GUEST EDITORIAL

Methamphetamine—what primary care practitioners need to know

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Introduction

General practitioners (GPs) and other primary care professionals such as practice nurses and mental health workers, operating in multidisciplinary care teams, have a key role to play in the prevention, early detection and management of substance abuse and addiction. Over 80% of patients will attend a GP at least once a year, GPs are seen as credible and trusted educators, and patients' attitudes towards lifestyle enquiry and interventions by GPs are positive. Moreover, people with addictions, particularly drug users, prefer to see their GP rather than attend outpatient drug dependency services.[1] Primary care practitioners can identify substance abuse problems early, prevent addiction, facilitate access to treatment and provide ongoing, holistic and non-stigmatising services and support to patients and their families—all core features of general practice.[2]

Methamphetamine is the most potent form of amphetamine available. There are estimated to be 26 million amphetamine and methamphetamine users worldwide, making these the most widely used illicit drugs after cannabis. Reported use of amphetamines is highest in the UK, Australia and New Zealand (NZ). This article reviews the epidemiology, pharmacology and clinical effects of methamphetamine, and treatment options for methamphetamine use.

Background

Amphetamines comprise a closely related family of drugs with psychoactive properties. They include amphetamines, methamphetamine, dexamphetamine and methylphenidate (Ritalin).[3]

Methamphetamine, also known as methylamphetamine, is the most potent form of amphetamine available. It is a synthetic drug that is sold under various street names including 'P', 'speed', 'base', 'meth', 'ice', 'crystal', 'whiz', 'goey', 'burn', 'tina', 'shabu', 'Ya Ba', 'pure', 'rock', 'crank', 'crack', 'chrissy', 'glass', 'go' and 'rock candy'.[4,5]

Methamphetamine is relatively easy to synthesise from commonly available medications in NZ, and it can be manufactured in laboratories small enough to fit into a room or car boot. These are often called 'clan labs' (clandestine laboratories). The number of 'clan labs' closed by police rose from one in 1997 to 200 in 2003.[6]

Methamphetamine is a 'Class A' controlled drug under the Misuse of Drugs Act 1975. The maximum penalty for production and distribution of methamphetamine is life imprisonment. Customs' seizures of pills to manufacture methamphetamine have escalated significantly from 10 300 in 2000 to 2.043 million at the end of 2005.[7]

There are four recognised ways of marketing methamphetamine at a street level:[4]

1. **Powder**—a white or off-white powder generally known as 'speed', typically of low purity, which can be snorted, injected or taken orally. It is usually adulterated with glucose.
2. **Base**—a damp or oily substance with a white to yellow or brown colour with a higher purity than powder. It can vary a lot in its appearance and is known by a range of terms, including 'paste' and 'wax'. This form is typically injected and sometimes swallowed. Base is sold in 'points' which weigh about 0.1 grams.
3. **Pills**—methamphetamine has also been sold in a pill form on the ecstasy (3, 4-methylenedioxymethamphetamine or MDMA) market.

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These pills contain only a small dose of methamphetamine, which is often combined with ketamine to give an ecstasy-like effect.

4. **Ice**—also known as 'crystal meth' or 'P'. This is methamphetamine in its purest and most potent form. It has a translucent to white crystalline appearance. Ice is usually smoked or injected.

Methamphetamine sells for about $100–180 per gram, and more pure forms for about $1,000 per gram.[8]

Epidemiology

There are estimated to be 26 million methamphetamine users worldwide. In Australia, it has been estimated that 6.3% of the population have used methamphetamine at some point in their lifetime and 2.4% within the last year.[9] Comparable figures for NZ are 11.1% and 4.2% respectively.[10] Consequently, enquiring about recreational drug use should be part of any assessment of lifestyle issues in the consultation.

When considering trends in methamphetamine use, population level surveys in Australia have not suggested a large increase in the overall numbers of users, and the most recent survey suggested that powder methamphetamine remained the form most commonly used, as opposed to crystal methamphetamine. However, there does appear to have been a shift towards the use of crystal methamphetamine among sentinel groups of ecstasy users and injecting drug users, whose use is likely to be heavier and through higher-risk (smoking or injecting) routes of administration.[11] In NZ there has been an increase in the level of use of both amphetamine and crystal methamphetamine in 2006 compared to 2003. These findings suggest that there has been some entrenchment in amphetamine use in recent years since the reported levelling out of its prevalence of use in 2003.[10]

Pharmacology

Amphetamines are prescribed legitimately for the treatment of a small number of clinical conditions:

KEY POINTS

- Methamphetamine is the most potent form of amphetamine available.
- Worldwide amphetamines are the most widely used illicit drugs after cannabis.
- An estimated 11.1% of New Zealanders have used methamphetamine at some point in their lifetime, and 2.4% within the last year.
- Methamphetamine can be taken by smoking/inhalation, snorting, orally, intravenously or rectally.
- Methamphetamine stimulates the central and peripheral sympathetic nervous systems.
- Regular methamphetamine use can cause long-term physical and psychological effects, including depression and psychosis.
- There is an association between methamphetamine use and violent behaviour.
- Treatment options are limited and most users quit through self-management.

- Narcolepsy
- Attention deficit hyperactivity disorder (ADHD)
- Obesity (rarely used).

Typical doses of therapeutic dexamphetamine are 10–40mg daily. Common abused doses of methamphetamine are 100–1000mg daily, and up to 5000mg in chronic binge use.[5] Methamphetamine is much more centrally acting than dexamphetamine.

Mechanism of action

Methamphetamine activates the central nervous system (CNS) and the peripheral sympathetic nervous system (PSNS). This is achieved by increasing synaptic (nerve junction) concentrations of the excitatory neurotransmitters dopamine, noradrenaline and serotonin. This occurs by two mechanisms. First, there is an increased release of neurotransmitters from storage sites in nerve terminals. Second, methamphetamine inhibits reuptake by blocking the transporters responsible for removal of neurotransmitter molecules from the synaptic cleft. Increased noradrenaline concentrations contribute to the anorectic (appetite suppressing), locomotor and sympathomimetic effects, while increased dopamine concentrations stimulate locomotor effects, psychosis and perception disturbances; and serotonin is responsible for delusions and psychosis.[3]

Through stimulating neurotransmitter release, and preventing their reuptake, methamphetamine use results in:

- **CNS effects**—euphoria; increased well-being, confidence and physical activity; improved cognitive and physical performance; suppression of appetite and need for sleep.
- **PSNS effects**—elevated blood pressure, tachycardia (rapid heart rate) or reflex bradycardia (slow heart rate), increased temperature. Large doses can cause cardiac arrhythmias (irregular heart rates).[3]

Routes of administration

Methamphetamine can be taken by mouth (oral), injection (intravenous), smoking/inhalation ('chasing the dragon'), snorting (intranasally) or rectally ('shelving'). Smoked methamphetamine is rapidly absorbed through the lungs and probably reaches the brain in six to eight seconds. Thus, the onset and peak effect occur within minutes of administration. Intravenous administration produces peak brain uptake in four to seven minutes. Intranasal and oral methamphetamine have a slower absorption and onset of effect (30–45 minutes), have a longer peak effect (about three hours post dose), and a more gradual decline from peak. The peak intensity of effect is weaker than with smoked or intravenous administration because less active drug reaches its site of action in the brain.[12] Overall, effects of methamphetamine typically last four to eight hours; residual effects can last up to 12 hours.[5]

Pharmacokinetics

Following oral administration, peak methamphetamine concentrations are seen in 2.6 to 3.6 hours, and the mean elimination half-life is 10.1 hours (range of 6.4 to 15 hours). Following intravenous injection, the mean elimination half-life is slightly longer (12.2 hours).[5] The acute effects of methamphetamine last about four to six hours, and disappear faster than the blood concentration falls, probably due to acute tolerance.

Between 30% and 40% of methamphetamine is metabolised by the liver, with the remaining 60–70% excreted by the kidneys. Acidification of the urine increases the rate of excretion (and may halve the half-life). Alkalinisation of the urine decreases the rate of excretion, prolonging the action of the drug and reducing the amount in the urine. Some users take large doses of sodium bicarbonate (an alkali) to achieve this.

Detection

Urine drug screening may identify recent use of methamphetamine. The drug and its metabolites can be identified in urine for 48 to 72 hours after last use, and in hair for weeks to months after last use.[1] Heavy chronic use may result in positive urine testing for up to one week after last use, and in hair for weeks to months after last use.[3]

Interactions

The primary interaction of methamphetamine that is of clinical concern is with other stimulants or with other medications that also enhance catecholamine (such as adrenaline, noradrenaline and dopamine) activity. Such interactions risk overstimulation of the sympathetic nervous system, with possible cardiac arrhythmias, hypertension, seizures, cardiovascular collapse, and death. The major potential for interaction is presented by monoamine oxidase inhibitors (MAOIs) which are used as antidepressants. Methamphetamines should not be used within two weeks of MAOI use. Other medications which can adversely interact with methamphetamine are tricyclic antidepressants, which can potentiate the effects of methamphetamine by enhancing its gastrointestinal absorption and slowing its liver metabolism.[5]

Tolerance and sensitisation

Repeated and prolonged use of methamphetamine leads to the development of marked tolerance (decreased drug response), and increasing doses are required to maintain the same effects. Sensitisation (increased drug response) tends to result from initial, low-dose, intermittent exposure, while tolerance tends to result from more frequent, high-dose or long-term exposure.[12] Prolonged use results in marked psychological dependence.[1] Individual differences in tolerance and sensitisation to methamphetamine may account

for the poor correlation between plasma methamphetamine concentrations and toxic effects.[12]

Clinical effects

Many people take small amounts of methamphetamine in specific social settings (e.g. dance parties, 'raves') and never meet the criteria for dependence. However, there are patterns of use that raise grave concerns:

- Heavy users tend to use in binges often lasting days (called a 'run'), followed by a 'crash', then a period of abstinence.
- Heavy users will often use methamphetamine concurrently with other drugs (especially alcohol, cannabis, benzodiazepines and heroin), and may use CNS depressants to help 'come down' after a binge.

The 'run' is usually terminated within one to three days because of the rapid development of tolerance and the emergence of sleep deprivation compounded by exhaustion due to low food intake. At this stage, if there has been repeated or high dose use, an acute paranoid state may be evident.[3]

Binge use of methamphetamine can be broken down into the following phases:[5]

- **Rush (5 minutes)**—intense euphoria, rapid flight of ideas, sexual stimulation, high energy, obsessive/compulsive activity, thought blending, dilated pupils.
- **Shoulder (1 hour)**—less intense euphoria, hyperactivity, rapid flight of ideas, obsessive/compulsive activity, thought blending, dilated pupils.
- **Binge use (1–5 days)**—the drug is frequently readministered in an attempt to regain or maintain euphoria.
- **Tweaking (4–24 hours)**—an overwrought state when the user is at their most violent and unpredictable state: dysphoria (unpleasant or uncomfortable mood), scattered and disorganised thought, intense craving, paranoia, anxiety and irritability, hypervigilance, auditory and tactile hallucinations (perceptions in the absence of a stimulus), delusions (fixed, false beliefs), and normal pupils.
- **Crash (1–3 days)**—intense fatigue, uncontrollable sleepiness and catnapping, continuing stimulation, drug craving.
- **Normal (2–7 days)**—apparent return to 'normalcy' although drug craving may appear.
- **Withdrawal**—anergia (lack of energy), anhedonia (lack of pleasure), waves of intense craving, depression, hypersomnolence (intense sleepiness), exhaustion, extreme fatigue.

Risk of dependence is exacerbated by route of administration (injecting or smoking), more frequent use, and the use of more potent forms of the drug. Recent Australian research suggests that half of methamphetamine users are dependent.[13]

Primary care practitioners should be mindful of the many symptoms, physical and psychological, which can be present in users of methamphetamine.

Table 1 shows the potential acute physical effects from using low and high doses of amphetamines.[14] The variable potency and presence of potentially lethal adulterants may increase the risks of toxicity.

Long-term physical effects of amphetamines include:[14]

- weight loss, malnutrition, lowered immunity, although with re-establishment of self-care and eating habits, likely to resolve over time;
- eating disorders, anorexia or nutritional deficiency;
- possible cerebral atrophy and impairment of neuropsychological functioning;
- Poorly maintained injection sites (e.g. infection) may cause callusing, scarring or abscesses;
- vascular and organ damage may occur due to blockages caused by particle blocking small blood vessels in organs (e.g. kidneys). Contaminants present in the blood stream (from acute injection or due to longer term accumulation) may result in lung or cardiac emboli, cardiac valve infections, or stroke;
- sexual dysfunction;
- cardiovascular symptoms consistent with shorter term use patterns (such as hypertension and cardiac arrhythmias).

Long-term psychological effects of amphetamines include:[14]

- Psychosis—psychological problems associated with amphetamine intoxication include delirium, paranoia, acute anxiety, and tactile hallucinations, which tend to readily resolve upon resolution of intoxication. Some people may experience a brief psychotic reaction of a few weeks' duration that was precipitated by amphetamine use. Amphetamine-induced psychosis tends to resolve on cessation of drug use and with short-term pharmacological treatment (usually risperidone, haloperidol and diazepam). Reinstatement of amphetamine use may increase the likelihood of further psychotic episodes; however, repeated episodes may not necessarily cause, nor be related to, schizophrenia-like disorders. Some people may experience a schizophrenia-like illness that appears to be precipitated by their use of amphetamines; however it remains unclear whether the drugs are responsible for the condition or rather increase the likelihood of its occurrence in susceptible individuals.
- Depression, other mood disorders (e.g. dysthymia), or eating disorders may be features of protracted withdrawal or become long-standing problems post-drug cessation.
- Highly dependent individuals show poorer performance on tests of cognitive functioning, especially with memory and concentration.

Table 1. Potential acute physical effects using low and high dose amphetamine

(Adapted from Gourlay, 2000; Latt et al., 2002; Victoria Police, 2002)

	Low doses	High doses
CNS, neurological, behavioural	• Overstimulation, insomnia • Dizziness, mild tremor • Euphoria/dysphoria, restless, talkative, excited with need to speak • Increased confidence, self-awareness • Mild confusion, panic (rarely psychotic episodes) • Appetite suppression • Pupillary dilatation • Increased energy, stamina and reduction in fatigue • Heightened alertness and psychomotor activity with improved performance or concentration on simple fatigue impaired tasks • With increasing doses, may increase libido • Headache • Teeth grinding	• Stereotypic or unpredictable behaviour, e.g. picking at skin especially on the face • Violent or irrational behaviour, mood swings, including hostility and aggression • Pressured or slurred speech • Paranoid thinking, confusion and perceptual disorders • Headache, blurred vision, dizziness • Psychosis (hallucinations, delusions, paranoia) • Cerebrovascular accident* • Seizures • Coma • Teeth grinding • Gross body image distortions
Cardiovascular	• Tachycardia (possibly brief bradycardia), hypertension • Palpitations, arrhythmias	• Cardiac stimulation (tachycardia, angina, arrhythmia*, MI) • Vasoconstriction/ hypertension • Cardiovascular collapse*
Respiratory	• Increased respiration rate and depth	• Respiratory difficulty/ failure*
Gastrointestinal	• Nausea and vomiting • Constipation, diarrhoea or abdominal cramps	• Dry mouth • Nausea and vomiting • Abdominal cramps
Skin	• Pale sweaty skin • Hyperpyrexia	• Flushing or pallor • Hyperpyrexia, diaphoresis • Crusting of skin from stereotypic picking or scratching
Skeletal	• Increased deep tendon reflexes	

(Items marked with * indicate that deaths have been attributed to amphetamine)

It is important to be aware that methamphetamine use can be associated with psychosis, depression, movement disorders and violence.

Association with psychosis

Chronic stimulant toxicity produces neuropsychiatric complications such as poor concentration and attention, memory impairment, sleep disturbances, hallucinations, flashbacks (vivid sense of reliving of a past drug experience), depression, anxiety and panic attacks. With repeated use of large doses of stimulants (a 'run' or binge), a psychotic state resembling acute paranoid schizophrenia can develop. This is characterised by severe agitation, anxiety, irritability, restlessness, paranoid delusions, hallucinations (predominantly visual but may be auditory or tactile), repetitive stereotyped behaviour, hostility and violence, and loosening of association of ideas in a setting of clear consciousness. Stimulant-induced psychosis is difficult to differentiate from acute paranoid schizophrenia. While psychotic symptoms generally subside as drug concentration declines, in a few individuals they may persist for weeks to months after cessation of use.[3]

Psychostimulant users are at high risk of experiencing psychotic symptoms if they suffer from pre-existing schizophrenia, mania or other psychotic disorders. Among such individuals, these drugs can precipitate or exacerbate psychotic episodes. Psychostimulant users, like all illicit drug–using populations, have elevated rates of pre-existing schizophrenia and other psychotic disorders. Despite this, the majority of psychostimulant users who experience psychotic symptoms after taking these drugs have no known history of schizophrenia, mania or other chronic, psychotic disorders.[15]

Symptoms of psychosis are most likely to occur among chronic, dependent users of the drug, rather than infrequent users. In one study 31% of dependent methamphetamine users had psychotic symptoms, as did 13% of non-dependent users[16] (compared to 1.2% of the general population); 23% of the methamphetamine users had experienced a clinically significant psychotic symptom in the past year. Psychotic symptoms are associated with longer term use, heavier use, dependence, injecting and a pre-existing history of psychotic symptoms.

Association with depression

Depression and suicide attempts are common. A third of methamphetamine users have received a diagnosis of depression at some point in their lives, and 11% have been diagnosed with an anxiety disorder. A quarter of psychostimulant users have a history of attempted suicide compared to 3.6% of the general population. Higher levels of depression, suicide and anxiety are associated with longer psychostimulant use.[15]

Association with movement disorders

Stimulant use is associated with a variety of movement disorders, presumably as a result of intense dopamine activity in the basal ganglia and other brain areas that control movements. Such disorders include repetitive stereotyped behaviours (such as repeated dismantling of objects, cleaning, doodling, and searching for imaginary objects), acute dystonic reactions (twisting and repetitive movements), choreoathetosis and akathisia (so-called 'crack dancers'), buccolingual dyskinesias ('twisted mouth' or 'boca torcida'), and exacerbations of Tourette's syndrome (a neuropsychological disorder characterised by multiple tics and at least one verbal tic) and tardive dyskinesias (involuntary repetitive movements).[12]

Although methamphetamine is a psychostimulant there is evidence that some patients with attention deficit hyperactivity disorder report a paradoxical calming effect of illicit stimulants, similar to that obtained through the medical prescription of these drugs.[3]

Association with violence

Violent behaviours appear to be common among psychostimulant users, particularly among people who inject these drugs. Recent Australian data indicated that 12% of methamphetamine users had committed a violent crime in the preceding year. According to McKetin et al.[17] such an association is plausible for three main reasons. First, there is experimental evidence that chronic use of the drug can increase aggressive behaviour. Second, acute intoxication may enhance or augment aggressive response in someone who is threatened or provoked. Finally, as discussed above, psychostimulant use is associated with a risk of psychosis, which can be accompanied by violent behaviours. McKetin states 'most of the violence associated with methamphetamine use occurs when users of the drug experience drug-induced psychosis. There is no direct evidence that simply taking the drug makes people become violent. Rather, it's a case of chronic users of the drug, who are experiencing drug-induced paranoia, reacting to situations in a violent way. Personality, drug withdrawal, alcohol use, and circumstantial factors, all play a role in precipitating violence.'[17]

Treatment options

Addiction should be seen in the same light as other chronic, relapsing conditions, where the aim is careful, long-term management and support, not cure. Treatment options are limited for users of methamphetamine because there are no established pharmacotherapies, as there are with alcohol and opioids. Management largely relies on psychosocial interventions, and cognitive behavioural therapy.[3] It appears that most stimulant

users become abstinent through self-management when they tire of their tumultuous lifestyle. Unfortunately behavioural and cognitive approaches, although effective during treatment, have not shown long-term benefits.[18]

Acute symptoms such as hyperactivity or agitation may be treated with dopamine-blocking agents such as haloperidol.[19] Behavioural and psychiatric intoxication may be treated with diazepam.[19]

Compared to usual treatment, contingency management (based on the premise that a behaviour is more likely to be repeated if it is followed by positive consequences) has produced a longer mean duration of drug abstinence, but this has not been sustained at three- and six-month follow-up.[20]

The Matrix model incorporates cognitive behavioural therapy principles, education about addiction and relapse prevention, 12-step or self-help programmes, and weekly urine monitoring.[21] One large-scale, multisite study found that the Matrix model produced superior benefits during treatment, but differences between the two groups were not observed at discharge or six-month follow-up.[22] However, potential therapeutic agents targeted to dopamine and nondopamine (e.g. opioid) systems, such as methylphenidate, are undergoing clinical trials and may offer hope for the future.[23]

Conclusion

NZ has one of the world's highest reported levels of methamphetamine use, and there has been a recent increase in the level of use of both amphetamine and crystalline methamphetamine, suggesting some entrenchment in amphetamine use. Primary care practitioners should be aware of the wide range of manifestations of methamphetamine use, particularly among younger patients presenting with agitation and/or psychosis.

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COMPETING INTEREST
None declared.

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