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EXECUTIVE SUMMARY

This feasibility study was a randomised controlled trial to test the reliability of urinary isomer monitoring to see whether individuals who consume street amphetamine could be distinguished from those who consume pharmaceutical amphetamine and those who consume amphetamine of both street and pharmaceutical origin. The study was conducted at the Kirketon Road Centre (KRC), a primary health care centre in Kings Cross in the inner city area of Sydney. KRC is involved in the care of injecting drug users, sex workers, 'at risk' youth and other disadvantaged or 'at risk' inner city communities primarily in the prevention and treatment of blood borne viruses and other transmissible infections. The centre offers both on-site and outreach medical, counselling and social welfare services, a methadone access program and a needle and syringe service.

Forty-one subjects, assessed as long-term dependent amphetamine users, were enrolled in the study over a period of 10 months from February to December 1998. Subjects were carefully assessed for amphetamine dependence, a history of chronic amphetamine use, and were only included if they gave a urine sample tested positive for amphetamine. Subjects were screened for active psychosis or any history of psychotic disorders (including schizophrenia) and underwent a medical assessment for any other chronic illness. Subjects who met the inclusion criteria were randomised after assessment to treatment (twenty-one subjects) or control groups (twenty subjects). Both groups were offered usual care including standard counselling offered by the KRC counselling unit for amphetamine users. The treatment group was in addition prescribed dexamphetamine to a maximum daily supervised oral dose of 60 mg for a period of up to 12 weeks.

The main finding of the study was that urinary isomer analysis did not distinguish pharmaceutical from street amphetamine in this study population. Methylamphetamine, which was not pharmaceutically available in Australia, was present in all baseline urine samples and could, therefore, be used as a marker of illicit amphetamine. Fortunately, this allowed the original aims of the study to be achieved with some minor changes to the study protocol. The urinalysis results obtained by testing for methylamphetamine rather than isomer monitoring confirmed that it was possible to use urinalysis to detect continued street amphetamine use in subjects who were receiving pharmaceutical dexamphetamine.

The study was designed in 1995. A pilot study conducted in 1996 confirmed the expected proportions of d:l urinary amphetamine isomers obtained in samples taken from subjects consuming street amphetamine and patients prescribed dexamphetamine for attention deficit hyperactivity disorder. The start of the study was considerably delayed by requirements to satisfy all relevant authorities that the present study met an important need, was sufficiently rigorous and did not infringe any policy or ethical requirements. During this period the availability of amphetamine precursors became more restricted presumably leading to changes in the main method used to synthesise street amphetamine. Urine tests indicated that, at the time of the study was conducted in 1998, illicit amphetamine was manufactured using pseudoephedrine as the major precursor, producing levels of d-amphetamine isomer equivalent to that produced by the ingestion of pharmaceutical dexamphetamine. Thus, changes in local illicit amphetamine supplies are an important consideration in selecting reliable monitoring techniques in future dexamphetamine trials.

This study also demonstrated that a trial to evaluate the effectiveness of controlled prescribing of amphetamine as substitution therapy for problematic amphetamine users was feasible. A number of components of such a study were tested and performed well. These included: subject recruitment, assessment, and retention; measurement of changes in amphetamine use and associated harms; the response of subjects to the control condition; the attractiveness of the intervention to potential subjects; its acceptability to clinical staff and the cost of the intervention. The study design was found to be appropriate as evidenced by acceptable recruitment, retention and outcome data. Recruitment proved the most difficult aspect of the study suggesting that the intervention may only be attractive to a sub-set of amphetamine users who experience the most severe physical and psychological harms associated with long-term, chronic amphetamine use. The overall study design, with some modifications, is feasible for a larger trial of efficacy and safety.

Assessment of the risks involved in providing dexamphetamine substitution therapy was an important concern of the investigators. It was reassuring that there were no serious adverse events reported during the course of the study. No psychotic symptoms or episodes were reported in the treatment group: a finding also reported in similar studies in the United Kingdom. The risk of psychotic symptoms developing in carefully screened and monitored subjects on the maximum dose used in this study appeared to be low. The recruitment experience gained in this study also suggested that the risk of inadvertently creating amphetamine dependence by treating non-dependent users was also very low. A concern that recreational users would be irresistibly attracted to substitution prescribing programs to increase their drug consumption was not supported in this study. There were no incidents of dexamphetamine being diverted from KRC with all doses dispensed under supervision and crushed in orange juice. The program proceeded with minimal disruption to KRC clinical services including the centre's methadone program.

Indications of the efficacy of an amphetamine substitution program were secondary aims of the study. Assessment of the effectiveness of this intervention was substantially limited by the relatively small sample size, short study duration and some important potential sources of bias. After 12 weeks, 61.5% of urine samples from the control group and 52.9% of urine samples from the treatment group tested positive for illicit amphetamine. According to an intention-to-treat analysis this difference was not statistically significant. The only statistically significant difference between study groups was in the uptake of counselling which was greater in the treatment group. This finding may, however, have been explained by the significantly higher proportion of females in the treatment group. Statistically significant improvements were found between baseline and follow-up in both groups in HIV risk behaviour (due to reduced injecting) and in the degree of amphetamine dependence as measured by the Severity of Dependence Scale. In the treatment group expenditure on illicit amphetamine also fell significantly.

Urinalysis and self-report were consistent in identifying a reduction in amphetamine use and related harms in both groups over the course of the study. Whether these changes endure or a difference exists between treatment and control groups can only be answered by an appropriately designed efficacy trial with a larger sample and longer duration of follow-up. The present study found that urinalysis can be used to distinguish illicit from pharmaceutical amphetamine consumption and therefore that it has a role in the evaluation of the efficacy of dexamphetamine as substitution therapy.

1.   Introduction

Amphetamine is the second most widely used illicit drug in Australia after cannabis (Makkai & McAllister, 1998). The most recent National Drug Strategy household survey, examined in *Patterns of drug use in Australia 1985-1995,* indicates that amphetamine has been widely available throughout the 1990s. The proportion of the population reporting they had been offered the drug and the reported lifetime prevalence of amphetamine use both increased. Lifetime prevalence was estimated at 10% of the population. Prevalence of reported lifetime use was higher (16%) among persons aged 20 to 29 years. The household survey suggested that amphetamine was easy to obtain and demonstrated that sizeable numbers were using amphetamine on a regular basis. This phenomenon of increased availability and use of amphetamine is not restricted to Australia; similar trends have been reported in Europe, the United States and parts of Asia (United Nations, 1997).

Harms associated with chronic amphetamine use have been well documented (Kamieniecki *et al.,* 1998). These include psychological morbidity, dependence, health problems, infections and other complications associated with injecting and unsafe sexual practices, financial, social and criminal problems. Psychological problems are common among regular amphetamine users. Depression, anxiety, hallucinations, paranoia, panic attacks and suicidal thoughts have been reported to occur commonly (Hando *et al.,* 1997; Vincent *et al.,* 1999; Klee, 1992). Regular amphetamine use has also been found to be associated with social, financial and personal problems (Hando *et al.,* 1997; Vincent *et al.,* 1999). Amphetamine use may not only increase risks of transmission of blood borne viruses through sharing of injecting equipment but also lead to disinhibition of sexual activity (Klee, 1992; Anderson & Flynn, 1997).

The number of people presenting to drug and alcohol services with primary amphetamine problems is increasing (Darke *et al.,* 1996; Torres *et al.,* 1996) but there are no specific services for amphetamine users. All current available treatments are abstinence based. This approach unfortunately appears unattractive to a considerable number of problematic users. There are currently no recognised pharmacotherapies for amphetamine users in Australia or overseas. Amphetamine users can attend general hospital emergency, general practitioners, psychiatric services, drug counselling services, detoxification and rehabilitation services, therapeutic communities and self-help groups such as Narcotics Anonymous. Amphetamine users rarely contact these treatment services, which they perceive to be targeted at people with alcohol and opiate problems (Klee, 1992). This low level of engagement with treatment services is reflected in several studies which have reported between 7 and 12% of long-term amphetamine users in treatment other than methadone maintenance (Hando *et al.,* 1997; Darke *et al.,* 1998; Ross *et al.,* 1994).

Interest in substitution therapy for amphetamine dependence has been revived as a consequence of increasing amphetamine use and intravenous administration during the 1980s and 1990s. The rationale for the provision of amphetamine substitution is similar to that for heroin substitution programs. The potential benefits of such programs embody major public health goals including: prevention of transmission of blood borne viruses such as HIV and hepatitis B and hepatitis C by means of sharing of injecting equipment; improvements in the health and social functioning of drug users; reduced illicit drug use; and reductions in the associated criminal behaviour undertaken to fund drug use (Ward *et al.,* 1998; Fleming, 1998;

Myles, 1997). The sharing of injection equipment by amphetamine injectors is an important public health concern requiring effective interventions to prevent the spread of infectious diseases. It has been argued that public health benefits may outweigh risks associated with prescribing of substitution drugs (Fleming & Roberts, 1994; Pates et al., 1996; Charnaud & Griffiths, 1998). Oral dexamphetamine substitution may allow stabilisation of some patients on a dose which causes neither withdrawal or craving and which may thereafter allow for gradual reduction and eventual cessation (Bradbeer et al., 1998; Sherman, 1990). In a discussion of the role of substitution therapy for amphetamine users, Mattick and Darke (1995) identified four criteria of appropriateness of a maintenance treatment program. These were: i) regular frequent use (usually daily); ii) clear evidence of dependence; iii) continued use representing severe adverse complications for the user; and iv) the harms associated with illicit use exceed the risks associated with the use of legal substitute drug.

Concern about possible risks of amphetamine prescribing has delayed serious consideration of substitution therapy until recent years. Potential complications of prescribing amphetamine may result from the use of additional street amphetamine by patients. These may include hypertension, high blood pressure, tachycardia, arrythmias, hyperthermia, convulsions, sub-arachnoid haemorrhages, cerebral infarctions and precipitating or exacerbating psychosis. However, the experience of several studies has been that "amphetamine can be prescribed safely without significant complications" (p.192 Lintzeris et al., 1996). Three recent clinical evaluations of dexamphetamine prescribing programs in the UK reported very low levels of psychosis and other side effects. A study of 63 patients receiving up to 40 mg of prescribed dexamphetamine daily in Wales, UK, was specifically designed to detect evidence of side effects from prescribed dexamphetamine, particularly psychosis (McBride et al., 1997). Three episodes of psychosis recorded over 4 years all followed consumption of large quantities of street amphetamine. No case of a first psychotic episode was detected in a study of 155 patients prescribed between 30 and 75 mg per day of dexamphetamine elixir in Cornwall (White, 1996). Six psychotic episodes were reported in patients with a history of psychosis who had taken additional illicit amphetamine. In a group of 60 patients prescribed between 15 and 75 mg per day of dexamphetamine elixir, five episodes of paranoia were reported over a two year period. In each case the paranoia coincided with consumption of street amphetamine and symptoms abated when street amphetamine use stopped (Charnaud & Griffiths, 1998).

Research evaluating amphetamine prescription conducted in the 1960s and early 1970s in London concluded that the benefits of psychostimulant prescribing were modest and the risks considerable. Seventy-four regular methylamphetamine injectors were prescribed methylamphetamine, some in an injectable form, in an attempt to treat problematic methylamphetamine and cocaine use (Hawks et al., 1969). The result was judged a therapeutic failure because of continuing illicit use and diversion of prescribed amphetamine. A study involving 35 methylamphetamine injectors and 65 oral amphetamine users reached a similar conclusion (Gardner & Connell, 1972). However, more recent studies and evaluations of clinical programs suggest that amphetamine users are attracted to services offering amphetamine prescription where they can be provided with advice, counselling and harm minimisation interventions such as needle and syringe programs (Fleming & Roberts 1994; McBride et al., 1997). Positive outcomes from amphetamine prescribing reported by these studies are summarised below.

Benefit	Author, Year
Reduced Injecting Behaviour	Fleming & Roberts, 1994; McBride et al., 1997; White, 1996; Pates et al., 1996; Charnaud & Griffiths, 1998
Reduced sharing of injecting equipment	McBride et al., 1997
Improved retention in treatment	McBride et al., 1997
Reduced use of illicit amphetamine	McBride et al., 1997; White, 1996; Sherman, 1990; Pates et al., 1996; Charnaud & Griffiths, 1998
Improved social functioning (reduced crime, stable housing, employment)	Fleming & Roberts, 1994; Pates et al., 1996; McBride et al., 1997
Reduced cravings	Sherman, 1990

These studies have relied mainly on self-report to measure changes in amphetamine use and have lacked effective control groups to confirm their positive outcomes. A recent survey of 149 medical specialists in drug dependence in England and Wales found that 46% of respondents were currently prescribing amphetamine and 60% saw a role for this therapy (Bradbeer et al., 1998). Although the practice of amphetamine prescription was found to be widespread, little scientific evidence was available to evaluate the efficacy or safety of the approach. Inability to distinguish street from pharmaceutical amphetamine consumption has been identified as an impediment to the evaluation of the effectiveness of substitution therapy in maintaining patients and monitoring abuse of such programs (Fleming, 1998; Bradbeer et al.,1998).

The present study was designed in 1995 with the primary aim of testing the reliability, under field conditions, of urinary amphetamine isomer analysis as a means of distinguishing between: (1) individuals who had consumed street amphetamine from (2) those who had consumed pharmaceutical amphetamine and (3) those who had consumed a mixture of street and pharmaceutical amphetamine. Chiral analysis of amphetamine isomers, which allows the separation of dextro (d) and levo (l) isomers, has been used to distinguish consumption of illicit amphetamine, a 50:50 racemic mixture, from pharmaceutical amphetamine, comprising primarily the d-isomer (Tetlow & Merrill, 1996). A pilot study conducted in 1996 using this technique confirmed the expected d:l ratios obtained in samples taken from subjects consuming street amphetamine and attention deficit hyperactivity disorder (ADHD) prescribed dexamphetamine. The pilot study indicated that it was possible to differentiate patients receiving prescribed amphetamine from street amphetamine by chiral determination of urinary amphetamine.

The technique was not applied to this trial until 1998 due to delays outside the control of the investigators. These delays were related to requirements to satisfy state and federal authorities that the study was not in breach of policy or ethical guidelines. During the period the study was delayed, the principal method of synthesis of illicit amphetamine appeared to have changed. This may have been due to a tightening of controls on precursor chemicals from which illicitly manufactured amphetamine is derived. These included phenyl-2-propynone which was scheduled under the Drug Misuse and Trafficking Act in July, 1995. This phenomenon has also been noted in the US (CSAT, 1999). The change in the composition of street amphetamine was apparent from the chiral analysis of baseline urine samples which revealed higher d:l ratios than found in either the pilot or previous UK studies.

All baseline samples were found to contain methylamphetamine isomers which are not produced by the ingestion of pharmaceutical amphetamine. Fortunately, this alternative technique involving testing for methylamphetamine in urine, allowed the primary aim of the study (to distinguish sources of amphetamine consumption by urinalysis) to be achieved without significant changes to the study protocol.

The investigators were also interested in assessing the feasibility of conducting and evaluating amphetamine substitution programs. The study provided valuable experience in the assessment, treatment and monitoring of suitable subjects and the provision of a controlled drug without diversion. The acceptability of the program to clinical staff and its attractiveness to subjects were also assessed. Components of the study design were also tested by examining recruitment, retention and compliance rates and procedures and measures used to detect changes in amphetamine use and related harms. The costs of the intervention were also estimated.

A secondary aim of the study was to obtain an indication of the safety and efficacy of amphetamine substitution. Urinalysis results and self-report data at baseline and follow-up were examined between groups. Data obtained from urinalysis included proportions of urine samples free of isomers indicative of illicit amphetamine use and the presence of other illicit drugs. Variables obtained from the Opiate Treatment Index included self-reported amphetamine use and other drug use, HIV risk taking behaviour, money spent on street amphetamine, criminal behaviour, health and psycho-social adjustment. Severity of Dependence Scale scores were compared at baseline and follow-up. Interpretation of data pertaining to the efficacy of this treatment was limited by the small sample size and study design.

2. Methods

2.1 Study design

This was an open, two-group, pre-post randomised clinical trial. Forty-one long-term amphetamine users who satisfied all inclusion criteria and had none of the exclusion criteria for the study were recruited over a seven month period. Subjects accepted into the study were randomly allocated to receive a daily oral dose of dexamphetamine for 12 weeks in addition to the usual care offered to amphetamine users at KRC (the treatment group), or were assigned to the control condition in which they received usual care only (the control group). Usual care consisted of weekly appointments with the KRC counselling service. Keeping clinicians and subjects blind to study conditions was not considered practical as the absence of a stimulant effect in any placebo preparation would have been too easily detected. Study participants were assessed at baseline and 12 weeks.

2.1.1 Eligibility criteria

The inclusion criteria for the study were as follows:

1. DSM-IV amphetamine dependence diagnosis using the Composite International Diagnostic Interview (CIDI, 1997);
2. two year history of amphetamine use;
3. regular, current amphetamine use (at least weekly);
4. motivation to reduce amphetamine use;
5. primary amphetamine user (current drug of choice);
6. amphetamine positive urine sample at intake;
7. aged 20 years or older;
8. residing within 1 hour commuting distance of KRC;
9. available for follow-up;
10. willingness to participate indicated by written informed consent.

Applicants who satisfied the inclusion criteria were ineligible if any of the following exclusion criteria were met:

1. pregnant, nursing or unwilling to take contraceptive precautions (if female);
2. driving vehicles or operating machinery in the course of employment;
3. any previous diagnosis of Attention Deficit Hyperactivity Disorder;
4. positive DSM-IV diagnosis for schizophrenia or other psychotic disorders (using the CIDI);
5. history of any other significant physical or mental illness.

2.1.2 Changes to eligibility criteria

Other drug use

Primary amphetamine users were targetted for recruitment as it was considered that dependence on other drugs may have impaired the effectiveness of amphetamine substitution. Heroin users and methadone patients were initially excluded as poly-drug users were

considered inappropriate due to opiate dependence and chaotic lifestyles. In the course of the study it became apparent that many chronic amphetamine users were also poly-drug users. The ready availability in Sydney of heroin, which was reported by many subjects to be easier to obtain than amphetamine, meant that many users who identified amphetamine as their drug of choice also used heroin.

As the primary objective of the study was to measure differences in urinary isomers, it was decided that the heroin exclusion criterion was not directly pertinent to this aim. Consequently the heroin dependence exclusion criteria was relaxed. Relaxing the heroin exclusion criterion made no difference to recruitment. No regular heroin users presented for treatment for amphetamine problems.

Current enrolment in methadone maintenance treatment (MMT) was the last poly-drug exclusion criterion to be relaxed. Methadone patients were originally considered to be inappropriate as participation in a methadone program suggested that heroin was the 'primary' drug of choice. However, as recruitment was expanded from KRC clientele, local GPs and methadone clinics reported that there were methadone clients who were also chronic amphetamine users. It was, therefore, decided to relax this exclusion criterion, subject to careful medical screening. It was noted that MMT subjects had been involved in UK studies (Fleming & Roberts, 1994).

Other changes to original protocol eligibility criteria

HIV infection

HIV infection was an exclusion criterion in the original protocol. This was amended to only exclude subjects diagnosed with AIDS and HIV positive subjects currently treated with protease inhibitors which have been reported to interact with amphetamine (Abbott Pharmaceuticals, 1997). Two HIV positive subjects were recruited. Both were randomised to the control group.

Operating machinery and driving

Subjects were warned about the dangers of driving and operating machinery particularly immediately after dosing. It was decided to exclude subjects who drove or operated machinery in the course of their employment.

Adult Attention Deficit Hyperactivity Disorder (ADHD)

It was agreed that subjects who believed they had ADHD or reported they had ever been diagnosed with ADHD would be referred to appropriate psychiatrists. No such subjects presented for assessment.

2.2   Subjects

2.2.1   Sample size

The sample size of 41 used in the study was considered adequate for the purposes of a feasibility study. Previous observational studies of amphetamine substitution suggested that

recruitment was likely to be slow. These included 26 subjects recruited over 3 years in Portsmouth, England (Fleming & Roberts, 1994); 10 subjects recruited over 24 weeks in Wales (Pates et al., 1996) and 155 subjects recruited over 4 years in Cornwall (White, 1996). The view that the treatment population would be small and difficult to recruit was also supported by previous descriptive studies of amphetamine users conducted in Sydney. These included a study of 200 regular amphetamine users where only three percent reported daily use and 18% expressed interest in substitution therapy (Hando et al., 1997) and a study of 301 users in which two percent reported daily use (Ross *et al.*, 1994).

2.2.2 Subject recruitment

Subjects were recruited from persons attending KRC by means of fliers posted in the waiting room, the outreach bus and a satellite needle and syringe service. KRC staff also mentioned the study to appropriate patients during consultations and outreach work. Potential subjects were encouraged to make contact with research staff to learn more about the study and make an appointment to be assessed for suitability.

In response to slow recruitment, an expanded and extensive recruitment strategy was adopted. This included publicity through other needle and syringe programs, methadone clinics, drug and alcohol services, community health services, hospital emergency centres, organisations representing drug users and target groups, media advertising, radio interviews and contact with selected doctors and pharmacies.

2.3 Study procedures

2.3.1 Intake procedure

a)   Individuals were initially assessed by the Research Officer to determine their eligibility. This assessment included a screening questionnaire to establish that the individual met the inclusion criteria. The automated version of the Composite International Diagnostic Interview (CIDI-Auto version 2.1, 1997) was administered to establish amphetamine dependence indicated by a positive diagnosis under Section L (Substance Related Disorders) and to exclude subjects receiving a positive diagnosis under Section G (Schizophrenia and Other Psychotic Disorders). The study and risks of participation was explained to the subject and informed consent obtained.

b)   Suitable subjects then proceeded to an assessment by a KRC Medical Officer (MO) authorised by the Pharmaceutical Services Branch, NSW Department of Health, to prescribe dexamphetamine for amphetamine dependence. The MO confirmed that the subject was amphetamine dependent and that there were no physical or psychiatric conditions precluding participation in the study. If there was any doubt about a potential candidate's psychiatric history a referral from the candidate's own GP was requested. The prescribers for subjects on methadone maintenance were likewise consulted. The risks of participation were repeated and informed consent confirmed. Medical officers had ultimate discretion as to whether individuals were included into the study.

c)   Subjects assessed as suitable by both the Research Officer and Medical Officer, provided baseline data in the study interview, a urine sample, received payment of

$20 as reimbursement for travel and time and were randomised. Randomisation was only performed if a urine sample tested positive for amphetamine as indicated by a Syva RapidTest™. Subjects who provided a negative urine sample at the time of interview were allowed to return 2 to 3 days later for a second urine test. If this sample tested positive, recruitment proceeded.

d)   Subjects randomised to the treatment group were registered with the Pharmaceutical Services Branch, NSW Department of Health. Once approval was received, usually within 3 days, the first dose of dexamphetamine was dispensed.

e)   Subjects in both groups were encouraged to attend individual counselling sessions offered on a weekly basis. The Research Officer made the initial appointment for subjects with the KRC counselling unit.

2.3.2   Follow-up

At the time of the baseline interview, subjects provided contact information for themselves and one significant other. Subjects were advised that the Research Officer would contact them again in 6 weeks for a urine sample and at 12 weeks for a follow up interview and urine sample. Subjects were compensated for time and travel costs at 6 weeks ($30) and the 12 week follow-up interview ($40).

2.3.3   Randomisation

The objective of the randomisation was to achieve block randomisation over the study period. Randomisation was achieved by means of Patient Identification Cards, indicating to which group the subject was allocated. These cards were sealed in opaque envelopes. Treatment or control group cards were shuffled in blocks of 10 containing 5 of each type of card. One extra envelope was added to each block of ten from a shuffled group of six envelopes containing equal numbers of treatment and control group cards. This was to ensure that the last card could not be guessed. Once the envelopes were prepared, they were numbered consecutively. It was decided *a priori* that couples would be randomised together. Subjects enrolling in the study were allocated case numbers consecutively. At randomisation, the corresponding envelope was opened and the subject advised to which group they had been allocated.

2.3.4   Treatment

Treatment subjects were prescribed dexamphetamine tablets (5 mg), up to a maximum of 60 mg daily which was dispensed under direct supervision by a nurse once a day. Tablets were crushed and taken orally with orange juice. Induction began at 20 mg, increasing by 5 mg daily until the maximum dose was achieved. A flexible dosing policy was adopted allowing subjects to vary their doses although the study objective was to achieve a relatively stable dose. In the first 4 weeks, subjects attended weekly medical appointments. This was reduced to once a fortnight in the last 8 weeks of the study. Subjects assessed as intoxicated by dosing staff were not dosed. Subjects were permitted to miss doses for up to one week without dose reduction or medical review. Subjects missing doses for longer than one week could only restart dosing after medical assessment for side effects. The dose was reduced in

the last two weeks by 5 mg every three days leaving a maximum dose of 40 mg at the conclusion of the trial. At this point, dosing ceased.

Potential candidates for the trial and referring clinicians advised that the dispensing hours at KRC (10 am to 5.45 pm) might not be feasible for subjects working between 9am to 5pm. In order to improve recruitment and retention of subjects, it was decided to offer subjects an alternative dosing site at a nearby methadone clinic (Rankin Court) which provided early morning dispensing from 7.45 am. To avoid the risk of subjects receiving doses at both clinics, subjects were dispensed at one clinic only. All subjects continued to see MOs and counsellors at KRC on a weekly basis for monitoring. This change to the study protocol was approved by relevant ethics and regulatory bodies. One subject transferred to Rankin Court after starting on the program at KRC.

The possibility of providing takeaway dexamphetamine and dispensing from pharmacies (for any future study) was also considered. The Pharmaceutical Services Branch, NSW Department of Health advised that any takeaway protocol would have to be similar to that for methadone prescribing i.e. patients would need to be stabilised on treatment for a period of at least 3 months. This was not feasible given the study period of 12 weeks.

2.3.5 Counselling

Counselling represented 'usual care' for individuals presenting for treatment for amphetamine-related problems in Australia. All subjects were offered counselling consisting of weekly sessions with drug & alcohol counsellors and qualified social workers employed at Kirketon Road Centre. The KRC counselling unit provides crisis counselling, counselling for emotional issues and drug and alcohol issues. Counsellors also effect referrals to drug treatment, rehabilitation and detoxification and social welfare (including housing, education and training, and income assistance). KRC counsellors are eclectic in approach with counselling tailored to individual needs. Counsellors were encouraged to build on the motivational aspects of the initial study assessment. Where subjects could not, or did not wish, to use KRC counselling services, they were referred to counsellors elsewhere. These included counsellors in private practice as well as in other public clinics. Subjects had limited exposure to counselling. Only 22% had attended counselling for amphetamine-related problems prior to joining the study.

2.3.6 Urinalysis

Urine samples were collected from all subjects at baseline. Urine samples were collected from treatment subjects every 2 weeks giving a total of seven samples per treatment subject. Treatment subjects who ceased treatment were only followed up for the midpoint (week 6) and follow up (week 12) samples. Control subjects gave urine samples at week 6 and week 12 for a total three samples. Jars with liquid crystal temperature monitoring strips were used to ensure a body temperature sample was provided and to avoid the need to directly observe urination.

Determination of chiral amphetamine

The presence of amphetamine and methylamphetamine was determined by immunoassay (EMIT™) using a cut off of 300 ng/ml (AS4308-1995, Standards Australia, 1995). "Positive"

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samples were confirmed by analysis of the pentafluoropropionic anhydride derivatives using gas chromatography-mass spectrometry operated in the selection ion monitoring mode. Chiral amphetamine and methylamphetamine were determined by gas chromatography-mass spectrometry of (trifluoroacetyl) propyl chloride derivatives using previously published methods (Cooke, 1994; Tetlow & Merrill, 1996). The chiral purity of dexamphetamine tablets was determined both at the commencement and conclusion of the trial. The d:l ratio was deemed to be >8.5:1. Due to chiral impurities in both dexamphetamine and the chiral derivation reagent, 100% chiral purity was not attainable. The maximum purity found was 88%.

Urine specimens testing for d:l isomer ratios less than 7 were assumed to indicate significant use of street amphetamine based on results from a pilot study. Urine samples were taken from seven attention deficit hyperactivity disorder (ADHD) patients receiving dexamphetamine, and 14 street amphetamine users attending metropolitan drug treatment centres. Chiral analysis of the ADD group showed d:l ratios of amphetamine to be approximately 7:1 (85% d-isomer), while the street group had ratios ranging from 0.6 to 1.2:1.

Other drugs

All urine samples were also subjected to immunoassay (EMIT™) for cocaine, benzodiazepines, opiates and methadone. High performance thin layer chromatography and mass spectrometry were used where required for a wide range of other therapeutic and illicit compounds.

2.3.7 Interview schedules

Demographics and Drug History

Data were collected on demographic characteristics, current drug use and general drug use history, previous treatment seeking, exposure to blood borne infections, prison history and any history of psychiatric illness.

Opiate Treatment Index (OTI)

The measures for this study were derived from the Opiate Treatment Index (OTI) (Darke et al., 1991) with minor modifications. The modifications were discussed with Dr Shane Darke, senior author of the OTI, who advised that they had no implications for the psychometric properties of the instrument. Amphetamine use was substituted as the major drug outcome in place of heroin. A Cost of Habit section was added to capture changes in average expenditure on amphetamine. Finally, the barbiturates use question, now redundant, was replaced by a more relevant question about ecstasy/MDA. Major outcomes measured by the OTI include amphetamine use, HIV risk behaviour, crime, drug-related health outcomes, other drug use, social functioning and psychological health. All outcome domains were assessed for the month prior to interview except the OTI Social Scale which referred to the previous three months. On all scales, higher scores indicate higher levels of dysfunction.

Severity of Dependence Scale

Current dependence on amphetamine was measured using the Severity of Dependence Scale (SDS) described by Gossop et al., (1992). This is a five item scale that measures psychological dependence over the preceding 12 months. In the present study, this period was reduced to the preceding three months in order to compare scores at baseline and follow-up. Subjects in the treatment group were asked to distinguish their street amphetamine use from prescribed dexamphetamine at follow-up. The SDS is designed primarily as a measure of compulsive use and does not include tolerance or withdrawal items. It has been considered suitable for use for drugs such as stimulants where withdrawal has not been clearly defined (Gossop et al., 1995). Scores range from 0-15, with higher scores indicative of a higher degree of dependence. The cut off for DSM III-R severe amphetamine dependence has been estimated at scores greater than 4 (Topp & Mattick, 1997).

Twelve week follow up interview schedule

The interview at twelve weeks repeated the measures taken at baseline for comparative purposes. In addition subjects were asked questions about their experience with the study - benefits of participation and problems. Subjects in treatment were asked whether they would have liked to continue with the treatment.

2.3.8 Data analysis

Data were collected and analysed using SPSS for Windows (Version 6.1). Results were divided into **primary results and analyses** consisting of outcomes from urinalysis and **secondary results and analyses** covering all other data collected.

An "intention-to-treat" analysis was adopted to examine differences in the primary and secondary outcomes between the two study groups at follow up. The "intention-to-treat" population was defined as those subjects who were enrolled in the study and randomised.

As this was the first randomised controlled trial of this treatment, no estimates as to the size or direction of the effect were assumed. All statistical tests performed were 2 sided tests using a 5% level of significance and 95% confidence intervals. For continuous variables *t-tests* were used. Categorical variables were analysed using *chi-square* tests.

Bias

Sources of bias were examined but because of the small sample and cell sizes no attempt was made to adjust for bias. Potential sources of bias were examined by comparing groups at baseline and follow up for selective attrition, comparing treatment and control groups at baseline for differences on baseline variables and comparing urinalysis with self-report at follow-up.

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3. Results

3.1 Study sample

One hundred and forty two amphetamine users made contact with research staff to enquire about the study. Forty-three (30 %) failed to attend appointments. Thirty (21%) did not proceed to assessment either because they were not interested in dexamphetamine or participation in an RCT or did not meet inclusion criteria. Many expressed interest in medication to assist with the withdrawal symptoms when coming off amphetamine and were not interested in dexamphetamine substitution. The second most common reason for not proceeding to assessment was the inability of potential subjects to attend KRC daily either due to work commitments or distance from residence (23%).

Sixty-nine amphetamine users were assessed for the study representing 49% of all users enquiring about the study. Twenty-eight (40%) did not meet study inclusion criteria and were excluded (see 3.1.1). Forty-one subjects were accepted into the study, completed valid baseline interviews and gave baseline urine samples. Twenty-one were allocated to the treatment group and twenty to the control group. Demographics for the group appear in table 3.1.

Table 3.1: Baseline demographic characteristics

	Entire sample (n=41)	Treatment group (n=21)	Control group (n=20)
Age (mean)	29	29	28.6
Male (%)	83	71	95
Gay/bisexual (%)	31.7	19	45
Duration of use (years)	9.7	9.6	9.9
Frequency of use (% daily or nearly daily)	71	67	75

The typical subject enrolled in the study was 29 years old (range 20 – 48), male and had been using amphetamines for 10 years (range 2 – 25). First reported use of amphetamine was at age 18. Regular use and also commencement of injecting started at age 21. Subjects reported currently using amphetamine twice daily, usually by injection (95%). Subjects reported spending an average of $56 per day on amphetamine.

The study group was generally well educated with 64% having completed 12 years of education. Fifty-four percent were in some form of employment. Levels of reported criminal behaviour were low (particularly when compared to opiate users). This is consistent with other research comparing opiate and amphetamine users (Darke et al., 1998). Criminal behaviour mainly involved shoplifting, social security fraud and amphetamine dealing. Ten percent had a history of imprisonment.

The prevalence of self-reported blood borne viral infections was low relative to opiate users. Fifteen percent were hepatitis C positive, 5% were HIV positive. Thirteen percent of injectors reported sharing injecting equipment with others in the month preceding intake. Poly-drug use was high. Tobacco (83%), marijuana (76%) and alcohol (73%) were the most prevalent other drugs used in the month preceding baseline interview. Use of cocaine (29%), ecstasy (27%), hallucinogens (19.5%) and inhalants (7%) was best described as recreational. Benzodiazepines had been used by 34% of subjects in the past month with two cases of problematic benzodiazepine use. Seventeen percent of subjects had used heroin in the past month but use was not regular. Fifteen percent of subjects (n=6) were enrolled in methadone maintenance treatment.

Subjects were questioned about previous help-seeking for amphetamine-related problems. Seventy-six percent had sought help: 44% had consulted a general practitioner, 22% had seen a counsellor and 22% had seen a psychiatrist. Twenty-two percent had attended hospital emergency centres and 17% had undergone a detoxification program at some stage. Twenty-four percent of subjects never sought treatment.

Differences between treatment and control

The two study groups were comparable on most key variables except that females were significantly over-represented in the treatment group (29%) compared to the control group (5%) (χ^2=4.4, df=1, p=0.04). Gay and bisexual males formed a large part of the sample and were somewhat over-represented in the control group (45%) compared to the treatment group (19%) (χ^2=3.2, df=1, p=0.14). These differences may have affected outcomes, for example, females may have been more likely to take advantage of counselling services. Gay or bisexual males may have been at higher risk of HIV (reflected in higher HRBS scores) due to the practice of anal sex and contact with larger numbers of sexual partners.

3.1.1 Excluded amphetamine users

The recruitment procedure required assessment for suitability by an initial assessment by the Research Officer and medical assessment for suitability by a Medical Officer. Users were only enrolled and randomised after both assessments were completed. Three amphetamine users were excluded for not completing the enrolment process (i.e. they did not present for a medical assessment). Twenty-eight amphetamine users (40%) were excluded as they did not meet inclusion criteria for the study or they decided they were not interested or unable to participate after initial assessment interview. Users were excluded for a variety of reasons including previous histories of major psychiatric illness (18%) and chronic illness such as AIDS and heart problems (18%). Twenty-one per cent were assessed as not chronic, regular users based on low frequency of use (less than weekly), short period of use (histories less than 2 years) or no CIDI diagnosis for amphetamine dependence. Fourteen percent were not interested in the treatment.

Limited data was collected for excluded users based on the assessment instruments. These are summarised and compared to the study sample in table 3.2.

Table 3.2: Comparison of excluded and included amphetamine users

	Excluded amphetamine users (n=28)	Included amphetamine users (n=41)
Mean age (years)	35	29
Frequency of use daily or nearly daily (past month) (%)	50%	71%
Duration of use (years)	14.6	9.7
Male (%)	75%	83%
Mean SDS Score	7.1	10.4

Excluded amphetamine users were significantly older (t=-3.58, df=67, p=0.001), had longer histories of amphetamine use (t=-2.71, df=67, p=0.009) but received lower SDS scores indicating lower levels of dependence (t=3.45, df=60, p=0.001) than included subjects. The means obtained for excluded users may obscure the different types of excluded users. Some were users with short histories of amphetamine use and low SDS scores while others had much higher SDS scores and longer histories of use but were excluded for reasons of psychiatric histories or chronic illness.

3.2   Urinalysis results

A total of 164 urine samples were analysed for amphetamine, amphetamine isomers and methylamphetamine over the course of the study.

3.2.1   Urinalysis results for baseline samples

Table 3.3: Urinalysis results for baseline samples

	Methylamphetamine Positive	Methylamphetamine Negative	Total (% of total)
Amphetamine d:l ratio < 7	6	0	6 (15%)
Amphetamine d:l ratio ≥ 7	29	0	29 (71%)
Amphetamine –ve	2	4	6 (15%)
Total (% of total)	37 (90%)	4 (10%)	41

The original hypothesis was that the source of amphetamine consumed could be distinguished by analysing the dextro (d) and levo (l) isomers in subjects' urine. It was assumed that specimens with ratios less than 7:1 indicated use of illicitly sourced amphetamine (See 2.3.6). However, it was apparent that street amphetamine did not conform to the expected d:l ratio. At baseline, only 6 (15%) out of 41 samples had d:l ratios less than 7. The majority of positive samples (29) had d:l ratios greater than 7. Two subjects gave samples which were methylamphetamine positive but with amphetamine levels too low to conduct d:l ratio analysis.

Excluding four subjects with amphetamine negative urine samples, all baseline samples were positive for methylamphetamine isomers, which are not produced by the ingestion of dexamphetamine or any other pharmaceutically available drug. Based on this evidence, it was decided that analysis based on the presence of methylamphetamine could be substituted for urinary isomer analysis to identify street amphetamine use, thereby enabling the study to meet the aims of the original study protocol.

3.2.2 d:l isomer ratio analysis

The proportion of urine samples within d:l ratio ranges by study group is presented in table 3.4. Four samples were methylamphetamine positive but specimens were insufficient to conduct chiral amphetamine testing and were not included in this analysis. Approximately half of control group samples were negative for any form of amphetamine over the study period, which together with study attrition, accounts for the low number of control group samples available for chiral analysis.

Table 3.4: d:l amphetamine isomer ratio ranges

Ratio range	Baseline (0 weeks)		Midpoint (6 weeks)		Follow-up (12 weeks)	
	Treatment (n=19)	Control (n=16)	Treatment (n=14)	Control (n=7)	Treatment (n=14)	Control (n=6)
1 – 6:1	10%	19%	14%	7%	0%	50%
7 – 13:1	15%	6%	79%	14%	71%	0%
14 – 20:1	65%	69%	14%	71%	29%	50%
21 – 27:1	5%	6%	0%	0%	0%	0%

The highest proportion of samples in both treatment and control groups at baseline were in the 14 – 20:1 d:l isomer ratio range. This persisted at follow-up in the control group while ratios in the treatment group fell. Note that ratios may be affected by a variety of factors including the time of sampling after the ingestion of amphetamine, the differing rates of metabolism between individuals and the interaction between methylamphetamine and amphetamine.

3.2.3 Comparison of treatment and control

Chiral Urinalysis results for all samples by group are presented in table 3.5. Methylamphetamine positive samples were deemed "positive" for street amphetamine use as were all samples with d:l amphetamine ratios less than 7.

Table 3.5: Urinalysis results for all samples by group

d:l isomer ratio	Methylam-phetamine	Treatment (n=114)	(%)	Control (n=50)	(%)
<7	+ve	5	4	5	10
<7	-ve	2	2	2	4
≥7	+ve	58	51	22	44
Amphet –ve	+ve	1	1	3	6
Total "positive"		**66**	**58%**	**32**	**64%**
≥7	-ve	39	34	0	0
Amphet –ve	-ve	9	8	18	36
Total "negative"		**48**	**42%**	**18**	**36%**

There was no evidence that this group of illicit amphetamine users had been exposed to diverted pharmaceutical dexamphetamine. Urine samples with d:l ratios greater than 7 and negative for methylamphetamine, characteristic of dexamphetamine use, were unique to the treatment group and were not found in any baseline or control group samples.

Table 3.6: Proportion of 'positive' treatment and control group samples over time

Positive samples	Baseline		Midpoint		Follow-up	
	%	n	%	n	%	n
Treatment	95.2	21	55.6	18	52.9	17
Control	85	20	41.2	17	61.5	13

Chi-square analysis at mid point and follow-up indicated there were no statistically significant differences between the groups at either point (Midpoint $\chi^2=0.72$, df=1, p=0.4, Follow-up $\chi^2 =0.22$, df=1, p=0.6). Missing samples have been excluded from this analysis consistent with data analysis approach used for other study outcomes. A more conservative approach would be to treat missing samples as positive for street amphetamine. Using this approach, 62% of treatment and 75% of control samples were positive at follow up. There was no statistically significant difference between groups using this approach (Midpoint $\chi^2=0.6$, df=1, p=0.4, Follow-up $\chi^2 =0.8$, df=1, p=0.4).

Figure 3.1 illustrates the proportion of urine samples deemed positive for street amphetamine use by group over the study period.

Figure 3.1: Proportion of urine samples deemed 'positive' for street amphetamine use over study period
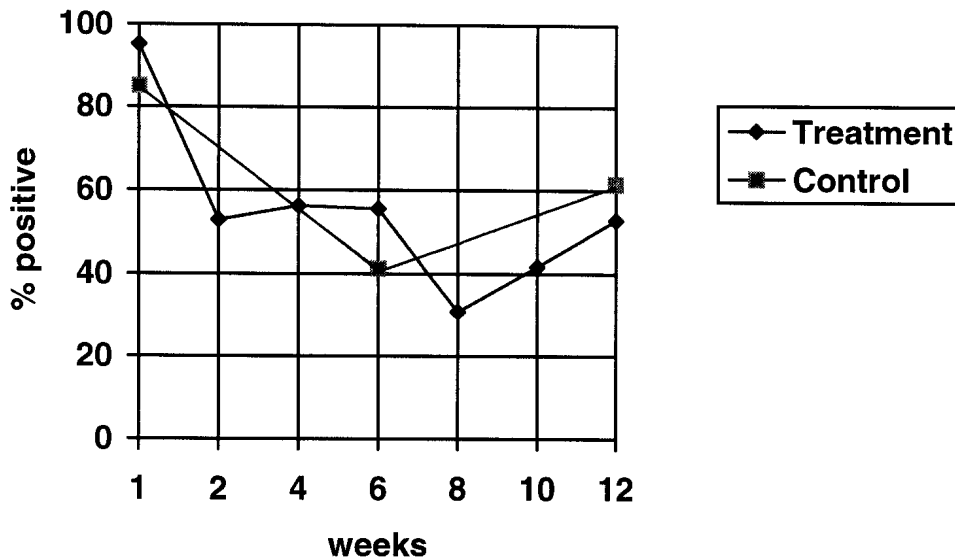
3.2.4 Treatment group results

Table 3.7: Proportion of treatment group urine samples deemed 'positive' for street amphetamine use

Positive samples	Baseline	Week 2	Week 4	Midpoint	Week 8	Week 10	Follow-up
(%)	(n=21) 95.2	(n=17) 52.9	(n=16) 56.3	(n=18) 55.6	(n=13) 30.8	(n=12) 41.7	(n=17) 52.9

The proportion of 'positive' urine samples in the treatment group fell by half at the study midpoint and then began to fall further until follow-up when the proportion increased to fifty percent. Note that the follow-up urine sample was taken after the dose of dexamphetamine for treatment subjects had been reduced to 40 mg and also includes subjects who had ceased treatment.

3.2.5 Power calculations

The Design-Power software package (Bavry, 1987) was used to retrospectively calculate the power of the study sample to reliably detect a difference between the study groups based on independent tests of proportions and an alpha level of 0.05. The effect size was based on differences between groups in the proportion of urine samples "positive" for street amphetamine at follow-up (Treatment 52.9% n=17: Control 61.5% n=13). This represented a modest treatment effect (8.6%) due, in part, to levels of abstinence indicated by "negative"

urine samples in the control group. The sample size necessary to reliably detect a statistically significant difference between groups was calculated to be 518 subjects per group. The power of the present feasibility study was calculated as 0.08 confirming that the sample size was insufficient to yield statistically reliable results.

A similar power calculation used an effect size estimate of 13% based on the more conservative approach of treating missing samples as "positive" (Treatment 62% n=21; Control 75% n=20). This increased the power of the study sample to 0.14 which was still well below the 0.8 conventionally accepted as an acceptable power level for determining the likelihood of detecting an effect. A sample size of 198 subjects per group was calculated as neccesary to reliably detect a difference between groups based on this approach. This is a feasible although large number of subjects for a clinical trial.

3.3   Other outcomes

3.3.1   OTI scores

Table 3.8: Mean OTI scores at baseline and follow-up

	Treatment (n=17)		Control (n=14)	
	Baseline	Follow-up	Baseline	Follow-up
Amphetamine use	1.9	1.4	2.2	1.0
HRBS	12.6	8.4 b	11.7	8.4 a
GHQ	7.7	4.5	9.9	5.1
Crime	1.0	0.6	1.5	1.6
Social	16.1	15.2	13.6	13.1
Cost	51.9	22.5 a	38.0	22.6
SDS	10.8	4.6 c	10.5	6.4 c
Health	15.8	12.4	14.9	13.1

a. $p = < 0.05$ for paired sample t-tests between baseline and follow-up within group.
b. $p = < 0.01$ for paired sample t-tests between baseline and follow-up within group.
c. $p = < 0.001$ for paired sample t-tests between baseline and follow-up within group

3.3.2 Amphetamine use (self-report)

Amphetamine consumption in the preceding four weeks was estimated using the OTI method based on the last three days of drug use. The intervals between days of use and the amounts used on those days, were averaged to estimate recent consumption. The derived value was equivalent to the estimated average number of 'hits' per day in the past month. The OTI technique seeks to overcome problems caused by relying on subjects' own estimates of the frequency and quantity of drugs used.

Average daily street amphetamine use at baseline was in the vicinity of two 'hits' for subjects in both groups. Self-reported street amphetamine use fell in both groups at follow-up. In the treatment group the number of 'hits' per day fell from 1.9 (SD 1.1) to 1.4 (SD 2.7), in the control group it fell from 2.2 (SD 2.5) to 1.0 (SD 1.3). Self-reported street amphetamine use was not significantly different between groups at follow-up (t=0.51, df=29, p=0.62).

Comparing these outcomes with the results of the urinalysis, the change is in the same direction although the control group had a higher proportion of positive urine samples at follow-up than the treatment group. The proportion of subjects reporting no street amphetamine use was also higher in the treatment group (23.5%) than in the control group (7%). Selective attrition may have affected comparisons between treatment and control groups as control subjects lost to follow-up had higher scores (mean 4.0) while treatment subjects lost to follow up had lower scores (mean 1.5) (See Losses to Follow Up 3.5).

3.3.3 HIV Risk Behaviour Scale

Two components of the HIV Risk Behaviour Scale of the OTI were used to assess HIV risk taking behaviour: injecting behaviour and sexual behaviour. The scale has a range of 0-55. It is designed to measure behaviour of injecting drug users that puts them at risk of either contracting or transmitting HIV.

Both groups experienced a significant reduction in HRBS scores, primarily due to reduction in drug consumption and therefore injecting behaviour (Treatment t=3.56, df=16, p=0.003; Control t=2.26, df=13, p=0.04). There was no significant difference between groups at follow-up (t=-0.03, df=29, p=0.973). The relatively high proportion of homosexual males in the control group may have elevated the HRBS score for this group due to higher number of sexual partners and anal sex. The mean score for the sample at baseline was 12 corresponding to the clinical category "above average". At follow up the mean score was 8.4 for both groups, corresponding to the clinical category of "average".

Sharing of injecting equipment

Reported levels of needle and syringe sharing were low. Two subjects in each group reported sharing needles in the month preceding baseline (12.5% of injectors in the treatment group (n=16) and 14% in the control group (n=14)). At follow-up, two treatment subjects (13% of injectors) and one control subject (8% of injectors) reported sharing needles and syringes.

Cleaning of injecting equipment

Cleaning of injecting equipment was mostly associated with personal re-use of needles. At baseline, fifty-eight per cent of treatment subjects reported cleaning re-used needles, although only 25% used bleach for this purpose. The number of treatment subjects who reported re-using needles at follow-up fell to twelve to eight, 87.5% of whom cleaned needles before re-using them, 25% using bleach. In the control group, seventy percent of subjects reported cleaning re-used needles at baseline with 40% using bleach. At follow-up the number of control subjects who reported re-using needles fell from ten to six. All reported cleaning re-used equipment, with only one using bleach.

Injecting Behaviour

Table 3.9: Frequency of injecting (any drug) in the past month

(%)	Treatment (n=17)		Control (n=14)	
	Baseline	**Follow Up**	**Baseline**	**Follow Up**
No injecting	6	12	-	7
Once a week or less	-	35	-	36
More than once a week (but less than daily)	35	41	64	43
Once a day	35	6	21	7
2-3 times a day	6	-	-	7
More than 3 times a day	18	6	14	-

As can be seen in table 3.9 there was a substantial change in self reported injecting frequency in both groups. Daily injecting declined in the treatment group from 59% to 12%, and from 35% to 14% in the control group. The proportion of subjects injecting "weekly or less" increased from nil in both groups at baseline to 35% (treatment) and 36% (control). However, only two subjects (one treatment, one control) actually ceased injecting altogether. Most subjects were injectors at baseline with the exception of one treatment subject.

3.3.4 Psychological adjustment

The GHQ provides a global measure of current psychological adjustment. It is made up of the following 4 sub-scales: Somatic symptoms, Anxiety, Social dysfunction and Depression. The scale has a range of 0-28 with 5 generally used as the cut-off point for the number of cases of psychopathology in any sample.

The mean GHQ scores in both study groups at baseline and follow-up fell into the clinical category of 'average' (bearing in mind categories were designed to classify opioid users).

At follow-up, improvements in psychological adjustment were noted in both groups but were not significant either within or between groups (t=-0.34, df=29, p=0.735). The proportion of treatment cases falling below the psychopathology cut-off point of 5 increased from 29% to 65%, while remaining stable at 43% among control cases.

3.3.5 Crime

The Criminality Scale of the OTI was used to measure property crime, drug dealing, fraud and violent crime committed during the month preceding baseline interview and follow-up interview. The scale has a range of 0-16. Higher scores denote greater criminal involvement.

Crime in the treatment group decreased and in the control group increased slightly although this difference was not statistically significant (t=-1.46, df=29, p=0.155). Crime reported involved mostly shoplifting, social security fraud and drug dealing (usually amphetamines).

3.3.6 Social functioning

The Social Functioning Scale of the OTI measures social adjustment, social support, and drug culture involvement over the preceding three months. The scale has a range of 0-48. Higher scores indicate poorer social functioning.

There were no statistically significant differences in the social functioning scale between groups at follow-up (t=0.92, df=29, p=0.37).

3.3.7 Drug expenditure

Daily expenditure on street amphetamine was estimated using the same method used for estimating subjects' street amphetamine use. Subjects were asked about the last three days on which they purchased street amphetamine for their own use. The intervals between days of drug purchase, and the amounts spent on those days, were used to estimate recent expenditure on street amphetamine. Four subjects were excluded from this analysis as they reported they were able to avoid payment for street amphetamine in the month prior to interview by obtaining street amphetamine through their drug dealing activities.

Treatment subjects spent significantly less on street amphetamine over the course of the study (t=2.4, df=15, p=0.03). Their estimated daily expenditure decreased from $52 (SD $32) to $22 (SD $30). Control subject daily expenditure also decreased from $38 (SD $30) to $22 (SD $36). This change was not significant due to the lower base (t=0.9, df=10, p=0.35). There were no differences between control and treatment for cost of habit at follow-up (t=0.14, df=26, p=0.89) but this may have been affected by selective attrition. Control subjects lost to follow-up spent an average of $104 on amphetamine daily compared to $40 for treatment cases lost to follow-up.

Average weekly expenditure on street amphetamine based on these daily estimates declined in the treatment group from $363 to $157 representing a reduction of $206 per week or $2,474 over the 12 week course of the study. In the control group, weekly expenditure declined from $266 to $158, a weekly saving of $107 or $1,291 over the 12 week course of the study. 'Saving money' was nominated as a benefit of research participation by the largest number of treatment subjects at follow up (See 3.9).

3.3.8 SDS Scores

Reduction in the SDS Score for both groups was the most dramatic improvement noted for both groups (Treatment t=-5.71, df=16, p<0.001; Control t=-4.66, df=13, p<0.001) although there was no difference between groups at follow-up (t=-1.37, df=29, p=0.182). The proportion of subjects with scores less than or equal to 4, estimated as the cut off for severe amphetamine dependence, increased from nil to 59% in the treatment group and from 7% to 36% in the control group. Control subjects with higher SDS scores and treatment subjects with lower SDS scores were lost to follow up representing a potential source of selective attrition bias (see Losses to follow-up 3.5).

3.3.9 Health

The Health Scale of the OTI is a symptom check-list designed to assess subjects current state of health. The scale is divided into items covering each of the major organ systems, with one section specifically focusing on injection-related health problems. The scale has a range of 0-52. Higher scores indicate poorer overall health. There was no significant difference between groups at follow-up on this scale (t=-0.23, df=29, p=0.82).

3.4   Other drug use

Use of other drugs was monitored by urinalysis and self-report. Each urine sample collected through the course of the study was subjected to a full drug screen. Treatment and control groups were compared at baseline, midpoint and follow up. Data regarding subjects use of other drugs were also recorded at the two OTI interviews at baseline and follow-up.

3.4.1   Other drug use detected by urinalysis

Table 3.10: Other drugs detected by urinalysis

	Baseline		Midpoint		Follow Up	
	Treatment (n=21)	Control (n=20)	Treatment (n=18)	Control (n=17)	Treatment (n=17)	Control (n=13)
No other drugs	62%	55%	39%	53%	53%	77%
Benzo-diazepines	14%	15%	6%	12%	6%	15%
Heroin	5%	0%	17%	6%	12%	15%
Cocaine	0%	5%	0%	6%	0%	0%
Pseudo-ephedrine	14%	30%	22%	35%	0%	8%
Methadone	24%	10%	22%	12%	35%	15%
MDMA	0%	10%	6%	6%	0%	0%

The lower level of cocaine positive urine samples compared to self-reported cocaine use may reflect the short window of detection of cocaine metabolites in urine samples which is similar to that of amphetamine (48 hours). The proportion of ephedrine and pseudoephedrine found in urines may be an impurity created by the manufacture of local illicit amphetamine. Ephedrine and pseudoephedrine decline sharply at follow-up consistent with reduced use of street amphetamine in both groups. The relatively high proportion of treatment subjects with methadone in urine samples may be a function of better retention of methadone patients in the treatment group.

3.4.2 Other drug use (self-report)

Table 3.11: Other drug use - OTI scores

	Treatment group		Control group	
	Baseline	Follow-up	Baseline	Follow-up
Drug type	Mean Score (n)	Mean Score (n)	Mean Score (n)	Mean Score (n)
Tobacco (cigarettes)	17.81 (16)	14.53 (15)	20.56 (9)	16.67 (9)
Cannabis (joints/bongs)	5.35 (13)	4.26 (13)	5.02 (11)	7.2 (11)
Alcohol (standard drinks)	2.82 (12)	1.47 (11)	3.7 (11)	3.64 (10)
Sedatives (pills)	0.7 (7)	0.12 (5)	3.7 (4)	4.2 (3)
Cocaine (hits)	0.55 (5)	0.42 (4)	0.64 (4)	0.66 (4)
Ecstasy (pills)	0.28 (3)	0.12 (3)	0.15 (5)	0.19 (6)
Heroin (hits)	0.08 (4)	0.12 (5)	0.04 (3)	0.07 (4)
Other opiates (hits)	0.14 (1)	0.48 (3)	Nil	Nil
Hallucinogens (tabs)	0.03 (2)	0.04 (1)	0.17 (4)	0.09 (3)
Inhalants (snorts)	0.14 (1)	0.1 (1)	0.35 (2)	0.12 (2)
Poly-drug Score	4.88	4.41	4.86	4.57

Data for other drug use were calculated for subjects who had used the drug in the past month. The small cell sizes for most drug groups preclude statistical analyses. However, there do not appear to be any major differences in other drug use between the two groups. The action of dexamphetamine substitution therapy, if any, would appear to be specific to amphetamine consumption. No changes in other stimulant consumption were apparent, although the use of cocaine and other stimulants was best characterised as recreational. A decline in alcohol

consumption in the treatment group and an increase in cannabis use in the control group was apparent, although the absolute number of subjects using each class of drug did not change markedly.

Other opiates refer to illicitly obtained methadone or morphine and not to prescribed methadone maintenance therapy. The high score for sedative use in the control group was caused by one outlier subject with exceptionally high use.

The poly-drug score was the number of drug classes subjects used during the month preceding interview including amphetamine, alcohol and tobacco. It can be used as a proxy for other drug use. No significant changes were noted in the number of other drug classes used either within or between groups.

3.5 Losses to follow-up

Six subjects from the control group and four from the treatment group were lost to follow-up. Contact was lost with seven subjects who were either untraceable or failed to respond to repeated messages. Two subjects moved away from Sydney. One subject withdrew from the study after being allocated to the control group.

Table 3.12: Losses to follow-up – Comparison of treatment and control

	Study Group at baseline (n=31)	Lost to follow-up Treatment group (n=4)	Lost to follow-up Control group (n=6)
Age (years)	28.4	26.5	32.5
Duration of amphetamine Use (years)	10.0	5.8	10.8
SDS score (mean)	10.7	8.3	11.2
OTI scores			
Amphetamine use	2.0	1.5	4.0
Social	15	15.7	14
Cost of habit	48.5	40.8	104.1
Crime	1.2	0.5	0
Health	15.4	11	9.5

The baseline demographic characteristics for subjects lost to follow-up were comparable to those completing the study on age and most OTI outcome scores but differed on OTI scores associated with amphetamine use, cost of amphetamine use and length of use. No statistically valid analyses can be conducted on these data, given the small cell sizes. Three control subjects lost to follow-up spent between $100 and $187.50 per day on amphetamine and reported consumption 5 to 10 times per day. These subjects accounted for most of the

difference between the study group and those lost to follow-up. The failure to retain control subjects with relatively severe amphetamine habits may represent a potential source of bias. With regard to losses to follow-up among treatment subjects, the data supported the impression that younger users with shorter histories of amphetamine use were less likely to be retained in treatment.

3.6 Treatment group data

3.6.1 Adverse Events

No serious adverse events were reported in the treatment group. No psychotic symptoms were reported for any subjects. Two subjects ceased treatment due to side effects. Both ceased at low doses during the induction phase. One felt uncomfortable after receiving the first two doses although it was unclear whether this was due to the medication itself or the clinical setting. The second subject ceased treatment after seven days, complaining of agitation and aggressive behaviour. Dose reduction was suggested, but the subject preferred to cease treatment.

The only notable other side effect was insomnia reported by three subjects. In all cases disturbed sleeping patterns were pre-existing complaints. Medical staff recommended dose reduction and earlier dosing to avoid disturbed sleep. Other strategies included avoiding stimulants such as coffee and non-pharmacotherapies such as baths and natural compounds such as valerian and hot milk. Prescription drugs such as benzodiazepines were not recommended although over the counter preparations such as antihistamines were suggested. Counterbalancing this, several subjects reported improved sleeping patterns once illicit amphetamine use was substituted with dexamphetamine therapy.

3.6.2 Compliance

Of the twenty-one subjects enrolled into the treatment arm of the study, four were lost to follow-up (19%), two terminated treatment due to side effects (9%) and three ceased treatment early to attempt abstinence (14%) leaving twelve subjects (57%) who completed the twelve week course of treatment. Treatment retention over study period appears in Figure 3.2.

The mean number of days all treatment subjects were dispensed dexamphetamine was 45 (range 2 – 91) over a mean attendance period of 61 days (range 6 – 98 days). This represented compliance to daily attendance of 74% (range 27% - 99%). Subjects completing treatment (n=12) presented for amphetamine doses a mean of 67 days over a mean attendance period of 87 days representing a compliance of 77%.

Figure 3.2: Retention in treatment over study period (n=21)
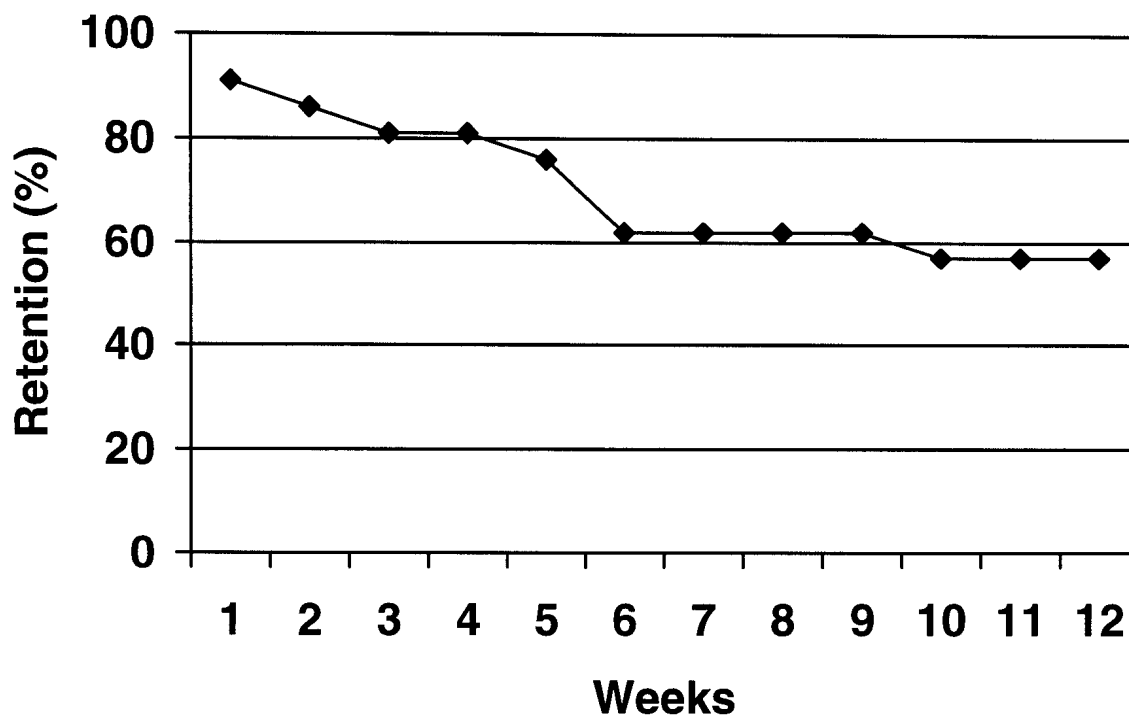
3.6.3 Dose Data

The mean daily dose of dexamphetamine received by all subjects was 49.4 mg (range 21.6 mg – 56.9 mg). Mean daily dose received was 52.3 mg (range 45 – 56.9 mg) for subjects compliant for the entire study period (n=12). These dose data include the induction and dose reduction periods.

The dose pattern at mid point may give a better picture of stabilised subjects. At week six, fourteen subjects were dispensed dexamphetamine. Ten received 60.0 mg every day during week six, three received 55.0 mg and one subject received an average of 22.9 mg indicating that most subjects remaining in treatment were stabilised at, or close, to the maximum dose.

3.7 Counselling

The number of counselling sessions subjects attended during the study period was obtained from subjects KRC records. Where subjects declined counselling, the Research Officer noted the reason.

Table 3.13: Uptake of counselling

	Treatment group (n=21)	Control group (n=20)
Attended KRC counsellors	57%	25%
Number of sessions	31	7
Mean	2.6	1.4
Range	1-7	1-3
Median	2	1
Reasons for non-attendance	**(n=9)**	**(n=15)**
- **Declined/failed to attend**	44%	73%
- **Other counsellor**	22%	7%
- **Work commitments**	11%	7%
- **Lost to follow-up**	22%	7%
- **Other referral**	0%	7%

Treatment subjects were significantly more likely than control subjects to attend counselling (χ^2=4.5, df=1, p=0.03) and attended more sessions. This outcome may have been affected by the higher proportion of females in the treatment group. Females accounted for 68% of counselling sessions attended by treatment group subjects. Most control subjects declined counselling or failed to attend counselling appointments. Some subjects declined counselling as they already attended counselling elsewhere or were unable to attend during clinic hours. No subjects attended regular weekly counselling sessions, most attended one or two sessions over the course of the study. Consequently no survival analysis was possible.

3.8 Cost of intervention

The costs of the intervention summarised here represent direct clinical costs and do not attempt to account for fixed or marginal costs of the health service. Research costs including subject payments, research personnel and data collection and analysis are not included.

Twenty-one subjects were in treatment for 182.9 person weeks. They attended 88 appointments with medical officers including the original assessment consultation and 31 sessions with KRC counsellors. One hundred and twenty-four urine samples were taken for analysis. Pharmacy handling charges were built into the study medication costs.

Clinical costs associated with the treatment are summarised as follows;

Study medication	$728	(9,432 5 mg doses @ 0.0772c per dose)
Medical Consultations	$2,640	(88 consultations @ $30)
Dispensing Costs	$1,908	(954 visits @ $2)
Counselling sessions	$620	(31 sessions @ $20)
Urinalysis	$1,860	(124 samples @ $15)
Total	$7,756	

Average clinical costs

Average clinical costs per person per week of $42.3 have been estimated by dividing total clinical costs by total person weeks in treatment for all subjects.

$$\frac{\text{Total clinical costs } (\$7,736)}{\text{Total person weeks } (182.9)} = \text{Average clinical costs per person per week } (\$42.30)$$

3.9   Comments by subjects at follow-up

At follow-up subjects were asked to comment on any benefits or problems they may have experienced whilst on the study. Sixteen treatment and thirteen control subjects provided comments on their experience. These comments have been summarised.

Problems

Treatment subjects reported the most difficulties with study participation. Side effects, travel difficulties, restricted dosing hours and concerns about withdrawal and the short study duration were all equally of concern with four subjects making comments about each problem area. No specific problem area attracted more than four comments. Confidentiality and tolerance were each of concern to two subjects. Two control subjects felt that the control condition did not offer them anything.

Benefits

In terms of benefits, 8 subjects (3 treatment, 5 control), reported 'a better understanding' of their amphetamine use. Five treatment subjects reported feeling either calmer, more confident or more 'in control'. Seven treatment subjects reported saving money as a benefit from the trial. Two treatment subjects (a couple) were able to secure stable housing due to reduced expenditure on amphetamine.

Six subjects (5 treatment, 1 control) reported ceasing amphetamine injecting as a benefit of participation in the study. Four subjects (3 treatment, 1 control) reported less injecting as a benefit. Two treatment subjects reported reductions in other drug use as a benefit. Two subjects (1 treatment, 1 control) nominated counselling as a benefit.

Treatment continuation

Subjects in treatment were asked whether they would continue treatment if it were available. Thirteen treatment subjects (81% of treatment subjects followed up) advised that they would continue treatment if available. Two treatment subjects would not have continued. No subjects were continued beyond the study period.

4. Discussion

4.1 Main findings

The primary aim of this study was to assess the feasibility, under field conditions, of urinary amphetamine isomer analysis to distinguish street from pharmaceutical amphetamine consumption in the context of the controlled prescribing of dexamphetamine to dependent users. Chiral analysis of baseline urine specimens revealed that street amphetamine consumption in this population of amphetamine users produced higher d:l isomer ratios than the expected 50:50 ratio found in the pilot study. The technique was, therefore, not able to reliably distinguish the source of amphetamine consumed in the treatment group from that used in the control group or for both groups at baseline where both were unexposed to the study medication. The technique was likewise unable to distinguish subjects in treatment who continued illicit amphetamine use from those who relied only on pharmaceutical amphetamine.

All baseline urine samples were, however, found to contain methylamphetamine isomers, which were not produced by pharmaceutical amphetamine and was not otherwise pharmaceutically available in Australia. The criterion used to detect illicit amphetamine consumption was changed to identifying the presence of methylamphetamine. This change in methodology did not affect the main aim of the study to monitor the controlled prescribing of amphetamine. This suggested that this population of amphetamine users was using methylamphetamine manufactured from ephedrine or pseudoephedrine, a finding also supported by the high levels of ephedrine and pseudo-ephedrine found in urine samples as an impurity. This phenomenon has also been noted in the United States (Malone, 1998; CSAT, 1999).

Interpretation of results

The results of this study should be interpreted with several caveats. The study was designed as a randomised controlled trial to examine the feasibility of urinalysis in reliably distinguishing persons consuming pharmaceutical amphetamine from those consuming street amphetamine or a combination of both. It was not designed to assess safety or efficacy aspects of amphetamine prescription. The limited sample size of forty-one and study duration of twelve weeks was inadequate to draw any definitive conclusions regarding efficacy. Potential sources of bias have been noted but no attempt to adjust results has been made. Sources of bias included selective attrition, incompatability of groups at baseline and differences in the frequency and timeliness of urine sampling.

An intention-to-treat analysis was adopted which compared subjects as assigned to study groups. Subjects lost to follow-up were not included in these analyses. Between group and within group comparisons on a series of variables were made. However, the total number of comparisons made was large and the risk of a type I error high. Comparability of self-report and urinalysis data was limited. Urinalysis was reported as a categorical variable while the OTI score was continuous. The time frame of the OTI was a four week estimate while urinalysis only detected drug use within the previous 48 hours. Subjects in the control condition were not required to attend regularly for medical monitoring after admission to the study. Consequently, the opportunity to detect fresh track marks, collect urine samples and self-reported drug use data was less than for treatment subjects. More regular and consistent

sampling in both groups would be needed in the design of any future effectiveness studies. Counselling representing "usual care" would ideally be more structured and standardised in an efficacy study. The results were sufficient, however, to indicate the feasibility of future studies of safety and efficacy.

4.2 Indications as to feasibility

4.2.1 Recruitment

One of the greatest challenges for the study was the recruitment of suitable subjects. A high proportion of potential subjects presenting for assessment for this study either failed to attend initial assessment interviews or failed to meet inclusion criteria for the study and were excluded or not interviewed. Recruitment targets for this study were achieved over a much longer recruitment period than originally anticipated. The target group was found to be small and geographically dispersed. Any future study will need to take this into account by using extensive recruitment efforts and, in Sydney at least, have a second clinical base located in a suburban area to allow subjects to present for daily dispensing. Difficulties experienced in recruitment may indicate this was a difficult treatment group to access or that the demand for this treatment was not great. Although the use of paid advertising was effective in attracting a large number of enquiries, the use of selected needle and syringe sites was particularly effective in attracting suitable subjects. Any future study should involve these services as early as possible in the recruitment process.

During recruitment it became apparent that substitution therapy was not "irresistibly" attractive to recreational users or those who were not severely dependent. Many amphetamine users expressed interest in non-substitution therapies including withdrawal medication and counselling rather than continued consumption of amphetamine. The clinical environment and commitment to regularly attend for treatment was unappealing for some. This experience challenges the preconception that recreational users would be tempted by any prescription program to enhance their drug taking. The finding that only a small subset of amphetamine users may benefit from this treatment, was consistent with the small numbers who have entered similar programs in the UK (Fleming & Roberts, 1994; Pates, 1996; White, 1996). Both the risk of creating amphetamine dependence by treating non-dependent users and the risk of abuse of such programs would appear to be low.

4.2.2 Assessment

The assessment procedure and admission criteria successfully recruited long-term dependent amphetamine users. The forty-one subjects accepted into the study had amphetamine use patterns and histories consistent with chronic problematic use. These included injecting amphetamine on a more or less daily basis and an average history of use of 10 years. The study group was not necessarily representative of all amphetamine users relying as it did on subjects who were able to attend an inner city clinic on a daily basis. The relatively high proportion of gay or bisexual males (31%) may limit the generalisability of the study. Key demographic characteristics of the group differed from those found in previous descriptive studies of amphetamine users conducted in Sydney between 1992 and 1998 (Hando et al., 1997; Darke et al., 1998; Hall & Hando, 1994; Ross et al., 1994). Subjects were older (29 years compared to between 25 and 26 years) and had longer histories of amphetamine use (10 years compared to 7 years). The proportion of amphetamine injectors was higher (95%

compared to 64%) and frequency of use was greater than in these previous studies (median "nearly daily" use compared to "1-2 times per week"). A greater proportion were male (83% compared to between 53 and 67%). In previous research, males were found to be more likely to seek treatment. This possibly explains the higher proportion of males recruited (Hando et al., 1997).

Subjects also exhibited higher levels of amphetamine dependence as measured by the Severity of Dependence Scale. The mean score obtained for the sample at baseline was 10.4. The SDS scores for the sample were significantly higher than those obtained in previous studies of amphetamine users in Sydney which ranged from 4.3 (Ross et al., 1994), 4.4 (Hando et al., 1997), to 5.6 (Darke et al., 1998). These previous studies were mainly based on non-treatment samples. Thus, the higher SDS scores obtained in the present study support the findings of Hando et al., (1997) who found dependence to be a key factor in prompting help seeking. They are also consistent with the findings of Hall & Hando, (1994) who found dependence linked to higher levels of injecting amphetamine use. The scores were comparable to results from a London study by Gossop et al., (1995) which found elevated SDS scores among heroin users who had presented to treatment agencies compared to those who had never received treatment (means of 10.3 and 6.6, respectively).

These results were unsurprising given that chronic long-term users seeking treatment were targeted for the research.

4.2.3 Comparison with opiate users

The results of this study were consistent with the findings of Darke et al., (1998) who compared opioid and amphetamine users using the OTI and concluded that amphetamine users reported less severe harms than opioid users. Compared to opiate users the subjects in the present study were socially more functional and were more likely to be employed and have higher levels of education. Self-reported exposure to hepatitis C and criminal involvement were also lower. A relatively large number of older long-term heavy users were excluded due to psychiatric and physical illness which may suggest that the harms associated with long term use were under-estimated.

The question then is whether the OTI, an instrument designed to assess treatment for opiate users, is also relevant to assessing treatment for amphetamine users. The positive changes detected in this study over a very brief study period suggest that the OTI was of value in assessing the treatment of amphetamine users. However, changes in the OTI score which suggested larger declines in amphetamine use in the control group than in the treatment group, were inconsistent with reductions in injecting frequency and with the proportion of subjects reporting abstinence, which were all greater in the treatment group. The higher scores in the treatment group may be attributed to two outliers representing relatively heavy users i.e., the type of user who tended to be lost to follow-up in the control group.

Binge behaviour may have also accounted for the relatively high score in the treatment group at follow-up. The OTI was designed for estimating opiate use, a less variable and continuous pattern of use than the binge patterns adopted by many amphetamine users. The OTI score estimates mean use during the last binge (i.e., last period of use) and extrapolates this to the entire month. This method did not present a problem at baseline as regular amphetamine use was a study admission criterion. A problem may have arisen at follow-up where, for

example, subjects who reduced illicit amphetamine consumption from daily use to less regular use or lapses usually in the form of a binge, may have received inflated OTI scores. This problem has been commented on by other investigators (Lintzeris et al., 1996).

Future study designs should better reflect and capture the common binge use patterns. The temporal component of the OTI method could be modified to avoid this problem by including the days between the interview and last day of use. Alternatively, a 30 day diary could be completed by subjects.

4.2.4 Adverse events

Over the short period of treatment no serious adverse events were noted. Some treatment subjects experienced sleep disturbance which was, in all cases, a pre-existing condition. No psychotic symptoms were noted in the treatment group (who were carefully monitored by prescribers and dosing staff). This experience is consistent with UK studies of dexamphetamine substitution (McBride et al., 1997; White, 1996; Charnaud & Griffiths, 1998). The risk of psychotic symptoms developing in carefully screened and monitored subjects on this dose of dexamphetamine would appear to be low. No subjects were excluded simply on the basis of a positive CIDI psychosis diagnosis. All five potential subjects excluded due to a psychiatric condition had clearly described a history of psychiatric illness or were currently on psychiatric medication. Consequently a briefer instrument than the CIDI for assessing psychosis is recommended in conjunction with a mental health assessment by a doctor.

4.2.5 Acceptability to staff

An important feasibility concern was the acceptability of dexamphetamine substitution to health care providers at KRC. Health care professionals at the clinic reacted positively to the program which proceeded with minimal disruption to the centre's clinical services. Dosing of treatment subjects proceeded without incident via the centre's methadone program. Dexamphetamine was stored in the same safe as supplies of methadone. Dosing was also offered at Rankin Court methadone clinic without incident. Health workers welcomed the opportunity to engage this group of drug users with counselling and other health services. The risk of diversion was reduced by supervised dosing and crushing dexamphetamine tablets which were taken with orange juice. No incidents of diversion either by staff or subjects occurred from the KRC program.

4.2.6 Cost of intervention

Costing data suggest that this was an affordable intervention. The direct clinical cost was estimated at $42 per treatment subject per week. The main components of clinical cost were medical supervision and supervised dispensing. This amount could be reduced for stabilised patients by improved flexibility of dispensing and monitoring. Following the UK experience, the aim of this intervention is withdrawal and abstinence from illicit use (Fleming, 1998). Thus for many patients, substitution therapy would not be a long or even medium term treatment. Subjects in the treatment group significantly reduced their expenditure on street amphetamine from $363 per week to $157. Given that many were employed, some patients could afford to contribute to the cost of treatment as is the case for private methadone patients in New South Wales who were estimated to have contributed between $40 and $50 per week

in dispensing fees in 1994 (Ward et al., 1998).

Other economic benefits for patients and the general community included reduced expenditure on illicit amphetamine, improvements in social functioning in areas such as employment and housing and reductions in crime. Employment and housing were not particular problems for the study group (unlike the situation for opiate users). Crime declined in the treatment group, albeit from a lower level than usually associated with opiate users. The long-term consequences of amphetamine dependence were not assessed by this study. These would include lost opportunities to develop careers and families, particularly in early adulthood, and potential costs to health services associated with treatment of long-term psychiatric and other chronic illness.

4.2.7 Acceptability to amphetamine users

The treatment was found to be acceptable to amphetamine users as evidenced by satisfactory levels of study retention and compliance in the treatment group. Study attrition was twenty-four per cent. Thirty per cent of control subjects and nineteen per cent of treatment subjects were lost to follow-up. In the treatment group, sixty per cent of subjects remained in treatment for the full twelve weeks. Retention compares favourably with a recent double blind trial of buprenorphine and methadone maintenance where retention of 50% and 59% respectively was reported at 13 weeks (Mattick et al., 1999). Compliance to daily attendance for doses while in treatment was seventy-four per cent. The majority of treatment subjects were stabilised at the maximum study dosing level. Eighty per cent of subjects in treatment, when asked at the follow up interview, indicated that they would continue in treatment if this option were available.

Barriers to treatment

The main barriers to treatment were the location and hours of KRC. These aspects could be a problem for any clinically based program. Dispensing was offered at Rankin Court, a nearby methadone clinic, for early morning dispensing to accommodate subjects working nine to five. Takeaway dispensing could be considered for carefully selected, stable and compliant subjects in order to improve the flexibility of treatment. Any takeaway protocol would need to include careful screening, approval and rigorous monitoring procedures. Takeaway times, whether they cover weekends, alternate days or special circumstances, would also have to be considered along with the risks posed by subjects injecting and diverting any takeaway drug. Flexibility could also be improved by the use of local general practitioners and pharmacies to dispense and monitor stabilised patients.

Control group

The reaction of subjects to allocation to the control condition was generally negative. However, only one subject withdrew from the study after objecting to allocation to the control group. The control group was variously perceived by subjects as offering no treatment or as a conspiracy. These sentiments may have reduced recruitment. An element of 'resentful demoralisation' may account for the low utilisation of counselling by the control group (Cook & Campbell, 1979). Rates of attrition between control and treatment were not significantly different. Although the numbers were too small to make definitive conclusions, losses to follow-up in the control group may have introduced an element of selective attrition

bias. That is, users who consumed more street amphetamine more regularly at baseline, were lost to follow up in the control group but were retained in the treatment group. Urine samples were taken less often in the control group than the treatment group. Access to follow-up the control group was much more difficult. This may have affected urinalysis results as control subjects may have been more likely to present during a recovery period than treatment subjects.

Given these problems and the desirability of a non-biased control group future efficacy trials should consider alternative control conditions such as cross-over or wait-list designs, sub-therapeutic doses or a placebo group.

4.3   Indications as to efficacy

4.3.1   Amphetamine use

At follow-up, subjects in both groups had reduced their consumption of illicit amphetamine. Urinalysis indicated that use had halved in both groups with 52.9% of treatment group urine samples and 61.5% of control group samples, positive for illicit amphetamine. These outcomes may be compared to a recent double blind trial of buprenorphine and methadone maintenance where the proportion of morphine positive urine samples was estimated at 58% and 54% respectively at 13 weeks (Mattick et al., 1999). Reduced street amphetamine use detected by urinalysis was consistent with self-reported changes. The reduction was not statistically significant by either measure in either group. Self-reported amphetamine use differed from the urinalysis results in so far as the fall in use was greater in the control group (over 50% decline in frequency of use) compared to a more modest decline of 25% in the treatment group. The proportion of subjects reporting no street amphetamine use was, however, higher in the treatment group (23.5%) compared to the treatment group (7%).

Reduced street amphetamine use was paralleled with reduced injecting frequency reported by both groups. The percentage of treatment subjects reporting daily injecting of any drug declined from 59% to 12%, compared to a decline from 35% to 14% in the control group. The reported level of needle sharing was too low to identify any intervention impact. Low levels of self-reported sharing of injecting equipment could indicate high utilisation of needle and syringe services among this group, the impact of other harm minimisation policies or under-reporting due to social desirability bias. It may also be a reflection of the relatively high education levels and social functioning of this group compared to other drug using populations. What actually caused these changes in illicit use cannot be determined by this study but some of the following factors may have been influential.

Treatment effect

Subjects in both groups were motivated to change their amphetamine use. The assessment procedure functioned as a motivational interview and was the first time some subjects had made contact with treatment services regarding their amphetamine use. This 'treatment effect' could explain the improvements noted in both groups. Counselling representing usual care was offered to both groups with treatment subjects significantly more likely to attend counselling sessions. However, it would appear that the control group was able to achieve improvements without pharmaco-therapy or counselling. The impact of selective attrition bias, although not adjusted for in this study due to small sample size, may have removed

many of the more severely dependent cases from the control group who may have been retained in the treatment group. It is doubtful whether many subjects would have presented for treatment without the incentive of substitution therapy.

Spontaneous cessation & study duration

The natural history of long-term amphetamine use, an important factor in treatment, is poorly understood. It could be argued that users are capable of ceasing use without intervention. Hando et al., (1997) found that 80% of a sample of 200 regular amphetamine users were able to reduce use without help. This effect has also been described as the 'maturation effect' - essentially young, recreational users grow out of their amphetamine using phase (Wickes, 1992; Myles, 1997). It could be argued that reductions in illicit amphetamine use in both study groups was attributable to 'spontaneous' cessation. This phenomenon was commented on by Charnaud & Griffiths (1998) as a possible factor explaining why patients in a dexamphetamine substitution program were much more likely to be discharged for non-attendance compared to patients in a methadone maintenance program.

Alternatively, older long-term users may have episodic patterns of use characterised by cycles of crises, recoveries and relapses. Such subjects are more likely to present at times of acute crisis which may explain the dramatic changes in SDS scores obtained for all subjects between baseline and follow-up as a regression to the mean. Whether treatment can break the cycle of problematic amphetamine use, prevent relapses and minimise short and long-term harms can only be assessed by a longer and larger study. Stabilisation of patients on dexamphetamine therapy has been estimated to take up to nine months (Fleming, personal communication, September 1997). Mean time to discharge in the Charnaud study was 10 months at which time 70% of subjects prescribed oral dexamphetamine had ceased injecting. This compares to 67% of subjects prescribed oral methadone who ceased heroin use in a similar period. Clearly a 12 week study period is insufficient to judge whether treatment and control subjects were successful in maintaining reduced illicit amphetamine use and associated harms. Urinalysis detected large declines in illicit use in the treatment group in the final six weeks of the study but these results were not sustained at follow-up. It is unclear whether this loss of effect was due to the dose reduction which took place in the last two weeks of treatment, subjects reacting to the impending conclusion of the study, or simply chance. Urinalysis and self-report data from this study show a change in illicit use in the same direction.

Sample size

Whether this change is sustained or a difference exists between treatment and control can only be addressed by a properly designed efficacy trial with adequate sample size and duration of intervention and follow-up. The power of the present study was calculated at 0.08 which was not sufficient to reliably detect a significant difference between treatment and control based on urinalysis outcomes. A large sample size of 518 per group was estimated as necessary to reliably detect a difference based on the modest observed treatment effect size of 8.6%. Based on the more conservative approach of treating missing samples as treatment failures or "positive" (giving an effect size 13%), the power of the study was 0.14. The necessary sample size, based on this approach, was reduced to 198 per group. Given the outcomes of UK observational studies and recommended improvements in study design and treatment duration it may be feasible to evaluate efficacy using a sample size calculated

assuming a greater but more clinically meaningful minimum treatment effect of 20%. Similar power calculations based on a 20% difference in proportions of "positive" urine samples between treatment and control yielded a sample size of 98 per group. Adjusting for 25% attrition experienced in the present study, a sample of 120 per group yields a power >0.8 which is a more feasible number of subjects for a clinical trial.

Improvements in study design necessary for an efficacy trial include reducing sampling and attrition bias. Study retention could be improved by use of alternative study designs including waitlist, cross-over or placebo. Such approaches may overcome 'resentful demoralisation' in the control group and any treatment termination effect in the treatment group. A more structured and standardised counselling intervention may also improve retention and outcomes. Whether the modest treatment effect observed at follow-up, unadjusted for potential sources of bias, would persist in a longer study is uncertain. Nevertheless these figures do suggest that a definitive safety and efficacy trial would require a significantly longer, larger and probably multi-site study. The power calculations suggest that a treating missing samples as "positive" or treatment failures was a more feasible approach.

4.3.2 Other outcomes

With the exception of the uptake of counselling, there were no other between group differences on secondary outcomes of the study. There were significant improvements on several outcomes within groups and outcomes on all variables changed in a positive direction in both groups. Statistically significant improvements occurred in HIV risk-taking behaviour as measured by the OTI within both groups, reduced expenditure on illicit amphetamine in the treatment group, and reduced dependence as measured by the SDS in both groups. These outcomes are consistent with the reductions in amphetamine use detected by urinalysis and self-reported injecting behaviour. The significant improvement in SDS scores suggests that the compulsive component of amphetamine dependence was reduced over the course of the study. This is consistent with improvements in psychological adjustment as measured by the GHQ and the follow-up reports of several subjects commenting that they felt calmer and more in control of their amphetamine use. The SDS was not used as a clinical screening instrument for this study. Screening was based on the CIDI for DSM-IV described under methods. However, only one enrolled subject received an SDS score of 4 or less compared to 24% of excluded subjects. This suggests that the SDS can function as an effective clinical screen for amphetamine dependence, as suggested by Topp & Mattick (1997).

The elevated SDS scores at baseline may also be explained in part by the context in which the instrument was administered. Subjects presenting for assessment were interested in participating in the treatment group and may have overstated their dependence in order to have a chance of receiving the treatment medication. At follow up there was no such incentive to qualify for inclusion. Nonetheless, reductions in other variables previously associated with higher SDS scores, such as, frequency of amphetamine use, positive urine samples and injecting behaviour, are consistent with the reductions in SDS scores.

4.4 Conclusions

The principal conclusion from the present study is that it is possible to distinguish street from pharmaceutical amphetamine consumption by means of urinalysis. This technique has an important role in any future research in this area. It can be concluded from the results of the present study that it is likely that problematic amphetamine users can be attracted to and retained in substitution therapy. The risks associated with substitution therapy including adverse events, the enrolment of inappropriate subjects and diversion, appear to be low. The intervention appears to be affordable and acceptable to health care workers in the field.

The study design and measurements used in the present research proved to be feasible in detecting changes in amphetamine use and related harms over the brief study period. The results yielded by the various measures were consistent and pointed to changes in a positive direction. This is consistent with the positive impressions of clinicians in UK substitution programs. The results also suggest that this treatment seeking group is highly responsive to treatment as evidenced by improvements in both study groups over the short duration of the study.

The serious harms associated with habitual, long-term amphetamine use warrant investigation of all potential treatments. If substitution therapy is a useful intervention, it is likely to be only appropriate for a sub-set of amphetamine users who experience the most severe physical and psychological consequences of long-term, chronic amphetamine use. Ultimately the most effective approaches to drug dependency consist of a range of options tailored, by appropriately trained medical practitioners, to the particular needs of individuals. Substitution therapy deserves further consideration as one of the range of interventions for problematic use, including counselling and medication for withdrawal.

The results of this study suggest that a multi-site randomised controlled trial of the efficacy of amphetamine substitution therapy be undertaken before this practice becomes too widely available (as has occurred in the UK). The time and effort required to conduct such a trial should not be underestimated.

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