using heroin, compared with 39% of those who were in residential programmes at intake (and were subsequently discharged). Although the study was not randomised, these results support North American research demonstrating that residential programmes are no more effective than community programmes, despite the greatly increased cost.

Other approaches

Drug treatment and testing orders were introduced in the UK under the Crime and Disorder Act 1998. Orders last from 6 months to 3 years. Under the relevant legislation, courts can require an offender to undergo treatment for drug misuse, subject to the offender's consent to such an order being made. Offenders are required to undergo testing for use of illicit substances and to 'submit' to treatment. If treatment is not satisfactory or clients reoffend, the court may sentence them again. Turnbull *et al* (2000) report the results of the pilot programmes, which involved 210 offenders. The percentage of opioid-positive urine tests (excluding methadone) fell from 42% to 13%. However, about half of the offenders were discharged from the orders for breach of terms. These results are disappointing, despite US reviews suggesting that coerced offenders do no worse than voluntary clients (Anglin & Hser, 1991). In the UK, a government report concluded that 'because of lack of investment in data and research, the nation is in no better position to evaluate the effectiveness of enforcement than it was 20 years ago' (National Research Council, 2002).

Needle exchanges have been widely adopted, their main purpose being to prevent transmission of HIV and hepatitis. Most surveys have concluded that they are effective in reducing needle sharing and blood-borne viruses and they encourage drug users to seek help. Needle exchange programmes do not appear to have caused an increase in injecting (Royal College of Psychiatrists, 2000: p. 161). An Australian study concluded that the cost-effectiveness of needle exchanges varied from Aus$50 to Aus$7000 per life-year saved. There are no randomised controlled trials of needle exchange schemes or drug treatment and testing orders.

Conclusion

What works in drug addiction? Methadone maintenance has been shown to be safe and very effective on a variety of measures, including preventing illicit drug use. Buprenorphine is probably equally effective, although it is more expensive in some countries. Reasonable evidence exists for the effectiveness of motivational interviewing. Few randomised controlled trials compare other psychosocial treatments and no or minimal contact. However, where evidence does exist, the effect size is often modest. Evidence for the effectiveness of detoxification is poor, even though this is one of the most widely used treatments. Residential treatments are not demonstrably more effective than community programmes.

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