Serotonin Syndrome Guidelines (Serotonin Toxicity)

Patterns of Psychostimulant Use

Psychostimulants are a group of drugs that stimulate the activity of the central nervous system, causing individuals to feel falsely or overly confident, euphoric, alert and energetic. The use and availability of psychostimulants, in particular methamphetamines ('meth', 'crystal meth', 'ice', 'base'), and amphetamine sulphate or hydrochloride ('speed') are increasing throughout Australia.

Users of amphetamines can be categorised as:

a) experimental (naïve users)

b) recreational (those who use irregularly, generally in a social setting)

c) binge users (an 'on again – off again' pattern of moderate to large quantities of use)

d) regular daily users.

Intranasal 'snorting' or oral ingestion 'bombing' are common routes of administration by experimental and recreational users. However, a significant proportion of users (particularly regular users) do choose to inject. Injection, while becoming increasingly common in Australia, is typically associated with greater potential for toxicity, higher levels of dependence and other physical, psychological and social problems as is smoking of some forms of psychostimulant drugs, such as the potent crystalline methamphetamine also known as 'ice'.

Definition of Psychostimulants

This policy refers to the range of substances collectively known as psychostimulants, which commonly include:

1. methylenedioxymethamphetamine(MDMA), 'ecstasy'
2. cocaine
3. amphetamine sulphate or hydrochloride, 'speed'
4. methamphetamine
    a) crystal methamphetamine, 'ice', 'crystal meth'
    b) methamphetamine tablets, 'pills'
    c) methamphetamine 'base', which is a moist, oily substance
    d) methamphetamine powder
5. paramethoxyamphetamine (PMA)
6. paramethoxymethamphetamine (PMMA)

Acute Psychostimulant Toxicity

Adverse effects (of psychostimulants) can exist on a spectrum of severity from minor symptoms to life threatening toxicity." The definition of 'acute psychostimulant toxicity' describes an individual who has administered psychostimulants and subsequently experiences acute symptoms of toxicity although it is recognised that intoxication with other drug classes such as alcohol, cannabis or opioid may also be evident, as patterns of use of psychostimulants suggest that co-administration of other drugs is extremely common.

Common consequences of significance from psychostimulant toxicity can include:

1. agitation, panic states and acute behavioural disturbances
2. psychosis (particularly paranoid hallucinations and delusions)
3. hyperthermia
4. cerebrovascular and neurological complications (e.g. CVA, cerebral vasculitis, disseminated intravascular coagulation, seizures, coma)
5. cardiovascular complications (e.g. myocardial infarction and ischaemia, hypertension, tachycardia, arrhythmia)
6. delirium
7. electrolyte disturbances (e.g. hyponatremia, hyperkalaemia)
8. hypoglycaemia
9. rhabdomyolysis
10. serotonin toxicity of varying severity.

It is important to recognise that psychostimulant toxicity can occur among both experimental (naïve) and regular users of psychostimulants. **(refer to Paramedical Services Protocol 29 – Drug Overdose).**

Management of Patients with Psychostimulant Toxicity

1. The use and availability of psychostimulants is increasing.
2. Adverse effects of psychostimulants fall along a continuum with mild symptoms at one end of the spectrum and life threatening toxicity at the other.
3. Psychostimulant toxicity has been identified among both naïve and regular users.
4. A thorough assessment should be undertaken which includes drug use history and presence of psychostimulant toxicity.

5. Calming communication to de-escalate potentially dangerous situations is recommended. Security or the police should always be called to any high-risk situation.
6. Urgent sedation should be administered to patients exhibiting acute behavioural disturbance secondary to psychostimulant intoxication or toxicity. Initially with normal dose benzodiazepines followed by higher doses if ineffective.
7. Oral sedation should be offered in the first instance, but if the patient refuses then intravenous (IV) sedation (or intramuscular sedation if a secure IV site cannot be obtained) should be administered promptly in an effort to rapidly and safely manage behavioural disturbance and medical complications of toxicity if present.
8. Medical complications are often serious and include hyperthermia, cerebrovascular accidents, seizures, myocardial ischaemia and infarction, serotonin toxicity, rhabdomyolysis, hypoglycaemia, hyponatremia, hyperkalaemia and others. Some peculiarities of medical management are specific to psychostimulant use being identified.
9. Patients should be referred to specialist alcohol and drug services for ongoing support and counselling following treatment.
10. For those who decline follow-up care, provision of information about psychostimulant use or other educational material is recommended.

Medical Treatment Summaries

- **Hyperthermia Temp > 38.0^{0}C**

Rapid external cooling, paralysis, intubation and deep intravenous sedation. Assess for rhabdomyolysis and electrolyte problems, hydrate adequately, urgent transport to tertiary level hospital. **(refer to Paramedical Services Protocol 36 – Heat Syndromes).**

- **Hyponatremia**

Assess total body water, fluid restrict if mild. Hypertonic saline if severe. Check blood sugar. Supportive care.

- **Serotonin Syndrome**

Control muscle rigidity. Monitor temperature for hyperthermia. Attend respiration, fluid and electrolyte status. Benzodiazepine first line therapy in mild cases.

- **Cerebrovascular Management**

Airway management, adequate oxygen, IV fluids, control seizures initially with benzodiazepines, avoid aspirin if cerebral haemorrhage is suspected. Urgent transport to hospital for head CT and attention to general supportive care, corticosteroids may be harmful.

- **Cardiovascular Management**

ECG, electrolytes, glucose, avoid beta-blockers, sublingual nitroglycerine for chest pain in combination with benzodiazepines. Avoid aspirin if uncontrolled hypertension. **(refer to Paramedical Services Protocol 24 – Chest Pain).**

Assessment and Diagnosis

Most commonly, initial management to rapidly control behavioural disturbance is the early priority and should occur concurrently with assessment. Failure to control the behaviour often prevents or delays assessment. Prudent consideration of the wide differential diagnosis for behavioural disturbance is required.

Drug Use History

A thorough drug history should be taken at the time of triage if possible. The following points may serve as a guide, although if the patient is obviously intoxicated or exhibiting signs of agitation or acute behavioural disturbance, an emphasis on rapidly controlling the behaviour and reassuring the patient take priority. Collateral information can be gained from friends, family members if in attendance, or from police and security officers.

If the Patient is Cooperative with Assessment, Record:

Psychostimulant use ('speed', 'go-ee', 'base', 'ice', 'meth', 'whiz' etc) type of psychostimulant used (e.g. methamphetamine, amphetamine, cocaine, MDMA, prescription drug) amount of psychostimulant used time of administration route of administration (intranasal, intravenous, oral, inhalation) frequency of use (e.g. regular daily use, binge pattern, recreational, experimental, etc) potency of psychostimulant used ("How long did the effect last", "Was it strong?") duration of current use and age of first use obtain a urine sample for a drug screen if possible.

Other drug use

Concurrent use of other drugs (particularly alcohol, benzodiazepines, opiates, party drugs), including criteria above concurrent use of antidepressant medication (e.g. TCAs, MAOIs, SSRIs, bupropion, venlaxafine) which may increase the serotonergic or catecholamine mediated effects of psychostimulants.

Medical History

Other conditions that might impact on management presence of concomitant physical illness including blood borne viruses, heart disease etc. presence of any physical injury (particularly head injury) that might have been recently sustained presence of concomitant psychiatric illness or psychiatric symptoms (psychosis, paranoia, depression, suicidal ideation etc.).

If the Patient is not Cooperative with Assessment or Denies Psychostimulant Use

The following signs might indicate the patient has recently used psychostimulants or is moderately to severely intoxicated (although some signs might be indicative of other medical conditions or intoxication with other drugs):

- dilated pupils that react sluggishly to light
- clenched jaw or muscle rigidity
- restlessness, agitation, tremor or repetitive movements
- rapid speech
- motor agitation or pacing
- hypertension
- tachycardia
- sweaty palms, flushed diaphoretic facial skin
- hypervigilance, paranoia.

The following signs might indicate long-standing or regular psychostimulant use:

- obvious signs of poor- or under-nutrition
- sores on face, arms or legs
- evidence of needle marks or thrombophlebitis.

Physical Observations and Key Investigations Relevant to Assessing for Psychostimulant Toxicity

- Vital signs including temperature; severe hyperthermia may develop (hyperthermia > 38.0^0C indicates severe, potentially life threatening toxicity and mandates immediate cooling and sedation)
- Bedside blood sugar level (BSL)
- Urine test (+ve blood if myoglobin present)
- An ECG should be obtained and continuous cardiac monitoring instituted in symptomatic patients
- Assess for signs of serotonin toxicity, a common area omitted in assessment.

Acute Behavioural Disturbance

Individuals suffering from psychostimulant toxicity can become extremely agitated, irrational, impulsive, paranoid and psychotic, which may lead the person to behave in an uncontrolled, aggressive and/or violent manner.

The primary aim of management of behavioural disturbance is to reduce the risk of harm to the patient, Paramedical Services staff and other people. It is necessary to utilise the established protocols for the management of behavioural disturbances in the event of such of an incident. Presence of security or police presence is mandatory until behaviour is controlled. **(refer to Paramedical Services Protocol 5 – Acute Behavioural Disturbance).**

Reliance on physical restraint alone is often not adequate for psychostimulant users experiencing acute behavioural disturbance, and may actually cause harm if agitation increases. Stimulant use has been suggested as a possible risk factor for sudden death of individuals being physically restrained.

Behavioural Management Strategy

Verbal de-escalation should be attempted in the first instance, if possible. Respond to the patient in a calm and confident manner. Be aware that if the person is acutely intoxicated with psychostimulants and experiencing great fear or paranoid symptoms, unexpected stimuli such as loud noises or sudden movements may worsen the situation. So at all times use calming, deescalating communication strategies. Individuals affected by psychostimulants are more likely to respond in a positive way to communication strategies that are not perceived to be aggressive, threatening or confrontational.

Recommended communication techniques include:

1. Listening to the patient
2. Using the patient's name to personalise the interaction
3. Calm, open-ended questioning to ascertain the cause of the behaviour
4. A consistently even tone of voice, even if the person's communication style becomes hostile or aggressive

Avoidance of the use of "no" language, which may prompt an aggressive outburst. Allow the individual as much personal space as is possible while still maintaining control of the situation. Encourage support and assistance from harm minimisation groups (e.g. DanceWize).

Avoid too much eye contact if possible as this can increase fear or promote aggressive outbursts in some hostile or paranoid individuals. These techniques will assist staff to determine the individual's level of responsiveness to de-escalation strategies and to further assess the degree of risk to all involved. This will allow clinicians to determine if administration of sedation is required and if the patient will voluntarily accept medication. If the patient requires sedation and will accept oral sedation this is preferred.

If however, the patient has a severe behavioural disturbance such that they pose a risk to themselves or others, and will not voluntarily take oral medication as required.

Intravenous sedation (or intramuscular sedation if no secure IV access can be achieved) should be administered as soon as possible to control the behaviour and to ensure physical observations and investigations can be safely undertaken **(refer to Paramedical Services Protocol 5 – Acute Behavioural Disturbance).**

Security presence and assistance is essential until behavioural control is obtained.

Intervention by a well-disciplined team in behavioural emergencies be developed that are suitable for the particular characteristics of the setting in which emergencies will be managed; if the police have brought someone in mechanical restraints (e.g. handcuffs), police officers and restraints should remain in place until decisions have been made regarding management, restraints can be removed once the individual has been assessed and it has been determined that it is safe to do so; and that the patient may need sedating medication before the restraints are removed.

In emergency situations it is often difficult to differentiate between a severe behavioural disturbance secondary to acute drug intoxication, drug-induced psychosis, or an exacerbation of a pre-existing psychotic disorder. Suspected drug-induced psychosis (or exacerbation of existing psychotic disorder) should not be considered a contraindication to urgent sedation.

Rather, a period of sedation and behavioural control will allow clinicians to re-assess the patient after the acute effects of the drug have worn off, allowing for a more accurate differential diagnosis.

Observations

Initial continuous direct physical and visual observation of the patient should occur during the first 10 minutes following administration of parenteral sedation. Patients should then be monitored for four hours, when possible, following the administration of a sedation protocol.

Observations should be undertaken every 10 minutes for 30 minutes, then every 15 minutes for 30 minutes

Transport to a tertiary level facility should be considered for all severe acute behavioural disturbance patients.

Observations should include:

- Airway
- Patient colour
- Continuous oxygen saturation
- End tidal CO2 if available
- Respiration rate
- Blood pressure
- Pulse
- Temperature
- Glasgow Coma Scale score
- Bedside BSL.

Management of Other Symptoms of Psychostimulant Toxicity

Cardiovascular Complications

The pharmacologic treatment of patients with cocaine-related (and to some degree amphetamine-related) ischaemic chest pain differs to conventional management in several important aspects. Patients with uncontrolled hypertension might be at risk for subarachnoid and intracerebral haemorrhage and therefore aspirin must be avoided. **(refer to Paramedical Services Protocol 38 – Hypertensive Crisis).**

Sublingual nitroglycerine, in a dose sufficient to reduce the mean arterial pressure by 10 to 15 percent, reverses cocaine-induced coronary artery vasoconstriction and relieves symptomatic chest pain. Therefore, nitroglycerine is recommended as a primary therapy for cocaine-associated myocardial ischaemia.

Adjunctive benzodiazepines should also be considered for patients with cocaine-associated myocardial ischaemia who are anxious, have tachycardia, or are hypertensive as they reduce blood pressure and heart rate, thereby decreasing myocardial oxygen demand in addition to their anxiolytic effects.

Hypertension is often transient and as such may not require pharmacological intervention unless severe. Hypertension requiring treatment often responds to sedation with IV benzodiazepines.

Beta-blockers, one of the mainstays of treatment of acute myocardial ischaemia **should be avoided** in patients who have recently used psychostimulants as these drugs enhance stimulant-induced vasoconstriction and increase blood pressure and may exacerbate adverse effects.

Cerebrovascular Emergencies

The use of cocaine or amphetamine derivatives is considered a strong risk factor for stroke or other forms of acute cerebrovascular emergencies.

Mechanistic processes might involve vasospasm of smooth muscles lining the cerebral artery and thrombus formation in the vasculature. Vasculitis is sometimes observed. Whilst a variety of abnormalities in cerebral vasculature may occur secondary to cocaine use including cerebral haemorrhage, the most common complications are haemorrhagic or thromboembolic strokes. **(refer to Paramedical Services Protocol 47 – Stroke).**

Additionally, symptoms of cerebrovascular complications have been reported to appear within six hours of methamphetamine use and include:

Localising neurological signs

1. Hypertension
2. Respiratory difficulties
3. Speech difficulties
4. Sudden severe headache
5. Atypical seizures (e.g. focal, recurrent).

Management of cerebrovascular emergencies where psychostimulants are implicated in the aetiology should be managed using standard cerebrovascular emergency procedures (except when subarachnoid or intracerebral haemorrhage is suspected and aspirin should be avoided).

Immediate management involves:

1. Airway management
2. Adequate oxygen
3. IV fluids to maintain adequate nutritional and fluid intake
4. Attention to bladder and bowel function.

Corticosteroids may be harmful. If present, fever, hyperglycaemia, heart failure, arrhythmias, or severe hypotension must be treated.

Serotonin Toxicity (including Hyperthermia)

The neurotransmitter, serotonin (5-hydroxytryptamine or 5-HT) is thought to be involved in a range of functions including: mood, appetite and sleep regulation; cognition; perception; motor activity; temperature regulation; pain control; sexual behaviour and hormone secretion. An excess of serotonin in the synaptic cleft leads to a range of symptoms that are intensified as serotonin levels increase. Hence, clinical researchers argue that the concept of a spectrum of serotonin toxicity is more clinically relevant than the notion of a discrete serotonin syndrome per se'.

Therefore, serotonin toxicity may be a mild, self-limiting condition or be potentially fatal with symptoms such as muscle rigidity, coma, seizures, hypertension or hypotension evident. When serotonin toxicity is severe, rhabdomyolysis with hyperkalaemia, acidosis and frank renal failure may subsequently result.

Serotonin toxicity has typically been associated with the use of antidepressant medication, particularly the SSRIs. However there is a growing recognition of the incidence of serotonin toxicity in relation to the use of psychostimulants particularly the potent serotonergic agent MDMA (ecstasy).

The treatment of serious serotonin toxicity involves early recognition, prompt supportive care and judicious use of specific agents. Supportive measures for severe toxicity include:

1. Hyperthermia > 38.0^{0}C requires rapid external cooling, paralysis and intubation with deep intravenous sedation **(refer to Paramedical Services Protocol 36 – Heat Syndromes).**
2. IV fluids/volume resuscitation for dehydration, hypotension or rhabdomyolysis (ensure adequate urine output in 1.5-2mls/kg/hr) **(refer to Paramedical Services Protocol 26 – Dehydration).**
3. Mechanical ventilation for respiratory compromise and sedation with IV benzodiazepines might be indicated
4. 5-HT2 antagonists such as olanzapine, chlorpromazine or cyproheptadine may be indicated (these specific antagonists should only be used if the diagnosis of serotonin toxicity has been established and anticholinergic agents have not been co-ingested)
5. Paralysis and intubation may have a role in cases of severe intractable rigidity
6. Management of secondary cardiac arrhythmias or seizures involves standard measures. **(refer to Paramedical Services Protocols 10-22 – Cardiac Protocols; Protocol 36 – Heat Syndromes; Protocol 34 Fits and Seizures).**

In all patients with suspected serious serotonin toxicity, glucose, renal function and ECG should be monitored.

Muscle rigidity should be controlled – if unchecked, it can lead to hyperthermia, rhabdomyolysis and respiratory compromise. Patients who develop coma, cardiac arrhythmia or respiratory insufficiency require more specific measures.

Hyponatremia

This can be life threatening and presents with confusion or reduced consciousness or seizures. It can occur due to water intoxication from excessive water intake at rave parties, from drug effects of MDMA and PMA particularly.

Treatment is guided by severity and warrants careful assessment of total body water status. Mild cases benefit from fluid restriction alone. Severe cases benefit from the use of hypertonic saline. Careful fluid balance is required. Patient weight can guide progress.

Conclusions

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