METHYLAMPHETAMINE REVIEW

A REPORT BY THE

ADVISORY COUNCIL ON THE MISUSE OF DRUGS

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CONTENTS

1. INTRODUCTION

Historical overview

1.1 There are records that from the 1st century AD, Chinese herbalists prescribed 'MaHuang' (the dried stems from the Ephedra Vulgaris plant) for treating asthmatic conditions. In the early 20th century, the moderately potent stimulant ephedrine extracted from the ephedra plant was used for its ability to dilate bronchial passages and for symptomatic relief in milder cases of asthmatic attack and also for brochial congestion and catarrh. As supplies of ephedra became more difficult to obtain pharmaceutical companies sought to identify a synthetic substitute (Yudko, Murray-Bridges, & Watson-Hauanio, 2003). Amphetamine (AMP) had been synthesized by the German chemist Leuckhart in 1887 (originally named phenylisopropylamine) but remained largely overlooked. In 1919 a Japanese chemist synthesized methylamphetamine (often referred to as 'methamphetamine' and abbreviated as MA herein) in 1919 (Burton, 1991) and in 1927 Gordon Alles a chemist from Los Angeles suggested that AMP could serve as a cheap alternative to ephedrine.

1.2 Medical use of AMP to treat narcolepsy, attention deficit disorders, depression and obesity was initially seen as a safe practice with many benefits (Grinspoon & Hedblom, 1975). But from the late 1930s, undesirable side effects were documented hypertension, depression, dependence, psychiatric disturbances associated with chronic use and non-medical usage for the stimulating effects of the drug. Perhaps the earliest report of non-medical use of AMP in the USA was an editorial in the Journal of the American Medical Association describing the non-medical use of benzedrine inhalers by students at the University of Minnesota as performance aid during study for examinations (JAMA, 1937). At this time one group of chemists in the UK decide to supply amphetamines on prescription only and in 1939 Benzedrine was placed on part one of the poisons list (Myles, 1997).

1.3 Both AMP and MA were widely distributed to allied and axis troops during World War II. It has been estimated that 200 million AMP or MA tablets were supplied to the US troops over the course of the war, and 72 million AMP tablets were supplied to British service men (Klee, 1997). In Japan AMP and MA were first marketed in 1941 under a range of different brand names. From 1942 onward MA (under the brand name 'Philopon') was increasingly administered to members of the Japanese forces and to workers in key industries (Suwaki, Susumu and Konuma, 1997). One of the factors involved in the increased use of illicit AMP after World War II was continued use by members of the military upon their return. Following the war, the misuse of AMP became common in a number of countries, notably the USA, Japan and Sweden. In response, stringent controls were enacted to restrict the prescribing and sale of AMP and MA preparations. As legitimate sources of AMP were cut off, black market sources were created to meet established demand. Supplies came in three ways: as diverted pharmaceutical products, as illicit AMP products trafficked into a country and domestically manufactured.

1.4 In some countries, notably in southern Europe and including the UK, AMP sulphate powder was and remains the most common AMP derivative used in the drugs scene. Alternatively in countries such as Japan and the USA MA has always been dominant type. In other counties

such as Australia, MA has displaced AMP, usually because of the enactment of controls on the precursor chemicals used in the production of AMP.

1.5 Illicit MA production and consumption is growing worldwide. MA is now the most commonly produced illicit synthetic drug (UNOCD, 2003a). Illicit MA consumption is firmly established in a number of countries including the USA, Czech Republic, Australia, Japan, Thailand, and the majority of nations in the East and Far East (UNOCD, 2004). Serious legal, health, social and environmental harms are associated with the production and use of MA.

Types of methylamphetamine

1.6 MA has two stereo isomers (see Appendix One): S (d- or (+)- methylamphetamine) and R (l- or (+)- methylamphetamine). There are three types of MA each of which is identified by the balance of the d- or l- isomers. The three types of MA are:

- l-MA (levo-methylamphetamine).
  l-MA only has the (l-) stereoisomer. In terms of CNS activity l-MA is the least potent type of MA. It is primarily active in the periphery systems (e.g. the cardiovascular system).

- dl-methylamphetamine (dextro-levo-methamphetylamine).
  dl- MA is the racemate (an equimolar mixture of the two enantiomeric isomers of a compound) form of MA containing equal proportions of (l-) and (d-) stereoisomer.

- d-methylamphetylamine (dextro-methylamphetamine).
  d-MA only has (d-) stereoisomer present. In terms of CNS activity d-MA is the most potent, and widely abused form, of MA and unless otherwise stated, this is the isometric form referred to herein.

This report

1.7 The illicit use of amphetamines, almost exclusively in the form of AMP sulphate powder, is widespread in the UK, but has been declining in recent years. At the same time, MDMA and the use of cocaine have increased. There is a paucity of information about the prevalence of MA use in the UK. What evidence there is suggests consumption of MA in the UK is very limited. However, given the experience of other countries such as the USA where MA misuse has become widespread the ACMD has been asked to review the harms posed by the drug now and the potential for its use to increase in the UK in the future.

2. MEDICAL USE OF AMPHETAMINE

2.1 In 1932 dl-amphetamine was first marketed as 'Benzedrine' by the pharmaceutical company *Smith, Kline & French* as inhaler to treat congestion. By 1935 the stimulant effect of AMP was recognized and physicians successfully used it to treat narcolepsy. In 1937 AMP was approved by the American Medical Association for sale in tablet form and it was sold by prescription for use in the treatment of narcolepsy.

2.2 In 1940 MA was marketed under the trade name 'Methedrine' by *Burroughs Welcome*. Between 1932 and 1949, 39 different types of medical use were accepted for AMP and MA including the treatment of schizophrenia, tobacco smoking, heart block, radiation sickness, morphine and codeine addiction (Lukas, 1985). In the USA, pharmaceutical MA is produced as 'Desoxyn' and contains 5mg of MA hydrochloride in tablet form. The British company *Shire Pharmaceuticals* manufactures 'Adderrall' for treatment of ADHD in the USA. Adderall is a combination of four AMP salts: dextroamphetamine saccharate; amphetamine aspartate; dextroamphetamine sulfate USP; and amphetamine sulfate USP. The drug is produced in 5mg, 10mg, 20mg, and 30mg tablets, and is designed to be taken twice a day. The manufacturer has recently developed 'Adderall XR' for adults. This is a once-daily controlled release version.

2.3 Current general medical use of AMP derivatives is limited to the treatment of narcolepsy and Attention Deficit and Hyperkinetic Disorder (ADHD). In the UK d-AMP is the only AMP compound recommended for narcolepsy. The most common treatment for ADHD in the UK is methylphenidate (Ritalin). D-AMP is chemically similar to methylphenidate, but is usually only prescribed after methylphenidate has not worked (Royal College of Psychiatrists, 2004).

2.4 An audit of the prescribing of controlled drugs in England between 2002 and 2003 was conducted by the Prescribing Support Unit (2003). Data obtained from the Prescription Pricing Authority was analysed. Therefore, the audit was restricted to GP prescribing on FP10 prescriptions. It found that three types of stimulants are being prescribed by GPs: methylphenidate hydrochloride; d-AMP sulphate and MA hydrochloride. A breakdown of the overall number of stimulant prescriptions in the period covered is presented in Table 2.1, with a more detailed breakdown of the MA prescriptions given in Table 2.2. Overall, the number of stimulant items prescribed is reported as increasing by 15% on the previous financial year but this growth was restricted to methylphenidate. There were reductions in the prescribing of both d-AMP sulphate and MA hydrochloride.

Table 2.1 Amphetamines derived products prescribed (England, 2002-2003)

BNF Name	Items	Increase on 2002
Methylphenidate Hydrochloride	201,674	20.0%
D-AMP	41,262	-2.8%
Methylamphetamine Hydrochloride	153	-8.9%

Table 2.2 Methylamphetamine products prescribed

	Items	Quantity
Methylamphet HCl_Cap 30mg	2	60
Methylamphet HCl_Cap 30mg	6	120
Methylamphet HCl_Cap 30mg	2	90
Methylamphet HCl_Inj 30mg/1.5ml Amp	44	2
Methylamphet HCl_Inj 30mg/1.5ml Amp	97	1
Methylamphet HCl_Inj 30mg/1.5ml Amp	1	28
Methylamphet HCl_Inj 30mg/1.5ml Amp	1	3

2.5 Between 2002 and 2003, just 153 MA hydrochloride items were prescribed – the most distinctive event being a single prescription for 28 x 30mg MA ampoules. The Prescription Pricing Authority records do not indicate the condition for which a drug is prescribed. There may well be more prescribing of AMP products on private prescriptions, but these were not included in the audit.

3. ILLICIT METHYLAMPHETAMINE

3.1 There are four forms of illicit MA: tablet, powder, 'base', and crystal.

Tablet. MA tablets usually contain a combination of MA hydrochloride and caffeine. In Thailand, *yaba* is the slang-term for the drug which translates as 'crazy drug' in Thai. In the Philippines, the drug is known as *shabu*. In the USA the tablets are reddish-orange or green, can be flavoured and scented, and carry a variety of logos. MA tablets can be taken orally, smoked or administered intravenously (NDIC, 2004). Most commonly MA tablets are crushed and smoked, by '*chasing the dragon*' over foil. In the UK, most MA tablets seized appear to be imitation ecstasy tablets stamped with a 'Mitsubishi' logo and contained ketamine, ephedrine and caffeine.

Powder. MA powder is the crystalline hydrochloride salt. It is bitter-tasting, water-soluble and ranges in colour from dingy white to reddish brown, depending on the chemicals used in the manufacturing process. MA powder is sometimes referred to as 'crystal MA' (DEA, 2002) but that term is more commonly used when referring to the '*ice*' form of MA described below. Powder MA can be taken orally, smoked, snorted and injected, but in the USA it is usually snorted or injected (DEA, 2002; NDIC, 2004). In New Zealand there have been reports of a powder form of MA of high purity (60% to 70%) which is usually smoked (UNODC, 2003a). It is referred to locally as *pure*, *p* or *burn*. Street slang terms for MA powder in the USA include *crank*, *crystal*, *Nazi crank*.

Base. In Australia a waxy or oily form of MA powder or paste has been reported, called *base* [1]by users (Topp et al., 2002). This type of MA is uncommon and it is thought that this substance is made by local producers who do not have the skill to produce the hydrochloride

[1] The term 'base' used in this context is a slang term and may not refer to same form of substance as when the term is used in chemistry i.e. a substance that can combine with an acid to form a salt.

salt MA or the 'ice' form of MA described below. 'Base' can be ingested orally, or administered intravenously, but is regarded as difficult to smoke or snort (ABCI, 2001).

Crystal. Crystal MA, is MA hydrochloride powder that has been re-crystallized from isopropyl alcohol or water. It is similar in appearance to cracked ice or slivers of glass, and typically tends to be much purer than the powder form. Crystal MA can be colourless or may have a blue, green or pinkish tinge depending on the specific manufacturing processes used and the skill of the person making it. This form of MA is usually smoked, most commonly in a pipe or a similar ad hoc device, but it can be also be injected, snorted or taken orally. The most common street name for crystal MA is '*ice*'. Other street terms include *crystal*, *glass*, *tina* and *christine*. The typical high purity of MA and the ease with which it can be smoked makes crystal MA potentially more harmful than the other forms of MA. Crystal MA, defined as d-MA with purity greater than 80% now attracts more severe penalties in the USA than MA of lower purity.

Administration, purity, dose and price

3.2 Illicit MA is mostly self-administered by one of four routes; oral, snorting, inhalation, and intravenously. The actual means of administration will in part be dependent on the norms of the peer group and the personal preferences of the person taking the drug. Smoking or injecting will produce a 'rush' or 'flash' followed by a sense of euphoria that can last 4-12 hours. With either the oral or snorting route there is no flash or rush. Effects are felt from oral ingestion in around 30 minutes, and via snorting in 3-5 minutes.

3.3 The purity of illicitly manufactured MA can vary considerably. In the USA the average purity of illicit MA decreased from 72% in 1994 to 35% in 2000, then increased to 40% in 2001 and 44% in 2002 (NDIC, 2004). Much of this variation in the USA was attributed to law enforcement activities against clandestine laboratories and increasing restrictions on precursors. A report from the Australian Illicit Drug Reporting system showed the average purity of MA seizure by the different state police forces in that country to be 5.5% in 2001/2002. An UNODC report showed the purity of MA in the Czech Republic as ranging from 40% to 80% (UNODC, 2003a). MA analysed by the Forensic Science Service (FSS) in the UK has generally been of low purity (see Appendix One). The average purity of MA seizures tested between April 2001 and June 2004 was 9% (calculated as base). Cutting agents, where identified, were mostly caffeine or glucose. There were nine seizures where the purity was 70% or greater.

3.4 The typical dose used by MA users will be dependent on a number of factors including tolerance and pattern of use. In the USA it is reported that typical doses by illicit users falls in the range 100-1000 mg (0.1gm-1gm) per day, increasing up to as high as 5 gm/day in chronic binge use (NHTSA, 2004). Given the high potency of some MA one strategy for new users is to take MA in very small doses, described as 'bumps', until the desired effect is achieved.

3.5 MA is typically sold in grams or 'points' (e.g. 0.1 of gram; i.e. 100mg). In the USA the price of powder MA is quoted as costing between $40 and $120 per gram, with crystal MA costing between $120 to $500 per gram (NDIC, 2004). In Australia in 2002 the median price of a gram

of powder MA was between $50 and $250 depending on the region where it was purchased. A median price for a point of crystal MA ranged from $25 to $50. The price of a gram of MA in Czech Republic was reported to be the equivalent of $26 in 2001 (UNODC, 2003a). There is scant information on the price of MA in the UK. Press reports have stated that the crystal MA sells in the UK for approximately £100 per gram (McClean, 2003). A further source reports crystal MA to cost £25 'for a large rock' (Drugscope, 2001).

Patterns of methylamphetamine use

3.6 Insights into initiation and early patterns of MA use have been described in one study of 203 users (Sommers and Baskin, 2004). The reasons given for starting to use MA were reported as either curiosity, having a friend who was using, seeking energy, and improved sex. For most of the sample, MA use was restricted to recreational events (e.g. clubs) at the weekend. For nearly a third of the sample (30%) their initial pattern of use and intensity of use remained stable for a number of years. The majority (95%) reported that they had binged on MA, with a '*run'* lasting an average of five days. A fifth of the sample (20%) reported a typical run as lasting for six to 10 days, with another 6% of the sample typically bingeing for 10 days or more. These reports characterise a user becoming both physically and mentally hyperactive while on a binge. As tolerance to acute effects of the drug increase, the user often shifts into depression, paranoia, and aggression. This mode of behaviour is known among MA users as tweaking.

4. METHYLAMPHETAMINE AND OTHER SUBSTANCE USE

4.1 It is common for MA users to use other mood altering drugs. Polydrug use can refer to the use of several different drugs over a short period of time or the use of two or more so that their effects are experienced simultaneously (variously defined as 'concurrent use', 'mixing' or 'simultaneous use')(Earleywine & Newcomb, 1997; Boys et al., 2001). Previous studies in the UK have noted that stimulant drug users tend to be poly-drug users (Farrell, 1998). Evidence from both Australia and the USA suggest that MA is used by polydrug users (CDCP, 1995; Degenhardt & Topp, 2003).

Heroin. Injecting heroin and cocaine is a well known practice among heroin injectors; commonly called a speedball or snowball. The practice of injecting a 'speedball' (originally a mixture of amphetamines and heroin) has been attributed to servicemen stationed in Korea and Japan in the early 1950s (Bercher, 1972). A survey by the Drug Awareness Warning Network (DAWN) in the USA found that in 1994 there were 433 MA related deaths and in 23% of these cases heroin was also present (CDCP, 1995).

Alcohol. Excessive alcohol use is common among some drug users (Gossop et al., 2001). In one survey of AMP and cocaine users 34% were screened as 'problem drinkers' (Farrell et al., 1998). An Australian study with 76 MA users reported that alcohol and ecstasy were the most common substances reported as being used with MA (Degenhardt & Topp, 2003). In the 1994 DAWN survey cited above, alcohol was present in 30% of MA related fatalities (CDCP,1995). In 2000, alcohol was mentioned in 22% of MA related visits to Emergency Departments (ED) in the USA (SAMHSA, 2002). There may be elevated health risks from concurrent MA and

alcohol use. In one study, the concurrent administration of MA and ethanol caused elevated cardiac activity compared to the use of MA alone, thereby potentially increasing the risk of adverse cardiovascular effects (Mendelson et al., 1995).

Cocaine. Some MA users are also users of cocaine. In one study of the USA treatment system, 7% of those seeking treatment reported joint use of cocaine and amphetamines (Derlet, Albertson, & Rice, 2004). While both cocaine and MA are powerful stimulants, there are substantial differences in the perceived effects (see Table 4.1). MA is often mentioned as a possible substitute for cocaine. There is some limited evidence from the USA that some cocaine users may use MA as an alternative but most do not see it as a an appropriate alternative.

Table 4.1: Characteristics of methylamphetamine and cocaine

	MA	**Cocaine**
Origin	Synthetic	Plant derived
Rush	5 to 30 minutes	3-6 minutes
Effect (high)	8-24 hours	20-30 minutes
Half life	12 hours	1 hour

Sources: Sommers and Baskin, 2004; NIDA, 2003

5. AMPHETAMINE & METHYLAMPHETAMINE IN THE UK

History of amphetamines in the UK

5.1 AMP was first prescribed in the UK in the 1920s. From the mid 1940s there was liberal prescribing of Drinamyl (d-AMP and amylobarbitone) and Dexdrine (d-AMP) as well as some retail pharmacy sales of AMP based preparations. In 1957, all over-the-counter preparations were classified prescription only medicines (Klee, 1997). In the early 1960s the use of AMP, usually diverted pharmaceutical products, reached epidemic proportions among young people. Dexedrine Tablets (*yellow bellies*) or capsules (*brown & clears*) or Durophet capsules (*black bombers*), and Drinamyl (*french blues*) were used most frequently. In 1964 and 1967 there were a series of amendments to the drug legislation which criminalized the possession, supply and importation of AMP.

5.2 In 1968, following an expression of concern by general practitioners in Ipswich about drug use in the town, a committee of physicians and other interested parties was set up to look into the issue. Initially there was a report that recommended a reduction in the overall prescribing of AMP. This occurred in 1968 and appeared to result in a small reduction in the detection of illicit AMP. However, in 1969 the police reported a small increase in AMP use. Through a series of negotiations and voluntary decisions it was agreed that all practitioners would desist from prescribing AMP medications and that pharmacies in the town would return or destroy all products containing AMP. This action appeared to eradicate all abuse in tablet form, but at this time AMP sulphate powder began to be used in the town (Wells, 1980).

5.3 Prior to 1968 there were only sporadic reports of MA use in London (Mitcheson et al., 1976). However, in 1968 there was an epidemic of intravenous MA use in the capital and incidents of

MA related psychosis began to be encountered at medical and social agencies. At this time there were a number of doctors in private practice prescribing MA (Methedrine ampoules) as a substitute to cocaine addicts. It was found that two doctors in particular were over subscribing with the surplus going onto the black market (Hawks, 1969). The epidemic was short lived as in late 1968 there was voluntary agreement on the part of the manufacturers with the Ministry of Health and the Council of Pharmaceutical Society to stop the sale of MA products to retail pharmacists. Further, recommendations were produced by a British Medical Association working party that amphetamines should only be prescribed for those conditions where there is no reasonable alterative (citing depression as an example) (ACDD, 1970). After 1968, the most common source of MA ampoules was the limited supplies that were diverted or stolen from hospitals, although illicit MA was available in powder from the 1970s.

5.4 There is a paucity of information about the use of amphetamines in the UK relative to other types of drugs in the 1970s and 1980s as research efforts focused on heroin (Klee, 1997). After an decrease in the early 1970s it is thought that the use of AMP increased throughout the rest of the 1970s and 1980s as a new generation of young people started using amphetamines in the nightclub scenes associated with punk rock and 'northern soul' dance events. In the 1990s the use of amphetamines in the rave scene ensured it remained a commonly used drug (ISDD, 1992). Since the 1970s illicitly manufactured AMP sulphate powder (the unsmokable salt form) has been dominant in the UK (Corkery, 2000). Both Belgium and the Netherlands have lower prevalence of AMP use than the UK (UNODC, 2003b) but are the main sources of the AMP consumed in the UK; 10% and 90% respectively (Corkery, 2002).

Legal status

5.5 Amphetamines are controlled under the Medicines Act 1968 and Misuse of Drugs Act 1971. AMP and MA are listed in Schedule 2, Part II, of the Misuse of Drugs Act 1971 and are classified as Class B Drugs. Any drug listed in Schedule 2 of the Act designed for administration by injection is classified as Class A. The maximum penalties for supply and possession of drugs in each class are as follows:

Class A:
Supply : Life imprisonment + unlimited fine
Possession : 7 years imprisonment + unlimited fine
Class B
Supply : 14 years + unlimited fine
Possession : 5 years imprisonment + unlimited fine
Class C
Supply : 14 years + unlimited fine
Possession : 2 years imprisonment + unlimited fine

5.6 The 2001 Misuse of Drugs Regulations set out the categories of people authorised to supply and possess drugs controlled under the different schedules of the Misuse of Drugs Act 1971:

- *Schedule 1*: includes drugs such as cannabis that are not, conventionally, used for medical purposes. Possession and supply are prohibited without specific Home Office approval.

- *Schedule 2*: includes morphine and diamorphine, amphetamine and methylamphetamine which are subject to special requirements relating to their prescription, safe custody, and the need to maintain registers.
- *Schedule 3*: includes the barbiturates which are subject to special prescription requirements and safe custody requirements.
- *Schedule 4*: includes the benzodiazepines which are neither subject to special prescription nor safe custody requirements.
- *Schedule 5*: includes preparations that, because of their strength, are exempt from most of the controlled drug requirements.

5.7 There have been efforts to control the supply of illicit synthetic drugs by restricting the availability of the precursor chemicals. The basis in international law for controls over precursor and essential chemicals is Article 12 of the 1988 United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (the Vienna Convention) to which the European Community is a signatory. European Union (EU) legislation reflects the principles of the 1988 UN convention and provides for control and monitoring of trade both within the Community and with third countries through a regime of licensing and registration of companies, end use declarations and authorization of exports. Ephedrine and pseudo-ephedrine are now the precursors most often used in the illicit manufacture of MA. Both of these substances are listed in Category 1 of the EU precursor legislation. Medicinal preparations are exempt from this legislation.

Seizures of amphetamines

5.8 The number of seizures involving AMP, mostly made by the police, rose steeply from 1990 to 1996 and levelled off in 1997 (Corkery, 2002). In 1999 there were 13,393 seizures of AMP, and 7073 seizures in 2000 (Corkery & Airs, 2003). The amount of AMP seized in 2000 was 1,744.5 kg, a 14% reduction on the previous year (2019.2 kg). Customs and Excise officers seized 41% of the total amount of AMP seized in 2000. The most common route of entry was in vehicles arriving in the UK Southern ports. In recent years the largest seizures of AMP have occurred in the UK, one third of the global total, reflecting that the UK is the world's largest market for AMP (UNODC, 2004).

5.9 The pattern of MA seizures in the UK is characterised by peaks and troughs. MA was popular in the UK during the 1970s, with seizures of MA becoming common by 1976 but reducing substantially by 1978. Seizures of MA peaked again in 1989, accounting for 16% of all seizures of amphetamines. In 1999 the Forensic Science Service was asked to report on MA seizures (Hansard, 1999). It was estimated that between 1995 and 1997 MA represented less than 0.1% of all seizures of amphetamines in the UK. Between April 2001 and June 2004, there were over 350 seizure records for MA, 10% of which contained AMP or 'ecstasy'. However, 265 of those seizures occurred in 2001 alone. In 2003 there were only 21 seizures.

5.10 While the amount of MA seized has been very small it must be noted that the current test for amphetamines by the Police does not differentiate between AMP and MA. Also, MA tablets may be passed off as ecstasy tablets, even having the same logo stamped onto both types in some cases (NCIS, 2004).

Amphetamine use in England and Wales

5.11 The British Crime Survey (BCS) is the most comprehensive source of illicit drug taking among the general population of England and Wales. Unfortunately, the survey does not attempt to differentiate between AMP and MA. The most recent wave of the BCS survey shows that AMP is the fifth most commonly used drug in England and Wales after cannabis, cocaine, ecstasy and amyl-nitrite (Condon & Smith, 2003). Among 15-59 year olds the best estimate is that 486,000 people used AMP in the previous year. In the 2000 BCS, a lifetime prevalence of 13% was reported for 16-19 year olds and 28% for 20-24 year olds (Ramsey et al., 2001). In the 2002/2003 wave, amongst 16-24 year olds it was stated that 3.7% had used AMP in the last year, and 1.7% in the previous month. From the 2002/2003 wave it was estimated that 62% of 16-24 years had only used one type of drug, with 4% estimated as having used six or more drugs in the last year (Condon & Smith, 2003). In recent years the prevalence of AMP in the UK has been reducing (Ramsey et al., 2001; Aust et al, 2002; Condon & Smith, 2003).

5.12 The prevalence of AMP is high among vulnerable groups such as young people in care and the homeless. In a study of 160 young homeless people (under 25 years old) Wincup et al. (2002) reported that 73% reported lifetime use of AMP. The past year and month mean prevalence rates were 32% and 12%. In a survey of 200 young people (14-24 years) leaving the social care system, 28% had used AMP (Ward, Henderson, & Pearson 2003). High levels of stimulant use are also found among young people who attend clubs and dance events. For example, a study of drug use by 492 clubbers in 1997 reported mean prevalence levels for lifetime AMP among 15-19 year olds and 20-24 year olds respectively of 83% and 86% (Release, 1997).

Methylamphetamine use in England and Wales

5.13 Beyond the seizure figures presented above there is limited data on the prevalence of MA in the UK. In the USA, MA is frequently found in the club scene, particularly among the Gay club scene. *Mixmag*, a magazine for club music devotees, conducts an annual survey about drug use among its readers. Since 2000 the survey has included a question about lifetime use of MA. Some caution must be taken since the data is self-report but as can be seen in Table 5.1 the reported prevalence of MA use among this high-risk population is low, but increasing. In future waves of the survey it is planned to expand the range of questions asked about MA.

Table 5.1: Methylamphetamine self-reported use amongst *Mixmag* readers (2000-2003)

Year	Sample size	Number reporting MA use
2000	797	3 (0.4%)
2001	987	8 (0.8%)
2002	493	4 (0.8%)
2003	1120	14 (1.3%)

Source personal communication: Neil Hunt

5.14 Figures collected through the National Drug Treatment Monitoring System (NDTMS) showed that very few drug users applying for treatment were reporting MA as either their primary drug (3) or as a secondary drug (7) (personal communication: Department of Health). A report from the Scottish Drug Misuse Database indicated that only two people in 2001/2002 reported MA, and that was as a secondary drug (personal communication: Scottish Office). There have been sporadic anecdotal reports about the level of MA use in the UK. MA has been reported as being sold as AMP in cities such as Glasgow (Drugscope, 2001). Reports in publications that target clubbers and the gay community suggest than in recent years MA is becoming more common (McClean, 2003).

Source of methylamphetamine used in the UK

5.15 There is little reliable information on where the MA consumed in the UK comes from or how it becomes available. It is likely that MA is brought into the UK by a number of different routes including relatively small scale trafficking by persons intending to sell the drug, persons bringing it from abroad for personal use, and MA posted to the UK from another country. There have been very few MA seizures by Customs and Excise officers. In 2000, 1330 tablets containing 32 milligrams of MA were seized. Between April 2000 and June 2004 there were only five seizures, the largest being 980 grams of powder in 2001. In 2004, 21 grams of crystal MA was seized.

5.16 The UK is not a major centre for the production of synthetic drugs and it appears that there is very little domestic manufacture of AMP. Nevertheless, between 1989 and 1994, 70 illicit laboratories were detected of which 11% were producing MA. In the 1990's about 15 AMP laboratories were detected each year (NCIS, 2004). Between 1993 and 2001 six laboratories were seized that had or had the potential to produce MA.

5.17 There is evidence of MA precursors being imported, although not necessarily for the production of MA. The Forensic Science Service has examined about 19 ephedrine powder seizures (total 13,884 grams) and about 397 Tablets seizures (total 58,393 tablets). In April 2002, 150,000 tablets of pseudo-ephedrine were seized by Customs and Excise officers at the postal parcel depot in Coventry (NCIS, 2004). In August 2004 two further large shipments were seized by Customs and Excise officers (totalling some 2 million and 2.5 million tablets, respectively). Current precursor controls in the UK only apply to bulk shipments of ephedrine

not single entity tablets, but there is potential for domestic production of MA to take place. Medicinal preparations containing ephedrine and pseudo-ephedrine are available, albeit controlled under the Medicines Act. Tablets containing 60 mg or more of ephedrine can be prescribed and tablets with a lower content can be bought from retail pharmacies.

6. PREVALENCE OF CONSUMPTION AND MANUFACTURE

6.1 The United Nations estimates that amphetamines are used by 30 million people (0.7% of the global population aged 15-64. This prevalence overshadows the use of opiates (15 million, 0.4%) and cocaine (13 million, 0.3%). Sixty-percent of users of amphetamines (mainly MA) live in East and South-East Asia and this region has an estimated prevalence of 1.3% of the population aged 15-64. The highest annual prevalence estimates for AMP in Western Europe among those aged 15-64 are as follows: Ireland (1.6%), Denmark (1.3%) and Spain (1.2%). The UN's estimated annual prevalence of consumption of amphetamines is shown in Table 6.1 (UNOCD, 2004).

Table 6.1: Annual prevalence estimates of consumption of amphetamines (2002-2003)

	Number of people (in million)	**In % of population age 15-64**
Oceania	1.94	2.78
Europe	2.37	0.44
- West Europe	1.79	0.58
- East Europe	0.59	0.25
Americas	4.96	0.89
- North America	3.46	1.25
- South America	1.50	0.54
Africa	2.13	0.44
Asia	18.16	0.76
Global	**29.56**	**0.73**

Source: UNOCD, 2004

6.2 Estimates of the annual production of amphetamines have been undertaken by UNODC based on various assumptions concerning the number of users and the volumes of drugs and precursors seized by the authorities. These are shown in Table 6.2 below.

Table 6.2: Estimated global annual production of methylamphetamine and amphetamine (excluding ecstasy)

Based on:	Estimated annual production (metric tons)
Consumption *	516
Drug seizures **	340 – 490
Precursor seizures ***	290 – 410
Mean and range	410 (290 – 516)

Source: UNOCD 2004

* Number of users and quantities consumed. Based on assumed consumption of 3.3 million users in Europe, 2.9 million users in North America and 22.5 million users in Asia, a standard unit of consumption (pill) of 30mg and consumption of 184 tons of AMP and 332 tons of methylamphetamine). ** Drug seizures. Based on assumed 7-10% of drugs seized by law enforcement agencies and a clandestine market amounting to 340 tons.
*** Precursor seizures. Using a similar approach to drug seizures.

Global seizures

6.3 The UN reports global seizures of amphetamines (excluding ecstasy) in metric tonne equivalents. The figures reported by the UNOCD (2003a) on the production and consumption of amphetamines and ecstasy (Table 6.3) emphasizes an almost continuous upward trend in the amount of amphetamines seized between 1992 and 2000; increasing by a factor of 10.

Table 6.3 Global seizures of amphetamines (metric tonnes)

1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
4	5	11	7	10	15	14	33	44	26

Source UNOCD, 2003a

6.4 The UN reports that there were sustained increases in the seizures of MA throughout the 1990s (a tenfold increase from 1990 to 2000). Seizures of MA reached a peak in 2000 and had declined by 27% in 2002 (attributed to the closure of laboratories in China), but still remains at a level some six times higher than in 1990. The majority of seizures of MA take place in East and South-East Asia (86.2% of all seizures in 2001/2002). Seizures of MA and AMP by percentage of world total in 2002 by weight (UNOCD, 2004) are as follows: Thailand (39%); China (14%); Australia (6%); USA (5%); Philippines (4%); Myanmar (3%); Belgium (2%); Netherlands (2%); Mexico (2%); Japan (2%); UK (8%) (2001 data). It is important to note the contrast with seizures of ecstasy in 2002. Here, the most active countries were Belgium (22% of the global total), the Netherlands (22%), UK (11%), USA (10%) and Australia (10%).

6.5 The UN reports that the indictors point to MA accounting for the majority of global production of amphetamines (UNODC, 2004). Some 8 countries are identified as sources of MA manufacture in 2002 (UNOCD, 2004). The main source countries were Myanmar (for Thailand), China, the Philippines, the People's Republic of Korea (North Korea) (identified by the Japanese authorities as a manufacturing or transit country) and Mexico for the USA. The Australian authorities reported that domestic MA seizures were mainly from China, Thailand

and the Philippines. In 2002, the largest reported seizures were from Thailand (some 56% of global seizures), China (21%), the USA (7%), Myanmar (6%), Japan (3%) and Mexico (3%). Just 8% of total ATS (Amphetamine Type Substance) seizures were reported from other areas. Twenty-one countries were identified as sources of AMP manufacture in 2002. The main source country is the Netherlands (UNOCD, 2004). The 2004 UN report shows that 58 countries reported seizures of AMP in 2002 and there was a 25% increase compared to 2001. Some 90% of AMP seizures were in Europe (predominantly Western Europe).

Detection of clandestine laboratories

6.6 Country returns to the UN's Annual Reports Questionnaire suggest that around 9,300 clandestine MA laboratories were detected and dismantled in 2002 (an increase of 14% on 2001). These data relate almost exclusively to the USA where the authorities shut down 9,024 MA laboratories in 2002. In the same year, there were 14 laboratory seizures in Canada and 10 in Mexico. There were13 laboratory seizures in China, 4 in Myanmar and 4 in the Philippines in that year. The UN note that these South-East Asian seizures related to manufacturing operations, although numerically small, are usually substantially greater in size than the US.

6.7 In Europe, a total of 104 laboratory seizures were made in the Czech Republic in 2002. In the same year, closure of laboratories was also reported in the Russian Federation, the Netherlands, Poland, Germany, Belgium, Bulgaria, the Baltic Countries (Estonia and Lithuania) and the UK. The UN also reports that there has been a shift in production from Western to Eastern Europe since the mid 1990s. In terms of precursor control, in 2002, 160 tons of pseudo-ephedrine and ephedrine were seized (an increase of 31 tons on 2001) with the majority originating in the East and South-East Asia region and South-Asia.

7. AMPHETAMINE EXPERIENCES IN OTHER COUNTRIES

Sweden

7.1 AMP was first placed on sale in Sweden in 1935 but by 1939 the potential hazards were recognised and the drug was only available on prescription (Ingne, 1969). By 1942 Swedish physicians were prescribing AMP to about 3% of the population (Ingne, 1969). A survey at that time found 209,000 users of AMP but judged only 200 to be 'abusers' with a further 3000 being 'borderline abusers' (Goldberg, 1968). In 1944 additional controls were placed on the prescription of AMP medications. However, by the 1950's a large black market for AMP was established. At the same time intravenous administration of stimulants began to be reported and AMP use became common among criminally active young people in the major cities (Kall, 1997). Also, there was an increase in the consumption of AMP substitutes; in particular phenmetrazine (an appetite suppressant) (Ingne, 1969).

7.2 However, in the early 1960s the bulk of drugs used illicitly still originated from prescriptions by doctors, often located in rural areas who provided prescriptions by telephone (Kall, 1997). In 1962 a strict limit was imposed by the National Board of Health on the number of narcotic drugs that could be prescribed by telephone. An experiment in substitute prescribing for users

of AMP and opioid users began in Stockholm in 1965. The experiment did not work, in part because it incorporated an opiate detoxification model unsuitable for stimulant users. The experiment ended in 1967 when a female patient died of overdose of morphine and AMP; in total 38 patients died while in the experiment (Kall, 1997). By 1968, in response to the increasing effectiveness of internal restrictions and controls over trafficking, manufacture of AMP and other stimulants in clandestine laboratories became more common in Sweden (Ingne, 1969). In 1968 the Swedes banned all prescribing of AMP with few exceptions; only 343 exceptions were granted in 1968 (Ingne, 1969).

7.3 There was a declining trend in the use of AMP in Sweden during the 1970s and 1980s followed by a strong increase in the 1990s which peaked in 1998 (UNODC, 2003b). Nearly all men aged 18 in Sweden are called for an examination for fitness for military service. Since 1971 all those attending have been asked to complete a confidential questionnaire about drug use; approximately 10% refused. In the most recent wave of the survey lifetime use of illicit drugs was reported by 18% and 3.2% reported lifetime use of AMP (Andersson et al., 2002). The dominant form of stimulant in Sweden is AMP. No evidence was found for the prevalence of MA.

Czech Republic

7.4 In 2000/2001, 0.1% of all MA seized in 2000/2001 worldwide was seized in the Czech Republic (UNODC, 2003b). MA (referred to locally as Pervitin) is the main problem drug in the Czech Republic (Reitox National Focal Point, 2002). In 2000 it was estimated that there were between 30,000-45,000 problem drug users (18,000–27,000 Pervitin users, and 12,000–18,000 users of heroin and other opioids). There is an increasing trend of injecting drug use in the Czech Republic. Some 80% to 90% of Pervitin users are thought to administer the drug intravenously (Polanecký et al., 2001 cited in Reitox National Focal Point, 2000; Reitox National Focal Point, 2002). Other countries in Eastern Europe where MA use is reported include Russia, Lithuania, Slovakia and the Ukraine (UNODC, 2003a).

7.5 The origins of MA use in the Czech Republic can be traced back to the use and manufacture of Pervitin during the Second World War. Pervitin is synthesized from ephedrine and is produced in numerous small clandestine laboratories and a limited number of larger ones. There are a number of prescribed drugs containing ephedrine and pseudo-ephedrine which are the precursors for MA. It has been reported that while consumption is primarily domestic, Pervitin has been exported from the Czech Republic to Germany and Canada (Reitox National Focal Point, 2000). Following improvements in controls of ephedrine the level of clandestine manufacture of MA has reduced from a peak in 1993 when 50 laboratories were seized to less that 30 laboratories a year seized in 2001 period (UNODC, 2003b).

7.6 In 2000 there were police reports indicating that the domestic production of Pervitin was being challenged by criminal networks in their attempt to take over the market (Národní protidrogová centrála, 2000 cited in Reitox National Focal Point, 2000). Heroin abuse in the Czech Republic increased in the late 1990s displacing Pervitin to some degree. This trend started in Prague in 1997, and has spread to other regions of the country. It has been suggested that a contributing factor to the increase of heroin use is the aggressive targeting of domestic Pervitin producers and the break-up of local networks which is relatively easier for the Police

than detecting and prosecuting sophisticated heroin distribution chains (Reitox National Focal Point, 2000).

USA

7.7 AMP could be purchased from retail pharmacies in the USA in tablet form until 1951 and as an inhaler until 1959 without prescription (Miller, 1997). However, afterward AMP products continued to be prescribed extensively; with a peak in 1967 when 31 million prescriptions for amphetamines were written. Production grew to keep pace with demand; from three and one half billion tablets in 1958 to 10 billion tablets in 1970 (Miller, 1997). Most of the black market in AMP was supplied by leakage from legitimate sources, with between 50% and 75% of legally produced AMP being diverted in any year (Grinspoon & Hedblom, 1975).

7.8 By the early 60s a number of doctors in the USA were prescribing injectable MA for heroin dependency and some became involved in writing illicit prescriptions (Lake & Quirk, 1984). These practices contributed to the high number of MA ampoules being dispensed: some 500,000 in the first half of 1962 alone (Brecher, 1972). Prompted by the Governor of California and the US Department of Justice both of the companies producing injectable MA (*Burroughs Welcome* and *Abbott*) withdraw their products from the market between 1962 and 1963. Clandestinely manufactured MA soon became the predominant form of illicit AMP in the USA (Millar, 1997).

7.9 In response to large scale diversion of pharmaceutical AMP and MA and the manufacture and trafficking of MA, a series of regulatory controls were enacted. In 1965 the Drug Abuse Control Amendments were passed requiring increased record keeping of the manufacture, distribution, and prescription of AMP. In 1970 the Department of Justice imposed a system of quotas on legal manufacture and Congress passed the Controlled Substances Act, Title II of the Comprehensive Drug Abuse Prevention and Control Act. This Act made AMP illegal to possess without a prescription (Miller & Hughes, 1994). Initially injectable MA was designated as a schedule II substance, and other AMP and non-injectable MA were listed in schedule III. In 1971 the other AMP and non-injectable MA were moved to the schedule II list.

7.10 In the 1960s and 1970s much of the manufacture and distribution of MA was controlled by outlaw motor cycle gangs and concentrated in areas along the west coast of California (Smith, 1970). A public information campaign ‘Speed Kills’ was run in the early 1970s and in part because of that campaign and the new controls and regulations there was a marked reduction in both AMP and MA use after 1972 (Miller & Hughes, 1994). Between 1972 and 1977 the characteristics of AMP and MA users changed from heavy users to light and moderate users, with more women becoming users (Newmayer, 1988).

7.11 In 1980 phenyl-2-propanone (P-2-P) was reclassified as a controlled substance which resulted in a shift among illicit MA manufacturers from the ‘amalgam method’ to the ‘ephedrine reduction method’ (Heischober & Miller, 1991). This production method results in the more potent d-MA form. This change combined with the intensified law enforcement activities targeting bikers led to production sites for MA shifting to the San Diego area and the

involvement of Mexican criminal gangs (Yudko, Murray-Bridges, & Watson-Hauanio 2003). By the 1990s, the sources of MA had became very numerous and diverse with independent 'cooks' producing small amounts of the drug, biker gangs being heavily involved in production in certain areas and in distribution, and Mexican criminal organizations being involved in large scale manufacture and trafficking of MA and precursors.

7.12 Separately to the situation on the mainland in the 1980s the highly pure form of crystal MA ('ice') became available in Hawaii. It was imported from the Far East by organised criminal gangs and distributed through extended kinship networks (Laidler & Morgan, 1997). By the 1990s crystal MA use was rampant across Hawaii. In part the market for crystal MA was created by a policy of eradicating marijuana cultivation and consumption in Hawaii. This left the consumers and locals who had derived their income from marijuana looking for alternatives. In 1996 the U.S. Congress passed the MA Control Act that established new controls over key ingredients and strengthened criminal penalties for possession, distribution and manufacturing. The MA Anti-Proliferation Act was passed in 2000 which strengthened sentencing guidelines (UNOCD, 2003a).

Australia

7.13 AMP is Australia's second most widely used illicit drug after cannabis (AIOHW, 2000). There were two small epidemics of in the 1960s and 1970s (Hando & Hall, 1997). These epidemics were driven by large increases in the prescribing of AMP by practitioners and leakage from this source led to increased usage among young people. The 1970 epidemic ended after a few years as a result of improved understanding among drug users of the adverse effects of stimulant use, and increased controls over the prescribing of AMP. There was resurgence in AMP use in the mid 1980s among injecting drug users because AMP sulphate was cheap to produce and the required chemicals were readily available. (Hando & Hall, 1997).

7.14 In recent years in Australia there has been a shift in the drug scene from AMP sulphate to MA. In 1990 controls were enacted to restrict the precursor chemicals used to manufacture AMP sulphate. This led to the 'pseudo-ephedrine-to-MA' conversion becoming the most widely used synthesis process (ABCI, 2001). Pseudo-ephedrine hydrochloride is extracted from cold and influenza medications. In 2000, 95% of all AMP seized in Australia were MA.

7.15 Monitoring systems in Australia have noted increases in the availability and use of crystal MA as opposed to MA powder made locally and of low purity. The staple drug in the party circuit remains 'ecstasy', but the use of crystal MA has increased among this population in recent years (Topp & Darke, 2001; Topp et al., 2002; Degenhardt & Topp, 2003).

New Zealand

7.16 The use of AMP increased rapidly in New Zealand between 1998 and 2001, especially among young people. Stimulants moved from being the third most popular illicit drug class in 1998 to being the second by 2001. As in Australia new more potent forms of MA have became more common (e.g. crystal MA trafficked from Malaysia). Organized crime groups (primarily outlaw motorcycle gangs) are thought to control most aspects of MA production and

distribution in New Zealand, including the precursor chemicals, the manufacture of MA in clandestine laboratories, and distribution of the end product.

7.17 Prior to 1998 there were few seizures of MA, and rarely over a kilogram. In recent times both the trafficking and domestic manufacture of MA has increased considerably. In 2002 6.4 kilograms of MA were seized at the border, and the number of laboratories detected in 2002 was 147, a 1600% increase since 2000. A specially tasked police unit for the detection of clandestine drug laboratories (the Clandestine Drug Laboratory Team) was formed in 2001. The prevalence of illicit use of AMP in New Zealand is relatively high compared with other countries in Asia with only Thailand (5.9%) reporting a higher last-year prevalence level among the 16-55 year old population (Wilkins et al., 2002).

7.18 The New Zealand Expert Advisory Committee on Drugs (EACD, 2002) produced an advisory report on MA in 2002. In May 2003 the Government of New Zealand presented a MA action plan informed by the EACD report (MAGD, 2003). The purpose of the plan was to integrate the various strategies and initiatives being developed by the different government departments to meet the growth in the trafficking, manufacture and use of MA, and the associated problems. The proposed changes included:

- Reclassify MA in the First Schedule of the Misuse of Drugs Act 1975.
- Changes to the Misuse of Drugs Act 1975 to allow increased powers for Police and Customs in relation to precursor supply control, particularly powers for Customs to seize unlicensed imports of precursors and extend warrant, search and seizure powers to Police for precursor substances.
- Improved drug monitoring and surveillance systems, including more specific Police offence codes for MA offences, the establishment of a comprehensive illicit drug monitoring system, and exploring the potential to add New Zealand sites to the Drug Use Monitoring Australia program of drug-testing people detained in police cells.
- The set up of Community Action Programmes to target communities with MA problems, focusing on community ownership and solutions with support from Public Health and public health providers.
- Improving public health and education drug resources with improved information on MA.
- Improved resources for treatment services to allow for a greater level of training.
- Develop, in consultation with treatment providers and clinical services, a MA treatment protocol.
- Workforce development for drug educators (e.g. teachers and public health nurses) and first interventions workers (e.g. youth workers) focused on information on MA and associated issues, recognition of problems and appropriate referral options.
- Assessment of training needs of emergency department hospital staff to deal with MA related admissions.
- Improve information gathering on MA, including ways of dealing with clandestine laboratories and their effects. This will be enhanced by placing a Health intelligence analyst at the National Drug Intelligence Bureau (funding for which has been provided in the Budget).

- Improved analysis of MA related apprehension and seizure statistics (this will be aided by the phasing in of more specific Police offence codes for MA offences, and establishment of a comprehensive illicit drug monitoring system).

7.19 In January 2004 the results of a rapid assessment of MA trends in New Zealand was published (Wilkins et al., 2004). The assessment process gathered reports from law enforcement officers and treatment agency workers. The key findings suggest a worsening of the situation:

- An increase in the popularity of smoking MA as opposed to the previous tradition of snorting.
- The emergence of users injecting MA.
- An increase in prevalence of pure crystal forms of MA as opposed to cut powder.
- Increased numbers of MA users coming to the attention of Police and drug treatment agencies.
- Easy availability of MA.
- Greater cross section of society using MA.
- Sale of MA from cannabis 'tinny' houses.
- Marketing of MA to lower socio-economic groups.
- Increased violence and property crime associated with MA use.
- Increased drug dealing by MA users.
- Serious violence and domestic violence associated with MA.

The results of the rapid assessment of MA trends described above do suggest that situation in New Zealand is continuing to get worse. However, the majority of the intervention strategies planned by the Government had either not been enacted at the time of the survey or had only been in place for few months.

Japan

7.20 Following World War II, Japanese pharmaceutical companies were left holding huge stocks of MA. These companies subsequently marketed the MA to the public as 'anti-fatigue stimulants'. This campaign led to the first MA epidemic in Japan. Illicit production of MA is considered to have commenced in the early 1950s (Konuma, 1994). In 1950 AMP was reassigned as prescription drugs and the Stimulant Control Law was established in 1951 to place controls on the production, sale and procession of AMP (Suwaki,Susumu & Konuma, 1997).

7.21 However, large amounts of diverted and illicitly produced MA continued to reach the black market until 1954 when a murder of young girl by a MA user and the resulting public outcry led to an amendment of the Stimulants Control Law to bring stricter implementation (Suwaki,Susumu & Konuma, 1997). The increased pressure from law enforcement agencies in tandem with public disapproval and other factors such as educational programs led to a decline in MA use to pre 1950 levels (Suwaki,Susumu & Konuma, 1997).

7.22 A second epidemic of MA abuse begin in the 1970s fuelled by increased trafficking of MA into Japan by organised criminal gangs and the continuing existence of a population of veteran

MA users (Suwaki, 1991; Suwaki, Susumu & Konuma, 1997). The Stimulant Control Law was strengthened but this action had limited effect. In 1981 a MA user killed two housewives and a child and the subsequent public outcry led to several law enforcement and public campaigns, which is thought to have reduced MA use after 1984 to some degree (Suwaki, Susumu & Konuma, 1997).

Thailand

7.23 In the 1990s and early 2000s Thailand experienced an astonishingly rapid epidemic of MA use which has overshadowed the entire region. MA was available first as a pharmaceutical product (Methedrine), known locally as ya-khayan (*diligence pill*) and was used widely in the work setting, it was especially popular among long-distance lorry drivers. As misuse became common the Government imposed strict controls, which in turn engendered an illegal trade in MA and its manufacture. The drug came in tablet form and was called ya-ma (*horse pill*) because a horse logo was commonly stamped on the tablets. In the mid-1990s MA became known 'yaba' (*crazy pill*).

7.24 At first clandestine MA production was domestic but soon the majority of MA was trafficked into Thailand across the border from Myanmar and the Yunnan Province in China. As a consequence of these developments, the Thai Ministry of Health reported a dramatic rise in numbers seeking help for MA dependence. Informal reports suggested that up to 50% of the population of Northern villages were yaba users and official estimates indicated that the number of MA abusers rose 10-fold between 1993 and 2001 (UNODC, 2003b). Prior to a government crackdown on MA in 2002, Thailand reported the highest MA prevalence rate worldwide (between 2.4% and 5.6% of the population aged 15-64 used MA in 2001; some 1-2.5 million people). The UN reports that police operations during the first quarter of 2003 led to the arrest of some 90,000 drug dealers and the mandatory government treatment of some 175,000 users.

China

7.25 There have been two epidemiological surveys of illicit drug use in the People's Republic of China (Xiao, Hao & Young, 1996; Hao et al., 2002). Both surveys were conducted in five major cities from the following Provinces (Yunnan, Guizhou, Shanxi, Gansu and Guandong), which are considered to have high prevalence of drug use (Chen, 1991`). The second survey interviewed some 67,000 respondents. The lifetime prevalence of illicit drug use was 1.6% (male, 2.6%, female, 0.6%) and one-year prevalence was 1.2% (male, 1.8%, female 0.5%). The majority of reports concerned opioids and the surveys appear to have detected few users of amphetamines. Just eight respondents only reported use of ATS , cocaine or cannabis. These estimates are at odds with the number of clandestine laboratories seized in China (10 in 2002) and the survey authors acknowledged that the sampling and methods and interview protocol may have lacked sufficient sensitivity to detect AMP use in China.

8. ILLICIT METHYLAMPHETAMINE PRODUCTION

Scale of Production

8.1 Illicit MA is produced either in large industrial scale 'superlabs', which produce 'multikilo' amounts each production cycle, or, particularly in the USA, by local MA 'cooks' operating small laboratories which typically produce 'gram' amounts (Scott, 2002). Single large-scale laboratories in the Far East have been reported as having the capacity to produce 400 kg of MA per week if the precursor and other essential chemicals are available (UNODC, 2003a).

8.2 Of the thousands of clandestine laboratories detected each year world wide only a few hundred are large-scale production 'superlabs' (UNODC, 2003a). Nevertheless, the majority of MA consumed worldwide is thought to be produced in these superlabs. Even in the USA, where small production laboratories are common, it is estimated that 80% of the MA consumed comes from these facilities (Scott, 2002). The total seizures of MA from the 17,070 laboratories detected in the USA in 2001/2 was 4,232 kg compared with the over 10,000 kg of MA seized from 84 mostly industrial scale laboratories in East and South East Asia (UNODC, 2004).

Chemicals involved in the production of methylamphetamine

8.3 The most common chemicals used for MA production are ephedrine, pseudoephedrine, phenylpropanolamine, red phosphorous, iodine, hydrochloric acid, ether, hydriodic acid, and anhydrous ammonia (NDIC, 2003). The chemicals used in the production of MA can be divided into four groups:

1. Precursors: the raw material that become part of the finished product such as ephedrine.
2. Reagents: chemicals that react with the precursor but do not become part of the finished product such as hydriodic acid.
3. Solvents: chemicals that are used to cool, mix or purify MA in the final stages of production such as acetone.
4. Gases: Using hydrogen chloride gas is the preferred method for converting MA freebase (oil) into powdered MA.

Types of methylamphetamine syntheses

8.4 Two types of synthesis are most frequently used to produce MA (Remberg & Stead, 1999):

- Syntheses starting from P-2-P that use aluminium, methylamine, and mercuric chloride, and typically produces gram amounts of low quality dl-MA.
- Synthesis routes beginning with ephedrine or pseudoephedrine producing d-MA, such as the hydriodic acid/red phosphorus method which is capable of yielding multi-kilo quantities of high quality d-MA or the Birch reduction method based on the use of anhydrous ammonia which produces 'gram' quantities of high quality d-MA.

Production processes

8.5 MA is not especially difficult to make and no previous knowledge of chemistry is required. Information and guidance on how to make MA are available in a number of publications, some of which can be obtained from commercial booksellers such as Amazon, and from a number of internet websites. The apparatus and many of the chemicals required are available over the counter (e.g. from simple coffee filters for straining, to metal 'lithium' from camera batteries and red phosphorus from matchbox strikers). The exact method of production used will depend on the knowledge and skill of the person making the MA, the type of laboratory available, and the chemicals and other materials available; in particular the precursors used.

8.6 The Birch method of synthesis has become very popular among the local producers in the USA since the mid 1980s. This production technique has spread and was being used in 20% of the MA laboratories seized by the DEA in 2000 (Cazenavette, 2000). It is a very quick, cheap and efficient method. This method is sometimes called 'Nazi' method but origin of this name is unknown.

8.7 Illicitly manufactured MA often contains a range of substances other tha MA including: impurities resulting from the manufacturing process and adulterants (e.g. bulk products such as caffeine, ephedrine or lactose) which are used in place of MA, and from other contamination. Contamination can originate from a variety of causes such as contaminated starting materials, subsequent reactions, intermediate products, laboratory equipment and bench dirt, and during the final packing of the drug (Anthonie & Verweij, 1989; Remberg & Stead, 1999). Contamination can also arise because purification procedures used to remove impurities are either inadequate or performed incorrectly (Windahl, 1995; Burton, 1991).

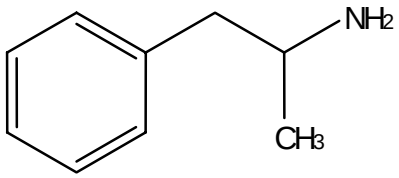
9. PHARMACOKINETICS AND NEUROCHEMISTRY

9.1 AMP has a simple molecular structure and there a large number of psychoactive compounds that can be derived from the basic prototype. AMP, MA and the ring substituted methylenedioxy AMP derivatives (3,4-methylenedioxy-methamphetamine, MDMA, 'ecstasy'; and 3,4-methylenedioxy-amphetamine, MDA) are the stimulants most commonly used illicitly. The methylenedioxy derivatives of AMP are synthesised with one or more substitutions (methoxy, methyl, halogen or sulphur), attached to the phenylring of AMP or MA (Christophersen, 2000). AMP is highly lipid soluble and can readily cross the blood-brain barrier. It exerts a number of effects in the central and peripheral nervous systems and concentrates also in the kidney, lungs and cerebrospinal fluid.

The chemistry of the amphetamines

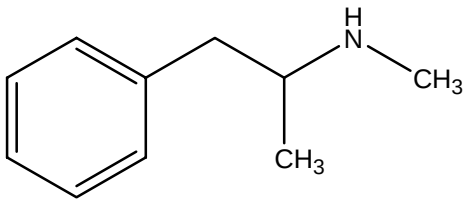
9.2 AMP and its derivatives are part of a broader class of compounds called phenethylamines. AMP is an acronym for alpha-methylphenehyltamine (1-phenyl-2-aminopropane). The basic AMP molecule has the following features: an unsubstituted aromatic ring, a two carbon side chain, the methyl group on the nitrogen ring and an amino group. The AMP molecule is shown in the figure below.

Structure of Amphetamine



9.3 MA is an AMP molecule with an additional methyl group attached to its nitrogen amine group. In its basic racemic form, MA consists of equal proportions of the two isomers: l- MA and d-MA. The additional methyl group results in MA having a slightly higher pKa value than AMP. This should mean that MA has a greater speed of absorption but at present there is no research evidence for this. The MA molecule is shown in the figure below.

Structure of Methylamphetamine



9.4 The chemical synonyms for MA are as follows:

- (+)-(S)-N, alpha-dimethylphenethyamine
- N a Dimethylbenzene-ethanamine
- d-N-methylamphetamine
- d-desoxyephedrine
- d-deoxyephedrine
- 1-phenyl-2-methylaminopropane
- d-phenylisopropylmethyl-amine
- 2-methylamino-1-phenylpropane.

9.5 The Chemical Abstracts Registry Service (CAS) number for MA is 53-74-62. The CAS number for AMP is 300-62-9.

Pharmacokinetics of amphetamine and methylamphetamine

9.6 There have been various studies have been undertaken into the pharmacokinetics of smoking (Cook 1991; Harris et al., 2003), intranasal (Harris et al., 2003) and oral (Cook et al., 1992) administration of MA. Bioavailability from the intravenous administration of any drug is always 100%. Harris and her colleagues reported the average bioavailability of MA by the intranasal route as 79% and between 37% and 67% via (pipe) smoking depending on the amount of drug retained in the pipe and variation in the temperature applied during the heating process (Harris et al., 2003). However, the bioavailability of MA by smoking may be 90% if heated to 300C (Cook, 1991). MA is readily absorbed though the gastrointestinal tract when taken orally with an average bioavailability of as 67% (Caldwell, 1973; Cook et al., 1993).

9.7 Most AMP sulphate in the UK is consumed orally or by injection. If AMP sulphate is heated it denatures before vaporization on heating and this compromises its bioavailability. The half lives of (d, +) and (l,-) AMP are 7+/ 1.2 hours and 11 +/2.1 hours respectively. Approximately 30% of a dose of *dl* AMP is excreted unchanged and the excretion rate of AMP is sensitive to urinary acidity (see 9.9). The volume of distribution of AMP has been found to range between 3 and 4.6 L/kg (Rowland, 1969).

9.8 The average plasma half life of MA by the different routes of ingestion is broadly similar: intravenous (11.4 hours), intranasal (10.7 hours), and smoked (via pipe) (10.7 hours), oral (10.1 hours) (Cook et al., 1992; Harris et al., 2003). The steady state volume of distribution is typically stated to be between 3 and 4.5 L/kg (Cook et al., 1992; Cook et al., 1993; Harris et al. 2003). However, plasma levels may be a misleading indicator of toxicity. A study using rats indicated that MA accumulates in the brain, resulting in concentrations 7-10 times higher than the plasma concentration (Melega et al., 1995).

9.9 Nearly all (90%) of an administered MA dose is excreted in urine (Shimosato, Tomita, & Ijiri 1986). The two main metabolites of MA are 4-hydroxymethamphetamine and AMP itself (Caldwell et al., 1972). In normal urine (pH 6-8) ~ 22% of MA is excreted unchanged and 4-7% is excreted as d-AMP (Caldwell, 1973; Schepers et al., 2003). Renal excretion is enhanced by acidification of urine which results in a shorter half-life and a greater clearance (Stern, Radovic & Buljubasic, 1965). The amount of the MA excreted unchanged can range from as low as 2% (pH >/ 8) in alkaline urine to 76% in acidic urine (pH </ 5)(Oyler et al., 2002).

9.10 One of the enzymes involved in the metabolic process of AMP in humans is CYP2D6, which exhibits genetic polymorphism with 10% of Caucasians deficient in the enzyme in the UK (Guengerich, 1993; Lin et al., 1997; Rege et al., 2002). These enzyme deficient individuals are potentially at greater risk of MA toxicity than others.

Neurochemistry of methylamphetamine

9.11 *In vivo* studies have shown that AMP interacts with the terminals of catecholaminergic neurons to release central stores of the neurotransmitters dopamine and noradrenaline, thereby increasing their transmission in the brain (Kuczenski, 1983). *In vivo* studies indicate that MA is approximately twice as potent at this release of neurotransmitters (Cho & Segal, 1994). *In vitro* studies have shown that the effects of AMP are mediated by the dopamine and noradrenaline systems. AMP induced effects appear to arise from the release of central stores of these neurotransmitters and their projections in the ventral tegmental area in the mesencephalon (Creese & Iverson, 1974). These studies suggest that the behavioural effects of AMP is closely tied to dose-dependent changes in dopamine and noradrenaline levels and the functioning of these neurotransmitter systems. The differential affinities of the monoamines and AMPs at monoamine transporters in the rat brain are shown in Table 9.1. One potential consequence of the long action of MA at monoamine synapse is the depletion of the available neurotransmitter for further release. The consequent effect is that MA is less potent after multiple administrations. In part this may explain the need for the chronic users to escalate the quantity of the drug during binges (Cho & Melega, 2002).

Table 9.1: Affinities of monoamines and amphetamines at monoamine transporters in rat brain

Compound	Ki NAT (nM)	Ki 5-HTT (nM)	Ki – DAT (nM)
Dopamine	40	6489	38
Noradrenaline	64	>50,000	357
Serotonin	3013	17	2703
d-Amphetamine	39	3830	35
d-Methylamphetamine	48	2137	114

Ki = nanomolar concentration needed to half-occupy monoamine transporter sites. NAT = noradrenaline transporter; 5-HTT = serotonin transporter; DAT = dopamine transporter *[Source:* Rothman & Baumann 2003).

9.12 All AMP compounds act on the serotonin neurotransmitter system at higher doses, but there are a sub-set of substituted derivatives that do strongly interact with the serotonin system, including: chloroamphetamine (PCA); (N)ethyl-meta-trifuromethylamphetamine (fenfluramine) and methoxyamphetamine.

9.13 It is widely believed that MA has a greater dependence liability and reduced peripheral nervous system action than AMP. But aside from the fact that MA is more commonly smoked there are few differences between the two forms and the precise underlying biological mechanisms are not known. The nucleus acumbens (NAC) and prefrontal cortex (PFC) are areas of the brain which are involved in the regulation of important survival functions relating to memory, motivation, decision making and response inhibition. These areas are implicated as mechanisms of AMP response and dependence. In an animal study, Shoblock and colleagues have shown that MA and AMP raise dopamine levels in the NAC to similar levels, but MA is less effective at raising dopamine levels in the PFC than AMP (Shoblock et al., 2003a). In terms of glutamate activity in the NAC, AMP raised levels while MA did not; while in the PFC MA raised glutamate levels while AMP did not.

9.14 Dopamine release in the NAC appears to be one of the primary sites for the reinforcing properties of AMP and it seems reasonable to suggest that large deviations below or increases toward an optimal level of PRC extracellular dopamine levels produces impairments or improvements in memory and behaviour and which mediate or suppress drug seeking and craving phenomena in response to environmental stimuli. The PFC may also mediate addictive behaviours by suppressing normal behavioural response inhibition thereby cueing drug craving, drug seeking and consumption which override negative drug-related effects. It has also been suggested that the neurotransmitter glutamate is also involved in stimulant reinforcement and locomotor activity in the PFC.

Behavioural Pharmacology

9.15 AMP produce individually variable but generally strongly reinforcing effects in the central nervous system resulting in increased arousal, increased motor activity, diminished fatigue and sleep, and appetite suppression. AMP are sometimes called ‘sympathomimetic’ agents because they have effects similar to the alerting effects of adrenaline and induce dose-dependent vasoconstriction, hypertension, and tachycardia. It is believed that the central activity effects

of MA are more pronounced than those of AMP and its peripheral effects (e.g. on heart rate) are less prominent (Hoffman & Lefowitz, 1996).

9.16 Animal studies have demonstrated that acute administration of AMP produces dose-dependent changes in locomotor activation. In rats, the most commonly studied species, low doses of d-AMP induce a very active and spontaneous movement response (Seiden, Sabol & Ricaurte, 1993). The lower doses that produce activation usually fall in the range (0.3 and 1.0 mg/kg), while at a higher dose higher dose (from 1.75 mg/kg upwards to 4.0 mg/kg) movement is much less varied and is progressively replaced by a distinctive stereotypy phase, characterised by repetitive movements (Segal & Kuczenski, 1997; Cho et al., 1999; Grilly & Loveland, 2001).

9.17 In further pre-clinical work, Shoblock, Maisonneuve & Glick (2003b) have shown although AMP and MA have dose-related effects on working memory, AMP produces relatively greater impairments in working memory than MA. Also, reinforced behaviour is quickly extinguished under AMP treatment conditions. In contrast, MA treated rats appear to be more resistant to behavioural extinction and do not extinguish food-reward seeking that was not rewarded and will continue seeking food reward. This suggests that MA significantly interferes with the ability to altered learned behaviour and thus interferes with behavioural inhibition. This provides some pre-clinical evidence that MA has a greater dependence liability.

10. AMPHETAMINE NEUROTOXICITY

Animal studies

10.1 AMP 'neurotoxicity' arises as morphological and neurochemical changes in catecholaminergic systems in the brain. There is now an established body of research demonstrating that chronic and acute administration of AMP, MA and other AMP analogues to experimental animals causes harmful neurochemical and neuroanatomical changes in comparison to untreated controls. AMP induced neurotoxicity appears to vary in severity and duration according to the species under investigation and the nature of the dosing regime employed. It is important to note that these neurotoxic effects are not necessarily permanent.

10.2 AMP neurotoxicity is generally seen as selective effects on the frontostriatal and prefrontal cortex monoamine neurotransmitter system nerve terminals (a region dense in dopamine and serotonin cells). Damage has also been reported in nonmonoaminergic sytems by studies examining nigral and striatal tyrosine and tryptophan hydroxylase in rats (Kogan, Nichols & Gibb, 1976; Hotchkiss & Gibb, 1980).

10.3 According to the AMP studied, neurotoxicity is also seen as damage or destruction to axons, and neurotransmitter transporter function in these areas as well as the anterior cingulated areas within the frontostriatal region (Gibb, Hanson & Johnson, 1994; Seiden & Ricuarte, 1987; Lew et al., 1997). Some studies have shown that chronic administration of MA can produce long lasting reductions in dopamine transporter activity which the researchers believe points to damage to dopamine nerve endings (Hogan, Staal & Sonsalla, 1994; Frey, Kilbourn & Robinson, 1997; Villemagne et al.,1998). It was initially believed that the transporter loss was

irreversible (Ricuarte & McCann, 1992) but several studies have now reported recovery of transported function following prolonged abstinence in rats (Cass & Manning, 1999) and primates (Melega et al., 1997) suggesting that nerve terminal damage is repaired. The precise mechanisms for AMP neurotoxicity and repair are not known. The current possible mechanisms focusing on glutamate activity within the striatum have been reviewed by Kita, Wagner & Nakashima (2003).

10.4 MA neurotoxicity was first reported in studies of rats (Koda & Gibb, 1973; Kogan et al., 1976) and rhesus monkeys (Seiden et al., 1977) and it has now been demonstrated in a number of other species including other primates, mice, cats and guinea pigs. To illustrate the nature of a typical dosing schedule used in early studies, rhesus monkeys were given low doses of MA eight times a day by subcutaneous injection or constantly by automatic pump infusion. Once behavioural tolerance had developed dosing increased over the next 4 or 6 months at which point subjects were receiving around 50mg/kg per day (Seiden, Fishman & Schuster, 1976).

10.5 It appears that AMP induced neurotoxicity requires an acute high-dosing or continuous low-dosing schedule. One report has shown neurotoxicity after a single MA administration, but this was a very high dose (Fukamura et al., 1998). In general the dose of MA that produces neurotoxic effects is around 20 to 30 times that required to produce behavioural effects such as reduced appetite, increased locomotion and stereotopy (Seiden & Dykstra, 1977).

10.6 Different species metabolise AMP in different ways and there appears to be differential sensitivity to drug effects. There is also evidence that primates appear to be more capable of recovery from neurotoxicity than rats. Nevertheless, it seems reasonable at this point to conclude that MA is capable of exerting neurotoxic effects in all mammals. There is evidence that among primates with chronically administered AMP and deceased dopamine levels locomotor stereotypies and decreased associative behaviour persist for 1-month and 6-months after, respectively, with increased levels of aggression detected for up to 2 years, although these negative behavioural effects are usually eventually reversed (Melega et al., 1997).

Human studies

10.7 It is important to note that animal studies employ a chronic and very high dose AMP administration schedule may poorly compare to self-administered doses in humans. One of the first investigations of AMP induced neurotoxicity in humans was reported by Wilson et al (1996). In this autopsy study, the brain tissue of chronic MA users was compared to non-drug misusing controls. The MA users had deficits in striatal dopamine, and tyrosine hydroxylase and significant loss of dopamine transporter activity. However, levels of DOPA decarboxylase and the vesicular monoamine transporter, known to be reduced in Parkinson's disease, were normal. This suggests that chronic exposure to MA may not cause permanent degeneration of striatal dopamine nerve terminals at the doses used by humans.

10.8 There is now an emerging body of brain imaging studies using positron emission tomography (PET) indicating neurotoxicity among chronic MA users following detoxification (McCann et al., 1998; Ernst et al., 2000; Sekine et al., 2001; Volkow et al. 2001a,b). Volkow and her colleagues assessed changes in dopamine transporter function with five MA users who were able to maintain longer-term abstinence over 12-17 months (Volkow et al., 2001c). The

findings indicated significant improvement, although improvements in neuropsychological test performance were not seen.

Neurocognitive impairment

10.9 There is now a fairly sizeable literature on the question of whether AMP is a risk factor for human neurocognitive impairment. Understanding whether people with AMP dependence have cognitive impairment is important, not least because this may compromise treatment planning and counselling and rehabilitative efforts that require memory and information processing and learning or relapse prevention skills.

10.10 There is some evidence that AMP can enhance as well as impair cognitive processes and acute effects of AMP can produce performance compared to controls (Soetens et al., 1995). But the focus of laboratory studies has been on chronic users. For example, Sato and her colleagues (2002) evaluated attention among chronic MA users using a computerized Stroop task. The Stroop task evaluates attention performance by assessing response latency and error responses to incongruent word, colour and word colour lists in which the subject is required to say the colour of ink (e.g. RED printed in BLUE) while ignoring the word. Eight male MA-dependent subjects were recruited from local treatment centres and an ongoing research study on MA and health. All had been abstinent from MA for between eight and 16 weeks. Twelve matched, male, community-recruited controls were also tested. There were significant differences between the MA users and controls on various attention-based response measures and the MA group exhibiting longer reaction times. The authors interpreted these differences as evidence for an impaired ability to focus attention, and manage distraction among dependent MA users. In Australia, McKetin & Mattick (1997) recruited 26 AMP users from the general community, 80% of whom had used in the past month but were drug free at the time of testing. Attention and memory deficits in AMP users were measured using the Wechsler Memory Scale-Revised neuropsychlological tests of visual and verbal memory and attention and also the block design and digit symbol tests form the Weschler Adult Intelligence Scale-Revised. Those subjects who were classified as higher AMP dependent had poorer visual memory, attention and delayed recall response measures. A history of heavy AMP use (marked by regular injecting) was also associated with impaired visual memory tasks. And in the UK Rogers and colleagues suggest that chronic AMP abusers show specific difficulties in the control of an attentional bias in a visual discrimination learning task believed to involve the functioning of the dorsolateral prefrontal cortex (Rogers et al., 1999).

10.11 Unfortunately, there are inconsistent findings in this literature. Some studies of verbal memory, for example, show that MA users have poorer performance than controls (Simon et al., 2002; Kalechstein et al., 2003) while other studies suggest that MA users perform in the normal range on standard neuropsychological tests albeit at a slower rate on tasks involving working memory (Chang et al., 2002). It seems possible that in some subjects the psychological and physical problems associated with AMP dependence which may be experienced at the time of testing (including chronic fatigue, general poor health, anxiety and depression) will lead to poor cognitive performance.

10.12 There does not appear to be a simple process of global cognitive impairment, and different cognitive abilities are affected and recover at different rates. In a study by Simon and

colleagues, MA users were shown to recover the ability to ignore irrelevant information after 3 months of abstinence, demonstrated unimpaired ability to manipulate information at 3 months, whereas verbal material declines for the first 5-6 months of abstinence (Simon et al., 2000). In a further study, Simon and colleagues studied the cognitive performance in 40 dependent MA users (recruited from treatment centres) and 40 dependent and current cocaine users compared to 40 matched controls by group (Simon et al., 2002). All drug using participants tested positive for their drug of choice on the day of the study via urinalysis. A battery was administered to all subjects containing the following: 3 memory tests; measures assessing manipulation of information and perceptual speed; the Stroop test; a brief IQ measure; measures of verbal fluency; and a measure of executive function using the Wisconsin Card Sort test. With a statistical adjustment for multiple comparisons, there was a slightly different pattern of results between the MA and cocaine samples in comparison to their respective controls. For the MA group, there were differences on test performance for the MA user's word recall, perceptual speed, the ability to manipulate information, IQ, executive function, and there was a slight negative difference on the colour work measure from the Stroop test. The cocaine-dependent sample were poorer that their matched controls on tests of word and picture recall, working memory, the colour work measure from the Stroop test, and on IQ. The authors concluded that cognitive problem profile is similar as seen with cocaine-dependence. The results suggest that MA users have problems with organising information and abstract thinking.

10.13 In their most recent study, Simon and colleagues (2004) investigated the cognitive performance of individuals receiving outpatient treatment for MA dependence. Three groups of 25 subjects per group were studied: those who remained abstinent throughout their treatment; those who were initially abstinence then relapsed; and a third group who continued to use MA throughout their treatment. A neuropsychological test battery was administered to all subjects monthly for 6 months. Comparison scores indicated that the abstinent and relapsing users had poorer performance than those that continue to use MA on a majority of the cognitive tests used. The relapsing group performed worst on tests of episodic memory than either the abstinent and continuous using group. The authors conclude that treatment services should expect cognitive problems among MA users to worsen during the first three months of treatment. There were some acknowledged problems with the study relating to the small numbers of participants and the fact that the relapsing group comprised individuals who relapsed at different points.

10.14 Finally, in two studies, Paulus and his colleagues (2002, 2003) used functional magnetic resonance imaging (fMRI) to identify deficits in decision-making among MA users. In their 2002 study, 10 MA-dependent subjects were compared with ten age and education-matched controls on a simple two-choice prediction task and a two-choice response task. In the second 2003 study, 14 MA-dependent subjects were compared to normal controls on a similar task. The results suggested that MA users have impairments in decision making tasks and that these are of a rigid stimulus-response nature and are not influenced by success or failure results. The fMRI data indicted that the MA subjects had significantly less activation in their dorsolateral, prefrontal, anterior cingulate and orbitofrontal cortex; all areas involved in normal information processing.

11. AMPHETAMINE PSYCHOSIS

Initial description

11.1 Since the late 1930s it has been recognised that repeated use of AMP can produce a psychotic state which may be characterised by paranoid ideas, auditory, olfactory and visual hallucinations, together with behavioural and body postural anomalies (Snyder, 1973). These symptoms are diagnostically very similar to the positive symptoms of paranoid schizophrenia. Most individuals who experience AMP psychosis recover quickly after stopping drug use but some suffer from long lasting residual symptoms including emotional blunting and volitional disturbances (e.g. loss of spontaneity). These symptoms may also be diagnostically identical to negative symptoms of schizophrenia. In 1938 in the USA, Young and Scoville (1938) first described a group of chronic benzedrine users who had been prescribed the drug for narcolepsy and who had subsequently developed paranoid-hallucinatory psychosis in an otherwise clear consciousness. This state was brief and resolved quickly following cessation of Benzedrine use. These cases were initially thought to be a rare and an idiosyncratic reaction, but there is now considerable evidence that some form of psychotic reaction is likely to follow prolonged use of AMP in most individuals.

11.2 Two decades later, at the Maudsley Hospital, Connell reported on the characteristics of 42 oral AMP users who had been admitted to hospital with behavioural disturbances (Connell, 1958). In over half of the patients their psychotic state recovered within a week, but in 24% the presenting psychotic state continued for over two weeks. Connell found that paranoid delusions were seen in approximately 80% of patients and hallucinations in various forms on 60-70%. On the basis of these observations Connell concluded that the clinical features of AMP psychosis were ‘indistinguishable from acute or chronic paranoid schizophrenia’. Although reviewers and commentators on this work acknowledged the similarities with schizophrenia, Slater in the British Medical Journal argued that AMP induced psychosis was distinguished by a higher level of anxiety than schizophrenia (Slater, 1959) while Bell (1973a,b) considered that schizophrenics had far more prominent thought disorder and that this was normally absent in AMP psychosis. Nevertheless, reports from clinical personnel treating schizophrenics described resolving psychosis amongst patients admitted to acute psychiatric wards who were subsequently screened positive for AMP and MA (Angrist & Gershon, 1969). In the late 1960s, Ellinwood described a further set of symptoms that were frequently seen among AMP users with psychosis: a sense of being watched, olfactory hallucinations, déjà vu experiences, and a sense of ‘crystal clear thinking’ and philosophical or mystical preoccupations (Ellinwood, 1968, 1971).

Laboratory studies

11.3 There have been a series of small-scale clinical laboratory studies reported which have sought to induce AMP psychosis directly. These studies have investigated reactions to AMP among volunteers some with a history of AMP use, but no prior psychiatric history. Griffiths, Oates & Cavanaugh (1968) investigated whether four male subjects with no psychiatric histories and who reported no regular use of AMP would develop psychosis when given the drug in controlled conditions. Subjects had abstained from AMP for at least 10 days and then were given 5-10mg d-AMP hourly for as long as they could tolerate it. All developed an abrupt

paranoid-type reaction (beliefs of being watched, secretly photographed, thought control, etc.) although no hallucinations were reported. Subsequently, Angrist & Gershon (1970) repeated this experiment using a dosing schedule of up to 50mg/hr in 4 subjects (described as having a schizoid personality). In the first study, the first subject received a total of 325mg dl-AMP over 29 hours. A steadily increasing set of paranoid symptoms were reported from 7hrs (100mg) onwards with pronounced olfactory hallucinations from 21 hours (230mg) which continued throughout the remainder of the study (patient reporting a 'vile' smell believed to be AMP in his perspiration). From 22 hours (235mg) the patient was hallucinating voices directed at him in the third person and became increasingly afraid and disturbed. A similar course was reported for the other three patients. In a series of further experiments Angrist, & Sudilovsky (1978) reported on subjects given doses between 465-595mg. At these levels subjects became floridly psychotic and experienced both auditory and visual hallucinations (e.g. coloured halos around lights; doors opening and closing in shadows; the image of a gangster in a white raincoat appearing on paper on a notice board). They concluded that while AMP psychosis could be said to be indistinguishable from schizophrenia, visual and olfactory hallucinations did seem to occur more commonly in drug induced psychosis.

11.4 On the basis of this work, the general conclusion appears to be that a range of symptoms that corresponds to those seen in schizophrenia can be induced by cumulatively high doses of AMP to non-schizophrenics in the laboratory. At the same time, there is also anecdotal clinical evidence that psychosis can also develop in individuals with no prior history of schizophrenia following administration of *low dose* AMP over a relatively short period of time (Griffiths, Fan & Oates, 1972; Abruzzi, 1977; Schiorring, 1981). Segal & Schukitt (1983) summarized the results of 13 clinical reports of patients who appeared to develop AMP psychosis with doses of 100mg/day or less (this aggregation included 19% of Connell's patients). In all of these cases the individuals concerned returned to normal levels of functioning within 2-10 days after cessation of AMP. Overall, this literature suggests that AMP psychosis is a condition that once manifest, progressively evolves into more and more abnormal symptoms. For example, auditory hallucinations begin with perception of simple noises but later become specific sounds and voices; visual hallucinations begin as shadowy images but gradually change to become specific images.

The Japanese experience

11.5 The Japanese experience of AMP induced psychosis deserves special mention. Since the epidemic of MA use in Japan following the Second World War, it has been claimed that some 200,000 cases were identified by psychiatric hospitals in which the psychotic symptoms observed were identical to acute or chronic schizophrenia (Tomiyama, 1990). The majority of this literature has not been translated into English. It is common in Japanese studies to observe that between one third and two thirds of patients with MA psychosis continued to experience paranoid symptoms for more than ten days after the stopping drug (Sato et al, 1992). The Japanese literature is important because it suggests that AMP psychosis can result from a low dose sensitization. For example, Sato et al. (1983) reported on 16 patients who developed MA psychosis; were then abstinent from 1-60 months (often spent in jail) and then relapsed to psychosis after just 1-6 injections of MA.

11.6 Japanese clinicians also suggest that some chronic MA users may have an enduring vulnerability to a relapse to a paranoid hallucinatory state caused by further use of MA. It is also been suggested that there may be a spontaneous recurrence of paranoid–hallucinatory states (defined in this literature as 'flashbacks') in reaction to stressful circumstances among patients with a history of MA psychosis but in the *absence* of resumed MA use (Yui, 1997a; Yui 1997b; Tomiyama 1990). Sato (1983) reported acute reappearances of paranoid states induced by one or more challenge injections of MA in 21 of 111 patients with a history of MA psychosis, even after a prolonged period of abstinence.

Recent experience in the Asia-Pacific region

11.7 In recent years a number of countries in the Asia-Pacific region (e.g. Thailand, Taiwan, Korea, the Philippines and China) have reported a high incidence of MA induced psychosis. In Thailand until 2003 there was a dramatic rise in the number of admissions to Thai regional psychiatric hospitals and a significant proportion (more than 20%) were attributed to acute MA-induced psychosis (Verachai et al., 2001). In Taipei, Chen et al. (2003) reported on 445 MA users were recruited from a psychiatric hospital and a detention centre. Among participants with a psychosis diagnosis: 85% had auditory hallucinations; 71% persecutory delusions; 63% delusions of reference. Compared those without psychosis diagnosis, these participants were younger at first MA use, used larger amounts of MA and had higher rates of major depressive disorder, alcohol dependence and antisocial personality associated with increased risk of psychosis. This study suggests that pre-morbid schizoid/schizotypal personality may predispose MA users to develop psychosis, and that the greater the personality vulnerability, the longer the psychosis will persist.

12. OTHER HARMS

Overdose and mortality

12.1 Acute and chronic MA use is associated with sudden cerebroascular crisis (Kia-Ping, 1999; Richards et al 1999a; Zhu et al 2000) and MA has been identified as a risk factor for the development of stroke in relatively young people (29-45 years)(Perez et. al., 1999). MA is known to be associated with intracerebral and subarachnoid hemorrhage stroke patterns (Yen et al., 1994). MA related stroke has been ascribed to the sympathomimetic effects of MA and the increase in pulse rate blood pressure and cerebral vasculitis (Kelly, Gorelick & Mirza, 1992, Kaku & Lowenstein, 1990). Moriya & Hashimoto (2003) reported a case where a massive intraventricular haemorrhage resulting from cerebral arterial spasm and hypertension occurred shortly after intravenous self-administration of MA. Swalwell and Davis (1999) found in a retrospective study of autopsies that among 35 people who died of acute aortic dissection, MA was the second most common risk factor after hypertension.

12.2 In England and Wales in 2002 there were 10 deaths were AMP was the only substance implicated in the death, a 28% increase on the previous year. In the same year AMP were present in 53 cases where multiple substances were implicated in the death, an increase of 60% on the previous year (Ghodse et al., 2003). Currently, the toxicology test undertaken at post-mortems does not distinguish between MA or AMP.

12.3 Data on AMP-related deaths has also been reported elsewhere. In the USA, for example, the Drug Awareness Warning Network (DAWN) survey indicates that during 1991-1994 MA related deaths increased from 151 to 443 (CDCP, 1995). In 1994, the majority of deaths were among white (80%) males (80%) aged 26-44 years (66%). Over nine tenths (92%) of the MA deaths involved at least one other drug, most often alcohol (30%), heroin (23%), or cocaine (21%). Logan, Fligner & Maddix, 1998 reported on the characteristics of 146 MA deaths from the US West Coast, noting 52 cases were a direct result of toxicity. Among the remaining 92 cases, where MA was present but not the direct cause of death, homicide (39) was most common cause, followed by traffic accidents (20) and suicide (18). The range of MA blood concentrations among the non-toxicity cases in the study was substantial (0.05-9.30 mg/L. In most cases death occurred with concentrations of 0.5mg/L or higher but death did also occur with a concentration as low as 0.05mg/L.

12.4 A study from Japan examined 646 autopsy cases that occurred during 1994-1998 in the southern half of Osaka city and surrounding areas (Zhu et al., 2000). MA was present in 15 cases (2.3% at a rate of 2-4 cases per year). The cause of death among the 15 cases were MA poisoning (4), homicide (4), accidental falls (4), fire (1), myocardial infarction (1) and cerebral haemorrhaging (1). About half of the cases had been transferred from emergency medical centres, with a survival time of up 30 hours.

Dependence and withdrawal

12.5 Chronic AMP users are at risk of dependence. The criteria for AMP dependence under DSM-IV are as follows: Increased tolerance; withdrawal; the substance is taken over a longer period than intended; a persistent desire or unsuccessful efforts to cut down; a great deal of time is spent on activities to obtain the substance; important social, occupational, or recreational activities are given up; the substance continues to be used despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by the substance. People who use AMP by intravenous injection and those who smoke crystal MA may be more susceptible to the development of dependence due to the speed of onset and the intense rush which reinforces use. There is some evidence that MA results in a faster progression from initial use to regular use and the need for treatment than cocaine (Castro et al., 2000; Kalechstein et al., 2000).

12.6 Tolerance to AMP often leads to an escalation of dose, conversely some users experience sensitization when small doses produce marked stimulant or mental health effects. Dependence is reflected by increased tolerance to the drug, problems in controlling use, and both physical and psychiatric withdrawal symptoms The DSM-IV criteria for withdrawal from AMP are: fatigue; vivid unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

12.7 Intensity of craving has been found to be a highly significant predictor for continued MA use among those in treatment for MA dependency (Hartz, Frederick-Osbourne & Galloway, 2001). MA dependent people often experience physical craving for the drug, often prompted by conditional cues, long after their last use of MA (Wermuth, 2000). These factors contribute to a loss of control over MA use (Anglin et al., 2000).

Blood borne viruses

12.8 Illicit AMP may be often administered in situations and via ingestion routes that increase the risk of viral cross infection of HIV, Hepatitis C and Hepatitis B, particularly as a result of sharing injecting equipment or other paraphernalia. However, the longer half life of MA makes for less frequent injecting than would typically occur with other stimulants such as cocaine. Some studies have reported that relative to heroin users primary injectors of MA display fewer risk behaviours, and have lower prevalence of antibodies for HIV, and viral hepatitis (Dolan et al., 1987; Murphy, 1987; Kall, 1990; Zeldis et al., 1992). Hutin et al., (2000) report that MA users are also at significantly increased risk of Hepatitis A infection and that the infection transmitted through fecal-oral and percutaneous routes.

12.9 Where relatively higher viral antibody prevalence rates have been found among MA injectors a significant proportion of the sample were either homosexuals or male to female transsexuals (Newmayer et al., 1989). While, MA injectors are at high risk from blood borne virus infection through risky injecting practices, they are more likely to have acquired a blood borne virus through risky sexual practice than other drug users (Zule & Desmond, 1999). MA also appears to have immunosuppressive properties. Among those diagnosed HIV positive, continued MA use has been shown to be associated with immunosuppression and risk of heart disease (Yu, Larson & Watson, 2003). Nath et al (2001) reported a case where a patient was experiencing rapidly accelerating HIV dementia and seizures despite receiving potent antiretroviral therapy. The reduction in health status was thought to be linked to use of MA and cocaine.

Sexual health

12.10 HIV and the other types of sexually transmitted diseases are on the increase in the UK. Chlamydia infection rates of up to 12% have been found in surveys, there are more reports of outbreaks of syphilis, and the number of HIV infections newly diagnosed in 2000 was the highest since reporting began (DoH, 2001). Several studies in the USA have identified an association between risky sexual behaviour and stimulant use, particularly among commercial sex workers (Carlson & Siegal, 1991; Inciardi, 1992; Inciardi, 2001; Yacoubian, 2000). AMP users are thought to be at greater risk of viral infection relative to heroin users because AMP enhances sexual drive while opioids may diminish interest in sex (Zule & Desmond, 1999).

12.11 Both research data and anecdotal reports suggest that MA use is strongly associated with risky sexual practices, because of the intensity and duration of drug effect (McClean, 2002; Rawson et al., 2002). MA use is associated with increased libido, unsafe sex and increased risk of disease transmission (Rawson et al 2000). A comparison of sexual functioning between primary MA users and primary users of alcohol, opioids and cocaine found that MA users regardless of gender reported relatively more highly positive aspects of sex under the influence of the drug (Rawson et al., 2002). MA use is associated with prolonged and rougher sex, which may lead to bleeding and abrasions. MA use has been found to be independently related to decreased condom use during sex (across both heterosexual and homosexual groups), prostitution, and sex with known drug users (Molitor, 1988). In a study of sexual HIV risk among gay and bisexual male MA users in Los Angeles, Frosch et al (1996) found a strong

association between MA abuse and high risk sexual behaviour with over two fifths of the sample reporting unprotected sex and frequent use of the drug before and after sex.

Prenatal exposure to amphetamine

12.12 There have been concerns about exposure to MA *in utero* with reports of an increased likelihood of small but significant decrements in cognitive, language and behavioural functioning (Eriksson et al., 1978). In a study of the effect of MA use on pregnant women found from an assessment of neonates that while there were no differences in infant growth between MA-exposed and MA-unexposed neonates, MA exposure throughout gestation was associated with decreased growth relative to infants exposed only for the first two trimesters (Smith et al., 2003). In a study to ascertain the impact of intrauterine MA exposure on the overall health of newborns in Bangkok, Thailand, birth records of somatic growth parameters and neonatal withdrawal symptoms infants born to MA using women were compared to other non-exposed newborns (Chomchai et al., 2004). Infants of MA using mothers were found to have a significantly smaller gestational age-adjusted head circumference and birth weight measurements. MA exposure was also associated with symptoms of agitation (5/47), vomiting (11/47) and tachypnea (12/47) when compared to the non-exposed group Overall, it is difficult to interpret this literature. The precise risk of MA exposure is hard to determine and it is possible that the health of women taking MA will generally be poorer than their non-MA using peers, resulting in lower birth weight.

Crime

12.13 AMP users are at risk of contact with the criminal justice system and some engage in acquisitive crime to support their drug use. In 2000 in the UK 6,637 people were found guilty, cautioned or fined for offences related to the use of AMP (Corkery, 2001). Klee & Morris (1994) examined the criminal activity of a group of heroin users and a group of AMP users in England. They found that while both groups reported similar crime rates, the heroin users' involvement in crime was more closely linked to their expenditure on drugs, whereas for AMP users, the frequency of drug use predicted crime.

12.14 AMP related driving impairment and fatalities have also been studied. Overwhelmingly alcohol and depressant medications are the substances most commonly found to be present in toxicology assessments in fatal accident investigations (Charlier, 1998; Christopherson, 1999; De Gier, 1999; Olaf, 2003). However, Logan (1996) evaluated the effects of MA on driving performance in 28 cases where drivers who had been arrested or killed in traffic accidents and had tested positive for MA. Typical driving behaviours reported by the arresting officers included drifting out of the lane of travel, erratic driving, weaving, speeding, drifting off the road, and high speed collisions. Combined alcohol and MA use was not common, but concurrent cannabis use occurred approximately 33% of the cases. It was judged that the effects of withdrawal from MA use such as fatigue, hypersomnnolence and depression were likely contributors to many of the accidents. Aitken et al (2000) conducted a series of focus groups in Australia about driving with different types of drug users including users of AMP and cocaine. The AMP users reported that their drug taking gave them 'sharpened reflexes'

and ‘great energy’ and some provided descriptions of particularly dangerous driving when going to buy drugs.

Violence

12.15 There is some evidence that regular AMP users are more likely to be engaged in violent acts and are significantly more likely to act impulsively with no planning compared to other types of drug users. In part, this may arise because of the increased likelihood of paranoid ideation associated with the use of these drugs and withdrawal from them (Maden et al., 1992). Wright & Klee (2001) reported that among a sample of 86 heavy AMP users in the UK, 47% reported committing a violent crime and 62% reported problems with aggression while 35% reported both. Approximately 24% of the sample reported that their involvement with violent crime was directly from AMP intoxication, withdrawal, mixing drugs or suffering from an AMP psychosis. In their study of 450 moderate to heavy crystal MA users in the USA, Morgan and Beck (1997) reported that 44% of the males in their sample reported being violent as a result of using MA. Logan (1996) observed a correlation between MA use and violence among drivers who were driving whilst intoxicated on alcohol and involved in accidents. In Spain, Lora-Tamayo, Tena & Rodriguez (1997) observed a high proportion on violent deaths recorded on autopsy reports of MA deaths.

12.16 MA is also implicated in violent domestic disputes. For example, police in California have contended that MA is involved in almost 90 percent of the domestic dispute cases investigated (US Justice Department 1999). Many MA users seen in the psychiatric emergency service in the US have reported long histories of aggression (Szuster, 1990). However, since some MA uses have personality disorder characterised by proneness to aggression this clouds the issue of how direct the relationship may be (Chen et al., 1999). Interviews conducted with a convenience sample of 205 chronic MA users from the San Francisco bay area, showed that 30% of males and 23% of females had committed violence while under the influence of the drug (Sommers & Baskin, 2003). Of these 55 respondents (36.4%) reported that they had never committed a violent crime before using the drug. This study suggests MA may well heighten aggressive behaviour in some people, but that violence is not a inevitable outcome even among chronic users.

Hazards of methylamphetamine manufacture

12.17 Clandestine AMP laboratories are dangerous to both those who operate the laboratories, those who are nearby such as neighbours and family members, law enforcement and other service personnel such as fire officers who are called to enter a laboratory. The main physical harms associated with the manufacture of MA are burns and toxic fume effects (CDCP, 2000; Scott, 2002). Chemicals used in MA production such as methylamine, phosphorus, ethanol, and lithium aluminum hydride are highly flammable and the use of red phosphorus in the production process creates phosphine, a lethal gas (Willers-Russo, 1999). Furthermore, phosphine, white phosphorus, lithium, sodium, and hydrogenation catalysts may ignite spontaneously on contact with air and/or water, which may account for the large number of laboratories detected as a result of fires or explosions. In the USA, it has been estimated that one in six laboratories is discovered because of explosion, fire, or toxic fumes (Scott, 2002).

A recent US study of contamination in domestic environments following the production of MA concluded that most individuals nearby to where production took place were contaminated with the drug and that several chemicals including iodine and hydrogen chloride would have spread throughout the building (Martyny et al., 2004).

12.18 Of the 1673 events reported to Hazardous Substances Emergency Events Surveillance Program in the USA between 1996-1999 that resulted in injuries, 112 (0.5%) events were associated with MA (53% of all MA related events). Of the 112 events, 79 (51%) of the injured were first responders: 55 (70%) were police officers; nine (11%) emergency medical team personnel; eight (10%) fire-fighters, and seven (9%) hospital employees. The most common effects were respiratory irritation (i.e. cough and difficulty breathing)(60%) and eye irritation (11%). The majority of those effected (77%) were treated at a hospital on an outpatient basis (Cooper et al., 2000). A survey of police personnel in the USA who had been involved with raiding a MA laboratory found that 50% had experienced symptoms, mostly chemical irritation, resulting from their work involving illicit MA laboratories (Martyny et al., 2004).

12.19 In the USA children of small-scale producers may be at risk either through ingestion of dangerous chemicals and MA or from burns to their lungs or skin from chemicals or fire. The number of children found at seized MA laboratory sites in the United States more than doubled from 1999 from 950 through to 2028 in 2001 and in that year approximately 35 percent (700) of the children found at MA laboratory sites tested positive for toxic levels of chemicals (NDIC, 2003).

12.20 In the USA, it is estimated that for every kilo of manufactured MA, five to six kilos of hazardous waste is produced (Pennell, et al., 1999). The operators of illicit laboratories may simply move on leaving the waste behind or dump it causing serious environmental problems (Irvine & Chin, 1991). In the USA the costs of cleaning up after a MA laboratory has been estimated as typically $150,000 for the large scale superlabs and $2500-$10,000 for average sized sites (Scott, 2002).

13. TREATMENT

Acute intoxication and overdose management

13.1 Emergency medical staff who attend to AMP users who are experiencing acute intoxication (overdose) of the drug may be faced with severe cardiovascular and neuropsychiatric effects. There may also be other related pulmonary, renal and gastrointestinal disorders also present. Hyperthermia is also common and seems to occur because of muscular hyperactivity, increased metabolic demands on the body or a malfunction of the hypothalamus. Overdose management usually involves gastric emptying via an activated charcoal agent, but this needs to be done within one hour of ingestion to be effective.

13.2 The severity of overdose symptoms is usually dose-related but appears also to be related to the patient's overall level of tolerance and toxicity (Lan et al., 1998). A patient's reaction to the overdose and the course of overdose symptoms and complications is likely to be affected by his/her overall levels of health and the health problems that are related to chronic MA use (e.g.

fatigue/exhaustion, malnutrition and systemic and soft tissue infection including abscesses due to injecting). Richards et al. (1999b) reported on the characteristics of 461 patients who presented to a Los Angeles emergency medical centre during a six-month study period and who had a positive toxicology screen for MA. The patients were most commonly white males in their early 30s and with no health insurance. The most common reason for hospital attendance was injury from blunt trauma (33%), with the most common causes being vehicle accident and assault followed by altered level of consciousness most commonly characterized by acute agitation (23%).

13.3 The most frequently encountered presentation is racing heartbeat (tachycardia), hypertension and also agitation, paranoia, confusion and violence. There are documented cases of severe overdose toxicity which is accompanied by hypotension (Chan et al., 1994) and early hypertension may be followed by hypotension after some hours following hospital admission. For example, Malay (2001) reported a case of male MA user who ingested an overdose and presented with blood pressure of 74/28 mmHg which then rose to 160/100 mmHg on the second day. Unlike opioid drugs there are no antagonist medications capable of quickly reversing the effects of MA. In emergency medical settings, clinical staff rely on benzodiazepines, or typical or atypical antipsychotyic medication for stabilisation of agitation of psychiatric symptoms (Malay, 2001). Antihypertensive agents and beta-blockers have been used to reverse cardiovascular symptoms. Phentolamine and nitroprusside are used to treat AMP induced hypertensive crisis, and tachycardia can be controlled by propranolol (Guharoy, 1999).

Stabilization-withdrawal management

13.4 The detoxification and stabilization phase of treatment is designed for people with substance withdrawal following active and prolonged use of drugs. Detoxification describes a process of supportive, usually medical care and pharmacotherapy to facilitate a return to abstinence and physiologically normal levels of functioning. This process is usually needed for the management of opioid, barbiturate, and benzodiazepine dependence, where a characteristic rebound physiological and emotional withdrawal syndrome is experienced usually around 8-12 hours after the last dose of the drug. Users of AMP may also experience substantial emotional and physiological symptoms and require a period of stabilizing treatment for their discomfort prior to entering rehabilitation.

13.5 Withdrawal from MA is characterised by a protracted period of anhedonia and dysphoria which is usually accompanied by intense urges to use the drug. These experiences are distracting, incentive-motivational or expectancy-based mental events taking the form of strong urges and desire to obtain and use the drug and are normally elicited by conditioned cues in the user's environment (people, places and objects) that have become associated with taking the drug. AMP use can also have automatic subjective aspects with little or no conscious appraisal (Tiffany, 1990).

13.6 Whilst craving is neither a necessary or sufficient condition for AMP use, researchers in the nicotine (e.g. Killen & Fortman, 1997) and alcohol treatment field (e.g. O'Connor et al., 1991) have shown that craving experiences are predictive of abstinence, relapse and retention in treatment. However, for psychostimulants there have been mixed findings. In the human

laboratory setting, craving does not appear to reliably precede cocaine use (Dudish-Poulsen & Hatsukami, 1997) nor does cue-elicited cocaine craving after treatment predict relapse (Margolin et al., 1994) or abstinence one year after treatment (Negrete & Emil 1992). On the other hand, Weiss et al. (1996) demonstrated that low craving scores predicted initiation of cocaine abstinence in the following month and in the single published report to date on MA craving during treatment, Hartz et al (2001) found that craving intensity *did* predict MA use in the week immediately following each craving report.

13.7 In Thailand, Srisurapanont, Jarusuraisin & Jittiwutikan (1999a) have reported on the effectiveness of the AMP-like, dopamine agonist antidepressant, amineptine to ameliorate MA withdrawal symptoms. In a two-week, inpatient, placebo-controlled double-blind trial, 44 MA dependent subjects who were abstinent from MA for 24-120 hours and had no psychotic symptoms were given either 300mg/day of amineptine or plabebo for two weeks. Results pointed to weak positive effects for amineptine on some aspects of withdrawal severity. However, the manufacturer (Servier Company, France) has since withdrawn this product following reports of non-medical abuse.

Amphetamine substitution pharmacotherapy

13.8 In London during the mid 1960s over-prescribing of Methedrine by several doctors established an illicit market and this led to the first presentation of young dependent MA users to the specialist drug dependency clinics. Mitcheson et al (1976) describes the treatment of a small case series of 23 patients (2 female) at the outpatient addiction clinic at the Maudsley Hospital. The average age of these users was 21 years (range 17-26 years). Previous use of other substances was the norm and most initiated to MA in the previous year. At entry to treatment all were injectors and were consuming a daily dose in the range of 1 ampoule (30mg) to 16 ampoules (480mg) a day. All patients were diagnosed with AMP psychosis. Twelve patients were given 4 ampoules of MA per day as maintenance treatment (these patients reported to be using an average of 7.5 ampoules a day on admission). The remaining patients either did not wish to be prescribed MA or dropped out of contact (3 patients) and were either using intermittently and at low levels or were not initially prescribed MA (7 patients). Of these latter patients 6 were subsequently given a variety of oral medications described as ‘diazepam MA’ tablets or ‘barbiturate/amphetamine mixtures’. The treated patients made an average of 8.5 contacts at approximately weekly intervals. The authors report that two patients made considerable progress and eventually they were successfully withdrawn from MA; a third made slow progress and for the remaining 17 there was little evidence of improvement – with the clinic regarding these patients as ‘therapeutic failures’.

13.9 Since the 1968 epidemic, there has been a small, local continued prescribing of d-AMP in other areas of England and Wales. Although insubstantial in comparison with opioid substitution pharmacotherapy in the UK, there has been a small but enduring clinical practice in the UK using d-AMP sulphate as a substitution agent for chronic AMP users. AMP injectors are mainly targeted for this treatment and the practice has been justified on harm reduction grounds (Fleming & Roberts, 1994). In Portsmouth, Fleming & Roberts (1994) conducted a case note review and patient questionnaire study with 26 AMP injectors (8 women) who were treated in the clinic during the first three years of its operation from 1989. Patients were prescribed 30mg/day oral AMP. The stated aims were to encourage users into

treatment so that they could stabilise their drug use, reduce their injecting behaviour, reduce the health risk from taking adulterated street AMP and receive HIV risk reduction education. Descriptive results suggested an overall improvement in all treated patients with reductions in injecting and criminal involvement. Pates, Coombes & Ford (1996) reported similar improvements in a group of 10 AMP injectors from Cardiff who were also substituted with d-AMP. In Manchester, Klee et al. (2001) reported on a group of 12 matched pairs of AMP maintained and non-prescribed AMP users. There was greater retention in treatment among the maintenance group but a non-significant difference for reductions in frequency and intensity of AMP use, which may have reflected insufficient statistical power. A recent small-scale, two-centre trial of d-AMP maintenance commissioned by the English Department of Health did not provide evidence for better outcomes over standard counselling. Current Department guidelines dictate that this practice must be carried out and closely monitored by experienced practitioners as part of a comprehensive package Merrill et al., 2004).

13.10 In Sydney, Australia, Shearer et al (2001) reported results of a feasibility study comparing 21 chronic MA injectors given 60mg/day d-AMP with a control group of 20 AMP users. Both groups received standard drug counselling. At follow-up, the experimental group engaged more with the counselling programme and attended a greater number of sessions. Both groups responded well to treatment as measured by reductions in injecting, positive urine tests for MA and lower severity of dependence but these improvements were significantly better among the experimental group. In Cornwall, White (2000) reported on the results of a AMP maintenance study with 148 users prescribed AMP at an average of 45mg/day (maximum daily dose – 90 mg). There was a 50% reduction in injecting during the first 2 months of treatment but retention was a problem, with some 34% dropping out. A single US study has evaluated d-AMP maintenance for chronic cocaine dependents (Grabowski et al., 2001). In a three arm, dose-ranging study 128 cocaine dependent patients were randomised to placebo, 15-30mg/day d-AMP or 30-60 mg/day d-AMP. The treatment regime was acceptable to the patients and positive trial results were obtained with dose-related improvements over placebo in terms of treatment retention and cocaine use.

Relapse-prevention

13.11 Rehabilitation is appropriate for patients who are no longer experiencing acute physiological or psychological effects of recent AMP use and who need behavioural change strategies to regain control of their urges to use. A practical goal of this stage of treatment is to prevent a return to AMP use and assist the person to developing control over urges to use alcohol or drugs, or both, usually through sustaining total abstinence from all drugs and alcohol; and to assist the patient in regaining or attaining improved personal health and social function, both as a secondary part of the rehabilitation function and because these improvements in lifestyle are important for maintaining sustained control over substance use.

13.12 In California, an intensive, multimodality outpatient therapeutic programme for MA dependence has been developed called the ‘matrix model’ (Rawson et al., 1991; Obert et al 2000). The model was developed in the 1980s as a highly structured community relapse prevention treatment for cocaine dependence (Rawson et al., 1998) and later adapted for patients with primary opioid problems (Rawson et al., 1995). In its early form, the programme

involved six months of active treatment during which patients attended the clinic three to four days a week. Therapy consisted of 56 individual sessions covering psycho-education, group relapse prevention; family involvement; self-help involvement (Narcotics Anonymous or Alcoholics Anonymous) and regular drug testing. Economic pressures to shorten treatment led to a condensed 16-week version which increased the group component and decreasing the number of individual sessions to 3x45 minute sessions. These individual sessions are seen as critical for personal treatment planning and goal setting and may sometimes involve significant others in the planning process.

13.13 There have been several published outcome evaluations of the matrix model. For example, 100 cocaine dependent patients (50% African American or Hispanic) were randomised to six months of Matrix treatment or to "other available community resources" (Rawson et al., 1995). At a three and six month follow-up 40% of the community resource group reported engagement in some form of treatment but the diversity in services accessed compromised the ability of this group to serve as an experimental control. Among the Matrix group, 24% completed treatment and although there were reductions in cocaine use in both conditions over 12 months there was not a significant difference between them. There was however a positive linear relationship between the amount of Matrix treatment received and the percentage of cocaine negative urine results but not for the community resources group.

13.14 An uncontrolled study by Rawson's group provided further evidence for the potential of the programme. Huber et al (1997) reported clinical data for 500 MA and 224 cocaine dependent patients who have received Matrix treatment. The MA patients remained in treatment for an average of 17.1 weeks versus 18.0 weeks among the cocaine group, and the percentage of weekly urinalysis positives for the primary drug were 13.3% for the cocaine group and 19.3% for the MA group, suggesting a similar response to treatment for MA users as seen for cocaine users. In a non-random convenience sample study, 183 (42%) were contacted from an eligible base of 437 patients in the MA group. Of these, 114 agreed to be interviewed. In this group, 17.5% reported MA use in the month before interview (compared to 86% in the month before entry to treatment). In a natural history study of MA use and treatment outcomes, Brecht et al (2000) investigated predictors of relapse to MA after treatment in sample of 98 patients who had been treated in publicly funded treatment programmes in Los Angeles and who were followed up 2-3 years after treatment admission. Half of the patients had resumed MA use after six months but almost half (49%) reported continuing abstinence at the time of the interview. Overall, all but three subjects had been abstinent for at least 18 months and two thirds of this continuing abstinence group remained MA-free for at least two years. Overall, a shorter time to relapse was related to a longer previous time in treatment a shorter time in the index treatment studied, older age at first use of any substance and lifetime reporting of selling MA.

13.15 Although design and implementation weaknesses limited the reliability of conclusions that could be drawn from the earlier study, these findings were sufficiently positive to pave the way for a formal US Centre for Substance Abuse Treatment (CSAT) funded evaluation. In 1998, CSAT initiated a parallel, eight-site randomised controlled trial in California (six sites), Montana and Hawaii with a six month post-admission follow-up. Between 1999 and 2001, 978 MA-dependent patients were randomised to 16-weeks of the Matrix model with the local

treatment agency's standard outpatient treatment programme (Huber et al., 2000). The standard treatment most commonly comprised Minnesota model and cognitive behavioural counselling approaches. Retention in treatment was superior (odds ratio = 1.38) among Matrix treated patients at all sites with the exception of a drug court programme. After adjusting for patient differences, the programme completion rate was 40.9% for Matrix patients and 34.2% among the treatment as usual patients. Matrix patients provided more MA-free urine samples and had longer periods of abstinence during treatment than those in the comparison programmes. Both groups self-reported statistically significant reductions in MA use at six month follow-up but there were no statistically significant differences by treatment condition.

13.16 In the UK, the National Treatment Outcome Research Study (NTORS) of the 1075 patients recruited a small subgroup of 80 cases reported that there main drug was a psychostimulant (AMP or cocaine) although 637 cases had used a stimulant in the 90 days before treatment entry. Among a group of 60 clients who cited AMP as their main drug and were followed up one year after entering treatment, there were improvements in AMP use and other problem behaviours at (Gossop, Marsden & Stewart, 2000).

13.17 There is small set of studies that have examined whether antidepressant medication can reduce the likelihood of AMP relapse (presumably through a general elevation in mood and possibly by reducing cravings). Srisurapanonent, Jarusuraisin & Kittirattanapaiboon (2004) have conducted a statistical review of four randomised controlled trials (two unpublished at the time of the review) of relapse-prevention pharmacotherapy with adult MA users (aged 18-65 years). The medications trialled were fluoxetine and amlodipine (two unpublished investigations by Batki et al. 2000), imipramine (Galloway et al., 1996) and desipramine (Tennant et al., 1986) were investigated in these studies. In all of these investigations the primary outcome measure was changes in MA use and the number of positive urine tests. The results of the review indicated that fluoxetine, amlodipine, imipramine and desipramine had little impact on MA abuse and dependence, although there was some evidence that fluoxetine can reduce craving for MA during treatment and imipramine may help to increase treatment attendance and retention.

14. CONCLUSIONS & RECOMMENDATIONS

14.1 MA is a potent derivative of amphetamines with a substantial health risk and dependence liability. However, based on our review, there does not appear to be a firm foundation and rationale for reclassifying the drug under the Misuse of Drugs Act 1971, at least at the present time. There does not appear to be evidence at present in the UK that MA is causing much harm - but there is evidence form other countries in terms of brain damage from heavy use – also there is evidence in preclinical studies as to why this might be and the fact that MA can be smoked means it is more addictive if used in this way – as AMP cannot be smoked. It is also possible that reclassification could have the unintended consequence of increasing interest in the drug amongst potential users.

14.2 However, although the current prevalence of MA is relatively low in the UK, The Advisory Council appreciates that this may change and that it is essential to have strategies in place to

detect any shifts in the pattern of prevalence of use. In order to assist with this the ACMD recommends:

14.3 Closer monitoring of **certain sub groups** within the UK who are more likely to use MA, for example, the Gay community and clubbers. General population surveys would not pick up the drug taking behaviour of such groups. In order to achieve this outcome we recommend;

i) Encouraging the commissioning of specific research studies / surveys for identified sub groups likely to use the drug.
ii) Encouraging additional questions on MA to be considered for inclusion in existing or future surveys / research that is being carried out on the identified sub groups or stimulants. As part of this the ACMD recommends -

iii) The profile of MA is raised at the National Treatment Association Research Steering Group so that it is considered for inclusion in any future stimulant-related research.
iv) The Home Office to consider funding the Amnesty Bins Project.
v) FRANK and its devolved equivalents to extend their options for MA to include MA in its powder form and crystal from as well as 'yaba'.

14.4 **Treatment Data**: The ACMD recommends that MA is differentiated from AMP and recorded by Drug Treatment Monitoring Systems.

14.5 **Arrestee Survey** (also referred to as the ADAM and NEW-ADAM Survey): This survey is designed to measure the drug use and self reported offending among a nationally representative sample of individuals at the first point of entry in the criminal justice system. The Arrestee Survey has an achieved sample size of about 9,000 arrestees a year. This is a very high drug-using population so it is more likely to pick up new drugs of use than a household survey. The ACMD recommends that thought is given to developing questions to be put forward for consideration in the Arrestee Survey for identifying MA use.

14.6 HMRCS (Her Majesty's Revenue & Customs Service) seizures of MA are very low. If the prevalence of MA was to increase this should in turn be reflected in HMRCS seizures. The ACMD recommends HMRCS forward all potential seizures of amphetamines that otherwise would not be analysed to the Forensic Science Service for further analysis. This should be done for an initial six months period and extended if required.

14.7 The ACMD recommends that attention is given to monitoring the heroin supply route from South East Asia to Europe. If this supply route became popular there would be the danger that MA would be brought into Europe along with heroin.

Precursors

14.8 Whilst not a firm ACMD recommendation, the Council feel it appropriate that policy makers are aware of the following development. There are inhibitors to prevent the extraction of precursors to produce MA, for example, the 'Pfizer Lock Technology'. There is also a product

called ‘Glowtell’ that can be added to liquid ammonia. This has the effect of turning MA tablets pink if this ammonia is used as a precursor. The ACMD feels it would be wise to keep these developments under review before making recommendations on how they could be used in the UK, as they are in early stages of development.

14.9 The ACMD recommends that the precursor chemicals; red phosphorus and hydroiodic acid are added to the European Precursor Legislation.

14.10 The ACMD recommends the removal of the exemption on ephedrine tablets under the European Precursor Legislation

Health

14.11 The ACMD recommends that St. George’s Medical School have provisions in place for differentiating and collecting data on MA when recording drug-related deaths.

14.12 Discuss with the Office of National Statistics on the monitoring of drug specific deaths through routine mortality data and drug related death database and potential implications of changes in coronial system, use of toxicology and verdicts on the monitoring of MA.

14.13 The ACMD recommends more investigation take place into AMP positive screenings amongst psychotic inpatient admissions to determine if any are due to MA.

Pharmacology

14.14 The ACMD recommends that closer links are forged with the National Institute of Drug Abuse (NIDA), as thy have undertaken research on MA in terms of its toxicity and addictiveness. Closer ties would ensure that not only was information shared but duplication of work was avoided. It was also felt that greater collaborative work with NIDA could take place in order to build a solid database on amphetamines.

14.15 The ACMD identified a number of specific areas regarding MA that required further research to be undertaken and wishes to bring this to the attention of research commissioners and policy makers. These were:

i) More research to be undertaken to determine why MA was different to AMP.
ii) MA seemed to have different effects to AMP on glutamate release in the brain. There was not much evidence as to why this was.
iii) Differential affects on cardiovascular symptoms to explain why users can take considerable amounts of MA in a short period without feeling any cardiovascular problem.
iv) Research should be encouraged to be undertaken on the neurotoxicity of MA as this would allow more thought to be given to effective treatment interventions.
v) Research should be encouraged to be undertaken on the differential brain entry/exit for MA compared with AMP.

Other Considerations:

14.16 The ACMD will look to forward its findings where appropriate to the DTI Foresight Project to

see if they would be willing to undertake further work on the topic.

14.17 The ACMD recommends that closer links are forged with The National Drug and Alcohol Centre, Sydney, Australia. They have an extensive MA using population and are undertaking an assessment on the harms associated with MA.

14.18 The ACMD recommends that the Home Office and the Department of Health consider adding MA to any stimulant research that they may be undertaking in the future.

14.19 The ACMD recommends that in an effort is made to improve the knowledge base on the cognitive harms of stimulant use in general. There maybe merit in undertaking research on the longer-term cognitive effects of stimulants such as cocaine and AMP sulphate. This would not only help firm up the knowledge base on stimulants the UK was currently experiencing problems with but it would also mean having the skills and expertise already in place when dealing with MA if it was to increase in prevalence in the UK.

14.20 The ACMD recommends that MA be a standing agenda item at its own Technical Committee meetings.

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