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Substitution therapy for amphetamine users

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At the commencement of the third millenium, the illicit use of amphetamines continues to be a growing problem in many countries around the world, yet treatment responses remain in need of further development. This is particularly true with regards to pharmacotherapy for amphetamine dependence. In this Harm Reduction Digest four authors who bring together considerable research and clinical experience in this area describe the nature of amphetamine-related problems and consider the role of amphetamine agonists in substitution therapy for amphetamine dependence. This is a timely paper which should be of interest to clinicians, researchers and regulators.

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Overview

While illicit amphetamine consumption and associated problems have increased steadily in many countries (including Australia) during the last decade, there has been a relative dearth of research into effective treatments, particularly for severely dependent users who are most vulnerable to the serious adverse consequences of illicit amphetamine use. It is likely that amphetamine-related harms disproportionately accrue to a minority of severely dependent amphetamine users, yet their relatively small numbers and treatment resistance may have resulted in this group being overlooked as a public health policy priority. Several forms of substitution therapies that aim to replace harmful illicit drug use with safer, legal pharmaceutical maintenance have been demonstrated to be safe and effective treatments for drug dependence. Although there is limited scientific evidence to support safety and efficacy, substitution therapy for amphetamine users has won a degree of clinical acceptance in the United Kingdom. Research into the rationale, safety and efficacy of substitution therapy for amphetamine dependence is at an early stage and is limited by the relatively few trials of generally observational nature, small numbers of patients and lack of controlled findings. However, the evidence to date consistently supports an expansion of efforts to evaluate this intervention. The natural history of amphetamine use and dependence involves a complex interplay of biological, psychological and social factors. Further controlled investigation of substitution therapy in combination with psychosocial interventions for severely dependent amphetamine users is indicated to assess the safety and efficacy (and later the cost-effectiveness) of this intervention in improving outcomes for selected amphetamine users.

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Trends in amphetamine use

Since first synthesized in 1887, amphetamine has had an enduring history of military, occupational, subcultural, recreational and therapeutic use [1]. At the dawn of the twenty-first century, epidemics of illicit amphetamine use have recently commenced or worsened in Asia, the Pacific, North America and Europe, perhaps reflecting the shift from plant-based drugs such as heroin to synthetic drugs like amphetamine [2]. Globalization, expanding trade and business networks and the accelerated pace of technological innovation and dissemination have driven an expansion of inexpensive, high purity and readily obtainable illicit amphetamine in Australia, the Asia Pacific region and internationally. Methamphetamine, the most potent amphetamine derivative, is the most commonly produced and consumed form of illicit amphetamine in Australia, Asia and North America. It is available in pill form, capsules, powder, oily base and crystalline form ('ice', 'shabu', crystal meth'). Depending on the formulation, the drug may be taken orally, intranasally, smoked or injected. In Australia, methamphetamine is produced predominantly using a simple manufacturing technique based on diverted pharmaceutical supplies of pseudo-ephedrine [3]. Easy access to precursors, production skills and materials, lower output of noxious fumes, fewer unstable by-products and smaller laboratories has increased the availability of methamphetamine and made control of supply increasingly difficult [4].

Australia has one of the highest per capita levels of non-prescription amphetamine use in the world [2]. The 1998 National Drug Strategy Household Survey estimated 3.7% of Australians aged 14 years or older had used non-prescription amphetamine in the previous 12 months, with 8.8% reporting lifetime use [5]. The age cohort 20–29 years had the highest lifetime prevalence of amphetamine use at 21% (increased from 16% in 1995) with prevalence of recent use (last 12 months) at 12% (increased from 7%). Most amphetamine users were male (outnumbering females 2:1), single and unemployed consistent with most previous studies [6]. It was estimated that 75 000 (or 70%) of injecting drug users injected amphetamine in 1998, with 51% reporting initiation to injecting drug use with amphetamine. Based on aggregated data from 1985 to 1995 it was estimated that 26% of people who had lifetime experience of amphetamine used the drug once a month or more [7]. More recently, the Illicit Drug Reporting System, an early warning system monitoring emerging drug trends, has identified increases in the prevalence of amphetamine use among injecting drug users across all states and territories since 1999 [8]. Recent heroin shortages in Australia have also seen a trend towards polydrug use of methamphetamine and cocaine among heroin injectors [9]. The proportion of people presenting to drug and alcohol services with primary amphetamine problems in Australia increased between 1995 and 2001 from 6.5% to 8.8% [10].

Nature of amphetamine-related harms

Amphetamines are central nervous system stimulants, which act by increasing synaptic concentrations of monoamine neurotransmitters in the brain. Amphetamine and cocaine bind to three major monoamine transporters: dopamine, serotonin and nor-adrenaline; but it is the action at dopamine transporters which is the principal reinforcing mechanism of psychostimulants [11]. A growing body of preclinical data also indicates that amphetamine at high doses has the potential to cause long-term changes to dopamine neurones [12]. Amphetamine use induces a sense of well-being, energy, euphoria, confidence, alertness and sexual arousal. Therapeutically, amphetamine-based preparations have been used as appetite suppressants, decongestants, for treatment of attention deficit hyperactivity disorders and sleep disorders. Although deaths are rare, and usually attributable to accidents and hypertensive or cardiovascular complications, substantial morbidity is common. Adverse consequences of chronic high-dose amphetamine use include psychological morbidity especially psychosis, dependence, medical complications, financial problems and other social problems [13]. The risk of these harms may increase depending on how the drug is taken (higher for injectors and smokers), drug purity and frequency of use. Injecting amphetamine users are at additional risk of exposure to blood-borne infections (including HIV and hepatitis B and C) [14], transitions to heroin use [15] and amphetamine dependence [16]. Amphetamine withdrawal has been characterized by cravings, depressed mood, agitation, anxiety, poor concentration, low energy, dysphoria and insomnia. The risk of developing dependence with amphetamine has possibly been underestimated due to comparisons with other drugs such as nicotine, opioids and cocaine. Amphetamine withdrawal may be milder than opioid withdrawal, with fewer severe physical problems, and may also be shorter; however, it appears to be sufficient to support a chronic, harmful and relapsing condition.

Current treatment services

Barriers to treatment for amphetamine users are high. There are no specific services and no recognized pharmacotherapies with treatment services perceived by amphetamine users as focused on assistance for people using opioids or alcohol [17]. Attracting and retaining amphetamine users in treatment is notoriously difficult. Lack of recognized effective treatments and

consequent lack of experience in treatment services to deal with amphetamine-related problems might well reinforce users' perceptions that treatment has little to offer, or worse, that amphetamine use is not a serious problem. A history of short binges or episodic use patterns may also disguise extensive periods of chronic use and the long-term personal and social harms which are so often overlooked. These latter problems include lost educational and career development, opportunities to develop personal and familial relationships and the financial consequences of long-term amphetamine use [18]. Apart from acute intoxication and amphetamine-induced psychosis, treatments for problematic amphetamine use, dependence and withdrawal have relied on psychosocial interventions. There is a dearth of amphetamine-specific treatment research and most reviews rely heavily on cocaine treatment studies conducted in the United States [19]. Generally the experience of cocaine treatment research has been very disappointing with high attrition rates, low follow-up rates and inadequate measurement of outcomes [20]. Psychosocial interventions in the form of cognitive behavioural therapy, therapeutic communities, self-help groups and other psychological interventions have shown some success among cocaine users [21] but few randomized controlled have been trails have been conducted among amphetamine users [22]. Pharmacotherapies, at least for cocaine, fare even worse, with recent Cochrane reviews finding the most commonly prescribed antidepressants, dopamimetics and anticonvulsants ineffective in reducing cocaine use as measured by positive urine analysis [23].

Substitution therapy rationale

The initial objective of substitution therapies for substance dependence is to replace harmful illicit drug use with a safer, licit pharmaceutical drug to achieve where possible a stable dose, avoidance of contaminants, reduced frequency of use, improved physical and psychological outcomes and benefits from a less hazardous route of administration. Substitution therapy aims to stabilize patients on a dose that prevents withdrawal and cravings and reduces substantially the risk of serious adverse consequences. Substitution therapies are recognized as highly effective for drugs such as nicotine [24] and heroin [25] where drug use is frequent (usually daily), associated with a hazardous route of administration (smoking and injecting), potential complications are severe (cancer, cardiovascular, HIV/hepatitis B and C, overdose) and achievement of abstinence by other methods is problematic. Once drug use is stabilised, treatment engagement may provide drug users with the psychosocial skills, support and experience to protect against relapse and ultimately and where possible achieve a drug-free lifestyle.

The potential benefits of substitution therapy for problematic amphetamine users according to Fleming (1998) [26] may include:

(1) Attraction and engagement of a broad range of problematic amphetamine users into treatment. Many users expressing initial interest in replacement treatment may subsequently be attracted into other forms of therapy.
(2) Amphetamine prescribing programmes recognize the gravity of amphetamine-related problems and send an important message about the potential dangers of amphetamine to users of the drug.
(3) Engagement of amphetamine users in treatment gives health-care professionals the opportunity to provide harm reduction advice and other services, including needle syringe programmes as well as other health care monitoring, advice and referral.
(4) Initial reduction and ultimate cessation of amphetamine use and reduced injecting are likely to reduce associated health, social and psychological harms.
(5) The risks of continued amphetamine use including long-term physical and psychological problems and blood-borne viral infections probably outweigh the small risks of prescribing amphetamine.

The intensity and chronicity of the subjective effects of central nervous system stimulants are important reinforcing characteristics of dependent use that vary according to the form, dose and route of administration of amphetamine. Dopamine depletion and sensitizing of dopamine receptors after chronic, long-term stimulant use has been postulated as the neurological basis of amphetamine and cocaine dependence [27]. Research into the neurobiological effects of cocaine and methylphenidate has provided insights into the neurological action of central nervous stimulants and the subjective experience of users which may have implications for potential stimulant agonists. Volkow and colleagues [28] used positron emission tomography to demonstrate that intravenous methylphenidate reached peak dopamine transporter occupancy within 9 minutes compared to 60 minutes for oral methylphenidate, after which brain concentrations cleared at the same gradual rate with a half-life of >90 minutes after peak uptake. The rapid onset of blockade of the dopamine transporter, rather than the subsequent continuous blockade, was associated with the subjective drug-induced 'high'. Volkow concluded from these data that the apparent low dependence liability of oral methylphenidate was due to the gradual onset of the drug's stimulatory effects. Put simply, oral methylphenidate did not produce the rush recreational drug users seek or the crash dependent drug users seek to avoid. In the language of dependence, it had weak 'appetitive and aversive' reinforcement. In comparison, cocaine reaches

peak dopamine transporter occupancy within 4 minutes and has a rapid rate of clearance (20 minutes from peak uptake) [29]. Similarly, cocaine transporter occupancy and subjective response has been found to vary by route of administration (more rapid for smoked than injected or intranasal) and by dose (for injected and intransal use) [30]. Further evidence in support of this hypothesis comes from Abreu *et al.* [31], who found that the subjective response to cocaine varied according to the rate of intravenous infusion.

If the dependence liability of stimulants varies according to dose, form and route of administration, then stimulants with significantly lower dependence liabilities may be suitable agonist candidates for treatment. Potential agonists must demonstrate efficacy in reducing amphetamine cravings and withdrawal symptoms triggered by dopamine deficiency syndromes at doses that are safe, do not cause hyperstimulation and from which users ultimately may comfortably reduce and cease therapy. In support of this proposition, patients receiving dexamphetamine in our clinical experience could reduce and cease dexamphetamine programmes very comfortably with no evidence of withdrawal. Further, we also did not find evidence of hyperstimulation among amphetamine-dependent patients receiving dexamphetamine.

History of amphetamine prescribing

Negative reports of amphetamine prescribing in the United Kingdom and Sweden in the 1960s and 1970s discouraged consideration of amphetamine prescribing for over two decades [32–34]. These early reports found only modest benefits outweighed by severe adverse consequences including psychosis, continued injecting use and diversion. Many of these early programmes involved the provision of injectable methamphetamine and all involved unsupervised consumption and limited measurement of outcomes. The provision of oral dexamphetamine treatment has increased slowly in England and Wales due to the resurgence of amphetamine use and the emergent threat of blood-borne viral infections such as HIV and hepatitis C among injecting drug users. Dexamphetamine programmes have existed in England and Wales for over a decade and have treated well over 1000 amphetamine users [35] and, although there is little scientific evidence to support the practice, the impression of clinicians appears to be generally positive.

Most studies of dexamphetamine replacement published to date have relied on self-report or case-note reviews and have lacked adequate control groups to confirm findings. Early observational reports described prescribing experiences in small groups of patients. One of the first observational reports published by a general practitioner [36] concerned the progress of 13 heavy, long-term intravenous amphetamine users in Melbourne, Australia who were prescribed 20–90 mg dexamphetamine supervised daily. About half of the participants were thought to have become drug-free (although this was never confirmed by urine analysis). The patients reported that dexamphetamine decreased drug craving and symptoms of amphetamine withdrawal. One male patient (age 40 years) from this group is still maintained on prescription dexamphetamine. He sought treatment in 1990 for amphetamine dependence of 5 years' duration. He was commenced on oral dexamphetamine, stabilized on 55 mg/day and has been successfully maintained for 12 years with no evidence of intravenous drug use or adverse side effects. The patient presents as fit, contented and productive with a stable marriage, four children and a successful professional business. A growing number of UK observational and quasi-experimental studies have consistently found evidence to support substitution prescribing in terms of safety, efficacy and achievement of harm reduction objectives. Fleming & Roberts (1994) [37] reported on 26 long-term intravenous amphetamine users in Portsmouth, England prescribed 30 mg oral dexamphetamine daily. They reported that over half had ceased injecting amphetamine while those who continued to inject had reduced the frequency of their injecting fivefold. Although no tests of statistical significance were provided, the authors also noted considerable reduction in criminal activity and in the sharing of injecting equipment. Pates *et al.* [38] described a similar reduction in amphetamine injecting and criminal activity in a small pilot study involving 10 intravenous users recruited in Cardiff, Wales.

Three retrospectively controlled studies, one randomized controlled trial and one large cohort study have since appeared. McBride *et al.* [39] retrospectively evaluated an existing programme in Mid Glamorgan, South Wales ($n = 63$) with a smaller control group of 23 amphetamine users who had attended the service prior to the commencement of dexamphetamine prescribing. Experimental subjects, who received up to 40 mg dexamphetamine daily, had statistically significantly more contact with services and reduced amphetamine injecting compared to controls. Charnaud & Griffiths [18] conducted a retrospective comparison of discharge notes for 60 primary amphetamine users (mean dose of 43 mg dexamphetamine daily) and 120 primary opiate users prescribed methadone (mean dose 44 ml daily). They concluded that dexamphetamine was at least as effective among amphetamine users as methadone for heroin users in reducing injecting behaviour, with 70% of discharged amphetamine users displaying no physical evidence of injecting compared to 67% of methadone patients. Klee *et al.* [40] while examining the effectiveness of treatment services for amphetamine users in North West England, case

matched a sub-group of patients prescribed dexamphetamine with patients not receiving a prescription (n = 12 matched pairs). They found significantly greater treatment retention in the dexamphetamine group; however, greater reductions in the amount and frequency of reported illicit amphetamine use did not reach statistical significance possibly due to the small sample size.

The first published randomized controlled trial was conducted by Shearer *et al.* [41] in Sydney, Australia, and this compared 21 long-term dependent amphetamine users receiving 60 mg dexamphetamine daily to a control group of 20 similar users, both groups receiving standard drug counselling. Although this feasibility study was limited by small sample size, both groups were found to respond positively to intervention with reduced injecting, reduced methamphetamine-positive urine samples and reduced severity of dependence. The only statistically significant between-group difference was in the uptake of counselling, which was greater in the treatment group. Between-group differences, while failing to reach statistical significance, were in the direction of treatment benefit. A definitive RCT was considered feasible and warranted. White [42] reported on the 4-year experience of a large cohort of 148 amphetamine users in Cornwall, England, prescribed up to 90 mg dexamphetamine elixir daily (mean dose 45.2 mg). The most notable outcome was a rapid 50% reduction in injecting behaviour achieved over an average of 2 months in treatment. White noted a high treatment dropout rate of 34%, a finding also reported by Charnaud & Griffiths.

Safety and feasibility issues

The selection of an appropriate agonist involves weighing risks against benefits of cessation of hazardous drug use. The development of psychotic symptoms is the most serious potential adverse consequence of dexamphetamine replacement therapy. Screening and monitoring for psychotic symptoms is integral to any prescribing programme. Exclusion of patients with a history of schizophrenia or bipolar affective disorder has been recommended [43]. Screening may be complicated by non-disclosure, as well as the common experience among amphetamine users of drug-induced transient psychotic symptoms and brief psychotic episodes. A history of drug-induced psychotic episodes may also make an individual more vulnerable to future amphetamine-induced psychotic episodes [44]. None of the studies described so far have reported first psychotic episodes among patients, leading several investigators to conclude that the risk of psychotic symptoms developing was small with low-dose, orally administered dexamphetamine. McBride *et al.* [39], noted three episodes of psychosis among 63 patients over 2 years, both associated with additional use of high-dose illicit amphetamine. White [42] reported five cases of psychosis among 220 dexamphetamine patients over 4 years, all with previous histories of psychosis and continued injecting drug use. In such cases amphetamine induced psychosis remitted rapidly on cessation of prescribed dexamphetamine.

Diversion is another issue of concern but has not been found to be a serious issue in the UK programmes, where dispensing has been unsupervised [40]. There are certainly advantages in unsupervised dispensing in terms of treatment flexibility and accessibility for employed patients. However, the impact of even occasional incidents of diversion could damage the credibility of dexamphetamine programme in the general community. Dose supervision, urinalysis and regular medical monitoring for side effects at least during the first 3-month stabilization period provides a fully informed basis for assessing the individual effectiveness of substitution and the appropriateness of continued maintenance. Unsupervised doses may be appropriate for stabilized patients where medication compliance indicates that diversion is unlikely. Patient commitment to supervised treatment protocols may also protect programmes from unsuitable or poorly motivated patients who may merely wish to obtain additional sources of drugs. Other potential side effects include disturbed sleep, hypertensive crises, agitation and the potential for accidents. The relative risk of these side effects can be determined only through controlled trials comparing patients receiving prescribed amphetamine with controls. Sensible precautions may include exclusion of subjects who operate machinery or drive in the course of employment and subjects with a history of serious cardiovascular illness.

Substitution therapy may only be appropriate for severely dependent amphetamine users, most probably daily, injecting users, although this should not preclude heavy non-injectors from programmes or studies. Ultimately, the most enduring treatment benefits are likely to be achieved by a combination of some form of pharmacotherapy in combination with a psychosocial intervention. We found that health-care professionals providing psychosocial interventions welcomed the opportunity to work with amphetamine users who had previously been difficult to attract or retain in treatment [41]. A parallel may be drawn with effective combined psychosocial and pharmacological treatment for nicotine and alcohol dependence that have demonstrated additive effects [45]. As mentioned previously, the existence of substitution programmes may be sufficient to increase contact with a wide range of problematic amphetamine users, most of whom will not need maintenance therapy. In severely dependent cases, substitution therapy may contribute to building therapeutic relationships through the motivational

aspects of assessment and the acknowledgement of the physical basis of cravings and dependence. Substitution therapy is not inconsistent with the goals of many psychosocial therapies, including cognitive behavioural therapy [6]. The duration of amphetamine substitution therapy may not need to be as long as methadone maintenance for heroin dependence; indeed, the relatively high rate of dropout and early drug-free discharge noted in several studies may be viewed as positive. This would be best assessed through adequate follow-up with analysis based on intention-to-treat principles. Short to medium term substitution combined with provision of relapse prevention and coping skills may offer more enduring benefits and help to achieve improved outcomes.

Dexamphetamine prescribing does not appear to increase the use of other drugs. Specifically no adverse interactions in patients concurrently receiving methadone have been noted. Increasing polydrug use among heroin injectors and methadone patients is a concern where it may undermine previously successful harm reduction strategies, particularly with regard to blood-borne infections. No specific problems with the six methadone patients in our original randomized controlled trial were noted and more recently we have completed a placebo-controlled trial of dexamphetamine for cocaine dependence which included 24 methadone patients. No apparent effect was noted on methadone dose, metabolism or opiate-specific efficacy [46]. Dexamphetamine replacement has also shown promise for cocaine dependence which has similar effects on dopamine transporters. In a three-arm trial (n = 128) including placebo, 15–30 mg d-amphetamine and 30–60 mg d-amphetamine groups, Grabowski and colleagues at the University of Texas [47] found dose-related changes in retention and cocaine use in favour of dexamphetamine treatment with no serious adverse events.

Previous studies have been limited by small sample sizes. The difficulty of recruiting subjects from this population should not be underestimated. Binge patterns do not encourage users to attend services because of chaotic lifestyles, while during recovery phases many seem to judge that treatment is not warranted. Attempting to recognize and break chronic relapsing patterns of amphetamine use, often occurring over many years, is challenging for both users and clinicians. Urinalysis monitoring of treatment compliance and efficacy can be achieved using detection of methylamphetamine as a marker of street amphetamine as methamphetamine is not a metabolite of dexamphetamine [48]. This technique is effective where illicit amphetamine is predominantly the methylamphetamine form, such as in Australia, Asia and North America. In Europe, where amphetamine sulphate is the predominant illicit form, chiral analysis of urinary amphetamine isomers can distinguish therapeutic from illicit amphetamine [49]. However, the composition of illicit amphetamine varies according to local precursor controls and availability and may be subject to rapid change.

Conclusion

At the beginning of the new millennium, amphetamine use is more prevalent and less easily controlled than ever before. Technological, cultural, social and economic change has driven a recent relentless worldwide expansion of amphetamine use. An incomplete understanding of the natural history of problematic amphetamine use and the more obvious short-term harms associated with heroin use may have delayed a comprehensive public health response to widespread amphetamine use. The advent of polydrug use has refocused public health attention towards effective treatments for amphetamine users, particularly dependent and injecting users. The efficacy of substitution therapy is not known, even though the practice appears to have gained a degree of clinical acceptance at least in the United Kingdom. The literature is not extensive and controlled trials are few. There is a strong and growing case for rigorous evaluation of substitution therapies combined with tailored psychosocial interventions to achieve improved outcomes for amphetamine users.

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