Interventions for Amphetamine Misuse

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and

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WILEY-BLACKWELL
A John Wiley & Sons, Ltd., Publication

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This edition first published 2010

Blackwell Publishing was acquired by John Wiley & Sons in February 2007. Blackwell's publishing programme has been merged with Wiley's global Scientific, Technical, and Medical business to form Wiley-Blackwell.

Registered office
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom

Editorial offices
9600 Garsington Road, Oxford, OX4 2DQ, United Kingdom
2121 State Avenue, Ames, Iowa 50014-8300, USA

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Library of Congress Cataloging-in-Publication Data

Interventions for amphetamine misuse / edited by Richard Pates and Diane Riley.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4051-7558-6 (pbk. : alk. paper) 1. Amphetamine abuse. I. Pates, Richard. II. Riley, Diane M. (Diane Mary), 1953-
[DNLM: 1. Amphetamine-Related Disorders–therapy. 2. Amphetamine-Related Disorders–complications. 3. Amphetamine-Related Disorders–epidemiology. 4. Amphetamines–therapeutic use. 5. Cross-Cultural Comparison. WM 275 I61 2010]
RC568.A45I58 2010
362.29'9–dc22

2009007670

A catalogue record for this book is available from the British Library.

Set in 10/12.5 pt Sabon by Aptara® Inc., New Delhi, India
Printed in Malaysia

1 2010

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DEDICATION

This book is dedicated to my wife, Gemma, and my beautiful daughter, Cleo, for keeping me sane and alive during the past two years.

Richard Pates

ACKNOWLEDGEMENTS

We thank all the contributors who have given their time and extensive knowledge to help produce this book, to Gemma Wallace for her help in preparing the manuscript and to Katrina Hulme-Cross for her patience and wisdom in getting this book into production.

Chapter 1
INTRODUCTION

Richard Pates and Diane Riley

Amphetamine-type substances (ATS) are the second most commonly used drugs in the world (UNODC, 2007). Their use occurs across Europe, North America, Asia and Australasia, and in many places the use of these drugs can be problematic. The chapters in this book describe the nature of this drug, the effects of the drug and patterns of use in various parts of the world. Despite the widespread use of the drug and the problems that it may cause, there seems to be little consensus on effective treatment. One of the aims of this book is to review this international evidence and try to draw together examples of good practice. Opiates such as heroin and morphine are drugs which cause problems in many parts of the world, and there is now a widespread consensus on how effective treatment can be managed, usually by using substitute medication such as methadone. There is no similar pharmacological answer for the amphetamine group of drugs as yet, despite the magnitude of the problems they cause. Whether this is because there is no similar option for amphetamines compared to heroin or because the impetus to develop pharmacological treatments has not been seen to be of sufficient importance is open to debate.

The majority of amphetamine users are polydrug users. Benzodiazepines may be used to self-medicate amphetamine-related problems, and they are commonly used by amphetamine users (Darke et al., 1994). Heroin is also used by stimulant users to self-medicate (Hando et al., 1997), and there are reports of a significant association between daily alcohol intoxication and methamphetamine smoking (Furr et al., 2000). This means that polydrug use (and interactions with medications such as those for HIV) always needs to be considered as a possibility when considering interventions for amphetamine users (Baker et al., 2004).

Where and when did the problem arise?

As we will see in many of the chapters in this book, ATS have been regarded in different ways across the decades. They have been seen as drugs which are useful in times of war for keeping troops alert, as drugs used by both the Allies and Axis countries during the Second World War and still used today, as a useful tool for doctors, nurses, students, truck drivers and others to stay awake during long shifts, and as a partying drug for many young people to keep them awake during the long hours of pleasure.

Bett in 1946 suggested that there were at least 39 clinical uses for amphetamine, including treatment for epilepsy, schizophrenia, morphine and cocaine addiction, behavioural problems in children, and migraine. In America, at least, it had become widely accepted at that time by the medical profession as a useful drug. These days the clinical uses of ATS are very few, partly because of the lack of evidence of many of the conditions that were supposedly helped by the drug and also by the recognition of the drug's dependence potential and long-term psychological effects.

The Benzedrine inhaler was introduced in 1932 (Grinspoon and Hedblom, 1975) and this became a popular way of treating both the effects of asthma and even head colds, as one of the effects of amphetamine is to dilate the nasal and bronchial passages. The use of Benzedrine from these inhalers became an early form of the illicit use of amphetamine. In 1946, Harry 'The Hipster' Gibson recorded a song called 'Who Put the Benzedrine in Mrs Murphy's Ovaltine' (http://mog.com/dermahrk/blog_post/134472; accessed 16 August 2008), which was a humorous take on the effects of taking Benzedrine and the supposed benefits it gave the user. The song was banned from broadcasting in 1947 and Gibson was blacklisted by the music industry. This indicates the fact that the drug use was in the public consciousness in the middle of the twentieth century.

Jack Kerouac's novel *On the Road* written in 1951 and published in 1957 was a defining novel of the 'beat generation'. This remarkable book, written almost as a stream-of-consciousness novel about a journey across America, was written under the influence of Benzedrine, and the phrenetic tone of the novel gives the reader the impression of that speed culture.

In the 1990s the emergence of methamphetamine as a potent, smokeable form of the drug was seen as the latest 'scourge' blighting our society following the warnings that we had about the dangers of crack cocaine in the late 1980s. Methamphetamine has clearly become a drug of choice in some areas and has been associated with violent motorcycle gangs, both on the west coast of North America and in New Zealand, and concern has been registered about the dangerous amateur laboratories producing the drug. These laboratories are dangerous both because of the potential for violent explosions during the production of the drug and because of the toxic by-products of the drug.

What are the dangers?

Is amphetamine really a 'scourge' or is current concern about it just another moral panic? It is, after all, part of the same drug family that until the 1960s was widely prescribed as a tonic and a slimming aid by general practitioners in many countries including the UK and America. Many drugs have this Jekyll-and-Hyde history of being thought to be useful and benign in the early days but become diabolic in their reputation as time passes and the true or other effects of the drug are known. One difficulty in labelling a drug as 'dangerous' is that for many occasional users there have been no ill effects. A study by Pates and Mitchell (1996) surveying the use of the drug in South Wales in the UK found that some people used very small

amounts, taken orally, on an occasional basis and experienced few problems with it. Other people surveyed were injecting up to 14 g/day and experiencing a host of psychological effects as a consequence.

What is clear is that these drugs, which have been used routinely by many people for purposes of alleviating fatigue in a work situation or for recreational purposes often without report of problems, are not benign. Chapter 2 of this book describes the physical effects and damage that may result from amphetamine use and Chapter 3 describes the psychological and psychiatric effects of the drug. One of the reasons that amphetamine use has not attracted as much publicity or been taken as seriously as other drugs such as heroin or cocaine (or even ecstasy) is that overdose from amphetamine use was rare (Pates, 1994), particularly in areas where the less potent amphetamine sulphate was in common use. With an increase in the use of methamphetamine, however, more concern has been expressed about the potential for fatalities from the use of this more potent form of amphetamine.

Kaye et al. (2008) reported on a survey of methamphetamine-related deaths in Australia. They comment that shift in the mid-1990s from the production and supply of amphetamine (sulphate) to that of the more potent methamphetamine has produced an increase in amphetamine-related problems. Examining the case notes of 371 individuals where coroners had decided that methamphetamine was a listed cause of death, they found that the great majority of deaths were accidental (only 14% being suicides). In the cases they reviewed, methamphetamine use or toxicity was identified as the direct cause of death, as an antecedent cause in 11% of the cases and as a significant contributory factor in 16% of cases. Cardiovascular problems were noted in more than half of the cases for which autopsy reports were available, the most common type of cardiac pathology being cardiac artery atherosclerosis. Cerebrovascular problems were found in 20% of the cases where autopsy findings were available, and non-traumatic cerebral haemorrhage was noted in half of these cases. Women were four times as likely as men to have had a cerebral haemorrhage. Kaye and colleagues comment that these deaths are not typically cases of death among young naive users. They also comment that there does not appear to be a clear dose–response relationship for methamphetamine toxicity.

In a study using electrocardiograms (ECG) obtained during screening in a previous trial, Haning and Goebert (2007) demonstrated that methamphetamine users showed abnormalities. They found that 36% of those studied had abnormal ECG results. The most frequent abnormality was a high frequency of prolonged QT intervals (the QT interval represents the interval of ventricular contraction or systole), 'which has implications for health of the myocardium, as the delay in the ventricular contractions may indicate cardiomyopathy or other cardio toxic injury' (p. 72). This is further evidence of the physical effects of methamphetamine.

Sexual risks of using amphetamine

The chapters in this book give descriptions of the problem of ATS use in various parts of the world. A number of papers have been published looking at its use

among various groups. For example, in a study of methamphetamine use and HIV risk in South Africa, Simbayi et al. (2006) surveyed 441 men and 521 women about their sexual behaviour and drug use; 18% of men and 12% of women had used methamphetamine. Methamphetamine use was associated with being male, having multiple sexual partners and having unprotected sexual intercourse. Condoms were used in less than half of the incidents of sexual intercourse. The authors comment that the association between methamphetamine use and sexual risk practices could fuel the spread of HIV infection in a part of the world where infectivity is already high. They also comment that although methamphetamine users were more likely to use condoms than other drug users, they were also more likely to exchange sex for money or goods. In a national study of young Americans, Iritani et al. (2007) looked at, among other things, criminality and sexual risk associated with methamphetamine use. They found that the unadjusted odds ratio showed that methamphetamine use among men was associated significantly with having more than one sexual partner, inconsistent or no condom use and regretting a sexual situation. The odds ratios were higher for women than for men, and there was a strong relationship between methamphetamine use, sexual risk behaviour, inconsistent or no condom use and regretting a sexual situation. When these odds ratios were adjusted to include sociodemographic characteristics, other illegal drug use and novelty-seeking behaviour, the odds ratio was no longer significant. The sociodemographic variables showed that men were twice as likely as women to be drug users, and Hispanics and Afro-Americans were much less likely to use drugs than white people but Native Americans were 4.2 times as likely to use as white people. Methamphetamine users were more likely to smoke cigarettes and use marijuana, cocaine and/or intravenous drugs in the previous year. Novelty-seeking behaviour was measured by Cloninger's Tridimensional Personality Questionnaire.

Halkitis et al. (2007) sought to understand the popularity of methamphetamine in the gay male community in New York. Using a longitudinal study for over a year where 450 club drug-using gay and bisexual men were assessed by quantitative measure, they found that the use of methamphetamine in this group is a multifaceted behaviour. This behaviour was driven by a desire to heighten sensations, especially in relation to sexual experience, as well as to overcome painful emotions. Methamphetamine is perceived to have aphrodisiac by-qualities and is often used to enhance and prolong sexual activity. In another study, Bolding et al. (2006) examined the use of crystal methamphetamine and its association with high-risk sexual behaviour among gay men in London. They surveyed 388 HIV-positive gay men attending HIV clinics, 266 HIV-negative gay men attending clinics for HIV testing, and 1592 gay men using gyms. They found that the percentage of men who had used methamphetamine in the last 12 months varied by sample (HIV treatment 12.6%, HIV testing 8.3% and gyms 19.9%). The majority of the men used methamphetamine only once or twice a year, but most methamphetamine users had taken other recreational drugs, and the users of methamphetamine plus other drug were more likely to report high-risk sexual behaviour than either other drug users or non-drug users. It is interesting to note that

methamphetamine appears to be popular amongst the gay male population especially in Britain.

Shoptaw and Reback (2007) reviewed the evidence regarding the prevalence of methamphetamine use amongst men who have sex with men and evaluated the factors that contribute to methamphetamine use and the potential for sexual transmission of HIV and other infectious diseases. They found that methamphetamine use is prevalent among men who have sex with men in the USA, Australia and in the UK and the use of methamphetamine may range from recreational through to chronic use and addiction. They found that the data indicated that the men who use this drug engage in concomitant HIV-related sexual behaviour. They also found that men who have sex with men using methamphetamine probably have higher rates of infection with HIV and syphilis than men who have sex with men who do not use the drug.

Will precursor regulation work?

Because most methamphetamine is made in 'kitchen' laboratories (i.e. non-pharmaceutical environments, often by amateurs) questions have been raised about whether controlling the precursors or substances required to make methamphetamine would reduce the supply of the drug. For example, in the USA, regulation of bulk ephedrine and pseudoephedrine was introduced in 1989, regulation of products containing ephedrine as the single active ingredient in 1995 and regulation of products containing pseudoephedrine in 1997. These were aimed at limiting access of these drugs to large-scale producers. Regulations aimed at small-scale producers were introduced on ephedrine products that included more than one medicinal ingredient in 1996 (Cunningham et al., 2008).

Cunningham et al. (2008) investigated whether the suppression of these substances affected the routes of administration of these drugs and thereby the relative potential risk of different routes. Using non-coerced admissions into treatment as a population sample, they found that admissions for snorting, smoking, swallowing and injecting initially rose sharply and then dropped when the 1995 regulations were introduced and snorting dropped after the 1997 regulations were introduced. Admissions for smoking showed a resurgence after the 1996 regulations and continued rising to higher levels than in 1995, and has continued to rise thereafter. This is interesting research because it used time series and a powerful quasi-experimental design to examine the effects of policy on drug use.

McKetin (2008) has suggested that as regulation of precursor chemicals in the developed world becomes more stringent the responsibility for controlling and policing chemical diversion may shift to the developing world which may have limited capacity to manage these problems. This could alter the relative availability of various drugs in different geographical areas of the world. As McKetin points out this may also increase levels of harm in these countries.

The chapters of this book closely examine the issues surrounding amphetamine use and the interventions provided to treat people with amphetamine-related

problems. Inevitably, there will be omissions in terms of countries and some of the issues around the use of amphetamine. We have tried to be as comprehensive and inclusive as possible.

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Chapter 2

THE PHYSICAL EFFECTS OF AMPHETAMINE USE

Zoe Hildrey, Sophie E. Thomas and Alyson Smith

Introduction

Amphetamines are synthetic stimulants and are taken either legally for medicinal reasons or illegally for recreational use. Internationally, the Convention of Psychotropic Substances classifies amphetamines as Schedule II drugs or Schedule I drugs if prepared for injection. Amphetamines are prescribed to treat sleep disorders, such as narcolepsy (Szabadi, 2006), and attention deficit/hyperactivity disorder (ADHD) (Biederman et al., 2005), to aid in street amphetamine dependence (White, 2000) and as a diet suppressant (Colman, 2005). They can also be used to augment antidepressant therapy in treatment resistant (Carlson et al., 2004).

Amphetamines are available in crystalline form, tablet form or as a powder. They can be ingested in many ways: snorted, swallowed, smoked, injected or dissolved in a drink. In this chapter, the word amphetamines will be used to describe all types of amphetamines, methylamphetamines or methamphetamines, used medicinally, and all other types of illegal amphetamine, for example, speed.

The effect of using amphetamines will usually persist for up to 6 hours (Tyler, 1998). The main effects of the drug are increased heart rate and breathing rate, increased wakefulness, suppressed appetite and feelings of well-being, exhilaration, power and confidence (Tyler, 1998). Some users may also experience a dry mouth, hallucinations, sweating and increased urinary frequency. The user may have an increased sexual drive, making them more likely to participate in risky sexual behaviours (Semple et al., 2004).

As the effects of the drug wear off, fatigue often follows. It is thought that amphetamine withdrawal peaks within 24 hours of the last dose (McGregor et al., 2005). This is characterised by increased sleeping and eating. Dysphoria and depression-related symptoms such as inactivity can occur. Anxiety, tension, agitation, vivid dreams, craving, poor concentration, and irritability may also be experienced.

In this chapter, we focus on the many long-term consequences of amphetamine use. See Table 2.1 for an overview. Anorectic, neurotoxic and smoking effects are discussed as well as effects on sleep, heart, teeth and unborn babies. Links with human immunodeficiency virus (HIV), ADHD and Parkinson's disease are addressed.

Table 2.1 Physical effect of amphetamines.

Addiction	Amphetamine users are at risk of dependence, reflected by increased tolerance to the drug and both physical and psychiatric withdrawal symptoms. Injecting amphetamine or smoking crystal methamphetamine sharply increases the risk of dependence.
Effects on sleep	Short-term use induces wakefulness and reduces the need for sleep. Long-term use reduces total and REM sleep time. On withdrawal hypersomnia is likely, followed by poor sleep patterns.
Anorectic effects	Amphetamines are an appetite suppressant, producing marked decrease in food intake on the first day of administration. However, a dose-dependent tolerance develops.
Risks associated with route of administration	Injecting is associated with risks of blood-borne viruses (BBV) and vein damage. Smoking is associated with an earlier onset of psychotic symptoms. Smoking and snorting can lead to nasal damage, particularly sinusitis, and can exacerbate asthma.
Oral damage	Amphetamine use can severely damage the mouth, causing tooth surface loss, flattening of the teeth, gingivitis and angular cheilitis, caused by bruxism and xerostomia.
Cardiac effects and stroke	Amphetamine use is a risk factor for heart problems such as cardiomyopathy, arrhythmia and myocardial infarction. Documented cases of amphetamine-induced stroke, both ischaemic and haemorrhagic.
Link with BBV	There is an association between amphetamine use and increasing incidence of HIV and HCV. Factors that contribute to this are risky sexual behaviours and unsafe injecting practices.
Prenatal effects	Amphetamine use could cause an unborn baby to be small for their gestational age, underweight or be delivered preterm. However, there are complex confounding variables, which make it hard to draw to any conclusions.
Neurotoxic effects	Amphetamine acts on monoamine neurotransmitters in the central nervous system. It is an indirect dopamine and serotonin agonist and can lead to extensive long-term neural damage.
Parkinson's disease	There is evidence to suggest that chronic amphetamine use may be a risk factor for the development of Parkinson's disease in later life.

Sleep problems

Amphetamines induce alertness and wakefulness (Pagel and Parnes, 2001; Smith, 2006), and reduce the desire for sleep (Srisurapanont et al., 1999). Consequently, they are sometimes prescribed to help with the symptoms of sleep disorders such as the daytime sleepiness present in narcolepsy (Szabadi, 2006). Although amphetamines have this valuable use, it is important to note that they can severely disrupt night-time sleep and act as a major risk factor for insomnia (Dollander, 2002). In a laboratory-based study of the effects of amphetamines on sleep, Comer et al. (2001) found that participants reported being significantly less satisfied with sleep, took longer to fall asleep and woke more through the night.

This stimulant-induced wake may be modulated by dopamine (Jankovic, 2002). Dopamine plays an important role in modulating sleep, and taking amphetamine increases the extracellular levels of dopamine (Wisor et al., 2001). The increased wakefulness may be caused by the amphetamine blocking dopamine re-uptake or by stimulating dopamine, or by both processes (Boutrel and Koob, 2004; Ebert and Berger, 1998).

Amphetamines are also known to reduce the total time spent in sleeping, reduce the total time spent in rapid eye movement (REM) sleep by up to 50% (Baekeland, 1967), and increase the time spent getting to REM sleep (Schafer and Greulich, 2000; Smith, 2006).

On withdrawal from amphetamines, there is an REM rebound where the total sleep time increases and the time to REM decreases. REM sleep gradually returns to normal after this rebound upon discontinuation of use (Baekeland, 1967). In addition to an REM rebound following withdrawal from amphetamines, hypersomnia is likely to set in. McGregor et al. (2005) report an acute phase and a sub-acute phase. During the acute phase of abstinence (1 week), the user may 'crash' and is likely to sleep for up to a few days. In the sub-acute phase, sleep time returns to normal, but the user may take longer to fall asleep. Increased night waking and low clear-headedness on waking may also be experienced (Smith, 2006).

Prolonged amphetamine use, medicinal or not, could induce a stimulant-dependent sleep disorder. However, it is possible that an underlying sleep disorder precipitated the stimulant use. Therefore, stimulant-dependent sleep disorder could be a consequence of amphetamine use or an inadvertent consequence of self-medication (Smith, 2006).

Anorectic

Due to their appetite-suppressing properties, amphetamine-based substances can be used on a short-term basis to treat obesity (Colman, 2005). They were commercially sold as appetite suppressants until recreational use began to increase in the late 1950s. It is due to these anorectic effects that there is a significant association between abuse of illicit drugs and the risk for eating disorders (Piran and Gadalla,

2007). Matsumoto et al. (2002) noted that amphetamine was being abused by a higher proportion of young females with eating disorders compared to women without eating disorders.

Studies have shown a marked decrease in food consumption after repeated administration of amphetamines, with intake being reduced by 35% compared to the baseline consumption. However after the first day of use, daily food intake gradually returned to baseline levels (Foltin, 1990; Kuo, 2003). Not only food intake but also caloric intake decreases (Comer et al., 2001), and in the initial period after amphetamine administration a reduction in drinking behaviour has also been observed (Hsieh et al., 2005).

The gradual reversion to normal food intake despite continued amphetamine use shows that individuals develop a tolerance to the anorectic effects. Development of tolerance is dose dependent; intake of food is directly proportional to the dose of amphetamine ingested (Foltin, 1989; Wolgin, 2004). Return to normal levels of food intake occurs more rapidly at lower rather than higher doses, and it has been reported that when treated with doses greater than 5 mg/kg tolerance does not develop and the anorectic effect persists (Kuo, 2003).

These anorectic effects are linked to neural activity in the brain, specifically dopamine activity. The co-activation of both D1 and D2 receptors plays a role in amphetamine-induced anorexia (Kuo, 2003). Activity of the orexigenic neuropeptide Y helps regulate feeding behaviour, and levels are altered after administration of amphetamine; therefore, it may play an important role in the anorexia observed (Hsieh et al., 2005; Kuo and Cheng, 2002).

Health risks associated with injecting, smoking and snorting

Amphetamine can be administered in several ways: orally, intravenously, smoking or snorting. The dangers of injecting are quite well known, with the risk of bloodborne viruses (BBVs) from sharing injecting equipment. Repeated injecting can cause veins to collapse and bad injecting practices can lead to sores and infections (Zule and Desmond, 1999).

Smoking amphetamine is the process by which the vapourised fumes are inhaled. This results in a less intense experience than injecting (Matsumoto et al., 2002), but reduces the risk of contracting HIV or hepatitis. However, it is connected with its own detrimental effects. Regular smoking of amphetamine can exacerbate asthma, induce sore throat and lead to a bloody sputum. It is also reported that individuals who smoke amphetamine experience psychotic episodes sooner than injectors or poly-administration users (Matsumoto et al., 2002).

Snorting is the ingestion of amphetamine powder through the nasal passage, and this method along with inhalation can cause a runny nose, lead to nasal ulcers and damage the epithelium and nasal septum (McCann and Ricaurte, 2000). In more chronic cases, this can lead to septum perforation and sinusitis. Sinusitis occurs when the membrane of the sinus cavity and sinus openings become inflamed, usually due to blockage of the sinus passage, and this prevents them from draining