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Models of intervention and care for psychostimulant users

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Models of intervention and care for psychostimulant users

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Introduction

Chapter 1

Background to the monograph

Amanda Baker

Chair of the Psychostimulant Monograph Consortium, Centre for Mental Health Studies, University of Newcastle, New South Wales

In response to the growing prevalence of psychostimulant use in Australia and the need for treatment and other community services to respond, the Australian Government Department of Health and Ageing commissioned a consortium of clinicians and researchers from the Centre for Mental Health Studies, University of Newcastle, New South Wales, the University of Queensland, Queensland Health, New South Wales Health and Turning Point Alcohol and Drug Centre Inc. to update the 1998 National Drug Strategy Monograph No. 32, Models of Intervention and Care for Psychostimulant Users (Kamieniecki, Vincent, Allsop & Lintzeris, 1998) and to produce management guidelines for ambulance officers, police, emergency department personnel and general practitioners. The management guidelines are published separately to the current monograph. Consortium members were:

Dr Amanda Baker (Chair), Centre for Mental Health Studies, University of Newcastle, New South Wales

Professor Vaughan Carr, Centre for Mental Health Studies, University of Newcastle, New South Wales

Dr Stefan Goldfeder, The Prince Charles Hospital and Health Service District (TPCH&HSD) Alcohol and Drug Service, Brisbane, Queensland

Dr Ed Heffernan, Integrated Forensic Mental Health Services, Royal Brisbane Hospital, Queensland

Ron Henderson, Queensland Ambulance Service

Linda Jenner, Centre for Mental Health Studies, University of Newcastle, New South Wales and JenCo Consulting

Frances Kay-Lambkin, Centre for Mental Health Studies, University of Newcastle, New South Wales

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Terry Lewin, Centre for Mental Health Studies, University of Newcastle, New South Wales

Professor John B Saunders, University of Queensland

John Sharples, Court Liaison, Hunter Mental Health Services, New South Wales

Associate Professor Ian Whyte, Department of Clinical Toxicology and Pharmacology, Newcastle Mater Hospital, New South Wales

As a member of the Expert Reference Group of the 1998 monograph, I am aware of the huge amount of academic work and consultation that contributed to the production of that seminal document. It drew together a large and disparate body of knowledge for the first time in order to inform Australia's response to the growing harms associated with psychostimulant use.

The present work builds upon the foundations of the previous monograph. Since that time, there have been substantial developments in the research into treatments for psychostimulant users and this monograph focuses on these.

Aims of the monograph

The aims of this monograph were to document the prevalence and risks associated with psychostimulant use, describe the pharmacology of psychostimulants, identify best practice in detoxification and clinical interventions for psychostimulant use, identify gaps in the literature and make suggestions for interventions and further research.

Key objectives of the monograph were to:

(i) critically review existing literature in the domains of prevalence, risks, pharmacology, detoxification and treatments for psychostimulant use;

(ii) obtain expert feedback from reviewers of each chapter;

(iii) update recommendations for practice with psychostimulant users; and

(iv) identify priority areas for further research.

Scope of the literature review

Experts in each domain were invited to contribute chapters to the monograph. Literature searches on databases, such as PsychInfo, Medline, Cochrane Database of Systematic Reviews and Addiction Abstracts were conducted. Existing review papers were obtained and reference lists reviewed. I would like to thank the following authors for their invaluable contributions to this publication:

Mr Anthony Arcuri, Ted Noffs Foundation, Sydney, New South Wales

Dr Sharon Dawe, School of Applied Psychology, Griffith University, Queensland

Dr Angela Dean, Department of Psychiatry, University of Queensland

Dr Linda Gowing, Evidence Based Practice Unit, Drug and Alcohol Services Council, South Australia (DASC)

Dr Leanne Hides, Substance Use Research and Recovery Focused (SURRF) Program, ORYGEN Youth Health, Department of Psychiatry, University of Melbourne

Dr John Howard, Ted Noffs Foundation, Sydney, New South Wales

Linda Jenner, Centre for Mental Health Studies, University of Newcastle, New South Wales and JenCo Consulting

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Dr Libby Topp, NDARC, New South Wales

Associate Professor Ian Whyte, Department of Clinical Toxicology and Pharmacology, Newcastle Mater Hospital, New South Wales

An Expert Steering Committee was established for the project. Members were asked to provide information on any previously unidentified research groups. I would like to thank the following Steering Committee members for their important contribution to the development of the monograph:

Professor Robert Ali, DASC

Michael Arnold, NSW Users and AIDS Association (NUAA)

Michael Lodge, NUAA

Professor Richard Mattick, NDARC

Professor Anne Roche, National Centre for Education and Training on Addiction (NCETA), Flinders University, South Australia

James Shearer, NDARC, New South Wales

Dr Libby Topp, NDARC, New South Wales

Dr Ingrid van Beek, Kirketon Road Centre, Sydney, New South Wales

Designation of levels of evidence

Chapter authors were asked to employ the method of Gowing, Proudfoot, Henry-Edwards and Teesson (2001) in designating levels of evidence in clinical studies (see Table 1). Gowing and colleagues (2001) had modified National Health and Medical Research Council (National Health and Medical Research Council, 1999) designations due to the limited availability of randomised controlled trials (RCTs) in the field of drug dependence by using a scale to provide an indication of the reliability and validity of evidence.

A brief statement of the reasons for the rating was also included. Gowing and colleagues (2001) noted that the rating system enabled a distinction between 'no evidence of effect' and 'evidence of no effect', or a 'negative effect'.

Table 1: Modified designation of levels of evidence (Gowing et al., 2001)

****** (4 stars) =**	**Strong evidence. Supported by a systematic review that includes RCTs or more than one properly conducted (unconfounded) RCT.**
***** (3 stars) =**	**Moderate evidence. Supported by qualified evidence from reviews limited by research factors OR one properly controlled RCT, or more than one qualified RCT limited by research factors, OR more than one well conducted level 111-1 or 111-2 study (see level explanation below).**
**** (2 stars) =**	**Some evidence. Supported by one qualified RCT limited by research factors, or more than one level 111-3 or level 1V study from different research teams OR one or more 111-1 studies limited by research factors.**
*** (1 star) =**	**A little evidence. Based on opinion (clinical anecdote or editorial) OR reviews unsubstantiated by data OR one level 111-3 or level 1V study OR 111-3 or level 1V studies limited by research factors.**
? =	**Unable to assess. No, insufficient or conflicting evidence preventing any conclusion from being drawn.**
Level 1 =	**Evidence obtained from a systematic review of all RCTs.**
Level 11 =	**Evidence obtained from at least one properly designed RCT.**
Level 111-1 =	**Evidence obtained from well-designed, pseudo-RCTs (alternate allocation or some other method).**
Level 111-2 =	**Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.**
Level 111-3 =	**Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.**
Level 1V=	**Evidence obtained from case series, either post-test or pre-test and post-test.**

Clinical recommendations have been based on the method employed by NDARC in preparing the Guidelines for the Treatment of Alcohol Problems (National Drug and Alcohol Research Centre, 2003). The strength of the recommendation is based on the best available evidence presented for the intervention or strategy in question (see Table 2), combined with clinical expertise. Three levels are used.

Table 2: Strength of clinical recommendation

Strength of recommendation	Descriptor
Strong	**The recommendation is supported by at least level 11 research and expert clinical opinion.**
Moderate	**The recommendation is supported by at least level 111 research and expert clinical opinion.**
Fair	**The recommendation is based on expert clinical opinion.**

Structure of the monograph

The monograph comprises three sections:

1. Background.
2. Prevalence, effects and risks (with chapters on prevalence, pharmacology and risks).
3. Clinical considerations (with chapters on psychosocial interventions; management of acute toxicity; withdrawal and detoxification; pharmacological interventions; specific populations; clinical recommendations; and future research directions).

Terminology and definitions

In this document, psychostimulants have been defined as amphetamines, cocaine and MDMA (ecstasy). Street names for these drugs can be found in the Glossary. The Glossary also contains definitions and explanations of a number of technical and medical terms used throughout the monograph. The term ATS (amphetamine-type stimulants) when used in this monograph specifically relates to amphetamines and methamphetamine and related substances. The term does not include other psychostimulants such as cocaine or MDMA. The term is typically used when describing law enforcement and customs data.

The terms psychostimulant abuse, use, misuse and dependence are sometimes used interchangeably. In this document, the terms 'abuse' and 'dependence' refer to the criteria defined by the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) (American Psychiatric Association, 1994), which are outlined in Tables 3 and 4. 'Use' refers to use that does not meet these criteria. We used 'misuse' only when referring to the inappropriate use of prescribed or otherwise licit psychostimulants.

Table 3: DSM-IV diagnostic criteria for substance abuse

1. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following occurring within a 12-month period:
a. recurrent substance use resulting in failure to fulfil major role obligations at work, school, or home;
b. recurrent substance use in situations in which it is physically hazardous (e.g., driving while intoxicated);
c. recurrent substance-related legal problems; and
d. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
2. The symptoms have not met the criteria for substance dependence.

Table 4: DSM-IV diagnostic criteria for substance dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three or more of the following, occurring at any time in the same 12-month period:

1. **tolerance, as defined by either:**
   a. **a need for markedly increased amounts of the substance to achieve detoxification or the desired effect; or**
   b. **markedly diminished effect with continued use of the same amount of the substance;**
2. **withdrawal, as manifested by either of the following:**
   a. **a characteristic withdrawal syndrome; or**
   b. **the same or closely related substance is used to relieve or avoid withdrawal symptoms;**
3. **the substance is taken in larger amounts or for a longer period than intended;**
4. **there is a persistent desire or unsuccessful efforts to cut down or control substance use;**
5. **a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects;**
6. **important social, occupational or recreational activities are reduced or given up because of substance use; and**
7. **substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.**

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Professor Robert Ali, DASC, South Australia

Professor Steve Allsop, Drug and Alcohol Office of Western Australia

Dr Lisa Amir, Centre for Women's Health in Society, University of Melbourne

Professor Robert Batey, Division of Medicine, John Hunter Hospital, Newcastle, Drug and Alcohol Clinical Services, Hunter Area Health Service and University of Newcastle, New South Wales

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Paul Gardiner, Turning Point Alcohol and Drug Centre Inc., Victoria

Tarra Adam, St Vincent's Hospital, Sydney, New South Wales

Section 2: Prevalence, effects and risks

Chapter 2

Prevalence and patterns of psychostimulant use

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Key points

- Use of psychostimulants is widespread nationally, with methamphetamine the most readily available type of amphetamine in Australia.
- The availability of psychostimulants to Australian consumers has increased substantially over the past five years.
- The use of cocaine, while still much less prevalent than the use of amphetamines, may be higher in New South Wales and Victoria than other states and use by primary heroin users in certain locations such as Sydney may have been influenced by the recent heroin shortage.
- Psychostimulants tend to be used in conjunction with other drugs particularly nicotine, cannabis and alcohol, and benzodiazepines are also frequently used by regular amphetamine users.
- Use of psychostimulants, particularly ecstasy, among certain groups such as dance party attendees, youth and the gay community is widespread.
- Injection of amphetamines is common and there are increasing reports of cocaine and to a much lesser extent ecstasy injection.
- Increasing popularity of injection increases public health concerns due to the adverse consequences of use and has implications for appropriate and timely interventions for this population.
- While numbers of users seeking treatment for psychostimulant use is still considerably lower than for other drug classes, treatment demand is increasing, particularly by injecting drug users (IDUs).
- Responses to psychostimulant-related incidents by emergency personnel such as ambulance services are reported to be increasing in some states (e.g. Queensland), which has implications for pre-hospital management strategies and resource issues.

Introduction

This chapter examines the international and Australian literature regarding the patterns and prevalence of use of psychostimulants including cocaine, amphetamines and ecstasy. The prevalence of use among certain groups such as injecting drug users, police detainees, Indigenous and gay communities is included and key emerging issues are addressed. The final section highlights significant gaps in knowledge in this area.

Historical context

In a previous review of the literature, Hall and Hando (1993) described the history of psychostimulant use in Australia and the United States of America (USA), which is briefly summarised here (the reader is referred to the original work for further details).

Since the medical introduction of cocaine in the 1880s, several 'epidemics' of use have been described. It has been proposed that such extensive use was due to a belief in the relative safety of the use of cocaine in conjunction with its wide availability. A second wave of widespread cocaine use occurred in the USA during the mid 1980s and included abuse of the newly introduced 'crack cocaine' which was the drug of choice for poor, marginalised African American youth. Crack was freely available, affordable and produced intense euphoria in the user. However, due to the short half-life of the drug and rebound dysphoria following abstinence, some heavy users experienced a severe dependence syndrome. The psychosocial impact of the United States (US) cocaine epidemic became increasingly clear.

Following the American experience and historical evidence to suggest that Australian drug use patterns tended to follow those of the USA, local authorities became concerned that a cocaine epidemic would also hit Australia. As a result, a substantial number of studies were undertaken to explore the prevalence and patterns of cocaine use among youth and known IDUs in Australia during the late 1980s and early 1990s (Hando & Hall, 1993). That body of evidence revealed that, although it was not uncommon for illicit drug users to have tried cocaine, and similarities in user demographics and patterns of use did indeed exist between the USA and Australia, the expected cocaine epidemic had failed to arrive.

Hall and Hando argued that while the focus of attention was on cocaine use during the 1980s, an emerging Australian amphetamine epidemic was somewhat eclipsed until the early 1990s. While undertaking the earlier cocaine studies, researchers became incidentally aware of the high prevalence of amphetamine use among illicit drug users, the discovery of which prompted a wave of amphetamine-specific research (see Hando & Hall, 1993 for a review of these studies).

Unlike cocaine, which needed to be imported from international markets, amphetamines were being locally produced from freely available chemical precursors and were therefore cheaper to purchase and readily obtained. Amphetamine use waned from the mid 1990s with the emergence of heroin as the major form of injecting or problematic drug use in Australia. This trend was most notable in the southeast of the country (i.e., Sydney, Canberra and Melbourne) while amphetamine use remained more common in other parts of Australia.

Several years on, cocaine emerged on the Sydney drug market. This trend was observed as the uptake of cocaine injection among the existing heroin using population in Sydney in late 1997 to 1998. Heroin users continued to use heroin, alongside cocaine. Cocaine use has since become a regular feature of the drug situation in Sydney, although the overall level of use has not continued to increase, with the exception of an increase in use among IDUs during the 2001 heroin shortage (MacDonald, Zhou & Breen, 2002). Similarly, use remains fairly circumscribed to Sydney and to a lesser extent other major cities in Australia.

Not long after the emergence of cocaine use in Sydney, reports of more pure forms of amphetamines began to emerge. By this time, amphetamines available on the Australian market were almost exclusively the more potent analogue of 'methamphetamine'. From the time of the first reports of more potent forms of methamphetamine in 1999 there has been a steady increase in use across a range of drug using populations, this being most apparent among IDUs during the heroin shortage of 2001 (McKetin, Darke, Bruno, Dwyer et al., 2000; Topp, Kaye, Bruno, Longo et al., 2002). There has been a corresponding increase in problems associated with methamphetamine use over this time as discussed later in this chapter.

Over this time ecstasy also emerged as a popular drug, especially its use in recreational or party settings. This amphetamine analogue, methylenedioxymethamphetamine (ecstasy), was legal in the mid 1980s until concerns over its widespread use and potentially negative effects led the American Food and Drug Administration (FDA) to schedule the drug. During the late 1980s ecstasy also became popular in Australia among subgroups of gay and heterosexual youth to enhance energy and sociability at all-night dance parties or 'raves' (Solowij, Hall & Lee, 1992).

Global overview of trends in psychostimulant use

Amphetamines

Regions with established amphetamine or methamphetamine use include parts of Southeast Asia, Australia and New Zealand, North America and certain parts of Europe (United Kingdom (UK), the Czech Republic and Scandinavian countries). The use of methamphetamine in particular is increasing in many regions and there is concern that the trend will continue despite heightened awareness of the adverse consequences (Rawson, Anglin & Ling, 2002; United Nations Office on Drugs and Crime, 2003).

The Americas

Use of methamphetamine in the Americas appears concentrated in North America, particularly in the USA, although there have been reports of increasing use in countries in Central and South America (United Nations Economic and Social Council, 2003). Clinical researchers in the USA have identified a growing market of methamphetamine consumers, particularly in the western and mid-western states (Rawson, Anglin et al., 2002). Clinical reports are supported by epidemiological data that reveal a three-fold increase in the incidence of methamphetamine use and a reduction in age of initiation from 22 years to 18 years (Substance Abuse and Mental Health Services Administration (SAMHSA), 2002). Methamphetamine is now being used along with other drugs at dance venues such as raves in the USA and use of the crystalline form of the drug ('ice') has been associated with significant problems. Use of methamphetamine is still at lower levels than seen in Australia, with around 4% of the general population having ever used the drug, although this should be interpreted in light of the relatively higher levels of cocaine use in the USA.

Europe

Most 'amphetamines' used in Europe are in the form of amphetamine sulphate. Methamphetamine problems have been largely restricted to the Czech Republic.

However, there has been some evidence of sporadic methamphetamine availability in other European countries. Use of amphetamines in Western Europe is still well below 5% lifetime prevalence for most countries — comparatively much lower than levels reported among the general population in Australia.

The UK (England and Wales) reports notably high rates of amphetamine use, with 11% of the general population having ever tried these drugs, although only 3% had used amphetamines in the past year. These levels of use are akin to those seen in Australia (see the prevalence and patterns of use section later in this chapter). Amphetamines are also dominant in the Scandinavian countries of Sweden, Finland and Norway where the majority of problem drug users (ie. injection or regular long duration use) primarily use amphetamines. This stands in contrast to other European countries where the majority of injectors or heavy drug users take opioids (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2002; Hibell, Andersson, Ahlström, Balakireva et al., 2000).

Asia-Pacific region

Over three-quarters of the world's production of amphetamine-type stimulants (ATS) occurs in Southeast Asia. Given this scenario it is not surprising that one of the most notable drug trends over recent years has been the dramatic increase in ATS use in this region. Particularly large increases in use have been seen in Thailand, while historically methamphetamine use has been the dominant pattern of drug use in Japan and the Philippines. Lower levels of use are seen in other parts of the region, although recently use in these areas also appears to be increasing, with use spreading to broader population groups.

In Thailand, methamphetamine use has been spreading since 1970 but this increase became more intense from 1996 and its use has now dispersed throughout the country. Methamphetamine has now replaced heroin as the most common drug for which drug users seek treatment, with over half of new treatment recipients in the country being methamphetamine users in 2000. Most methamphetamine available in Thailand is in the form of tablets, referred to locally as 'yaabaa', which is typically smoked 2-3 times per day. Young people and students have become the main users of methamphetamine, while drugs like ecstasy, ketamine and cocaine are more commonly used by youth in entertainment places (Chaiyawong, 2002).

Japan has experienced several waves of widespread methamphetamine use, the first immediately following the Second World War when stockpiles used by combat personnel became widely available to the general public. Although drug use among the general population is low, methamphetamine is reported to be 'the most widely abused drug in Japan' (Matsumoto, Kamijo, Muiyakawa, Endo et al., 2002) and accounts for the majority of reported cases of drug dependence or abuse in Japan. Injection is the predominant mode of administration, although smoking the drug has increased in popularity over the past decade (Ministry of Health, Labour and Welfare, 2002).

Methamphetamine is also the most common illicit drug used in the Philippines, where there is an estimated 1.8 million users of the drug (1999 National Household Survey) and methamphetamine accounts for the majority of drug-related treatment admissions. The main form of methamphetamine used in the Philippines is the high purity crystalline form called *shabu* (or 'ice'). Most users smoke the drug, although there have been reports of methamphetamine injection (Balmes, 2002).

Use of ATS has also increased in China where there is also substantial production and trafficking of the drug, including the high purity crystalline methamphetamine that is used in the neighbouring countries of Japan and the Philippines. Use of amphetamine-type drugs in China includes 'ice' but also other forms of ATS, particularly ecstasy, known locally as 'shake head pill'. There has been an increase in the use of ATS pills in several other Southeast Asian countries, such as Vietnam, Laos People's Democratic Republic (PDR) and Cambodia. Use in these countries is still relatively low. However, there are signs that use is beginning to spread (Zhimin, Xianxiang & Jiaqi, in press).

The dramatic increase in the supply and consumption of ATS within the Southeast Asian region has implications for Australia because of the geographic proximity and the potential 'spill over' of the market into Australia. Importation of high purity crystalline methamphetamine from Southeast Asia to Australia is already occurring. The use of this form of the drug presents a particular concern because of the increased risk of dependence, psychosis and other health and social consequences. At the same time, domestic production and use of methamphetamine has also increased. New Zealand has witnessed a similar increase in methamphetamine use, with past year prevalence increasing from 2.9% in 1998 to 5.0% in 2001 (Wilkins, Bhatta & Casswell, 2002) and increased availability of more pure forms of methamphetamine, referred to locally as 'pure' or 'p'. The increased use of methamphetamine, particularly more pure forms of the drug, has also prompted concern about the impact on increasing levels of psychosis and violent behaviour associated with use of the drug and options for treating dependence. A later section of this chapter discusses patterns of methamphetamine use in Australia in more detail.

Ecstasy

Experimental or infrequent use of 'ecstasy' type drugs appears to be on the rise in many regions of the world. This increase is most noticeable across the Americas and in Central and Eastern Europe, where increased exposure to ecstasy use among young people has been documented. Increases in ecstasy use have also been noted in Australia and in some countries in Southeast Asia.

In Europe the use of ecstasy type drugs has become an established aspect of specific recreational settings (dance parties) where the drug is taken among youth, combined with increasing experimentation with other synthetic drugs. With respect to the use of ecstasy there has been a clear upward trend in both Western and Eastern European cities (Bless, Kemmesies & Diemel, 2000). However, the most recent data from the European Union region shows that lifetime experience of ecstasy among the general population is still well below 5% in most countries (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2002), which is slightly lower than levels seen in Australia (6%) (Australian Institute of Health and Welfare, 2002a). However, much of the 'ecstasy' taken in Australia may actually be methamphetamine pills, so it is difficult to make accurate comparisons across countries (Australian Bureau of Criminal Intelligence, 2002).

Increased ecstasy use is a particular concern in the USA at the moment. Around 4% of the population have ever used ecstasy, with exposure to the drug having increased significantly since 2000 (2.9% vs. 3.6%) (Substance Abuse and Mental Health Services Administration (SAMHSA), 2002). Increased ecstasy use has been noted in

many regions of the country and has been reflected in a rise in the number of emergency room admissions where ecstasy has been implicated (Community Epidemiological Work Group (CEWG), 2002). Increased use of ecstasy was particularly notable among older school students where levels of use in the past year have risen sharply from around 4% in 1996-98 to just over 9% in 2001 (Johnston, O'Malley & Bachman, 2002). Designer drugs such as ecstasy have also emerged as popular drugs in Canada, mainly among youth. In Ontario, past-year ecstasy use among students had increased from 0.6% in 1993 to 6% in 2001 (Adlaf, Paglia & Ivis, 2000).

Ecstasy is typically the domain of Western and developed countries; however, increasing ecstasy use has not been restricted to these areas. Over the past decade ecstasy use has increasingly become the concern of other regions, including Africa, South and Central America and the Caribbean and parts of Asia (United Nations Economic and Social Council, 2003). In Southeast Asia, ecstasy use is typically restricted to youth from higher socio-economic brackets where the drug is taken in at entertainment venues. However, there have been reports of ecstasy use among other population groups, but an increase in the consumption of 'pills' that may contain either methamphetamine, ecstasy or other drugs has made it difficult to monitor trends in use (Poshyachinda, Perngparn & Ngowabunpat, 2002; Zhimin et al., in press). This is particularly the case in Australia, where it has been estimated that 80% of the pills sold as ecstasy contain methamphetamine (Australian Bureau of Criminal Intelligence, 2002).

Cocaine

Consumption of cocaine tends to be concentrated in the Americas, with relatively lower levels in other parts of the world. This is hardly surprising considering that the global supply of cocaine originates almost exclusively from the South American countries of Peru, Bolivia and Columbia. Trafficking of cocaine in this region dwarfs other regions, with over 200 tonnes of the drug seized annually — around 90% of global cocaine seizures.

In line with supply-side trends, cocaine is the second most common illicit drug used after cannabis in North America. Exposure to cocaine among the general population in the USA is high, with around one in ten people (11.2%) having ever used the drug. An estimated 1.7 million people (0.7%) were current cocaine users, while 406,000 (0.2%) were current crack users, having used the drug in the past month (Substance Abuse and Mental Health Services Administration (SAMHSA), 2001). Similar to the USA, cocaine is the second most common illicit drug used in Canada after cannabis. Cocaine is also the most commonly injected drug, although smoking of crack cocaine has become more popular among IDUs in recent years, especially in Vancouver, where crack cocaine is also injected (Archibald, 2002). Mexico is also experiencing high levels of problematic cocaine use. The Drug Information Report System (DIRS) in Mexico noted that cocaine use surpassed use of cannabis and inhalants in 1998 to be the most common form of drug use among problematic drug users. Cocaine use among school students in Mexico also increased over the last decade with 5.2% of students reporting first use, to be the second most common illicit drug used after cannabis (5.8%) (Natera Rey, 2002). Levels of cocaine use also appear high in other parts of the Americas, with relatively high levels of cocaine use found among school students in Columbia, with crack cocaine using being the dominant form of

problematic drug use seen in the Caribbean (Caribbean Epidemiology Centre (CAREC), 2001; Secretaría Nacional Antidrogas (SENAD), 2002).

Lower levels of cocaine use are seen in Western Europe where the drug has been tried by between 1% and 6% of the population. Prevalence of recent use is usually less than 1% although this is not without exception (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2002). Cocaine use is increasing among young people in the UK. Of those in the 16–24 years age group interviewed for the British Crime Survey, 5% reported use of cocaine in the previous year, which was five times more than those who reported recent use in 1994 (Boys, Marsden & Strang, 2001). There has also been concern about high or increasing levels of cocaine use in selected European countries (e.g. Denmark, Germany, Greece and Spain) (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2002).

Use of cocaine is also relatively low in other parts of the world. Pockets of cocaine use have been noted in some major urban areas in Africa, including cities in Nigeria, Morocco, Kenya and South Africa, some of these centres being transit points for trafficking of cocaine. Use of cocaine in these areas appears to be confined to small groups in urban areas, although lack of comprehensive data makes assessment of the situation difficult. Cocaine use is not a salient feature of the drug situation in Asia, while use in Australia is a relatively recent phenomenon and even then cocaine has remained at low levels, as discussed later in this chapter.

Prevalence and patterns of psychostimulant use in Australia

The similarity in the chemical action and arousal-producing effect of psychostimulant drugs is not reflected in similarly homogeneous use patterns. Patterns of use include chronic and dependent abuse by the socially marginalised, use by young, often socially well-integrated people in recreational settings, and the instrumental use of psychostimulants by certain occupational groups or in particular work settings. The morbidity and mortality associated with psychostimulant use is also influenced by the route of administration. Recreational use is usually associated with occasional use by swallowing and snorting these drugs. Injection is typically associated with higher levels of dependence and other health and social problems, as is smoking of some forms of psychostimulant drugs, such as crystalline methamphetamine or crack cocaine, where smoking results in a similar rapid onset and high bioavailability to that seen with injection of the drug.

There has been a significant increase in reported lifetime use of psychostimulant drugs in Australia since 1993 (Table 5) according to the Australian National Drug Strategy Household Survey (Australian Institute of Health and Welfare, 2002a)[1]. Amphetamine use is particularly prevalent and is the second most commonly used illicit drug after cannabis. In this sense, amphetamine use is relatively more common in Australia than many other countries (see preceding section on international trends for details). The following sections discuss the prevalence and patterns of each type of psychostimulant drug in more detail.

1 Note that the wording of the question relating to lifetime use of illicit drugs was altered slightly for the 2001 survey. In previous surveys, respondents were asked if they had ever 'tried' drugs, but in 2001 they were asked if they had ever 'used' drugs. Hence, lifetime use data in 2001 is not strictly comparable to previous years and care must be taken when comparing prevalence rates across time.

Table 5: Prevalence (%) of use of amphetamines, cocaine and ecstasy/designer drug use, 1993–2001 (Australian Institute of Health and Welfare, 2002a)

	1993	1995	1998	2001
Past year				
Amphetamines	2.0	2.1	3.7	3.4
Cocaine	0.5	1.0	1.4	1.3
Ecstasy/designer drugs	1.2	0.9	2.4	2.9
Lifetime				
Amphetamines	5.4	5.7	8.8	8.9
Cocaine	2.5	3.4	4.3	4.4
Ecstasy/designer drugs	3.1	2.4	4.8	6.1

Note: Lifetime prevalence for 2001 represents 'ever used' in comparison with 'ever tried' in earlier years.

Amphetamines

According to the 2001 National Drug Strategy Household Survey (Australian Institute of Health and Welfare, 2002a), almost 1.5 million Australians had used amphetamines at least once in their lives and half a million people had used these drugs at some time during the preceding year. Those aged 20-29 years were most likely to have recently used amphetamines (11%), followed by those in the 14-19 years age group (6%), while recent use of illicit drugs including amphetamines was uncommonly reported by those in the over 40 age group (0.4%). The mean age of initiation to amphetamine use of approximately 20 years has remained largely unchanged since 1995 (Australian Institute of Health and Welfare, 2002a).

The most popular setting for the use of amphetamines by participants of the Australian National Drug Strategy Household Survey was 'in a home' (59% of recent users), then private parties (47%) and dance parties (46%). However, 13% of recent users reported that a car or other vehicle was the usual setting for amphetamine use, 8.5% used in public places and 8% used at work, school, TAFE or university. Most recent users reported obtaining the drug from friends or acquaintances (71%), while 23% used a 'dealer' (Australian Institute of Health and Welfare, 2002a).

It is rare for people to use only amphetamines and use of multiple drug classes is common. For example, 88% of recent users in the National Drug Strategy Household Survey reported concomitant use of alcohol, 71.5% cannabis and 43% ecstasy (Australian Institute of Health and Welfare, 2002a). Similarly, Darke and Hall (1995) found high levels of concomitant nicotine, alcohol and cannabis use (>90%) and hallucinogen, benzodiazepine and opiate use (>50%) among a sample of 301 primary amphetamine users.

The frequency of amphetamine use in Australia varies, particularly among user groups described above. Among the estimated 534,000 recent users of amphetamines in 2001, 12% reported regular daily or weekly consumption, although 45.5% reported only yearly or twice yearly use (Australian Institute of Health and

Welfare, 2002a). Recent users used around 1 gram of amphetamines on a typical using day, with 'powder' form the most frequently used (84% of respondents) followed by 'crystal' (38%) (Australian Institute of Health and Welfare, 2002a).

Users of amphetamines can be loosely categorised as 'recreational' (those who use irregularly in a social setting), intermittent binge users or regular daily users. Occupational users of amphetamines may also represent a distinct group, as may those who use the drug as an anorectic to effect weight loss. Intranasal or oral ingestion are common routes of administration by novice and recreational users, while a significant proportion (particularly regular users) move on to injecting (Hall & Hando, 1994).

Overall, injection is a common route of administration particularly among heavier dependent users, with amphetamine injectors accounting for around one in five injecting drug users (IDUs) in Australia (Australian Institute of Health and Welfare, 2002a; Breen, Degenhardt, Roxburgh, Bruno et al., 2003). Once users make the transition to injecting, they are unlikely to return to snorting or swallowing as their preferred mode of administration. On the whole, injection of methamphetamine is associated with more frequent use, higher risk of dependence, poorer social functioning and psychological morbidity (Darke, Cohen, Ross, Hando & Hall, 1994).

Injection of amphetamines is also seen among established populations of heroin users. For example, during the heroin shortage of 2001 there was a shift toward injection of psychostimulant drugs, including amphetamines, among IDUs who would otherwise see heroin as their drug of choice (Weatherburn, Jones, Freeman & Makkai, 2003). However, transitions back and forth between the injection of amphetamines and heroin were demonstrated prior to this time (Darke, Cohen et al., 1994). Use of amphetamines by those on methadone maintenance programs for opioid dependence has also been highlighted (Swensen, Ilett, Dusci, Hackett et al., 1993).

In summary, the use of amphetamines is most commonly seen as part of a polydrug use pattern among IDUs (Darke & Hall, 1995).

Cocaine

Cocaine use among the general population in Australia has always been low in comparison to other psychostimulant drugs (amphetamines and ecstasy). Cocaine use in Australia is also much lower than levels of cocaine use seen in the Americas and is probably more similar to levels of use seen in European countries. Use tends to remain more concentrated among younger people in conjunction with social occasions and among subgroups of IDUs. In Australia, a little more than 4% of the general population reported using cocaine at least once in their lives and 1.3% reported use in the previous 12 months (Australian Institute of Health and Welfare, 2002a). Cocaine is often used in combination with other drugs in Australia, particularly alcohol and cannabis (Australian Institute of Health and Welfare, 2002a) and this polydrug use pattern has been reported elsewhere (Chen & Kandel, 2002; John, Kwiatkowski & Booth, 2001; Pennings, Leccese & Wolff, 2002).

Like amphetamines and other drugs generally, males more commonly reported lifetime use of cocaine than females (5.3% compared with 3.5%), while the highest lifetime ever use was found among those aged 20–29 years (10%), followed by the 30–39 year age group at 6.5%. Those who had used in the previous 12 months

(4.3%) were more likely to be males and aged between 20 and 29 years. The mean age of initiation to cocaine use has been fairly stable since 1995 and is approximately 22 years of age (Australian Institute of Health and Welfare, 2002a).

Like users of amphetamines, users of cocaine can be classed as occasional or recreational, intermittent binge users, or regular users. Of the recent users in the 2001 Household Survey, 65% reported yearly or twice yearly use; approximately 20% used every few months; and 16% used daily, weekly or once per month. The most common route of administration of cocaine by respondents in the 2001 Household Survey was intranasal snorting, which is consistent with reports from other countries (e.g., Boys et al., 2001; Chen & Kandel, 2002). However, there has been a significant increase in those reporting cocaine as the last drug injected by users of needle and syringe programs nationally (see 'Specific Populations' Section in this chapter for details). This is consistent with work by Hando et al in the late 1990s that found two distinct groups of cocaine users in Sydney, those from a low socio-economic group who predominantly injected cocaine and those from a higher socio-economic group who tended to prefer intranasal administration.

Cocaine can be snorted, ingested or injected. Crack cocaine, the use of which remains uncommon in Australia, is usually smoked.

Injecting cocaine users in Australia tended to be heroin users who began injecting cocaine with its increased availability around 1997–98. From 1995–2000, reports of recent cocaine injection were fairly stable at 1–2% of respondents but in 2001, this rose considerably to 7% (MacDonald et al., 2002) during the heroin shortage when it was thought to 'fill the gap' from the decreased supply of heroin (Weatherburn et al., 2003). Injection of cocaine was related to increased risk of a variety of physical and mental health problems, such as injection-related problems, chaotic lifestyle and paranoia (Kaye, Darke & Topp, 2001; van Beek, Dwyer & Malcolm, 2001). Female sex workers in Sydney who used cocaine heavily were also found to be at greater risk for a wide variety of adverse physical and psychological health consequences including sexually transmitted diseases and hepatitis (van Beek et al., 2001).

In line with low levels of cocaine use in Australia, few people receive drug treatment primarily for cocaine use or are admitted to hospital for cocaine-related mental disorders relative to other psychostimulant drugs (see later section in this chapter). Despite this, significant harms have been noted even among non-injecting users, such as death from cardiac toxicity (see Chapter 6: *Management of acute toxicity*, for a detailed discussion). The potentially life-threatening nature of problems related to cocaine use highlight the need not to be complacent about this form of drug use.

Ecstasy

Ecstasy use has also increased in Australia. Data from the National Drug Strategy Household Survey indicated that nearly one million people had used ecstasy at some time during their lives and levels of use in the past year reached around 3% of the adult population in 2001 (Australian Institute of Health and Welfare, 2002a). As was the case with amphetamines, younger age was associated with ecstasy use. Nearly one in five of the 20–29 year old group had ever used ecstasy and one in ten had used it in the preceding 12 months. Again, users were more likely to be male.

The mean age of initiation to ecstasy use has been fairly stable since 1995 and like cocaine was approximately 22 years of age for those in the Household Survey. However, an Australian study of 329 ecstasy users reported a median age of initiation (ie. the age at which first use most frequently occurred) as 18 years (Topp, Hando, Dillon, Roche & Solowij, 1999). This discrepancy probably reflects the latter sample being comprised mainly of regular users of the drug, who in general are likely to initiate use at a younger age.

The majority of users (73%) procured ecstasy from a friend or acquaintance, while 23% obtained the drug from a dealer. Similar to the settings for use of other psychostimulants, many people used at home (46%) or private parties (54%), but the use of ecstasy at dance parties or a rave was higher at 70% (Australian Institute of Health and Welfare, 2002a). Monitoring of ecstasy use among 'party drug users' also suggests an increased demand for the drug although patterns of use have remained reasonably stable since the mid 1990s (Topp, Breen, Kaye & Darke, 2002). One recent trend is that a large proportion of 'pills' that are often sold as ecstasy actually contain methamphetamine (Australian Bureau of Criminal Intelligence, 2002). In Australia as elsewhere in the world, ecstasy users report high levels of recent alcohol, cannabis, amphetamine, LSD and tobacco use (>70%), while recent use of solvents and benzodiazepines were lower but still notable (>30%) (Topp et al., 1999).

Results of a descriptive study undertaken in the late 1990s demonstrated patterns of use among a sample of 329 ecstasy users recruited from Sydney, Brisbane and Melbourne (Topp et al., 1999). Mean duration of use was three years and female subjects reported a younger age of initiation (17 years) than the male participants (19 years). Most (89%) had used ecstasy at least monthly and the median days of ecstasy use in the preceding six months was ten (12% had used on more than 24 days). Subjects tended to use one tablet on a typical using day, although almost half (44%) reported using more than one tablet. A third of the respondents had 'binged' on ecstasy (used continuously without sleep for 48 hours or more), the longest binge reportedly lasting for 14 days. Ecstasy was most often swallowed, although it had been injected by 16% of the sample at some time in their using career and 10% had injected it in the preceding six months (Topp et al., 1999).

As pointed out by Topp et al (1999), the results of early studies into ecstasy painted a fairly benign picture of the natural history of use: a spontaneous tapering or cessation of mainly oral use by many individuals, limited adverse physical or psychological effects and few cases of injecting ecstasy use were reported.

Data obtained in 1990 from 100 ecstasy users in Sydney led Solowij, Hall and Lee (1992) to conclude that ecstasy did not lend itself to regular use due to a high tolerance potential for positive effects, coupled with experiences of increased negative effects over time. Typically, users took ecstasy intermittently or recreationally, in combination with other drugs, to enhance sociability and increase energy, particularly for all-night dance parties. Although more recent international research has demonstrated that while there is still a strong likelihood that many users will spontaneously cease ecstasy use (von Sydow, Lieb, Pfister, Hofler & Wittchen, 2002), a range of serious adverse effects of use, some fatal, have been reported in Australia (eg, Gowing, Henry-Edwards, Irvine & Ali, 2002) and elsewhere (Kalant, 2001; Parrott, 2002).

Prevalence and patterns of psychostimulant use among specific populations

Student populations

This chapter includes a brief overview of the extent of psychostimulant use among students. The reader is referred to Chapter 9: *Psychostimulants and young people*, for a detailed description of patterns of psychostimulant use among youth and related issues.

Psychostimulant drugs have been tried by between 4% and 7% of Australian school students aged 12 to 17 years, with use increasing to levels similar to the overall general population by 16-17 years of age (see Table 6). Amphetamines are the most commonly used psychostimulant drug, also being the third most commonly used illicit drug after cannabis and inhalants (White, 2001). The use of amphetamines among school students occurs in about 7% of students, although exposure to amphetamines ranges from around 3% of students aged 12 years to 10–12% of those aged 16–17 years. Recent use of amphetamines (past year) had occurred among 5.5% of students and again is highest among 16–17 year olds (8.2% and 9.6% respectively). While use may be low among the younger age groups, it is important to note that early onset of use, alongside other factors, is a risk factor for development of drug dependence in later life (Glantz & Pickens, 1992). Use of cocaine and ecstasy was lower than for amphetamines, with 3.5% and 4% of students having ever used these drugs respectively.

Use of psychostimulant drugs was only slightly higher among boys than girls compared with gender ratios seen among the general population (two males: one female). This was particularly true for amphetamine use, with 7.7% of boys and 6.5% of girls ever having used the drug and a similar ratio for recent use (6.0% male vs. 5.1% female). This ratio is roughly equivalent to a ratio of approximately six males to every five females. Higher rates of amphetamine use among young women than seen in older age groups may reflect a relative increase in use of psychostimulant drugs among young females.

Similar to patterns of use among the general population described in the previous section, use of psychostimulant drugs in the previous week (a proxy for more regular use of the drug) occurred among less than 2% of students.

Table 6: Prevalence of psychostimulant use among Australian school students, 1999

		Amphetamines	Ecstasy	Cocaine
Past year use	**Boys**	**6.0**	**3.5**	**2.9**
	Girls	**5.1**	**2.7**	**2.1**
	Total	**5.5**	**3.1**	**2.7**
Ever used	**Boys**	**7.7**	**4.6**	**4.1**
	Girls	**6.5**	**3.4**	**3.0**
	Total	**7.1**	**4.0**	**3.5**

Party drug scene

Use of psychostimulants, particularly ecstasy type drugs, is commonplace among the dance party scene. Sentinel surveys of ecstasy users among the dance party scene in Sydney have found that most used two to three times a month and swallowed one to two tablets per occasion (Topp, Breen et al., 2002). The other psychostimulant drugs — amphetamines, methamphetamine and cocaine — were also taken by a large group of ecstasy users and were used more often than other drugs such as LSD, benzodiazepines, inhalants (amyl nitrate and nitrous oxide), heroin and ketamine. These were used infrequently by less than half of the ecstasy users sampled. Alcohol and cannabis were also commonly and frequently used by this group.

Use of methamphetamine became more prevalent among the Sydney dance party scene in 2001. One in five party drug users interviewed in Sydney during 2001 had used base methamphetamine recently, while one-quarter had used the crystalline form of the drug. Even though similar numbers had been exposed to both ice and base, the base form of the drug was used more often. Most of this group used base once a month compared with only having used ice once in the past six months. Similar to use among IDUs, powder methamphetamine was still by far the most common form of the drug used in the dance party scene (Topp, Breen et al., 2002). By way of comparison, cocaine was typically used less than once a month by around half the sample, this level of use remained stable across the period from 1997–2001.

Gay community

The use of psychostimulants among members of the gay community in Australia is widespread (see Table 7), particularly among those who are socially 'attached' to the gay community (Ireland, Southgate, Knox, van de Ven et al., 1999). In Australia, the use of drugs in combination with music, dancing and sexual contact has been identified as a means to celebrate gay identity with psychostimulants in particular being used to enhance energy for dancing and partying (Ireland et al., 1999). Although drug use has frequently been found to increase the risk of engaging in unsafe sexual practices in many studies, there appears to be various other contributing factors among the gay community such as the nature of sexual relationships, misunderstanding of risks, impulsivity, the situational context of sexual activity, stress responses and age (see Ireland et al for a review of these studies).

Overall, ecstasy is the most common drug used among the gay community. Although similarly high levels of methamphetamine use can be seen in Queensland and Adelaide, methamphetamine is also more common among other population groups in these areas. Use of cocaine among gay men is lower than for ecstasy and methamphetamine (Hull, Rawstorne, van de Ven, Prestage et al., 2002). Levels of psychostimulant use are not as high among all subgroups of gay men. For example, among Asian men in Sydney levels are lower with 16% having used ecstasy recently, followed by methamphetamine (9%) and then cocaine (4%) (Mao, van de Ven, Prestage, Wang et al., 2003).

An interesting feature to note is that methamphetamine was the most commonly injected drug among gay men, with relatively few indicating injection of other drugs including heroin. This stands in contrast to IDUs surveyed through needle and syringe programs (NSPs), where heroin is still commonly injected (see IDU section below for details).

Table 7: Prevalence of psychostimulant use in the past six months among gay men in different Australian regions, 2001

		Sydney	Melbourne	Queensland	Adelaide
Use	Ecstasy	47.6	32.4	31.3	17.2
	Speed	35.0	23.1	29.6	18.4
	Cocaine	23.3	11.0	9.0	7.3
	Any drug	–	–	–	55
Injection	Ecstasy	1.9	1.1	2.2	1.4
	Speed	5.3	2.7	7.6	3.5
	Cocaine	2.1	0.5	1.4	1.1
	Any drug	–	–	10	4.1

Police detainees

The Australian Institute of Criminology Drug Use Monitoring in Australia (DUMA) project collects information from people detained by police in seven sites across Australia every three months. To validate the self-report data, a urine drug screen is also obtained from participating detainees. Information is confidential and voluntarily supplied and the data obtained is an indicator of current drug use by those involved in criminal activity. Across years 2000 to 2002, Perth had the highest number of adult male detainees test positive to amphetamines, 33%–42%; followed by Adelaide (31%–38%); Southport (26%–33%) and Brisbane (21%–29%) (Makkai & McGregor, 2003).

The investigators reported an increase in positive urine screens for MDMA across the data collection period from 0.5% in 2000 to 1.1% in 2002, although prevalence of use in this population remains fairly low. Similarly, cocaine use was infrequently detected among this sample, with an average of only 4% across all sites testing positive to cocaine. However, the DUMA data supported the findings from the Illicit Drug Reporting System (IDRS) of an increase in use of other drugs, particularly cocaine, in the context of reduced availability of heroin in 2000-01 (Makkai & McGregor, 2003).

Indigenous community

There is scant published data regarding IDU among Indigenous communities. However, one study by Larson, Shannon and Eldridge (1999) reported that amphetamines were the most commonly injected drugs by a group of 77 known illicit drug users in Brisbane. All but one respondent had injected amphetamines and 73% reported amphetamines to be the last drug injected.

In the same year, an examination of hospital separation data recorded between 1980–95 was undertaken in Western Australia to determine the extent of recorded illicit drug problems among Indigenous and non-Indigenous Australians (Patterson, Holman, English et al., 1999). Data revealed a substantial increase in admissions of Indigenous people for amphetamine abuse, dependence and psychostimulant poisoning from 1980–85 to 1991–95 (Table 8). Despite similar increases in admission

rates for non-Indigenous patients, the proportion of Indigenous admissions for amphetamine abuse and dependence are proportionately greater than would be expected, given that Indigenous people represent about 3% of the population.

Table 8: Numbers of first-time hospital admissions with illicit drug problems in Western Australia, 1980 –1995 (Patterson et al., 1999)

	Indigenous admissions (numbers)			Non-Indigenous admissions (numbers)		
	1980–1985	1986–1990	1991–1995	1980–1985	1986–1990	1991–1995
Cocaine abuse	–	–	–	6	10	43
Cocaine dependence	–	–	–	6	7	7
Amphetamine abuse	–	3	81	31	89	980
Amphetamine dependence	–	3	28	13	32	200
Psychostimulant poisoning	–	4	10	35	84	134

More recently, Shoobridge, Vincent, Biven and Allsop (2000) reported results of interviews conducted with 25 Indigenous people in South Australia (19 males, median age 30 years), to determine the prevalence and impact of IDU on a small community. The investigators reported that injection of more than one drug class during the preceding 12 months was common (mean two classes). Amphetamines (76%) were the third most commonly used drug after tobacco (96%) and cannabis (88%) during the previous 12 months and a total of 96% of the sample had used amphetamines some time during their lives. Nearly half of the sample nominated an amphetamine as the first drug they had injected and the investigators noted unsafe injecting practices including some needle or other equipment sharing. Those interviewed reported considerable concerns regarding the negative social, financial and health consequences of their IDU on the small community (Shoobridge et al., 2000).

Further studies into the impact of psychostimulants on the Indigenous community in various locations throughout Australia is required to inform the development of culturally and geographically appropriate public health interventions.

Injecting drug users (IDUs)

Methamphetamine and cocaine are the most commonly injected psychostimulants, with injection of ecstasy being rare. Methamphetamine injection is far more common than cocaine injection, with cocaine injection occurring mostly in Sydney. The Australian Needle and Syringe Program Survey reports data collected from a cross section of national needle and syringe program users, including information on the last drug injected and hepatitis B, C and HIV status (MacDonald et al., 2002). About 2% of IDUs surveyed through the annual NSP Survey reported cocaine as their last injection, in comparison with around 20-30% for amphetamines (mostly methamphetamine).

There are vast inter-jurisdictional differences in methamphetamine injection, with the highest proportion seen in Queensland, South Australia and Western Australia.

It is not possible to say whether this means there are 'more' methamphetamine injectors in these states, as it is not known how many IDUs exist within each state.

Table 9: Percentage of IDUs who report methamphetamine as their last drug injected, 2000-01 (MacDonald et al., 2002)

	Methamphetamine last injection (%)	
	2000	2001
Australian Capital Territory	6	41
New South Wales	12	17
Northern Territory	27	36
Queensland	38	51
South Australia	30	52
Tasmania	22	21
Victoria	6	25
Western Australia	23	56
Total	21	37

Note: Data represent findings from the Australian Needle and Syringe Program Survey, NCHECR.

Evidence suggests that there has been a recent swing away from heroin injection towards the injection of amphetamines among IDUs. According to MacDonald, Zhou and Breen (2002), "there was a consistent pattern of increased reporting of amphetamines and decreased reporting of heroin as the last drug injected in all states and territories" (p. 1). Reports of heroin as the last drug injected dropped from 56% in 2000 to 36% in 2001. Conversely, reports of an amphetamine as the last drug injected rose from 22% in 2000 to 37% in 2001. A preference for amphetamines over heroin may be due, in part, to a reduction of supply and the subsequent increase in cost of heroin during 2000-2001 (eg, Rouen, Dolan, Day, Topp et al., 2002) and the wide availability and comparatively low cost of amphetamines nationally (Topp, Kaye et al., 2002). However, the increase in the use of amphetamines was reported several years before the so-called heroin 'drought' and has continued since, suggesting that increasing methamphetamine injection seems to be an ongoing trend.

The IDRS, coordinated by the National Drug and Alcohol Research Centre (NDARC), New South Wales, has been collecting data from IDUs and key informants from selected locations nationally since 1997. Data regarding availability, purity, price and patterns of drug use is collected and combined with data from other key sources to provide an opportunity for comparisons across specific jurisdictions.

Data from the IDRS confirms that cocaine use is prevalent among IDUs in some cities (e.g. Sydney, New South Wales) (Darke, Kaye & Topp, 2002b), while cocaine is virtually unobtainable in others (e.g. Hobart, Tasmania) (Bruno & Mclean, 2002).

During the heroin shortage, reported use of cocaine by IDUs in New South Wales rose from 63% in 2000 to 84% in 2001 and six-month frequency of use increased from 12 as the median number of using days to 90 using days (Darke et al., 2002b; Day, Topp, Rouen, Darke et al., 2003). Similar rises were detected in Victoria, with Melbourne IDUs reporting an increase in the last six-month injection of cocaine from 6% in 2000 to 20% in 2001 (Fry & Miller, 2002). Research suggests that injectors use cocaine more frequently than non-injectors and are more likely to be dependent (Kaye & Darke, 2000; van Beek et al., 2001). Due to the short half-life of cocaine and rapid reduction in acute effect, users tend to inject the drug more frequently than those whose first drug of choice is heroin or an amphetamine (van Beek et al., 2001). This has particular implications for the health of cocaine users due to risks associated with frequent use (e.g. vein damage and mental health disorders), particularly in the context of the increasing popularity of injection. Risks associated with cocaine use are discussed in detail in Chapter 4: *Risks associated with psychostimulant use.*

The increase in the use of base and ice methamphetamine also became very apparent among IDUs during the 2001 heroin shortage. At this time an estimated 76% of IDUs in Australia had recently used methamphetamine, a notable increase from previous years. The increase of 2001 appeared to have stabilised in 2002. Still, 73% of IDUs reported recent use of methamphetamine and the presence of the more potent forms of methamphetamine was still evident. For example, one-quarter of the IDUs surveyed through the IDRS in Sydney had recently used crystalline methamphetamine and/or methamphetamine base, while exposure was substantially higher than this in South Australia (56%), Western Australia (74%) and Queensland (39%). This level of exposure to methamphetamine base and ice was similar to that seen in 2001, although markedly higher than previous years. For example, in 1999 only a handful of injectors in Sydney reported use of ice (3%) and 'base' methamphetamine was being reported for the first time. Even though exposure to base and ice were similar among injectors, ice was used less frequently than either base or powder methamphetamine. Powder methamphetamine was still the most common form of the drug used by injectors.

Trauma and emergency settings

Data pertaining to emergency presentations is not routinely recorded in Australia. However, investigators are able to track trends in the USA and the prevalence of psychostimulant use among acute presentations to emergency departments appears to be increasing in some areas of the USA. Schermer and Wisner (1999) reviewed toxicology results of all patients admitted to a large emergency department in California from 1989–1994. They found that the prevalence of methamphetamine positive toxicology nearly doubled from 7.4% in 1989 to 13.4% in 1994, while positive cocaine toxicology had only a modest rise from 5.8% to 6.2%. Methamphetamine-positive patients were most commonly injured in motor vehicle collisions or motorcycle collisions; cocaine-positive patients were most commonly injured by assaults, gunshot wounds, or stab wounds.

However, in Australia, emergency incidents related to the use of psychostimulants are also emerging as an area of concern. In 2001 the Queensland Ambulance Service (QAS) recorded more attendances to ATS-related incidents (n=219) than to non-fatal heroin overdoses (n=196) (Bates, Clark, Henderson & Davey, 2003).

The mean age of the patients requiring emergency assistance for ATS use was 23 years for females and 25 years for males. Although the data relating to ATS-related attendances in preceding years is not yet available for comparison, QAS staff have reported an increased demand for emergency responses to ATS cases over the past three years, with attendances complicated by the need to manage patients' behavioural disturbances such as agitation and potential for aggression (Australian Crime Commission, 2003).

Treatment settings

The Alcohol and Other Drug (AOD) Treatment Services National Minimum Data Set (NMDS) collects data on a routine basis on clients attending government and non-government treatment agencies (Australian Institute of Health and Welfare, 2003a). These data do not include treatment data from Queensland and also exclude methadone maintenance treatment, half-way houses, sobering up shelters and correctional institutions. However, they still provide an indication of the numbers seeking treatment primarily for psychostimulant use.

Data on the overall treatment demand for psychostimulants relative to other drugs can be seen in Table 10. Amphetamines represent the principal drug of concern for 9% of all clients that received treatment during 2000-01, being the third most common illicit drug for which Australians sought treatment after cannabis and opioids (30.6% and 14.2% of all drug and alcohol treatment clients respectively). In comparison less than 1% of treatment clients sought help primarily for ecstasy or cocaine.

Data from the NMDS has only been collected routinely since 2000-01. However, the national census on Clients of Treatment Service Agencies (COTSA) has been undertaken in 1990, 1992, 1995 and 2001 (Shand & Mattick, 2001) and provides a snapshot of people seeking treatment from government and non-government services on the day of the census. These have shown a steady increase in the proportion of amphetamine-related treatment admissions from around 4% (174 and 226 cases for 1990 and 1992 respectively) in the early 1990s to 6.5% in 1995 (308 cases) and 8.3% in 2001 (412 cases).

Gender breakdown among amphetamine treatment clients is very similar to that among amphetamine users in the general population, being a ratio of 64% male to 36% female and most are aged between 20–29 years (56%). Treatment seeking amphetamine users tend to be slightly older than the amphetamine users in the general population (73% vs. 78% under 30 years of age) as would be expected due to the natural lag between uptake of drug use and treatment seeking.

Relative to opioid drugs or alcohol, methamphetamine users appear to have relatively low contact with treatment services specifically for their amphetamine use. Roughly 7,000 methamphetamine users received treatment in 2000-01[2], in comparison with the 63,000 who used the drug regularly during this period. The low level of contact with services may reflect a low demand for services, or lack of appropriate and accessible services for this population. Around one-third (35%) of amphetamine clients self-refer for treatment, which is typical for drug treatment clients in general (34%).

2 Note. This figure excludes people seeking drug treatment in Queensland.

Table 10: Number and percentage of drug and alcohol treatment clients by drug type, 2000-01 (Australian Institute of Health and Welfare, 2003a)

	Number of clients			% of sample (N=76,944)[a]
	Male	Female	Total	
Alcohol	18,221	7,500	25,889	33.6
Opioids	14,867	7,871	23,230	30.2
Cannabis	7,775	2,930	10,798	14.0
Amphetamines	4,451	2,499	6,979	9.1
Cocaine	225	60	291	0.4
Ecstasy	91	48	139	0.2
Benzodiazepines	768	852	1,635	2.1
Other	3,977	2,922	6,968	9.1

[a] Includes 1,065 missing cases.

The majority of amphetamine clients inject the drug (75%) with smaller proportions smoking (3.3%), swallowing (9.5%) or snorting (3.8%) the drug. This is not surprising given evidence of injecting being associated with higher levels of dependence, but has important implications for treatment interventions targeting amphetamine users, particularly in terms of preventing the spread of blood borne viruses.

Hospital settings

In the year 2000–01, there were 2,384 hospital separations in Australia for mental and behavioural disorders due to psychostimulant use including caffeine (see Table 11) (Australian Institute of Health and Welfare, 2003b), this representing a stark increase on previous years. Most of this increase is due to psychotic disorders due to psychostimulant use, which increased from 200 in 1998-99 to 1,028 in 1999–2000 and a further but smaller increase to 1,252 in 2000–01. While this may be associated with the change in diagnostic coding from ICD-9 to ICD-10 in 1997–98, such a dramatic increase was not seen for disorders related to other drug classes. Hospital separations for psychostimulant use do not include those due to cocaine use. In comparison with other psychostimulant drugs there were few hospital admissions due to cocaine use, with 146 in 1998–99, 92 in 1999–2000 and 164 in 2000–01.

Most psychostimulant separations were for a psychotic disorder due to psychostimulant use (52%) followed by dependence (24%) and harmful use (15%). Of those with psychosis, most were treated in specialised psychiatric facilities (84%). Care of dependence was more likely to occur outside of psychiatric hospitals, with 70% of dependence separations being from a general hospital facility.

Average duration of hospital care for psychostimulant use was approximately five days. In terms of the duration of care required to treat problems, psychostimulants accounted for 12,194 patient days of care in 2000–01, similar to the number of care days for cannabis (14,060) and just under half that for opioids (29,464).

Patients seen in hospitals for psychostimulant use were older than psychostimulant users in the general population, but most were still aged less than 30 years (67%). Similar to the gender breakdown among the general population and the treatment population, 67% of hospital separations due to psychostimulant use were male.

It should be noted that these data represent only mental and behavioural problems due to psychostimulant use and not physical health problems. Moreover, these data do not reflect the incidence of mental and behavioural disorders due to psychostimulant use in the overall population. Also, trends seen in these data may be affected by variations in factors such as service provision, hospital practices and diagnostic coding practices.

Table 11: Australian hospital separations for mental and behavioural disorders due to use of psychostimulants including caffeine by principal diagnosis, 1998–99 to 2000–01 (Australian Institute of Health and Welfare, 2003[a])

	1998–99		1999–00		2000–01	
Acute intoxication	30	(3.2%)	132	(6.5%)	112	(4.7%)
Harmful use	87	(9.3%)	288	(14.1%)	318	(13.3%)
Dependence	370	(39.5%)	453	(22.2%)	545	(22.9%)
Withdrawal	25	(2.7%)	75	(3.7%)	97	(4.1%)
Withdrawal with delirium	1	(0.1%)	11	(0.5%)	9	(0.4%)
Psychotic disorder	200	(21.3%)	1,028	(50.3%)	1,252	(52.5%)
Amnesic syndrome	0	(0%)	5	(0.2%)	2	(0.1%)
Residual and late-onset psychotic disorder	1	(0.1%)	4	(0.2%)	1	(0.0%)
Other mental and behavioural disorders	5	(0.5%)	12	(0.6%)	13	(0.6%)
Unspecified	219	(23.4%)	36	(1.8%)	35	(1.5%)
Total	938	(100%)	2,044	(100%)	2,384	(100%)

Note: These figures do not include hospital separations for cocaine.

Arrests and seizures

Arrest and seizure data refer to ATS as a class of drugs including amphetamines, methamphetamine and ecstasy related drugs. The supply of ATS in Australia has increased dramatically over the past five years, with seizures increasing tenfold from 156 kg in 1996–97 to just over 1.8 tonnes in 2001–02 (Australian Bureau of Criminal Intelligence, 2002). Of ATS, most 'amphetamines' consist of domestically produced methamphetamine, although there has been a recent increase in the importation of methamphetamine, particularly high purity crystalline methamphetamine. Most ecstasy available in Australia is thought to be imported. Table 12 shows the increase in both arrests for ATS providers and consumers over the past five years.

Overall, the number of arrests in Australia for ATS is over tenfold more than for cocaine. Border detections of cocaine have increased since 1998-99 from under 100 kg per year to the largest ever seizure of 938 kg in Western Australia in July 2001.

Table 12: Number of arrests for ATS and cocaine in Australia, 1997–98 to 2001–02

		1997–98	1998–99	1999–00[a]	2000–01[b]	2001–02[c]
ATS						
	Consumer	**3,349**	**4,976**	**6,252**	**6,721**	**5,815**
	Provider	**1,417**	**1,608**	**1,829**	**2,113**	**2,212**
	Total	**4,766**	**6,584**	**8,081**	**8,834**	**8,027**
Cocaine						
	Consumer	**378**	**462**	**253**	**405**	**378**
	Provider	**146**	**109**	**180**	**246**	**234**
	Total	**524**	**571**	**433**	**651**	**612**

a 1999–2000 data exclude 493 arrests where drug type was not recorded and 1,725 arrests where consumer/provider information was not recorded.

b 2000–01 data exclude 1,543 arrests where consumer/provider information was not recorded. Figures for 2000-01 have been amended to include revised figures from South Australia.

c 2001–02 data exclude 588 arrests where consumer/provider information was not recorded.

A recent trend in ATS is the emergence of different physical forms of methamphetamine. Most 'amphetamines' available in Australia are actually methamphetamine and this has increasingly been the case over the past decade. In 2001–02 methamphetamine made up 97% of all seizures of either methamphetamine or amphetamines. While the most readily available form of the drug remains low purity powder methamphetamine, increasing availability of so-called 'base' methamphetamine and high purity crystalline methamphetamine has steadily increased since around 1998. It is assumed that the 'ice' available in Australia is imported rather than locally produced, although there has been a single recent detection of a clandestine laboratory in Australia producing ice. The so-called base methamphetamine available in Australia is probably not actually true base methamphetamine, which is an oil, but the same form of methamphetamine found in the powder form of the drug (ie. methamphetamine hydrochloride). The gluggy, oily or wet appearance is thought to result from residual products left over from the manufacture process. This form of methamphetamine is usually more pure as it has not been 'cut' to the same extent as the classic powder form of the drug.

Methamphetamine tablets also appear to be increasingly common, the main market for these being among the 'party drug' scene where they are sold as ecstasy (INCSR, 2002). The Australian Bureau of Criminal Intelligence in its Australian Illicit Drug Report 2000–01 estimated that 80% of the tablets sold as 'ecstasy' in Australia today are actually locally manufactured methamphetamine tablets.

Conclusion

The availability and subsequent use of psychostimulants, particularly amphetamines and methamphetamine, is prevalent in Australia and ecstasy is commonly used by youth. The use of cocaine, while not as widespread as the use of other psychostimulants, is nonetheless a considerable concern due to its impact on the physical and mental health of problematic users. Use of ATS is more common among specific groups such as young people and IDUs and psychostimulants appear to be an integral part of the 'dance party scene' in this country and internationally. The increasing availability of more potent forms of psychostimulants such as methamphetamine and the increasing trend towards injection has corresponded with an increase in treatment demand and preliminary reports of additional demands for emergency services in some locations. Despite this, we still have no clear picture of the natural history of methamphetamine use among the general population or specific subgroups such as pregnant women, the Indigenous community and those in rural and remote areas. Nor can we estimate accurately the current number of dependent users to inform the planning and coordination of responsive treatment services. As indicated in Chapter 13: *Future Research Directions*, a considerable amount of research is required to shed light on this issue for the Australian context.

Chapter 3

Pharmacology of psychostimulants

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Key points

- Psychostimulants all act to increase activity of the neurotransmitters dopamine, noradrenaline and serotonin. MDMA and amphetamines act to enhance release of monoamines, whereas cocaine inhibits monoamine reuptake as well as blocking sodium channel activity.
- Psychostimulants all produce euphoria, wellbeing, energy, wakefulness and alertness. Additionally, MDMA is known for producing a greater sense of closeness to others.
- Psychostimulant use may lead to diverse toxicity presentations, including psychiatric, neurological, cardiovascular, cerebrovascular and metabolic presentations. These are not always dose-related and identification of risk factors is not yet consistently possible.
- Concurrent administration of psychostimulants and other drugs may alter desired drug effects and their toxicity profile.

Introduction to the monoamine system

Psychostimulants exert their effects by acting on a range of biological systems. One of the primary targets of psychostimulant activity is the monoamine system. Monoamines refer to the particular neurotransmitters dopamine, noradrenaline and serotonin. Dopamine and noradrenaline are sometimes also referred to as catecholamines. These neurotransmitters are involved in mediating a wide range of physiological and homeostatic functions, which vary with the part of the brain being examined.

Dopamine

Dopamine is a modulatory neurotransmitter. It is important in the regulation of movement, cognitive processes such as attention and working memory and motivational behaviour (Tzschentke, 2001; Vallone, Picetti & Borrelli, 2000). It is the primary neurotransmitter involved in reward pathways that is considered important in mediating effects of drugs of abuse (Tzschentke, 2001). Dopamine acts on a range of dopamine receptors located in various brain regions and the periphery.

Noradrenaline

Noradrenaline (also called norephinephrine) acts on the adrenergic (or sympathetic) nervous system and is involved in mediating cardiovascular effects, arousal, concentration, attention, learning and memory (Ressler & Nemeroff, 1999). Noradrenaline acts on adrenergic receptors in the Central Nervous System (CNS)

and the periphery. There are two types of adrenergic receptors (a and b) and for each type there are a number of subtypes (Lynch, Harrison & Pearson, 1994; Michelotti, Price & Schwinn, 2000).

Serotonin

Serotonin is a neurotransmitter in the CNS, but is also present in platelets and the gastrointestinal mucosa. It is also known as 5-hydroxytryptamine, or 5-HT. It is involved in a variety of physiological processes, including regulation of smooth muscle function, blood pressure regulation and both peripheral and CNS neurotransmission. In the CNS it is involved in complex behaviours such as mood, appetite, sleep, cognition, perception, motor activity, temperature regulation, pain control, sexual behaviour and hormone secretion (Kema, de Vries & Muskiet, 2000; Saxena, 1995). Serotonin acts on serotonin (5-HT) receptors, of which there are many types and subtypes (e.g. 5-HT1A, 5-HT2C).

Neurotransmitter action

These neurotransmitters are synthesised within particular neurons and stored in vesicles. To exert an effect, they are released into the synapse where they are able to act on receptors. Their action at receptors is terminated either by being broken down by enzymes such as monoamine oxidase or being returned to the nerve terminal by a reuptake transporter. Psychostimulants may increase or enhance the activity of dopamine, noradrenaline or serotonin by either increasing release, blocking reuptake, inhibiting metabolism or acting directly on a receptor.

Pharmacology of amphetamines

Chemistry

Amphetamines and methamphetamine are synthetic substances that do not exist in nature. They are weakly basic substances and can exist as either in a free base form or react with various acids to form salts such as amphetamine hydrochloride. The salt forms of the amphetamines are highly water-soluble whereas the free base forms are less so (Budavari, 1996).

Amphetamines

Amphetamines are structurally similar to dopamine and noradrenaline. They are a chiral molecule; that is, they can exist in two different chemical forms (enantiomers) that are identical in two dimensions, but in three dimensions they are mirror images of each other. The enantiomers of amphetamines are usually referred to as dexamphetamine (also denoted as S(+)-amphetamine) and levoamphetamine (also denoted as R(-)-amphetamine). Dexamphetamine is more centrally active and therefore more of a 'typical' amphetamine than levoamphetamine (Ferris & Tang, 1979).

Methamphetamine

Methamphetamine only differs from amphetamines in the addition of a methyl group on the chain. As with amphetamines, it exists in two chemical forms (+) methamphetamine and (-) methamphetamine (Budavari, 1996).

Pharmacokinetics

Amphetamines may be administered orally, intranasally or intravenously. The peak response occurs one to three hours after oral administration (Angrist, Corwin, Bartlik & Cooper, 1987) or approximately 15 minutes after injection (Jonsson, Anggard & Gunne, 1971). A single dose may maintain an effect for up to 7–12 hours (Cook, Jeffcoat, Hill, Pugh et al., 1993). However, when urine is alkaline (pH greater than 6.7), the half-life may increase to 18–34 hours (Anggard, Jonsson, Hogmark & Gunne, 1973; Wan, Matin & Azarnoff, 1978).

Amphetamines are metabolised by the liver by a range of enzymes, including cytochrome P450 2D6 (Li, Wang, Pankiewicz & Stein, 2001; Wu, Otton, Inaba, Kalow & Sellers, 1997). Metabolites include 4-hydroxyamphetamine, 4 hydroxynorephedrine, hippuric acid, benzoic acid and benzyl methyl ketone (Kraemer & Maurer, 2002; Musshoff, 2000). Methamphetamine is metabolised to amphetamine. Some amphetamines are also excreted unchanged in the urine.

Pharmacodynamics

Amphetamines increase the activity of monoaminergic systems. The primary mechanism is by increasing release of dopamine from nerve terminals (Kegeles, Zea-Ponce, Abi-Dargham, Rodenhiser et al., 1999; Silvia, Jaber, King, Ellinwood & Caron, 1997). Amphetamines are thought to enter the nerve terminal via the transporter, disrupt storage vesicles of dopamine and reverse the direction of the dopamine transporter through which large amounts of dopamine are released (Leviel, 2001). The ability of amphetamines to release dopamine is dose-related (Kuczenski, Segal, Cho & Melega, 1995).

In addition to this, amphetamines are able to inhibit dopamine metabolism and its reuptake. Amphetamines are able to increase the release of noradrenaline and serotonin (Berridge & Stalnaker, 2002; Kuczenski et al., 1995; Rothman, Baumann, Dersch, Romero et al., 2001).

Methamphetamine acts by similar mechanisms, although some research suggests that amphetamines and methamphetamine may possess different neurochemical profiles in different brain areas (Shoblock, Sullivan, Maisonneuve & Glick, 2003).

Sex differences

There may be sex differences in acute responses to amphetamines and other psychostimulants. In animal studies, oestrogen enhances the acute behavioural and neurochemical responses to psychomotor stimulants in female compared to male animals (Becker, 1999).

Effects on the user

Sought-after effects

The psychological effects produced by amphetamines are dependent on dose, the characteristics of the individual and the context in which they take the drug. Amphetamines produce euphoria, mood elevation and a sense of wellbeing (Becker, 1999; de Wit, Enggasser & Richards, 2002; Johanson & Uhlenhuth, 1980). This is combined with an increase in energy and wakefulness, a reduction in fatigue and increased concentration and alertness (Chapotot, Pigeau, Canini, Bourdon & Buguet, 2003; Pigeau, Naitoh, Buguet, McCann et al., 1995).

Other behavioural effects

An increase in motor and speech activities may present as increased talkativeness (Higgins & Stitzer, 1989). Amphetamines can improve physical performance (Chandler & Blair, 1980). Performance of simple mental tasks may also improve (Brauer & De Wit, 1997; Soetens, Casaer, D'Hooge & Hueting, 1995; Wiegmann, Stanny, McKay, Neri & McCardie, 1996), although higher doses or chronic use are associated with deficits in cognitive and motor performance (Ornstein, Iddon, Baldacchino, Sahakian et al., 2000; Rogers, Everitt, Baldacchino, Blackshaw et al., 1999; Simon, Domier, Carnell, Brethen et al., 2000).

At higher doses, the euphoria becomes more intense, but adverse effects also increase. They include restlessness, tremor, changes in libido, anxiety, dizziness, tension, irritability, insomnia, confusion and aggression (Degenhardt & Topp, 2003). Teeth grinding may occur and may produce distinctive wearing of teeth (Richards & Brofeldt, 2000).

Psychosis, delirium, auditory, visual and tactile illusions, paranoid hallucinations, panic stages and loss of behavioural control (Angrist, Sathananthan, Wilk & Gershon, 1974; Degenhardt & Topp, 2003; Iwanami, Sugiyama, Kuroki, Toda et al., 1994; Janowsky & Risch, 1979; Miczek & Tidey, 1989) may occur. Delusions of being monitored with hidden electrical devices are common, as is the preoccupation with 'bugs' that are felt and seen on the skin, leading to picking and excoriation of the skin. Restless, choreoathetoid and tic-like movements are often present. Experienced amphetamine users may describe the combination of paranoia and compulsive movements as 'tweaking' (Forster, Buckley & Phelps, 1999). Alterations in consciousness may also occur (Nakatani & Hara, 1998).

Physiological effects

Amphetamines are sympathomimetic agents associated with a range of cardiovascular effects. Increases in both systolic and diastolic blood pressure are typically observed after amphetamine administration (Angrist, Sanfilipo & Wolkin, 2001; Brauer, Ambre & De Wit, 1996; Brauer & De Wit, 1997; Rush, Essman, Simpson & Baker, 2001). Effects on heart rate are varied. Amphetamines may have little effect on heart rate at low doses (Angrist et al., 2001; Rush et al., 2001), although higher doses may lead to increased heart rate (Brauer et al., 1996; Brauer & De Wit, 1997). Physiological effects of amphetamines may vary with the social context of use (de Wit, Clark & Brauer, 1997).

Adverse effects reported by methamphetamine users include sweating, palpitations, chest pain, shortness of breath, headache, tremors and hot-cold flushes (Degenhardt & Topp, 2003). In addition to their cardiovascular effects, amphetamines and methamphetamine are able to increase body temperature and stimulate the respiratory centre, increasing rate and depth of respiration (Mediavilla, Feria, Fernandez, Cagigas et al., 1979). They reduce appetite and may also increase metabolic rates (Jones, Caul & Hill, 1992).

Methamphetamine produces similar effects to amphetamines, but at smaller doses, it produces prominent CNS stimulation with fewer significant peripheral effects. At higher doses methamphetamine similarly increases blood pressure and cardiac output.

Toxicity

Use of amphetamines can lead to a range of toxic presentations. The toxic dose of amphetamines varies widely and whilst higher doses are more likely to produce toxic effects, toxicity is sometimes idiosyncratically observed after ingestion of low doses. Some studies have suggested that polymorphisms in the cytochrome P450 enzyme system (mainly CYP2D6) are responsible for individual variations in drug toxicity, although these findings have been largely refuted (Kraemer & Maurer, 2002).

Toxic central effects include psychosis (Iwanami et al., 1994), hyperthermia (Callaway & Clark, 1994) and seizures (Alldredge, Lowenstein & Simon, 1989; Hanson, Jensen, Johnson & White, 1999). Rhabdomyolysis may also occur (Richards, Johnson, Stark & Derlet, 1999).

Cardiovascular toxicity includes ventricular arrhythmias (Sloan & Mattioni, 1992), acute myocardial infarction (Bashour, 1994; Costa, Pizzi, Bresciani, Tumscitz et al., 2001; Hung, Kuo & Cherng, 2003) and cardiomyopathies (Hong, Matsuyama & Nur, 1991). Cerebrovascular crises may occur including stroke, aneurysm and cerebral haemorrhage (Biller, Toffol, Kassell, Adams et al., 1987; Buxton & McConachie, 2000; Chen, Liang, Lu & Lui, 2003; Moriya & Hashimoto, 2002; Perez, Arsura & Strategos, 1999; Sloan & Mattioni, 1992; Yen, Wang, Ju, Chen et al., 1994).

Use of methamphetamine may also produce neurological changes that may persist after cessation of drug use, often referred to as neurotoxicity. Research in both primates and humans suggests that chronic methamphetamine use leads to dopamine depletion, accompanied by reductions in other markers of dopamine function, such as dopamine transporters and enzymes (Davidson, Gow, Lee & Ellinwood, 2001). Changes may persist after periods of abstinence and may also occur in markers of serotonergic function (Davidson et al., 2001).

Although the precise mechanisms associated with these changes are not entirely clear, it is thought that they may be associated with excessive dopamine concentrations within the synapse (Davidson et al., 2001). However, excessive dopamine may not be essential for neurotoxic effects (Yuan, Callahan, McCann & Ricaurte, 2001). Other contributing factors may include hyperthermia, formation of reactive oxygen species or increased glutamate activity (Davidson et al., 2001; Miller & O'Callaghan, 2003). It has been suggested that these changes may be associated with motor and cognitive impairments (Volkow, Chang, Wang, Fowler, Leonido-Yee et al., 2001).

Pharmacology of cocaine

Chemistry

Cocaine (benzoylmethyl ecgonine) is the psychoactive alkaloid of the coca plant (Erythroxylon coca). Cocaine is the only naturally occurring local anaesthetic. Unlike amphetamines, which structurally resemble dopamine and noradrenaline, cocaine has a similar structure to other synthetic local anaesthetics. Like amphetamines, cocaine is a weakly basic substance and can exist in a free base form or as the salts of various acids (Budavari, 1996). The salt forms of cocaine are water-soluble; the free base form ('crack cocaine') is sufficiently volatile for it to be inhaled

via smoking. Salts of cocaine (e.g. cocaine hydrochloride) are both water and fat soluble (Budavari, 1996). Like amphetamines, cocaine also exists in two enantiomeric forms (Gatley, 1991).

Pharmacokinetics

Cocaine is well absorbed when administered via mucous membranes (e.g. intranasally), the gastrointestinal tract and intravenously. Peak concentrations occur within five to ten minutes after intravenous injection or smoking and within 60 minutes after intranasal administration (Cone, 1995). Cocaine is shorter acting than amphetamines and effects or blood levels may diminish after as little as one hour (Inaba, 1989).

Some cocaine is excreted unchanged in the urine, but the majority is metabolised to benzoylecgonine, ecgonine methyl ester, norcocaine and other metabolites (Jufer, Wstadik, Walsh, Levine & Cone, 2000; Klingmann, Skopp & Aderjan, 2001). Although cocaine has a short half-life, elimination half-lives of cocaine metabolites are substantially longer (Jufer et al., 2000). The half-life of cocaine may increase after chronic dosing (Jufer et al., 2000; Moolchan, Cone, Wstadik, Huestis & Preston, 2000).

Pharmacodynamics

Cocaine also enhances the activity of dopamine. It does this by blocking its reuptake into the nerve terminal via the transporter and thus increasing the amount of dopamine available to act at receptors in the synapse (Silvia et al., 1997; Volkow, Wang, Fischman, Foltin et al., 2000). Cocaine may also block reuptake of noradrenaline and serotonin (Rasmussen, Carroll, Maresch, Jensen et al., 2001; Ritz, Cone & Kuhar, 1990), with some authors suggesting that it may enhance noradrenaline release (Tuncel, Wang, Arbique, Fadel et al., 2002).

In addition to these effects cocaine is also a local anaesthetic agent. Like other local anaesthetics, it produces direct effects on cell membranes — cocaine blocks sodium channel activity and thus prevents the generation and conduction of nerve impulses in electrically active cells, such as myocardial and nerve cells (Knuepfer, 2003).

Effects on the user

Sought-after effects

Like amphetamines, cocaine produces euphoria and sustained mood elevation (Epstein, Silverman, Henningfield & Preston, 1999; Mendelson, Mello, Sholar, Siegel et al., 2002). It also increases energy and self-confidence, promotes talkativeness, alleviates fatigue and enhances mental alertness (Brownlow & Pappachan, 2002).

Other behavioural effects

Aspects of psychomotor performance may be enhanced (Stillman, Jones, Moore, Walker & Welm, 1993). At higher doses or during chronic use adverse effects increase. Euphoria may be replaced with restlessness, excitability, sleeplessness, loss of libido, nervousness, aggression, suspicion and paranoia, hallucinations and delusional thoughts (Estroff, Schwartz & Hoffmann, 1989).

Physiological effects

Cocaine use produces a wide spectrum of physiological effects. One of the most studied involves the effects of cocaine on the cardiovascular system. The cardiac effects of cocaine are complex and whilst they act as sympathomimetic agents, the actual effects observed vary with dose and route of administration.

In animal studies, results have been conflicting. Cocaine has been reported to produce increases in arterial systolic and diastolic blood pressures, left ventricular pressure, cardiac output and heart rate (Schwartz, Janzen, Jones & Boyle, 1989), whereas others demonstrated a decreased cardiac performance, reporting a dose-dependent decrease in blood pressure, coronary blood flow and cardiac output (Beckman, Parker, Hariman, Gallastegui et al., 1991).

Cocaine may produce a transient slowing of heart rate after use (Tuncel et al., 2002). It appears that at more moderate doses, the sympathomimetic effects of cocaine predominate, leading to an increase in blood pressure and heart rate. However, at higher doses or more rapid infusion rates, blood pressure and cardiac output are negatively influenced. With increasing doses of cocaine, the peripheral sympathomimetic effects may be limited by either the direct negative inotropic effects of cocaine (slowing heart rate) or by myocardial ischaemia (Baumann, Perrone, Hornig, Shofer & Hollander, 2000).

In human studies, cocaine administration leads to increased heart rate, systolic blood pressure and pupil diameter and reduced skin temperature (Stillman et al., 1993). Increases in myocardial (heart) oxygen consumption may be related to cardiovascular adverse events (Summers, Bradley, Piel & Galli, 2001). Cocaine also inhibits endogenous fibrinolysis, increases thrombogenicity and enhances platelet aggregation via increased production of thromboxane (Auer, Berent & Eber, 2001; Baumann et al., 2000).

Cocaine has a range of effects on the body's heat regulatory (thermoregulatory) system. It may lead to increased core body temperature, decreased heat perception and impairment of sweating and skin blood flow (Crandall, Vongpatanasin & Victor, 2002). This combination of increased heat production, impaired heat dissipation and altered behavioural responses to increased body temperature may lead to dangerous or fatal hyperthermia (Crandall et al., 2002). These effects may be amplified by the context of cocaine use, such as dancing in crowded nightclubs. Cocaine use may also produce headaches (Satel & Gawin, 1989).

Toxicity

Symptoms of intoxication include bizarre, erratic and violent behaviour. Users experience tremors, vertigo, muscle twitches, paranoia and other symptoms of psychosis. Physical symptoms include chest pain, nausea, intense thirst, blurred vision, fever, muscle spasms, convulsions and coma (Brownlow & Pappachan, 2002).

Chronic cocaine use can lead to a range of cardiac complications. Acute myocardial infarction and myocardial ischaemia are the most common cardiac complications associated with cocaine use (Hollander, Hoffman, Burstein, Shih & Thode, 1995; Qureshi, Suri, Guterman & Hopkins, 2001). A range of cocaine-related effects are thought to contribute to myocardial ischaemia and infarction risk. These include increased oxygen demand, vasoconstriction of coronary arteries, increased platelet

aggregation and thrombus formation (Lange & Hillis, 2001). Potentially fatal arrhythmias and dysrhythmias may also occur (Benchimol, Bartall & Desser, 1978; Nanji & Filipenko, 1984).

Longer-term complications include accelerated atherosclerosis, cardiomyocyte apoptosis, sympathoadrenal-induced myocyte damage, chronic arrhythmias, cardiac hypertrophy and dilated cardiomyopathy (Brownlow & Pappachan, 2002; Knuepfer, 2003).

Regular cocaine use has also been associated with a number of abnormalities in the cerebral vasculature. The most common complications are haemorrhagic or thromboembolic strokes, but cerebral haemorrhage may also occur. The pathogenesis of cocaine-related cerebrovascular events is complex. It has been suggested that contributing factors may include cocaine-related rapid increases in blood pressure, smooth muscle effects producing vasospasm and ischaemia, vascular malformations and enhanced platelet aggregation (Auer et al., 2001). Other neurological complications include seizures (Dhuna, Pascual-Leone, Langendorf & Anderson, 1991; Lason, 2001; Lathers, Tyau, Spino & Agarwal, 1988; Satel & Gawin, 1989); sensitivity to seizures may be increased by chronic exposure.

Some individuals are vulnerable to cocaine-induced excited delirium. This is characterised by hyperthermia, extreme behavioural agitation and, in some cases, violent behaviour. This may also result in cardiac collapse and sudden cardiac death. Rhabdomyolysis may also occur (Merigian & Roberts, 1987). This may be part of the same syndrome as delirium, induced by changes in dopamine processing associated with chronic use of the drug rather than acute toxic effects (Ruttenber, McAnally & Wetli, 1999).

Regular intranasal use of cocaine may lead to damaging effects on the nasal mucosa. This ranges in severity from chronic rhinitis, reduced sense of smell, nosebleeds and septal perforation (Schwartz et al., 1989) to more serious damage such as necrosis of the sinonasal tract and oronasal fistula (Braverman, Raviv & Frenkiel, 1999; Gertner & Hamlar, 2002; Mari, Arranz, Gimeno, Lluch et al., 2002). This is thought to be mediated by ischaemia secondary to vasoconstriction, although adulterants may also play a role (Mari et al., 2002). Smoking of crack cocaine can lead to a variety of acute pulmonary complications, including severe exacerbations of asthma and an acute lung injury syndrome associated with a broad spectrum of histopathologic changes ('crack lung') (Tashkin, 2001). Habitual cocaine smoking may also produce more subtle long-term pulmonary consequences due to chronic alveolar epithelial and microvascular lung injury (Brownlow & Pappachan, 2002; Tashkin, 2001) including pulmonary oedema and pulmonary haemorrhage.

It is unclear whether cocaine use produces neurotoxicity. Since cocaine does not induce dopamine release, it may pose a lower risk for neurotoxic effects than other agents such as methamphetamine (Cappon, Morford & Vorhees, 1998). Cocaine use has been associated with certain neurological abnormalities (Fein, Sclafani & Meyerhoff, 2002; Franklin, Acton, Maldjian, Gray et al., 2002; Li et al., 2001). However, whether this represents neurotoxicity, neuroadaptation or other aetiology has not been established.

Pharmacology of MDMA (ecstasy)

Chemistry

MDMA is structurally related to amphetamines. One important difference between MDMA and amphetamines is the presence of the methylenedioxy group (-O-CH2-O-) attached to the aromatic ring. This attachment makes it also resemble the structure of the hallucinogen mescaline. Like amphetamines, MDMA is a synthetic substance that does not exist in nature.

Similarly to amphetamines and cocaine, MDMA can exist as a free base or as salts of various acids. Unlike these drugs, however, MDMA tends not to be inhaled in its free base form. This is because the methylenedioxy group raises the boiling point of the free base so high that it becomes too difficult to use in such a manner (Shulgin, 1986).

The salts are not volatile, but are quite soluble in water and thus can be administered intravenously, orally or intranasally. 'Ecstasy' tablets sold on the street do not always contain MDMA, but may contain methylenedioxyethylamphetamine (MDEA), methylenedioxyamphetamine (MDA), paramethoxyamphetamine (PMA), ephedrine, ketamine or a range of other compounds (Becker, Neis, Rohrich & Zorntlein, in press; Byard, Gilbert, James & Lokan, 1998; Holden & Jackson, 1996).

MDMA is a chiral molecule, meaning that it exists in two forms, which are denoted as S(+) MDMA and R(-) MDMA. S(+) MDMA is thought to possess greater central pharmacological effects (Steele, Nichols & Yim, 1987).

Pharmacokinetics

MDMA is readily absorbed from the gastrointestinal tract. Onset of action is within 30 minutes and peak serum levels occur after one to three hours (Mas, Farre, de la Torre, Roset et al., 1999). The elimination half-life is approximately seven hours (Mas et al., 1999). Like amphetamines, alkaline urine can increase the half-life of MDMA to 16-31 hours.

MDMA is metabolised in the liver to an active metabolite (methydioxyamphetamine), which has a longer half-life (16–38 hours). Whilst the enzyme cytochrome P450 2D6 is mainly responsible for the metabolism, other enzymes are also involved (Lin, Di Stefano, Schmitz, Hsu et al., 1997; Ramamoorthy, Yu, Suh, Haining et al., 2002; Tucker, Lennard, Ellis, Woods et al., 1994). Some of these are saturable, which means that once the enzymes are saturated, as the dose increases, disproportionately large increases in blood and brain concentrations occur, increasing risk of toxicity (de la Torre, Farre, Ortuno, Mas et al., 2000).

Pharmacodynamics

The primary mode of action of MDMA is as an indirect serotonergic agonist, increasing the amount of serotonin released into the synapse (Kalant, 2001). MDMA acts on the serotonin transporter and is transported into the nerve terminal. This promotes release of serotonin through the serotonin transporter by a process of transporter-mediated exchange. Whilst within the terminal, MDMA interferes with the storage of serotonin within the vesicles and thus increases the amount of serotonin available to be released (Rothman & Baumann, 2002). This process can lead to significant increases in serotonin available in the synapse.

MDMA is also able to enhance release of dopamine (Gold, Hubner & Koob, 1989; Lyles & Cadet, 2003) and noradrenaline (Frei, Gamma, Pascual-Marqui, Lehmann et al., 2001). It is presumed that MDMA's effects on dopamine and noradrenaline release are mediated in a similar manner to the serotonin release. MDMA can also inhibit monoamine reuptake and delay metabolism by inhibition of monoamine oxidase (Leonardi & Azmitia, 1994).

In addition to increasing extracellular levels of monoamines (Kalant, 2001), there is some evidence to suggest that MDMA might also have a range of other receptor effects, acting on 5HT2 receptors, a2-adrenergic receptors and M1 muscarinic cholinergic receptors (Battaglia, Brooks, Kulsakdinun & De Souza, 1988; McDaid & Docherty, 2001). It has relatively low affinity for D1 and D2 dopamine receptors (Battaglia et al., 1988).

Effects on the user

Sought-after effects

The sought-after effects for which MDMA is used are similar to those of amphetamines (Tancer & Johanson, 2001). Psychological effects include a sense of euphoria and wellbeing (Vollenweider, Gamma, Liechti & Huber, 1998), but unlike amphetamines, MDMA users particularly report a sense of closeness to others, greater sociability, sharpened sensory perception, extraversion and greater tolerance of others' views and feelings (Greer & Tolbert, 1986; Peroutka, Newman & Harris, 1988; Siegel, 1986). 'Positive mood state' has been cited as an important desired outcome of MDMA use (Solowij et al., 1992). Users have reported the sensation of 'an expanded mental perspective' and 'improved self-examination'. Hallucinations are sometimes reported (Peroutka et al., 1988).

Although MDMA can also produce wakefulness, increased energy and alleviation of fatigue (Tancer & Johanson, 2001), these effects need not be present at doses required to enhance mood (Vollenweider et al., 1998).

Repeated use of MDMA over a short time frame may lead to reduced drug effects, or tolerance. This has been observed in animal (Frederick, Ali, Slikker, Gillam et al., 1995) and human studies (Peroutka et al., 1988). Although the mechanisms of tolerance to MDMA are not well established, they may include short-term inhibition of serotonin synthesis or depletion of serotonin (Lyles & Cadet, 2003).

Other behavioural effects

Other psychological effects occurring during or after use of MDMA may include hyperactivity, racing thoughts, insomnia, mild hallucinations, depersonalisation, anxiety, agitation and bizarre or reckless behaviour (Cohen, 1995; Siegel, 1986). Occasionally, this may lead to panic attacks, delirium, or brief psychotic episodes. Although increases in sexual arousal are reported (Cohen, 1995), impairments in sexual functioning may also occur (Zemishlany, Aizenberg & Weizman, 2001). In the few days following drug use, reduced appetite, depression, anxiety, difficulty concentrating, muscle aches and fatigue have been reported (Cohen, 1995; Peroutka et al., 1988; Vollenweider et al., 1998). Chronic use may also be associated with depression, anxiety or cognitive impairments (Krystal, Price, Opsahl, Ricaurte & Heninger, 1992; Parrott, Buchanan, Scholey, Heffernan et al., 2002).

Physiological effects

Common adverse effects reported during the drug experience and shortly afterwards include dry mouth, ataxia, stiffness and pain in the back and limbs, headache, nausea, loss of appetite, blurred vision, insomnia and increased muscle tension, experienced as jaw clenching, tooth grinding and restless leg movements (Cohen, 1995; Downing, 1986; Greer & Tolbert, 1986; Vollenweider et al., 1998). Other physical symptoms may include reduced appetite and pupil dilation (Cohen, 1995; Greer & Tolbert, 1986; Mas et al., 1999). Increased body temperature stems from the drug's effects on the thermoregulatory system in the brain, but is not always observed in experimental conditions (Mas et al., 1999; Vollenweider et al., 1998).

As with amphetamines (O'Cain, Hletko, Ogden & Varner, 2000), acute cardiovascular effects of MDMA include dose-dependent increases in heart rate, blood pressure and cardiac output (Lester, Baggott, Welm, Schiller et al., 2000; Mas et al., 1999; Peroutka et al., 1988; Vollenweider et al., 1998), although animal studies suggest that these effects may be influenced by other factors such as ambient temperature (Irvine, Toop, Phillis & Lewanowitsch, 2001).

In an examination of responses during MDMA 'binge' administration in rats (Badon, Hicks, Lord, Ogden et al., 2002), the first binge led to an increase in mean arterial pressure and a biphasic effect on heart rate (decrease then increase). In subsequent binges, the reduction in heart rate was more pronounced and was accompanied by hypotension, suggesting that binge administration may produce a different profile of cardiovascular effects than that observed from alternative dosing regimes. Increases in heart rate and blood pressure or myocardial oxygen consumption may be clinically relevant in producing adverse reactions.

Toxicity

Severe MDMA overdoses are associated with intense sympathomimetic responses and active hallucinations as well as thermoregulatory, neurologic, cardiovascular, hepatic and electrolyte disturbances (Gowing, Henry-Edwards et al., 2002; Kalant, 2001). Neurological symptoms include agitation, hallucinations, seizures, coma and acute and chronic psychiatric symptoms (Kalant, 2001; Vaiva, Boss, Bailly, Thomas et al., 2001). Serotonin toxicity may occur in combination with antidepressants (Kaskey, 1992; Vuori, Henry, Ojanpera, Nieminen et al., 2003) or after MDMA alone (Brown & Osterloh, 1987; Henry, Jeffreys & Dawling, 1992; Screaton, Singer, Cairns, Thrasher et al., 1992). It has been suggested that jaw clenching commonly experienced by MDMA users may be a result of serotonergic overactivity (Parrott, 2002).

Cerebrovascular crises may also occur. One case study describes right-sided subarachnoid haemorrhage and middle cerebral artery aneurysm occurring after MDMA ingestion (Auer, Berent, Weber, Lassnig & Eber, 2002). MDMA-induced hyperthermia is modulated by serotonergic and dopaminergic systems. Severe hyperthermia can be associated with rhabdomyolysis, renal failure, disseminated intravascular coagulation, multiorgan failure and death (Kalant, 2001; Screaton et al., 1992). There is a strong correlation between hyperthermia and poor survival rates in patients who have ingested ecstasy (Kalant, 2001).

Cardiovascular effects include hypertension, which results from the enhanced vasoconstrictive effects of monoamines. Hypotension resulting from depletion of these chemicals may also occur. Supraventricular and ventricular tachyarrhythmias

with or without haemodynamic instability may also be present (Kalant, 2001). Unlike other amphetamine derivatives, MDMA has not been reported to result in acute myocardial infarction.

Use of MDMA may lead to various electrolyte disturbances. These include hypoglycaemia, hypernatraemia (related to reduction in body water) and hyponatraemia (may be related to the syndrome of inappropriate secretion of vasopressin or to hypervolaemia resulting from excess water ingestion) (Holden & Jackson, 1996; Traub, Hoffman & Nelson, 2002). Fatal hyponatraemia and cerebral oedema after MDMA use has been reported (Milroy, Clark & Forrest, 1996; Parr, Low & Botterill, 1997). In healthy volunteers, a single ingestion (47.5 mg) of MDMA led to increased vasopressin secretion and reduced sodium concentrations. There are isolated case reports of inappropriate vasopressin levels in MDMA users presenting with severe hyponatraemia.

Growing evidence suggests that MDMA may be hepatotoxic (Jones & Simpson, 1999). Liver damage may occur via a range of mechanisms (Beitia, Cobreros, Sainz & Cenarruzabeitia, 2000), but may be secondary to hyperthermia (Brauer, Heidecke, Nathrath, Beckurts et al., 1997; Carvalho, Carvalho & Bastos, 2001).

Ring substituted amphetamine derivatives, such as MDA, MDEA or PMA, may confer a riskier toxicity profile than MDMA. In particular, PMA is considered responsible for a number of ecstasy-associated deaths (Becker et al., in press; Felgate, Felgate, James, Sims & Vozzo, 1998), producing life threatening hypertension or hyperthermia. Fatalities have also occurred after MDEA ingestion (Weinmann & Bohnert, 1998).

A considerable amount of research examining psychostimulants and neurotoxicity has focused on MDMA. In animal studies, administration of high dose MDMA leads to long-term depletion of serotonin, accompanied by reductions in other markers of serotonergic function including serotonin metabolites, transporters and serotonin-specific enzymes, degeneration of serotonergic axons and axon terminals and increased numbers of glial cells (Commins, Vosmer, Virus, Woolverton et al., 1987; Ricaurte, DeLanney, Irwin & Langston, 1988; Rothman & Baumann, 2002; Schmidt & Taylor, 1987; Sprague, Everman & Nichols, 1998). Although some animal studies have been criticised for utilising doses that are not representative of doses consumed by humans, other research in primates has demonstrated serotonergic alterations using doses similar to those used by humans (Ricaurte et al., 1988; Ricaurte, Yuan, Hatzidimitriou, Cord & McCann, 2002).

A range of human studies suggest that MDMA users demonstrate reduced levels of serotonin metabolites, blunted neuroendocrine responses to serotonergic drugs, reduced density of serotonin reuptake sites, reduced glucose metabolism in certain brain regions and EEG patterns resembling those of ageing and dementia (Boot, McGregor & Hall, 2000). Challenges in this area include the difficulty in establishing causality in cross-sectional research and establishing the clinical significance of observed neurological changes (Kish, 2002; Lyles & Cadet, 2003). Nonetheless, it has been suggested that MDMA users at high risk for neurotoxic effects are those who use two or more street doses of MDMA at a time, those who use the drug fortnightly or more frequently, those who inject MDMA and those who use it for 24 hours or more (Boot et al., 2000).

The exact mechanisms of MDMA induced neurotoxicity are not known. Factors that may be involved in development of neurotoxicity include hyperthermia, formation of toxic metabolites, inhibition of serotonin synthesis, oxidative stress and free-radical formation, dopamine release and glutamate and nitric oxide pathways (Lyles & Cadet, 2003; Rothman & Baumann, 2002; Sprague et al., 1998).

Psychostimulants and other drug use

Psychostimulants are frequently used in combination with other substances. Use of other drugs in combination with psychostimulants may influence either the acute effects of either drug, or the longer-term risks associated with psychostimulant use.

Ethanol

Ethanol is often consumed before or during cocaine use. Some research suggests that the concurrent use of alcohol and cocaine leads to greater increases in blood pressure and heart rate than when using cocaine alone (Foltin & Fischman, 1988) and may increase the risk of cardiodepression, cardiac myopathies and other cardiovascular toxicities. It has been suggested that this toxicity may result from the formation of an active, ethanol-induced metabolite, cocaethylene, which is more toxic than cocaine or ethanol alone (Knuepfer, 2003). Studies suggest that cocaethylene is more euphorigenic and reinforcing than cocaine and that its pharmacological effects are additive or synergistic to cocaine and potentially more toxic (Hearn, Rose, Wagner, Ciarleglio & Mash, 1991; Landry, 1992; Randall, 1992).

In humans, the combination of cocaine and ethanol appears to exert more cardiovascular toxicity than either drug alone (Foltin & Fischman, 1988). In addition, ethanol appears to potentiate cocaine hepatotoxicity (Jover, Ponsoda, Gomez-Lechon, Herrero et al., 1991; Katz, Terry & Witkin, 1992; Landry, 1992).

Some evidence suggests that concurrent alcohol and methamphetamine use may slow metabolism of methamphetamine, potentially increasing risk of adverse effects (Shimosato, 1988). Mendelson and colleagues (1995) report that the concurrent administration of methamphetamine and ethanol reduced the subjective effects of ethanol, but did not alter the subjective effects of methamphetamine. The combination also increased systolic blood pressure without any changes in heart rate; they suggest that this increase in cardiac work associated with the combination could produce more adverse cardiovascular effects than observed when either drug is taken alone.

Laboratory studies suggest that cocaine may reverse certain alcohol-related psychomotor deficits (Pennings et al., 2002). One study (Hernandez-Lopez, Farre, Roset, Menoyo et al., 2002) reported that concurrent use of MDMA and alcohol produced greater MDMA plasma concentrations and greater euphoria. The combination also reversed the perception of alcohol-related sedation but did not reverse psychomotor impairment, which the authors conclude may impact upon issues such as road safety.

Nicotine

Cocaine has also been reported to interact with nicotine, producing a synergistic effect on dopamine release in the reward areas of the brain. Amphetamines are considered by some to be behavioural psychostimulants (Kolta, Shreve, De Souza &

Uretsky, 1985), meaning that use of amphetamines increases the rate of learned and stereotypic behaviours. One study has demonstrated that use of dexamphetamine led to dose-related increases in the number of cigarettes smoked, total puffs, weight of tobacco consumed, expired air carbon monoxide levels and subject-rated satisfaction derived from smoking (Henningfield & Griffiths, 1981).

Cocaine and nicotine may also exert synergistic effects on myocardial oxygen supply, arterial pressure and cardiac contractility (Moliterno, Willard, Lange, Negus et al., 1994). Since nicotine, like cocaine, is a risk factor for cardiac disease, it is thought that smoking may increase the incidence of cardiac complications arising from cocaine use (Lange & Hillis, 2001).

Smoking methamphetamine in combination with tobacco produces the pyrolysis product cyanomethylmethamphetamine (Sekine & Nakahara, 1987). This is thought to possess psychostimulant properties (Sekine, Nagao, Kuribara & Nakahara, 1997), but the potential toxicity of this product has not been established.

Cannabis

A number of reports suggest that cannabis may increase the subjective effects of cocaine, reduce duration of dysphoric effects and cause a greater increase in heart rate compared to use of either drug (Foltin, Fischman, Pedroso & Pearlson, 1987; Lukas, Sholar, Kouri, Fukuzako & Mendelson, 1994). Concomitant marijuana use may increase the pharmacologic and toxic effects of cocaine. Cannabis levels seem to be unaffected by cocaine. The mechanism of this interaction is not well established. It has been suggested that cannabis-induced vasodilation of the nasal mucosa leads to increased cocaine absorption, although these effects have also been demonstrated using intravenous cocaine (Foltin et al., 1987). Whether such an interaction exists between amphetamine-related compounds and cannabis has not been demonstrated.

Opiates

There are no particular interactions documented between opiates and psychostimulants. However, it has been reported that opiate withdrawal may increase the risk of aggressive behavioural reactions to psychostimulants (Miczek & Tidey, 1989).

Antidepressants

Antidepressants may be co-ingested with psychostimulants for a number of reasons such as concurrent treatment of depression, treatment of psychostimulant dependence or inappropriate attempts to enhance the effects of psychostimulants (MDMA in particular). A number of antidepressants can interact with psychostimulants to increase the risk of harms arising from psychostimulant use.

Increased risk of serotonin toxicity

Most antidepressants enhance serotonergic activity, sometimes acting on the serotonin transporter, which is also the site of action for MDMA. Concurrent use with other serotonergic agents may increase the risk of serotonergic side-effects. Assessment and management of serotonin toxicity is discussed in more detail in Chapter 5: *Psychosocial interventions.*

Vuori and colleagues (Vuori et al., 2003) describe four deaths following ingestion of MDMA and the antidepressant, moclobemide. The mode of death in each case was consistent with a serotonin syndrome. Another report (Kaskey, 1992) describes what was probably a serotonin syndrome after ingestion of MDMA and phenelzine. These antidepressants are monoamine oxidase inhibitors (MAOIs), which inhibit the enzyme responsible for metabolism of serotonin, noradrenaline and dopamine.

Reuptake inhibitors — a special case?

Most antidepressants used in Australia act by inhibiting reuptake of serotonin, rather than interfering with its metabolism, e.g. selective serotonin reuptake inhibitors (SSRIs). Both MDMA and SSRIs act on the serotonin transporter. Via this transporter, MDMA produces serotonin release and SSRIs remove serotonin from the synapse. The drug interaction arising from concomitant administration of MDMA and SSRIs depends on the temporal ordering of drug use.

Initial use of an SSRI will inhibit serotonin transporter function, impairing the activity of any subsequently used MDMA. The ability of pre-treatment with an SSRI to block the effects of MDMA has been demonstrated in animal studies (Shankaran, Yamamoto & Gudelsky, 1999; Stein & Rink, 1999). However, in the reverse scenario, if SSRIs are used after MDMA, the opposite interaction may occur. Initial use of MDMA increases release of serotonin; use of an SSRI after this release may prevent its removal from the synapse, leading to potentiation of serotonergic effects and possible toxicity.

The actual clinical outcome produced in real situations is difficult to predict. One report (Lauerma, 1998) describes a case where ingestion of the SSRI citalopram and an unknown quantity of MDMA led to symptoms resembling 'serotonin syndrome' which improved after cessation of the citalopram. Another case (Prior, Isbister, Dawson & Whyte, 2002) describes a patient maintained on dexamphetamine (15 mg daily) who developed signs of serotonin toxicity after initiating venlafaxine (a noradrenaline and serotonin reuptake inhibitor). After venlafaxine was discontinued and symptoms abated, he was initiated on citalopram, which led to re-emergence of serotonergic symptoms.

Sympathomimetic toxicity

Sympathomimetic toxicity may also occur. Concurrent use of amphetamine-related substances and non-selective MAOIs results in severe hypertension. Acute elevations in blood pressure have also been noted after co-ingestion of methylphenidate and a tricyclic antidepressant (Flemenbaum, 1971). This interaction has the potential to occur with other antidepressants that enhance noradrenergic activity, including moclobemide, tricyclic antidepressants and venlafaxine.

Changes in metabolism

Amphetamines, methamphetamine and MDMA are metabolised in the liver by a range of enzymes, one of which is cytochrome P450 2D6 (CYP2D6). Many antidepressants inhibit this enzyme and thus may have the potential to increase the blood levels of the psychostimulant and alter toxicity profiles (Ramamoorthy et al., 2002). Antidepressants which may inhibit CYP2D6 include paroxetine and fluoxetine and to a lesser extent sertraline (Hemeryck & Belpaire, 2002).

Conclusion

Much is known about the pharmacokinetics, pharmacodynamics, effects and toxicity of psychostimulants. Effects include euphoria, wellbeing, energy, wakefulness and alertness. Toxic effects include psychiatric, neurological, cardiovascular, cerebrovascular and metabolic presentations. Risks are a result of many factors and are not exclusively dose related. Several other drugs, including antidepressants, licit and illicit drugs, may alter psychostimulant effects and toxicity.

Chapter 4

Risks associated with psychostimulant use

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Key points

- Psychostimulant use, especially heavy use, has been associated with dependence; adverse effects on neurological, neuropsychological and physiological functioning and mental health; high levels of injecting and sexual risk-taking behaviour; and pharmacological risks concerning drug content and purity.
- Lack of knowledge about contents of pills is a significant pharmacological risk and although users operate with a range of 'safeguards' to reduce risk, users tend to become increasingly blasé over time.
- Many of the risks associated with psychostimulant use are influenced by the context of use.
- Users are often naïve to the risks associated with using psychostimulants and many believe that these drugs are relatively safe and benign.
- Users should be made aware of the potential health and other risks and given information to reduce the possible harms associated with psychostimulant use.

Introduction

The prevalence of psychostimulant use has increased (see Chapter 2: *Prevalence and patterns of psychostimulant use*) and some psychostimulants are perceived as relatively safe drugs by some users. Consequently, there is a growing body of literature examining the risks associated with varying levels of psychostimulant use. Risk domains reviewed in this chapter include neurological, neuropsychological, physiological, psychiatric, injecting, sexual and social risks. Research suggests that there are some significant risks associated with psychostimulant use, especially from heavy use. However, available evidence is sparse and often inconclusive.

Neurotoxicity

Risk of brain toxicity and receptor changes have been the subject of much research in the psychostimulant area, particularly for ecstasy. Chapter 3: *Pharmacology of psychostimulants*, details the literature on neurotoxic effects of psychostimulants.

Evidence of neurotoxicity has come mainly from animal studies and evidence in humans is inconclusive. Neurotoxic risks associated with psychostimulant use may include short- and long-term disruption to brain neurotransmitters that can result in significant health risks, such as hyperactivity, mental confusion, agitation, fever, tachycardia and tremor (known as the 'serotonin syndrome'), the effects of which can be fatal. Monoamine depletion can also lead to low mood, anhedonia and lethargy post-use ('come down'). Similar deficits have been identified after

methamphetamine use. Neurotoxic effects appear to persist for extended periods post-administration in animals (Parrott, 2002).

Given the risk of neurotoxic effects, users should limit their intake, especially new users, and be aware of possible signs of neurotoxic effects. Harm minimisation messages should include a psychoeducational component about the possible effects of psychostimulants.

Neuropsychological risks

Some identified long-term effects of ecstasy use include memory and neurocognitive deficits. Parrott (2002) has summarised the literature identifying significant memory deficits on neuropsychology tests in heavy long-term users and in young ecstasy users, particularly in immediate and delayed memory recall.

There has been a substantial amount of research into the neurocognitive deficits experienced by ecstasy users and evidence suggests that even in early and light users there is some evidence of attentional and working deficits (see Gowing, 2002). These may reflect serotonergic changes (Parrott, 2002) and may be permanent (Kalant, 2001).

Other cognitive functioning does not appear to be consistently affected, although there is some evidence that executive functioning (including decision-making, reasoning and problem-solving) may be reduced and that impulsivity may be increased (Kalant, 2001). However, some researchers have indicated that caution must be exercised in interpreting the data concerning long-term cognitive effects, as ecstasy use is most often seen in the context of polydrug use and the role of concomitant cannabis use in cognitive impairment has yet to be adequately described (Croft, Mackay, Mills & Gruzelier, 2001). Functional consequences of long-term use of ecstasy will remain uncertain until large epidemiological studies have been conducted (Gowing, Henry-Edwards et al., 2002).

Kosten, Malison and Wallace (1996) have described two broad categories of neuropsychological deficits from cocaine use. Mood changes, including depression, are likely to be a result of abnormalities in catecholamine receptors and are probably reversible, although in some cases have been found to be long lasting and may trigger an underlying propensity for mood disorder. Cognitive deficits may be due to neural loss (Kosten et al., 1996) and include an increase in theta brain activity and cerebral atrophy as a result of lowered cerebral blood flow leading to cognitive deficits even after use has ceased (Daras, 1996). The most common deficits are spatial learning, concentration and recent memory, but abnormalities have been found in motor tasks, including parkinsonian-like symptoms, such as motor deficits (Kosten et al., 1996).

Physiological risks

There are significant toxic effects from psychostimulant use. These are discussed in detail in Chapter 3: *Pharmacology of psychostimulants.*

Primary physiological toxicity effects of ecstasy use include liver toxicity (including jaundice); cardiovascular toxicity (including hypertension and tachycardia resulting in heart failure); brain haemorrhage; and cerebral toxicity leading to seizures and

disruption of respiration and circulation (Kalant, 2001). Hyperthermia and disturbance of metabolite balance are also commonly reported effects (Gowing, Henry-Edwards et al., 2002).

Volkow, Fowler and Ding (1996) have noted that the most frequent complication of cocaine use is cardiac toxicity, including myocardial infarction and fatal arrhythmias as a result of release of adrenaline and noradrenaline and the inhibition of noradrenaline reuptake. Daras (1996) noted that the risk of these cardiovascular events is substantially increased by the concurrent use of alcohol, which is a common pattern of polydrug use (Topp, in press). Hypertension is an acute effect that appears to subside (Daras, 1996).

Neurovascular complications of cocaine use that have been documented include ischaemic and haemorrhagic stroke, probably as a result of dose-related rises in arterial pressure and heart rate, as a result of inhibited reuptake of noradrenaline. Headaches, seizures and abnormal movements such as tics and choreoathetoid have also been documented (Daras, 1996).

Physiological effects of amphetamines include hyperthermia (Callaway & Clark, 1994) and seizures (Alldredge et al., 1989; Hanson et al., 1999). Cardiovascular toxicity (including ventricular arrhythmias, acute myocardial infarction and cardiomyopathies) have been noted (Bashour, 1994; Costa et al., 2001; Hung et al., 2003). Cerebrovascular problems may also occur such as stroke, aneurysm and cerebral haemorrhage (Biller et al., 1987; Buxton & McConachie, 2000; Chen et al., 2003; Moriya & Hashimoto, 2002; Perez et al., 1999; Sloan & Mattioni, 1992; Yen et al., 1994).

Risk reduction strategies should include a psychoeducational component to increase awareness and understanding of physiological risks of psychostimulant use. These effects are usually dose related, but low doses have also been known to produce acute physiological symptoms (see Chapter 3: *Pharmacology of psychostimulants*).

The effects of hyperthermia and metabolite imbalances can be exacerbated by the context of use, such as the rave or dance party environment. Users should be made aware of strategies to reduce these risks, including drinking appropriate amounts of water, reducing other concomitant drug use (including alcohol) and ensuring breaks from dancing.

Drug contents and purity

A significant pharmacological risk that may lead to additional complications, as with most illicit drugs, is the variable and unknown contents of street psychostimulant products. Content is highly variable across time and for individual doses. Until very recently, the majority of tablets seized in Australia as ecstasy have been found to be primarily methamphetamine (IDRS, 2002) and although the percentage of ecstasy in seizures has increased, it is still estimated to be only around 50% (IDRS, 2002). Often tablets sold as ecstasy have been found to contain a variety of other drugs such as ketamine (IDRS, 2002).

Hansen, Maycock and Lower (2001) surveyed 31 ecstasy users in Perth, Western Australia about the risks of using MDMA. One of the primary risks identified was lack of knowledge of the contents of the drug. They found that users relied on

'acceptable safeguards' to reduce risk (e.g. using a regular supplier and using with friends). They also found that over time, users became more blasé about their use and the risks involved, suggesting that regular and accurate psychoeducational interventions targeted at high-risk groups may be useful. Pill testing, although advocated by some as a harm reduction measure, is unreliable and subjective (Winstock, Griffiths & Stewart, 2001) and not likely to reduce the harms associated with unknown pill contents.

The purity of psychostimulants is variable and changeable. In Australia, the Illicit Drug Reporting System (IDRS) has documented changes in purity over several years and found that the purity of cocaine is relatively high (Darke, Kaye & Topp, 2002a) and the purity of methamphetamine, although much lower, has been increasing (IDRS, 2001).

Risks of injecting

In addition to the usual risks of injecting (such as blood borne virus transmission and vein care), there are some specific risks to injectors of psychostimulants.

Injecting of ecstasy is rare (see Chapter 2: *Prevalence and patterns of psychostimulant use*) and potential strategies to reduce initiation to injecting may be useful for ecstasy users, especially if they are likely to or currently inject other drugs (see Chapter 5: *Psychosocial interventions*) for an overview of strategies to reduce initiation to injecting).

However, injection of cocaine and methamphetamine is much more common. Following a survey among users of cocaine, van Beek et al. (2001) noted that the prevalence of injecting use of cocaine had recently increased. This is a particular problem given the short half-life of cocaine, making injecting typically more frequent than other drugs. Injectors tend to be former heavy snorters or injectors of other drugs who have added cocaine to their repertoire (Topp, Day & Degenhardt, in press).

van Beek et al (2001) noted that because of the short half-life of cocaine, the initial rush was often quickly followed by a rapid reduction in brain concentration, experienced as a 'crash', easily remedied by further use. They concluded that this pattern of use may result in binges lasting several days. Respondents in this study averaged 15 injections per day on their highest use days, with some injecting up to 60 times a day. The authors noted that the frequency of cocaine injecting resulted in problems with vein access and other skin problems, with thrombosed veins, unexplained cuts and bruises and abscesses frequently reported by injecting users. Compulsive skin picking and scratching in response to tactile hallucinations were also reported by chronic users. The authors also noted that cocaine users were at high risk of re-using needles when availability was limited, particularly because the nature of cocaine often induced a feeling of invincibility. Social support appears to reduce injecting risk and interventions that increase non-using social supports may be useful (Stein, Charuvastra & Anderson, 2002).

Topp, Degenhardt, Kaye and Darke (2002) have noted that base amphetamine, due to its consistency, has been associated with increased vascular damage among amphetamine users. In addition, Kaye and Darke (2000) noted that because amphetamine use tends to be a social activity, there may be more opportunities for

needle sharing than for other drug users. In this study, social dysfunction was related to degree of dependence among injecting users. Since injecting has a higher dependence potential than other forms of use (Gossop, Griffiths, Powis & Strang, 1992), injecting users are also at higher risk of both dependence and declining social functioning.

It is generally considered rare for injecting users to return to non-injecting practices. However, non-injectors may benefit from strategies aimed towards preventing initiation into injecting (see Chapter 5: *Psychosocial interventions* for a review).

Blood borne viruses and sexual risk-taking behaviour

Several studies have shown that psychostimulant users have higher levels of sexual risk-taking behaviour than non-users. Lenton et al. (1997) noted that young inexperienced users were largely unaware of the higher risk of unsafe sex whilst using psychostimulants.

Klitzman, Greenberg, Pollack and Dolezal (2002) found that gay ecstasy users tended to have more partners and more unprotected anal sex than non-users. These researchers and others (e.g. Binson, Woods, Pollack, Paul et al., 2001) have also noted that psychostimulant users are more likely to use 'sex-on-premises' venues than those who did not. This is an important finding as most new human immunodeficiency virus (HIV) infections in Australia are a result of unsafe sexual activity (National Centre for HIV Epidemiology and Clinical Research, 2002), particularly by men who have sex with men (MSM). In addition, Malbergier and Guerra de Andrade (2001) noted that cocaine dependence was more prevalent among users with HIV infection than those without HIV infection. Together, these results suggest that use of psychostimulants may be associated with an increase in sexual risk-taking behaviour and hence risk for blood borne virus (BBV) infection, as both are high in psychostimulant users.

van Beek et al. (2001) have identified sexual risk-taking behaviour as a special concern among cocaine users in Sydney. They noted that feelings of invincibility may lead to increased willingness to engage in unsafe sex and to take other sexual risks. Of particular concern was the high proportion (27%) of sex workers in their study. Most said they engaged in sex work to pay for cocaine and most used while they were sex working. The authors suggest that this pattern increases the likelihood of a cycle of using to work and working to use that may be difficult to break. According to some key informants, this may also increase willingness to engage in unsafe sex in order to get the work needed to pay for their use.

Psychostimulant exposure during pregnancy

There has been a relatively substantial amount of research into the effects of prenatal exposure to psychostimulants. Chapter 11: *Psychostimulant use in pregnancy and lactation* in this monograph details the studies in this area. Briefly, animal and human studies have found that although there is some transfer of psychostimulants from mother to foetus, there is little evidence of long-term effects on the child, neither in utero nor during development.

As noted in Chapter 11, while many drugs can induce pharmacological effects in the foetus during pregnancy, the number of drugs able to cause congenital malformations is small. Many factors (e.g. pattern of drug use or dose in relation to gestational age) influence potential drug effects on the foetus rather than drug use per se.

Binge administration of psychostimulants during pregnancy should be avoided and if drug use occurs once daily or less frequently, infant exposure to the drug can be minimised by breast-feeding just prior to the dose and avoiding feeding for a minimum of two to three hours after the dose. If drug use occurs more frequently (many times per day or in a binge), breast-feeding should be avoided during these times.

In a systematic review, Frank, Augustyn, Knight, Pell and Zuckerman (2001) concluded that there was no evidence of a consistent relationship between prenatal cocaine use and growth, intellectual development or language in early childhood, confirming the findings of earlier reviews (Lutiger, Graham, Einarson & Koren, 1991). They noted some evidence that motor development was impaired, but this did not extend past seven months and may have been related to tobacco exposure. Furthermore, there were no parent or teacher reported effects on child behaviour, but there was some evidence to suggest decreased attentiveness and emotional expressiveness. The authors concluded that in children under six years of age there was no clear evidence of toxic effects of cocaine use pre-birth and much of the deficits previously attributed to prenatal cocaine exposure are likely to be a result of exposure to other drugs, including tobacco and alcohol.

Hurt et al. (2001) also found that inner city children with and without prenatal cocaine exposure performed poorly on developmental tests and concluded that test scores reflect the socio-economic conditions of these children rather than the effects of prenatal cocaine exposure. Likewise, Ho, Karimi-Tabesh and Koren (2001) found that users of ecstasy were likely to have a cluster of socio-economic risk factors that increased a range of risks for the unborn child and to isolate ecstasy effects was difficult.

Das Eiden (2001) observed that mother-infant interactions may be diminished in cocaine exposed infants. The author suggested that interventions focusing on enhancing the quality of these interactions may be helpful for this population.

Flavin (2002) noted the significant socio-economic, emotional and physical disadvantage of cocaine using women. They suggested that such women were willing and able to engage in harm reduction activities, including reducing or quitting use. They further suggested that drug use treatment, as well as prenatal and maternal care, should be targeted at this group.

Dependence

Although psychostimulant use tends to be characterised by intermittent rather than daily use, a clear dependence syndrome has been described (e.g. Topp & Mattick, 1997b). Withdrawal is a key but not necessary feature of dependence (see Chapter 7: *Psychostimulant withdrawal and detoxification* for a review of withdrawal). Amphetamine dependence has been identified as a key factor in prompting users to moderate use and seek treatment (Hando, Topp & Hall, 1997). The reader is

referred to Chapter 1: *Background to the monograph* for an outline of the diagnostic criteria for dependence. Regular users (several times a week) are considered to be heavy users and are likely to manifest at least some symptoms of dependence.

Mental health risks

Psychostimulants have been implicated in a range of mental health problems and there has been an increasing interest in these sequelae. Issues related to comorbidity of mental health and psychostimulant use are reviewed in Chapter 10: *The psychiatric comorbidity of psychostimulant use*. Mental health effects such as these appear to be more often documented for amphetamine users than cocaine and ecstasy users.

In a review of the psychiatric case study literature, Soar, Turner and Parrott (2001) found that there were a substantial number of cases where ecstasy users had developed psychiatric symptoms, including psychotic symptoms (29%), anxiety and panic attacks (26%), delusions, hallucinations, illusions (26%) and depression (16%). These symptoms occurred with as little as one occasion of use and usually without a family or personal history of mental illness. Some of these case studies presented evidence that symptoms were potentially long term, continuing long after ecstasy use ceased. They also presented evidence from studies that showed that a significant proportion of users experienced subclinical symptoms. Clearly, however, there needs to be caution in interpreting these data, given the anecdotal nature of the studies and the likelihood of publishing bias (e.g. a bias towards publishing unusual or particularly interesting cases). These data do, however, support the commonly held view that there is a significant relationship between ecstasy use and psychiatric symptoms, although polydrug use and polydrug dependence may also influence the interpretation of these results.

In a longitudinal study, Lieb et al (2002) conducted detailed assessments with 2,462 adolescents and young adults over a 4-year period and found that ecstasy users were significantly more likely to attract a psychiatric diagnosis (according to DSM-IV criteria), including other substance use disorders, than both non-drug users and other drug users. They reported higher rates of prescription medication use than non-users, but not higher rates of health service utilisation. Interestingly, analyses showed that, in the majority of cases, these psychiatric symptoms occurred prior to ecstasy use, suggesting that adolescents and young people with symptoms of mental disorders are at an increased risk of using ecstasy.

van Beek et al (2001) noted that after a binge the crash, often increasingly more intense each time, is characterised by depression, fatigue and sleeping difficulties. Similar patterns of use and effects have been identified for amphetamine users, although the half-life of amphetamines is substantially longer that cocaine. In this group, depression and suicidal behaviour have been identified as significant risks during the 'crash' period (Kamieniecki et al., 1998).

Most respondents in the van Beek et al. study reported paranoia, hallucinations, depression, anxiety and obsessiveness. Other psychological problems identified by these users included low self-esteem, an altered sense of reality and feelings of hopelessness. The study did not identify any users who reported psychosis, but key informants reported that psychosis was common and problematic among users in

treatment. In addition, because of the significant paranoia and irritability common in cocaine users, referral to mental health services is often a difficult process. Informants noted that symptoms typically subsided when treated or when cocaine use ceased but often reoccurred when use resumed.

Back et al (2001) note that post-traumatic stress disorder (PTSD) is highly prevalent among cocaine users, with studies reporting up to 45% for lifetime diagnosis. Nearly a quarter would meet criteria for a current diagnosis of PTSD, significantly higher than the general population at around 8%. They also note a number of studies that have shown that cocaine use is associated with more severe psychiatric symptomatology, higher rates of DSM-IV Axis II (personality disorder) psychopathology and higher risk of re-victimisation. In a study of exposure therapy for cocaine users with PTSD, Brady, Dansky, Back, Foa and Carroll (2001) found that dropout rates were high but those who completed treatment reduced both cocaine use and PTSD symptoms.

Several studies have identified a higher than usual risk of suicidal behaviour among cocaine users. Roy (2001) compared a group of cocaine users who had attempted suicide with cocaine users who had never attempted suicide and found that suicide attempters were more likely to be female, have a family history of suicide, had more childhood trauma, comorbid substance use and depression and had particular personality characteristics, including introversion, neuroticism and hostility. However, in a study of IDUs, Malbergier and Guerra de Andrade (2001) concluded that depression was associated with suicide attempts but not with cocaine use in both HIV positive and HIV negative users.

Field, Diego and Sanders (2001) noted that adolescents at risk for depression were, among other factors, more likely to use cocaine and cannabis. However, in this study their relationship with parents and other indicators of wellbeing accounted for a majority of the variance.

In a review of adverse effects of psychostimulants, Kamieniecki et al.(1998) noted a particularly high prevalence of mental health symptoms among amphetamine users. For example, these authors noted that between 50% and 90% reported symptoms of depression, between 60% and 80% reported anxiety symptoms and between 30% and 80% had experienced symptoms of psychosis.

Israel and Lee (2001) and Kratofil, Baberg and Dimsdale (1996) both presented several case studies of self-mutilation after amphetamine use. In each case this was attributed to psychosis. Self-mutilation behaviours have also been seen in animal studies (Kratofil et al., 1996). Kratofil et al. (1996) noted that the behaviour was commonly motivated by religious, sexual and 'neurotic' themes, such as self-punishment and control. Self-mutilation included enucleation (amputation) of limbs and eyes, genital mutilation, stabbing and cutting injuries. The behaviours appear to be relatively rare and virtually unknown among women who use psychostimulants, but are probably under-reported (Israel & Lee, 2001).

Other mental health and psychological symptoms that have been noted as a result of psychostimulant use include agitation and anxiety, paranoia, hostility and aggression, confusion, delirium and hallucinations (especially auditory and tactile) (Baker & Lee, in press; Topp, in press).

Social risks

Strote, Lee and Wechsler (2002) conducted a survey of ecstasy use among college students. They noted that, although they spent less time studying, ecstasy users were not academic under-achievers and were as satisfied with education as non-using students.

Riley, James, Gregory, Dingle and Cadger (2001) identified four main risks for young people using ecstasy: driving on drugs, unprotected sex, over indulgence and injecting. They found that 85% of ecstasy users reported concurrent polydrug use, 30% had unprotected sex while using, 35% reported driving while intoxicated and nearly 1% reported injecting.

In a survey of users, van Beek et al. (2001) identified a number of significant social risks. 60% of respondents admitted to committing crimes they wouldn't normally engage in whilst using, 77% agreed that it made people socially unreliable and 64% believed that cocaine use interferes with relationships. Cocaine use has also been associated with violent injury (Chermack & Blow, 2002; Macdonald & Wells, 2001) as has amphetamine use (Wright & Klee, 2001).

Similarly, Winstock, Griffiths and Stewart (2001) found that dance music enthusiasts in London used substantial doses of multiple substances, including alcohol at hazardous levels. Over 5% of the sample injected, primarily amphetamines and heroin. They noted that purchasing patterns (an average of eight pills bought at a time) and the prevalent selling-on put users at risk of legal consequences. They also noted use patterns that put users at high risk of dependence.

Other risks

Lenton et al (1997) noted that inexperienced users were less likely to have knowledge of the risks of using psychostimulants. They also found that nearly two-thirds of ecstasy users tried ecstasy for the first time at a rave. Given the increased risk of the rave environment for physiological harms it is important that new users are educated about potential risks. They also cited studies that noted that new users of psychostimulants have romanticised notions of the drug's effects and are unaware of many of the negative effects of use. These authors also noted that users were largely unaware of the legal consequences of possession and selling of party drugs increasing their risk of police contact.

Conclusion

There is a range of risks that have been associated with the use of psychostimulants. Users, often naïve to the extent of the risks, should be made aware of them and ways to reduce the harms associated with using psychostimulants.

Section 3:
Clinical considerations

Chapter 5
Psychosocial interventions

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Key points

- There are clear signs that amphetamine use is increasing, however, there are few services in Australia that offer amphetamine-specific interventions;
- several assessment instruments with good psychometric properties are available to assess aspects of psychostimulant use and dependence;
- the literature is very limited in the number of well-conducted, controlled studies, but the available evidence suggests that outpatient cognitive behaviour therapy appears to be current best practice, although there is also some evidence that contingency management is effective;
- the service context in which interventions are provided is important in attracting and retaining people who present at treatment facilities;
- psychosocial approaches to psychostimulant dependence include outpatient interventions, residential treatment and therapeutic communities (TCs);
- completion of treatment (both outpatient and in the TC context) is associated with better outcomes;
- enhancement of residential treatment with behaviour therapy or cognitive behaviour therapy (CBT) is also associated with better outcomes; and
- service delivery may be enhanced by considering the following issues: attracting and retaining clients; establishing treatment partnerships; and monitoring and evaluating services.

This chapter has drawn on key major reviews of the effectiveness of psychosocial interventions for psychostimulant users (Baker & Lee, 2003; Gowing et al., 2001; Kamieniecki et al., 1998; Proudfoot & Teesson, 2000). The literature on psychosocial interventions among users of amphetamines, cocaine and ecstasy is examined. The information in this chapter summarises material from existing major reviews and considers more recent significant published studies from expert knowledge of the area of IDU.

Survey data pertaining to treatment seeking

The service context in which interventions are provided is important in attracting and retaining people who present at such treatment facilities. This is particularly important for users of amphetamines as they have not traditionally sought treatment

(Klee, 1997). Services are often reported by amphetamine users as not being amphetamine-oriented or attractive (Kamieniecki et al., 1998). There is little in the way of specific treatment available for amphetamine users and existing psychosocial treatment has often been designed to manage alcohol or opiate dependence (Vincent, Shoobridge, Ask, Allsop & Ali, 1998).

There are no controlled trials that we are aware of that have examined the impact of treatment context on entry into, or retention in, treatment among amphetamine users. However, researchers in the UK (Klee, Wright, Carnwath & Merrill, 2001; Wright & Klee, 1999; Wright, Klee & Reid, 1999) and Australia (Hando, Topp et al., 1997; Vincent et al., 1998; Vincent, Shoobridge, Ask, Allsop & Ali, 1999) have conducted surveys among amphetamine users to determine their treatment needs and preferences and barriers to effective service delivery.

In Sydney, Australia, Hando et al. (1997) conducted interviews with 200 regular amphetamine users and reported a growing need for treatment that focuses on amphetamine–specific issues. Amphetamine users who had attended treatment reported being most satisfied with natural therapies, consulting a general practitioner (GP), or moderating use either alone or with the support of friends and relatives. Amphetamine dependence was determined to be a key factor in prompting users to moderate use and seek treatment. Hando et al. recommended that interventions should aim to increase users' awareness of dependence symptoms and adverse consequences of dependence. The most popular treatment option reported was amphetamine substitution, although nominated by only 18% of the sample. Counselling was the second most popular treatment option with the authors recommending that evaluations of motivational interviewing (MI) and cognitive behaviour therapy (CBT) be conducted. The availability of natural therapies, such as massage and acupuncture, was recommended due to their attractiveness among amphetamine users (see Chapter 8: *Pharmacological interventions* for a brief review of alternative therapies). A range of goals, including abstinence and controlled use, was seen as important. Hando and colleagues (1997) have reported that most health practitioners remain largely unfamiliar with amphetamine-related problems and that education is required.

Vincent et al. (1999) conducted a survey among 100 amphetamine users in Adelaide, South Australia and compared 15 dependent amphetamine users who felt the need for treatment with 37 who did not feel they required treatment. Compared to the latter, those expressing the need for treatment were more likely to have experienced aggressive outbursts since starting to use amphetamines, to have experienced depression both before and after starting amphetamine use, and to report experiencing hallucinations and panic attacks since starting to use the drug. The best independent predictors of feeling the need for treatment were greater time spent unemployed, poor general health and the development of aggression since using amphetamines. Having previously sought help for amphetamine-related problems was best predicted by higher severity of dependence and poorer social functioning.

Given the extent of psychological morbidity among amphetamine users feeling the need for treatment, Vincent et al. (1998) have recommended that clinicians treating amphetamine users need to be skilled in the assessment, management and appropriate referral of people with comorbid mental health problems. Comorbidity experts have suggested that treating only one disorder, when a comorbid disorder is

present, can increase relapse risk for both disorders (Jenner, Kavanagh, Greenaway & Saunders, 1998).

In terms of services, the survey conducted by Vincent and colleagues (1999) revealed that GPs were seen by users as important sources of assistance. Vincent and colleagues suggested that GPs should be trained on the issues and that shared care arrangements between treatment agencies and GPs be encouraged. Peer support and education were also identified as potentially important, given the importance users placed on peer information and help. In addition to training GPs, peer educators and clinicians, Vincent et al. suggested that existing drug treatment services need to be improved to more adequately meet the needs of amphetamine users.

In Manchester, UK, Klee and colleagues have reported data on amphetamine users' attitudes towards treatment (Wright et al., 1999), factors associated with sustained abstinence (Klee, Wright & Morris, 1999), characteristics of amphetamine users who present to treatment and do not return (Wright & Klee, 1999) and on violent and aggressive behaviour among users (Wright & Klee, 2001). A matched case control study among 58 amphetamine users was conducted, where for each drug agency client interviewed, another amphetamine user (not in contact with drug services) was also interviewed (Wright & Klee, 2001; Wright et al., 1999).

Wright et al. (1999) recommended several methods to attract more amphetamine users into treatment. These included increased information about services available to amphetamine users, public display of agency policies on confidentiality, education and training of health professionals, availability of resources to improve staff credibility, consideration of specialist services for amphetamine users, drop-in centres that allow users to seek advice and support, partnerships between non-specialist services and drug agencies and interventions to inform and support families.

Similar to Australian findings, Klee and colleagues (1999) reported that motivation to abstain from amphetamines was driven initially by psychological health problems and severe social dysfunction. Maintenance of abstinence was achieved through professional support and/or informal support from partners, parents and friends during treatment. On the basis of these findings, Klee et al. (1999) recommended that interventions should be sensitive to the motives underlying the use of the drug and the functions it performs and aim to increase self-awareness; evaluate individual needs and potential for change; and focus on coping and interpersonal skills. They also recommended the development of treatment protocols.

Wright and Klee (1999) further argued that staff should have experience of working with stimulant users and offer support and guidance, especially at the user's first appearance at an agency. As many amphetamine users find it difficult to seek help, often because of their paranoid and aggressive behaviour, the development of effective treatment services would require effective responses to such presentations (Wright & Klee, 2001). Staff should be trained in communication strategies and safety procedures necessary to deal with aggressive behaviour (Centre for Mental Health, New South Wales Health Department, 2002).

John, Kwiatkowski and Booth (2001) compared AOD use, psychological morbidity and entry into treatment for substance abuse among 583 out-of-treatment IDUs. Compared to IDUs who used opiates only or opiates plus stimulants, those using only psychostimulants reported the most severe alcohol problems and had the

highest psychological symptom scores for paranoia, hostility and psychoticism and were far less likely to enter treatment. The authors recommended that clinicians should be able to treat potential psychological problems and alcohol abuse among psychostimulant users in order to offer a comprehensive and attractive treatment approach.

Thus, survey data have highlighted a number of key issues regarding service delivery to amphetamine users.

Clinical interventions

Drug use can be considered to exist along a continuum (Epstein, 2001), with experimental use at one end and regular (hazardous, harmful and dependent) use at the other. Other common types of use include instrumental or situational use and heavy although infrequent use (Wickes, 1992). Accordingly, interventions should be tailored to the client's point on the continuum (Wickes, 1992).

Approaches applicable to all psychostimulant users

Given the risks associated with psychostimulant use (detailed in Chapter 4: *Risks associated with psychostimulant use*), Hando and Hall (1993) recommended that all users be encouraged to practise safer sexual behaviours and use sterile injecting equipment if injecting. They further recommended that all users be informed about the adverse consequences of heavy use so that they can moderate or cease their use if adverse consequences are experienced (see Chapter 4: *Risks associated with psychostimulant use*) and if resources allow, be provided with a self-help guide (e.g. Lintzeris, Dunlop & Thornton, 1999; Topp, McKetin, Hando & Dillon, 2001).

Polydrug use

The majority of amphetamine users are polydrug users (Darke & Hall, 1995). Benzodiazepine use among amphetamine users is common (Darke, Ross & Cohen, 1994) and may be used to assist with amphetamine-related problems (Hando, Topp et al., 1997). Heroin has also been used to self-medicate or as a substitute for amphetamines (Hando, O'Brien, Darke, Maher & Hall, 1997). Furr, Delva and Anthony (2000) have reported a significant association between daily alcohol intoxication and methamphetamine ('ice') smoking, independent of potentially confounding factors such as other recent drug use, age and sex. The authors hypothesised that heavy drinkers may use ice to counteract the performance deficits arising from the CNS depressant effects of alcohol.

In their review of the physical and mental health problems experienced by amphetamine users, Vincent and colleagues (Vincent et al., 1998) recommended that an appropriately tailored management program should be negotiated with each client, that polydrug use needs to be considered and that the client may be placed on withdrawal or maintenance programs for other drugs while being treated for amphetamine use. O'Connor and Bradley (1990) have reported a case study successfully employing cognitive therapy for the treatment of amphetamine and benzodiazepine abuse.

Approaches to experimental psychostimulant use

Recommendations regarding approaches to experimental psychostimulant users have primarily focused on reducing transition to injecting. Hall, Darke, Ross and Wodak (1993) recommended that for people at risk of experimenting with amphetamines, clinicians should discuss the hazards of injection, without exaggerating the risks of occasional low dose oral use. For current users, advice to avoid injection and daily use has been recommended (Hando & Hall, 1993). Presently, there are no recommended safe limits for amphetamine use, but Hall and Hando (1994) have offered the following suggestions to reduce the risk of experiencing adverse effects of amphetamine use: to use less than twice a week and to use small amounts.

Darke, Cohen, Ross, Hando and Hall (1994) reported survey data from 301 regular amphetamine users regarding transitions between routes of administration of amphetamines. The main reasons given for the transition to injecting were enjoying the 'rush' from injecting and viewing it as a more economical and healthier way to use. Only 9% reported a transition away from injection, the main reason being concern over vascular damage. Darke et al. (1994) recommended that interventions to encourage safer use of amphetamines needed to address misconceptions that injecting is more economical and healthy and to emphasise the vascular problems associated with injecting.

Des Jarlais, Casriel, Friedman and Rosenblum (1992) conducted a randomised controlled trial (RCT) in order to evaluate the effectiveness of CBT in preventing transition to injecting among 104 intranasal heroin users in four sessions conducted across two weeks. The four-session small group prevention program has been described in detail by Casriel and colleagues (1990). At nine-month follow-up interviews there was a reduction in injecting in the intervention group with only 15% injecting during the follow-up period, compared to 33% of the control group. Thus it would appear that the intervention had a modest effect in reducing IDU. The authors suggested that intranasal heroin users needed to develop skills to manage social pressures to inject and resources to cope with a reduction in or elimination of their intranasal use. The study by Des Jarlais and colleagues represents a progressive utilisation of CBT among people at an early stage of change (Prochaska, DiClemente & Norcross, 1992) for injecting. Replication of the study with a larger sample of primary amphetamine users is necessary to determine its appropriateness for that group, although the intensity and extent of the intervention needed for sustained change is not yet known.

Hunt and colleagues (1998) reported three-month follow-up data from an uncontrolled study of a brief intervention (less than one hour) among current IDUs. Subjects reported increased disapproval of initiating non-injectors into injecting; reduced requests from non-injectors for subjects to assist with initiation into injecting; and reduced rates of injecting in front of non-injectors. Results suggested that brief interventions with the aim of preventing initiation of non-injectors into injecting are feasible, acceptable and potentially effective. However, only 27% of the sample of 73 subjects reported amphetamines as the main drug injected. Further RCTs of such interventions among amphetamine users are recommended.

Approaches to infrequent, heavy use of psychostimulants

Ten years ago, simple suggestions for interventions with infrequent heavy users were provided by Hando and Hall (1993). These included encouraging awareness of the purity of the drug; adverse consequences of heavy use; the need for moderation or cessation of use if adverse consequences were experienced; a false sense of psychomotor competence that may be produced when used in combination with alcohol; the need to avoid driving when using; and the need to take precautions to reduce harmful side-effects (e.g., obtaining the drug from reliable sources and using smaller amounts per occasion). However, there has been no published research since this time providing an evidence base for such simple interventions.

Approaches to instrumental use of psychostimulants

Instrumental users are those who use amphetamines for specific (non-recreational) purposes. They include, for example, long distance truck drivers, chefs, shift workers and students. No studies have been identified that offered specific harm reduction measures for this group. The advice for experimental and infrequent, heavy users (above) may be appropriate. CBT interventions such as those described below may be indicated. There may be additional opportunities for peer education among different occupational groups, but again these have not been systematically studied.

Approaches to ecstasy use

In general, ecstasy users do not present for treatment, except in instances of adverse effects serious enough to require medical assessment, or in instances of significant concomitant use of alcohol or other drugs. This is likely to largely be a reflection of typical patterns of ecstasy use. It also determines the type of interventions that can be considered for ecstasy users.

Ecstasy is generally used infrequently, in small amounts (1 to 2 tablets a time, taken orally), in association with social events. This pattern of intermittent use, that is usually self-limited, does not suggest the need for treatment specifically directed at ecstasy use. The occasional occurrence of significant adverse effects, particularly the highly publicised deaths of young people in Australia and the UK subsequent to ecstasy use, have negated the benign image of ecstasy to some extent. Such events have triggered primary prevention initiatives directed at the youth dance party culture.

Given the low numbers of ecstasy users seeking treatment, interventions need to be largely opportunistic. An approach that is well suited to these purposes is that of brief interventions (Barry, 1999). Brief interventions aim to investigate a potential problem and motivate an individual to begin to do something about their substance use. The primary goal of a brief intervention is to reduce the risk of harm that could result from continued substance use. Brief interventions on their own can promote behaviour change, or can act as the first stage of more intense treatment. Furthermore, brief interventions are applicable to individuals from a wide range of cultures and backgrounds and they can be used in a variety of settings, both opportunistic or within specialised substance abuse treatment.

Potential settings for opportunistic use of brief interventions to address ecstasy use include emergency departments of hospitals, subsequent to attendance for acute adverse effects, support services at major events such as dance parties, primary health care (doctors and dentists may detect ecstasy use in the context of other

consultations), law enforcement settings (subsequent to being found in possession of an illicit drug) and computer-based applications (the target group is likely to be frequent internet users).

These strengths identify the potential value of brief interventions in addressing ecstasy use, but brief interventions need to be structured and much of the evidence of their effectiveness relates to tobacco and alcohol abuse. The development and evaluation, through structured research, of brief interventions appropriate to ecstasy users and the various contexts for delivery of the interventions is required.

More intense forms of psychological interventions are appropriate to those with problematic ecstasy use. However, as discussed previously, this group is likely to constitute a minority of ecstasy users who are likely to be polydrug users and hence may require additional interventions appropriate to other drugs that are being used. In general, the psychosocial intervention modalities appropriate for cocaine and amphetamine users would also be appropriate for ecstasy users. This is particularly relevant as most ecstasy sold in Australia is actually methamphetamine as detailed in Chapter 2: *Prevalence and patterns of psychostimulant use*.

Assessment of regular amphetamine use

Teesson, Degenhardt and Hall (2002) have reviewed a number of self-report questionnaires for psychostimulant users, all of which have good reliability and validity. They emphasise the importance of conducting an assessment within the context of a non-confrontational, empathic and mutually respectful therapeutic relationship. The instruments they recommended were:

- Severity of Dependence Scale (SDS) (Gossop, Darke, Griffiths, Hando et al., 1995) for a quick and informative five item instrument that assesses subjective aspects of dependence, with a cut-off score of four (Swift, Copeland & Hall, 1998) (see Chapter 10: *The psychiatric comorbidity of psychostimulant use* for specific items).
- Voris Cocaine Craving Scale (Smelson, McGee, Bergstein & Engelhart, 1999) and the Drug Impairment Rating Scale (Halikas, Crosby & Nugent, 1992; Halikas, Nugent, Crosby & Carlson, 1993) for self-reported impairment and treatment outcome purposes.
- Cocaine Selective Severity Assessment (CSSA) (Kampman, Volpicelli, McGinnis, Alterman et al., 1998) for measurement of symptoms of early cocaine withdrawal.

Topp and colleagues (Topp & Darke, 1997; Topp & Mattick, 1997b) have validated the Severity of Amphetamine Dependence Questionnaire (SamDQ) (Churchill, Burgess, Pead & Gill, 1993) as an instrument measuring dependence and capable of discriminating between individuals with different use patterns. Proudfoot and Teesson (2000) also suggest that broad instruments such as the Opiate Treatment Index (OTI) (Darke, Hall, Heather, Wodak & Ward, 1992) and the Addiction Severity Index (ASI) (McLellan, Luborsky, Cacciola, Griffiths et al., 1985), which have good psychometric properties, are useful to assess drug use.

Psychosocial approaches to regular psychostimulant use (hazardous, harmful or dependent users)

Pharmacological approaches to psychostimulant dependence are reviewed in Chapter 8: *Pharmacological interventions.* Most of the psychosocial approaches described below are compatible with pharmacotherapy and many people are likely to benefit from a combination of both types of intervention.

Motivational interviewing (MI)

Following their survey of treatment preferences among regular amphetamine users, Hando et al. (1997) have suggested that MI may be appropriate for users who have difficulty perceiving amphetamine-related problems or who are not motivated to attend treatment. Vincent et al. (1998) have suggested that emphasising the associations between severity of dependence on amphetamines and poor mental and physical health may help improve motivation. They suggest that this information could be most effective if provided within the context of the damage to social functioning with which such problems may be associated. Hando et al. (Hando, Topp et al., 1997) have suggested that key factors in defining amphetamine use as a problem, such as dependence and financial difficulties, should be emphasised, increasing awareness of dependence symptoms and the possible adverse consequences of dependence. Treatment seeking amphetamine users have reported that they are especially interested in interventions that are amphetamine-specific, non-judgemental and allow a variety of goals, including abstinence and controlled use (Hando, Topp et al., 1997).

Behaviour therapy and cognitive behaviour therapy

There have been very few studies of non-pharmacological approaches for the treatment of amphetamine use (Baker, Boggs & Lewin, 2001a, 2001b) and the effectiveness of different types of psychological therapy for cocaine use has been found to be variable (Gowing et al., 2001). The American Psychiatric Association (APA) (1995) emphasises that the different findings may be due more to intensity of treatment than type of therapy. However, outcomes of the Collaborative Cocaine Treatment Study (Crits-Christoph, Siqueland, Blaine, Frank et al., 1999) suggest that differences may be due to the quality of treatments provided.

Psychosocial therapy for cocaine dependence has traditionally been based on the 12-step approach and much of the controlled research in this area has concentrated on comparing newer therapies with this approach. The APA (1995) concluded that attendance at self-help groups (which are generally based on the 12-step model) might improve long-term outcomes. They also noted that psychodynamic approaches have been the subject of little research to date, but that two psychotherapeutic approaches based on behavioural and cognitive behavioural theory have shown promise. These are discussed below, following consideration of assessment strategies.

Behavioural reinforcement

There is some evidence of the effectiveness of behavioural reinforcement and CBT from the cocaine literature that may be extrapolated for use with amphetamine users. However, caution is warranted because of both the differences between cocaine and amphetamine use and the fact that much of the research on the

treatment of cocaine use has come from the USA, which has a strong abstinence orientation and may influence the treatment goals and outcomes measured.

As reviewed by Proudfoot and Teesson (2000), Higgins and colleagues, in research on non-drug reinforcers, used vouchers that were exchangeable for retail items or housing and job opportunities as positive reinforcers for cocaine abstinence (Higgins, Budney, Bickel & Badger, 1994; Higgins, Budney, Bickel, Foerg et al., 1994). Vouchers were employed in combination with a community reinforcement approach (CRA). This intervention produced substantial reductions in rates of cocaine use. CRA involves individual therapy directed at relationships and other living skills in order to increase non-cocaine reinforcers in the individual's environment. The researchers found this approach to be superior to standard outpatient drug abuse counselling. In addition, there were significant improvements in outcomes for the voucher plus CRA compared with CRA condition (Higgins & Wong, 1998). Higgins et al. (1998) also found significantly greater abstinence rates for a group given contingent vouchers compared with another group given non-contingent vouchers. These researchers also incorporated monitored disulfiram therapy in their program for those cocaine users also abusing alcohol and found promising reductions in cocaine as well as alcohol use. Considering that it is estimated that some 60% of cocaine abusers are also alcohol dependent, this finding is important.

In his general review of literature on cocaine addiction, Platt (1997) commented that research had indicated that the magnitude of reinforcement and immediacy of reinforcement might be critical in determining efficacy of a voucher system. He also pointed to some research that has not supported the use of vouchers to encourage abstinence from cocaine, especially on a longer-term basis. In attempting to explain the disparities in the literature, he suggests that the study samples were from widely divergent social settings — those that obtained best results were from a rural environment, whilst those with negative findings were from an inner-city environment.

Subsequent to publication of Platt's review, there have been a number of published studies investigating the effectiveness of voucher systems. In two studies involving 90 severely socio-economically disadvantaged cocaine users (88% crack cocaine), Kirby et al. (1998) investigated the effect of adding voucher payments for cocaine-free urine screens to a comprehensive treatment package. The treatment package consisted of 26 sessions of CBT plus 10 one-hour sessions of interpersonal problem solving carried out over the 12 weeks of the study. In the first study, voucher delivery was on a weekly basis with initial values low, increasing with production of consecutive negative urine results and reset to zero on production of positive screens. In this study the use of vouchers was found to have no effect. This is consistent with Platt's view that negative results tend to be associated with an inner-city environment.

The second study involved 23 subjects. Half the group received vouchers on a weekly basis while the other half received vouchers immediately upon producing the cocaine-free urine. The values of the vouchers started high ($30 for the first nine cocaine-free specimens) with no punishment for positive screens. Repayments became more intermittent after this, but overall maximum earnings were greater. There was a trend for this system of voucher delivery to improve retention and attendance outcomes, but low numbers are likely to have prevented these differences from being significant. There were also significant improvements on measures of

abstinence for immediate compared with weekly voucher delivery. About half the participants on immediate voucher delivery completed treatment and showed continuous abstinence at one month following treatment, whereas no participant on weekly voucher delivery achieved one month of continuous abstinence. This finding provides some support to Platt's conclusion that immediacy of reinforcement may be an important determinant of efficacy.

Further support for this is provided by an RCT comparing behavioural day treatment (DT) only with DT plus abstinent-contingent housing (available immediately on achievement of four consecutive urine samples over two weeks) and DT plus work therapy during aftercare in a sample of homeless persons with substance use disorders (primarily crack cocaine) and non-psychotic mental disorders. DT was associated with greater abstinence at two and six months and more days of treatment attendance (Milby, Schumacher, McNamara, Wallace et al., 2000). The odds of being cocaine-abstinent increased with days of treatment attendance (Schumacher, Usdan, Milby, Wallace & McNamara, 2000).

Cognitive behavioural interventions

CBT for cocaine use is aimed at helping individuals to recognise that they have a problem with their cocaine use, to understand their problem and to assist users to modify the dysfunctional cognitions underlying this problem behaviour. Therapy typically involves skills training and practise to deal with craving, monitoring thoughts about drugs and monitoring high-risk situations associated with relapse (Carroll, 1998). Cognitive behavioural interventions have not generally been demonstrated to be superior to other psychotherapies in initiating abstinence, but research suggested that its effects may be more durable and thus protective against relapse. Furthermore, CBT may be more effective with more severely dependent users (Carroll, 1998). This was also the conclusion of the APA (1995).

Baker and colleagues (2001b), in an RCT, compared a brief cognitive behavioural intervention (either two or four sessions duration) with a self-help booklet (control condition). Participants were regular (at least monthly) users of amphetamines. Moderate reductions of amphetamine use were reported by both groups, but significantly more people in the CBT condition abstained from amphetamines at six-month follow-up compared to the control condition. This study demonstrated the feasibility of brief CBT for the treatment of regular amphetamine use.

Over a decade ago, Hawkins, Catalano, Gillmore and Wells (1989) reported 12-month follow-up data for a randomised trial of CBT (Hawkins, Catalano & Wells, 1986) among people in the re-entry phase of residential therapeutic communities (TCs). The intervention consisted of drug refusal and avoidance skills, problem-solving, social and stress coping skills, how to deal with depression or with being treated unfairly, coping with a slip into drug use and coping with personal high-risk situations. Community volunteers also became involved in sessions and attended bimonthly support groups for six months. Subjects were expected to remain in treatment during the 10-week period when the CBT group received their intervention. At 12-month follow-up subjects who completed CBT had significantly higher skill scores than did controls. The CBT intervention did not significantly affect subjects' drug use except for a marginal effect on amphetamine use ($p<.05$) at 12 months for the entire sample and for fully treated subjects at 6 months compared to controls. Urinalysis results corroborated self-reported drug use.

Hawkins et al. (1989) stated that the generalisability of their findings is questionable given that the subjects were a highly select sample of volunteers who had completed a lengthy and demanding drug treatment program. They also noted that the design, in which CBT was in addition to an already intensive and lengthy program, does not address the effectiveness of CBT as the primary treatment modality or in combination with other treatments (e.g. methadone maintenance treatment). In addition, these studies were not conducted among primary amphetamine users. However, this study provides some initial evidence that adjunctive CBT may be effective within the context of residential programs in reducing amphetamine use.

Maude-Griffin and colleagues (1998) compared CBT with 12-step facilitation in a randomised study involving 128 crack cocaine smokers. This was a socio-economically disadvantaged group with 75% homeless or marginally housed, 84% unemployed, 82% with comorbid psychiatric disorders (and almost half with two other psychiatric disorders) and a mean length of cocaine use of 19 years. Participants attended three groups and one individual therapy session per week over 12 weeks. Treatments were manualised and administered by counsellors with extensive experience, with the same counsellors administering both therapies. The 12-step facilitation group was encouraged to attend Cocaine Anonymous, while the CBT group was encouraged to attend Rational Recovery, a cognitively based self-help group.

Attendance at treatment groups was low — only 17 participants (13%) attended at least 75% of both group and individual sessions. Overall, 44% of the cognitive behavioural group and 32% of the 12-step facilitated group achieved four consecutive weeks of abstinence from cocaine ($p<0.05$). However, the outcomes varied for different subgroups of participants. For those assessed as having high levels of abstract reasoning, 50% in the cognitive behavioural group achieved four weeks of abstinence compared to 25% in the 12-step facilitated group. This result was virtually reversed (18% compared to 48%) for those assessed as having low levels of abstract reasoning.

For those assessed as having a low degree of religious belief, 48% in the cognitive behavioural group achieved four weeks of abstinence, compared to 12% in the 12-step facilitated group. For those assessed as having a high degree of religious belief there was little difference between the two groups: 35% in the cognitive behavioural group and 40% in the 12-step facilitated group achieved four weeks of abstinence. This variability indicates the importance of providing treatment that is relevant to the individual.

Monti et al. (1997) compared the effects of adding brief coping skills training or 'attention placebo' to a comprehensive treatment package incorporating both 12-step and social learning principles. The coping skills training was directed towards high-risk situations while the 'attention placebo' involved the same number of hours in manualised meditation and relaxation training, which the researchers regarded as a credible but ineffective treatment. Both approaches were administered on an individual basis in eight one-hour sessions. Self-reported cocaine use at six months pre-treatment and one-month and three-month follow-up assessments was confirmed with urine tests as well as collateral reports. Demographic information and indices of psychosocial wellbeing were also obtained at pre-treatment and 3-month follow-up.

Monti et al. found that there were no differential effects of the two additional interventions in terms of total abstinence during the 3-month follow-up period, or on longest continuous abstinence. However, there were significant reductions in days of use as well as length of bingeing for participants in the coping skills treatment condition compared with placebo, variables that are considered to be more sensitive than the categorical abstinence measure.

Overall, the authors concluded that the brief coping skills intervention led to shorter and less severe relapses. These results fit with prior findings that interventions based on cognitive behavioural principles may have more impact on longer-term relapse prevention than on more immediate broad measures of drug use or abstinence.

In a multicentre collaborative cocaine treatment study, supported by the National Institute on Drug Abuse in the US (NIDA) (Crits-Christoph et al., 1999), 487 participants were randomised to four treatment conditions:

(1) individual drug counselling plus group drug counselling;

(2) cognitive therapy plus group drug counselling;

(3) supportive-expressive therapy plus group drug counselling; and

(4) group drug counselling alone.

All treatments were manualised with a six-month active phase and a three-month booster phase. The individual drug counselling and group drug counselling were based on the disease model of substance use, with strong encouragement to participate in 12-step programs, and they taught participants how to progress through stages of recovery from addiction. Cognitive therapy followed a program for substance abuse based on social learning theory. Supportive-expressive therapy was based on the psychoanalytic approach to treatment for substance abuse.

The Crits-Christoph et al. study employed a composite outcome measure of cocaine use, which ascribed the rating 'abstinent' or 'not abstinent' for each month. Any indication of drug use from either urine tests, Addiction Severity Index responses or a weekly cocaine use inventory led to a 'not abstinent' rating. Where no measures were available (which occurred on 19% of possible occasions) participants were rated as 'not abstinent'. However, as only 42.6% of all potential urine specimens were collected, this global abstinence rating may have been unreliable.

Participants in the study conducted by Crits-Christoph et al. (1999) were obtained from a total of 2,197 persons screened by phone, of whom 1,777 met inclusion criteria and 870 were considered to have begun what was termed the orientation phase of treatment. During this phase participants were required to attend three clinic visits within 14 days to demonstrate their motivation. At this time the participants were encouraged by group counsellors to attend self-help groups based on 12-step principles. Housing, employment and financial needs were also addressed during the orientation phase. Only 487 (56%) proceeded to randomisation and the active therapy stage.

It was found that participants in the three groups which received individual therapy had significantly better outcomes than those who received only group drug counselling. Despite poorer retention, it was also found that individual counselling plus group drug counselling was more effective than cognitive therapy plus group

drug counselling or supportive-expressive therapy plus group drug counselling in promoting abstinence (in the past 12 months).

However, as the authors point out, the superiority of individual counselling plus group drug counselling in this study may be due to the additive effect of the single focus (on 12-step principles). Further, as Carroll (1999) comments, a focus on the 12-step principles in the orientation phase may have proven selective for those who were more amenable towards this approach. This, along with possible differential attendance at AA-type self-help meetings, would also help explain the need for less treatment in this group and thus lower retention rates. These factors are yet to be examined by the researchers.

Crits-Christoph et al. (1999) suggested that one reason for the effectiveness of individual counselling, when it had not been found to be effective in previous studies, was the use of high quality manualised counselling with highly selected and experienced counsellors. Thus, the greater intensity of treatment provided by individual counselling plus group drug counselling compared with group drug counselling alone may be interpreted as a response to a higher dose of treatment. On the other hand, the interaction of two approaches based on different models (as with the psychotherapies plus 12-step orientated group drug counselling) may be counterproductive.

It could be argued that this study demonstrates that a singular concerted approach may be more effective than the more eclectic approach often found in drug counselling in community settings. This point was also raised by Carroll (1999) in relation to the transfer from orientation to active phase. The Crits-Christoph et al. study demonstrates that manualised individual therapy in addition to group counselling leads to significant improvements in outcome. However, because of the correlation of selection (orientation), group and individual counselling procedures offered, it is difficult to draw definitive conclusions from this study regarding the relative merits of individual counselling versus cognitive therapy and supportive-expressive therapy.

Characteristics of amphetamine users in outpatient treatment and retention

Copeland and Sorensen (2001) investigated differences between primary methamphetamine and cocaine-dependent outpatients in a retrospective chart review of 345 admissions to the Stimulant Treatment Outcome Program (STOP) in San Francisco during 1995–1997. Methamphetamine users were found to engage in higher rates of injecting risk-taking behaviour, were more likely to be HIV positive, have a psychiatric diagnosis and be prescribed psychiatric medications. Only 18% of all clients completed the six-month treatment program and there were no differences in retention rates between methamphetamine and cocaine patients.

The authors suggested that the findings highlighted the need for more effective treatments for psychostimulant abuse and dependence, although not necessarily the development of novel treatments for amphetamine users. They suggested it might be more productive to provide ancillary services in order to address amphetamine users' more severe medical and psychiatric problems.

Maglione, Chao and Anglin (2000) examined retention among 2,337 methamphetamine users entering public outpatient treatment programs from the California Alcohol and Drug Database System (CADDS) between January 1994

and September 1997. Dropout was defined as receiving less than 180 days of treatment. Overall, 23% completed treatment and the average stay in treatment was 112 days. Men were 1.35 times more likely to drop out of treatment than women and people 40 years of age and older were significantly less likely to drop out. Referral from the criminal justice system was a strong predictor of treatment retention. Those who reported injecting drug use (IDU) were 1.5 times more likely to drop out compared to those who smoked or snorted the drug. In addition, daily users were more likely to drop out. Thus, it appears that completion of lengthy outpatient treatments is low and strategies to improve treatment completion rates of men, younger people and IDUs are needed.

As part of an ongoing study to describe use ecology and drug use motivation among amphetamine users, Von Mayrhauser, Brecht and Anglin (2002) have interviewed 260 participants from the CADDS study. Thus far, the most commonly stated reasons for amphetamine use are as a substitute for other psychostimulants (28%); to cope with mental illness, mental distress or trauma (28%); to stay awake (23%); to enhance sexual experience (11%); and to lose weight (10%). Von Mayrhauser and colleagues expect that developing a profile of amphetamine users will help the development of locally relevant treatment protocols for amphetamine users and identify areas worthy of further research.

Matrix Model program

The outpatient Matrix Model program for psychostimulant users was designed to integrate several interventions into a structured approach (e.g. Huber, Ling, Shoptaw, Gulati et al., 1997). Elements of the treatment include individual therapy, family education groups and relapse prevention groups, conjoint sessions and 12-step involvement.

Specific goals are to stop drug use, learn about issues critical to addiction and relapse, educate family members regarding addiction and relapse, become familiar with self-help programs, and receive weekly urine screening and breath alcohol testing. Treatment materials are manualised. The recommended treatment duration was 26 weeks (52 individual sessions, two stabilisation groups, 24 relapse prevention groups, 12 family education groups and numerous 12-step groups) from 1987 to 1990 and 16 weeks from 1991 to the present (Huber et al., 1997; Shoptaw, Rawson, McCann & Obert, 1994).

The program has been employed extensively in Southern California for over 15 years. Currently, a seven-site randomised controlled trial is being conducted among methamphetamine users in the USA, with subjects being randomly assigned to either the standardised Matrix 8- and 16-week protocols or usual treatment (Freese, Obert, Dickow, Cohen & Lord, 2000; Galloway, Marinelli-Casey, Stalcup, Lord et al., 2000; Herrell, Taylor, Gallagher & Dawud-Noursi, 2000; Huber, Lord, Gulati, Marinelli-Casey et al., 2000; Obert, McCann, Marinelli-Casey, Weiner et al., 2000; Rawson, McCann, Huber, Marinelli-Casey & Williams, 2000; Reiber, Galloway, Cohen, Hsu & Lord, 2000).

A number of studies describing outcomes of the program have been published (Rawson, Huber, Brethen, Obert et al., 2000; Simon, Richardson, Dacey, Glynn et al., 2002). Rawson et al (2000) compared the characteristics and treatment retention among 500 methamphetamine and 224 cocaine users between 1989 and 1995 in

California. Cocaine users reported more episodic use patterns, spent more money on purchasing their drugs and used alcohol more heavily. Methamphetamine users included a higher proportion of women, individuals who tended to use on a daily basis, used cannabis more often and experienced more severe medical and psychiatric consequences. Despite these differences in sample characteristics, there were no differences in treatment retention between the samples. Mean retention was 118 days for methamphetamine users and 125 days for cocaine users.

Recently, Rawson et al. (2002) described the outcome status at 2–5 years of a convenience sample of 114 of the 500 methamphetamine users recruited in the original sample. Methamphetamine and other drug use were significantly reduced from pre-treatment levels and the follow-up status of the sample was much improved. However, the authors note that this type of follow-up data does not allow conclusions regarding the specific impact of the Matrix program. Also, as the follow-up group stayed longer in treatment than that which was not followed up, it should be assumed that this outcome is better than would be reported for the sample as a whole. Nevertheless, these results are promising and we await the results of the seven-site study with great interest, particularly whether there are differences in effectiveness between the 8- and 16-week programs.

However, this sort of therapy is resource intensive, even in the eight-week form, and it may be that shorter interventions may be suitable for some people. For example, there is evidence from a randomised controlled trial (see CBT section above) that briefer outpatient CBT can be effective among regular amphetamine users (Baker et al., 2001b).

Residential rehabilitation

Psychosocial approaches vary considerably in their setting (outpatient, residential, self-help group) and treatment orientation (Swindle, Peterson, Paradise & Moos, 1995). Research evidence in this area is limited. The evidence that exists comes mainly from observational studies (Gowing, Cooke, Biven & Watts, 2002) such as the Drug Abuse Reporting Program (DARP), the Treatment Outcome Prospective Study (TOPS), the Drug Abuse Treatment Outcome Study (DATOS), all undertaken in the USA, and the National Treatment Outcome Research Study (NTORS), undertaken in the UK. In part the limited research evidence reflects ethical and procedural difficulties in conducting randomised controlled trials with clients of residential rehabilitation facilities (Toumbourou & Hamilton, 1993).

Residential rehabilitation is based on the principle that a structured residential setting provides an appropriate context to address the underlying causes of addictive behaviour. These programs assist the client to develop appropriate skills and attitudes to make positive changes towards a dependence-free lifestyle. Wickes (1993) has noted the comparative efficacy and cost-effectiveness of outpatient versus in-patient treatments among cocaine users. She cited recommendations by Taylor and Gold (1990) that in-patient treatment may be considered when there is polysubstance dependence; severe withdrawal is a possibility; medical complications may require close observation or treatment; there may be psychiatric complications; living conditions are undesirable; outpatient treatment has repeatedly failed; or social supports are absent. The duration of stay should be tailored to the individual and their goal to be achieved and in all cases be long enough for resolution of withdrawal symptoms (Wickes, 1993).

Several studies of the effectiveness of residential treatment among drug users have reported results separately for amphetamine users. Thirty years ago, Melin and Gotestam (1973) reported on a residential contingency management program for injecting amphetamine users. Significantly more people who had received the program were drug free at 6 and 12 months compared to a comparison group who received residential treatment without the contingency management program. They suggested further research was required to establish appropriate schedules and the most appropriate contexts for these. The effectiveness of these interventions for amphetamine users has not been investigated. In addition, Australian trials of these interventions were needed, as the methods used in US research may not easily translate to Australian treatment services.

The study by Hawkins, Catalano, Gillmore and Wells (1989) reported above (CBT section) provided some initial evidence that adjunctive CBT may be effective within the context of residential programs in reducing amphetamine use. However, these results need to be replicated among primary amphetamine users.

Evidence of the effectiveness of a CBT program adjunctive to residential treatment among primary amphetamine users was reported in a non-randomised comparative study by Smith, Volpe, Hashima and Schuckit (1999). Data from two groups of consecutive admissions of male veterans with alcohol dependence, dependence on amphetamines or cocaine, or both, were reported for the 383 subjects who completed at least 21 days of the 28 day in-patient treatment. All patients were assigned to aftercare groups for up to six months and after discharge approximately 71% went to abstinence-oriented recovery houses for two months. The enriched program consisted of all the elements of the standard program, including the aftercare and recovery housing, to which psychostimulant-focused elements were added for a total of 10 additional hours per week. Two one hour relapse prevention group sessions per week were conducted and two hours of related homework was required per week. Two one and a half hour sessions of interpersonal counselling groups per week were held, along with two hours per week of related homework. Both groups utilised a therapist manual. The remaining one hour per week came through additional educational material focused on psychostimulants added to the weekly meeting of the family and friends group. Follow-up occurred at 3 and 12 months. At 3 months, abstinence from substances were 63% and 49% for the standard and enhanced groups respectively and 43% and 24% at 12 months respectively.

Although the enhanced program showed a lower percentage of subjects returning to psychostimulant use than for the entire group, the results were difficult to interpret for the small numbers of subjects remaining who were dependent on psychostimulants only. Smith and colleagues (1999) concluded that despite the enhanced treatment focus on psychostimulants, both alcohol and stimulant-dependent participants appeared to benefit from the enhanced treatment, suggesting that different substance problems do not require different treatment interventions and that more intense interventions produce better outcomes.

The absence of randomisation of subjects in this study is a serious flaw and the study should be replicated with RCT methodology. Although different treatment interventions may not be required for different drug classes, it is important to note that the intervention in this study was manual driven and delivered by therapists

who received six weeks of training. Furthermore, the results are only generalisable to those subjects who had remained in treatment for at least 21 days.

Overall, there is support from three trials that enhancing residential treatment with behavioural (contingency) management or CBT is associated with better outcomes for amphetamine users. However, further randomised controlled trials among primary amphetamine users are required. In addition, longer-term residential treatment may only be suitable for a small proportion of psychostimulant users. Hando, Topp and Hall (1997) reported that as most of their sample of 200 regular users of amphetamines in Sydney was employed, home detoxification or short-term residential treatments may be more appropriate for this population.

Therapeutic communities

Therapeutic communities (TCs) represent a subset of residential rehabilitation where residents participate in the management and operation of the community. The community is the principal means for promoting behavioural change and there is a focus on social, psychological and behavioural dimensions of substance use (Gowing, Cooke et al., 2002). The philosophies of TCs and 12-step groups are such that they tend to be available to AOD users in general. Hence research evidence is generally not related to specific illicit drugs, although psychostimulant users are often included in studies of these approaches.

Residential rehabilitation originally was based around lengthy periods of stay. However, in the last two decades, short-term residential rehabilitation programs have emerged. There is also a developing trend for both therapeutic community and 12-step approaches to be used in conjunction with other treatment approaches (both pharmacological and psychosocial). This diversity of intervention approach complicates the task of assessing the effectiveness of general drug-free approaches.

Gowing et al. (2002) recently reviewed the research literature on the effectiveness of TCs. They noted that there have been very few comparative studies of the effectiveness of TC treatment with good control of bias and confounding factors, making it difficult to form an accurate view of the effectiveness of this approach relative to other treatment modalities. Furthermore, the major longitudinal studies, such as DARP, DATOS and NTORS, combine TCs with other residential rehabilitation approaches, further limiting the data available specific to the effectiveness of TCs. Consequently Gowing et al. made their assessment of effectiveness based on the consistency of outcomes to the multiple follow-up studies that are available.

Concern has been expressed over a period of many years regarding high rates of dropout from TCs, particularly early in treatment. At the same time, there is a long-standing view among residential treatment services that three months or more in treatment is necessary for enduring behavioural change. The studies reviewed by Gowing et al. (2002) indicate that between 30% and 50% of those entering TCs remain in treatment at around the three month mark. Reported median or mean lengths of stay ranged from 54 to 100 days. Hence the majority of those entering TCs do not remain in treatment for the length of time considered necessary for enduring change.

Some strategies, such as preparatory interventions prior to entry, have the potential to improve retention rates, as do approaches such as providing additional services to meet individual needs. Perhaps the strongest message from the reported retention rates is that the TC approach does not suit all people and individuals are likely to vary in their receptiveness to the approach at different stages of substance abuse and recovery. This emphasises the importance of linking TCs to other treatment approaches to ensure there are alternatives available for those who find themselves unable to complete treatment.

As with other forms of treatment, relapse to substance use is common following TC treatment. Nonetheless, overall levels and frequency of drug use are significantly reduced by TC treatment, with the reduction still apparent one to two years after exit. The degree of reduction is at least similar to and possibly more enduring than the changes achieved with methadone maintenance treatment. Findings in relation to levels of criminal behaviour are similar. Other aspects of health, particularly psychological symptoms, are also significantly improved with TC treatment and there is a trend of increasing participation in employment and education or training. These reported areas of significant improvement indicate the benefits that can be gained by those who respond positively to the TC approach and justify the continued availability of this approach as part of a treatment system.

There is a strong indication provided by the studies reviewed that time in treatment is a significant determinant of treatment outcome, but this is a complex issue with time being something of a proxy indicator for engagement, participation and progress in treatment. Nonetheless the evidence from the studies reviewed here is consistent with the accepted benchmark of at least three months in treatment before enduring behaviour change is likely to be seen. Given that time is a proxy for other factors, it would be useful to give greater attention to issues of participation and motivation during treatment, with a view to increasing the average length of stay in TCs and therefore potentially improving outcomes on average. Other factors worthy of consideration include involvement of the family, childcare, comorbidity (particularly psychiatric conditions) and cultural issues. Information on the cost effectiveness of the TC approach is particularly lacking.

Self-help groups

Self-help or mutual support groups are most commonly based on the principles of Alcoholics Anonymous (AA) or Narcotics Anonymous (NA), which espouse a disease concept of drug and alcohol dependence with the potential for recovery, but not cure, for those who adhere to it. The '12 steps' of AA/NA contain a strong spiritual component. They emphasise the importance of reconstructing relationships with other people, including confession, restitution and an injunction to help other alcoholics or addicts. They contain an implication that a decision to change is within the power of the individual, even if the power to effect that change is not (Cook, 1988). One of the perceived benefits of self-help or mutual support groups is that they provide a mechanism to promote alternative social networks that do not support drug use. It has been found that abstinence is more likely in individuals who have formed new social networks (Powell & Taylor, 1989).

The efficacy of self-help groups based on the 12-step approach of AA to support the maintenance of abstinence has been briefly reviewed by Fiorentine (1999).

Fiorentine (1999) noted that claims by AA of efficacy are often based on testimonies of long-term, abstinent participants, which may exaggerate the effectiveness of AA if those who drop out are more likely to continue or resume alcohol or drug use. Fiorentine (1999) identified more rigorous studies; both observational after-treatment studies and some controlled studies and noted that both groups of studies offer mixed results as to the effectiveness of the 12-step approach. One possible explanation given for the inconsistent findings is that some 12-step groups are more effective than others, but it remains unclear what comprises an effective or ineffective 12-step approach. It is also probable that some individuals will respond better to the 12-step approach than others (Maude-Griffin et al., 1998).

Fiorentine and colleagues (1999; 2000) have used a longitudinal study of more than 400 adult clients entering 25 outpatient treatment facilities in Los Angeles to investigate a number of aspects of 12-step programs, with attempts to control for the confounders of motivation and simultaneous activities. In this group the primary drugs most commonly used in the year prior to treatment were crack cocaine (56%), cannabis (46%), methamphetamine (24%) and cocaine (22%), with around half the cohort being polydrug users. Key conclusions were:

- weekly or more frequent 12-step participation may be an effective step in maintaining relatively long-term abstinence;
- less than weekly participation does not seem to be any more effective than non-participation;
- formal drug treatment and 12-step programs were seen as integrated recovery activities, rather than alternatives;
- individuals with pre-treatment involvement in 12-step programs stayed in treatment longer and were more likely to complete a formal 24-week treatment program; and
- individuals who participated in both formal drug treatment and a 12-step program had higher rates of abstinence than those who participated only in formal treatment (consistent with findings that intensity and duration of treatment is important for a successful outcome).

Weiss et al. (1996) made the point that attending self-help groups in itself is not sufficient — it is participation in self-help group meetings that is critical. They support this view with data from a survey of 519 cocaine-dependent people entering a psychotherapy study. In the week prior to study entry 34% had attended a self-help group. Of those who attended and actively participated in a self-help group meeting, 55% initiated abstinence within the next month, compared with 40% of non-attenders and 38% of non-participating attenders. The majority of self-help attendees may not continue with the program for long enough to accrue significant benefit, with more than half dropping out by three months (Fiorentine, 1999). Many find the heavy emphasis on spirituality difficult to reconcile and the 12-step method has been criticised for emphasising reliance on external forces for recovery (Li, Feifer & Strohm, 2000) with some professionals expressing concern about potential disempowerment of users in treatment.

As a result of some of these limitations other self-help groups have been developed to provide an alternative to the 12-step model. SMART Recovery (Self Management And Recovery Training) is an abstinence-based self-help group based on a cognitive

behavioural model designed to provide similar support mechanisms and be more compatible with mainstream drug treatment, which is also based on a cognitive behavioural model. Unlike AA, SMART recovery has group facilitators, some of whom are professionals, and professional volunteer advisers, and the groups are more focused on developing skills and education (Fletcher, 2001). However, because it is relatively new, like AA, little research has been conducted into its efficacy, although the advisers point out that it is based on an evidence-based treatment intervention.

Conclusion

The literature on amphetamine treatments is limited in both quantity and quality. The literature is particularly hindered by a paucity of well-conducted studies among primary amphetamine users, especially outcome studies. The available evidence suggests that cognitive behavioural approaches, such as relapse prevention, and behavioural approaches, such as contingency management, are the most effective treatments for amphetamine users to date. The effectiveness of other types of intervention is not well supported. Until more research is undertaken comparing different treatment modalities in Australian settings, CBT, coupled with motivational approaches, appears to represent current best practice.

Summary of evidence

Psychosocial approaches to all psychostimulant use

Key points	Strength of evidence
Transition to injecting can be prevented with CBT intervention.	*
Brief interventions among current injectors can reduce initiation into injecting among non-injectors.	**
Infrequent, heavy users of psychostimulants and instrumental users should be encouraged to be aware of symptoms of heavy use and the need for moderation or cessation.	*
Brief, opportunistic interventions are most appropriate for ecstasy users.	*

Psychosocial approaches to regular psychostimulant use

Behavioural reinforcement

Key points	Strength of evidence
Positive reinforcers for abstinence, in combination with psychological treatment, can reduce cocaine use.	***
The magnitude, immediacy and relevance of reinforcement to the target group may be critical to efficacy of positive reinforcement.	*

CBT

Key points	Strength of evidence
Cognitive behavioural therapy (CBT) has been effective in reducing amphetamine use.	***
CBT is more effective at moderating cocaine use than equivalent time in non-therapeutic activities, but has not been shown to increase abstinence.	***
Findings in relation to 12-step approaches have been equivocal.	***
The effects of cognitive behavioural interventions may be more durable than other psychotherapies and hence be more protective against relapse.	***
The use of high quality, manualised counselling with experienced counsellors may be an important factor contributing to outcomes.	?
A single concerted approach may be more effective than several different counselling approaches.	?

Matrix model

Key points	Strength of evidence
Low rates of retention have been reported for programs of up to 6-months duration and it is currently not possible to identify effective strategies to encourage retention, or to relate treatment duration to outcome.	*

Residential rehabilitation

Key points	Strength of evidence
Rates of dropout from residential rehabilitation programs are very high in the early stages of treatment (>40% dropout in the first month), but rates of attrition then decline. (Not specific to psychostimulants).	**
For those who complete residential rehabilitation programs, drug use and criminal behaviour is reduced and legal employment increased, following treatment. (Not specific to psychostimulants).	**
Treatment progress, not just time in treatment, is predictive of good outcomes. (Not specific to psychostimulants).	*
For psychostimulant users, enhancing residential treatment with behaviour therapy or CBT improves outcome.	*

Self help

Key points	Strength of evidence
The effectiveness of 12-step (self-help) approaches is equivocal.	**?**
Participation in self-help group meetings (not just attendance) is important in determining outcomes.	*****
Attendance at self-help group meetings should not be mandated.	**?**

Chapter 6

Management of acute psychostimulant toxicity

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Key points

- Consequences of psychostimulant toxicity including cardiovascular and cerebrovascular emergencies, acute behavioural disturbances, psychosis and serotonin toxicity of varying severity may occur among both experimental and regular users of psychostimulants.
- Some evidence regarding the emergency management of complications related to cocaine toxicity is available, although studies related specifically to the management of amphetamine and MDMA toxicity are few.
- Individuals who have used psychostimulants and soon after experience symptoms of chest pain, rapidly increasing body temperature, psychotic features (hallucinations, severe paranoia, delusions or thought disorder), severe agitation or uncontrollable behavioural disturbance; seizures; severe headaches, or breathing difficulties are encouraged to seek medical attention urgently.
- Skilful management of the various manifestations of toxicity involves accurate assessment, the provision of a safe environment, careful monitoring, a prompt response, attention to special precautions (including medication contraindications) and the use of urgent sedation for the emergency management of acute behavioural disturbances and severe psychosis when indicated.

Introduction

Psychostimulants produce a broad range of effects. Adverse effects can exist on a spectrum of severity from minor symptoms to life threatening toxicity. Although regular use or use of high doses increases risk of adverse events, many adverse events requiring emergency intervention may occur even in the naïve user.

Early symptoms of potential psychostimulant toxicity include hyperactivity, restlessness, tremor, sweating, talkativeness, tenseness and irritability, weakness, insomnia, headache and fever (Brownlow & Pappachan, 2002; Derlet, Rice, Horowitz & Lord, 1989; Kalant, 2001). Vomiting, diarrhoea, cramps and anorexia may occur. Symptoms may progress to agitation, hyperactive reflexes, confusion, aggression, delirium, illusions, paranoid hallucinations, panic states and loss of behavioural control. Chorea, dystonia, fasciculations, muscle rigidity, tics and tremors (all disorders of movement) may develop. Seizures and coma may occur with severe intoxication. Other neurological effects have included stroke and cerebral vasculitis. Increased body temperature can progress to severe hyperthermia (Gowing,

Henry-Edwards et al., 2002), which may be associated with rhabdomyolysis, renal failure, disseminated intravascular coagulation, multi-organ failure and death.

Hypertension and tachycardia are common. More severe cardiovascular toxicity includes ventricular arrhythmias, acute myocardial infarction or hypertensive crises. Acute left ventricular dysfunction and aortic dissection may occur. Respiratory complications such as tachypnea are common. Pulmonary oedema and adult respiratory distress syndrome (ARDS) are unusual complications of severe exposure. Hepatic (liver) injury is common in patients who develop severe hyperthermia and/or vasospasm. Electrolyte disturbances include hypoglycaemia, hypernatraemia (increased blood sodium related to reduction in body water) and hyponatraemia (may be related to the syndrome of inappropriate secretion of vasopressin or to hypervolaemia resulting from excess water ingestion) (Gowing, Henry-Edwards et al., 2002; Traub et al., 2002). Hypo- and hyperkalemia have been reported. Dehydration is common. Renal ischaemia may occur. Metabolic acidosis occurs with severe poisoning (Burchell, Ho, Yu & Margulies, 2000).

Assessment

Clinical observation of potentially toxic signs and symptoms is more relevant than estimating the ingested dose. If objective confirmation of psychostimulant use via urine or blood screening is not possible, reasonable suspicion of psychostimulant use may be inferred from the information provided by significant others or bystanders, the recent activities of the patient (e.g. a dance party) and their clinical presentation, including vital signs, behavioural presentation and the presence of symptom complexes.

Pupils are usually mydriatic (dilated) and often sluggishly reactive to light (Chan, Graudins, Whyte, Dawson et al., 1998). The skin is usually flushed and diaphoretic. Core temperature should be monitored, as severe hyperthermia may develop. Hyperthermia above 39.5 degrees C indicates severe, potentially life-threatening toxicity and mandates immediate cooling and sedation. Serum electrolytes should also be monitored, along with renal and hepatic function and creatine phosphokinase. An electrocardiogram (ECG) should be obtained and continuous cardiac monitoring instituted in symptomatic patients.

Management of toxicity

Overall, treatment of psychostimulant toxicity should involve prompt supportive care and judicious use of specific agents. Good management relies upon early recognition and the initiation of supportive care in the emergency department. Unfortunately, some individuals avoid or delay seeking emergency care due to fears about negative legal ramifications associated with use of an illicit substance. It is important to seek emergency care when any of the following symptoms are present:

- chest pain;
- rapidly increasing body temperature;
- psychotic features (hallucinations, severe paranoia, delusions or thought disorder);
- behavioural disturbance to the extent that the individual may be at risk to themselves or others;

- seizures; and
- uncontrolled hypertension.

The role of gastric decontamination where toxicity develops from recent excessive oral doses is not established. Ipecac-induced emesis is not recommended (Krenzelok, McGuigan & Lheur, 1997). Gastric lavage is unlikely to be of benefit if instituted more than one hour after ingestion (Vale, 1997) and there is no evidence to support its use in these patients even if they present within one hour. The possible neurological and cardiovascular toxicity could make such an intervention potentially dangerous. Similarly, activated charcoal is unlikely to be of benefit if instituted more than one hour after ingestion (Chyka & Seger, 1997) and it is unclear whether earlier administration would be of any benefit.

Management of intoxication

Uncomplicated intoxication may only require observation and monitoring for several hours in a subdued environment until symptoms subside (Henry, 1992; Rawson, 1999; Williams, Dratcu, Taylor, Roberts & Oyefeso, 1998). Management is predominantly supportive, with an emphasis on sedation and reduction of body temperature. Most patients with a minor elevation in core temperature do not require any specific measures, but rapid cooling measures are essential if body temperature is above 41 degrees C. Strategies to promote cooling in a community or pre-hospital environment include moving the patient to a shady, cooler environment, removal of insulating clothing, application of ice packs to neck, axillae (armpit) and groin and dousing the patient with water and fanning to promote evaporative heat loss. Emergency departments also utilise evaporative cooling techniques and cold water immersion (Roberts & Hedges, 1998; Wexler, 2002). Muscle paralysis and intubation may be necessary if external cooling measures fail.

The following sections address specific aspects of toxicity.

Acute behavioural disturbances and psychoses

Introduction

Urgent sedation in an emergency (sometimes referred to as chemical restraint) is a procedure for administering drug treatment to rapidly control extremely agitated, aggressive behaviour of an individual at risk of causing physical harm to themselves or others. The primary aim of emergency sedation is to attenuate specific symptoms of behavioural disturbance rather than as a treatment for an underlying cause or psychiatric condition. Nonetheless, effective sedation may provide a safe environment in which to determine and treat the cause of agitated behaviour.

Urgent sedation should be distinguished from procedures aimed at rapidly treating psychoses. Procedures such as 'rapid neuroleptisation' consist of giving high loading doses of antipsychotics to attenuate psychotic symptoms. These procedures are no longer recommended in an emergency setting where high or frequently repeated doses of antipsychotics may exacerbate the emergency situation through side-effects including dysphoria, akathisia or acute dystonia (Keckich, 1978; Siris, 1985).

Reliance on physical restraint alone is often not adequate for psychostimulant users experiencing acute behavioural disturbance and may actually cause harm if agitation increases. Stimulant use has been suggested as a possible risk factor for sudden death of individuals being physically restrained (Stratton, Rogers, Brickett & Gruzinski, 2001). Sedation using sedative drugs is acceptable to patients (Sheline & Nelson, 1993), provides a humane alternative to physical restraint (Richards, Derlet & Duncan, 1998) and ensures simpler and safer essential physiological monitoring than other types of restraint.

Presentation

Use of psychostimulants has been associated with violent or agitated behaviour, which may lead to fatal outcomes (Dowling, McDonough & Bost, 1987). Behavioural effects are influenced by dose used, characteristics of the individual and the social context of the psychostimulant use (Miczek & Tidey, 1989). Violent behaviour is more common in chronic high-use psychostimulant users than occasional users. Other factors such as coincident opiate withdrawal may increase risk of aggressive behaviour (Miczek & Tidey, 1989).

Common acute effects of amphetamines include panic or motor agitation. With prolonged use, hypervigilance and euphoria gradually give way to auditory, visual and tactile illusions, hallucinations and paranoia. Delusions are common, as is the preoccupation with 'bugs' that are felt and seen on the skin, leading to picking and excoriation of the skin. Restless choreoathetoid and tic-like movements are often present. Experienced amphetamine users may describe the combination of paranoia and compulsive movements as 'tweaking'. Delirium may occur (Forster et al., 1999).

Assessment

Conducting an exhaustive differential diagnosis is less important when sedating an acutely agitated patient than when formulating longer-term treatment in an in-patient unit (Citrome & Volavka, 1999). Indications for urgent sedation in suspected psychostimulant users include:

1. failure of other attempts to control the patient such as de-escalation and other non-drug interventions;
2. the patient is uncooperative;
3. the patient is at known or imminent risk to themselves or others; and
4. there is a perceived need for medical intervention (requirement of the Guardianship Act).

In some emergency situations, it may be difficult to differentiate between behavioural disturbance and potential drug-induced psychosis. Suspected drug-induced psychosis should not be considered a contraindication to urgent sedation. Rather, a period of sedation and behavioural control will allow clinicians to re-assess the patient after the acute effects of the drug have worn off, allowing for a more accurate differential diagnosis. In general, treatment of patients with psychostimulant-induced psychosis is similar to treatment of acute mania or schizophrenia (Forster et al., 1999) and establishing a 'safe' environment should be the first priority.

Management

Non-specific sedation is frequently used in the management of acutely agitated or violent patients. The setting of clinical contact (emergency department versus ambulance attendance) may influence drug selection and route of administration.

Ideal medications for urgent sedation should possess rapid sedative action, providing quick control of dangerous behaviour. Sedation should generally be titrated to the point of rousable sleep, not unconsciousness. The aim of sedation is to control dangerous behaviour sufficiently to facilitate assessment and management.

Over-sedation in the form of loss of consciousness should be avoided. Health care providers who provide sedation, regardless of practice setting, should have access to advanced airway assessment and management skills so that successful 'rescue' of patients can be made should an adverse sedation event occur.

Benzodiazepines

Forster and colleagues (Forster et al., 1999) suggest that benzodiazepines should be the agent of choice when there is unlikely to be an ongoing need for antipsychotic medication after acute treatment, warning that little data support frequent administration of 'as needed' antipsychotic medication. They suggest that benzodiazepines influence fewer neurotransmitter systems than antipsychotic agents and are thus a safer (pharmacologically 'cleaner') choice of drug. Consistent with other survey findings (Sheline & Nelson, 1993), their clinical experience predicts that most agitated patients are more willing to accept treatment with a benzodiazepine than with an antipsychotic and that following such treatment, patients tend to be calmer and better organised.

Secondary benefits of selecting a benzodiazepine are that they are also part of first line treatment for cardiac toxicity associated with psychostimulant use (Albertson, Dawson, de Latorre, Hoffman et al., 2001) and may exert some benefit in the agitation of serotonin toxicity (Graber, Hoehns & Perry, 1994). In cases of adverse events, a pharmacological antagonist (flumazenil) is available to reverse benzodiazepine effects (Hunkeler, Mohler, Pieri, Polc et al., 1981).

Neave (Neave, 1994) suggests that parenteral midazolam may be effective in controlling agitated or aggressive patients. The dose administered should be based on the patient's general health, age, weight and level of agitation or aggression; usually 5, 10, or 15 milligrams are given incrementally at 15-minute intervals until the desired effect is achieved. The advantages of midazolam over other benzodiazepines include its rapid onset (onset of action: intravenous (IV) three to five minutes; intramuscular (IM) 15 minutes) (Nordt & Clark, 1997), shorter duration of action, less potential to cause hypotension and that prolonged administration results in more rapid awakening (Dundee, Halliday, Harper & Brogden, 1984; Simpson & Eltringham, 1981).

Although some commentators suggest that lorazepam is an "excellent choice" for sedating violent patients (Citrome & Volavka, 1999), few studies have demonstrated its superiority over other agents. It is considered to be at least as effective as haloperidol (Bick & Hannah, 1986) and demonstrates a better safety profile than typical antipsychotics (Lenox, Newhouse, Creelman & Whitaker, 1992), mainly attributed to its lack of extrapyramidal side-effects. However, lorazepam does not have a rapid onset

of action (IV 15-20 minutes; IM two hours) (Dundee, Lilburn, Nair & George, 1977; Greenblatt, Ehrenberg, Gunderman, Scavone et al., 1989), which is also a slower onset of effect than that of droperidol (Richards et al., 1998). It must be noted that neither IM nor IV preparations of lorazepam are available in Australia.

Typical antipsychotics

It is sometimes considered that using antipsychotics for sedation purposes may also confer a benefit via their antipsychotic actions. However, this putative benefit would only be evident after the acute episode of agitation or violence has subsided (Citrome & Volavka, 1999).

Haloperidol, a butyrophenone antipsychotic, is frequently used for urgent sedation. Compared with other neuroleptics, haloperidol causes less hypotension, fewer anticholinergic side-effects and less decrease in the seizure threshold. Despite this, haloperidol is not the most sedative of neuroleptics and may thus be less appropriate than more sedating agents for emergency sedation purposes (Citrome, 2002; Citrome & Volavka, 1999).

In an uncontrolled study (Clinton, Sterner, Stelmachers & Ruiz, 1987), 136 patients were treated primarily with IM haloperidol although IV and oral routes were also utilised. Haloperidol alleviated the problem behaviour in 83% of patients; two patients experienced dystonic reactions.

Another butyrophenone used to treat acute agitation is droperidol. Droperidol is fast acting, rapidly eliminated from the body and may be administered IM or IV. Small, uncontrolled studies indicate that droperidol is useful in controlling methamphetamine intoxication (Gary & Saidi, 1978), severely agitated psychotic patients (Granacher & Ruth, 1979; Hooper & Minter, 1983), acute agitation related to traumatic brain injury (Stanislav & Childs, 2000), or agitated patients in a pre-hospital setting (Hick, Mahoney & Lappe, 2001). Chambers and Druss (1999) recommend that droperidol be considered a drug of choice in psychiatric emergencies due to its efficacy and rapidity of action.

Two placebo-controlled studies (Rosen, Ratliff, Wolfe, Branney et al., 1997; van Leeuwen, Molders, Sterkmans, Mielants et al., 1977) assessed the utility of droperidol in acute agitation and found that it provided greater sedative effect than placebo within 3-5 minutes of administration. Limitations of both studies include small sample size and no longer-term follow-up of participants.

Comparisons between lorazepam and droperidol have demonstrated that droperidol may have greater efficacy. One randomised study (Richards et al., 1998) compared the effectiveness of lorazepam versus droperidol in a heterogenous sample of agitated patients (N=202) in the emergency department. Agitation was attributed to methamphetamine toxicity in 72% of cases and cocaine toxicity in 14% of cases. Patients received either lorazepam 4 mg IV or droperidol 5 mg IV; sedation levels and vital signs were monitored for 60 minutes. Droperidol provided more rapid sedation than lorazepam and achieved higher levels of sedation that were maintained over the 60 minutes and required less frequent repeat dosing. No patients experienced adverse effects on their vital signs; no patients required airway intervention. There were no significant advantages to either drug with regard to net change in pulse, systolic blood pressure, respiratory rate or blood pressure.

One patient who received droperidol experienced an acute dystonic reaction. Results were similar in the subset of patients whose agitation was attributed to methamphetamine toxicity (Richards, Derlet & Duncan, 1997).

The main benefit demonstrated for droperidol in this study was its rapid onset of action. Given that lorazepam does not have a rapid onset of action (see above) it may have been more appropriate to compare droperidol with more rapidly acting benzodiazepines such as midazolam.

Potential problems associated with use of droperidol include dystonia and akathisia, hypotension, prolongation of the QTc interval on ECG, lowering of the seizure threshold and respiratory depression (Chase & Biros, 2002; Granacher & Ruth, 1979; Heard, Daly, O'Malley & Rosen, 1999; Stanislav & Childs, 2000). However, some authors suggest that serious QTc interval prolongation associated with droperidol is uncommon in practice, where it is safe and effective for the treatment of violence and agitation (Shale, Shale & Mastin, 2003). These problems may be more of an issue in a psychostimulant-affected population although data supporting this contention are lacking.

The Cochrane Review of droperidol for acute psychosis (Cure & Carpenter, 2001) concludes that this area is under-researched and that use of droperidol in an emergency situation is currently based on experience rather than evidence from well-conducted clinical trials. In comparison studies (Resnick & Burton, 1984; Thomas, Schwartz & Petrilli, 1992), droperidol (5 mg IM) produced more effective sedation than haloperidol (5 mg IM), although there were no differences between the two drugs when given by the IV route (Thomas et al., 1992). Although some research has examined the role of atypical antipsychotics to treat agitation (e.g. Currier & Simpson, 2001), little evidence supports their use for urgent sedation.

Combination regimens

A combination of lorazepam (2 mg IM) and haloperidol (5 mg IM) was compared with 2 mg lorazepam alone in 20 agitated patients presenting to a psychiatric emergency service (Bieniek, Ownby, Penalver & Dominguez, 1998). The combination group exhibited greater improvements in some, but not all, outcome measures. Both groups improved over time.

Battaglia and colleagues (1997) compared three regimens: lorazepam 2 mg IM alone, haloperidol 5 mg IM alone and a combination of both drugs at the same doses. All medications led to significant improvements in aggression over 12 hours; the combination group demonstrated a greater improvement in some measures and experienced less extra-pyramidal symptoms than those receiving haloperidol alone. These three treatment groups were compared in a similar study (Garza-Trevino, Hollister, Overall & Alexander, 1989) although doses of lorazepam used were 4 mg instead of 2 mg. They report that the combination was superior to either of the single agents and that lorazepam alone was slightly superior to haloperidol alone.

These studies support the use of benzodiazepines and antipsychotics in combination as safe and effective options. Whilst these results also seem to indicate that combination therapies are superior to single agent regimes, it is important to note that doses in each arm are not necessarily equally effective and that superior efficacy of a combination regime may merely reflect that patients in the combination group received a greater total dose of drug than those in a single agent group.

Serotonin toxicity

Introduction

Serotonin excess is best thought of as a spectrum of toxicity, rather than a defined clinical entity (syndrome) with clear prognostic importance (Gillman, 1998). Serotonin toxicity is a symptom complex that arises from an increase in the biological activity of the neurotransmitter serotonin (also called 5-hydroxytryptamine or 5-HT). Serotonin influences multiple organ systems, mediating its effects via a range of central and peripheral receptors.

It used to be thought that serotonin toxicity was mediated via 5-HT1A receptors, but recent evidence suggests that it is mediated mainly via 5-HT2 receptors. Most reports in the literature of serotonin toxicity are triggered by a combination of antidepressant medications, although reports also implicate agents such as atypical antipsychotics (Hamilton & Malone, 2000; Haslett & Kumar, 2002), pethidine and dextromethorphan (Bowdle, 1998) or metoclopramide (Fisher & Davis, 2002).

Psychostimulants have the potential to cause serotonin toxicity, although since MDMA is the most serotonergic drug in this group, it may pose a greater risk than other agents. MDMA is able to produce serotonin toxicity in animals (Fone, Beckett, Topham, Swettenham et al., 2002). In humans, there are a number of reports of MDMA toxicity that exhibit features of excess serotonin (Brown & Osterloh, 1987; Henry et al., 1992; Screaton et al., 1992), with one of these being fatal (Mueller & Korey, 1998). Other reports implicate MDMA or other amphetamine derivatives in combination with antidepressants (Kaskey, 1992; Lauerma, 1998; Prior et al., 2002; Vuori et al., 2003).

Assessment

Diagnosis of serotonin toxicity is made by clinical examination. Serotonin toxicity can be thought of as a triad of clinical features consisting of: 1) autonomic signs; 2) neuromuscular changes; and 3) altered mental status (Dunkley, Isbister, Sibbritt, Dawson & Whyte, in press). Laboratory abnormalities may occur, but they are non-specific. Blood serotonin levels are not meaningful since they do not represent the concentration of serotonin in the brain. Diagnosis using the Sternbach criteria (1991) requires the suspected recent use of a serotonergic agent and the presence of at least three of the following criteria:

- altered mental status (confusion, hypomania);
- agitation;
- tremor;
- shivering;
- diarrhoea;
- hyperreflexia;
- myoclonus (jerking movements may be severe enough to mimic seizure activity);
- ataxia;
- fever; and
- diaphoresis.

There are problems with these criteria, which were derived from a small collection of case reports (Radomski, Dursun, Reveley & Kutcher, 2000). This has led to efforts to derive more useful diagnostic criteria (Dunkley et al., in press; Hegerl, Bottlender, Gallinat, Kuss et al., 1998). These analyses have demonstrated that the combination of a few well-defined clinical features (clonus, agitation, diaphoresis, tremor, hyperreflexia, hypertonia and temperature) is both sensitive and specific for serotonin toxicity (Dunkley et al., in press).

The clinical course of serotonin toxicity varies — it may be a mild, self-limited state or potentially fatal. Serious cases present with symptoms such as muscle rigidity, coma, hypertension or hypotension (LoCurto, 1997). When the toxicity is severe, rhabdomyolysis with hyperkalaemia, acidosis and frank renal failure may result. This occurs secondary to sustained muscle contraction. Disseminated intravascular coagulation is described in advanced cases and seizures may also occur rarely. Temperatures in excess of 41°C correlate with a poor prognosis (LoCurto, 1997).

Management

Overall, treatment of serious serotonin toxicity should involve prompt supportive care and judicious use of specific agents. Good management relies upon early recognition and the initiation of supportive care in the emergency department. General supportive measures for severe forms include IV fluids/volume resuscitation for dehydration, hypotension or rhabdomyolysis, antipyretics, external cooling, muscular paralysis with neuromuscular blocking agents, mechanical ventilation for respiratory compromise and sedation with IV benzodiazepines (Bodner, Lynch, Lewis & Kahn, 1995). Paralysis and intubation may have a role in cases of severe intractable rigidity. Management of secondary cardiac arrhythmias or seizures involves standard measures.

In all patients with suspected serious serotonin toxicity, serum electrolytes, glucose, renal function, creatine kinase levels and ECG should be monitored. Hepatic function and arterial blood gases should also be monitored in more severe cases. Muscle rigidity should be controlled — if unchecked, it can lead to fever, rhabdomyolysis and respiratory compromise (Carbone, 2000; Mills, 1997). Patients who develop coma, cardiac arrhythmia, disseminated intravascular coagulation or respiratory insufficiency require more specific measures.

Cyproheptadine

Cyproheptadine is a first generation antihistamine (H1 blocking agent) that also possesses non-specific antagonist properties predominantly at the 5-HT2 receptors — this action is most likely to be responsible for its effects in treating serotonin toxicity. A number of case reports exist describing use of oral cyproheptadine for serotonin toxicity (Goldberg & Huk, 1992; Graudins, Stearman & Chan, 1998; Horowitz & Mullins, 1999; Lappin & Auchincloss, 1994; McDaniel, 2001; Weiner, Tilden & McKay, 1997).

Cyproheptadine also has some anticholinergic activity and would be relatively contraindicated in cases of suspected overdose of another anticholinergic drug. If the cause of the agitation is anticholinergic delirium (as can occur with specific anticholinergic agents and drugs such as the tricyclics) then cyproheptadine will not provide any clinical benefit and may indeed worsen the situation. It should be used cautiously in cases of unknown or mixed overdose.

Benzodiazepines

Benzodiazepines are of use in treating muscle rigidity, agitation and seizures if present. A range of benzodiazepines has been used in the treatment of serotonin toxicity, including diazepam (Fisher & Davis, 2002), lorazepam and clonazepam. It is important to note that use of benzodiazepines is often based on clinical experience rather than prospective research evaluation and that they may not be of use in all patients (Graudins et al., 1998; Lappin & Auchincloss, 1994).

Chlorpromazine

Chlorpromazine is a typical antipsychotic agent that also is a potent 5-HT2 antagonist. A number of case reports suggest that it may have a role in management of serotonin toxicity (Gillman, 1996; Graham, 1997). Other reports describe using it in combination with other agents (Chan et al., 1998) or report it being effective when other agents such as cyproheptadine were ineffective (Gillman, 1997).

One advantage of chlorpromazine is its availability in a parenteral (injectable) form, but it may cause hypotension, dystonic reactions or reduce the seizure threshold, which may compromise patient care in serotonin toxicity. Antipsychotics and other dopamine antagonists should be avoided if a clear diagnosis excluding neuroleptic malignant syndrome (NMS) has not been made.

Other agents

A role for alternative pharmacotherapies has not been established. Although some case reports suggest that propranolol may be effective (Dursun, Burke, Nielsen, A. & Reveley, 1997; Guze & Baxter, 1986), other studies suggest it is ineffective (Gillman, 1997; Lappin & Auchincloss, 1994), however, beta blockers are not recommended in the management of psychostimulant toxicity (Lange, Cigarroa, Flores, McBride et al., 1990).

Dantrolene, a skeletal muscle relaxant, is sometimes used in serotonin toxicity to reverse prolonged muscle rigidity and related complications (Graber et al., 1994; Hall, Lyburn, Spears & Riley, 1996; Mallick & Bodenham, 1997). However, little evidence currently supports its utility in this context and clinical opinion regarding its role is conflicting (Campkin & Davies, 1993; Tehan, 1993; Watson, Ferguson, Hinds, Skinner & Coakley, 1993).

Cardiovascular emergencies

Presentation

One of the most common emergency presentations occurring after cocaine use is chest pain (Baumann et al., 2000; Brody, Slovis & Wrenn, 1990), although cardiac profiles show wide variability. In one study (Baumann et al., 2000), patients with cocaine-associated chest pain described their pain as pressure (63%); it was usually located substernally (48%) or in the left anterior chest (37%). The most common associated symptoms were shortness of breath (74%), light-headedness (69%), nausea (67%) and palpitations (65%). Although 56% of these patients were given a diagnosis of possible ischaemia and 88% of patients were hospitalised in a monitored setting, only one sustained a myocardial infarction (4%). After review of the hospital records, none of the patients experienced any cardiac complications, including arrhythmias, hypotension, or congestive heart failure (Baumann et al., 2000).

Most patients experience onset of symptoms within 24 hours of drug use, although cocaine withdrawal may also result in myocardial ischaemia (Hollander, 1995a). Although most of the literature examining cardiovascular toxicity and psychostimulants focuses on cocaine use, myocardial ischaemia may also occur after amphetamine use (Costa et al., 2001). Other possible presentations related to psychostimulant use may include hypertensive crisis, acute myocardial infarction and ventricular arrhythmias (Baumann et al., 2000; Dowling et al., 1987).

Assessment

The typical patient with cocaine-associated myocardial infarction is a young tobacco-smoking man with a history of repetitive cocaine use but few other cardiac risk factors. The following variables cannot reliably predict or rule out acute myocardial infarction in subjects with cocaine-associated chest pain: demographic characteristics, drug use history, location, or duration or quality of chest pain (Hollander, 1995a). As there may be no clinical differences between those who experience myocardial infarctions and those who do not, it is important to test all patients with cocaine-related chest pain for possible myocardial infarction (Hollander, Hoffman, Gennis, Fairweather et al., 1994).

Diagnosis of heart attack in cocaine users with chest pain is difficult but may be assessed with ECGs, measurements of creatinine kinase and cardiac troponin I (Hollander, 1995b). Interpreting the ECGs of patients with cocaine-associated chest pain is difficult. ECGs are abnormal in 56% to 84% of patients with cocaine-associated chest pain and as many as 43% of cocaine-using patients without infarction meet the standard electrocardiographic criteria for the use of thrombolytic agents. J-point and ST-segment elevation due to early repolarisation or left ventricular hypertrophy often makes the identification of ischaemia more difficult in these patients (Hollander, 1995a).

Increased concentrations of creatine kinase and creatine kinase MB (the cardiac component of creatine kinase) may occur even in the absence of unequivocal electrocardiographic evidence of myocardial infarction. A pattern of continuously rising enzyme concentrations is more likely to occur in patients with myocardial infarction; initial elevations that rapidly decline indicate infarction less commonly (Hollander, 1995a). The immunoassay for cardiac troponin I has no detectable cross-reactivity with human skeletal-muscle troponin I, making it a more specific test than that for creatine kinase MB in assessing myocardial injury when concomitant skeletal-muscle injury exists. Use of the immunoassay for cardiac troponin I may therefore enhance the accuracy of a diagnosis of myocardial infarction in patients with cocaine-associated ischaemia (Hollander, 1995a).

Those patients experiencing recurrent symptoms, increased levels of markers of myocardial necrosis, or dysrhythmias should be monitored more thoroughly and for longer periods (Weber, Shofer, Larkin, Kalaria & Hollander, 2003).

Most serious complications of cocaine-associated myocardial infarction occur before or soon after hospital presentation (Hollander et al., 1995). Consequently, monitored patients with cocaine-associated chest pain who do not have evidence of ischaemia or cardiovascular complications over a 9 to 12 hour period in chest pain observation units have a very low risk of death or myocardial infarction during the

30 days after discharge (Weber et al., 2003). Hollander and colleagues report that all patients with cardiovascular complications were identified within 12 hours after presentation by observing ischaemia or infarction on an initial electrocardiogram, or by elevated creatine kinase MB (Hollander et al., 1995).

No single explanations of the causes of myocardial ischaemia can explain all cases. Explanations include increased myocardial oxygen consumption (Summers et al., 2001) and coronary artery vasoconstriction, intracoronary thrombosis and accelerated atherosclerosis (Benzaquen, Cohen & Eisenberg, 2001). Signs of occlusive disease or significant risk factors (other than smoking) are rarely present.

There is much less information available about amphetamine-related chest pain. Cocaine-associated chest pain has a variety of additional aetiological mechanisms (see above) that are not known for amphetamines.

Management

The pharmacologic treatment of patients with cocaine-related ischaemic chest pain differs in several important ways from that of patients with the usual type of myocardial ischaemia. Treatment recommendations based on the pathophysiology of cocaine-associated myocardial ischaemia must take into account the toxic effects of cocaine on the CNS and other vital organs. For example, aspirin must be avoided in patients at risk for subarachnoid haemorrhage. If treatment strategies could be altered by the knowledge of recent cocaine use, rapid bedside toxicological assays for the drug or its metabolites may be useful, since the patient's own reporting is not entirely reliable (Hollander, 1995a). The appropriate management of amphetamine-related chest pain is unknown although some of the principles of the management of cocaine-associated chest pain are likely to be valid.

Hollander (1995a; 1995b) recommends a stepped approach to the treatment of patients with cocaine-associated myocardial ischaemia. He suggests that after treatment with oxygen and the establishment of intravenous access, benzodiazepines, aspirin and nitroglycerine should be administered. Patients who continue to have severe chest pain after such an intervention may be treated with either low-dose phentolamine, or verapamil as second-line therapy. If evidence of continued myocardial infarction persists after medical management, the strategy is then to establish reperfusion with either primary angioplasty or thrombolytic therapy. When possible, the patient's current ECG should be compared with earlier ones. If the ST-segment elevations are unchanged from prior electrocardiograms, diagnostic cardiac catheterisation may be indicated and reperfusion, if necessary, can be accomplished with primary angioplasty. If the ST-segment elevations are new, it is reasonable to give the patient thrombolytic agents, in the absence of the traditional contraindications.

Hypertension is often transient and as such may not require pharmacological intervention unless severe. Hypertension requiring treatment often responds to sedation with IV benzodiazepines. Benzodiazepines are recommended for patients with cocaine-associated myocardial ischaemia who are anxious, have tachycardia, or are hypertensive (Albertson et al., 2001; Hollander, 1995a), as they reduce blood pressure and heart rate, thereby decreasing myocardial oxygen demand in addition to their anxiolytic effects. Hypertension not responding to benzodiazepines is best managed with IV nitroprusside, titrated slowly to response.

A small, randomised controlled trial examined the efficacy of diazepam, nitroglycerine or both in the treatment of acute cocaine-induced cardiovascular effects. (Baumann et al., 2000) reported that both medications, alone or in combination, led to a reduction of chest pain and improvements in cardiac performance. The small sample size (N=40) limited detection of any differential benefit of one treatment regimen above the others.

Aspirin should be administered to prevent the formation of thrombi. This recommendation is based on theoretical considerations, the drug's good safety profile and the extensive investigation of aspirin in patients with ischaemic heart disease unrelated to cocaine, although there are no clinical data on the use of aspirin in patients with cocaine-associated myocardial ischaemia (Hollander, 1995a).

Nitroglycerine limits the size of acute myocardial infarction and reduces infarct-related complications in patients with myocardial ischaemia unrelated to cocaine. Sublingual nitroglycerine, in a dose sufficient to reduce the mean arterial pressure by 10% to 15%, reverses cocaine-induced coronary-artery vasoconstriction and relieves symptomatic chest pain. Therefore, nitroglycerine is recommended as a primary therapy for cocaine-associated myocardial ischaemia (Hollander, 1995a).

Alpha-adrenoceptors are critical for many haemodynamic responses to cocaine. Phentolamine, an alpha-adrenergic antagonist, reversed the increase in arterial pressure and heart rate and the decrease in coronary vessel diameter produced by cocaine (Lange, Cigarroa, Yancy, Willard et al., 1989). The use of a low dose (1 mg) may avoid the hypotensive effects of the drug while maintaining the anti-ischaemic effects (Hollander, 1995a).

There are a number of reports suggesting that calcium channel antagonists, such as verapamil, may be able to prevent some of the pathological effects of cocaine on the heart (discussed by Hollander, 1995a; Knuepfer, 2003), but they may only be effective when administered prior to cocaine ingestion, limiting their usefulness as treatments for cocaine toxicity.

Beta-blockers, one of the mainstays of treatment of acute myocardial ischaemia unrelated to cocaine use, should be avoided in patients who have recently used psychostimulants (Hollander, 1995a). Research on this issue is conflicting (Knuepfer, 2003), as is clinical opinion (Blaho, Merigian & Winbery, 1996; Derlet & Horowitz, 1996; Rajput & Sunnergren, 1996). However, these drugs enhance stimulant-induced vasoconstriction and increase blood pressure (Albertson et al., 2001; Lange et al., 1990) and may exacerbate adverse effects (Sand, Brody, Wrenn & Slovis, 1991). Some authors suggest that their use in combination with a vasodilator such as nitroglycerin or nitroprusside may reduce such risks (Lester et al., 2000).

Some authors have cautioned against the use of thrombolytic therapy in cocaine-associated acute myocardial infarction (Hollander, 1995a). Concerns raised include potentially fatal complications of thrombolytic agents (Bush, 1988), the low mortality of patients in this group and the possibility of misdiagnosis because of the high incidence of J point elevation in this population. Hypertension is a relative contraindication in both cocaine-associated and traditional S-T elevation acute myocardial infarction. One study argues that the risk-benefit analysis favours use of

thrombolysis for S-T elevation acute myocardial infarction with or without associated cocaine use (Boniface & Feldman, 2000). They suggest that standard treatment of aspirin, nitrates and opiate analgesics followed by reperfusion (thrombolytic therapy) for non-responders should also be appropriate for those with suspected use of cocaine or other amphetamine derivatives.

It has been recommended that strategies for substance-abuse treatment should be incorporated into management, since there is an increased likelihood of non-fatal myocardial infarction in patients who continue to use cocaine (Weber et al., 2003).

Cerebrovascular emergencies

The use of cocaine or amphetamine derivatives is considered a strong risk factor for stroke or other forms of acute cerebrovascular emergencies (Heye & Hankey, 1996; McEvoy, Kitchen & Thomas, 2000; Perez et al., 1999; Petitti, Sidney, Quesenberry & Bernstein, 1998; Qureshi et al., 2001).

Mechanistic processes that mediate cocaine's effects on the cerebral vasculature are not well understood, but may involve vasospasm of smooth muscles lining the cerebral artery and thrombus formation in the vasculature (Johnson, Devous, Ruiz & Ait-Daoud, 2001). Vasculitis may (Merkel, Koroshetz, Irizarry & Cudkowicz, 1995) or may not be observed (Aggarwal, Williams, Levine, Cassin & Garcia, 1996; Nolte, Brass & Fletterick, 1996). Whilst a variety of abnormalities in cerebral vasculature may occur secondary to cocaine use including cerebral haemorrhage, the most common complications are haemorrhagic or thromboembolic strokes.

The pathophysiology of stroke related to amphetamine abuse is also multifactorial. It may produce transient and extreme increases in sympathetic output and blood pressure. This abnormal blood pressure change can precipitate intracerebral haemorrhage either alone or in association with an underlying vascular lesion such as an aneurysm or vasculitis. Unlike cocaine use, cerebral vasculitis or vasculopathic changes are well-described consequences of amphetamine use (Biller et al., 1987; Diez-Tejedor, Tejada & Frank, 1989; Harrington, Heller, Dawson, Caplan & Rumbaugh, 1983). In most reports, the clinical presentation of stroke is intracerebral haemorrhage.

Presentation

Heye and Hankey (1996) describe seven cases of amphetamine-associated stroke. The types of strokes observed were clinically and pathologically heterogenous. Five patients had ischaemic strokes; the other two patients had intracranial haemorrhages. All patients had consumed amphetamines hours before the onset of their symptoms. For three patients, it took more than four weeks of enquiry for disclosure of amphetamine use to occur, which led the authors to conclude that the incidence of amphetamine-induced stroke may be higher than currently thought.

Perez and colleagues (1999) describe four cases of stroke in young people associated with use of methamphetamine. Patients presented with a range of symptoms including weakness, hypertension, respiratory difficulties, speech difficulties, facial droop, temporal sudden headaches and partial paralysis. Most symptoms appeared within six hours of methamphetamine use. Another case describes a ruptured aneurysm of the right internal carotid artery in a young man with amphetamine

abuse (Chen et al., 2003). It grew rapidly within two weeks. Surgery revealed fibrosis and fibrinoid necrosis around the aneurysm. This type of presentation is quite rare.

Fessler and colleagues (Fessler, Esshaki, Stankewitz, Johnson & Diaz, 1997) describe 33 cases of neurovascular complications associated with cocaine use. Fourteen patients presented with headache, 12 with partial paralysis, 13 with nausea or vomiting and 8 experienced difficulty speaking. Sixteen of the 31 patients receiving a computerised tomography (CT) scan had subarachnoid haemorrhage. Eighteen cerebral arteriograms were performed, revealing 12 patients with intracerebral aneurysms, two with intracerebral haemorrhage and three with vessel occlusions consistent with ischaemic stroke and vasculitis. One patient had an arteriovenous malformation. Most patients experienced onset of symptoms whilst using cocaine or within six hours of cocaine use. Between 25-60% of cocaine-induced strokes can be attributed to cerebral ischaemia. About 80% of the infarcts occur in the regional distribution of the middle cerebral artery in young adults typically without pre-existing vascular malformations. Another case (Auer et al., 2002) describes a young man presenting with severe occipital headache following use of MDMA. Cerebral CT revealed right-sided subarachnoid haemorrhage and cerebral angiography showed right-sided middle cerebral artery aneurysm.

Since one of the earliest reports of intracranial haemorrhage associated with amphetamine use (Goodman & Becker, 1970), there are now numerous publications describing cerebrovascular problems associated with psychostimulant use. These include spinal cord infarction following cocaine use (Weidauer, Nichtweiss, Lanfermann & Zanella, 2002), intraventricular haemorrhage following methamphetamine use (Moriya & Hashimoto, 2002), intracranial haemorrhage following amphetamine use (Buxton & McConachie, 2000), massive intracerebral haemorrhage following amphetamine use (Chaudhuri & Salahudeen, 1999), intracerebral haemorrhage within the posterior right frontal lobe with no evidence of underlying aneurysm or vascular malformation (Byard et al., 1998), intracranial haemorrhage secondary to concurrent use of cocaine and enoxaparin (Khellaf & Fenelon, 1998) and cerebral (berry) aneurysms following methamphetamine use (Davis & Swalwell, 1996).

Assessment

Cocaine-induced cerebral ischaemia can result in marked hypoperfusion abnormalities. One study (McEvoy et al., 2000) reports that of 13 patients who had sustained intracerebral haemorrhage after psychostimulant use, they observed intracranial aneurysm in six and arteriovenous malformations in three. In only one patient was the angiogram normal.

A history of severe headache immediately after using amphetamines, MDMA or cocaine should alert doctors to the possibility of intracranial haemorrhage (McEvoy et al., 2000). They suggest that cerebral CT should always be performed when severe headache or altered consciousness or both occur in relation to use of these compounds. Arteriography should be part of the evaluation of most young patients with non-traumatic intracerebral haemorrhage (Auer et al., 2002).

Management

It has been suggested (McEvoy et al., 2000) that mortality and morbidity of patients sustaining drug-related intracerebral haemorrhage may be greater than that observed in similar patients with no substance use history, although not all studies support this (Conway & Tamargo, 2001; Nanda, Vannemreddy, Polin & Willis, 2000). At this stage treatment options targeted specifically at psychostimulant-induced cerebrovascular disease have not been explored. Management of cerebrovascular emergencies where psychostimulants are implicated in the aetiology should be managed using standard cerebrovascular emergency procedures.

Immediate management involves airway management, adequate oxygen, IV fluids to maintain nutritional and fluid intake and attention to bladder and bowel function. Corticosteroids may be harmful. If present, fever, hyperglycaemia, heart failure, arrhythmias, or severe hypotension must be treated.

Conclusion

Experimental and regular use of psychostimulants has been associated with severe adverse consequences including cardiovascular and cerebrovascular emergencies, acute behavioural disturbances, psychosis and serotonin toxicity. While some evidence regarding the emergency management of complications related to cocaine toxicity is available, studies related specifically to the management of amphetamine and MDMA toxicity are few. Despite a lack of strong evidence, it is widely accepted that skilful management of behavioural disturbance, psychosis and other manifestations of toxicity involves accurate assessment in a safe environment, adequate monitoring, a prompt response, attention to special precautions and the use of urgent sedation when indicated. Further studies into the efficacy of rapid sedation, particularly in regard to short-term effects, are required to improve emergency responses for this group.

Summary of evidence

Management of acute agitation and violence

Key points	Strength of evidence
Urgent sedation is a useful technique for management of acutely agitated or violent patients in an emergency setting.	**
A range of drugs may be useful, including droperidol, haloperidol, midazolam and lorazepam.	**
In the doses studied, droperidol produces more rapid sedation than haloperidol and lorazepam.	**
Benzodiazepines and antipsychotics may be used in combination and may be more efficacious than the use of single agents.	*

Serotonin toxicity

Key points	Strength of evidence
Serotonin toxicity may occur after ingestion of amphetamine derivatives alone or if ingested with other serotonergic agents such as antidepressants.	*
Pharmacological agents which antagonise the effects of serotonin such as cyproheptadine and chlorpromazine may have a limited role in attenuating symptoms of toxicity.	*
Non-specific agents such as benzodiazepines may assist in reducing muscle rigidity, agitation and seizures.	*

Cardiovascular complications

Key points	Strength of evidence
Psychostimulant-related chest pain is a common presentation.	*
It is more common after cocaine than amphetamine use but can occur with both.	*
Benzodiazepines can be particularly useful.	**
Continued psychostimulant use is associated with an increased risk of subsequent infarction.	*

Cerebrovascular complications

Key points	Strength of evidence
Use of psychostimulants is a risk factor for several cerebrovascular events.	*
Onset of symptoms occurs during or within hours of use.	*
Cerebrovascular events occur in patients with little in the way of additional risk factors.	*
Management should follow standard procedures with early consideration of angiography.	*

Chapter 7

Psychostimulant withdrawal and detoxification

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Key points

- Agreement on the natural history of psychostimulant withdrawal is yet to be reached.
- The phasic model of withdrawal is commonly applied but not well supported.
- The 'crash' period is not universally experienced but where it exists, it should be viewed as a recovery period and does not in itself constitute a clinically significant withdrawal syndrome.
- The withdrawal syndrome for psychostimulants, unlike CNS depressants, may mimic intoxication.
- Symptoms of depression and associated suicidal ideation may complicate psychostimulant withdrawal.
- Dependence on other substances, particularly alcohol, is common among those who are psychostimulant dependent.
- Attempts to self-detoxify from amphetamines may be common and relapse rates are high following both self and hospital detoxification.
- A thorough mental health and AOD assessment is recommended for those undergoing psychostimulant detoxification.
- Detoxification on its own is of little long-term value and should be considered only as the first component of an individually tailored intervention plan that at least addresses motivational enhancement and relapse prevention.
- Due to the high prevalence of comorbid mental health and other drug use disorders, careful and thorough assessment of both areas should be undertaken prior to detoxification with particular emphasis on depression and psychotic symptoms. Training should be provided to clinicians unfamiliar with these assessments.
- Detoxification from psychostimulants can usually be undertaken in the home or community, but evidence of severe psychotic symptoms that cannot be safely managed in the community, significant poly drug dependence, severe depression or other risk factors indicate that a hospital setting might be more suitable.
- The use of medications is of little general value in psychostimulant withdrawal and should be informed by individual presentation and specific circumstances according to existing guidelines until further research is undertaken.

- No strategy for specific psychological therapy during detoxification has as yet been evaluated, but due to the variability of withdrawal syndromes, people undertaking detoxification from psychostimulants should be informed about the range of potential symptoms that they could experience.

Introduction

The use of psychostimulants has increased considerably in Australia over the past decade, particularly among certain groups such as youth and IDUs. The use of cocaine is less widespread, however pockets of problematic users may be located in cities such as Sydney (see Chapter 2: *Prevalence and patterns of psychostimulant use*). Prescription stimulants, such as methylphenidate ('Ritalin™') are also misused, often in a quest to lose weight or with the diagnosis of adult attention deficit hyperactivity disorder used as a pretext. Similarly, prescription anorectics such as 'Duromine™' can also be misused.

This chapter reviews the national and international literature pertaining to cocaine and amphetamine withdrawal and recommended management. Recommendations for assessment and monitoring are included and a one-page decision tree has been developed for quick reference. Gaps in the literature are identified throughout, in addition to brief recommendations for further research. As the pattern of MDMA use is unlike that of amphetamines and cocaine (see Chapter 2: *Prevalence and patterns of psychostimulant use*), it is unusual for someone to become dependent and require withdrawal specifically from MDMA, hence withdrawal management of MDMA is not addressed in this chapter.

The psychostimulant withdrawal syndrome

The dependence potential of psychostimulants is well established. For many years the dependence was considered to be entirely 'psychological' (Senate Standing Committee on Social Welfare, 1977). However, the existence of a withdrawal syndrome is now well recognised. The literature pertaining to psychostimulant withdrawal is inconsistent and of mixed quality. Similarly, despite an exhaustive search, no studies that describe the natural history of methamphetamine withdrawal among dependent individuals could be located and as a result that particular process is still poorly understood.

In spite of this, there is some agreement that the psychostimulant withdrawal syndrome is unlike the withdrawal syndromes that occur in people who are dependent on CNS depressant drugs such as opioids or alcohol, the features of which are the opposite to those of the acute pharmacological effects of these drugs. In contrast, several features of the psychostimulant withdrawal syndrome actually mimic those of intoxication, particularly agitation and hyper-arousal.

'Crash' period

It is important to note that many users of psychostimulants will experience what is commonly called a 'crash' or brief period of recovery that may last for a few days following binge use. This recovery period may be planned or unplanned, but does not in itself constitute a clinically significant withdrawal syndrome (although it may herald it in some cases). Rather it is a process of recovery from a period of CNS over-stimulation and is usually characterised by excessive sleeping and eating and irritability of mood.

Such a recovery period may be compared to the experience of a 'hangover' from alcohol characterised by irritability, tiredness, headache and nausea, which is widely recognised as time-limited and not a withdrawal syndrome in itself. A withdrawal syndrome, therefore, manifests as a cluster of symptoms, enduring for a meaningful duration (according to drug class and severity of withdrawal), which impairs the functioning of an individual to a clinically significant degree. The key features of intoxication and withdrawal from heroin, alcohol and psychostimulants are compared in Table 13.

Table 13: Comparison of key features of intoxication versus withdrawal from heroin, alcohol and psychostimulants (includes cocaine and amphetamines)

	Intoxication	Withdrawal
Alcohol	**Relaxation, sociability, euphoria, disinhibition, reduced motor coordination, reduced respiratory rate, sleepiness/ sedation (respiratory arrest in toxicity state).**	**Tremulousness, agitation, anxiety perspiration, insomnia, sleep disturbance, increased blood pressure, pulse and temperature, nausea, vomiting and diarrhoea (seizures and delirium tremens in complicated withdrawal). Onset 6–24 hours after last drink, peaks day 2–3, resolves by day 5 (may last up to 10–14 days if complicated withdrawal).**
Heroin	**Intense euphoria, extreme relaxation, calmness, sleepiness, constricted pupils, dulled responses, potent pain relief, constipation and reduced respiratory rate (respiratory arrest in toxicity state).**	**Restlessness, insomnia, agitation, irritability, dilated pupils, piloerection (gooseflesh), hot and cold flushes, watering eyes and nose, perspiration, muscle aches, leg cramps, joint pain, abdominal cramps, diarrhoea, nausea, vomiting and craving to use. Onset 8–12 hours after last dose, peaks day 2–3, usually resolves by day 5.**
Psychostimulants	**Increased confidence, anxiety, agitation, motor hyperactivity, insomnia, excitement, talkativeness and rapid speech, irritability, hypervigilance, muscle twitches, hand tremor, sweating, rapid heart rate, elevated blood pressure, heart palpitations, poor appetite, dilated pupils, increased body temperature, dry mouth and jaw clenching (psychosis, hyperthermia and seizures in toxicity state).**	**Following a possible initial 'crash' period: dysphoria, depression, slowing of physical movements, poor concentration, agitation, insomnia, irritability, lethargy, exhaustion, craving to use, anxiety, variable (often increased) appetite and anhedonia. Onset and duration variable according to type of stimulant used: amphetamine sulphate withdrawal may last up to 4 weeks, some symptoms of methamphetamine withdrawal may last for many months.**

Clinical picture

Unfortunately, the number of individuals who are dependent on psychostimulants and are likely to experience a withdrawal syndrome following cessation or reduction in use is not yet able to be estimated, although the presence of a withdrawal syndrome is not necessary for a person to meet criteria for dependence (which includes psychological factors). Similarly, the roles that tolerance (neuroadaptation) and acute toxicity play in long-term withdrawal are also unclear (Davidson et al., 2001). Having said this, the incidence, severity, course and subjective experience of the withdrawal syndrome are likely to be influenced by:

- the severity of dependence;
- duration of use;
- frequency of psychostimulant use (irregular use versus regular, daily use);
- potency of psychostimulant used (e.g. methamphetamine versus amphetamine sulphate);
- duration of action of psychostimulant (e.g. cocaine versus methamphetamine);
- the presence of other physical or psychiatric disorders; and
- psychosocial factors (e.g. physical environment, fears and expectations).

The clinical picture of psychostimulant withdrawal tends to be mixed. Dominant signs of CNS hypoactivity such as lethargy, slowed movements and poor concentration are interspersed with agitation and insomnia. Dysphoria and depression are also particularly common, especially after toxicity symptoms have resolved (Miller, Summers & Gold, 1993).

At least two mechanisms may be involved with this. The first is the depletion of monoamine neurotransmitter stores, specifically of serotonin, norepinephrine and dopamine that affect mood regulation (Cho & Melega, 2002). The second involves alteration in brain structure identified by brain imaging studies of current and past methamphetamine users, particularly the loss of dopamine transporters, the effect of which is slowed motor function and impaired memory (Volkow, Chang, Wang, Fowler et al., 2001).

The onset of withdrawal following cessation of high-level, regular use varies between the subgroups of psychostimulants according to their half-lives and route of administration.

The cocaine withdrawal syndrome

Natural history of cocaine withdrawal

Most of the literature pertaining to the cocaine withdrawal syndrome has predictably emerged from studies undertaken in the USA where the use of cocaine is prevalent. However, general agreement on the natural history of a 'typical' cocaine withdrawal has yet to be reached. Due to the relatively short half-life (time required for half of the drug dose to be cleared from the body) of cocaine of 90 minutes (Cho & Melega, 2002), withdrawal symptoms may occur quite rapidly following the last dose.

The most commonly cited study into cocaine withdrawal was undertaken by Gawin and Kleber in 1986. Using data collected from 30 cocaine-dependent outpatients, the investigators reported three distinct phases ('crash', 'withdrawal' and 'extinction') of the withdrawal process:

Phase one, 'the crash', developed rapidly following abrupt cessation of heavy cocaine use and was characterised by acute dysphoria, irritability and anxiety, increased desire for sleep, exhaustion, increased appetite, decreased craving to use.

Phase two, 'withdrawal' was characterised by increasing craving to use, poor concentration, some irritability and some lethargy, which persisted for up to 10 weeks.

Phase three, 'extinction', comprises intermittent craving to use in the context of external cues.

The phasal model is pictorially represented in Figure 1.

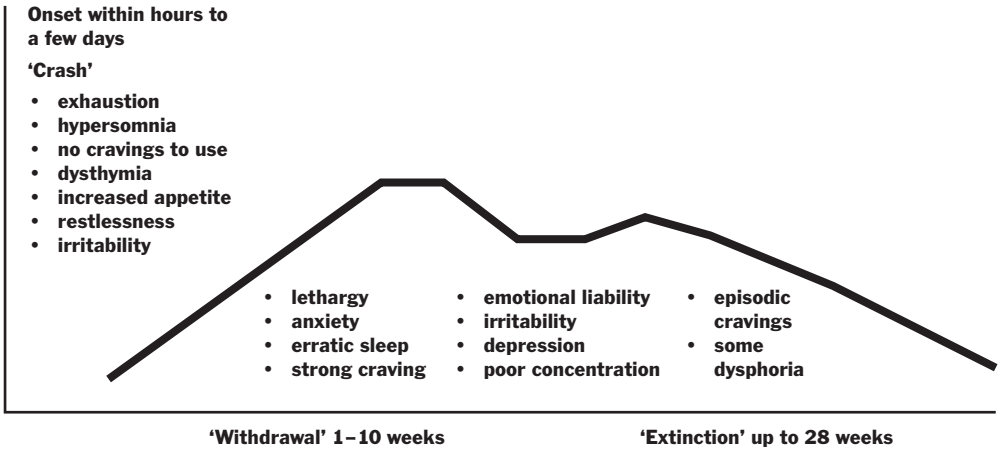


Figure 1: Gawin and Kleber's Phasal Model of Cocaine Withdrawal (1986)

Despite the relative persistence of the clinical application of the phasal model to cocaine withdrawal (and to some extent amphetamine withdrawal), results from several other studies have not supported this model, but rather have found a gradual return to normative functioning over time (Coffey, Dansky, Carrigan & Brady, 2000; Miller et al., 1993; Satel, Price, Palumbo, McDougle et al., 1991; Weddington, Brown, Haertzen, Come et al., 1990).

For example, Miller and colleagues (1993) reported self-described and clinically observed withdrawal symptoms among a group of 150 cocaine-dependent (DSM-III-R criteria) in-patients of an alcohol and drug treatment facility in Florida. The age range was 18–55 years (mean 26 years). Males comprised 64% of the sample. Half of all participants smoked crack cocaine and 29% snorted powder. The investigators reported that following rapid cessation of cocaine use, withdrawal symptoms consisted of 'craving, hyperactivity, slight tremor, insomnia and apprehension' (p. 30), which decreased in a linear fashion. No participants required medication during the withdrawal and no significant psychological problems

emerged. Unfortunately, no specific time periods associated with the symptoms were presented, although only 12 patients (8% of the sample) left the 28-day treatment program prior to completion.

A more recent prospective study of cocaine withdrawal was undertaken in the USA by Coffey and colleagues (2000). A small sample of 24 mixed in-patient and outpatient subjects (42% female) who completed all measures over a 28-day period were included in the final analysis (82 cocaine-dependent participants comprised the whole sample). The investigators reported a linear reduction in withdrawal symptoms over the time period, particularly anger and depression, with a corresponding increase in concentration. Interestingly, craving to use cocaine was not identified as a significant issue among this sample, nor were appetite fluctuations and sleeplessness.

Several explanations have been offered for the lack of consistency across studies. These include differences in exposure to drug use cues between in-patient and outpatient samples and variations in sample size and research methodology, such as prospective versus retrospective designs (Lago & Kosten, 1994). Mixed in-patient and outpatient samples as described above may also cloud the clinical picture, particularly when small sample sizes are relied upon. Prospective studies examining the natural history of cocaine withdrawal among both in-patients and outpatients, with attention to gender differences in withdrawal characteristics among dependent cocaine users, are required to clarify some of these issues for the Australian situation.

Diagnosis of cocaine withdrawal

For a formal diagnosis of cocaine withdrawal to be made, the DSM-IV-TR (American Psychiatric Association, 2000) lists the following criteria:

A. cessation of, or reduction in, heavy or prolonged cocaine use;

B. dysphoric mood plus two (or more) of the following, developing within a few hours or several days after A:
   - fatigue;
   - insomnia or hypersomnia;
   - psychomotor agitation or retardation;
   - increased appetite; and
   - vivid, unpleasant dreams;

C. the criterion symptoms in B are clinically significant or cause distress in social, occupational or other important areas of functioning; and

D. are not due to a medical condition or another cause.

Interestingly, cravings and anhedonia (lack of enjoyment in activities that were previously enjoyed), which were included in the 1994 DSM-IV criteria, may be present, but are not part of the diagnostic criteria in the revised edition.

While depression is commonly present during cocaine withdrawal and dysphoria (sadness) is a mandatory criteria as stated above, there is some evidence to suggest that depression (lifetime and current) affects the onset and course of cocaine withdrawal.

In a recent study of 146 cocaine users (who used more than 10 times in any one-month period), those with a lifetime history of depression (according to DSM-IV diagnosis) were five times more likely to self-report ever having experienced a withdrawal syndrome than those with no history of depression (Helmus, Downey, Wang, Rhodes & Schuster, 2001). Unfortunately, the investigators did not determine if the depressed subjects used larger amounts of cocaine than their non-depressed counterparts, as quantity and frequency of use significantly impacts on withdrawal.

In another study, Schmitz, Stoots, Averill, Rothfleisch et al. (2000) reported more severe craving for cocaine among those with comorbid cocaine dependence and depression (n=50) than those with cocaine dependence alone (n=101).

Finally, Roy (2001) reported that of a sample of 214 cocaine-dependent patients admitted to a Department of Veterans' Affairs sponsored drug treatment service in the USA, 39% (n=84) had at least one attempt at suicide during their life (mean 2.1 attempts, range 1-9) and 87% met DSM-IV criteria for lifetime major depression. Those who attempted suicide were more likely to be female (p=<0.001), have a family history of suicide (p=<0.0001) and were more likely to have experienced childhood sexual, emotional or physical abuse than cocaine-dependent individuals with no history of suicide attempts (p=<0.0001).

Assessment issues in cocaine withdrawal

Individuals presenting for treatment should be thoroughly assessed for concomitant mental health disorders due to the high rates of comorbid depression and cocaine dependence (eg, Falck, Wang, Carlson, Eddy & Siegal, 2002; Rounsaville, Anton, Carroll, Budde et al., 1991), the potential role of untreated depression in relapse to problematic substance use (Hasin, Liu, Nunes, McCloud et al., 2002) and the potential for suicide (Falck et al., 2002; Roy, 2001). The issue of comorbid mental health disorders and their impact on assessment and management of psychostimulant users are discussed in detail in Chapter 10: *Psychiatric comorbidity of psychostimulant use*.

Due to the high prevalence of concurrent dependence on other drugs, particularly alcohol (Carroll, Nich, Ball, McCance et al., 2000; Kampman, Pettinati, Volpicelli, Kaempf et al., 2002; Miller et al., 1993) the cocaine withdrawal syndrome may be complicated by withdrawal from other drugs, hence a thorough assessment of the use of all drug classes is recommended (see Assessment section of this chapter). Should concomitant withdrawal syndromes occur, both should be managed simultaneously.

The amphetamine withdrawal syndromes

Natural history of amphetamine withdrawal

Studies examining the natural history of amphetamine withdrawal are significantly fewer than those examining cocaine. This is probably due to the more recent recognition of the widespread use of amphetamines.

The phasal model of cocaine withdrawal has typically been applied to withdrawal from amphetamines with symptoms believed to persist for a longer duration due to the longer half-life of amphetamines (e.g. methamphetamine has a half-life of

between 6–34 hours) (Davidson et al., 2001) or authors have simply described withdrawal from 'psychostimulants' without discriminating between cocaine, amphetamines, methamphetamine or dexamphetamine (e.g. West & Gossop, 1994).

Clinicians in the UK have reported that following cessation of regular daily use of intravenous amphetamines, dependent individuals:

> *"…complain of fatigue and inertia, an initial period of hypersomnia followed by protracted insomnia and an onset of agitation, usually within 36 hours of cessation, that exists for between 3–5 days. The degree of mood disturbance, while influenced by the previous level of consumption, ranges from dysphoria to severe clinical depression. Subjectively, such patients report symptoms that, although differing from that of opiate withdrawal, require support and in some cases urgent psychiatric attention."*
>
> (Myles, 1997, p.69).

The variability in sleeping patterns during amphetamine withdrawal, particularly hypersomnia during early withdrawal, has been supported by some studies (Gossop, Bradley & Brewis, 1982) but not others (e.g. Srisurapanont, Jarusuraisin & Jittawutikan, 1999a). To investigate the psychometric properties of a scale to assess the severity of amphetamine withdrawal (AWQ) (Srisurapanont, Jarusuraisin & Jittawutikan, 1999b), which is described in the Monitoring section of this chapter, 102 subjects in early withdrawal (1-5 days) were asked to rate the presence and severity of eleven symptoms prior to receiving treatment and a subgroup completed additional ratings on days 7 and 8. The analysis revealed that in order of ranking, craving for sleep, increased appetite, decreased energy, dysphoric mood, slowing of movement and loss of interest or pleasure attracted the highest mean scores. Contrary to the clinical observations described by Myles above, the symptom of insomnia was removed from the final version of the AWQ due to its low mean score (28 patients rated insomnia as 'not at all' present or rated it as causing 'very little' distress). It should be noted, however, that the AWQ was administered to subjects in different stages of withdrawal, which is likely to affect sleeping patterns.

Diagnosis of amphetamine withdrawal

Interestingly, the DSM-IV-TR criteria (American Psychiatric Association, 2000) for amphetamine withdrawal are exactly the same as those for cocaine withdrawal and while sleep disturbance is included, it is not critical for a diagnosis:

A. The cessation of, or reduction in, heavy or prolonged amphetamine (or a related substance) use.

B. Dysphoric mood plus two (or more) of the following, developing within a few hours or several days after A:
   - fatigue;
   - insomnia or hypersomnia;
   - psychomotor agitation or retardation;
   - increased appetite; and
   - vivid, unpleasant dreams.

C. The criterion symptoms in B are clinically significant or cause distress in social, occupational or other important areas of functioning.

D. Symptoms are not due to a medical condition or another cause.

Self-detoxification from amphetamines

Attempts to self-detoxify from amphetamines appear to be common among dependent users. Cantwell and McBride (1998) explored the detoxification experiences of a small sample of amphetamine dependent individuals (according to ICD-10 and DSM-IIIR criteria) in Britain. Of the 50 participants, 48 had injected regularly and seven were abstinent at the time of the study (mean 2.8 years of abstinence). A total of 43 subjects (86%) reported withdrawal symptoms following cessation of amphetamine use. 66% of the sample (n=33) reported that they had attempted self-detoxification at least once (n=47 occasions of self-detoxification), including six of the ten subjects who had also undertaken a medically supervised withdrawal (n=16 occasions of in-patient and outpatient detoxification).

Amphetamine withdrawal symptoms

The most frequently reported withdrawal symptoms in the Cantwell and McBride (1998) study were irritability (78%), aches and pains (58%), depressed mood (50%) and impaired social functioning (46%). Participants reported that symptoms persisted for between five days and three weeks. Relapse was common (most within four weeks of cessation) and the reasons given for reinstatement of use following self-detoxification included the wide availability of amphetamines, depression, boredom, peer pressure, persistent withdrawal symptoms and enjoyment of using. Interestingly, no participants reported craving as a reason for relapse.

Animal and human studies have confirmed that the methamphetamine withdrawal syndrome may be protracted (the mood disturbance may last up to a year in some cases) and tends to be more severe than cocaine withdrawal (see Cho & Melega, 2002 for a thorough review; Davidson et al., 2001; Volkow, Chang, Wang, Fowler, Franceschi et al., 2001). Similarly, there is some evidence to suggest that individuals who have experienced a methamphetamine-related psychosis are at risk of further psychotic episodes, even in the absence of further psychostimulant use (Yui, Ikemoto, Ishiguro & Goto, 2000). Clearly, the amphetamine and methamphetamine withdrawal syndromes may be complex and clinically challenging. Due to the widespread use of potent methamphetamine in Australia, studies that describe the natural history of withdrawal among dependent Australian users in a range of settings, with mixed gender samples, are urgently required to inform the development of appropriate services and responses.

Detoxification and withdrawal management

Cessation of psychostimulants may be a planned (elective) or unplanned experience (e.g. due to incarceration or drugs being unavailable). The planned cessation of drug use in someone who is dependent is termed 'detoxification'. In this monograph the management of someone who has already developed a withdrawal syndrome is termed 'withdrawal management' and may be applicable to various settings including general or psychiatric hospitals or custodial environments such as watch houses or remand centres.

As discussed in Chapter 5: *Psychosocial interventions*, psychostimulant users are more likely to present for treatment when their use of these drugs has impacted negatively on their lives in regard to behaviour (anger and aggression), aversive psychological symptoms (depression, anxiety, paranoia and panic) and social factors

(damage to family or social relationships and unemployment) (Vincent et al., 1999). Beliefs about the relative safety of amphetamines among some users and the lack of identification with treatment-seeking opiate users (Wright et al., 1999), coupled with the inability of many existing drug treatment agencies to appropriately respond to amphetamine users (Lintzeris, Holgate & Dunlop, 1996) may also inhibit treatment-seeking until the adverse consequences are severe. Many psychostimulant users may have had several previous attempts to self-detoxify before seeking formal treatment (Cantwell & McBride, 1998). Hence, the management of people seeking detoxification support should take into account all of these factors to ensure that people are initially engaged in appropriate treatment and retained in aftercare to ensure the best possible outcomes are obtained.

General principles of detoxification from psychostimulants

Detoxification is a process by which the psychostimulant dependent person may withdraw from the effects of the drug in a supervised manner to ensure that withdrawal symptoms and the attendant risks are minimised. As a stand-alone treatment, detoxification is generally considered to be of little long-term value (Gowing et al., 2001), but it is invaluable as a gateway to more extensive services and interventions (National Campaign Against Drug Abuse (NCADA), 1992), which have been discussed in Chapter 5: *Psychosocial interventions* and Chapter 8: *Pharmacological interventions* of this monograph. Due to the high rates of relapse following treatment for psychostimulant use disorders (Brecht, von Mayrhauser & Anglin, 2000), psychosocial interventions are an extremely important component of post-detoxification treatment.

Detoxification from psychostimulants is usually undertaken outside a hospital setting if the home environment is supportive and there are no stimulants or other psychoactive drugs available. However, if the person is homeless, has a history of protracted or multiple withdrawals, is severely dependent, or has a concomitant significant medical or psychiatric illness that cannot be appropriately managed in the community, a supervised or hospital setting may be more appropriate.

To date, there is no clear strategy for the psychological and pharmacological management of psychostimulant withdrawal that is based on sound empirical evidence (Proudfoot & Teesson, 2000; Srisurapanont, Jarusuraisin & Kittirattanapaiboon, 2001, 2002). However, there is clinical agreement that management strategies essentially involve:

(1) the provision of psychosocial support in a safe, non-threatening environment; and

(2) the prescription of symptomatic relief medication when indicated on an individual basis (Murray, Lintzeris, Gijsbers & Dunlop, 2002, Cruickshank & Dyer, unpublished; Pead, Lintzeris & Churchill, 1996).

The reader is referred to Chapter 5: *Psychosocial interventions* and Chapter 8: *Pharmacological interventions* of this monograph for a thorough review of psychosocial and pharmacological approaches to treatment.

Assessment for detoxification

The assessment process for psychostimulant detoxification is similar to the process for other drug detoxification. The essential components of an accurate assessment include:

Psychostimulant use

- Amount of psychostimulant used[3].
- Type of psychostimulant used (e.g. methamphetamine, amphetamines, cocaine).
- Route of administration (e.g. intranasal, intravenous, oral or inhalation).
- Frequency of use (e.g. regular daily use or irregular 'binge' pattern).
- Duration of current use and age of initiation.

Other drug use

- Use of other drug classes (particularly alcohol, benzodiazepines and opiates), including criteria above.

Dependence

- Meets criteria for a diagnosis of dependence for psychostimulants and/or other drugs.
- Severity of dependence on each drug used.
- Evidence of tolerance (uses more of the drug to achieve the same effect).

History of withdrawal

- Experience of previous withdrawal symptoms, severity, course and treatment outcomes.

Other conditions

- Presence of concomitant physical illness including blood borne viruses (HCV, HBV and HIV).
- Presence of concomitant psychiatric illness or psychiatric symptoms (psychosis, paranoia, depression, suicidal ideation etc).

Other factors that may impact on completion of detoxification include:

- precipitants to treatment-seeking;
- social/family supports;
- parenting status and other familial responsibilities;
- employment status;
- accommodation (stability, exposure to psychostimulants etc);
- unresolved legal/social issues;
- understanding/knowledge of withdrawal process;

3 The amount of amphetamines used can be measured either in dollars spent on the drug or in 'points' or grams or number of 'pills'. The street value of amphetamines (powder, 'base', pills) varies considerably across cities and states and clinicians should determine local costs so an accurate assessment can be made if using amount of money spent as a guide to consumption. IDRS data for each state is a useful indicator of local prices and purity.

- readiness to change drug use behaviour;
- client's goal for treatment; and
- confidence in ability to complete withdrawal and expectation of the process and outcomes.

Settings for detoxification

Home or ambulatory detoxification

Most people identify the home setting as the preferred option for supervised detoxification and many might be more willing to undertake detoxification if they do not require hospitalisation (Saunders, Ward & Novak, 1997). The option to detoxify at home might be especially appealing to psychostimulant users who are often reluctant to access mainstream treatment services for reasons previously noted. In addition, as the withdrawal syndrome from psychostimulants may be protracted, a hospital setting may be inappropriate for many individuals.

During home detoxification, the person is supervised in their home by a carer and receives daily visits from a registered nurse or a general practitioner. There are several community agencies in Australia that provide this type of service. These agencies may be identified by calling the state alcohol and drug telephone information service.

During ambulatory (or outpatient) detoxification, the person attends the local drug treatment service or the local hospital (in some regional areas) daily, or sees his/her general practitioner daily or second daily.

The detoxification process should be monitored and appropriate interventions undertaken. The aim of ambulatory or home-based detoxification is to:

- manage the symptoms of withdrawal in a supportive environment;
- monitor the person's mood;
- provide an opportunity for early intervention if adverse consequences arise;
- educate people about the course of withdrawal and the likelihood of enduring symptoms;
- maintain commitment to withdrawal; and
- plan for and co-ordinate aftercare.

Ambulatory or home detoxification treatment can be considered suitable if the following criteria are met (Saunders et al., 1997; Topp et al., 2001):

- no severe or complicated withdrawal is anticipated;
- no medical complications requiring close observation or treatment in a hospital setting are evident;
- psychiatric symptoms such as psychosis or depression are able to be safely managed in a community setting;
- has strong social supports (family members and carers require education and support themselves);
- has a drug-free, supportive and stable home environment;

- has not previously failed detoxification in the community; and
- is committed to withdrawal.

Community residential setting

When the home environment is not supportive of detoxification or where one or more previous attempts at ambulatory or home detoxification have been unsuccessful, the person can be referred to a community residential setting for detoxification. This setting is suitable for persons who meet the criteria outlined below:

- no severe or complicated withdrawal is anticipated;
- no medical complications requiring close observation or treatment in a hospital setting are evident; and
- psychiatric symptoms such as psychosis or depression are able to be safely managed in a community residential setting.

Hospital or specialist detoxification setting

The need for admission to a hospital or a specialist detoxification unit may be less warranted than for other drug types, such as alcohol or benzodiazepines. There is also considerable variation in criteria for admission among specialist detoxification settings throughout Australia and the following criteria are intended as a guide only:

- simultaneous dependence on alcohol or other drugs that would satisfy criteria for hospital admission;
- severe dependence such that complicated withdrawal is anticipated;
- serious medical complications requiring close observation or treatment in a hospital setting are evident;
- significant psychiatric complications, specifically psychotic symptoms or severe depression and/or suicidal ideation that pose significant risk to the person or others and cannot be adequately or safely managed in a community setting;
- has an unfavourable home environment or is homeless; and
- the person has had multiple previously failed attempts at ambulatory detoxification.

Individuals and clinicians should confirm admission criteria with their local agency to determine if referral is appropriate. If in-patient treatment is considered necessary the duration of stay should be tailored to the individual. In all cases it should be long enough for the resolution of the psychotic and acute withdrawal symptoms to occur.

Due to the high prevalence of sub-clinical and acute psychotic symptoms among regular amphetamine users (Dawe, Saunders, Kavanagh & Young, unpublished) and those presenting specifically for detoxification from amphetamines (Cruikshank & Dyer, unpublished), individuals may voluntarily or involuntarily present to mental health services for treatment in the first instance. As discussed in Chapter 2: *Patterns and prevalence of psychostimulant use*, there has been a six-fold increase in the numbers of Australians receiving treatment for psychosis due to psychostimulant use between 1998 and 2001 (Australian Institute of Health and Welfare, 2003b).

In the mental health setting, management of psychosis, severe depression or other disorders will occur according to standard treatment. However, to complement the usual psychiatric assessment a thorough alcohol and other drug use history should also be obtained by the mental health service and include collateral information gained from friends or relatives, which will inform the concurrent management of the psychostimulant withdrawal.

Similarly, it is essential that all AOD treatment providers undertake a thorough mental health history or mental state assessment on all psychostimulant-using clients, with a particular emphasis on psychotic symptoms and depression. For clinicians unfamiliar with such assessments, adequate training and supervision should be offered.

It is also important that services involved in the person's care collaborate to coordinate the management of individuals who require both mental health treatment and management of psychostimulant withdrawal and aftercare. Collaborative service provision may entail alcohol and other drug clinicians offering primary or secondary consultation to mental health services and vice versa and prompt assessments by either service to a person experiencing concomitant mental health and psychostimulant use problems, regardless of the initial place of presentation.

Monitoring the withdrawal syndrome

The person should be monitored throughout the course of the withdrawal and various observation charts exist for this purpose. The Amphetamine Withdrawal Questionnaire (AWQ) is a 10-item self-report instrument designed to detect severity of amphetamine withdrawal symptoms based on the DSM-IV criteria for withdrawal and published literature (Srisurapanont et al., 1999b). Following a trial among a small sample of 102 amphetamine-dependent individuals undergoing withdrawal, the investigators reported good test-retest reliability (mean test-retest correlation score 0.77) and validity ($r=0.62$, $p=0.00$). A factor analysis revealed a three-factor model comprising a hyperarousal factor (craving, agitation and unpleasant dreams), a reversed vegetative factor (decreased energy, increased appetite, craving for sleep) and an anxiety factor (loss of interest or pleasure, anxiety and slowing of movement).

A scale for assessing severity of cocaine withdrawal has been developed by Kampman, Volpicelli, McGinnis, Alterman et al. (1998) and is reported to be a valid and reliable measure. The Cocaine Selective Severity Assessment instrument is an 18-item instrument designed for use by clinical staff to assess severity (0 = no symptoms to 7 = severe) of signs and symptoms of cocaine withdrawal. Domains measured include craving, depressed mood, appetite changes, sleep disturbance, lethargy, low pulse rate (bradycardia) and irritability.

It must be emphasised, however, that unlike withdrawal from alcohol or opioids, medication is not specifically or immediately administered in response to a specific score on a psychostimulant withdrawal scale (symptom-triggered treatment). The observations monitor the person's progress through detoxification, however a rating of the person's subjective experience of withdrawal symptoms, particularly agitation, sleep disturbance, depression and symptoms of psychosis, will inform the need for, or dose of, relevant medications during the course of withdrawal or aftercare.

Irritability is very common and angry outbursts have been noted among some individuals experiencing withdrawal from psychostimulants. Clinical staff and carers should be mindful to provide appropriate support and adequate physical space during detoxification. The use of medications might be indicated in some instances.

The place of pharmacotherapies

Detoxification from psychostimulants may proceed without the assistance of medications. Unlike withdrawal from substances such as alcohol or opioids, pharmacotherapy for psychostimulant withdrawal is of limited value, with most studies undertaken to date failing to demonstrate significant clinical effects (Gowing et al., 2001) (see Chapter 8: *Pharmacological interventions* for a thorough review).

There is also no evidence that tapered withdrawal from psychostimulants is preferable to abrupt cessation (Wickes, 1992). Psychostimulant withdrawal is rarely life-threatening but users with profound depression may develop suicidal ideation, or psychotic symptoms may manifest during the acute intoxication/toxicity phase and worsen during the early stages of withdrawal (Murray et al., 2002). In this case, medications may be prescribed as indicated for those disorders.

Use of anxiolytics and sedative hypnotics

Anxiety may be a prominent feature of cocaine and to a lesser extent amphetamine withdrawal. A recent animal study demonstrated the effectiveness of benzodiazepines to reduce cocaine withdrawal-induced anxiety (Paine, Jackman & Olmstead, 2002). Benzodiazepines (particularly long-acting diazepam) if indicated for anxiety or to initiate sleep in early withdrawal should be prescribed for a maximum of two weeks, with dispensing on a daily basis if possible. Results from a recent Australian study revealed that patients who were prescribed a sedative hypnotic (temazepam) were more than twice as likely to complete an in-patient amphetamine detoxification program than those who were not (Cruikshank & Dyer, unpublished).

Use of antidepressants

There are several guidelines currently available for the pharmacological management of amphetamine withdrawal in Australia if it is indicated. Briefly, Murray and colleagues (e.g. Murray et al., 2002), suggest that an SSRI or tricyclic antidepressant may be prescribed if necessary, with frequent reviews and careful monitoring, as tricyclic antidepressants are cardiotoxic in overdose. Similarly, as relapse to psychostimulant use is common, special care must be taken when prescribing SSRIs as toxicity (due to increased serotonin levels) has been reported with concomitant use of psychostimulants (Barrett, Meehan & Fahy, 1996). It must be recognised, however, that antidepressants need to be taken for about 2 weeks before a therapeutic effect is evident and individuals prescribed these medications must be suitably informed to encourage compliance during this window period. Australian researchers intend to investigate the role of the faster-acting SNRIs in psychostimulant withdrawal in the near future (Dyer, K. pers. comm.).

Use of antipsychotics

If psychotic symptoms manifest, antipsychotic medication such as phenothiazine or haloperidol may be prescribed in the short term (one to two weeks). However if psychosis persists or is severe, an immediate psychiatric assessment is indicated and general psychosis management and treatment principles should be applied (Murray et al., 2002).

There is some clinical interest in the prescription of the newer atypical antipsychotic medications during psychostimulant withdrawal, but their role is yet to be empirically determined and further studies are required before clinical recommendations can be confidently made (Srisurapanont et al., 2002). The reader is referred to Chapter 6: *Management of acute toxicity* and Chapter 10: *Psychiatric comorbidity* of *psychostimulant use* in this monograph for a detailed review of the management of psychosis.

It is important to recognise that some clinical investigators have found withdrawal from at least cocaine to be a relatively benign process that can be generally undertaken without the assistance of medication (Miller et al., 1993).

Psychological therapies for psychostimulant detoxification

Like other investigators (e.g. Proudfoot & Teesson, 2000), we could locate no specific recommendations for psychological therapies specifically for the acute detoxification period. However, any psychological and other supportive therapies initiated during detoxification should be aimed at assisting the person to safely complete withdrawal and to engage in aftercare. As fear of the withdrawal process may play a role in non-completion of detoxification, it is essential that people are properly prepared for what they may experience in both the short and long term. This involves education about possible withdrawal symptoms and the variable course of withdrawal and ongoing supportive management through what may be a protracted process for some people.

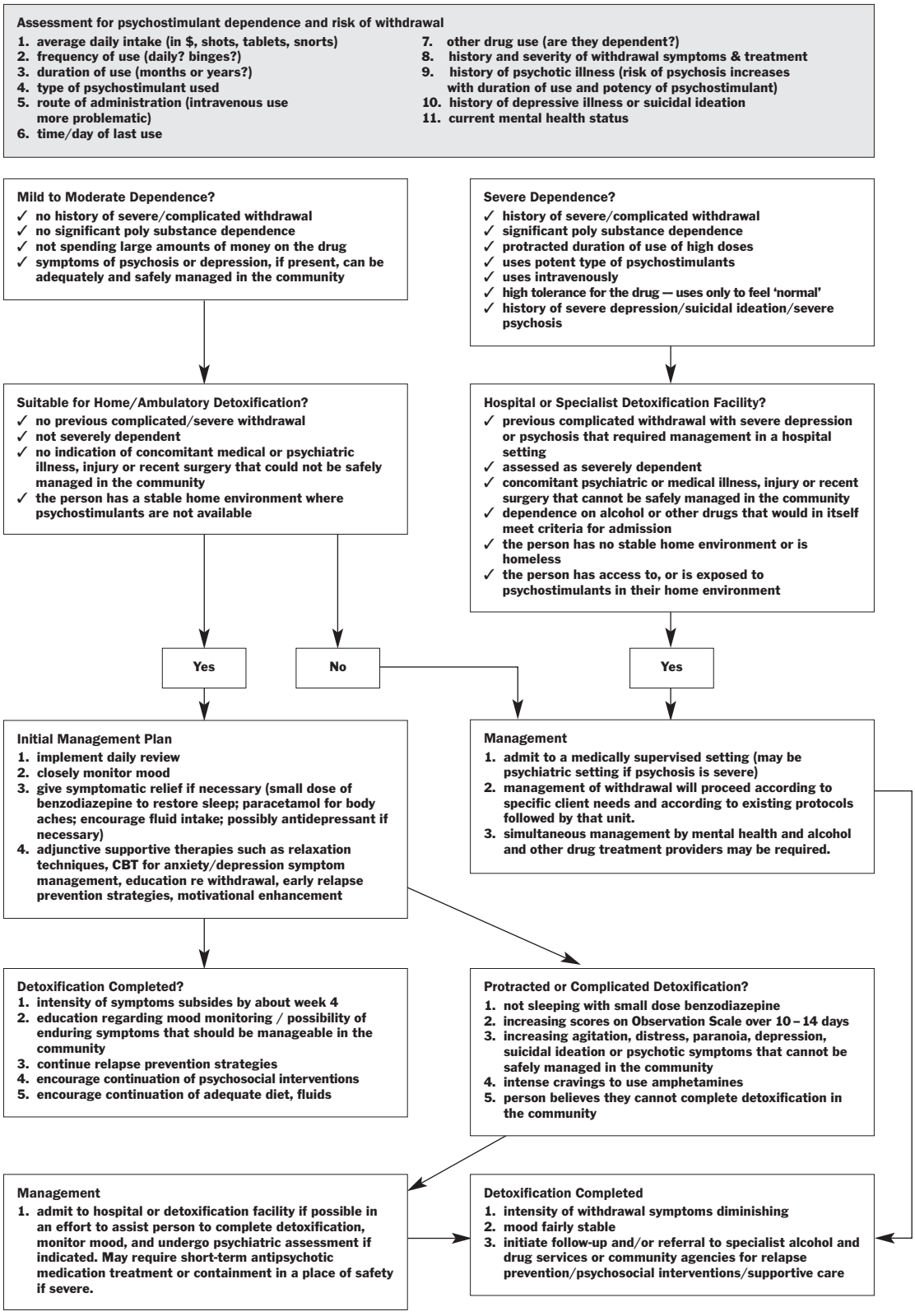
Conclusion

The evidence pertaining to psychostimulant withdrawal is sparse in comparison to that available for alcohol and opioid withdrawal. No studies describing the natural history of withdrawal among methamphetamine-dependent persons have been published. Recommendations for psychostimulant detoxification and withdrawal management, the presentation of which is a mixture of CNS hypoactivity with irritability and insomnia of variable duration, tend to be based on clinical opinion and therefore management strategies may vary from setting to setting. The role of pharmacotherapies is currently limited, however benzodiazepines, antipsychotics and antidepressants if necessary are currently considered by clinicians to be the major components of a medicated psychostimulant withdrawal program. Prospective studies into cocaine and amphetamine (particularly methamphetamine) detoxification and withdrawal management with mixed gender samples of outpatients and in-patients are required to inform Australian service development and appropriate responses.

Summary of evidence

Key points	Strength of evidence
Symptoms of depression and associated suicidal ideation may complicate cocaine withdrawal.	*
Dependence on other substances, particularly alcohol, is common among cocaine dependent persons.	*
Symptoms of severe depression and psychosis may complicate amphetamine withdrawal.	*
Detoxification from psychostimulants can usually be undertaken in a community setting with appropriate support and individualised management plans in place.	*
No pharmacotherapies have been empirically found to be effective for the treatment of psychostimulant withdrawal.	****
Specific pharmacotherapies (e.g. antidepressants, benzodiazepines and antipsychotics) may be effective for concurrent management of specific comorbid symptoms.	**

Decision Tree for the Management of Psychostimulant Detoxification



Chapter 8

Pharmacological interventions

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Key points

- With the exception of pharmacotherapies targeted towards accurately and appropriately diagnosed comorbid conditions such as affective disorders, psychotic disorders, attention deficit disorders and opioid dependence, no pharmacotherapy has been shown to be effective in the management of psychostimulant disorders.
- The inherent risks of pharmacotherapy suggest that the use of pharmacotherapeutic agents should be limited to users who experience the greatest burden of psychostimulant-related harms.

Introduction

This chapter has drawn on key major reviews of the effectiveness of pharmacological interventions for psychostimulant users (Gowing et al., 2001; Shearer & Gowing, submitted).

Despite substantial research effort directed primarily at cocaine dependence, no broadly effective pharmacological therapy has been identified for cocaine or amphetamine dependence (Gowing et al., 2001). Nonetheless, several agents have been commonly used in the USA for cocaine detoxification and relapse prevention including amantadine, bromocriptine, l-tryptophan and desipramine (Halikas et al., 1993). In the UK, dexamphetamine substitution therapy has been available for amphetamine dependence (Bradbeer, Fleming, Charlton & Crichton, 1998).

The great majority of clinical trials in this area have been conducted in the USA among cocaine users, most often crack cocaine users. Clinical studies of pharmacotherapies for amphetamines are uncommon and controlled studies even rarer. Indeed, a recent systematic review (Srisurapanont et al., 2002) identified only four randomised controlled trials of treatment for amphetamine dependence.

Cocaine and amphetamines elevate mood by binding to monoamine transporters and increasing synaptic concentrations of monoamine neurotransmitters (see Chapter 3: *Pharmacology of Psychostimulants*). Changes induced at dopamine transporters have been postulated as the principal reinforcement underlying both cocaine and amphetamine dependence although other transporter sites may also be involved. The sensitisation of dopamine receptors and dopamine depletion through chronic stimulation may play a role in withdrawal and cravings underpinning both cocaine and amphetamine dependence (White & Kalivas, 1998). Given the apparent similarities in neurological effects of cocaine and amphetamines, the rationales

underlying pharmacotherapeutic strategies for each condition have also been similar. The rationales for pharmacological interventions have been categorised in several ways. Potential strategies have included:

(i) drugs aimed at alleviating the discomfort of psychostimulant withdrawal, including low mood and cravings;

(ii) aversive drugs;

(iii) blocking drugs;

(iv) IV drugs that treat comorbid disorders such as depression, psychosis and attention deficit hyperactivity disorder; and

(v) replacement therapy.

The treatment potential of some medications, such as antidepressants, has been investigated under more than one treatment rationale. Accordingly, the following brief review is structured around the broad classes of drugs that have been studied.

Antidepressants

Antidepressants have been investigated in the treatment of comorbid depression, depressive symptomatology associated with psychostimulant withdrawal, or for their dopamine agonist properties. Agents have included tricyclic antidepressants, SSRIs and MAOIs. Generally, results of clinical trials of antidepressants have been equivocal, with a recent systematic review concluding that there was no evidence to support the use of antidepressants in the treatment of cocaine dependence (de Lima, Soares, Reisser & Farrell, 2002). Imipramine, a tricyclic antidepressant associated with more side-effects than desipramine, demonstrated no differential efficacy compared to placebo in reducing drug use in 113 cocaine users (Nunes, McGrath, Quitkin, Opeceek-Welkikson et al., 1995) or in 32 methamphetamine users (Galloway, Newmeyer, Knapp, Stalcup & Smith, 1996).

Among the SSRIs, fluoxetine (Prozac™) has attracted most research attention, but with equivocal results. The review by de Lima et al. (2002) found too few fluoxetine trials to analyse. However, they noted a similarity in urinalysis results to those reported in early desipramine trials. Two further large-scale trials, both conducted at the same centre, arrived at negative conclusions. Grabowski et al. (1998) found fluoxetine ineffective in reducing cocaine use in 228 cocaine users with superior retention in the placebo group. Schmitz et al. (2001) found no improvement in cocaine use or depressive symptoms in 68 dually diagnosed patients in a double blind trial of placebo and 40mg/day fluoxetine. Indeed, the latter study concluded that fluoxetine may potentiate cocaine effects. Other smaller controlled trials of fluoxetine for cocaine users have found fluoxetine less effective than placebo in reducing cocaine use or craving (Batki, Washburn, Delucchi & Jones, 1996; Petrakis, Carroll, Nich, Gordon et al., 1998), less effective than desipramine or amantadine (Oliveto, Kosten, Schottenfeld, Falcioni & Ziedonis, 1995) and less effective than interpersonal psychotherapy (Covi, Hess, Kreiter & Haertzen, 1995). A placebo controlled trial of 40 mg/day fluoxetine in 60 methamphetamine users found no difference in retention, amphetamine positive urines or reported amphetamine free days although amphetamine craving was significantly reduced (Batki, Moon, Delucchi, Bradley et al., 2000).

Significant proportions of problematic psychostimulant users may have pre-existing untreated affective disorders or other concomitant psychiatric disorders that may predispose them to psychostimulant dependence (Tutton & Crayton, 1993). One possible reason for the variability in findings is that antidepressants may have differential effectiveness dependent upon the underlying pre-existing psychiatric conditions. For example, there is a tendency for desipramine and other tricyclic antidepressants to be more effective where there is pre-existing depression than in non-depressed cocaine users (Donovan & Nunes, 1998). Sevarino, Oliveto and Kosten (2000) also point to the heterogeneity among cocaine users and the need to develop specialised treatments for distinct subgroups of users.

The way in which pharmacotherapies are used may also influence outcomes. For example, it has been suggested that fixed dosages of desipramine may be counter-productive and that results might be improved by individually managing serum drug levels (Campbell, Nickel, Penick, Wallace et al., 2003; Platt, 1997). Another approach to the use of antidepressants that has been suggested but not yet trialed, is as an adjunct to a behavioural intervention aimed at teaching alternative reinforcers to cocaine, with the antidepressants used to reduce craving (Fischman & Foltin, 1998).

There are disadvantages to the use of antidepressants. As identified above, fluoxetine may potentiate cocaine effects (Schmitz, Averill et al., 2001) and desipramine may be associated with negative cardiovascular side-effects (Platt, 1997). Furthermore, there is a two to three week delay before antidepressants such as desipramine become effective. As dropout rates in this early period tend to be very high, these medications may not have an opportunity to demonstrate efficacy.

MAOIs have also been used for their potentially aversive interaction with cocaine and amphetamines. However, no controlled studies exist and the risk of hypertensive reactions make their use questionable (Tutton & Crayton, 1993).

Early interest in buproprion (Zyban™) was not sustained after a placebo controlled trial of 149 cocaine-dependent methadone patients found no significant differences between placebo and buproprion (Margolin, Kosten & Avants, 1995). Buproprion had no effect on the subjective or cardiovascular effects of intranasal cocaine in an open label drug interaction study involving ten primary cocaine users (Oliveto, McCance-Katz, Singha, Petrakis et al., 2001).

Srisurapanont et al.(2002), from a systematic review of treatment for amphetamine dependence and abuse, found that fluoxetine, amlodipine, imipramine and desipramine have very limited benefits. These reviewers found that fluoxetine decreased craving in short-term treatment and imipramine may increase duration of adherence to treatment in medium-term treatment.

Dopamine agonists

The treatment rationale for dopamine agonists or dopamimetics is to increase dopamine concentrations to overcome the dopamine depletion that has been theorised to underlie psychostimulant craving and withdrawal.

Pergolide mesylate, which is used in the treatment of Parkinson's disease, is more potent, has a longer duration of action than bromocriptine and has been suggested

to have a more favourable side-effect profile. However, a large (N=255 cocaine users) five-year study of pergolide mesylate, found that subjects receiving placebo had significantly better retention and treatment outcomes (Malcolm, Herron, Sutherland & Brady, 2001). This outcome may be due to pergolide mesylate increasing cocaine craving (Fischman & Foltin, 1998). As cardiovascular complications are potentially the most serious side-effects of pergolide mesylate, Malcolm, Moore, Kajdasz and Cochrane (1997) recommend baseline screening, a cautious approach and close monitoring of users with current or past heart disease who are prescribed the drug.

A recent systematic review (Soares, Lima, Reisser & Farrell, 2002) found that current evidence does not support the clinical use of dopamine agonists in the treatment of cocaine dependence. This review identified 12 studies, most of which compared amantadine or bromocriptine to placebo. The main efficacy outcome presented was positive urine sample for cocaine metabolites, with no significant differences between interventions. Rates of retention in treatment were also similar in both placebo and active drugs. A recent study of amantadine for cocaine dependence (Shoptaw, Kintaudi, Charuvastra & Ling, 2002) found no significant difference in cocaine abstinence at the end of 16 weeks of treatment among 69 patients. Bromocriptine is associated with nausea, headache, orthostatic hypotension and psychotogenic effects (Sevarino et al., 2000; Tutton & Crayton, 1993).

Dopamine antagonists

Dopamine antagonists have been used for their euphoria-blocking effects via receptor blockade although their ability to influence cocaine self-administration is problematic. Many dopamine receptor antagonists have had initial success in pre-clinical work and acute dosing studies but have failed in clinical trials. Ecopipam is a recent example of a dopamine antagonist where early success in attenuating cocaine effects was not sustained in clinical trials and indeed in one study increased cocaine induced euphoria and cocaine use (Haney, Ward, Foltin & Fischman, 2001; see also editorial by McCance-Katz, Kosten & Kosten, 2001; Nann-Vernotica, Donny, Bigelow & Walsh, 2001). Flupenthixol is a dopamine blocker that acts as an antidepressant at low oral doses (1-3 mg/day) and as a neuroleptic at higher intramuscular doses (30-100 mg/two week depot). It has shown promise in cocaine users with schizophrenia (Levin, Evans & Kleber, 1998) and also potential as an aversive agent (Gawin, Khalsa-Denison & Jatlow, 1996). However, a double blind placebo controlled study of the safety and tolerability of both oral and intramuscular flupenthixol in 23 cocaine users found low doses were well tolerated but ineffective in attenuating subjective and cardiovascular responses to intravenous cocaine, while high neuroleptic doses produced unacceptable dystonic reactions in subjects (Evans, Walsh, Levin, Foltin et al., 2001). The neuroleptic, haloperidol, produces receptor supersensitivity making it unsuitable for long-term treatment (Sevarino et al., 2000).

Antipsychotic agents have been examined due to their potential for those with comorbid psychostimulant dependence and psychotic disorders, for the treatment of psychostimulant-induced psychosis and for their dopamine antagonist properties. A randomised, double-blind study of risperidone, an atypical antipsychotic with 5HT and D2 antagonist properties, was conducted in 193 cocaine users without other psychiatric diagnoses (Grabowski, Rhoades, Schmitz, Silverman et al., 2000).

The study was terminated early due to poor retention and numerous side-effects in the risperidone groups with no reduction in cocaine use. The investigators speculated that highly selective antagonists would not be successful because they may not block the full range of neurobiological actions of psychostimulants or that the doses needed to effectively block drug effects could not be tolerated by patients. Antipsychotic agents may be useful in cocaine users with concurrent psychotic illness. However, as Sevarino et al. (2000) have commented, the high prevalence of cocaine use among neuroleptic-maintained individuals with schizophrenia does not auger well.

The anticonvulsant carbamazepine has been trialled in humans because it has been shown in animal studies to selectively inhibit the "kindling" effects (of increased limbic seizures) resulting from chronic cocaine use. Several open trial studies carried out in the late 1980s and early 1990s led to some optimism that this medication may effectively reduce cocaine use through reduced craving and blocking of euphoria. However, subsequent randomised controlled trials found no evidence for the superior efficacy of carbamazepine compared with placebo. Carbamazepine was the subject of a systematic meta-analysis including five placebo controlled trials and 455 cocaine-dependent subjects (de Lima et al., 2002). De Lima and colleagues concluded that there was no evidence supporting the clinical use of carbamazepine in the treatment of cocaine dependence. Furthermore, Withers, Pulvirenti, Koob and Gillin (1995) have cautioned that at least one study has noted increased cardiovascular effects of cocaine used in combination with carbamazepine. No benefits for carbamazepine either in retention or cocaine free urine results were found in a comparison with desipramine and placebo in 146 crack cocaine dependent users (Campbell et al., 2003).

Crosby et al. (1996) assessed the effects of another anticonvulsant, phenytoin, and found that this drug was significantly associated with reduction in cocaine use compared with placebo. The study commenced with 44 subjects and ran for 12 weeks, at which time only 12 subjects (6 in each group) remained. The high dropout rate and the fact that 85% of the phenytoin group believed they were taking phenytoin, means that these results are inconclusive.

Disulfiram

Disulfiram (Antabuse™) is principally used in the treatment of alcohol use disorders for its aversive properties. The cocaine-specific action of disulfiram is thought to be based on the suppression of alcohol-related cues for cocaine use or through inhibition of a dopamine metabolising enzyme that leads to excessive dopamine levels associated with aversive effects including heightened anxiety and paranoia. Cocaine administration in subjects pre-treated with disulfiram has been associated with dysphoria and anxiety that was initially attributed to elevated plasma cocaine concentration (McCance-Katz, Kosten & Jatlow, 1998). A study of 122 people dependent on both cocaine and alcohol randomised into five groups (12-step n=25; CBT n=19; clinical management + disulfiram n=27; 12-step + disulfiram n=25; CBT + disulfiram n=26) found disulfiram was significantly associated with better retention and abstinence from alcohol and cocaine use compared to no pharmacotherapy (Carroll, Nich, Ball, McCance & Rousanville, 1998). Encouragingly, the main effects of disulfiram on cocaine and alcohol use were

sustained at one-year follow-up (Carroll et al., 2000). While the role of alcohol as a potent conditioned cue for cocaine craving may have been explanatory, cocaine-specific effects were also possible. Two placebo controlled studies have reported positively on the effect of disulfiram in promoting cocaine abstinence in 20 buprenorphine maintained patients (George, Chawarski, Pakes, Carroll et al., 2000) and 67 methadone patients (Petrakis, Carroll, Nich, Gordon et al., 2000). Alcohol use was minimal in both studies. Another potential mechanism for disulfiram is the inhibition of dopamine β-hydroxylase, an enzyme that metabolises dopamine. When combined with cocaine-boosted neural dopamine, excessive dopamine levels may cause unpleasant effects, including anxiety and paranoia, (Petrakis et al., 2000) and consequently may increase cocaine toxicity (McCance-Katz et al., 1998).

CNS stimulants

CNS stimulants have been proposed as beneficial in the management of psychostimulant dependence as substitution therapy and withdrawal management and in the treatment of underlying Attention Deficit Hyperactivity Disorder (ADHD).

Amphetamine dependence

Dexamphetamine substitution programs have been available for amphetamine users in the UK although the efficacy and safety of the practice has not been adequately tested by randomised controlled trials (Bradbeer et al., 1998; Shearer, Sherman, Wodak & van Beek, 2002). Substitution therapies aim to replace harmful drug use with safer modes of drug use in terms of dose, route of administration and adverse effects. Effective substitutes may allow patients to stabilise on doses that prevent withdrawal and craving and to reduce the harms associated with illicit drug use. Attracting and retaining problematic cocaine users in treatment may also facilitate engagement with health care services, including psychosocial interventions. Mattick and Darke (1995) have suggested that amphetamine maintenance may be appropriate where amphetamine use is frequent (usually daily), attempts to achieve abstinence have been unsuccessful, dependence is evident, severe adverse complications have occurred and maintenance is likely to cause less harm than continued illicit use. Risks associated with maintenance include psychiatric and cardiovascular complications, particularly when additional illicit psychostimulants are consumed. Carnwath et al. (2002) reported that six out of eight patients with schizophrenia who had received prescribed dexamphetamine both reduced amphetamine use and improved psychiatric health. There was no exacerbation of psychosis in any patient while compliance with neuroleptics improved in most cases. A retrospective case note evaluation of a Welsh dexamphetamine program found three episodes of psychosis in 63 patients receiving amphetamine substitution treatment over two years, all associated with additional use of street amphetamines (McBride, Sullivan, Blewett & Morgan, 1997). In a large cohort study, five cases of psychosis in 220 patients over four years were reported, all with prior histories of psychosis and continuing injecting drug use (White, 2000).

Evaluations of amphetamine prescription conducted in the 1960s and early 1970s in London concluded that the modest benefits were outweighed by serious negative consequences including psychosis, continuing illicit use and diversion of prescribed amphetamines (Gardner & Connell, 1972; Hawks, Mitcheson, Ogborne & Edwards, 1969). More recent evaluations of clinical programs have suggested that

amphetamine users are attracted to services offering amphetamine prescription where they can also be provided with advice, counselling and harm minimisation interventions such as needle and syringe programs (Fleming & Roberts, 1994; Klee et al., 2001; McBride et al., 1997). Reported positive outcomes of amphetamine prescribing included reduced illicit amphetamine use, reduced injecting, reduced sharing of injecting equipment, improved social functioning and retention in treatment (Charnaud & Griffiths, 1998; Fleming & Roberts, 1994; Klee et al., 2001; McBride et al., 1997; Pates, Coombes & Ford, 1996; Shearer, Wodak, Mattick, van Beek et al., 2001; Sherman, 1990; White, 2000). A retrospective comparison of discharge notes for 60 dexamphetamine program patients (mean dose 43 mg/day) and 120 methadone program patients (mean dose 44 mg/day) found both treatments equally effective in reducing injecting behaviour, with 70% of amphetamine users showing no physical evidence of injecting compared to 67% of methadone patients (Charnaud & Griffiths, 1998). The first published prospective pilot RCT (Shearer et al., 2001) found modest gains in favour of dexamphetamine treatment (60 mg/day) compared to counselling alone but these did not reach statistical significance, possibly due to the small sample size.

Cocaine dependence

Dexamphetamine has also been investigated for cocaine dependence in two studies. A 13-week controlled study (N=128) of sustained release dexamphetamine (placebo, 15–30 mg/day dexamphetamine and 30-60 mg/day dexamphetamine) found dose related changes in retention and cocaine use in favour of dexamphetamine treatment with no serious adverse events or cardiovascular complications (Grabowski, Rhoades, Schmitz, Stotts & Daruzska, 2001). Findings were limited by high study attrition. An Australian 14-week placebo controlled study (N=30 cocaine injectors) of dexamphetamine 60 mg/day found outcomes (cocaine use, crime, cocaine craving and severity of dependence) favoured dexamphetamine treatment with no improvement in the placebo group (Shearer, Wodak, van Beek, Mattick & Lewis, 2003).

Other agonist agents used in cocaine dependence have included methylphenidate (Ritalin™) and oral forms of cocaine. Levin et al. (1998) reported significantly reduced cocaine use and cravings in a group of 12 patients diagnosed with comorbid adult ADHD and cocaine dependence receiving 40 mg/day sustained release methylphenidate. However, a placebo controlled trial of 48 cocaine-dependent adult ADHD patients found improvements in reported ADHD symptoms in subjects receiving active methylphenidate but none between group differences in cocaine use or cravings (Schubiner, Saules, Arfken, Johnasen et al., 2002). Further, in a randomised placebo controlled trial of 49 patients without adult ADHD, methylphenidate (20 mg twice daily slow release) was ineffective in reducing cocaine use (Grabowski et al., 1998). Grabowski et al. suggested consideration of other psychostimulants that may be more adequate reinforcers.

Oral formulations of cocaine including coca tea infusions and tablets have been investigated in Peru for coca paste smokers (Llosa, 1994a, 1994b, 1996). Overall results suggested that a low dose of oral cocaine (20-60 mg/day) significantly reduced relapse to heavy use and cravings (Llosa, 1994a). Interestingly, in the open trial involving 23 subjects, while all accepted coca tea as a treatment, 78% agreed they would have preferred to take the same medication in capsules. Walsh et al. (2000) tested the safety and utility of oral cocaine in a laboratory study where oral

cocaine was administered in a range of doses (0-100 mg/day) to eight subjects with cocaine use histories. Intravenous cocaine challenges (0-50 mg) were administered during each new dose sequence. They found that oral cocaine modestly attenuated the subjective and physiological responses to intravenous cocaine and was safely tolerated.

Modafinil

Human laboratory studies (Rush, Kelly, Hays, Baker & Wooten, 2002) and early case reports have prompted interest in modafinil, a novel wake promoting agent, recently approved for narcolepsy. Modafinil promotes wakefulness, vigilance and alertness and may have value in treating psychostimulant withdrawal symptoms such as hypersomnia, poor concentration and low mood. Case reports pointed to positive responses in both cocaine and amphetamine-dependent patients with no apparent over-stimulation or abuse (Comacho & Stein, 2002; Malcolm, Book, Moak, DeVane & Czepowicz, 2002). No medical risks in terms of blood pressure, pulse, temperature or electrocardiogram measures were identified in a placebo-controlled drug interaction study of modafinil and cocaine in seven subjects who received infusions of cocaine or modafinil (200 mg/day or 400 mg/day) over four days (Dackis, Lynch, Yu, Samaha et al., 2003).

Vaccines

Cocaine vaccines aim to reduce the amount of cocaine reaching the brain by stimulating enzymes or antibodies that target cocaine molecules in the bloodstream. They differ from other pharmacological approaches that have targeted neurotransmitter sites within the brain. There are several types of cocaine vaccine that have been tested in animal models and more recently in human volunteers. These include:

(i) compounds that stimulate antibodies that bind to psychoactive cocaine metabolites and make them too large to cross the blood brain barrier;

(ii) compounds that stimulate antibodies that increase the rate of cocaine metabolism, reducing the amount that crosses the blood brain barrier; and

(iii) 'passive' inoculation of cocaine antibodies to block cocaine crossing the blood brain barrier.

The effectiveness and duration of these effects vary and may not be permanent. Therapeutic potential includes overdose, relapse prevention and detoxification. The most advanced trial involves the therapeutic vaccine, TA-CD, currently in dose optimisation trials after initial dose and safety trials found it was well tolerated in a group of 34 abstinent cocaine users (see also Hall & Carter, 2002 for a discussion of ethical issues; Kosten, Rosen, Bond, Settles et al., 2002).

Calcium blockers

Pre-treatment with isradipine, a calcium channel antagonist, produced significant reductions in positive subjective effects of d-methamphetamine in 18 healthy volunteers. Studies in methamphetamine users are underway (Johnson, Roache, Bordnick & Ait-Daoud, 1999). An unpublished controlled study of another calcium

channel blocker, amlodipine, found that 5-10 mg/day in 77 methamphetamine users resulted in no difference in treatment retention or in any other outcome measures including amphetamine use and cravings (Batki, Moon, Delucchi & Bradley, 2001).

Opioid agonists and antagonists

The role of opioid agonists and antagonists has been explored in psychostimulant users with and without concurrent opioid dependence. Increasingly polydrug use is a common feature both among recreational drug users and dependent opioid users. Cocaine use has been identified as a significant treatment impediment in methadone maintenance patients that undermines the effectiveness of methadone maintenance (Condelli, Fairbank, Dennis & Rachal, 1991) and is a commonly reported reason for treatment failure (Strug, Hunt, Goldsmith, Lipton & Spunt, 1985). There have been reports of subgroups of methadone patients using cocaine to obtain the euphoria not available when receiving methadone (Grabowski, Rhoades, Elk, Schmitz & Creson, 1993; Tutton & Crayton, 1993; van Beek et al., 2001). Buprenorphine was believed by some earlier reviewers (Platt, 1997; Tutton & Crayton, 1993) to hold promise in treating comorbid cocaine-opioid dependence. However, no evidence for cocaine specific efficacy or differential efficacy compared to methadone was found in a recent meta-analysis involving five studies and 779 participants (Mattick, Kimber, Breen & Davoli, 2002).

The opioid antagonist, naltrexone, may have potential in cocaine use via its euphoria blocking effects on opiate pathway reinforcers, similar to its postulated mechanism of action in alcohol dependence. In a placebo-controlled study of relapse prevention treatment, 85 abstinent cocaine-dependent volunteers were randomised into one of four combined conditions; naltrexone (0 vs. 50 mg) with relapse prevention versus drug counselling (Schmitz, Stotts, Rhoades & Grabowski, 2001). The combined naltrexone/relapse prevention group significantly reduced cocaine use over time compared to the other conditions. This study represents an encouraging contribution to integrated behavioural and pharmacological treatment approaches although it is limited by the selection of an abstinent study population and by the difficulties and risks of naltrexone induction and maintenance for opioid dependent patients. Intriguingly, cocaine use (measured by self-report and urinalysis) declined in a cohort of 266 heroin and cocaine users receiving prescribed heroin maintenance from 84% to 48% over 18 months (Blätter, Dobler-Mikola, Steffen & Uchtenhagen, 2002). The study sample was drawn from the participants in the first Swiss trial of prescribed heroin that included older, treatment-refractory heroin users. The authors suggested that high treatment retention in an extensively structured medically prescribed heroin program may have been explanatory. Declines in factors associated with cocaine use including criminality, prostitution and drug scene contact may also have contributed.

Ecstasy

While the majority of ecstasy users take small doses infrequently, a proportion use more frequently (monthly to weekly) and/or use larger amounts. There may also be a trend of increasing use by injection rather than orally (Topp et al., 1999). This study found it was young, female, polydrug users and those who binged on ecstasy (ie. administered high doses to maintain intoxication over a period of hours to days)

who were most likely to report physical, psychological, financial, relationship and occupational problems which they attributed, at least in part, to their ecstasy use. Those who inject ecstasy are also likely to be at increased risk of harm arising from the more rapid onset of effects and higher peak levels in the blood following injection, thereby increasing the effect on the cardiovascular system and the liver and the possibility of physical trauma from loss of control during the 'rush' (Hunt, Jones & Shelley, 1993). Those who inject ecstasy are also at risk of vein damage and blood borne viruses due to their injecting behaviour. These groups of ecstasy users therefore may be appropriate targets for preventive interventions.

In the absence of research into specific interventions for ecstasy users, the closest approximation is interventions for users of other psychostimulant drugs, ie., cocaine and amphetamines. It is cocaine dependence that has been the subject of most research in this area. While cocaine and amphetamines are related to MDMA, it should be noted that there are substantial differences in the context and patterns of use, as well as pharmacology. Furthermore, it is now generally accepted that cocaine and amphetamine users can exhibit a dependence syndrome, while the existence of ecstasy dependence remains questionable (Topp, Hall & Hando, 1997).

Considerable research effort has been directed towards the identification of effective pharmacotherapies for cocaine users. To date these efforts have been largely unsuccessful and even if an effective pharmacotherapy were found, any transfer to the treatment of ecstasy users is questionable because of the differing pharmacology of the drugs — cocaine acts primarily through the dopamine system (Rawson, 1999) whereas MDMA acts through the serotonin system. Hence pharmacotherapies for ecstasy users should be innovative and specific to the action of MDMA. If taken concurrently with MDMA, SSRIs have been shown to block the usual subjective effects of MDMA (Stein & Rink, 1999). However, administration of SSRIs (e.g. fluoxetine, citalopram) subsequent to MDMA may potentiate the effects of the released serotonin, worsening any adverse effects (Green, Cross & Goodwin, 1995) and limiting their value as a treatment agent.

Alternative therapies

The lack of effective pharmacotherapies for psychostimulant dependence has created substantial interest in alternative or complementary therapy approaches. Auricular acupuncture for cocaine dependence has been widely practised in the USA and Europe. Although the specific mechanism of action is unclear, it may have potential through calming patients, reducing or assisting with the management of cravings and in the retention of patients in psychosocial treatment. However, evidence for the effectiveness of auricular acupuncture is weak and early promise has not been sustained in larger, more rigorous trials.

Auricular acupuncture

Recently a large single blind controlled trial involving 620 cocaine users recruited in six US cities compared auricular acupuncture, a needle insertion control condition and relaxation (Margolin, Kleber, Avants, Konefal et al., 2002). The investigators had previously found, in an RCT involving 82 cocaine-dependent methadone patients, that those who had received auricular acupuncture were significantly more likely to provide cocaine-negative urine samples (Avants, Margolin, Holford &

Kosten, 2000). However, these early positive findings were not replicated in the subsequent trial with no differences between the treatment conditions in the principal outcomes of cocaine positive urine samples and retention in treatment and no differences in any secondary outcome measures. These negative findings were consistent with those reported in an earlier trial of true and sham acupuncture in 236 residential treatment clients (Bullock, Kiresuk, Pheley, Culliton & Lenz, 1999).

Hypericum

Hypericum (St John's Wort) has been used as a treatment for mild to moderate depression in Europe. In a 55-subject placebo controlled trial, the dosage of hypericum had little effect on cocaine use and further investigation was not considered warranted (Watson, Shoptaw, Rawson, Reiber & Ling, 2002).

Conclusion

This brief review of pharmacological approaches suggests that, with the exception of pharmacotherapies targeted towards accurately and appropriately diagnosed comorbid conditions such as affective disorders, psychotic disorders, attention deficit disorders and opioid dependence, the use of pharmacotherapies for the promotion or maintenance of psychostimulant abstinence or the management of psychostimulant withdrawal continues to be experimental. The inherent risks of pharmacotherapy may suggest that the use of pharmacotherapeutic agents should be limited to users diagnosed with more severe dependence who experience the greatest burden of psychostimulant-related harms. Indeed recent re-analysis of trials of the dopamine agonist amantadine (Kampman, Volpicelli, Alterman, Cornish & O'Brien, 2000) and the beta blocker propranolol (Kampman, Volpicelli, Mulvaney, Alterman et al., 2001) found that subjects displaying significant cocaine withdrawal (suggestive of neuroadaption) responded selectively to treatment (see also Dackis & O'Brien, 2002). The absence of good data on the natural history of psychostimulant use and psychostimulant induced neuroadaption has, in the past, contributed to a 'scatter gun' approach to investigating potential pharmacotherapies, especially for cocaine. Research on treatment for amphetamine dependence is at a much earlier stage and may benefit by lessons already learned from the cocaine experience. This experience particularly points to the need for rigorous, controlled studies with adequate follow-up, sample sizes, selection of appropriate subjects and the integration of psychosocial interventions.

Summary of evidence

Antidepressants

Key points	Strength of evidence
Transition to injecting can be prevented with CBT intervention.	*
There is no current evidence supporting the clinical use of antidepressants in the treatment of cocaine dependence.	***
Antidepressants have very limited benefits in the treatment of amphetamine dependence.	***
Antidepressants may be suitable in cases of concomitant cocaine dependence and depression.	?

Dopamine agonists

Key points	Strength of evidence
There is no current evidence supporting the clinical use of dopamine agonists in the treatment of cocaine dependence.	***

Dopamine antagonists

Key points	Strength of evidence
There is no current evidence supporting clinical use of carbamazepine in the treatment of cocaine dependence.	****
Phenytoin may be more effective than placebo in reducing cocaine use.	**
Flupenthixol, haloperidol and risperidone are probably not useful due to side-effects.	***

Disulfiram

Key points	Strength of evidence
Disulfiram as an adjunct to buprenorphine or methadone maintenance may reduce cocaine use in opioid-dependent people.	***

CNS stimulants

Key points	Strength of evidence
Prescription of oral amphetamines is of potential value as a substitution treatment for dependent, injecting amphetamine users.	**
Methylphenidate is not generally effective in reducing cocaine use.	***
Dexamphetamine may be of value in reducing cocaine use.	**

Vaccines

Key points	Strength of evidence
Cocaine vaccines may provide therapeutic support by reducing the psychoactive effect of cocaine.	?

Calcium blockers

Key points	Strength of evidence
Calcium blockers may, or may not, have therapeutic effect.	?

Opioid agonists and antagonists

Key points	Strength of evidence
Combined behavioural and pharmacological treatment for cocaine users who are also opioid dependent may reduce cocaine use.	**
Buprenorphine is no more effective than methadone in reducing cocaine use amongst opioid dependent clients.	****

Alternative therapies

Key points	Strength of evidence
Auricular acupuncture does not appear to significantly reduce cocaine use.	**

Chapter 9

Psychostimulants and young people

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Key points

- The rate of psychostimulant use among young people in Australia is comparable to that in Southeast Asia, but higher than Europe, North America and Africa.
- Injecting is the most popular route of administration of psychostimulants by young people.
- Prevention and early intervention activities are considered to have a positive impact, but they have not been extensively evaluated.
- Adult models of intervention have been applied to young people, but very few specific interventions have been studied among psychostimulant users.
- There is evidence that some treatment is superior to no treatment in reducing substance use and improving functional outcomes, but there is insufficient evidence to compare the effectiveness of treatment types.
- In the absence of well-controlled studies amongst psychostimulant users, a multi-component approach is recommended, including Cognitive Behaviour Therapy and Family Therapy.
- A great deal more research is required into effective interventions for young people who use psychostimulants.

Introduction

Adolescence and early adulthood are critical developmental periods within which a number of key tasks must be accomplished in order for 'normal' development to occur. Early initiation of substance use and subsequent problematic use may impede this development. Understandably, the recent global rise of psychostimulant use, particularly methamphetamine use among young people, has caused concern. As such, it is pertinent to focus on psychostimulant use as it specifically relates to young people.

The term 'young people' is used within the United Nations (UN) system to identify those aged 10 to 24 years. More specifically, the period of 'adolescence' comprises the ages of 10 to 19 years, while 'youth' describes those between the ages of 15 and 29. The World Health Organisation (WHO) defines adolescence as the second decade of life and stresses that it is a phase rather than a fixed period of time in a person's life.

During this phase enormous physical and psychological changes occur, as do changes in social perceptions, experiences and expectations (World Health Organisation, 2002). This transitional phase is characterised by a time of curiosity, discovery and exploration, during which there are a number of tasks that need to be accomplished.

Some of the tasks of adolescence include developing a stable sense of identity and moving from a stage of dependence to independence (Papalia, 1989). In early adulthood there is an emphasis on the wider community, in which the family, social relationships and 'vocation' become the key focal points. Being 'stuck' within a culture of problematic substance use can impede these vital development stages.

Prevalence and patterns of psychostimulant use among young people

Prevalence

Population

Population based secondary school surveys have indicated that in Australia there is a growing trend towards the use of psychostimulants among students, despite overall low levels of use. For example, data from the 1999 Secondary School Survey indicated that 11% of students reported having ever used amphetamine-type stimulants (ATS), compared to 9% in 1996 (White, 2001). The data also indicated that 3% of 12 year olds and 12% of 17 year olds had ever used an ATS, while around 6% of all students had used amphetamines in the past year, with prevalence increasing with age — 2% of 12 year olds and 10% of 17 year olds. Only 1–2% of students reported recent use of an ATS. Gender differences were minimal.

These rates of ATS use for 14 to 19 year olds were mirrored in the 2001 National Drug Strategy Household Survey (Australian Institute of Health and Welfare, 2002b) where 8.4% of young people reported lifetime use of ATS, 6.2% reported recent use and 1.2% of young people in this age group reported use in the last week. Approximately 10% of ATS users aged 14–19 years reported daily or weekly use. Gender differences were minimal although females reported slightly higher rates of lifetime and recent ATS use than males. However, there were higher rates of ATS use amongst males than females in the 20 to 29 year old age group, with 25% of males and 19% of females reporting lifetime use and 14.1% of males and 8.2% of females reporting recent use. The drug most likely to have been injected by both age groups was an amphetamine.

Youth populations reported low rates of lifetime cocaine use (3–4%). Prevalence rates of MDMA use tended to increase with age, with 4% of secondary students and 7% of 14 to 19 year olds reporting lifetime use (Australian Institute of Health and Welfare, 2002b; White, 2001). Significant gender effects occurred, with males reporting greater rates of cocaine and MDMA use than females (Australian Institute of Health and Welfare, 2002b; White, 2001). For 20 to 29 year olds, 22.5% of males and 16.9% of females reported lifetime MDMA use, with 12.5% of males and 8.3% of females reporting recent use (Australian Institute of Health and Welfare, 2002b). Recent use of ATS and MDMA tended to increase with age, but this pattern did not emerge for cocaine, the use of which was fairly even across the ages (Australian Institute of Health and Welfare, 2002b; White, 2001).

Comparisons with international data

While different data collection methodologies make global comparisons of youth populations difficult, some broad trends can be observed. Stable, but elevated, levels of cocaine use have been noted among youth in the Americas (4–5%), which are somewhat higher than rates in Australia and Europe (2–3% and 1–2% respectively) (Maxwell, 2003; United Nations Office on Drugs and Crime, 2003).

The highest reports of ATS use by young people come from East and Southeast Asia and Australia with prevalence rates ranging from 8–10% (United Nations Office on Drugs and Crime, 2003). Europe, the Americas and Africa largely report lower levels of ATS use by young people (approximately 2–5%), with some pockets of higher-level use, which often correspond to areas of methamphetamine production or transhipment routes.

For MDMA use, surveys in Australia, the USA and Canada report similar prevalence rates (about 7%). In contrast, the average lifetime prevalence of MDMA use in 32 European countries among 15 to 16 year olds was only 2.5% (Maxwell, 2003; United Nations Office on Drugs and Crime, 2003).

Juvenile detention and treatment samples

A 1999 survey of 300 clients in New South Wales (NSW) Juvenile Justice Centres found significantly higher lifetime rates of amphetamine (56%) and cocaine (34%) use than in the general population (Copeland, Howard, Keogh & Seidler, 2003). These rates also represented an increase from the levels of use reported in a 1994 survey (Copeland et al., 2003).

The number of young people admitted to residential AOD treatment services with problematic psychostimulant use (particularly ATS use) has also increased (Degenhardt & Topp, 2003; Howard & Arcuri, 2003a). Howard and Arcuri (2003a) profiled 178 young people assessed for a state-wide adolescent residential treatment agency across five sites finding that more than a quarter of clients nominated psychostimulants as their major drug of concern.

Patterns

Route of administration

In the Howard and Arcuri study (2003a) the most popular route of administration for first psychostimulant use was intranasal ingestion (26%), whilst injection was the preferred route of administration for recent use (55%). 83% of clients who nominated ATS as their primary drug of concern preferred injection as their route of administration. A similar pattern was observed for cocaine use, where inhalation (61%) was the most popular initial route of administration, whilst injection (51%) was the most popular recent route of administration. Likewise, rates of injection of designer drugs increased substantially from first to most recent route of administration (9.1% to 12.2%), a finding similar to that of Topp and colleagues (Topp, Breen et al., 2002; Topp et al., 1999).

Reasons for and patterns of psychostimulant use by young people

Like most drug use, the reasons given by young people for initiating psychostimulant use are not necessarily the reasons they maintain use. Understandably, congruent with the developmental stages of adolescence, the reasons for initiation of psychostimulant use include 'curiosity/experimentation' and the 'influence of peers' (Dennis & Ballard, 2002; Howard & Arcuri, 2003a).

In contrast, reasons for continued psychostimulant use are largely associated with 'the effect' or 'dependence' and because psychostimulants are 'fun' (Howard & Arcuri, 2003a). Other reasons proposed for continuation of use include the management of trauma or symptoms of depression (Buckstein, Dunne, Ayres, Arnold et al., 1997; Herman, 1992).

Psychostimulants are often included in the colloquially termed 'party drugs' category (Topp, Breen et al., 2002) and their use has been linked to raves (dance parties), good times and celebrations (Dennis & Ballard, 2002; Weir, 2000). In contrast to heroin use, daily use of psychostimulants for extended periods is considered to be relatively rare (Topp, Kaye et al., 2002) and the withdrawal from this class of drugs is relatively benign. Thus, psychostimulant users are less likely to seek and access treatment than heroin users (Hall et al., 1993; Shearer et al., 2002).

Psychostimulant use amongst young people is characterised by three distinct patterns of use:

(i) Experimental use — this type of use can be seen as a part of normal adolescent risk-taking. Experimentation or occasional psychostimulant use is most common in the younger Australian population. Data show that the majority of young people do not experience extensive problems or continue psychostimulant use and 'recent' psychostimulant users only reported using the drug every few months (Australian Institute of Health and Welfare, 2002b).

(ii) Rave or club scene use — these young people are often regarded as 'functional users', in that their use is restricted to weekend or event-specific use. A UK survey of 16–29 year olds found that 91% of members of the dance club scene had used psychostimulants, particularly MDMA (Weir, 2000).

(iii) Problematic use — this pattern of psychostimulant use is characterised by chaotic and dependent use, is usually associated with injecting drug use and often results in negative outcomes (e.g. homelessness and criminal behaviour).

These three patterns of psychostimulant use are not mutually exclusive and a large body of research has attempted to tease out the factors associated with these patterns of use (Bond, Thomas, Toumbourou, Patton & Catalano, 2000; Commonwealth Department of Health and Aged Care, 2000; Gregg, Toumbourou, Bond, Thomas & Patton, 2000; National Crime Prevention, 1999a, 1999b; Rutter, 1985; Toumbourou, Patton, Sawyer, Olsson et al., 2000; Vakalahi, 2001).

Risk, protection, transitions and connectedness

Simplistic cause and effect models of problematic substance use have not proved helpful and pathological explanations can confuse efforts to understand and respond to drug use by young people (Moore & Saunders, 1991). It should be clear then that the aetiology of problematic drug use during adolescence is multi-determined and

that the individual, the environment and the drugs themselves cannot be considered in isolation (Dielman, Butchart, Shope & Miller, 1990–1991; Moncher, Holden & Schinke, 1991; Spooner, Hall & Lynskey, 2001).

However, most adolescents who engage in substance use do not develop a substance use disorder, such as abuse or dependence. Researchers have identified a number of risk factors which may directly or indirectly make young people more vulnerable to the development of problematic substance use (Gilvarry, 2000; Spooner et al., 2001).

Individual factors such as genetic/biological, temperamental, neurobiological and psychological variables and an earlier age of initiation of substance use may increase the likelihood of problematic substance use (Buckstein et al., 1997; Gilvarry, 2000; Newcomb & Felix-Ortiz, 1992; Spooner et al., 2001).

Community factors including the physical environment in which young persons live and their legal, social and cultural context may also play a role (Buckstein et al., 1997; Gilvarry, 2000; Newcomb & Felix-Ortiz, 1992; Spooner et al., 2001). Family influences are vitally important and young people living in families where there is conflict, dysfunction and parental substance abuse and psychopathology are at increased risk of substance use (Gilvarry, 2000; Newcomb & Felix-Ortiz, 1992; Spooner et al., 2001; World Health Organisation, 2002).

The final group of factors found to influence young people's substance use are school and peer factors. Young people who have positive relationships with teachers and feel 'connected' to and are rewarded for their involvement in their school environment are less likely to have problems with substance misuse (Spooner et al., 2001). Peers are of critical importance, as young people with substance using peers with positive attitudes towards substance use are more likely to initiate and maintain substance use (Buckstein et al., 1997; Gilvarry, 2000).

A number of 'protective factors' which may decrease the vulnerability of a young person by enhancing resiliency and ameliorating the effects of existing risk factors have also been identified (Newcomb & Felix-Ortiz, 1992). These include a positive temperament, intellectual ability, a supportive family environment with clear structure and boundaries, prosocial peers and a strong sense of 'connectedness' with family, school or external support systems (Rutter, 1985; Spooner et al., 2001).

It is important to note that exposure to risk and protective factors varies with the developmental stage, perceived meaning of (attribution) and current life circumstances of young people. Risk and protective factors may have direct, indirect interactional and even reciprocal effects on substance misuse (Farrell, 1993; Rutter, 1985). However, methodological difficulties abound in studies on causation and recent research has stressed that there are multiple pathways to substance misuse.

Adverse effects

Adverse effects can be categorised into three general areas: physical health, mental health and psychosocial problems. These effects can be exacerbated by concurrent use of other drugs, especially alcohol. Adverse effects can occur as a result of psychostimulant intoxication, withdrawal and long-term use and the safety of the contexts within which they are used.

Physical health problems

The physiological and health effects from psychostimulant use are well documented (Arcuri, 2000; Dennis & Ballard, 2002; Hall & Hando, 1994; McKetin & McKenna, 2000; Topp, Breen et al., 2002; Topp et al., 1999; Weir, 2000; World Health Organisation, 1997). Chapter 3: *Pharmacology of psychostimulants* outlines the pharmacology and effects of psychostimulant use. Among young people accessing residential AOD treatment, physical health problems were most likely to be reported by those who nominated ATS as their primary drug of concern (Howard & Arcuri, 2003a).

Mental health problems

There is increasing evidence of the mental health problems associated with adult psychostimulant use (see Chapter 4: *Risks associated with psychostimulant use* and Chapter 10: *The psychiatric comorbidity of psychostimulant use* for reviews). However, only two studies have documented rates of comorbid mental health problems in young people.

An American study found significantly higher rates of attention deficit hyperactivity disorder (ADHD), major depression, oppositional defined disorder, post-traumatic stress disorder (PTSD) and sexual and physical abuse amongst adolescent amphetamine users compared to other drug users (Hawke, Jainchill & DeLeon, 2000). Howard and Arcuri (2003a) found Australian primary ATS users were more likely to report feeling trapped, have trouble concentrating and were more likely to have had suicidal thoughts. However, they were less likely to have seen a mental health professional than primary heroin and cannabis users.

The relationship between psychostimulant use and depression has received particular attention. A number of researchers have reported on the relationship between excessive psychostimulant use and resultant depression, in part due to their impact on serotonin and dopamine (Hall, Hando, Darke & Ross, 1996; McKetin & McKenna, 2000; Shearer et al., 2002; Weir, 2000). Others have found pre-existing depression is one of the strongest predictors of young people taking up and continuing psychostimulant use (Sussman, Dent & Stacy, 1999).

Psychosocial problems

Howard and Arcuri (Howard & Arcuri, 2003a) found primary psychostimulant users were more likely to have committed a crime against a person during the three months prior to admission than primary heroin, cannabis and alcohol users. Furthermore, a history of sexual assaults and risky sexual behaviour were most likely to have been reported amongst clients who nominated ATS as their primary drug of concern.

Prevention and population-based interventions

Few studies of prevention and population-based interventions have been reported that focus specifically on younger people and psychostimulants. However, given the popularity of psychostimulants amongst this age group, a large proportion of the sample in broader population studies will have been drawn from psychostimulant users. As such, the findings reported in the previous chapters may be applicable to this younger population.

General prevention that targets risk and protective factors

Addressing multiple risk and protective factors results in a decrease not only in problematic substance use but also in rates of homelessness, mental health issues, suicide and criminality. For a comprehensive review of the risk and protection literature, see Bond et al. (2000), Commonwealth Department of Health and Aged Care (1999) and National Crime Prevention (1999a; 1999b).

Prevention programs can focus on the child, the family or the community. They occur within health centres, homes, schools, whole communities or a combination of these. Preventive interventions range from identification (such as hospital or school screening and referral services), to diagnostic and direct intervention programs.

Early intervention may begin at any time as long as it occurs prior to the development of problematic substance use and impaired functioning. Strategies focus on enhancing the child's development via building resiliency skills and providing family support and assistance.

Examples of prevention programs include:

- intensive nurse home visitation aimed at at-risk mothers;
- early intervention programs for high-risk infants and pre-schoolers;
- early childhood education;
- mental health services for young children;
- parenting programs;
- programs that ease the transition from primary to secondary school;
- child protection casework;
- foster care;
- family support agencies; and
- AOD treatment for the young person's parents.

Many of these programs have been extensively reviewed with findings indicating they are cost effective and have positive effects on a range of child and adult outcomes, including lowered rates of licit and illicit substance use. For a comprehensive review of prevention programs, see Mitchell et al. (2001) and National Crime Prevention (1999a; 1999b).

Generic drug prevention interventions for young people

Mass media campaigns

Mass media campaigns mostly attempt to prevent the onset of substance use and subsequent problems. Well-designed campaigns have been shown to impact on smoking and drug use among young people (Strasburger & Donnerstein, 1999). One study that utilised anti-marijuana public service announcements decreased marijuana use by more than 25% among high-sensation-seeking adolescents (Palmgreen, Donohew, Lorch, Hoyle & Stephenson, 2001). The impact of such campaigns are contingent upon targeting a clearly defined audience, a clear understanding of their prevailing attitudes and beliefs, and the design of credible messages that are frequently presented during programs watched by that audience

(Bertram, Barbir, Ball & Carroll, 2003). The pre-testing of these messages for their effectiveness and appropriateness to the target audience is crucial (National Institute on Drug Abuse, 2002). Governments periodically release media campaigns targeted at young people, most often around alcohol.

School-based prevention programs

There have been a number of criticisms levelled at the limited capacity of school-based prevention programs to address the complex range of factors associated with the onset, escalation and maintenance of substance use. An additional concern is that many young people most in need of an effective intervention are not currently enrolled in or have been excluded from the school system for a variety of reasons (e.g. truancy and expulsion).

Both school-based and media campaigns focused on the need for young people to 'Just Say No' to drugs have been criticised for their naïve and simplistic nature. Such school-based interventions need to be based on an assessment of local need, be comprehensive and culturally sensitive, provide life skills and be delivered over a significant period of time with booster sessions. A number of authors have developed guidelines to effective school-based education programs (Dennis & Ballard, 2002; Hansen, 1997; Lohrmann & Wooley, 1998; Midford, Munro, McBride, Snow & Ladzinsji, 2002; National Institute on Drug Abuse, 1997; UNICEF, WHO, World Bank & UNFPA, in press; World Health Organisation, 1994).

However, a recent meta-analysis indicated there is limited evidence for the effectiveness of school-based programs (White & Pitts, 1998). More intensive and comprehensive programs with both educational and skills training components and booster sessions had the most evidence for their effectiveness. An example of an effective prevention program is the 'Life Skills Training Program' (Botvin, Baker, Dusenbury, Botvin & Diaz, 1995). The program comprises a three-year prevention curriculum intended for late primary and early secondary school students and covers three major content areas: drug resistance skills and information, self-management skills and general social skills. A randomised controlled trial found the Life Skills Training program had a positive impact on both drug and polydrug use outcomes on students compared to controls which were maintained at six-year follow-up (Botvin et al., 1995; White & Pitts, 1998). While initially this program was used largely with middle-class white populations, recently similar results have been reported for other groups of youth (Botkin & Griffin, 2001).

A need for targeted interventions for different groups of young people, particularly for high-risk youth, has also been identified (Gilvarry, 2000). An example of a promising targeted school-based program is the Reconnecting Youth Program (Eggert, Thompson, Herting & Nicholas, 1994). This program targets young people who show signs of poor school achievement and potential for dropping out of high school, as well as young people with multiple problems. Through personal growth classes, social activities and school bonding, the program teaches resiliency skills to moderate the effect of risk factors and the early signs of substance abuse. Participants in this program have shown improved school performance, self-esteem, personal control, school bonding and social support; and reduced drug involvement, deviant peer bonding, depression, anger, aggression, hopelessness, stress and suicidal behaviours, although there was no comparison group (Eggert, Thompson, Herting & Nicholas, 1995).

Other interventions have targeted high-risk, out of school youth and the promotion of drug free activities (Substance Abuse and Mental Health Services Administration (SAMHSA), 2003). The former include formal and informal projects directed toward high-risk, out-of-school youth, delivered as 'outreach' or 'centre-based' by a mix of peer educators and professionals. The latter include various activities such as rock concerts and sporting events sponsored by the health promotion sector. The rationale for such events is two-fold: first, linking pleasurable activities with drug-free experiences and messages reinforces the strength of the drug-free message and, second, to combat boredom that is often associated with substance use. However, these programs have not been extensively evaluated.

Prevention strategies specifically targeting psychostimulants

In the knowledge that much psychostimulant use by the younger population is experimental or social in nature, the emphasis of many interventions has been aimed at reducing the harm caused by this time-limited or lower-level use (Weir, 2000). This has included the dissemination of information on the effects and risks of taking psychostimulants or placing oneself in a position where psychostimulants are freely available.

The aim of prevention strategies that specifically target individuals who have used psychostimulants is to assist them to minimise the harm associated with use. Prevention strategies include teaching early signs of problematic use, how to assist peers with problems and where help is available for individuals with problems (Dennis & Ballard, 2002). One example is 'Venue Safety', a harm minimisation strategy for raves and clubs which has been adopted by the rave community and municipal and public health authorities (Weir, 2000). Many information booklets, such as 'Rave Safe' (Marinelli, 1996), 'Club Drugs' (Dillon & Degenhardt, 2000) and 'Ecstasy — Facts and Fiction' (Topp, Dillon & Hando, 2002), have been developed to give young people relevant information on the different drugs used, short-term and long-term effects, risks involved with use and hints and tips on safer use, as well as emergency responses to adverse effects. The provision of sterile injection equipment should also be part of any harm reduction strategy.

In prevention and harm reduction strategies, much emphasis has been placed on information conveyed at schools, or raves and dance parties. As noted earlier, these prevention strategies and harm reduction initiatives need to better target possibly more 'at-risk' groups (e.g. homeless youth, juvenile justice youth and non-school attending youth) and other settings like parties and general celebrations where young people are likely to use psychostimulants. One attempt at targeting these areas involved the development of a psychostimulant-specific comic entitled 'On the Edge' (Streetwize Communications, 2002). This was distributed to youth centres, refuges and other locations in which various populations of young people were likely to be present. Integral to the development of this publication was qualitative research carried out via focus groups into the information needs of young psychostimulant users. The result was a language appropriate publication, in the form of a comic, which addresses the issues of side-effects (in particular drug induced psychosis), harm reduction techniques and treatment availability and accessibility. Evaluation reports have consistently shown that comics are more successful than other print media in disseminating information to young people. Additionally, research on previous issues has shown that 80% of young people recalled the main message of a

Streetwize comic up to four months after they had read it. Research has also shown that young people are more likely to pass Streetwize resources onto their friends (www.streetwize.com.au/publications).

In any prevention and population based intervention, attention needs to be given to the following:

- providing accurate, unbiased information;
- attending to personal variables that may be associated with increased vulnerability to negative peer influence for some individuals or groups;
- teaching of coping and decision-making skills and those associated with resistance to negative influences;
- challenging and changing incorrect normative beliefs about the extent of use in a particular area or among a particular target population;
- improving communication between young people and their parents, teachers and other adults;
- providing harm minimisation strategies (e.g. safer using techniques) as appropriate; and
- exposing participants to satisfying and acceptable alternatives to substance use.

Assessment

A comprehensive assessment is the critical first step in the treatment of adolescent substance use, due to the plethora of factors involved in the aetiology of AOD misuse. A well-conducted assessment can increase engagement in treatment and be a therapeutic intervention in and of itself. However, clinical judgement is required so that it does not become an intrusive process that can negatively impact on the engagement with the young person.

The type of assessment conducted depends largely on the professional's role. For an outreach worker, where brief contact usually occurs, the worker may simply obtain information on demographics and presenting issues and conduct a risk assessment (if required). For a specific AOD service, the assessment is likely to be more comprehensive. With the young person's consent, valuable information may be sought from the young person's family, other supportive persons and other treatment agents (Buckstein et al., 1997).

There are a number of key areas that should be covered in any assessment with a young person (Buckstein et al., 1997; Department of Human Services, 2000; Howard & Arcuri, 2003a):

- Chief complaint/issue — elicit from the young person his or her understanding of what has brought him or her to the point of assessment. If the chief issue is not an AOD problem, then assess the history of the chief issue, ie. duration, impact upon the young person's life, steps taken to resolve the issue and the results of these steps. Then appropriate referral would follow. If the chief issue is primarily AOD related, then move to the areas described below.
- Background demographic information — include here any important relationships (family or significant others) and other important connections, current vocational and educational pursuits and current living arrangements.

- Initial drug use history — given that polydrug use is the norm for young people, all drug groups should be covered. Explore current intake, type and levels of use and how long they have used each drug.
- Comprehensive substance use history — a systematic enquiry of all drug classes and differentiating the psychostimulants, as there are many of them with differing impacts on individuals. For each drug, include age at first and last use, reasons for continued use, method of administration (including any changes), sharing of injection equipment, where they use (e.g. street, home, dealer's place) and whether they use alone or in a group, impact of drug use on functioning, periods of non-drug use, attempts to control/stop use and the young person's goals in relation to his or her drug use.
- Severity of the problem — use of standardised measures to assess the severity of the problem is recommended; e.g. Severity of Dependence Scale (SDS, Gossop et al., 1995), Diagnostic and Statistical Manual of Mental Disorders — IV (DSM-IV, American Psychiatric Association, 2000), or the International Classification of Mental and Behavioural Disorders (World Health Organisation, 1992).
- Previous treatment — include perceived usefulness of such treatments and reasons for cessation/continuation of treatment.
- Leisure and social functioning — include connections with family, school, peers and significant others. Working with these connections is vitally important in enhancing protection and minimising risk.
    a. Family — explore who is in the young person's family, who resides with whom, the family's place of residence, how the young person gets along with parents and siblings (possibly using simple scales, such as the psychometrically sound General Functioning scale of the 'Family Assessment Device' (Byles, Byrne, Boyle & Offord, 1988); contacts with extended family; young person's wishes for family involvement; and likelihood that family may become involved in treatment.
    b. Peers — investigate how they spend their time together, the young person's perspective of how they compare to peers, the young person's wishes for peer involvement in treatment (where appropriate) and the likelihood that peers may become involved in treatment.
    c. Hobbies and leisure activities — including any changes in these over time (particularly as a result of escalation of problems related to drug use). Explore whether the young person wishes, or perceives the possibility, that he/she might re-engage with these activities.
    d. Educational/employment history — investigate the young person's attitude to school, highest grade attained, best subject(s), worst subject(s), changes of school, special education, attendance, disciplinary record (suspensions and expulsions) and ability/desire to return to schooling or alternative education. Include work history and current employment, if relevant, employment aspirations and current income source.
- Physical and mental health — included in this part of the assessment is an examination of past medical history, any allergies, past psychiatric history (individual and family) and current medications and medical compliance.

Upon completion of assessment, a more comprehensive assessment could be undertaken in any of the aforementioned areas, by a more specialised medical practitioner, if required.

a. Given the potential for mental health problems, a comprehensive assessment may be necessary, especially where harmful use of psychostimulants is evident. As such, a mental state examination should be conducted with every young person. This includes questions about:
   - — General feelings and moods — possible questions could cover areas such as how the young person feels about him or herself, how the young person generally feels (e.g. sad, happy, irritated) and other specific indicators of depression, such as whether the young person cries a lot or isolates him or herself, has reduced levels of energy or activity, or if 'acting out' may indicate avoidance of negative mood.
   - — Suicidal ideation — a suicide screen should be conducted with the young person, exploring any ideation and/or attempts by the young person to deliberately harm or kill him or herself, the reasons behind any such attempt and any current thoughts about, intentions or plans to kill him or herself.
   - — Cognition — thought processes and thought content (delusional, hallucinatory or suicidal thoughts).
   - — Attention should be paid to general appearance, attitude, behaviour, mood, speech and gait of the young person.

- Offending history — include the number of offences, types of offences and links with substance use, number of times incarcerated (and length of time), current legal status and any upcoming legal appearances.
- Trauma history — explore abuse, violence, torture and experience of armed conflict and natural disasters (e.g. fire, flood and famine).
- Sexual practices — investigate past sexual activity, number of partners, gender of partners and the practice of safe sex.

Reassessment and monitoring will need to occur over time, especially during the first two weeks, as withdrawal and other symptoms may develop during the first week of abstinence.

Assessment instruments can be useful tools in screening for and determining the frequency, quantity and severity of substance use in young people. Furthermore, structured interviews such as the Structured Clinical Interview for DSM-IV (SCID) (Spitzer, Williams & Gibbon, 1994) and the Composite International Diagnostic Interview (CIDI) (Training and Reference Centre for WHO and CIDI, 1993) may be useful in determining whether young people meet DSM-IV or ICD-10 criteria for abuse or dependence, potentially requiring more intensive intervention. However, most assessment tools are not youth specific, or they require adaptation for Australian populations. A comprehensive review of diagnostic and screening instruments was recently conducted (see Dawe, Loxton, Hides, Kavanagh & Mattick, 2002).

Management and treatment

Across the board, there is a paucity of research into interventions for young psychostimulant users (Deas & Thomas, 2001; Deas-Nesmith, Brady & Campbell, 1998; Gilvarry, 2000; Muck, Zempolich, Titus, Fishman et al., 2001). Most studies utilise samples of older, predominantly cocaine users. The translation and applicability to younger, primary psychostimulant users can be problematic. This review of management and treatment options will, where possible, discuss the effectiveness of these interventions with psychostimulants, but will also cover these interventions as they apply to young drug users generally.

Management of psychostimulant intoxication

Accepted practice in working with clients presenting with intoxication-induced psychosis and aggression or violence is stabilisation in a medically supervised treatment setting, where short-term use (48–72 hours) of antipsychotics and tranquilliser medications can be administered to reduce symptoms (Rawson, Gonzales & Brethen, 2002). A Cochrane Review of the literature found no controlled trials of treatment for amphetamine psychosis (Srisurapanont, Kittiratanapaiboon & Jarusuraison, 2003).

Withdrawal management

Detoxification, particularly medically supervised or hospital-based, is rarely required for young people because of their often more limited history of overall drug use and their enhanced capacity to recover from long-term use of psychostimulants (Bailey, 1989; Buckstein et al., 1997). Rather, the provision of a caring and soothing environment is seen as the most effective method of assisting young psychostimulant users during the withdrawal period. In this environment, the young person should:

- have a high level of support;
- be surrounded by people who can understand what they are going through;
- be comfortable;
- be provided with guidance;
- have their levels of depression and signs of potential suicide/deliberate self-harm, monitored and responded to; and
- be assisted with any cravings, taught relaxation strategies (e.g. oils, massages, guided imagery and warm baths) and provided with nutritious meals and assistance in gaining professional help if required.

Acupuncture and a variety of herbal preparations are becoming more and more popular as a means for withdrawal management. While they lack an evidence base, they have anecdotally been found to alleviate withdrawal symptoms and may assist with engagement. There is a need for these procedures to be subject to more rigorous evaluation. The role of medication to assist the management of ATS withdrawal is limited and no agents have been identified which reliably and demonstrably improve the situation (see Chapter 7: *Psychostimulant withdrawal and detoxification* and Chapter 8: *Pharmacological interventions* for reviews). The prescription of benzodiazepines and antidepressants has become common practice. Because of the high potential toxicity in overdose of some tricyclic antidepressants, such as amitriptyline, the newer, safer antidepressants should be considered for this group, but none are side-effect free (Cantwell & McBride, 1998).

It needs to be remembered that withdrawal is merely a part of treatment, and in order to maintain change it should be linked with support and other interventions. During withdrawal, young people have time away from substance-using peers and their community to contemplate their situation, appropriate information and to explore their ambivalence about and receive encouragement to make a decision about changing their substance use.

Treatment of young people with alcohol and other drug problems

Purpose

The purpose of adolescent substance use treatment is to provide interventions that address the needs of young people who exhibit problems associated with substance use. The primary aim of treatment may be cessation of use, detoxification or controlled use. In addition, there are usually broader objectives, such as reduction of criminal activity and risk behaviour (e.g. safer routes of administration and reduction in equipment sharing and unsafe sex), increased school performance, vocational preparation, improved family functioning, improved living and interpersonal skills and self-care and improved physical and psychological health.

Goals

A suitable goal for treatment with young people is to increase the capacity of the young person involved in treatment to manage their life more effectively. There may need to be a reconsideration of the traditional abstinence goal of many programs in situations other than those that involve physical or organ damage of the young person. This is particularly pertinent for young people, as a focus solely on abstinence from substance use may have the effect of undermining other gains and thus decrease the value of those gains for the young person, their family or the treating agent.

A range of treatment options is essential (Gowing et al., 2001; Howard, 1994; Howard & Arcuri, 2003b; Kaminer, 1994; Spooner, Mattick & Howard, 1996; Wagner & Waldron, 2001), the intensity of which should ideally be matched to the severity of the young person's substance use and the level of impairment in personal, school, social and family functioning (see Table 14) (Winters, 1999).

Youth friendly?

Whatever the intervention, access issues require attention, as does engagement. The WHO has distilled the features of effective youth friendly services, which include the active involvement of young people and policies that guarantee confidentiality. In line with relevant legislation, they recommend that parental consent is not required and that provision of services or products should not be withheld in the absence of parental consent.

Easy registration, prompt screening and assessment, short waiting times, 'drop-ins' with or without prior appointment possible, and strong linkages to other social service providers are important ingredients that have been identified as increasing the attractiveness of services to young people. Further, there is a need for increased participation by young people in all aspects of interventions including prevention, treatment, assessing need, planning, delivery of interventions, monitoring and evaluation (Kirsch, 1995; World Health Organisation, 1999, 2001).

Table 14: Types of treatment options available for adolescents

Treatment Type	Client Assessment Criteria	Typical Treatment Options
Primary prevention	**No history of current use.**	**Individuals, family, school or community interventions including psychoeducation, brief CBT or FT and ST.**
Early intervention	**No history of or low levels of use, with few problems arising from substance use.**	**Counselling or brief individual, group or family interventions including psychoeducation, HR, MI, CBT and FT and ST.**
Outreach and drop-in centres	**Low to severe levels of use, for difficult to engage young people (treatment non-completers, pre-contemplators) and support treatment completers.**	**Emphasis on engagement with young people and improved health and access to services, interventions may include psychoeducation, HR, MI, brief CBT and FT, counselling, recreational activities and ancillary services (e.g. educational and vocational activities, legal assistance and support).**
Outpatient treatment	**Low to moderate levels of substance use/dependence with problems resulting from use with largely intact social supports (ie. family, accommodation and school/ employment).**	**Individual, group and family counselling, or interventions including psychoeducation, MI, HR, CBT, FT and ST (educational/vocational activities, life/living skills).**
Semi-supported residential	**Low to severe levels of substance use or dependence with problems resulting from use and there is a need for residential support.**	**These include hostels or group homes and can be used to accommodate young people who are attending a day program, or exiting a residential unit.**
Short-term residential (usually less than three months)	**Moderate to severe levels of misuse or dependence, usually requiring detoxification or ongoing assessment and respite, with problems resulting from substance misuse and few social supports.**	**Detoxification, individual, group and family counselling and interventions including MI, HR, CBT, FT and ST (educational/vocational activities and life/living skills).**
Longer-term residential (usually three months)	**Severe substance misuse or dependence usually requiring detoxification, limited social supports and health concerns are elevated (including mental health).**	**As above but are usually 'therapeutic communities' adapted to better suit the needs of young people.**

Note: CBT: Cognitive Behavioural Therapy; FT: Family Therapy; ST: Skills Training; MI: Motivational Interviewing; and HR: Harm Reduction.

Specific treatment interventions

There is a dearth of information on treatments for adolescent substance misuse and few well-controlled studies of specific treatment modalities have been conducted. Traditionally, studies have failed to demonstrate the superiority of any one treatment, although there is a general consensus that some treatment is better than none (Catalano, Hawkins, Wells, Miller & Brewer, 1990-1991). More recently, several clinical trials have demonstrated the efficacy of psychosocial treatment interventions for adolescent substance use disorders, including family based, behavioural and cognitive behavioural therapies (CBT) (Azrin, Donohue, Besalel, Kogan & Acierno, 1994; Deas & Thomas, 2001; Deas-Nesmith et al., 1998; Kaminer, Burleson & Goldberger, 2002; Muck et al., 2001; Waldron, Slesnick, Brody, Turner & Peterson, 2001). However, these studies have a number of methodological limitations including the use of small sample sizes, uncontrolled designs, non-standardised measures and inadequate follow up (Kaminer et al., 2002).

Pharmacotherapies

Psychostimulant substitution has been common practice in some countries (White, 2000), but is not widely available in Australia. A full review of the literature is available in Chapter 8: *Pharmacological interventions.* Most of the literature describes studies of adult populations and although many of the studies include clients in the 18-25 year old age bracket, no specific conclusions can be drawn about the outcomes of these studies for young people.

Other pharmacotherapies have also received mixed reviews and there are currently none that have been identified as highly effective for detoxification or aftercare (see Chapter 7: *Psychostimulant withdrawal and detoxification* and Chapter 8: *Pharmacological interventions*). Again, although there have been many trials of pharmacotherapies for the treatment of adult substance use disorders, none that we have located have focused on their effectiveness for a younger population. Thus, given their questionable efficacy for adults, controversy remains as to whether any of these drugs are efficacious with young people. However, two controlled trials of lithium and sertraline have found positive results in the treatment of adolescent substance users with comorbid psychopathology (Deas-Nesmith et al., 1998; Geller, Cooper & Sun, 1998).

Cognitive behavioural interventions

Cognitive Behavioural Therapy (CBT) is a psychotherapeutic approach that focuses on the interaction between behaviours, cognitions and emotions (Buckstein et al., 1997). Typical CBT approaches to the treatment of youth substance misuse include behavioural contingency management, skills training and relapse prevention (Deas & Thomas, 2001). Relapse prevention is a core component in which environmental, intra- and inter-personal triggers are identified and strategies for coping with stressors, cues and lapses into substance use are developed (Heather & Tebbutt, 1989; Jarvis, Tebbutt & Mattick, 1995). CBT skills training may include relaxation and stress management, drinking/drug refusal, problem solving, coping, self-control, and social and living skills training (Muck et al., 2001).

Although there are no studies on the use of CBT in young people with psychostimulant use problems, CBT is considered best practice in the treatment of problematic psychostimulant use and dependence in adults (see Chapter 5: *Psychosocial interventions*). Furthermore, there is a growing evidence base for the use of CBT in the treatment of child and adolescent internalising (e.g. depression) (Compton, Burns, Egger & Robertson, 2002; Deas & Thomas, 2001; Lewinsohn & Clarke, 1999; Muck et al., 2001) and externalising psychiatric disorders (e.g. conduct disorder, ADHD) (see Farmer, Compton, Burns & Robertson, 2002 for a review). However, the majority of these trials have excluded young people with comorbid substance use disorders (Muck et al., 2001).

Several RCTs have recently provided preliminary evidence for the efficacy of CBT in the treatment of youth substance misuse. For example, Azrin and colleagues (1994) found significant reductions in substance use and positive urine screens amongst young people receiving behaviour therapy compared to supportive therapy. Similarly, a small pilot study comparing CBT and insight-orientated interactional therapy (IT) group treatments found adolescents in the CBT group had significant reductions in the severity of their drug use compared to the IT group at three-month follow-up (Kaminer, Burleson, Blitz, Sussman & Rousanville, 1998). At 15-month follow-up, no treatment group differences were found, although reductions in substance use were maintained in both the CBT and IT groups (Kaminer & Burleson, 1999). In a later study, Kaminer and colleagues (2002) compared the efficacy of a CBT Coping Skills group and a psychoeducational therapy (PET) group amongst 88 adolescent substance users with comorbid psychopathology. At three-month follow-up, male participants and older youth in the CBT group had significantly lower rates of positive urinalysis than the PET group. However, similar relapse rates for both groups were found at nine-month follow-up, although both treatments resulted in an overall reduction in substance use.

Finally, Waldron and colleagues (2001) conducted an RCT comparing individual CBT, functional family therapy (FFT), combined CBT and FFT, and a group intervention amongst 114 substance abusing adolescents. All interventions had some efficacy, although there were differences in outcomes. Adolescents in the combined FFT and CBT and FFT-only interventions had significantly fewer days of cannabis use and achieved minimal levels of use post treatment. Youths in the individual CBT condition also achieved minimal levels of use following treatment. However, these treatment gains were not maintained at seven-month follow-up, although they were maintained when CBT was combined with FFT.

Thus, whilst CBT has not been used in the treatment of youth psychostimulant users, there is promising evidence for its effectiveness in the treatment of adolescent substance use disorders either alone or in combination with FFT. Future research determining the short and long-term outcomes of individual and group CBT in the treatment of youth psychostimulant and other substance use is warranted.

Family and multi-systemic interventions

The family and other social environments of young people including peer relations, school and the community play an important role in adolescent substance use (Deas & Thomas, 2001). Thus, family therapy is considered to be a critical component of the management of adolescent substance use problems. The early involvement of the

family in treatment via assertive outreach can assist with the engagement and retention of young people (Buckstein et al., 1997; Hando, Howard & Zibert, 1997; Kalajian, 1992).

Family and Multi-Systemic Therapies have received the most attention in the adolescent substance use literature. Whilst there are many theoretical approaches to family therapy, most approaches are based on four models including strategic, structural, behavioural and functional approaches or a combination of these (Muck et al., 2001). Common components include family and individual psychoeducation, parent management training and communication skills training (Buckstein et al., 1997).

Several reviews of the literature on family therapies in the treatment of adolescent substance use have been published elsewhere (Liddle & Dakof, 1995; Ozechowski & Liddle, 2000; Waldron et al., 2001). A number of RCTs comparing family therapy with other treatment modalities have been conducted. Family therapy was found to be superior to family education and adolescent group therapy in reducing drug use severity in several studies (Joanning, Quinn, Thomas & Mullen, 1992; Lewis, Piercy, Sprenkle & Trepper, 1990). Furthermore, although Functional Family Therapy (FFT) was equivocal with a parent group and CBT in reducing substance use over a 9 and 4 month period respectively (Friedman, 1989; Waldron et al., 2001), it was superior to individual CBT in reducing substance misuse at 7 months follow-up (Waldron et al., 2001). Finally, a comparison of Multidimensional Family Therapy (MDFT, Liddle, Dakof, Diamond, Barrett & Tejeda, 2001), adolescent group therapy and family psychoeducation, found that reductions in drug use were superior in the MDFT group at 6 and 12 months follow-up compared to the other treatments.

Multi-Systemic Therapy (MST) takes the family therapy approach further by providing interventions in a variety of systems and processes known to be related to psychosocial problems in young people. These include the family, peer group, educational and vocational settings, as well as the individual (Henggeler, Bourdin, Melton, Mann et al., 1991).

Three large-scale RCTs have evaluated the efficacy of MST compared to individual counselling and Department of Youth Services (DYS) treatment as usual in young offenders (Henggeler et al., 1991). In the first study, a significant reduction in the number of substance-related arrests was found in the MST group compared to individual counselling over a four-year follow-up period. Similarly, offenders receiving MST had significantly lower levels of alcohol and marijuana use in a second study compared to the DYS treatment as usual group post treatment. However, mixed results were found in youth offenders with substance abuse or dependence when MST was compared to outpatient community substance abuse treatment (Henggeler, Clingempeel, Brondino & Pickrel, 2002). No differences between groups emerged on marijuana, alcohol or other drug use at four-year follow-up, although the MST group had higher rates of abstinence for cannabis use according to biological measures (Henggeler et al., 2002).

Whilst no single approach to family therapy has emerged as superior in the clinical research literature, there is solid empirical support for the use of family therapy in the treatment of adolescent substance misuse (Overall & Gorham, 1962;

Ozechowski & Liddle, 2000; Stanton & Shadish, 1997). Thus, family interventions are a promising area for development in the treatment of youth psychostimulant users.

Residential treatment

Questions have long been raised as to the appropriateness of residential treatment for young psychostimulant users (Brook & Whitehead, 1973; Coulson, Went & Kozlinski, 1974). Howard and Arcuri (2003a) found that clients presenting to residential treatment with psychostimulant dependence were not dissimilar to those presenting as primarily heroin or alcohol dependent on admission. This was despite low retention rates, with close to 60% leaving in the first 30 days of the 90-day in-patient treatment.

However, of those clients who completed a substantial component of the program (at least six weeks), at three-month post treatment, the psychostimulant group did |as well as other groups, showing significantly less drug use from a self-reported pre-treatment base-line. This is important when one considers the more problematic pre-treatment presentation of the psychostimulant group in this study. Psychostimulant users were more likely to have reported greater mental and physical health problems, more financial problems and, during the three months prior to treatment, were more likely to have overdosed, committed person and property crimes and to have had more sexual partners.

Similarly, an American study of amphetamine users admitted to a residential therapeutic community drug treatment program found that the treatment outcomes of amphetamine users did not differ from other drug users despite having a more extensive history of drug use, criminal behaviour, family dysfunction, psychopathology and HIV risk-taking behaviours (Hawke et al., 2000). Both amphetamine and other drug users reported significant reductions in drug use (including amphetamines), criminal behaviour and HIV risk-taking behaviour and improved psychological functioning at 12-month follow-up (Hawke et al., 2000).

Thus, whilst there is some support for the efficacy of residential treatment for young amphetamine users, it is an expensive and potentially invasive option and, as such, should only be considered where external supports (e.g. family, school/work, accommodation, income, etc) have broken down, are openly hostile, are non-existent, or where there are significant mental health and other behavioural concerns present. Other risks associated with residential treatment include removing the young person from the functional aspects of their lives and exposing them to drug using peers.

Contingency programs

Contingency management programs have been shown to be effective in improving abstinence rates among adult drug users in treatment and there is some evidence for their effectiveness with psychostimulant users (see Chapter 5: *Psychosocial interventions* for a fuller review). A comprehensive description of contingency management procedures for adolescent substance misusers was recently provided by Kaminer (2000) and there is some evidence for its effectiveness in the treatment of adolescent smoking (Corby, Roll, Ledgerwood & Schuster, 2000). However, a recent study amongst adolescent and adult cocaine users found a voucher incentive

program for multiple drug use was not effective (Katz, Chutuape, Jones & Stitzer, 2002) and overall there is little evidence of the efficacy of contingency management in the treatment of youth substance misuse.

12-step programs

Twelve-step approaches to the treatment of substance use such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) are the most commonly used model for the treatment of adolescent substance abusers in the USA (see Muck et al., 2001). They are based on the tenet that substance abuse and dependence is a disease, which can only be managed with a goal of abstinence (Winters, Stinchfield, Opland, Weller & Latimer, 2000). The approach is considered most appropriate for severely substance dependent youth with high levels of motivation (Kelly, Myers & Brown, 2002). Whilst some evidence has emerged for the effectiveness of this approach in reducing substance use amongst psychostimulant (cocaine and amphetamines) dependent youth over a four-year follow-up (Brown, D'Amic, McCarthy & Tapert, 2001), its overall suitability for the developmental level of young people is questionable as no RCTs have been conducted.

Peer programs

The popularity of peer programs for young people has increased immensely (World Health Organisation, 2001). This is largely due to the validity and acceptability of health peer-conveyed messages to young people. The WHO (2001) reviewed many peer programs that mainly targeted sexual and reproductive health, most of which had positive outcomes, including benefits for peer promoters, short-term individual behaviour change for participants (no long-term evaluations exist) and increased service utilisation.

One concern regarding the use of peers in this type of intervention is the question of how long peer educators can remain 'peers'. Educating young people to become educators or promoters places them in a privileged position whereby they are no longer peers and covert pressure may be exerted in some settings for them to remain in high-risk environments to positively influence others.

Conclusion

To date there is a paucity of rigorous research on the effectiveness of treatment for young people experiencing problematic psychostimulant use. Much of the research that has looked at young people has tested models developed for adult populations. Primary and secondary prevention programs are considered to have the greatest impact, although very few have been rigorously evaluated. Multiple, age-appropriate interventions are recommended over one-dimensional approaches. There is promising evidence for CBT and increasing evidence of the effectiveness of family therapy approaches and a combination of the two approaches appears most beneficial.

Generally clinicians consider that treatment interventions, while addressing any deficits, must acknowledge and build on strengths inherent in the young person and take into account the specific needs of young people. Young people using psychostimulants may require specialised care at particular times but generally they

require the same assistance as other young people. There is a clear need for well-controlled studies into a range of, particularly psychosocial, interventions for young people using psychostimulants.

Summary of evidence

Key points	Strength of evidence
CBT and family therapy approaches appear to be most promising with young people, but there is little difference between different treatment modalities. A wide range of comprehensive interventions that target a range of factors needs to be offered.	**
Pharmacotherapies appear to be of little value except for specific psychopathology.	**
Treatment needs to be readily available, accessible and attractive to young people.	*
A comprehensive assessment is the critical first step in the treatment of young people due to the plethora of risk and protective factors, which may be targets for intervention.	*
The intensity of treatment intervention offered to young people should ideally be matched to the severity of substance misuse and the level of impairment in functioning. The least intrusive options should be tried first.	*
Coexisting mental disorders should be assessed and addressed.	
Detoxification is only a stage of treatment and by itself does little to change long-term use.	

Chapter 10

The psychiatric comorbidity of psychostimulant use

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Key points

- Comorbid disorders are common among psychostimulant users.
- The most common comorbid psychiatric disorders among psychostimulant users are depression, anxiety and drug-induced psychosis.
- Standardised screening, diagnostic tools and symptom checklists are available for psychostimulant use and comorbid psychiatric disorders and their use is highly recommended.
- Comorbid psychiatric conditions among psychostimulant users should be diagnosed and treated.
- Pharmacological interventions for the treatment of psychostimulant withdrawal, intoxication and comorbid psychiatric conditions are guided by principles of good clinical practice.
- In practice, the primacy of psychiatric and substance use disorders is difficult to establish and both disorders should be addressed.
- Following treatment of the acute presentation, integrated treatment for comorbid psychiatric disorder and psychostimulant use should follow.
- All clinicians working in the mental health and substance use fields should have sound suicide risk assessment skills and know when to appropriately refer to a specialist service when and if it is required.
- Many psychostimulant users, particularly those whose use is not heavy, may benefit from short interventions such as brief motivational interventions.
- Adequate resourcing for mental health and AOD staff will be needed to ensure adequate training, supervision and ongoing referral, consultation, liaison and collaboration in service delivery.
- Monitoring of service outcomes and the effectiveness of training and supervision on client outcomes should be a priority.

Overview

Parts of this chapter are based on a paper currently under editorial review (Dawe, McKetin & Kingswell, unpublished).

There has been a growing acknowledgement that comorbid psychiatric and substance use disorders require careful assessment and treatment. For example, the Australian National Comorbidity Project has brought together for the first time both the National Drug Strategy and the National Mental Health Strategy with the aims of providing an opportunity for information sharing among key stakeholders working in comorbidity and identifying actions for progression of issues (Teesson & Burns, 2001).

There are now major epidemiological and clinical studies in which the prevalence of such comorbidity has been well documented for substance use disorders generally. There has, however, been considerable variability in the extent to which the relationship between individual substances or combinations of substances and mental health problems has been investigated.

Understandably, given the high rates of alcohol use across the western world, we know a great deal about comorbidity in people with alcohol use disorders. Although the use of amphetamines and other psychostimulants is increasing, there has been relatively less investigation of mental health problems in relation to this class of substances. In this chapter we have focused predominantly on amphetamines, the psychostimulant most widely used in Australia (Australian Institute of Health and Welfare, 2002a).

An overview of prevalence, clinical course, pharmacological management and possible psychosocial interventions is presented for both psychostimulant-induced psychosis and psychostimulant-induced mood and anxiety disorders. Issues related to the assessment of comorbid conditions are presented next. A range of assessment strategies is presented, including the use of diagnostic and screening instruments and measures of symptom severity. Finally, the emerging literature on psychosocial approaches to comorbidity is briefly presented.

Prevalence of comorbid psychiatric conditions and substance use

Both epidemiological catchment area studies and clinical studies indicate that there are high rates of comorbid psychiatric problems among people with substance use problems. Epidemiological surveys conducted in North America such as the Epidemiological Catchment Area study and the National Comorbidity Survey found that substance use disorders were twice as likely to co-occur amongst people who also had a psychiatric diagnosis. Conversely, psychiatric disorders were three times more likely to co-occur in people with a substance use disorder compared to those without such a disorder (see Sinha & Schottenfeld, 2001 for a review). People with severe mental illness such as schizophrenia or bipolar disorder are at greatest risk of having a comorbid substance use disorder. For example, alcohol use disorders, such as alcohol dependence, abuse and hazardous and harmful use, affect approximately 30-40% of people diagnosed with schizophrenia (Regier, Farmer, Rae & Myers, 1993), with recent Australian data reporting a lifetime prevalence of up to 48% (Fowler, Carr, Carter & Lewin, 1998). The use of illicit drugs such as cannabis and psychostimulants such as amphetamines and cocaine is also higher amongst young adults with severe mental illness compared to either the general population or to other psychiatric comparison groups (Degenhardt & Hall, 2001; Degenhardt, Hall & Lynskey, 2001; Regier et al., 1993).

In the following section, comorbid disorders have been broadly classified into three major groups: psychotic disorders; mood disorders; and anxiety disorders. Each of these three selected diagnostic groups will be discussed in terms of presentation, clinical course and pharmacological management. A comprehensive review of effective psychosocial treatments for psychostimulant users has been presented in Chapter 5: *Psychosocial interventions*.

Psychotic disorders among psychostimulant users

There has been a growing research focus on comorbidity and psychostimulant use in recent years with particular attention paid to psychotic symptoms. It is well established that a psychostimulant-induced psychosis may occur following either prolonged use of the psychostimulant or after binge use (Griffith, Oates & Cavanaugh, 1968). The symptom profile is similar to that found in other non-drug induced psychoses and typically the psychostimulant-induced psychosis resolves after discontinuation of psychostimulant use. Psychosis is higher among psychostimulant users than amongst the general population and is higher after amphetamine use than after cocaine use (King & Ellinwood, 1992).

The emergence of more pure forms of crystalline methamphetamine 'ice' and the so-called 'base' methamphetamine product (poorly purified crystalline methamphetamine), has been associated with an increase in psychotic behaviour among methamphetamine users in Australia (Topp, Kaye et al., 2002). Psychotic symptoms can be induced in healthy subjects with no history of psychosis or substance use (Griffith et al., 1968) and in patients previously dependent on amphetamines (Bell, 1973). Psychostimulant use can exacerbate psychotic symptoms in people with schizophrenia (Janowsky & Davis, 1976; Janowsky, El-Yousef, Davis & Sekerke, 1973; LeDuc & Mittleman, 1995; Snyder, 1976).

Despite the recent increase in the use of psychostimulants in Australia (Australian Institute of Health and Welfare, 2002a; McKetin et al., 2000; Topp, Kaye et al., 2002) there is little information on the rates of amphetamine psychosis in Australia. Hospital morbidity data show a dramatic rise in the number of psychotic disorders due to psychostimulant use from 200 in 1998–99, to 1,028 in 1999–2000 and a further but smaller increase to 1,252 in 2000–01 (Australian Institute of Health and Welfare, 2002a). Furthermore, the relationship between amphetamine dose, duration of use and psychosocial factors that have been implicated in the precipitation of other, non-drug-induced psychotic episodes is essentially unexplored.

Whilst it is clear that amphetamine-induced psychosis resolves rapidly for many people, from the earliest studies we find that there are a proportion of people whose psychotic symptoms are protracted.

Data from cross-sectional studies of amphetamine users in Australia indicate that a significant proportion of amphetamine users report experiencing a range of acute, periodic or chronic 'low grade' or 'sub-clinical' psychotic symptoms and behaviours (Hall, Hando et al., 1996). However, whether these symptoms are due to the direct effect of the drug or whether they are prodromal symptoms that will lead to a psychotic episode with continuing amphetamine use is not clear.

Prospective cohort studies are clearly needed to determine the proportion of amphetamine users who will have a psychotic episode; the course of the disorder; and in particular, whether there are identifiable risk factors or variables that may indicate a longer course or poorer outcome for a particular subgroup of amphetamine users.

Presentation and clinical course

It is now well established that high doses of psychostimulants can result in a transient psychosis that is almost indistinguishable from an acute non-drug-related psychotic disorder (Angrist & Gershon, 1970; Connell, 1958). Further, it would appear that with the exception of those individuals with a pre-existing vulnerability to schizophrenia, the induction of psychostimulant psychosis occurs with a high dose binge pattern of use, especially with a multiple binge pattern that includes escalating doses (Segal & Kuczenski, 1999). The symptoms typically include paranoid ideation and hallucinatory experiences that have paranoid themes, often related to drug use and potential apprehension by authorities for illicit drug use or related illegal activities (Rosse, Collins, McCarthy, Alim et al., 1994).

There has been relatively little investigation of the course of psychostimulant-induced psychosis. Early experimental work has clearly demonstrated that with discontinuation of substance use the symptoms resolve rapidly (Griffith, Cavanaugh & Oates, 1969). More recent studies on clinical populations of amphetamine-induced psychotic patients confirm these findings on the whole (e.g. Iwanami et al., 1994). However, symptoms persist for more than one month in a small but significant minority of patients raising the possibilities that those with persisting symptoms may in fact have had either prodromal symptoms of schizophrenia that were exacerbated by psychostimulant use or a pre-existing vulnerability to schizophrenia that was triggered by psychostimulant use.

Finally, it is possible that psychostimulant-induced psychosis has a similar presentation to early episodes of schizophrenia and that there are some similarities between the course of the illness and non-drug induced schizophrenia (Flaum & Schultz, 1996). In a review of the literature from Japan, Sato et al. (1992) concluded that methamphetamine-induced psychotic episodes could persist long after methamphetamine use had stopped. Further relapse to a psychotic state could occur following the reuse of methamphetamine, alcohol and non-specific psychological stressors.

The high rates of re-presentation without recent amphetamine use described by Suwaki provide further support for this hypothesis. There is some evidence that repeated or long-standing use of methamphetamine results in a process known as 'behavioural sensitisation' or 'reverse tolerance' such that lower doses of the psychostimulant are required to produce the same response in laboratory animals (see Ujike, 2002). In humans, this may be manifest as a recurrence of a psychotic episode following the use of a lower dose of the psychostimulant than was previously used (Sato et al., 1992) or after non-specific stressors (Yui, Goto, Ikemoto, Nishijima et al., 2001).

Sensitisation to the effects of methamphetamine use in humans, unlike tolerance, is not a well-documented phenomenon. It is not clear, based on the existing evidence, to what extent methamphetamine use increases vulnerability to psychosis, or

whether recurring psychosis is merely a manifestation of a pre-existing vulnerability to psychosis among certain individuals. Once again, we do not know whether methamphetamine use increases vulnerability to psychosis, or what proportion of people who have experienced a psychostimulant-induced psychosis are at risk of relapse. At the least, there appears to be variation among individuals' vulnerability to sensitisation that may, in turn, be influenced by genetic factors (Ujike, 2002).

Pharmacological treatment of methamphetamine-induced psychosis

Typical protocols for treating methamphetamine-induced psychosis include administration of antipsychotics, sedatives or a combination of both drugs. Injection of antipsychotic drugs has been associated with a decrease in symptoms (e.g. Angrist, Lee & Gershon, 1974) although it may not be necessary in all cases. Sedation alone can be sufficient in some cases of extreme agitation and apparent acute intoxication. While there is limited literature on the treatment of psychostimulant-induced psychosis, general principles for management of the acutely agitated patient should apply. Sedating medication may be required. An oral or intramuscular benzodiazepine alone or in combination with a high-potency conventional antipsychotic (such as haloperidol) is generally the treatment of choice.

Another option to consider is the combination of a benzodiazepine and an atypical antipsychotic (such as risperidone or olanzapine). Individuals who abuse psychostimulants may be more prone to develop extrapyramidal side-effects, which may make benzodiazepines preferable. Cocaine toxicity can result in seizures, so drugs that significantly reduce the seizure threshold are best avoided. Diazepam 10–20 mg or more orally repeated every one to two hours is commonly used. Higher doses may be required if the individual is a polydrug user, particularly if benzodiazepines have been used regularly.

There is insufficient evidence supporting a particular regime in the treatment of amphetamine psychosis and therefore the principles of good clinical management need to be used (Srisurapanont et al., 2003). In a review of treatment options for amphetamine-induced psychosis, these authors conclude by stressing the importance of further systematic investigation of the use of conventional antipsychotics, atypical antipsychotics and benzodiazepines in the treatment of amphetamine psychosis.

Affective and mood disorders in psychostimulant users

The mixed presentation of mood and anxiety symptoms in amphetamine users is reported in both surveys of forensic populations (Kalechstein, Newton, Longshore, van Gorp & Gawin, 2000) and cross-sectional community samples (Goodwin, Stayner, Chinman, Wu et al., 2002; Hall, Hando et al., 1996; Vincent et al., 1999). In an Australian study Hall et al. (1996) found that injecting amphetamine users reported a high occurrence of psychological problems, particularly depression and anxiety. At least three-quarters of the sample experienced symptoms of depression and anxiety. Although these high levels are partly due to the prevalence of anxiety and depression prior to amphetamine use (48–62%), around half of the sample (48–58%) reported experiencing symptoms after an episode of amphetamine use. Following first use of amphetamines, substantially more users reported experiencing symptoms of anxiety, panic, depression, mania, hallucinations and paranoia. Significant increases in violence also occurred after first use.

Hall et al. (1996) found that the best predictors of poor psychological morbidity were frequent use of amphetamines in the past six months, injecting amphetamines rather than snorting or swallowing them and the self-report of psychological symptoms prior to drug use. Similarly, Vincent and colleagues (1999) found that the factors that were significantly associated with mental health problems occurring since the first use of amphetamines were severity of amphetamine dependence; number of mental health problems predating first use of amphetamines; recent amphetamine use; and frequency of benzodiazepine use.

There is some indication that amphetamine use is associated with higher rates of mental health problems compared to other psychostimulant users (e.g., cocaine). In a community sample of drug users with relatively low levels of dependence, psychostimulant use was associated with a range of adverse events. Further, amphetamine use was associated with the greatest number and most severe adverse events such as sleep disturbances, paranoia, depression, anxiety and irritability compared to ecstasy and cocaine use (Williamson, Gossop, Powis, Griffiths et al., 1997). Rawson et al., (2000) compared medical and psychiatric symptoms at admission for methamphetamine users (n=55) and cocaine users (n=224) who presented to treatment from 1989–1995. Hallucinations were reported by over a third of methamphetamine users compared to a quarter of cocaine users; approximately 20% of methamphetamine users were rated as severely depressed compared to 12% of cocaine users and 7% of methamphetamine users reported suicidal ideation compared to 3% of cocaine users. Whilst there was no difference in retention in treatment between the two groups, a later paper (Rawson, Huber et al., 2002) reported that the methamphetamine users appeared to experience a longer period of depressive symptoms after cessation of use.

One factor that has been proposed as contributing to the apparent higher rate of psychological symptoms in current amphetamine users compared to cocaine users is the differential duration of action with the relatively short half-life of cocaine (40–60 minutes) compared to methamphetamine (approximately seven hours) contributing to the increased symptoms (Rawson, Huber et al., 2000). However, it is also possible that there may be differences in rates of a primary mood disorder that predate drug use. Using data from the Drug Abuse Treatment Outcome Studies (DATOS), Rieman et al., (2002) found partial support for this hypothesis with higher rates of depressive symptoms in amphetamine/methamphetamine users (35%) compared to cocaine users (26%) at intake. However, they found no evidence that these depressive symptoms persisted after cessation of drug use in either amphetamine/methamphetamine users or cocaine users.

Presentation and clinical course

Psychostimulant users may experience a range of anxiety and mood symptoms that are due to the direct effect of the drug during intoxication and withdrawal. High dose, regular use of psychostimulants produces dependence that is followed by a withdrawal syndrome on discontinuation of the drug. Whilst many of these symptoms are of short duration, four to five days, a number of studies suggest that some of the symptoms may continue for several weeks (e.g. Cantwell & McBride, 1998). It appears that these withdrawal symptoms fall into three groups, those related to hyperarousal such as craving, agitation and dreams, those related to reversed vegetative features such as loss of interest or pleasure and slowing of

movement and, finally, those related to anxiety (Srisurapanont et al., 1999a). Dysphoric mood is also noted to be a major feature of the withdrawal syndrome.

Symptoms of withdrawal associated with amphetamine use are usually strongest within the first week after the initial 'crash' or 'come-down' from amphetamines and then wane over the following weeks. Most withdrawal symptoms abate between one and three months after cessation of amphetamine use. Clearly, further work is required to investigate the reliability of this grouping of symptoms and, more importantly, to determine the course of the withdrawal syndrome to ascertain which features are more enduring and should be medicated.

Whilst both mood symptoms and anxiety symptoms can occur during psychostimulant intoxication and psychostimulant withdrawal (see Chapter 7: *Psychostimulant withdrawal and detoxification*), there are occasions when the symptoms are considered to be in excess of those usually associated with either intoxication or withdrawal and warrant independent clinical attention (American Psychiatric Association, 1994). Under these circumstances, the DSM-IV (American Psychiatric Association, 1994) provides diagnostic categories that allow for the substitution of Psychostimulant Withdrawal with either Psychostimulant-Induced Mood Disorder or Psychostimulant-Induced Anxiety Disorder. A prominent and persistent disturbance in mood must dominate the clinical picture and there must be clear evidence that the symptoms developed during or within one month of substance intoxication or withdrawal for a diagnosis of Psychostimulant-Induced Mood Disorder. Similarly, there must be prominent anxiety, panic attacks, obsessions or compulsions dominating the clinical presentation with evidence that such symptoms developed during or within one month of substance intoxication or withdrawal for a diagnosis of Psychostimulant-Induced Anxiety Disorder.

Pharmacological treatment of mood and anxiety symptoms during withdrawal

There has been a substantial research effort directed at determining effective medications for cocaine dependence and withdrawal with a primary focus on the treatment of mood and anxiety that occurs on cessation of use. As the severity of cocaine withdrawal symptoms is predictive of retention in treatment and (short-term) abstinence (Kampman et al., 2001), an individualised symptom-focused approach may be necessary. Chapters 7 and 8 review the evidence for the effectiveness of pharmacological treatment during withdrawal.

There has been little focus on possible pre-existing mood disorders that may persist beyond withdrawal and require a long-term intervention. A complex issue for research in this area is to be able to differentiate between patients with a pre-existing disorder at the start of treatment and then, in turn, ascertain whether pharmacological management of a comorbid mood or anxiety disorder improves prognosis.

Assessment of comorbidity in psychostimulant users

Determining an accurate diagnosis in people with co-occurring severe mental illness and substance use is a complex task. In the first instance, the clinician needs to take a careful history of psychiatric symptoms and the use of substances (see Table 15). Having established the temporal relationship between the onset of substance use and symptoms it is then possible to determine whether there have been changes in substance use over time, e.g., periods of abstinence or increased use and the impact

that this had on symptoms. Zimberg (1999) developed a helpful typology to guide clinical practice. He distinguishes between three subgroups of comorbidity. The first, referred to as Type I: Primary psychiatric disorder, describes the case of a person whose psychiatric disorder clearly began before regular substance use and the substance use disorder is influenced by the course of the psychiatric disorder. One example may be of a person who uses amphetamines only during a manic episode. Type II: Primary substance use disorder occurs when the substance use clearly existed prior to the onset of the psychiatric disorder and the psychiatric symptoms are present only during active phases of substance use. Finally, Type III: Dual primary disorder occurs when both psychiatric and substance use disorders are present and do not coincide with one another in either onset or course.

Table 15: Prompts in assessing the comorbidity of substance use disorder and psychiatric illness

- **Ask for recent drug and alcohol use.**
- **Consider the range of symptoms that the use of each identified substance may cause.**
- **Determine whether substance use predated the psychiatric symptoms:**
  a. **How old were you when you first experienced ... (symptoms)?**
  b. **How old were you when you started using (substance) regularly[1]?**
- **Has there been a time when you have not used (substance)?**
  c. **(If YES) How did this affect your (symptoms)?**
- **Has there been a time when you have not experienced (symptoms)?**
  d. **(If YES) How did this affect your use of (substance)?**

Adapted from Shaner, Roberts, Eckman, Racentein et al. (1998);
[1] regular use defined as at least weekly use of substance.

In the case of psychostimulant use, both withdrawal and intoxication states have many similarities with mood and affective disorders. Amphetamine withdrawal is characterised by dysphoric mood, fatigue, sleep difficulties and psychomotor retardation, all symptoms that occur in depression. The agitation and anxiety that often occurs during psychostimulant intoxication and withdrawal share many features of an anxiety disorder (American Psychiatric Association, 1994). Symptoms that are similar to hypomania and mania can also be seen during amphetamine intoxication. If these symptoms clearly follow a substantial period of amphetamine use, for example, and remit over a two-week period, then a diagnosis of amphetamine-induced anxiety disorder or amphetamine-induced mood disorder is appropriate (Larson, 2002). Repeated, high-dose binge patterns of amphetamine use can result in a psychostimulant-induced psychosis that closely mimics symptoms of paranoid schizophrenia (Segal & Kuczenski, 1997, 1999). If the symptoms resolve within a one-month period after the discontinuation of amphetamine use, then a diagnosis of amphetamine-induced psychosis is appropriate with either delusions or hallucinations listed as the predominant symptom (American Psychiatric Association, 1994). However, it is not always possible to distinguish at presentation whether the symptoms are drug-induced or are indeed part of a primary and pre-existing disorder that may have been exacerbated by substance use (e.g. Shaner et al., 1998).

The DSM-IV (American Psychiatric Association, 1994) provides diagnostic criteria that will enable a clinician to ascertain whether the patient is experiencing a substance-induced mental disorder. As the use of structured diagnostic interviews provides more accurate diagnoses than less structured clinical interviews across a range of disorders (e.g. Miller, Dasher, Collins, Griffiths & Brown, 2001), we recommend that such interview schedules are used whenever possible. Two possible diagnostic interviews are the Structured Clinical Interview for DSM (SCID, Spitzer et al., 1994) and the Composite International Diagnostic Interview (CIDI) developed by WHO (Wittchten, 1994). Both structured interviews are widely used in research settings, they are less often used in clinical settings although diagnostic accuracy is always enhanced when they are used. Thorough training in the administration of either structured interview is necessary in order to ensure that overall diagnostic accuracy is achieved (Ventura, Liberman, Green, Shaner & Mintz, 1998). Training in the administration of the CIDI can be obtained from the Clinical Research Unit for Anxiety Disorders, St. Vincents Hospital in Sydney, New South Wales (URL:http://www.unsw.edu.au/crufad/cidi/cidi.htm).

Once the presence or absence of particular symptoms has been established, it is often helpful to assess the severity of symptoms in order to quantify symptom change over time. The use of valid and reliable instruments that are sensitive to change over time is strongly recommended. Whilst a comprehensive review of potential measures is beyond the scope of this chapter, we have provided a brief overview of some available symptom measures that are widely used.

Symptom severity ratings for psychosis include the Positive and Negative Symptoms Scales (Kay, Opler & Lindenmayer, 1988) and the SANS and the SAPS (Kay et al., 1988). One of the most widely used is the Brief Psychiatric Rating Scale. The Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) is a clinical rating scale widely used in psychiatric practice. Ratings for each symptom are made after a brief (15-20 minutes) semi-structured interview. Each item is rated on a 7-point scale ranging from 'not present' to 'extremely severe'. The BPRS is a reliable and valid measure of symptom severity when used by trained mental health clinicians. There are also a number of measures for mood and anxiety symptoms. One such instrument that has been developed in Australia and is readily available is the Depression and Anxiety Stress Scales (Lovibond & Lovibond, 1995). Those in the public domain which may be used without cost but with due acknowledgement of their source are described in detail in Dawe et al. (2002).

There are a number of settings where psychostimulant users may present with clinically significant levels of psychotic or mood and anxiety symptoms in which the clinician is not able to conduct a structured diagnostic interview. Such settings may include needle and syringe programs, primary care settings, community mental health services or emergency departments. A screening instrument is particularly useful if the client presents with some or all of the following:

- a strong family history of a mood disorder;
- if there is a clear pre-existing history of a mood disorder; and
- if the individual has ongoing significant affective symptoms after one month of abstinence.

The use of screening instruments such as the General Health Questionnaire (GHQ) is recommended to determine whether there are mood or anxiety disorders. In relation to determining possible psychosis or sub-clinical symptoms of psychosis a Psychosis Screener (Jablensky, McGrath, Castele, Gureje et al., 2000) may also be administered (see Table 16). In addition, below are some helpful practical tips adapted from the "Users' guide to speed" (see Table 17) (Topp et al., 2001). Practitioners treating methamphetamine users may also find it helpful to train their clients to recognise the early signs of drug-induced psychosis and to cut down their use in response to these signs and seek medical help if necessary.

Once the presence or absence of particular symptoms has been established, it may be helpful to ascertain whether there is a pre-existing disorder and to assess the severity of symptoms in order to quantify symptom change over time. The use of valid and reliable instruments that are sensitive to change over time is strongly recommended. Whilst a comprehensive review of potential measures is beyond the scope of this chapter, we have provided a brief overview of some available symptom measures that are widely used.

Table 16: Psychosis Screener from Jablensky et al. 2000

(i) Delusional mood

(a) Has the person ever felt something strange, unexplainable was going on?

0 = No

1 = Yes ☐

(b) If yes, was this so strange that others would find it very hard to believe?

0 = No

1 = Yes ☐

(ii) Grandiose delusions

(a) Has the person ever believed they have special powers, talents that most people lack?

0 = No

1 = Yes ☐

(b) If yes, do they belong to a group that believes they have special powers, talents?

0 = No

1 = Yes ☐

(iii) Delusions of reference/persecution

(a) Has the person ever felt people were too interested in them?

0 = No

1 = Yes ☐

(b) If yes, did they feel harm might come to them?

0 = No

1 = Yes ☐

(iv) Delusions of control

(a) Has the person ever felt thoughts were directly interfered with, controlled by others?

0 = No

1 = Yes ☐

(b) If yes, did this happen in a way others would find hard to believe, e.g. telepathy?

0 = No

1 = Yes ☐

(v) Hallucinosis

(a) Has the person ever heard voices or had visions when there was no-one around?

0 = No

1 = Yes ☐

(vi) Diagnosis of Psychosis

(a) Has the person ever been prescribed psychotic medicine, diagnosed as psychotic by a doctor?

0 = No

1 = Yes ☐

Please specify: _____

(vii) Rating of Psychosis by Key Worker

(a) Using clinical judgement, is this person psychotic or has ever been psychotic?

0 = Definitely not

1 = Possibly

2 = Definitely

Additional comments:_____

_____

NOTE: The cut-off point applied for recording a person as screen positive for psychosis is at least 2 positive items (Items 1–6) subject to the following provisos:

- **'yes' to item 6 only and 'definitely positive' to item 7 = positive for psychosis;**
- **'yes' to item 6 and 'yes' to one other item 1- item 5 and 'maybe' in item 7 = positive for psychosis;**
- **'yes' to item 6 only and 'possibly' in item 7 = negative for psychosis.**

If the clinician considers the person to have screened positive for psychosis, then ensure that appropriate referral is made.

Table 17: Tips for speed users (adapted from Topp et al., 2002)

Have a break from speed if you:

- **Keep having odd thoughts that won't go away.**
- **Feel overly suspicious of your friends or other people.**
- **Are imagining things that aren't really there — seeing things that other people can't see or hearing things other people can't hear.**
- **Often feel like other people are noticing you so that you begin to avoid people, especially strangers in public places.**
- **Feel extreme jealousy.**
- **Have used speed for more than three days in a row or have used it more than three weekends in a row.**
- **If you are feeling anxious or depressed avoid using more speed, these may be warning signs of speed psychosis.**
- **Try to get a few good nights sleep.**

Factors affecting the reliability of self-report

As with any clinical assessment, the accuracy of the information obtained during the history is influenced by a number of factors including the rapport established between the client and the interviewer and the context or circumstances surrounding the interview. Additional factors need to be considered, however, in the case of a client with both a substance use disorder and suspected co-occurring mental health problems. Recent drug use and accompanying intoxication or the severity of withdrawal symptoms will influence the client's attention and concentration. Further, the presence of symptoms associated with psychosis will influence the amount of information a client may be prepared to divulge. For example, symptoms of suspiciousness and hostility that are sub-clinical symptoms of psychosis may reduce the likelihood of obtaining accurate information. The presence of acute psychotic symptoms such as delusions and hallucinations may reduce this even further. Managing the clinical situation and appreciating that aggressive or hostile features of the presentation may be due to a direct effect of amphetamine use rather than indications of other enduring personality features is always necessary. Whenever possible, interviews should be conducted across a period of days to determine the course of such features.

Quantitative measures of alcohol and other drug use

Obtaining information on drug consumption using well-validated and reliable instruments is good clinical practice. However, there are relatively few measures from the substance use field that have been validated in people with amphetamine use disorders. The Timeline Follow Back (TLFB, Sobell & Sobell, 1992) uses a calendar method to provide memory aids to help people reconstruct their recent drinking and drug use patterns and typically covers the last 30 days of use. This method has been used successfully in samples of people with schizophrenia-spectrum disorders (Carey, 1997), in people with cannabis use and early onset psychosis (Hides, Dawe, Kavanagh & Young, unpublished) and in amphetamine users attending a needle and syringe exchange program (Dawe, Saunders et al., unpublished). While the TLFB method provides a detailed picture of recent drug use, additional information regarding the age of onset of all substance use, age of regular use and periods of abstinence are also necessary. A more detailed description of other standardised measures of drug and alcohol use may be found in Carey et al., (Carey, 2002; Carey & Correia, 1998) and Dawe et al. (2002).

In addition to assessing recent frequency of use, it may be wise to consider severity of dependence. Diagnostic criteria for dependence can be found in the DSM-IV and ICD-10 under substance use disorders (see Chapter 1: *Background to the monograph*). A simple way to obtain an estimate of the current level of dependence is by using the Severity of Dependence Scale (see Table 18). This five-item scale has been validated against DSM-IV criteria for dependence and a cut-off score of greater than four was found to correspond to a diagnosis of severe amphetamine dependence (Topp & Mattick, 1997a).

Table 18: Severity of Dependence Scale (adapted from Gossop et al., 1995)

(i)	**Have you ever thought your speed use is out of control?**			
	Never (0)	**Sometimes (1)**	**Often (2)**	**Always (3)**
(ii)	**Has the thought of not being able to get any speed really stressed you at all?**			
	Never (0)	**Sometimes (1)**	**Often (2)**	**Always (3)**
(iii)	**Have you worried about your speed use?**			
	Never (0)	**Sometimes (1)**	**Often (2)**	**Always (3)**
(iv)	**Have you wished that you could stop?**			
	Never (0)	**Sometimes (1)**	**Often (2)**	**Always (3)**
(v)	**How difficult would you find it to stop or go without?**			
	Never (0)	**Sometimes (1)**	**Often (2)**	**Always (3)**

Total Score: _____

Psychosocial approaches to comorbid psychiatric disorders and psychostimulant use

Comorbid psychiatric and substance use disorders can be treated sequentially (one disorder is treated before the other), in parallel (two separate disorders are treated by two different treatment teams) or within an integrated treatment model in which both disorders are treated within the context of a single treatment program (Minkoff, 1989). Integrated treatments among people with psychotic disorders and substance abuse or dependence have been shown to be more effective to parallel or sequential approaches (Drake, Yovetich, Bebout, Harris & McHugo, 1997). A recent randomised controlled trial (Barrowclough, Haddock, Tarrier, Lewis et al., 2001) compared routine care and routine care plus an integrated intervention, addressing motivation for change and CBT for psychotic symptoms, plus family sessions and practical assistance. The mean percentage of change in days abstinent from all substances was greater in the integrated group. In practice, the primacy of psychiatric and substance use disorders is difficult to disentangle and both the psychiatric disorder and the substance use disorder should be addressed (Kavanagh, Mueser & Baker, in press). In acute settings, priority is given to treating symptoms that may be life threatening, for example, suicidal behaviour and integrated treatment for the psychiatric disorder and substance use may follow, once the immediate crisis has resolved. All clinicians working in the mental health and AOD fields should have sound suicide risk assessment skills and know when to appropriately refer to a specialist service when and if it is required.

Integrated treatments for depression and substance use problems are currently being investigated in several randomised controlled trials in Australia. Integrated psychotherapy and pharmacotherapy treatments have been advocated for psychostimulant dependence (Stitzer & Walsh, 1997) and for comorbid psychiatric and substance use disorders (Carroll, 1997) with the aim of broadening and enhancing outcomes.

Integrated interventions for comorbid psychostimulant use and anxiety disorders have not been widely researched. A small uncontrolled study by Brady and colleagues (Back et al., 2001; Brady et al., 2001) evaluated a treatment program for people with post-traumatic stress disorder (PTSD) and comorbid cocaine dependence that included imaginal and in vivo exposure for PTSD and CBT for cocaine dependence (see Chapter 5: *Psychosocial interventions* for a description of CBT for cocaine dependence). The dropout rate was high (38.5% attended at least 10 of 16 therapy sessions), but large effect sizes for both disorders were reported for those who remained in treatment.

Many psychostimulant users, particularly those whose use is harmful or hazardous, may benefit from short interventions such as MI. It may be possible to extrapolate from research performed among people with psychiatric disorders using drugs other than psychostimulants. Hulse and Tait (2002) have reported results of a randomised controlled trial of a brief motivational intervention among psychiatric in-patients who were drinking at a hazardous but not dependent level. At 6-month follow-up, the MI group reported a significantly greater reduction in weekly consumption of alcohol compared to an education group. MI has been found to be effective among people with psychotic illnesses and substance use disorders (Baker & Hambridge, 2002; Kavanagh, Young, White, Saunders et al., in press) and can be employed to enhance engagement in treatment for mental health problems (Baker & Hambridge, 2002).

As part of the National Comorbidity Project Workshop, Kavanagh outlined principles for the development of treatments and services that are applicable to all people with psychiatric and substance use disorders (Teesson & Burns, 2001):

(i) effective management of comorbidity is likely to be cost-effective;

(ii) service deployment should take into account factors such as the prevalence of disorders (e.g. anxiety and depression are common conditions) and the impact of substance use (e.g. amphetamine use may have stronger impact on people with schizophrenia);

(iii) treatment services need to be responsive to heterogeneity in the type and severity of comorbidity and changes in presenting problems and motivation to change, and for treatment over time;

(iv) treatment services need to be able to address multiple morbidities;

(v) confrontation and punitive communication styles should be avoided in the interests of improving engagement and retention in treatment; and

(vi) existing treatments for individual disorders are likely to be useful in comorbidity, with more modifications needed among people with severe disorders.

In order for services to meet these principles, adequate resourcing for mental health and AOD service staff will be needed to ensure adequate training, supervision and ongoing referral, consultation, liaison and collaboration in service delivery.

Monitoring of service outcomes and the effectiveness of training and supervision on client outcomes should be a priority.

Conclusion

Symptoms of comorbid disorders are common among psychostimulant users, as they are among other types of drug users. The most commonly documented comorbid conditions are drug-induced psychosis, depression and anxiety. Well-validated screening, diagnostic instruments and symptom checklists are available and their use is strongly recommended.

Overall, there is a paucity of research on the effectiveness of diagnosing and treating comorbid conditions among psychostimulant users and few well-controlled evaluations of specific interventions for comorbid conditions among psychostimulant users per se. Consequently, it is not possible to recommend any specific interventions for comorbid conditions at this point, although a general recommendation would be to encourage diagnosis and integrated treatment of comorbid conditions among psychostimulant users.

Chapter 11

Psychostimulant use in pregnancy and lactation

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Key points — drug use in pregnancy and breast-feeding

- While many drugs can induce pharmacological effects in the foetus during pregnancy, including foetal toxicity in third trimester, the number of drugs able to cause congenital malformations is small.
- Many factors (e.g. pattern of drug use or dose in relation to gestational age) influence potential drug effects on the foetus rather than drug use per se.
- It is prudent to avoid binge administration of psychostimulants during pregnancy.
- If drug use occurs once daily or less frequently, infant exposure to the drug can be minimised by breast-feeding just prior to the dose and avoiding feeding for a minimum of two to three hours after the dose.
- If drug use occurs more frequently (many times per day or in a binge), it is sensible to avoid breast-feeding during these times. If ongoing breast-feeding is desired, milk may be expressed and discarded during times of heavier use.

Key points — cocaine use during pregnancy and breast-feeding

- Cocaine does not possess any specific teratogenic effects.
- Cocaine use during pregnancy may increase the risk of abruptio placenta and premature rupture of membranes.
- Women who use cocaine are at higher risk of a range of obstetric complications such as reduced birth weight — most of these outcomes are not specific to cocaine but influenced by other drug use and lifestyle factors.
- Exposure to cocaine in utero may influence prenatal brain development, but the clinical significance of these changes is unclear.
- Children who were exposed to cocaine in utero may experience cognitive or behavioural deficits during childhood, but there is insufficient evidence to attribute these deficits to cocaine.
- Risk of neonatal withdrawal symptoms and other adverse events may be minimised by avoiding regular use in late third trimester.
- The American Academy of Paediatrics considers use of cocaine incompatible with breast-feeding.
- To minimise infant exposure to cocaine via breast milk, feeding should occur just prior to or as long as possible after the dose.

Key points — amphetamine use during pregnancy and breast-feeding

- Amphetamine use in controlled doses during pregnancy is unlikely to pose a substantial teratogenic risk.
- Binge dosing of amphetamines during pregnancy is not recommended.
- Women who use amphetamines are at higher risk of a range of obstetric complications such as reduced birth weight — many of these outcomes are not specific to amphetamines but influenced by other drug use and lifestyle factors in addition to amphetamine use.
- Exposure to amphetamines in utero may influence prenatal brain development, but the nature of this influence and potential clinical significance are not well researched.
- Risk of neonatal withdrawal symptoms and other adverse events may be minimised by avoiding regular use in late third trimester.
- To minimise infant exposure to amphetamines via breast milk, feeding should occur just prior to or as long as possible after the dose.

Key points — ecstasy use during pregnancy and breast-feeding

- Existing evidence suggests that use of MDMA during first trimester poses a potential teratogenic risk. It is strongly recommended that use of MDMA be avoided during the period of organogenesis (between week two and week eight post conception or between week four and week ten using an obstetric calendar).
- Limited information exists about the other possible pregnancy effects of MDMA.
- MDMA will enter breast milk. Until clinical outcomes data is available, it would be prudent to avoid breast-feeding during times of MDMA use.

Key points — management of the pregnant and lactating psychostimulant user

- Even if psychostimulants have been used in the earlier stages of pregnancy, there are possible benefits for reducing or ceasing use in the later stages of pregnancy.
- Reduction of other substance use, especially nicotine and alcohol, can improve neonatal and early childhood outcomes.
- Provision of good antenatal care with interventions to improve maternal nutrition and reduced psychological distress may improve neonatal outcomes.
- Avoid breast-feeding during periods of heavy psychostimulant use.
- Provision of parenting interventions may have a positive impact on childhood outcomes.

Introduction

Epidemiological surveys suggest that 30% to 60% of women will take at least one medication during pregnancy (Cordero & Oakley, 1983). It is difficult to estimate what proportion of pregnant women may be taking psychostimulants (amphetamines, amphetamine derivatives such as MDMA, or cocaine) during their pregnancy. In the National Household Survey on Drug Abuse conducted in the USA (Ebrahim & Gfroerer, 2003), 2.8% of pregnant women reported that they used illicit drugs, and one-tenth of these were using cocaine. In an Australian study

describing characteristics of 96 infants born within a chemical dependence unit (Kelly, Davis & Henschke, 2000), 6% of mothers were using amphetamines alone and 66% were using intravenous drugs and receiving methadone maintenance. However, it was not stated what proportion of this latter group were using psychostimulants. Up to 10% of the Australian population has reported use of a psychostimulant and usage is increasing (Topp, Kaye et al., 2002). It is therefore likely that rates of concurrent psychostimulant use during pregnancy will increase.

Health professionals are often asked for advice on the safety of drugs (licit or illicit) during pregnancy and lactation. Generally, drug use during pregnancy is an issue that is associated with high levels of anxiety. Despite this, the numbers of drugs associated with teratogenicity are few. In order to best assess the risks of drug ingestion and make appropriate recommendations, it is necessary to have an understanding of: (i) changes in maternal physiology during pregnancy; (ii) developmental phases of the embryo; (iii) the variable effect that the same drug may have at different times during the pregnancy; and (iv) mechanisms of drug transfer into breast milk.

Part I of this chapter reviews the above four areas. In part II of this chapter, the impact of different psychostimulants on the foetus is reviewed. Part III provides an overview of the management of pregnant and lactating psychostimulant users.

Part I: Pathophysiological considerations

Pregnancy associated changes in maternal physiology

Pregnant women experience a number of physiological changes that can impact on drug pharmacokinetics (Table 19). They have increased cardiac output and renal function. In addition to increased body weight, high hormone levels and fluid retention, pregnant women also exhibit increases in plasma volume. In contrast, there is a decrease in plasma albumin and intestinal motility (Tuchmann-Duplessis, 1977). Because of this, drugs with a high renal clearance may need to have their dosage increased, while drugs with a high hepatic clearance require no dose change (as maternal liver size and hepatic blood flow remain unchanged). In addition, emesis, constipation and iron deficiency are common (Llewellyn-Jones, Abraham & Oats, 1999).

Table 19: Pregnancy associated physiological changes (Chamberlain & Broughton-Pipkin, 1998; Tuchmann-Duplessis, 1977)

In pregnancy:	Increased	Decreased
Cardiac output	+	
Renal function	+	
Body weight	+	
Sex hormone levels	+	
Fluid retention	+	
Plasma volume	+	
Plasma albumin		+
Intestinal motility		+

Stages of foetal development

Clinicians use an obstetric calendar for clinical convenience, where day 0 is defined as the date of the last menstrual period. However, when considering potential drug effects on the foetus, it is more accurate to define day 0 as the moment of conception (approximately two weeks prior to the last missed menstrual period).

Pre-implantation

After fertilisation of the ovum, the embryo takes about 10 to 14 days for implantation in the uterus to occur. Prior to implantation, the embryo (or blastocyst) floats freely in endometrial fluid, depending on uterine secretions for nutrition. During pre-implantation, exogenous agents can become toxic to the blastocyst. However, lack of organ formation precludes the development of organ specific foetal anomalies. Slight injuries to the blastocyst can be overcome without harmful sequelae since the cells retain their ability to segment and produce varied cell lines. At this stage, the woman is usually unaware she is pregnant and inadvertent drug ingestion may occur. Provided she has taken the drug before implantation (roughly prior to her expected menstrual period), there will be little danger of malformations.

Teratogenic period

Once the embryo has implanted, it undergoes very rapid and important transformations (Table 20) (Chamberlain & Broughton-Pipkin, 1998; Tuchmann-Duplessis, 1977). Most organ and tissue differentiation takes place between week three (implantation) and week eight. This is the potential teratogenic period when drug exposure, in sufficient doses, has the potential to cause gross and irreversible malformations. Teratogens taken during this period only affect the vulnerable organ or tissue if drug exposure occurs as the organ is being formed. Thus, exposure to thalidomide after week eight (post-conception) has not been associated with adverse effects such as phocomelia.

The foetal period

The foetal period begins at the end of week eight. This is a time of relative drug safety as organ differentiation is largely complete. Thus, drugs given during the foetal period do not cause major malformations. However, CNS development continues throughout pregnancy and for some months after birth; the possibility of drugs producing subtle effects on neural development cannot be excluded (American Academy of Pediatrics Committee on Drugs, 2001). In addition, the foetus demands considerable nutrition for normal growth and development to occur. Drugs that decrease the flow of oxygen and nutrients to the foetus (e.g. vasoconstrictors such as amphetamines and nicotine) have the potential to cause intrauterine growth retardation (Zuckerman, Frank, Hingson, Amaro et al., 1989) and should therefore be avoided during mid pregnancy.

Table 20: Key organ differentiation in first trimester (Tuchmann-Duplessis, 1977)

	Drug impact on foetus	Weeks post conception
FIRST TRIMESTER		
Pre-Implantation		
No organ differentiation.	**Minimal**	**</= Week 2**
Transformation		
Development of neural groove (from which spinal cord and brain develop). Heart begins to form.		**Week 3**
Gut differentiates into fore and hind gut. Optic vessels, liver and pancreas form. Limb buds (arms and legs) develop.	**Potential for teratogenicity**	**Week 4**
Eyes and olfactory organs develop. Heart divides into different cavities.		**Week 5**
Limbs grow and differentiate. Heart structures completely form. Anal membrane ruptures. Bones begin to develop. Sex is determined.		**Weeks 5–8**
Effects primarily on nutrition and growth.	**Minimal**	**Weeks 9–11**
SECOND TRIMESTER		
Effects primarily on nutrition and growth.	**Minimal**	**Weeks 12–24**
THIRD TRIMESTER		
Drug accumulation and associated toxicity reported.	**Foetal toxicity**	**Week >/=24**

Third trimester

In third trimester, the foetus prepares to function independently of its mother. He or she gradually adapts to performing more of its own nutrient and toxin elimination. However, by 26 weeks gestation, the foetal half-life of many drugs is still up to twice that of the mother. Thus, it is not surprising that drug accumulation and potential for foetal toxicity occur in late third trimester. Drugs that are lipophilic or with long half-lives are more likely to cause foetal toxicity. Many psychostimulants fall into this category. The major consequences of psychostimulant accumulation in the foetus are the potential to influence labour and for the development of neonatal withdrawal symptoms postpartum.

Prevalence of birth defects

Approximately 2% of all births in Australia are associated with congenital malformations (National Perinatal Statistics Unit, 2001). Discovery of internal organ anomalies may not be noticed until later life, which may double the prevalence statistic. Whilst most gross abnormalities cannot be attributed to any specific cause, genetic influences and chromosomal abnormalities have been estimated to cause about 20% of these malformations while environmental factors in the uterus

(poor maternal nutritional status, poor folate status, diseases such as diabetes or infection) account for about 10%. Drug ingestion is believed to cause an additional 3% of birth defects, although this may be underestimated due to poor recall and reporting of medicine ingestion (Iams & Rayburn, 1982). For a drug to be implicated as a teratogen, it must therefore cause a dose-related, consistent pattern of anomaly, with an incidence higher than the population 2%.

Classification of drug risk in pregnancy

The Australian Drug Evaluation Committee's (ADEC) classification on medicines in pregnancy is internationally recognised (Table 21) (ADEC, 1999). This drug risk classification system is similar to those developed in Sweden and by the Food and Drug Administration in the USA. Despite the thousands of medicines marketed internationally, there are few (less than 25) proven teratogens. In this categorisation of drugs commonly used in Australia, ADEC has included two psychostimulants — dexamphetamine as category B3 and methylphenidate as category B2. It should also be noted that the categorisation of an individual drug, assigned by the manufacturer and listed in their approved product information, might differ from the ADEC categorisation.

Table 21: ADEC categorisation of drugs in pregnancy (ADEC, 1999)

A	**Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.**
B	**Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformations or other direct or indirect harmful effects on the human foetus having been observed. As experience of effects of drugs in this category in humans is limited, results of toxicological studies to date (including reproduction studies in animals) are indicated by allocation to one of three subgroups:**
B1	**Studies in animals have not shown evidence of an increased occurrence of foetal damage.**
B2	**Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.**
B3	**Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.**
C	**Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.**
D	**Drugs which have caused, are suspected to have caused, or may be expected to cause an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.**
X	**Drugs that have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.**

Breast-feeding

Factors influencing the excretion of a psychostimulant into breast milk can be broadly divided into those relating to the mother, the child and to the drug itself. As with all drugs, psychostimulants have a chemical structure that determines their pharmacokinetic parameters and the extent to which they pass into breast milk. For simplicity, the term drug will be used in describing these processes.

Maternal factors

Breast milk content and yield capacity

Breast milk is a suspension of protein and fat dispersed in an aqueous medium containing carbohydrates and inorganic mineral salts. The extent to which psychostimulants diffuse into the milk depends on fat content, which varies during the day, with duration of lactation, frequency of feeding and the volume of milk produced by the mother (Briggs, 2002; Chaplin, Sanders & Smith, 1982; O'Brien, 1974). The ratio of fat to volume of milk tends to be higher toward the end of a feed (hindmilk) compared with the milk available to the infant at the beginning of the feed (foremilk). Larger babies require larger milk volumes (approximately 165 mg/infant kg/day) and therefore may be exposed to higher levels of psychostimulants. If the mother is undernourished or dehydrated, milk supply is likely to decrease.

Milk is separated from maternal plasma by a membrane that allows selective drug movement from plasma to milk and back diffusion. For the most part, drugs pass by simple passive diffusion from a solution of high concentration to that of a lower concentration, until equilibrium is reached or circumstances are changed, such as the mother receiving her next dose (McGuire, Mitchell, Wright & Noordin, 1987; O'Brien, 1974). Active transport may also occur.

Underlying illness

Milk quality may be dependent on maternal wellbeing. If, for example, a mother using psychostimulants is unable to maintain adequate nutrition, hydration status and rest, this may impact on milk quality and quantity (Wilson, Brown, Cherek, Dailey et al., 1980).

Drug parameters

When the mother takes a drug, a proportion of the dose will peak in her plasma. Generally, peak blood levels for oral, non-sustained release dose forms occur within two hours of administration, whereas smoking or intravenous injection produces peak drug levels within minutes.

As the drug reaches peak levels in the blood, the drug will be distributed into various body compartments, including breast milk. Once equilibrium is reached and the drug peaks in the milk, back diffusion takes place; the drug is cleared rapidly from the milk back into plasma and from there cleared by the body. This process is repeated with each new dose. Drug transfer and accumulation into breast milk depends on various factors (Table 22) (McGuire et al., 1987; O'Brien, 1974).

Infant status

Gestational age

The infant's gestational age at birth affects suckling behaviour and duration on each breast, the quantity of milk consumed per feed (130 to 180 ml/infant kg/day) and the interval between feeds (McGuire et al., 1987). The neonate's immature liver enzymes will also decrease drug metabolism and excretion. A premature infant, particularly if of low birth weight, is likely to feed more frequently and for longer, making manipulation of feeds to minimise infant drug exposure through breast milk more difficult.

Time of feeding in relation to maternal dose

On the presumption that the drug is in an immediate release and not a sustained or controlled release dose form, the amount of drug transferred into the milk of a breast-feeding mother may be limited or reduced by the following strategies (Anderson, 1977; Berlin, 1981; Wilson et al., 1980).

If the drug is taken once daily, it should be taken around the time of the feed to allow the longest period of time to elapse until the next feed. Often, this would be at the time of the last feed at night to allow the maximum time for maternal drug elimination. Controversy exists over whether it is best to take a drug immediately before, during or immediately after the feed; whichever is most practical should be chosen.

If the drug cannot be taken as a single daily dose, feeds and drug consumption need to be timed to allow the maximum possible time from administration to the next feed. Usually, for non-sustained release dosage forms, this is best achieved if the mother takes the dose at the next feed. Ideally, the mother should wait at least one half-life after the peak milk concentration is achieved before feeding again as this will significantly decrease (by about 50%) the amount of drug excreted into the milk (Berlin, 1981). Feeding away from the time of the peak milk concentration will minimise the infant's drug exposure. In practice, other factors, such as chaotic lifestyle, may influence a mother's ability to ensure breast-feeding occurs away from peak drug concentrations. Any clinical recommendations should take these factors into account.

Table 22: Drug parameters that impact on drug excretion into breast milk

Parameter	Comment	Psychostimulant Example
Molecular weight	**Molecular weight (MW) determines extent of drug passage through membrane pores between plasma and milk.**	**Amphetamines (base) = 135.2** **Amphetamine sulphate = 368.5** **Methamphetamine HCL = 185.7**
	If MW < 200 — passive diffusion and extensive milk excretion are expected to occur.	**Cocaine = 303.4** **MDMA (free base) = 193.2**
Lipid solubility	**As the drug increases in lipophilicity (less water soluble), passage through the membrane and excretion into the milk increases.**	**Methamphetamine (base) — quite fat soluble** **Methamphetamine sulphate — low fat solubility**
Plasma protein binding (ppb)	**Extent of drug and plasma protein binding determines the amount excreted into the milk.** **Only free, unbound drugs can pass membrane, so highly bound drugs are minimally excreted into milk.**	**Amphetamine ppb = 20% (low)** **Methylphenidate ppb = 15% (low)** **Cocaine ppb = 20%-50%** **MDMA ppb = 35%**
Ionisation	**The membrane separating the milk from plasma favours transfer of drugs in non-ionised (non-dissociated) state. Milk is more acidic than plasma, thus weak bases ionise more in milk than plasma, producing higher milk to plasma (M/P) ratio. Weak acids ionise preferentially in plasma and have a low M/P ratio.**	**Amphetamines, cocaine and MDMA are weak bases** **Amphetamine M/P 2.8-7.5**
	M/P ratio: deceptive parameter for predicting the quantity of the drug excreted into the milk, as it is only measured at the moment in time when the drug peaks in the milk and does not represent the amount retained in the milk over a 24 hour period.	**Milk plasma ratios of most illicit psychostimulants have not been determined**
Elimination half-life ($t_{1/2}$)	**ie. length of time taken for drug plasma concentrations to drop by half. It takes five half-lives for a therapeutic dose to be eliminated from the body.**	**Dexamphetamine $t_{1/2}$ = 16–31 hrs** **Methamphetamine $t_{1/2}$ = 12–34 hrs** **Cocaine $t_{1/2}$ = 1.5 hrs**
	Short half-life means less potential for drug accumulation in milk.	**Benzoylecgonine $t_{1/2}$ = 5 hours** **MDMA $t_{1/2}$ = 9–31 hours**

Table 22: Drug parameters that impact on drug excretion into breast milk (continued)

Parameter	Comment	Psychostimulant Example
Pharmacological activity	**Adverse effects are commonly dose related and may cause unwanted extension of pharmacological activity.**	
Dose/ frequency	**Increased daily dose increases the quantity excreted into the milk.**	
	Maintaining same daily dose but increasing administration frequency does not increase the quantity excreted into the milk, but can increase amount ingested by infant.	

Part II: Profile of individual drugs

In pregnancy, the mechanisms underlying the effects of psychostimulants on the developing foetus are complex. Currently available theories are that they block the neuronal reuptake of catecholamines in the mother, resulting in cardiac stimulation and vasoconstriction. This leads to decreased uterine blood flow and thus to a decrease in the transfer of oxygen and other nutrients to the foetus. In addition to these mechanisms, psychostimulants act on serotonergic or noradrenergic transporters expressed in placental cells (Ramamoorthy, Ramamoorthy, Leibach & Ganapathy, 1995). This may increase levels of monoamines in the intervillous space (further adding to the vasoconstrictive effect) and restricting blood flow to the placenta. Elevation of serotonin and noradrenaline levels occurring via this mechanism may also alter uterine contractility.

If the mother continues to use psychostimulants when breast-feeding, the effects on the infant are variable. While risks of infant exposure are extended, this may be offset by the amelioration of withdrawal symptoms in the first month of life.

Although psychostimulants share a common spectrum of pharmacological activity, it cannot be assumed that their impact on a developing foetus is also the same. For this reason, the following section is separated into individual drugs.

Cocaine

Most of the clinical and animal research conducted into effects of psychostimulants in pregnancy and lactation have focused on cocaine. Cocaine and its metabolites do cross the placenta. Cocaine does accumulate in the placenta (Ursitti, Klein & Koren, 2001), where it may be metabolised by placental microsomes. Whilst this may protect the foetus after bolus administration, placental retention may also prolong foetal exposure.

Cocaine exerts a number of actions on the foetus. Inhibition of noradrenaline reuptake leads to maternal vasoconstriction, which reduces uterine and placental blood flow (Lipton, Vu, Ling, Gyawali et al., 2002; Patel, Laungani, Grose & Dow-Edwards, 1999; Sutliff, Gayheart-Walsten, Snyder, Roberts & Johnson, 1999). Cocaine also has a direct effect on the foetus, resulting in foetal vasoconstriction and other cardiovascular changes (Fomin, Singh, Brown, Natarajan & Hurd, 1999; Shearman & Meyer, 1999; Yakubu, Pourcyrous, Randolph, Blaho et al., 2002).

Cocaine and teratogenic effects

Although a large volume of animal research has examined this issue, there are conflicting results with regard to its teratogenic potential. This is partly due to differences in teratogenic effects between animal species, which highlight the need for caution when extrapolating results from animal research to humans.

In humans, case reports describe a range of congenital malformations occurring in infants exposed in utero to cocaine. These include malformations of the genitourinary tract, heart, limbs and face (Bingol, Fuchs, Diaz, Stone & Gromisch, 1987; Chasnoff, Chisum & Kaplan, 1988; Little, Snell, Klein & Gilstrap, 1989; Viscarello, Ferguson, Nores & Hobbins, 1992).

However, many controlled studies fail to demonstrate such anomalies (Addis, Moretti, Syed, Einarson & Koren, 2001; Frank et al., 2001). In particular, one study reported that women who used cocaine in the first trimester only (which is the teratogenic period), demonstrated similar obstetric outcomes to drug free controls (Chasnoff, Griffith, MacGregor, Dirkes & Burns, 1989). In a large, blinded prospective study (Behnke, Eyler, Garvan & Wobie, 2001), there was no evidence to suggest that cocaine contributes to the development of gross abnormalities in humans. The authors state that "if cocaine does produce human malformations, it seems to do so at a very low rate or only under certain conditions, perhaps related to such events as the amount and timing of the exposure, or to the simultaneous ingestion of other substances" (Behnke et al., 2001).

The number of reports of cocaine-associated malformations is of concern to many clinicians. However, interpreting these studies requires caution due to the lack of a consistent pattern in the anomalies described and the inconsistencies in research results (Buehler, Conover & Andres, 1996). Infants exposed to in utero cocaine may have a higher risk of malformations but evidence to date has failed to consistently link cocaine exposure with organ specific anomalies (teratogenicity).

Other outcomes associated with cocaine exposure during pregnancy

Obstetric complications

A large amount of research has examined the relationship between cocaine use during pregnancy and obstetric outcomes. Although a range of poor obstetric and neonatal outcomes have been attributed to foetal cocaine exposure, research results are conflicting. It is thought that the cardiovascular effects of cocaine (producing maternal vasoconstriction and direct foetal effects) may be the main drug effects influencing obstetric outcomes.

In human studies, cocaine use during pregnancy has been associated with reduced growth such as lower birth weight, reduced length and reduced head circumference (Bada, Das, Bauer, Shankaran et al., 2002; Richardson, Hamel, Goldschmidt & Day, 1999), still birth related to abruptio placenta (Bauer, Shankaran, Bada, Lester et al., 2002; Bingol et al., 1987; Little, Snell, Trimmer, Ramin et al., 1999), intracranial haemorrhage in the neonate (Spires, Gordon, Choudhuri, Maldonado & Chan, 1989) and sudden infant death syndrome (Durand, Espinoza & Nickerson, 1990). Other studies have found no relationship between cocaine exposure and pre-term births (Savitz, Henderson, Dole, Herring et al., 2002), sudden infant death syndrome (Fares, McCulloch & Raju, 1997) or between cocaine exposure and

morbidity associated with pre-term premature rupture of membranes (Refuerzo, Sokol, Blackwell, Berry et al., 2002).

One issue that may influence results of these studies is timing of cocaine exposure. Chasnoff and colleagues (Chasnoff et al., 1989) compared women who had used cocaine in first trimester only with those who continued to use cocaine throughout pregnancy. Those who used cocaine throughout pregnancy had increased rates of pre-term births, low birth-weight infants and intrauterine growth retardation. Those who used cocaine in first trimester only had similar outcomes to a drug free control group.

One of the challenges with interpreting research in this area is that many studies have failed to take into account potential confounding factors (Gressens, Mesples, Sahir, Marret & Sola, 2001). Women who use cocaine whilst pregnant are more likely to use other drugs, especially alcohol and tobacco (Bada et al., 2002; Singer, Arendt, Minnes, Farkas & Salvator, 2000) and are more likely to exhibit other risk factors for poor obstetric outcomes, such as greater levels of maternal distress (Singer, Salvator, Arendt, Minnes et al., 2002), low socio-economic status, low levels of education and poor maternal nutrition (Savitz et al., 2002). As such, only limited conclusions regarding the role of cocaine as the causal agent can be made from such research. One author suggests that nicotine and cocaine produce similar effects on the foetus, but pharmacokinetic characteristics of cocaine and its patterns of use mean that periods of recovery exist and the "eventual consequences are much less severe" when compared with tobacco use (Slotkin, 1998).

One meta-analysis (Addis et al., 2001) attempted to untease the relationship between cocaine exposure and other risk factors. Outcomes assessed included rates of major malformations, low birth weight, premature birth, placental abruption, premature rupture of membranes and mean birth weight, length and head circumference. After adjusting for confounding factors, only the risk of placental abruption and premature rupture of membrane remained attributable to cocaine use.

In a systematic review, Frank and colleagues (Frank et al., 2001) report that there is no convincing evidence that prenatal cocaine exposure confers a greater risk of developmental toxic effects than multiple other factors. They report that although some decrements in measures of physical growth such as birth weight or head circumference are reported after cocaine exposure, once studies have controlled for alcohol or tobacco use, no negative effects of cocaine are observed. Such reports highlight the complexity of interpreting research in this area — many findings once thought to be specific effects of in utero cocaine exposure can be explained in whole or in part by other factors including prenatal exposure to tobacco, marijuana or alcohol and the quality of the child's environment. Birth weights may in fact be improved by the provision of prenatal care (Racine, Joyce & Anderson, 1993). It is likely that there is a complex interaction between dose response effects of the drug, cumulative environmental and other risk factors (Kaltenbach, 2000).

Neurobehavioural development

In addition to cardiovascular effects, cocaine produces a range of neurochemical effects. This has led to concern that prenatal cocaine exposure may influence brain development.

A range of animal studies have been conducted. They report that cocaine exposure may produce abnormal neocortex development (Lidow, Bozian & Song, 2001), lasting metabolic changes within specific brain regions associated with arousal, attention and stress responses (Dow-Edwards, Freed-Malen & Gerkin, 2001), changes in dopaminergic activity (Lipton, Ling, Vu, Robie et al., 1999), changes in circadian activity (Strother, Vorhees & Lehman, 1998) and disruption of short-term memory (Morrow, Elsworth & Roth, 2002). A meta-analysis of research of prenatal cocaine exposure on the development of the nigrostriatal dopamine system in animals (Glatt, Bolanos, Trksak & Jackson, 2000) found that cocaine exposure led to negligible effects on most indicators of dopamine function. Some authors suggest that neurodevelopmental changes observed in animals may explain behavioural changes observed in human studies. However, this has not been adequately explored.

The results of human research into neurobehavioural development have been conflicting. Some clinical research suggests that prenatal cocaine exposure may lead to problem behaviours (Delaney-Black, Covington, Templin, Ager et al., 1998), deficits in attentional processing (Coles, Bard, Platzman & Lynch, 1999), behavioural abnormalities such as jitteriness (Singer et al., 2000), poorer cognitive, motor and language development and reduced emotional responsivity (Singer, Hawkins, Huang, Davillier & Baley, 2001).

In a study examining children at three, five and seven years (Bandstra, Morrow & Anthony, 2001), a stable influence of prenatal cocaine exposure was observed on indicators of sustained attention and task vigilance. These effects were maintained after controlling for prenatal exposure to other substances and additional medical and sociodemographic variables. They also observed a more pronounced effect for children whose mothers had a heavy alcohol intake in addition to cocaine use.

In a prospective study (Morrow, Bandstra, Anthony, Ofir et al., 2001), a range of subtle deficits across the spectrum of neurobehavioural functioning were observed within the first postnatal week in infants with cocaine exposure. These deficits were partly correlated with reduced foetal growth. The deficits in functioning were larger as the number of trimesters of exposure increased. The authors suggest that prenatal cocaine exposure may produce more problematic effects in infants born prematurely and that cocaine exposed full-term infants may be more resilient. Other authors also suggest that any effect of cocaine on longer-term development is an indirect association, mediated by reduced birth weight, head circumference, other drug use or other prenatal issues (Behnke, Eyler, Garvan, Wobie & Hou, 2002; Bendersky & Lewis, 1999). In addition, one controlled study reports that mothers in a cocaine-exposed group had less frequent emotional contact with their infant and tended to have maladaptive coping strategies compared with a non-exposed group (Singer et al., 2001). The authors suggest that interventions targeted at maternal parenting skills may be of some benefit.

Bennett and colleagues (Bennett, Bendersky & Lewis, 2002) found that in utero cocaine exposure was largely unrelated to IQ and adjustment skills at four years, particularly for girls. The systematic review by Frank and colleagues (Frank et al 2001) reports a lack of relationship between cocaine exposure and cognitive performance, behaviour and affect after controlling for alcohol and tobacco use.

In conclusion, it is likely that cocaine use contributes to infant neurobiological and behavioural outcomes in cumulation with other drug exposure, maternal and environmental factors.

Cocaine and ethanol

In animal studies alcohol alone or cocaine alone may lead to reduced foetal weights or foetal mortality (Ohnaka, Ukita, Yamamasu, Inoue et al., 2001). When alcohol is used concurrently with cocaine, liver esterases transesterify cocaine to produce cocaethylene, which is considered a more potent vasoconstrictor than cocaine. As such, it is thought that exposure to a combination of alcohol and cocaine may be more deleterious to pregnancy and foetal outcome than either drug alone (Randall, Cook, Thomas & White, 1999; Snodgrass, 1994).

Cocaine exposure and neonatal withdrawal syndromes

The literature on prenatal cocaine exposure is unclear whether immediate postpartum effects on the infant are transient, related to either acute toxicity of cocaine, or to a withdrawal effect. Infants born after cocaine exposure may exhibit a range of symptoms including tone and movement abnormalities, brisk or excessive reflexes, jitteriness, irritability and poor feeding (Eyler et al 2001). One of the difficulties of interpreting this area of research is the lack of consistent measures used to describe infant behaviours and the frequent inclusion of neonates concurrently exposed to opiates in utero.

In a recent prospective study (Eyler, Behnke, Garvan, Woods et al., 2001) examining 154 neonates with prenatal cocaine, no dramatic effects of toxicity or withdrawal were observed. Deficits in neurobehavioural functioning were minor and improved in most infants within the first week. The presence or severity of a neonatal withdrawal syndrome may be influenced by extent and frequency of exposure during the period immediately prior to parturition.

Cocaine and risk during lactation

Cocaine and its metabolites pass into the breast milk. Chasnoff and Lewis describe a case of cocaine intoxication in a breast-fed infant (Chasnoff, Lewis & Squires, 1987). The baby experienced irritability, vomiting, diarrhoea, tremulousness and seizures subsequent to maternal cocaine. In light of such case reports, the American Academy of Pediatrics Committee on Drugs questions the appropriateness of breast-feeding a baby where the mother is using cocaine (American Academy of Pediatrics Committee on Drugs, 2001).

Amphetamines/methamphetamine

Amphetamines and teratogenic effects

Animal studies have reported that amphetamine use is associated with cardiac malformations (Nora, Trasler & Fraser, 1965) or other malformations (Acuff-Smith, George, Lorens & Vorhees, 1992; Kasirsky, 1971). In humans, there are a number of case reports linking amphetamine exposure with malformations (Gilbert & Khoury, 1970; Matera, Zabala & Jimenez, 1968). One study found a positive relationship between dexamphetamine exposure and heart defects (Nora, Vargo, Nora, Love & McNamara, 1970).

A number of other studies have failed to demonstrate a relationship between malformations and amphetamine exposure (Heinonen, Slone & Shapiro, 1977; Little, Snell & Gilstrap, 1988; Milkovich & van der Berg, 1977; Nora, McNamara & Fraser, 1967). One report from a teratogen information service (Felix, Chambers, Dick, Johnson & Jones, 2000) found that methamphetamine abuse was not associated with increased rates of congenital anomalies. However, exposed infants did have minor physical anomalies, irritability or other signs of neurological dysfunction. This is consistent with theoretical data.

In contrast to these earlier studies, Sherman and colleagues (2000) reported major congenital abnormalities in 16% of infants whose mothers had used methamphetamine, often in combination with alcohol or other illicit drugs. Most of the anomalies found were cardiac defects, but also included gastroschisis and hydronephrosis. It is not established if this rate of anomalies is higher than would be expected. Approximately 5% of infants in the exposed group also had neonatal thrombocytopaenia. Unfortunately, this study was uncontrolled and conducted retrospectively. A recent controlled study examined full-term neonates exposed to methamphetamine in utero (Smith, Yonekura, Wallace, Berman et al., 2003). Although examining foetal growth and withdrawal symptoms were the aims of this study rather than teratogenicity, 134 neonates were assessed to have no malformations or anomalies.

From these studies, it would seem that use of amphetamines in regular low doses (e.g. when prescribed for therapeutic purposes such as ADHD) poses little teratogenic risk. Further research is required to address the possible risk of cardiac malformations and whether dependent or binge patterns of amphetamine use may confer a greater risk to the foetus. Alternatively, any possible increase in negative outcomes associated with amphetamine use may be attributed to causes such as other drug use or environmental factors associated with illicit drug use.

Other outcomes are associated with amphetamine exposure during pregnancy

Obstetric complications

Similarly to cocaine, prenatal exposure to methamphetamine may cause cardiovascular alterations including increased maternal and foetal blood pressure, reduced foetal oxyhaemoglobin saturation and a decrease in uterine blood flow (Nora, 1968). At least some of these effects seem to be dose-related (Yamamoto, Yamamoto, Fukui & Kurishita, 1992).

A number of studies have reported an association between amphetamine exposure and outcomes related to growth retardation such as reduced body weight, reduced length and head circumference at birth (Little et al., 1988; Naeye, 1983; Smith et al., 2003). Other adverse effects include stillbirth (Dearlove, Betteridge & Henry, 1992) and intracranial haemorrhage (Dixon & Bejar, 1989).

Neurobehavioural development

Williams and colleagues (Williams, Vorhees, Boon, Saber & Cain, 2002) report that rats exposed to methamphetamine between postnatal days 11 to 20 developed behavioural and spatial learning impairments. Methamphetamine may lead to alterations in dopaminergic (Heller, Bubula, Freeney & Won, 2001) or serotonergic (Tavares, Silva, Silva-Araujo, Xavier & Ali, 1996) systems. One review (Frost &

Cadet, 2000) suggests that exposure to methamphetamine is likely to produce changes in neural circuitry in a wide variety of brain regions, but assessing the clinical and functional significance of this remains a challenge.

One prospective study examined 65 children who had been exposed to amphetamines in utero (Cernerud, Eriksson, Jonsson, Steneroth & Zetterstrom, 1996). Deficits in learning in children with prenatal amphetamine exposure were observed compared to matched controls.

Amphetamine exposure and neonatal withdrawal syndromes

Neonatal withdrawal syndromes have been reported after methamphetamine exposure (Oro & Dixon, 1987; Ramer, 1974). Symptoms included poor feeding, abnormal sleep patterns, tremors and increased muscle tone. A study on 134 neonates with prenatal methamphetamine exposure reported that 49% of neonates experienced withdrawal symptoms, although only 4% required pharmacological intervention (Smith et al., 2003).

Amphetamines and risk during lactation

Amphetamines are excreted into breast milk and, depending on the dose, measurable amounts can be detected in the urine of the infant. In one study of 103 nursing infants whose mothers were taking amphetamines, no neonatal insomnia or stimulation was observed over a 24 hour period (Ayd, 1973).

MDMA

MDMA is a substituted amphetamine. In addition to a range of amphetamine-like properties, it has a greater range of serotonergic and potentially hallucinogenic properties. There have been limited animal studies exploring the effects of MDMA during pregnancy and within existing research, results have been mixed.

MDMA and teratogenic effects

At this stage, there is insufficient evidence to make firm conclusions about the potential teratogenicity of MDMA. One animal study found no effects of MDMA on rates of malformations (St Omer, Ali, Holson, Duhart et al., 1991). Doses utilised were 0, 2.5, or 10 mg/kg of MDMA.

There are only a few studies on the effects of MDMA on human pregnancy. One case of congenital heart disease was reported in an abstract examining 489 pregnancies (Rost van Tonningen, Garbis & Reuvers, 1998). In another abstract examining 38 pregnancies, one case of congenital heart disease and one possible case of omphalocele were reported (van Tonningen, Garbis & Reuvers, 1998).

The UK National Teratology and Information Service (NTIS) collected prospective follow-up data from 1989 to 1998 on 136 pregnancies following primarily first trimester exposure to MDMA (McElhatton, Bateman, Evans, Pughe & Thomas, 1999). 35% of these women had elective terminations (one after prenatal diagnosis of malformations) and 10% had miscarriages. Of the remaining 78 live-born infants, over 15% had congenital malformations, especially cardiovascular and musculoskeletal anomalies. This is five to sevenfold higher than the expected incidence of 2-3%. Although other factors were not well controlled for, the high rate of anomalies reported in this study indicates a possible association between MDMA

exposure and congenital anomalies. MDMA shares many pharmacological properties with amphetamines. However, its structural differences (namely the methylenedioxy ring substitution) may mean that it displays a different teratogenic profile. Further controlled studies are required in this area.

Other outcomes are associated with MDMA exposure during pregnancy

Obstetric complications

Animal studies have reported that MDMA exposure led to no effect on litter size or birth weight (St Omer et al., 1991) and no effect on body, brain and liver weight (Bronson, Barrios-Zambrano, Jiang, Clark et al., 1994). In contrast, other studies have reported reduced maternal weight gain and litter size (Colado, O'Shea, Granados, Misra et al., 1997) and reduced embryonic motility (Bronson, Jiang, Clark & DeRuiter, 1994).

Although no research has examined the relationship between MDMA and obstetric complications, given that MDMA shares many pharmacological effects with amphetamines, it is likely that MDMA shares similar effects to amphetamines such as intrauterine growth retardation.

Neurobehavioural development

Animal studies have reported that MDMA exposure is associated with increases in serotonergic and dopaminergic markers (Won, Bubula & Heller, 2002) or long-term effects on cerebral function (Kelly, Ritchie, Quate, McBean & Olverman, 2002). Some studies demonstrate vulnerability to MDMA-related neurotoxicity (Meyer & Ali, 2002), whereas Colado and colleagues (1997) reported that although female rats demonstrated signs of neurotoxicity, this was not observed in their offspring.

In another study (Broening, Morford, Inman-Wood, Fukumura & Vorhees, 2001), rats exposed to MDMA in the late stages of pregnancy showed dose-related impairments of sequential and spatial learning and memory, while rats exposed at an earlier time (equivalent to early third trimester) showed no significant impairment. This might suggest vulnerability of the brain to MDMA later in its development but drawing any further conclusions from a single animal study is clearly tenuous.

No studies in humans have been undertaken on the effects of prenatal MDMA exposure on neurobehavioural development.

As discussed in earlier sections, psychostimulant users often display a range of other risk factors associated with poor neonatal outcomes. Ho and colleagues (Ho et al., 2001) compare pregnant women reporting use of MDMA with pregnant women not exposed to MDMA. They report that women using MDMA were more likely to binge drink during pregnancy, use tobacco and other illicit drugs. Pregnancies were more likely to be unplanned and women were more likely to be young, single and experiencing a range of psychological problems. This reaffirms the need to account for a range of confounding risk factors when undertaking research in this area.

MDMA exposure and neonatal withdrawal syndromes

No studies have been identified that examine the potential for prenatal MDMA exposure to produce neonatal withdrawal symptoms.

MDMA and risk during lactation

No case reports were identified that examined MDMA and lactation. However, due to low molecular weight and lipophilicity of MDMA, it would be expected to concentrate in breast milk. Given the lack of clinical outcomes data available, it would be prudent to avoid breast-feeding during periods of MDMA use.

Part III: Management of the pregnant and lactating psychostimulant user

Psychostimulant use during pregnancy is part of a spectrum of complex, high-risk behaviours that have been reported to result in significantly increased complications for both the mother and infant. Even though questions remain about the impact of psychostimulants on the developing foetus or lactating neonate, psychostimulant use during pregnancy may be a marker for subsequent risk of poor child health or impaired care giving. Psychostimulant use during pregnancy may be associated with poor nutrition, poorer socio-demographic characteristics (Savitz et al., 2002), higher rates of both licit and illicit substance use (Bada et al., 2002), less involvement in antenatal care and increased likelihood of being victims of violence (Bauer et al., 2002). These factors (especially smoking, alcohol use and low folate intake) may be more strongly associated with poor pregnancy outcomes than the pharmacological effects of psychostimulants alone.

Management strategies should address both psychostimulant use and the associated risk factors. Pregnant women and mothers who use psychostimulants should be encouraged to seek pre, peri and postnatal care; such care has been shown to optimise infant outcome (Racine et al 1993).

Non-judgmental environments are essential to ensure disclosure of psychostimulant or other drug use and maintain involvement with antenatal and postnatal care. If mothers perceive that they are likely to have their infants removed, then many will either avoid antenatal care altogether or attend but conceal their drug use (Cairns, 2001). Cairns suggests that the goals of antenatal care are to engage the family, stabilise the mother's drug use, assess other areas such as nutrition, poverty, infection, housing and home environment and to educate the mother.

It has been observed (Corse, 1998) that reductions in substance use are less likely to occur if a women enters prenatal care late in her pregnancy and thus there is an important role for encouraging pregnant substance users to seek prenatal care early in their pregnancy. Prenatal care is important; however, it is equally important to continue provision of care and support throughout the postnatal period. This area is not well addressed by the literature.

Psychostimulants do pass into breast milk. The decision to engage in or avoid breast-feeding should be influenced by an individual's pattern of drug use. It is prudent to avoid breast-feeding during periods of heavy psychostimulant use. If use occurs once daily or less frequently, it may be possible to minimise the infant's drug exposure by breast-feeding away from the time of peak milk levels. Patient factors such as personal preferences or presence of a chaotic lifestyle should be considered in clinical decision-making.

Conclusion

Advice on the safety of psychostimulant drugs during pregnancy and lactation should be based on a good understanding of pathophysiological considerations in pregnancy and breast-feeding and the impact of different psychostimulants on the foetus. Management of the pregnant and lactating psychostimulant user should address psychostimulant use and associated risk factors within the context of a non-judgmental environment.

Chapter 12

Clinical recommendations

Edited by Amanda Baker, Nicole K. Lee and Linda Jenner

This chapter presents key points of chapter authors' recommendations for clinical interventions based on findings from Chapters 4 to 11. A decision tree to assist clinicians with appropriate options for management and interventions is included as Figure 2 at the end of this chapter. The following criteria (National Drug and Alcohol Research Centre, 2003) have been used throughout this chapter:

Strength of recommendation	Descriptor
Strong	**The recommendation is supported by at least level 11 research and expert clinical opinion.**
Moderate	**The recommendation is supported by at least level 111 research and expert clinical opinion.**
Fair	**The recommendation is based on expert clinical opinion.**

Risks associated with psychostimulant use

Recommendation	Strength of recommendation
Psychostimulant users, especially new users, should be informed of possible adverse effects of the drug even in low doses and advised to limit their intake and avoid injecting.	**Fair**
Psychostimulant users should be informed of the potential for the context of use (e.g. rave or dance party environment) to exacerbate physiological risks, such as hyperthermia and metabolite balances.	**Fair**
Users should be made aware of strategies to reduce health risks, including drinking appropriate amounts of water, reducing other concomitant alcohol and drug use and ensuring breaks from dancing.	**Fair**
Users should be made aware of the legal consequences of possession and selling party drugs.	**Fair**

Psychosocial interventions for psychostimulant users

Recommendation	Strength of recommendation
Services should offer treatment and treatment contexts that are attractive to, and appropriate for, psychostimulant users.	**Fair**
A range of interventions should be available for psychostimulant users.	**Fair**
Partnerships between agencies and referral networks should be developed.	**Fair**
All users should be encouraged to practise safer sexual behaviours and use sterile injecting equipment if injecting, be informed about the symptoms of heavy use, and be provided with a self-help guide.	**Fair**
Polydrug use is common and polydrug dependence should be assessed and addressed in the treatment plan.	**Fair**
Hazards of injecting should be discussed with experimental users, without exaggerating the risks of occasional oral use of low doses.	**Fair**
Advice to avoid injection and daily use should be provided to current users.	**Fair**
CBT interventions to reduce transition to injection should be implemented for non-injectors.	**Moderate**
Brief interventions among current injectors should be implemented to reduce initiation into injecting among their non-injecting peers.	**Fair**
Infrequent, heavy users of psychostimulants and instrumental users should be encouraged to be aware of symptoms of adverse consequences of heavy use and the need for moderation or cessation.	**Fair**
Brief, opportunistic interventions should be undertaken among ecstasy users to reduce harm and alert users to possible adverse consequences of use.	**Fair**
Motivational interviewing should be a standard intervention.	**Fair**
CBT should be a standard intervention.	**Moderate**
Behavioural approaches, such as contingency management, may be considered.	**Moderate**
A single concerted approach or an integrated structured approach should be used rather than an eclectic approach.	**Fair**
Residential treatment should be enhanced with behavioural or cognitive interventions to improve their effectiveness.	**Moderate**
The use of residential rehabilitation and therapeutic communities for psychostimulant users should be limited to those who are likely to stay for 3 months or more.	**Fair**
Given the limited evidence of effectiveness, attendance at self-help groups should be optional not mandatory.	**Fair**

Management of acute psychostimulant toxicity

General issues

Recommendation	Strength of recommendation
Treatment of psychostimulant toxicity should involve prompt supportive care and judicious use of specific agents. It is important to seek emergency care when any of the following symptoms are present: • **Chest pain.** • **Rapidly increasing body temperature.** • **Psychotic features (hallucinations, severe paranoia, delusions or thought disorder).** • **Behavioural disturbance to the extent that the individual may be at risk to themselves or others.** • **Seizures.** • **Uncontrolled hypertension.**	**Fair**
Once in the Emergency Department, clinical observation of potentially toxic signs and symptoms is more relevant than estimating the ingested dose. If objective confirmation of psychostimulant use is not possible, reasonable suspicion of psychostimulant use may be inferred from: • **information provided by significant others or bystanders;** • **the recent activities of the patient (e.g. a dance party); and** • **clinical presentation (pupils are usually dilated and sluggishly reactive to light; the skin is usually flushed and diaphoretic; hyperthermia above 39.5 degrees C indicates severe, potentially life-threatening toxicity and mandates immediate cooling and sedation).**	**Fair**

Behavioural emergencies and psychosis

Recommendation	Strength of recommendation
Urgent sedation may be indicated for extreme behavioural disturbance associated with psychostimulant toxicity or if a patient is extremely agitated or severely psychotic.	**Fair**
If a patient requires urgent sedation, medical staff should ensure that they have sound airway management skills and access to appropriate equipment.	**Fair**

Serotonin toxicity

Recommendation	Strength of recommendation
Diagnosis of serotonin toxicity is made by clinical examination and the Sternbach criteria may be used.	**Fair**
Management of serious serotonin toxicity should always involve supportive measures such as IV fluids/volume resuscitation for dehydration, hypotension or rhabdomyolysis; antipyretics, external cooling, muscular paralysis with neuromuscular blocking agents, mechanical ventilation for respiratory compromise and sedation with IV benzodiazepines. Paralysis and intubation may have a role in cases of severe intractable rigidity. Management of secondary cardiac arrhythmias or seizures involves standard measures.	**Fair**
In all patients with suspected serious serotonin toxicity, serum electrolytes, glucose, renal function, creatine kinase levels and ECG should be monitored.	**Fair**
Hepatic function and arterial blood gases should be monitored in more severe cases.	**Fair**
Muscle rigidity should be controlled — if unchecked, it can lead to fever, rhabdomyolysis and respiratory compromise.	**Fair**
Patients who develop coma, cardiac arrhythmia, disseminated intravascular coagulation or respiratory insufficiency require more specific measures.	**Fair**

Cardiovascular complications

Recommendation	Strength of recommendation
As there may be no clinical differences between those who experience myocardial infarctions and those who do not, all patients with cocaine-related chest pain should be tested for possible myocardial infarction.	**Fair**
Diagnosis of heart attack in cocaine users with chest pain is difficult but may be assessed with electrocardiograms, measurements of creatinine kinase and cardiac troponin I.	**Fair**
The pharmacologic treatment of patients with cocaine-related ischaemic chest pain differs in several important ways from that of patients with the usual type of myocardial ischaemia. Treatment recommendations based on the pathophysiology of cocaine-associated myocardial ischaemia must take into account cocaine's toxic effects on the CNS and other vital organs.	**Fair**
Aspirin must be avoided in patients at risk for subarachnoid haemorrhage. If treatment strategies could be altered by the knowledge of recent cocaine use, rapid bedside toxicological assays for the drug or its metabolites may be useful, since the patient's own reporting is not entirely reliable.	**Fair**

Cardiovascular complications (continued)

Recommendation	Strength of recommendation
Beta-blockers should not be used for the treatment of acute myocardial ischaemia related to psychostimulant use, as these drugs enhance stimulant-induced vasoconstriction, increase blood pressure and may exacerbate adverse effects.	**Fair**

Cerebrovascular complications

Recommendation	Strength of recommendation
Cerebral computed tomography should always be performed when severe headache or altered consciousness or both occur in relation to use of these compounds. Arteriography should be part of the evaluation of most young patients with non-traumatic intracerebral haemorrhage.	**Fair**
Immediate management involves airway management, adequate oxygen, IV fluids to maintain nutritional and fluid intake and attention to bladder and bowel function. Corticosteroids may be harmful. If present, fever, hyperglycaemia, heart failure, arrhythmias, or severe hypotension must be treated.	**Fair**
Management of cerebrovascular events secondary to psychostimulant use should follow standard procedures with early consideration of angiography.	**Fair**

Psychostimulant withdrawal and detoxification

Recommendation	Strength of recommendation
A thorough assessment of the use of all drug classes should be undertaken. Should concomitant withdrawal syndromes occur, both should be managed simultaneously.	**Fair**
The management of people seeking detoxification support should ensure that people are initially engaged in appropriate treatment and retained in aftercare to optimise outcomes.	**Fair**
Due to the high rates of relapse following treatment for psychostimulant use disorders, psychosocial interventions should be offered post-detoxification.	**Fair**
Detoxification from psychostimulants is usually undertaken outside a hospital setting unless severe psychotic symptoms or other risk factors indicate that a supervised setting would be more appropriate.	**Fair**
A thorough mental health assessment should be undertaken by those monitoring withdrawal, focusing on psychosis and depression, and mental health staff should undertake a thorough substance use assessment.	**Fair**

Psychostimulant withdrawal and detoxification (continued)

Recommendation	Strength of recommendation
Those involved in the client's care should collaborate to coordinate their management of individuals.	Fair
Detoxification from psychostimulants may proceed without the assistance of drugs. Unlike withdrawal from substances such as alcohol or opioids, pharmacotherapy for psychostimulant withdrawal is of limited value.	Strong
Clients should be educated about possible withdrawal symptoms and the variable course of withdrawal, and be provided with ongoing supportive management.	Fair

Pharmacological interventions for psychostimulant users

Recommendation	Strength of recommendation
Medications, including antidepressants, dopamine agonists and antagonists, disulfirum, and most CNS stimulant drugs have not been found to be useful in the treatment of psychostimulant dependence. The use of pharmacotherapies should be limited except where targeted towards accurately and appropriately diagnosed comorbid conditions.	Moderate

Psychostimulants and young people

Recommendation	Strength of recommendation
A wide range of comprehensive interventions that include CBT and family therapy approaches and target a range of factors should be offered.	Moderate
The use of pharmacotherapies should be limited, except for specific comorbid psychopathology.	Moderate
Treatment should be readily available, accessible and attractive to young people.	Fair
A comprehensive assessment should be undertaken as a first step in the treatment of young people focusing on risk and protective factors, which may be targets for intervention.	Fair
The intensity of treatment intervention offered to young people should be matched to the severity of substance misuse and the level of impairment in functioning. The least intrusive options should be tried first.	Fair
Co-existing mental disorders should be assessed and addressed.	Fair
Detoxification by itself does little to change long-term use and should be offered as part of a comprehensive treatment program.	Moderate

The psychiatric comorbidity of psychostimulant use

Recommendation	Strength of recommendation
Comorbid conditions among psychostimulant users, including drug use and psychiatric symptoms, should routinely be screened, assessed and monitored over time using valid and reliable instruments.	**Fair**
Although it is not possible to recommend any specific interventions for comorbid conditions at this time, comorbid conditions should be diagnosed and treated in an integrated way.	**Fair**
Psychostimulant-induced psychosis is usually treated with conventional antipsychotic medication, sedation with benzodiazepines, or a combination of both types of medication.	**Fair**
Affective and anxiety disorders can be treated with interventions designed for these conditions.	**Fair**
Clinicians should be provided with guidelines on screening, assessment, referral options, information on different treatment protocols available, and access to clinical evaluation tools.	**Fair**

Psychostimulant use in pregnancy and lactation

Recommendation	Strength of recommendation
Management strategies should address both psychostimulant use and the associated risk factors.	**Fair**
Pregnant women and mothers who use psychostimulants should be encouraged to seek pre, peri and postnatal care.	**Fair**
The clinical environment should be non-judgmental to maintain involvement in antenatal and postnatal care.	**Fair**
Provision of good antenatal care with interventions to improve maternal nutrition and reduce psychological distress may improve neonatal outcomes.	**Moderate**
Even if psychostimulants have been used in the earlier stages of pregnancy, there are possible benefits for reducing or ceasing use in the later stages of pregnancy and pregnant users should be encouraged to reduce or cease use.	**Moderate**
Pregnant users should be advised to reduce other substance use, especially nicotine and alcohol, as this can improve neonatal and early childhood outcomes.	**Strong**
Pregnant users should be advised to avoid binge administration of psychostimulants during pregnancy.	**Fair**
If the pregnant user continues to use, infant exposure to the drug can be minimised by breast-feeding just prior to the drug use and avoidance of feeding for a minimum of two to three hours afterwards.	**Fair**

Psychostimulant use in pregnancy and lactation (continued)

Recommendation	Strength of recommendation
Pregnant users should be advised to avoid breast-feeding during periods of heavy psychostimulant use.	**Fair**
Parenting interventions should be considered for those who continue to use as they can have a positive impact on childhood outcomes.	**Fair**

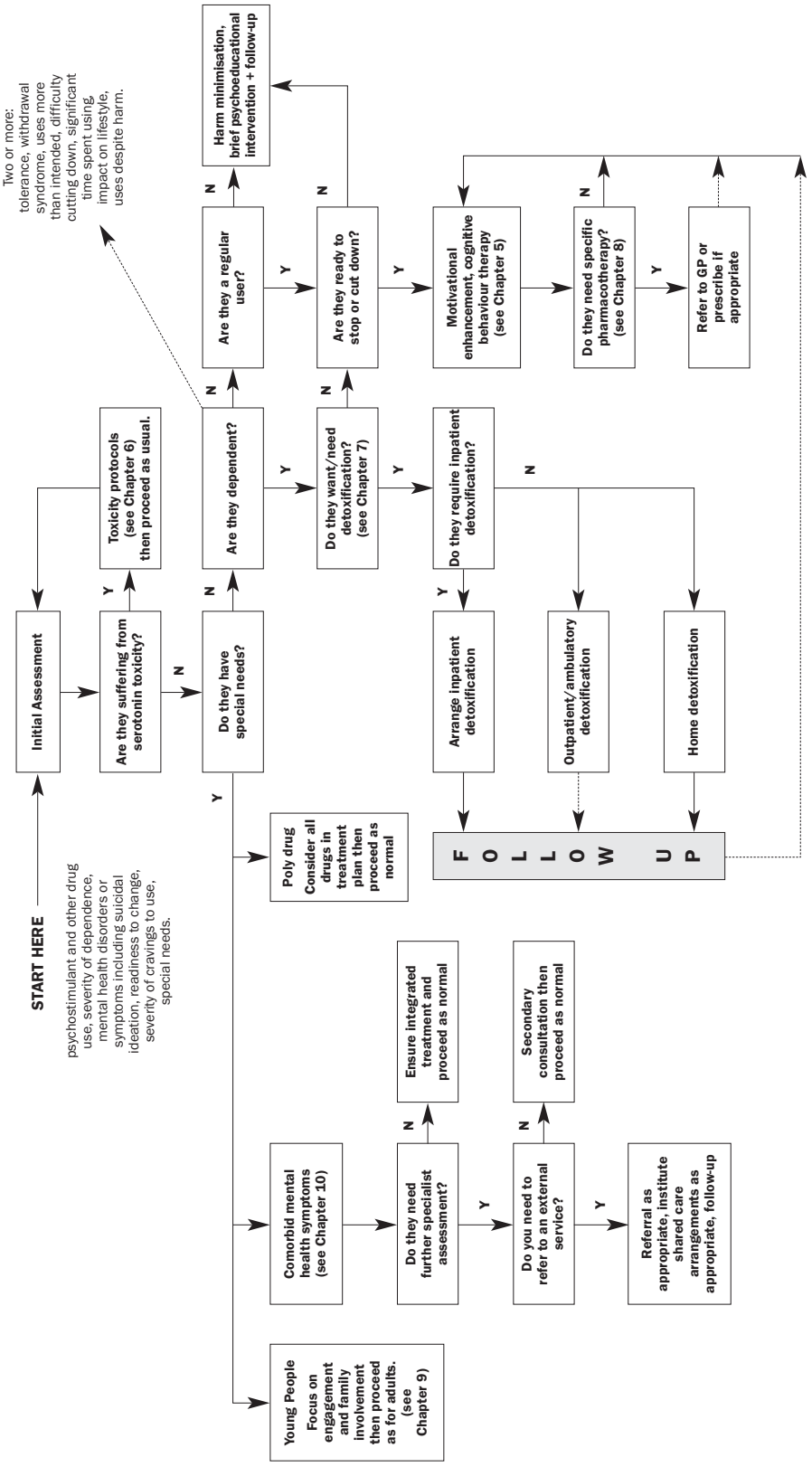

Figure 2: Decision Tree

Chapter 13
Future research directions

Edited by Amanda Baker, Nicole K. Lee and Linda Jenner

This chapter presents key points of chapter authors' recommendations for addressing identified gaps in the literature based on findings from the indicated monograph chapters. The symbol *, when it appears, denotes the research recommendation is considered a high priority.

Prevalence and patterns of psychostimulant use

1. Monitoring systems that focus on understanding patterns of use among specific populations are required, including for:
   - pregnant women;
   - children whose parents use drugs, including a focus on generational transfer of patterns of use;
   - Indigenous Australians, including a focus on social and health impacts;
   - those in rural areas, especially effects of use on individuals and communities and implications for treatment options and access; and
   - those at high risk of blood borne viruses, sexual risk-taking and mental health problems, such as injecting methamphetamine use, the gay community (including implications for HIV treatment), and those with a history of mental health disorders.
2. Research examining gender differences among psychostimulant users including reasons for use, route of administration, health and social effects and treatment considerations.
3. *Cohort and retrospective history studies are required to gain an understanding of the natural history of psychostimulant use, including protective and risk factors for continued use and/or later problematic use.
4. Integration of treatment demand data into routine monitoring on psychostimulant use is required to improve responsiveness of treatment services to the needs of psychostimulant users.
5. Studies that assist our understanding of the prevalence and nature of physical harms (e.g., cardiovascular and cerebrovascular pathology) associated with psychostimulant use and also associated risk of mortality.
6. More accurate estimates of the number of dependent or injecting methamphetamine users who are more likely to impact on services in Australia.
7. Research is required to understand the impact of psychostimulant use on frontline workers such as ambulance and emergency workers and police officers and to identify the training and resource needs of these groups to effectively manage psychostimulant users.

Risks associated with psychostimulant use

1. *Continued monitoring of drug purity, such as via the Illicit Drug Reporting System (IDRS), is necessary to document changes in drug purity and inform harm minimisation interventions among users.
2. The possible relationship between psychostimulant use and sexual risk-taking behaviour among sex workers and men who have sex with men should be investigated using quantitative and qualitative research methodologies.
3. Due to the high prevalence of tobacco use among psychostimulant users and illicit drug users in general, interventions for tobacco dependence should be evaluated among users.

Psychosocial interventions for psychostimulant users

1. *Further RCTs of brief versus intensive outpatient interventions employing MI and CBT are urgently needed among different groups of amphetamine users (infrequent but heavy; instrumental and regular).
2. RCTs evaluating the effectiveness of CBT in preventing transition to injection and regular use of amphetamines are needed.
3. Service evaluations of the characteristics of clients, client outcome and staff training needs are required.
4. *The issue of retention in outpatient and residential treatment also requires urgent attention. There is a lack of information about the possible mechanisms that may enhance retention.

Management of acute psychostimulant toxicity

1. There are few research papers evaluating efficacy and safety of sedation protocols specifically in psychostimulant use populations within an emergency setting. Further research needs to explore use of urgent sedation techniques in a range of emergency settings, especially the pre-hospital setting.
2. A clear and unambiguous case definition for serotonin toxicity is lacking; diagnostic criteria have been proposed but not tested prospectively. No prospective studies have been done to evaluate the treatment of serotonin toxicity. Prospective studies of serotonin toxicity are required to:
   - test diagnostic criteria;
   - determine long-term outcomes for psychostimulant users; and

   Controlled studies are required to:
   - evaluate the treatment of serotonin toxicity and determine an optimal dosing regime.
3. Prospective studies of cardiovascular toxicity are required, particularly among those with amphetamine and MDMA use complications.
4. Prospective studies of cerebrovascular complications secondary to psychostimulant use are required.

Psychostimulant withdrawal and detoxification

1. Prospective studies examining the natural history of cocaine withdrawal among both in-patients and outpatients, with attention to gender differences in withdrawal characteristics among dependent cocaine users are required to clarify issues for the Australian situation.
2. *Due to the widespread use of potent methamphetamine in Australia, studies that describe the natural history of withdrawal among dependent Australian users in a range of settings, with mixed gender samples, are urgently required to inform the development of appropriate services and responses.
3. The role and efficacy of psychosocial interventions in withdrawal management should be determined.

Pharmacological interventions for psychostimulant users

1. *Future controlled trials of pharmacotherapies in Australia should focus on those treatment groups experiencing the most harm including cocaine injectors, methamphetamine injectors, methamphetamine smokers and dually dependent opioid/stimulant users. Such research should be integrated with psychosocial interventions.

Psychostimulants and young people

1. RCTs are required to determine the efficacy of various treatment modalities for young people using psychostimulants.

The psychiatric comorbidity of psychostimulant use

1. There needs to be more systematic investigation of comorbid conditions among psychostimulant using populations employing diagnostic instruments to determine the proportion, duration and severity of affective, anxiety and other psychiatric disorders among this population.
2. *Prospective cohort studies are needed to determine the proportion of amphetamine users who will have a psychotic episode, the course of the disorder and, in particular, whether there are identifiable risk factors or variables that may indicate longer course or poorer outcome for a particular group of amphetamine users.
3. *There needs to be more consideration of the relative effectiveness of treatment modalities for comorbid conditions among psychostimulant users.
4. *Further research is required into non-psychotic comorbid conditions and their treatment among amphetamine users.
5. There needs to be further systematic investigation of the use of conventional antipsychotics, atypical antipsychotics and benzodiazepines in the treatment of amphetamine psychosis.
6. Further work is required to investigate the reliability of the symptoms associated with withdrawal and to determine the course of the withdrawal syndrome to ascertain which features are more enduring and should be medicated.

7. Research into mood and anxiety disorders among psychostimulant users should aim to improve differentiation between people with pre-existing disorders at the start of treatment from those with current disorders and, in turn, ascertain whether pharmacological management of a comorbid mood or anxiety disorder improves prognosis.
8. The course of residual or sub-clinical symptoms persisting beyond an acute episode of stimulant-induced psychosis is not well documented and should be studied.

Psychostimulant use in pregnancy and lactation

1. Large prospective studies are required to accurately assess the relationship between psychostimulant use in pregnancy and neonatal/early childhood outcomes, particularly for methamphetamine and MDMA.
2. The role of engagement in prenatal care in contributing to improved neonatal/early childhood outcomes needs to be further evaluated. Barriers to participation in prenatal care and methods to enhance participation should also be explored.
3. Parenting interventions should be evaluated among psychostimulant users.

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Glossary of Terms

Acute: having severe symptoms and a short course.

Aetiology: science dealing with the cause of disease.

Age of initiation: age at which drug was first used.

Agonist: see dopamine agonist.

Akathisia: a condition marked by motor (movement) restlessness and anxiety.

Alkaline: having a low pH value (e.g. base).

Alkaloid: organic, basic substances found in plants (e.g. cocaine and caffeine).

Alveolar: thin walled chamber or follicle surrounded by networks of capillaries.

Ambient temperature: environmental temperature.

Ambulatory: having the physical ability to access an outpatient facility, walking or able to walk.

Amphetamine hydrochloride: salt form of amphetamine mixed with hydrochloric acid.

Amphetamine sulphate: salt form of amphetamine mixed with sulphuric acid.

Amphetamines: a synthetic group of drugs that includes amphetamine and methamphetamine salt and base forms (speed, pills, base and ice).

Anaesthetic: an agent that produces a loss of feeling or sensation or induces sleep.

Aneurysm: a sac formed by dilation of the walls of a blood vessel and filled with blood.

Anhedonia: an inability to experience pleasure from things previously enjoyed.

Anorectic: a drug that suppresses the appetite.

Antagonist: see dopamine antagonist.

Anxiolytic: A group of drugs described as minor tranquillisers, prescribed to reduce anxiety and used as muscle relaxants e.g. benzodiazepines.

Arrhythmia: variation or irregularity of the rhythm of the heart.

Ataxia: lacking coordination of movement.

Atherosclerosis: degeneration and hardening of the wall of an artery or arteries.

Axon: part of the nerve cell that conducts impulses from one cell toward the next cell's neuron.

Base methamphetamine: a high potency, low purity paste.

Behavioural reinforcement: an effect that strengthens a specific behaviour.

Binge use: irregular heavy drug use.

Cardiac myopathy: disease of the heart muscle leading to heart failure.

Cardiomyocyte apoptosis: the death of heart muscle cells.

Cardiomyopathies: see cardiac myopathy.

Cardiovascular: pertaining to the heart and blood vessels.

Cerebral artery aneurysm: a sac formed by dilation of the walls of the cerebral artery and filled with blood.

Cerebral haemorrhage: the rupturing of a blood vessel, usually an artery, in the brain (a cause of cerebral vascular accident (CVA/stroke)).

Cerebral oedema: an abnormal accumulation of fluid in the brain.

Cerebrovascular: pertaining to the blood vessels of the brain.

Choreoathetoid: involuntary/irregular/slow movement.

Clearance: the rate at which a substance or drug is removed from the blood by various organs or processes e.g. hepatic (liver) clearance, renal (kidney) clearance.

Cocaethylene: psychoactive substance formed exclusively during the simultaneous administration of cocaine and alcohol.

Cocaine: a naturally occurring, psychoactive alkaloid of the coca plant.

Cognitive: pertaining to thoughts or thinking.

Cognitive behaviour therapy: a talking therapy that seeks to modify dysfunctional or distorted thoughts and beliefs.

Coma: state of profound unconsciousness, unable to be roused.

Comorbidity: the co-occurrence of any two or more disorders, in this monograph the term refers to amphetamine use disorders and mental health disorders.

Compulsive movements: overwhelming urge to perform an irrational or ritual act or movement.

Contingency management: behavioural management technique that involves the application of rewards and/or punishments to modified behaviour.

Convulsions: 'fits', 'seizures' induced by abnormal electrical stimulation of the brain.

Crack cocaine: the free base form of cocaine (i.e. not mixed with a salt) sufficiently volatile for it to be inhaled via smoking.

Craving: intense desire.

Crystalline methamphetamine: a high potency, high purity salt form of amphetamine, crystals or course powder (ice, crystal, shabu).

Cue exposure: exposure to a stimulus (cue), either internal (e.g. mood, thought) or external (e.g. exposure to a drug) that increases risk of using the drug.

Cytochrome: a pigment present in aerobic cells.

Delirium: mental state characterised by excitement and illusions.

Dementia: progressive mental deterioration due to organic brain disease.

Depersonalisation: a feeling of unreality or strangeness related to one's self or the environment.

Depression: a mood disorder or state that meets diagnostic criteria characterised by blunted affect (appearance), psychomotor retardation (slowed physical movements and thinking), dysphoria (flat mood) and anhedonia (inability to experience pleasure).

Designer drug: a drug artificially manufactured for a specific effect or purpose.

Detoxification: the planned cessation of drug use in someone who is dependent is termed detoxification.

Dexamphetamine: a synthetic amphetamine available on prescription (pills).

Dilation: to make larger or bigger.

Dopamine: a neurotransmitter involved in the control of movement, thinking, motivation and reward.

Dopamine agonist: used to increase dopamine concentrations, thereby overcoming dopamine depletion, such as in stimulant substitution therapy.

Dopamine antagonist: used for its euphoria-blocking effect via receptor blockade, to limit the effects of stimulants.

Dysphoria, dysphoric mood: emotional state characterised by discontent, depression, anxiety and malaise.

Dysrhythmias: alteration of normal heart rhythm.

Ecstasy: see MDMA.

Electrocardiogram: the graphic recording from the body surface of variation in electric potential produced by the heart.

Electrolyte: a compound that when dissolved is capable of conducting an electric current, essential to the workings of a cell.

Elimination: discharge from the body of substances not usable.

Enzymes: a substance that initiates and accelerates a chemical reaction.

Epidemic: the simultaneous occurrence in the community of a great many cases of a specific disease or condition.

Euphoria: a subjectively pleasant feeling of wellbeing.

Euphorigenic: able to induce euphoria.

Excoriation: a superficial loss of substance (e.g. loss of skin by scratching).

Excretion: removal from the body via waste products (urine, faeces, breath, sweat).

Fibrinolysis: the dissolution of fibrin leading to poor blood clotting or haemorrhage.

Free radical: atoms or group of atoms with an odd number of electrons often formed when oxygen interacts with specific molecules, damaging to cell membranes.

Glial cell: a specialised cell that is part of the supporting structure of the brain and spinal chord.

Glutamate: excitatory neurotransmitter.

Haemodynamic: blood movement.

Hallucinations: sensory impression having no basis in external stimulation.

Harm minimisation/harm reduction: refers to a range of strategies that aim to reduce harms associated with drug use.

Hepatic: pertaining to the liver.

Hepatotoxic: toxic to the liver.

Histopathologic: the science of diseased tissues.

Hospital separation: episodes of care or the event of discharge from a hospital.

Hyperactivity: excessive activity.

Hypernatraemia: elevated levels of salt in the blood.

Hypersomnia: excessive sleep.

Hypertension: elevated blood pressure.

Hyperthermia: higher than normal body temperature.

Hypervolaemia: lower than normal blood volume.

Hypoactivity: slowed or reduced activity.

Hypoglycaemia: lower than normal levels of blood sugar.

Hyponatraemia: lower than normal levels of salt in the blood.

Hypotension: lower than normal blood pressure.

Ice: see crystalline methamphetamine.

Illusions: mental impression derived from misinterpretation of an actual sensory stimulus.

Incidence: number of new cases.

Inhalants: group of substances, usually volatile, that are inhaled for their specific effects e.g. petrol, glue, paint, and nitrites.

Insomnia: inability to fall or remain asleep.

Intranasal: method of administering drugs by sniffing through the nose (snorting).

Intravascular coagulation: clotting of blood inside a blood vessel.

Intravenous: method of administering drugs into the blood through direct vein injection (shooting up, i/v).

Ketamine: anaesthetic used by veterinarians that produces profound hallucinatory effects in humans and may lead to death in toxic doses.

Lethargy: weariness or stupor.

MDMA: a synthetic drug structurally related to amphetamines with the added presence of the methylenedioxy group of molecules. Most locally made MDMA contains a large proportion of methamphetamine and ketamine (pills).

Median: the central tendency of a set of data i.e. most frequently occurring number.

Meta-analysis: a defined systematic method for statistically integrating the results from independent controlled research studies.

Metabolite: any compound produced during metabolism.

Methamphetamine, methylamphetamine: amphetamines with the addition of a methyl group on the molecular chain, which are typically more potent in effect (can include salt and base forms).

Methylphenidate: prescription drug 'RitalinTM'. Synthetic stimulant used primarily to treat Attention Deficit Hyperactivity Disorder.

Microvascular lung injury: injury to small vessels of the lung.

Monoamine neurotransmitters: mood regulating substances produced by the body such as serotonin, norepinephrine and dopamine.

Motivational interviewing: a non-confrontational cognitive behavioural style of interviewing used to assist clients to recognise and address their health concerns leading to behaviour change.

Motor: physical activity.

Myocardial infarction: see heart attack.

Myocardial ischaemia: reduced blood flow to the heart muscle.

Neuroadaptation: the body's ability to adapt to exposure to higher levels of a drug, also when an individual requires higher doses of a drug to create the intended effect (tolerance).

Neuroendocrine: pertaining to the relationship between nervous and endocrine systems.

Neurology: scientific study of the functions and disorders of the nervous system.

Noradrenaline: see norepinephrine.

Norepinephrine: a neurotransmitter secreted by the adrenal glands promoting energy and alertness.

Occupational use: drug use intended to benefit work performance.

Oestrogen: female sex hormone.

Palpitations: a heartbeat that is unusually rapid, strong or irregular enough to make a person aware of it.

Paranoia: mental disorder characterised by delusions of persecution.

Parenteral: by injection.

Pathogenesis: origin of disease.

Pharmacodynamics: the action of a drug on the body and brain.

Pharmacokinetics: refers to the processes involved in mediating the concentration of a substance or drug in the body over time, including absorption, distribution, metabolism and elimination.

Pills: see MDMA or Dexamphetamine.

Platelet aggregation: the binding or clumping of red blood cells.

Polymorphism: the quality of existing in several different forms.

Potency: relating to the level of effect from a specific dose of the drug.

Prevalence: frequency or occurrence.

Psychoactive: any substance that activates brain neurotransmitters.

Psychomotor agitation: increased motor effects or movement (stimulated).

Psychomotor retardation: decreased motor effects or movement (depressed).

Psychosis: a mental health disorder characterised by a separation from reality, may include symptoms such as delusions, hallucinations, disorientation and confusion.

Psychosocial factors: involving a range of psychological and social variables.

Psychostimulants: a group of central nervous system stimulants, which act to increase the activity of dopamine, noradrenaline and serotonin.

Pulmonary haemorrhage: lung haemorrhage.

Pulmonary oedema: fluid in the lungs.

Pyrolysis: the decomposition of a substance at high temperatures in the absence of oxygen.

Rave: dance party where psychostimulant drugs are often utilised to enhance energy for dancing.

Recreational use: irregular drug use in a social setting.

Regular use: recurring, routine pattern of drug use.

Renal failure: failure of kidney function.

Residential rehabilitation: medium to long-term treatment option offered in a home-like setting.

Respiratory: pertaining to breathing (respirations).

Reuptake: reabsorption.

Rhabdomyolysis: disintegration of muscle tissue due to very high body temperatures.

Rhinitis: inflammation of the nasal passage.

Route of administration: path into the body by which drugs are used or administered.

Self-detoxification: undertaking withdrawal without professional assistance.

Self-mutilation: self-initiated act of disfigurement, which may include cutting, burning etc.

Sentinel surveys: studies designed to monitor specific occurrences or trends.

Septal: of the nasal septum.

Serotonergic agonist: see dopamine agonist.

Serotonin: neurotransmitter involved in complex behaviours such as mood, appetite, sleep, cognition, perception, motor activity, temperature regulation, pain control, sexual behaviour and hormone secretion.

Sex on premises venues: venues that allow or promote sexual activity on site, usually for gay men, typically anonymous.

Shabu: see crystalline methamphetamine.

Stroke: lay term for cerebrovascular accident (CVA), which describes occlusion of a blood vessel in the brain, which leads to varying degrees of brain damage and possibly death.

Subacute: a condition that is not a severe acute condition but has not progressed to a chronic, long-term state.

Subarachnoid haemorrhage: haemorrhage beneath the arachnoid layer that encases the brain.

Substitution therapy: prescription of an agonist or partial agonist drug, which aims to reduce the harms associated with illicit drug use.

Suicidal ideation: thoughts or preoccupation with suicide.

Supraventricular: above the ventricle of the heart.

Sympathomimetic: mimics the action of the sympathetic nervous system.

Systolic blood pressure: the degree of pressure placed on the walls of blood vessels when the heart is in contraction (diastolic, degree of pressure when the heart is at rest).

Tachycardia: rapid pulse rate.

Teratogenic: the ability of a substance or drug to produce specific congenital anomalies. (The period during pregnancy where the foetus is susceptible to teratogens is during the period of organ differentiation (weeks 2-8 from conception in humans). There are fewer than 25 drugs considered to be teratogens; for a drug to be considered teratogenic, it must produce a dose-related, consistent pattern of anomaly, with an incidence higher than the population rate of approximately 2%.)

Thermoregulatory: regulation of body temperature.

Thromboembolism: obstruction of a blood vessel with a solid mass (e.g. clot).

Thromboxane: produced by the body to initiate an inflammatory response and platelet aggregation (clotting).

Tic-like movement: involuntary spasmodic twitching movement.

Toxicity: the capacity of a substance to produce toxic or poisonous effects.

Tremors: shakes, usually of hands, or limbs, can be fine or coarse.

Urine drug screen: analysis of a specimen of urine to detect the presence of drug metabolites.

Vasoconstrictive: decreases the size and blood-carrying capacity of a blood vessel.

Vasodilation: increases the size and blood carrying capacity of a blood vessel.

Vasopressin: water soluble principle from the pituitary gland that increases blood pressure and influences reabsorption of water by the kidneys.

Vasospasm: spasm of a blood vessel.

Ventricular: pertaining to the larger chambers (ventricles) of the heart.

Ventricular tachyarrhythmias: rapid and irregular contraction of the ventricles of the heart.

Volatile: combustible, able to be ignited.

Withdrawal: the progress and time-course of detoxification.

Yaabaa: tablet form of methamphetamine (Thai street name).

List of abbreviations

ADEC: Australian Drug Evaluation Committee

ADHD: attention deficit hyperactivity disorder

AOD: Alcohol and other drug/s

ATS: amphetamine type stimulants (synthetic CNS stimulants including amphetamines and methamphetamine)

BBV: blood borne virus

BPRS: Brief Psychiatric Rating Scale

CIDI: Composite International Diagnostic Interview

CNS: Central nervous system

COTSA: Census of Treatment Service Agencies

DSM: Diagnostic and Statistical Manual

DUMA: Drug Use Monitoring in Australia (Australian Institute of Criminology)

ECG: Electrocardiogram

FDA: Food and Drug Administration (American)

GHQ: General Health Questionnaire

GP: General practitioner

HIV: human immunodeficiency virus infection

IDU: Injecting drug user

IM: intramuscular

IV: intravenous

MAOI: monoamine oxidase inhibitor

MDMA: methylenedioxymethamphetamine

MI: motivational interviewing

MSM: men who have sex with men

NSP: Needle and Syringe Program

NMDS: National Minimum Data Set

NTIS: The United Kingdom National Teratology and Information Service

PTSD: post-traumatic stress disorder

RCT: randomised controlled trial

SANS: Scale for Assessing Negative Symptoms

SAPS: Scale for Assessing Positive Symptoms

SCID: Structured Clinical Interview for DSM

SSRI: selective serotonin reuptake inhibitor

UK: United Kingdom

US: United States

USA: United States of America