Management of patients presenting with acute methamphetamine-related problems: evidence summary.

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Introduction

Acute intoxication with amphetamine-type stimulants such as crystal methamphetamine ("ice") can be associated with disturbed behaviour including agitation and psychotic symptoms such as delusions and hallucinations. The possibility of adverse cardiovascular and cerebrovascular effects makes it important that a full assessment is undertaken to guide further management.

In 2016, Drug and Alcohol Services South Australia (DASSA) identified the need for a guideline on acute methamphetamine presentations through its Consultation Liaison Service provided in the major metropolitan hospitals, and the phone-based Drug and Alcohol Clinical Advisory Service. A working group was established to develop the guideline, and research literature was reviewed to inform the deliberations of the working group.

This document presents a summary of the literature review.

Medline and PsycINFO were searched via Ovid Online. Details of the search strategies used are provided in the appendix. The initial searches included terms to identify amphetamine use disorders, but this overly restricted the search and retrieved very few relevant studies. The final searches combine terms to identify disturbed behaviour, an acute hospital setting, and medications likely to be used in response to disturbed behaviour.

Reference lists of recent studies and review articles retrieved by the Medline and PsycINFO searches were checked to identify any additional studies, and members of the working group were asked to identify studies they were aware of.

This review is not systematic in the sense that inclusion and exclusion criteria were not defined in advance, and studies included in the review were not formally assessed for risk of bias. However, the literature search was systematic in nature so that this document represents a comprehensive overview of research related to acute methamphetamine-related problems.

Linda Gowing
Principal Research Officer, Evidence-Based Practice

Chris Holmwood
Director, Primary and Tertiary Liaison

1. What is methamphetamine?

Methamphetamine is the most common form of amphetamine used illicitly in South Australia. It is usually sold as a powder, or in crystal form (known as 'ice'). The powder form is usually snorted or injected; crystal methamphetamine is usually smoked or injected. The crystalline form is suitable for vapour inhalation because high purity S-methamphetamine hydrochloride vaporizes without pyrolysis. Relative to lower purity forms, crystalline methamphetamine is associated with an increased incidence of dependence (Cruickshank & Dyer, 2009).

Methamphetamine is a powerful central nervous stimulant. For most users, the desired effects are feelings of wellbeing, and increased confidence, energy, stamina, concentration and sex drive. Use often causes excitability, hyperactivity, wanting to talk a lot and a loss of interest in sleep (Bramness et al., 2012).

2. Acute effects of methamphetamine

The acute effects of methamphetamine that are most likely to result in presentation to a hospital emergency department largely relate to the stress on the heart, high blood pressure, and psychological effects, particularly paranoia, hallucinations, aggression, anxiety, and unpredictable behaviour (Pasic, Russo, Ries, & Roy-Byrne, 2007; Zweben et al., 2004).

The acute subjective effects of methamphetamine diminish over four hours, while cardiovascular effects tend to persist. In regular users this decline in subjective effects may drive repeated use within intervals of around four hours, with consequent increased risk of adverse cardiovascular effects (Cruickshank 2009). The combination of alcohol and methamphetamine increases heart rate and blood pressure beyond that seen for methamphetamine use alone (Darke, Kaye, McKetin, & Duflou, 2008). The use of diazepam in combination with amphetamines may increase the risk of myocardial ischaemia (Starcevic & Sicaja, 2007).

Physical symptoms of psychostimulant overdose include nausea and vomiting, chest pain, tremors, increased body temperature, increased heart rate, breathing irregularities and seizures. Psychological symptoms such as extreme anxiety, panic, extreme agitation, marked paranoia, hallucinations and excited delirium are also indicative of methamphetamine overdose (Darke et al., 2008). Stroke, acute coronary syndrome and hypertension are among the vascular complications associated with methamphetamine abuse (Carvalho et al., 2012; Chin, Channick, & Rubin, 2006; Darke et al., 2008; Jacobs, 2006).

Serotonin syndrome or neuroleptic malignant syndrome associated with methamphetamine use appears to be rare. Reports identified through a literature search all involved ecstasy (MDMA) or "bath salts" (mephedrone), and not methamphetamine.

Pasic *et al*. (2007) compared patients presenting to a psychiatric emergency service in Washington (USA) with positive methamphetamine urine toxicology with a comparison group of patients presenting on the same day without methamphetamine use. Methamphetamine patients were significantly younger, and more likely to be male. They were less likely to have a past diagnosis of schizophrenia or any other past psychiatric history, and less likely to have a history of suicide attempts than the non-methamphetamine patients. Methamphetamine patients were more likely to present with hypertension and tachycardia, dysphoria and psychosis. Pasic *et al*. note that methamphetamine patients most often present in a state that has been described by the term "tweaking", a state of high arousal, agitation and bizarre uncontrollable movements, with prominent dysphoria, hallucinations, and paranoia that are uncontrollable and distressing to the patient. They suggest this as a reason why many methamphetamine patients accepted medications to help with their symptoms. Most methamphetamine patients in this study accepted the rapidly dissolvable forms of medication, most often olanzapine.

3. Sedation to manage disturbed behaviour

3.1 Medications

This section summarises the rationale for the use of the different medications in the management of disturbed behaviour. The table in section 3.2 summarises studies of various medications, separately and in combination, for sedation in acute care settings. The table in section 3.3 considers studies of medications for the treatment of amphetamine-induced psychosis.

3.1.1 Benzodiazepines

Benzodiazepines, in particular lorazepam, midazolam and diazepam, are appropriate first-line medications for sedation. They cross the blood-brain barrier and bind to gamma-aminobutyric acid receptors, the major inhibitory neurotransmitter system in the central nervous system, and enhance its inhibitory effects at all levels. This has a calming influence and a depressant effect on psychomotor and cognitive functions.

Potential side effects are sedation, hypotension, and respiratory depression, which can be synergistic with ongoing use of alcohol, opioids and other depressants (Knott, Taylor, & Castle, 2006; Rossi, Swan, & Isaacs, 2010; Wilson, Pepper, Currier, Holloman, & Feifel, 2012).

Lorazepam, administered orally, has a quick onset, moderate half-life, and a route of elimination with no active metabolites. It is given in 0.5- to 2-mg increments as frequently as every 15 minutes.

Midazolam, administered intramuscularly or intravenously, provides rapid sedation of short duration, making it appropriate for brief symptom control (Rossi et al., 2010).

3.1.2 Atypical antipsychotics

In the context of acute behavioural disturbance, antipsychotic medications such as olanzapine (oral) and droperidol (intramuscular or intravenous), provide an alternative, or supplementary, means of sedation when benzodiazepines alone are not effective. The most relevant adverse effects of antipsychotic medications, in the acute context, are QT interval prolongation, and extrapyramidal symptoms.

Droperidol

Droperidol is a potent antagonist of dopamine subtype 2 receptors in the limbic system. It also produces mild alpha-adrenergic blockade and peripheral vascular dilation (Kao, Kirk, Evers, & Rosenfeld, 2003; John R. Richards & Schneir, 2003).

Droperidol has a shorter half-life than haloperidol, a more rapid onset of action, absence of long-term side effects, potent sedative properties without long-term cognitive impairments, and is generally as effective as haloperidol in controlling aggressive and disruptive behaviour. For these reasons droperidol is preferred over haloperidol in patients requiring rapid sedation (Rossi et al., 2010). Droperidol does not cause respiratory depression even in high doses, and has equivalent IM and IV dosing (John R. Richards & Schneir, 2003).

Droperidol is listed on the Australian Register of Therapeutic Goods with indicated uses in anaesthesia to produce tranquillisation and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures, and in psychiatry for the management of severe agitation, hyperactivity, or aggressiveness in psychotic disorders[1].

In 2001 the FDA issued a black box warning for droperidol due to reported cases “of QT prolongation and/or torsade de points” at doses at or below recommended doses. The black box warning recommends reserving the use of droperidol “for use in the treatment of patients who fail to show an acceptable response to other adequate treatments” and that all patients should undergo a 12-

[1] Product Information – Droleptan® Injection, downloaded from https://www.tga.gov.au/ 8/12/2016

lead ECG prior to administration. However, as noted by others (Kao et al., 2003), obtaining a 12-lead ECG in a combative patient is often not feasible (Knott et al., 2006).

Product information for preparations registered in Australia[2] indicates that droperidol should not be used:

- in female patients with a QTc greater than 450 msec or male patients with a QTc greater than 440 msec
- in patients with acquired long QT interval
- in patients with known congenital long QT interval or family history of congenital long QT syndrome.

Acute alcohol intoxication is listed as a relative contraindication.

Kao *et al*. (2003) reviewed published studies and available postmarketing surveillance data of the association between droperidol and QT prolongation or torsades de points. Mullins *et al*. (2004) also reviewed postmarketing data (MedWatch reports).

As noted by Kao *et al*. (2003) and Mullins *et al*. (2004), sudden death caused by torsades de pointes is uncommon and difficult to assess. For this reason QT prolongation has become a surrogate marker for potential arrhythmogenicity. QTc prolongation was one factor explored in the Rotterdam Study, a prospective cohort study involving 3,105 men and 4,878 women aged 55 years and older. An abnormally prolonged QTc interval (>450 ms in men, >470 ms in women) was associated with an increased risk of death during follow-up (on average, 6.7 years) (Straus et al., 2006). However, the implications of short-term QTc prolongation are unclear.

Hundreds of drugs are known to prolong the QT interval (John R. Richards & Schneir, 2003), with widely variable degrees of evidence for clinical dysrhythmias. In addition to QT prolongation, other risk factors for the development of torsade de pointes include female sex, bradycardia (<50 beats/min), heart disease, electrolyte imbalance, hepatic or renal dysfunction, and concomitant use of specific drugs, such as azole antifungal agents. Kao *et al*. (2003) concluded that although droperidol has been associated with prolonged QT intervals, clinically significant adverse cardiovascular events appear to be rare. Based on a review of 35 articles, Perkins *et al*. (2015) concluded that droperidol is an effective and safe medication in the treatment of nausea, headache, and agitation, that mandated electrocardiogram or telemetry monitoring was not supported for doses less than 2.5 mg (im or iv), and that doses of up to 10 mg were as safe and effective as other medications used for sedation of agitated patients.

3.1.3 Ketamine

Ketamine has been widely used in ED settings for children and adults, mostly for procedural sedation or as the induction agent for intubation (Hopper et al., 2015) with few adverse events. Ketamine is seen as being particularly useful in settings without capability for inhalational anaesthetics (Green & Li, 2000; Le Cong, Gynther, Hunter, & Schuller, 2012).

Ketamine has a rapid onset of action (dissociative anaesthesia in 1-2 min IV, 3 min IM), does not affect airway reflexes, can be administered IM or IV, sedation is often achieved reliably with one dose, and has a relatively short duration of effect (up to 25 minutes), potentially “allowing more rapid disposition of agitated patients” (Hopper et al., 2015).

However the dissociative state induced by ketamine may reduce the capacity of patients to participate in their own care. Ketamine does not treat underlying cause of agitation, and subanaesthetic doses may worsen psychosis (Hopper et al., 2015).

[2] ibid

Green and Li (2000) discuss the possibility that the sympathomimetic activity of ketamine might provoke ischaemia in patients with underlying coronary artery disease. However, they also note that pretreatment with benzodiazepines or droperidol appears to blunt the cardiovascular effects of ketamine. Concurrent use of benzodiazepines may also reduce the incidence and magnitude of any unpleasant emergence reactions in adults.

Richards *et al*. (2015) suggest that a catecholamine surge after administration of ketamine may be problematic in patients experiencing amphetamine toxicity.

3.2 Studies of sedation in acute care settings for agitation of various aetiologies

Study design and setting	Medications	Participants	Sedation outcomes	Adverse effects
Battaglia *et al*. (1997), randomised controlled trial, N=98, hospital emergency departments, 5 sites, USA.	Lorazepam (IM, 2 mg), haloperidol (IM, 5 mg) or two medications combined. Maximum 6 doses with first 3 at least 1 hour apart, then at least 2 hours apart. 2nd and subsequent doses if clinically indicated.	Psychotic, agitated, aggressive, average age 34, 74% male.	Tranquilisation most rapid with combination. Up to 3 injections in 74% of lorazepam group, 91% of combination group and 71% of haloperidol group. At 3 hours 65% lorazepam, 61% combination, 32% haloperidol group asleep.	No significant difference in adverse effects, but more extrapyramidal symptoms with haloperidol alone.
Richards *et al*. (J. R. Richards, Derlet, & Duncan, 1997; 1998), randomised trial, N=202, emergency department, California, USA	Lorazepam (IV, 2 mg if <50 kg, 4 mg if >50 kg) or Droperidol (IV, 2.5 mg if <50 kg, 5 mg if >50 kg)	Acutely agitated, average age 34, 62% male, methamphetamine toxicity in 72%	Lower sedation scores (less agitation) with droperidol at 10, 15, 30 and 60 mins. Repeat doses at 30 mins for 40% lorazepam, 8% droperidol.	No airway intervention required. Acute dystonic reaction in 1 person treated with droperidol (treated with IV diphenhydramine).
TREC Collaborative Group (2003), randomised controlled trial, N=301, 3 psychiatric emergency rooms, Rio de Janeiro, Brazil	Midazolam (7.5-15 mg, IM) or haloperidol (5-10 mg IM) plus promethazine (25-50 mg IM)	Adults, requiring IM sedation for agitation and dangerous behaviour, 49% men, mean age 38 years, substance misuse presumed cause in 17%.	*Tranquil or asleep after 20 minutes* Midazolam 89% Haloperidol + promethazine 67%	1 transient respiratory depression with midazolam, 1 grand-mal seizure with haloperidol-promethazine
Nobay *et al*. (2004), randomised controlled trial, N=111, emergency department, California, USA	Midazolam (5 mg IM), Lorazepam (2 mg IM) or Haloperidol (5 mg IM)	Violent or severely agitated, average age 40.7; recreational drug use in 26%, alcohol in 32%; 48.6% had prior psychiatric history.	*Mean ±SD time to sedation* Midazolam 18.3 ±14 mins Haloperidol 28.3 ±25 mins Lorazepam 32.2 ±20 mins *Time to arousal* Midazolam 81.9 mins Haloperidol 126.5 mins Lorazepam 217.2 mins	No significant differences in effects on vital signs. Two adverse events in haloperidol group (1 hypotension, 1 apnoea).

Study design and setting	Medications	Participants	Sedation outcomes	Adverse effects
Martel *et al*. (2005), randomised double-blind trial, emergency department, Minneapolis, USA	Droperidol (5 mg IM), Ziprasidone (20 mg IM) or Midazolam (5 mg IM)	Acute undifferentiated agitation, average age 37, 68% male; alcohol intoxication in 94%, illicit substance intoxication in 11%.	*Agitated at 15 mins* Midazolam 31.3% Droperidol 40.0% Ziprasidone 60.9% *Agitated at 30 mins* Midazolam 22.9% Droperidol 12.0% Ziprasidone 30.4% *Agitated at 45 mins* Midazolam 29.2%% Droperidol 18.0%% Ziprasidone 19.6% *Rescue medication required* Midazolam 50.0% Droperidol 10.0% Ziprasidone 19.6%	No cardiac dysrhythmias in any group. *Respiratory depression requiring oxygen* Midazolam 20.8% Droperidol 8% Ziprasidone 15.2% None required endotracheal intubation. *Akathisia developed in* Midazolam 2.1% Droperidol 2% Ziprasidone 8.7%
Knott *et al*. (2006), randomised controlled trial, N=153, emergency department, Melbourne, Australia	Midazolam (IV, median dose 5 mg) Droperidol (IV, median dose 10 mg)	Acutely agitated, age range 15-76, 65% male; 40% with intoxication (mainly alcohol, ¼ due to drugs)	*Median time to sedation* Midazolam 6.5 minutes Droperidol 8 minutes *Adequately sedated at 5 minutes* Midazolam 44.6% Droperidol 16.5% *Sedated at 10 minutes* Midazolam 55.4% Droperidol 53.2% *Further sedation within 60 minutes* Midazolam 18.9% Droperidol 10.1%	Adverse events Midazolam 13.1% Droperidol 11.6% Dystonic reactions (3) and 1 arrhythmia in droperidol group; 3 in midazolam group required active airway management. QTc longer in droperidol group but not clinically significant.

Study design and setting	Medications	Participants	Sedation outcomes	Adverse effects
Veser *et al*. (Veser, Veser, McMullan, Zealberg, & Currier, 2006), randomised controlled trial, N=30, medical emergency department, South Carolina, USA	Risperidone (2 mg oral) or Haloperidol (5 mg oral) or Placebo, all with Lorazepam (2 mg IM)	Adults with acute agitation and/or psychosis, willing to take oral and IM medications, average age 40, 77% male. Drug screen positive for marijuana or cocaine in 30% and alcohol in 33%.	No significant group differences at any point. In all cases symptoms improved and none required further medication.	No complications.
Huf *et al*. (2007), psychiatric emergency room, Rio de Janeiro Brazil.	Haloperidol (5-10 mg IM) plus Promethazine (up to 50 mg), or Haloperidol (5-10 mg IM) alone.	Agitated and aggressive, substance misuse likely cause in 18%, 53.8% male.	Those who received combination medication more likely to be tranquil or asleep by 20 minutes compared to haloperidol alone (RR 1.30, 95% CI 1.10 to 1.55, P=0.002). No group differences after 20 minutes.	Dystonia in 7% treated with haloperidol alone, but none treated with haloperidol plus promethazine.
Raveendran *et al*. (2007), randomised controlled trial, N=300, emergency services of hospital psychiatry department, Vellore, India	Olanzapine (10 mg IM) or Haloperidol (10 mg IM) plus Promethazine (25 mg or 50 mg)	Agitated or violent with mental illness, average age 30, 63% male, 63% with a diagnosis of mania, 7% with substance induced psychosis	*Tranquil or asleep at 15 minutes* Olanzapine 87% Haloperidol 91% *Tranquil or asleep at 240 minutes* Olanzapine 96% Haloperidol 97% *Required additional drugs over 4 hrs* Olanzapine 43% Haloperidol 21%	No significant adverse events. Minor adverse events for 3% olanzapine, 0.6% haloperidol-promethazine.
Newton & Fitton (2008), N=92, emergency department of hospital, London, UK.	Ketamine (0.5-1.0 mg/kg IV)	Adults, requiring procedural sedation for injuries, median 38 years, 67% male	Adequate sedation in 99%	Adverse events in 21.7% (4 clonic movements, 12 recovery agitation (7 treated with IV midazolam), 4 vomiting, 2 hypersalivation.

Study design and setting	Medications	Participants	Sedation outcomes	Adverse effects
Isbister *et al*. (2010), randomised controlled trial (the DORM study), N=91, Newcastle, Australia.	Droperidol (10 mg IM) or Midazolam (10 mg IM) or Droperidol (5 mg IM) plus Midazolam (5 mg IM)	Violent and acute behavioural disturbance requiring physical restraint and parenteral sedation; age range 22-45, 49% male; alcohol intoxication in 70%, drug-induced psychosis in 9%.	*Required additional sedation* Droperidol 33% Midazolam 62% Combination 41% *Median (IQR) duration of behavioural disturbance* Droperidol 20 (11-37) Midazolam 24 (13-35) Combination 25 (15-38)	*Proportion with adverse events* Droperidol 6% Midazolam 8% Combination 7% Effect of IM midazolam unpredictable, most likely due to differing patient tolerance, with both over- and undersedation.
Szwak & Sacchetti (2010), retrospective case note review, N=79, hospital pediatric emergency department, New Jersey, USA.	Droperidol as initial therapy or rescue medication (20%). Doses administered ranged from 1.0 to 10 mg, IV in 77.9%, IM in 17.6%, and both in 4.3%.	Age range 15-21 years, 62% male, agitation (86%), nausea/vomiting, headache, or other pain. Of those with agitation, drugs detected in 51.5%, drugs and alcohol in 22.1%, alcohol only in 17.6%. Drug detected was amphetamines in 4%, cocaine in 4% - cannabinoids, alcohol and PCP were most common.	Droperidol alone was effective in 87% of patients with agitation.	All patients placed on cardiac monitoring – no arrhythmias noted.
Burnett *et al*. (2012), retrospective case note review, paramedic treatment prior to transport, N=13, Minnesota, USA.	Ketamine (200-500 mg IM)	Excited delirium, age range 24-54, 8 male; 3 drug/alcohol intoxication.	Time to peak sedation <5 minutes in 11 cases, 20 minutes in 2 cases; 5 required additional sedation.	3 developed hypoxia (2 intubated), 1 hypersalivation, 3 emergence reaction.

Study design and setting	Medications	Participants	Sedation outcomes	Adverse effects
Le Cong *et al*. (2012), prior to aeromedical transport, N=18, Queensland, Australia.	Ketamine (0.5-1 mg/kg IV); if 2 doses required in first 60 mins, infusion started at 1-1.5 mg/kg/hour and titrated to effect.	Agitated, with a psychiatric illness (none of the cases involved amphetamine use).	Effective sedation (calm, cooperative patient, able to respond to verbal commands) in all cases.	No significant adverse effects during retrieval or following 72 hours.
MacDonald *et al*. (2012), retrospective chart review, N=146, emergency departments of 2 hospitals, California, USA.	Haloperidol (IM) or Olanzapine (IM)	Agitated, 65% male, mean age 41 years; drugs and/or alcohol detected in 58%.	*Additional medication required* Haloperidol alone 43% Haloperidol & benzodiazepine 18% Olanzapine alone 29% Olanzapine & benzodiazepine 18%	No evidence of clinically significant adverse effects
Chan *et al*. (2013), randomised controlled trial, N=336, emergency departments of 3 hospitals, Australia	Droperidol (5 mg) or Olanzapine (5 mg) or Placebo (saline), all IV bolus followed by midazolam (2.5-5 mg IV boluses) until sedation achieved.	Adults <65 years, requiring IV drug sedation for acute agitation, median age 34, 59% male; 30% intoxicated, 91% history of substance abuse.	*Sedated at 10 mins* Placebo 48.7% Droperidol 66.1% Olanzapine 67.9% *Sedated at 30 mins* Placebo 78.3% Droperidol 92.0% Olanzapine 89.9% *Median (IQR) minutes to sedation* Placebo 10 (4-25) Droperidol 6 (3-10) Olanzapine 5 (3-10)	No group differences in adverse events of length of stay.

Study design and setting	Medications	Participants	Sedation outcomes	Adverse effects
Macht *et al*. (2014), retrospective case note review, N=532, paramedic treatment prior to transport, Colorado, USA	Haloperidol (median 10 mg, 92% IM) or droperidol (median 2.5 mg, 61% IM)	Undifferentiated agitation, median age 31, 69-75% male	No significant difference in use of additional sedating medications within 30 mins of emergency department arrival	No significant group difference in median QTc or adverse effects. Cardiopulmonary arrest (resuscitated) in 1 in droperidol group (with history of congenital heart disease).
Scheppke *et al*. (2014) retrospective case note review, N=52, paramedic treatment prior to transport, Florida, USA	Ketamine (average 4 mg/kg IM), single dose; 50% also received midazolam (2-2.5 mg IV) to prevent emergence reactions.	Violent, aggressive behaviour, age range 17-86, 77% male, 44% considered due to alcohol and other drugs.	50/52 rapidly sedated (<3 minutes) sufficiently to enable transport.	Respiratory depression in 6% who had also received midazolam.
Calver, Drinkwater *et al*. (2015), randomised controlled trial, N=228, psychiatric intensive care unit, Newcastle, Australia	Droperidol (10 mg IM) or haloperidol (10 mg IM)	Adults with acute behavioural disturbance requiring parenteral sedation, median age 33, 63% male; 31% related to psychostimulant use.	*Sedation successful* (sedated within 120 mins, no additional medications, no adverse effects) Droperidol 83% Haloperidol 79% *Additional medication within 1 hr* Droperidol 5% Haloperidol 13% *Median (IQR) time to sedation* Droperidol 25 (15-30) mins Haloperidol 20 (15-30) mins	Adverse effects Droperidol 5% Haloperidol 1% Most common adverse effect transient hypotension.
Calver, Page *et al*. (2015), prospective cohort study, N=1403 (N=1009 with ECG recorded), 6 hospital emergency departments, New South Wales and Queensland.	Droperidol, 10 mg IM or IV, additional dose after 15 minutes if patient did not settle. Further doses of droperidol or other medications as clinically indicated.	Adults with acute behavioural disturbance at risk to themselves or others, median age 34, 59.9% male, 52.6% related to alcohol intoxication, 13.8% related to psychostimulants.	97% sedated within 120 minutes, 69.0% sedated with initial dose of droperidol. Sedation failed in 49 patients. Oversedation occurred in 7.8% - in 15% of these cases benzodiazepines were also administered.	Adverse events occurred in 5.0% of patients, most commonly hypotension, desaturation and airway obstruction. An abnormal QT interval was detected in 1.3% with an ECG.

Study design and setting	Medications	Participants	Sedation outcomes	Adverse effects
Hopper *et al*. (2015), case note review, N=27 (32 episodes), emergency department, California, USA	Ketamine (IM 17 episodes, IV 15 episodes). Mean initial dose 150 mg, average dose 157.5 mg. Other medications (antipsychotic, benzodiazepine) prior to ketamine in 18 episodes.	Agitated; 70% male, age range 9-77; intoxication with alcohol or other substances in 38% of episodes.	Additional medication required (ketamine, antipsychotic or benzodiazepine) in 62.5% of episodes. Additional medication required in 84.6% of episodes involving intoxication, compared to 47.4% not involving intoxication.	Average increase in heart rate 8±17 bpm, no cases of hypoxia.
Isbister *et al*. (2016), subgroup (N=49) of DORM study, multiple hospitals, Australia	Ketamine (median 300 mg)	Acute behavioural disturbance not responding to droperidol; median age 37, 57% male; 16% "intoxicated", 14% with "psychostimulants".	Sedation effective (within 120 mins of ketamine administration, no further ketamine required within 1 hour) in 90%.	Three patients (6%) experienced adverse effects – 2 vomiting, 1 oxygen desaturation to 90%.
Taylor *et al*. (2017), randomised controlled trial, (N=349), emergency department of two hospitals, Australia	Midazolam (5 mg) plus droperidol (5 mg), or droperidol (10 mg), or olanzapine (10 mg), all as IV bolus. Two additional doses at 5 min intervals if needed. If sedation still not adequate, further medications as needed.	Adults, mean 34 years, 61% male; requiring IV sedation for acute agitation. Half intoxicated with drugs or alcohol, >80% history of substance abuse.	*Proportion sedated at 10 mins* Midazolam-droperidol 74.6% Droperidol 49.6% Olanzapine 49.2% *Proportion sedated at 15 mins* Midazolam-droperidol 89% Droperidol 60.4% Olanzapine 65.8% *Median (IQR) minutes to sedation* 5 (3-11) 11 (6-23) 11 (5-25)	Respiratory events (airway obstruction, SaO_2 <90%) somewhat more common with midazolam-droperidol. Other adverse events (dystonia, prolonged QT interval) were rare.

3.3 Studies of medications for amphetamine-induced psychosis

Study design and setting	Medications	Participants	Outcomes
Leelahanaj *et al*. (2005), randomised controlled trial, N=58, Thailand	Olanzapine or haloperidol, commenced at 5-10 mg/day, 5 mg adjustments weekly in range 5-20 mg/day	All with amphetamine-induced psychosis	At 4 weeks, 93% in olanzapine group and 79% in haloperidol group were clinically improved. Extrapyramidal symptoms more often and more severe with haloperidol.
Sulaiman *et al*. (2013), randomised controlled trial, N=37, Malaysia	Aripiprazole (5-10 mg/day) or placebo, 8 weeks.	Methamphetamine dependent with a history of psychosis, mean 35 years, 94% male	*Retention in treatment, mean±SD* Aripiprazole 48.7±4.0 days Placebo 37.1±5.0 days Psychotic symptoms decreased more with aripiprazole but no group differences in methamphetamine use. Akathasia occurred in 5 patients treated with aripiprazole compared to 1 receiving placebo. Adverse effects mild to moderate in intensity.
Farnia *et al*. (2014), randomised controlled trial, N=45, psychiatric hospital, Iran	Risperidone (4 mg) or aripiprazole (15 mg), once daily at bedtime for 6 weeks. Benzodiazepines as need in both groups.	Admitted for amphetamine-induced psychotic disorder by DSM-IV, adults, mean age 40, all male, abstinent from amphetamines 1-4 weeks.	Both medications effective. Risperidone may have greater effect on positive symptoms. Patients with negative symptoms may respond better to aripiprazole.
Verachai *et al*. (Verachai et al., 2014), randomised controlled trial, N=80, substance abuse treatment centre, Thailand	Quetiapine (100 mg/day, oral), or Haloperidol (2 mg/day, oral, 4 weeks. Doses of medication increased every 5 days until no psychotic symptoms observed.	Adults with amphetamine-induced psychotic episode, 76% male, average age 24.	*In remission at end of study* Quetiapine 89% Haloperidol 84% No significant group differences in adverse effects.

4. Psychosis

4.1 Amphetamine use as a risk factor

Psychiatric symptoms that are commonly associated with methamphetamine use include irritability, anxiety, and mood disturbances (Glasner-Edwards & Mooney, 2014). Prominent psychotic symptoms in methamphetamine users include auditory and tactile hallucinations, ideas of reference, and paranoid delusions (Bousman et al., 2015; C. Chen et al., 2003; Glasner-Edwards & Mooney, 2014). Aggressive behaviour is frequently associated with paranoid delusions (Dawe, Davis, Lapworth, & McKetin, 2009; Glasner-Edwards & Mooney, 2014).

It has been variously estimated that between 8 and 46% of regular users of amphetamines experience drug-induced psychosis (Alharbi & el-Guebaly, 2016; Bramness et al., 2012; Vallersnes et al., 2016). A number of factors are likely to underlie the wide range of estimates, including methods of assessment and diagnostic criteria (Bramness et al., 2012; Glasner-Edwards & Mooney, 2014; Vallersnes et al., 2016).

The signs and symptoms of substance-induced psychosis in the absence of an underlying primary psychosis are very similar to primary psychosis that is triggered or exacerbated by substance abuse (Bramness et al., 2012; C. Chen et al., 2003; Glasner-Edwards & Mooney, 2014; McKetin et al., 2016; Medhus, Mordal, Holm, Morland, & Bramness, 2013; Srisurapanont et al., 2011) although methamphetamine-induced psychosis may be associated with more visual and somatic or tactile hallucinations and less severe negative affect (Wang et al., 2016). Furthermore, there is evidence of a shared genetic risk between methamphetamine-induced psychosis and schizophrenia (Ikeda et al., 2013).

Given the difficulty in distinguishing clinically, in the acute setting, between these aetiologies, priority is given initially to treating the acute psychosis. However, a plan of care to effectively treat a patient with a primary diagnosis of psychosis who uses methamphetamine will be different to that for a methamphetamine user who developed acute and transient psychosis in the context of use (Glasner-Edwards & Mooney, 2014).

Vallersnes *et al*. (2016) used data on presentations to emergency departments in Europe (Euro-DEN) to describe the association between cases of psychosis and drug use. Over 12 months there were 5529 cases with acute drug toxicity; psychosis was a clinical feature in 6.3% of cases. Of the patients presenting with psychosis, the median age was 29 years, 79.3% were male, 63.2% had agitation, and 43.7% had hallucinations. Cannabis was present in 25.9% of psychosis presentations, amphetamine in 25.0%, and cocaine in 16.1%. Multiple drugs were involved in 54.3% of presentations with psychosis. Amphetamine was the drug most frequently associated with psychosis when only one substance was reported. Treatment was required in 55.2% of the presentations with psychosis, usually sedation.

McKetin *et al*. (McKetin et al., 2016) followed a cohort (N=164) of methamphetamine users for one year, with monthly assessments. Those who met the criteria for a lifetime primary psychotic disorder were excluded. Methamphetamine use exacerbated positive psychotic symptoms (suspiciousness, unusual thought content, hallucinations, bizarre behaviour), affective symptoms (depression, suicidality, guilt, hostility, somatic concern, self-neglect) and psychomotor symptoms (tension, excitement, distractability, motor hyperactivity) but did not significantly increase negative symptoms. The authors suggest this might be an aspect to explore as the basis for differential diagnosis of amphetamine-induced psychosis from primary psychosis.

Possible risk factors for psychosis associated with methamphetamine use may include the level of use (amount over time, amount on one occasion), use of other drugs, particularly cannabis, in addition to methamphetamine (McKetin, Lubman, Baker, Dawe, & Ali, 2013), age at first use, the duration of the current binge (with sleep deprivation as a potential factor), vulnerabilities in the user such as a family history of schizophrenia (Cruickshank & Dyer, 2009), the route of administration (Hall, Hando, Darke, & Ross, 1996) and the form of methamphetamine used. There is considerable variability in the reported dose of methamphetamine and time interval prior to onset of psychotic symptoms (Cruickshank & Dyer, 2009).

Arunogiri *et al*. (2015) reported on ambulance attendances in Melbourne between January 2012 and August 2014, where patients presented with psychosis symptoms. In 6.1% of cases methamphetamine was implicated, and in 13.4% of methamphetamine-related presentations cannabis was also involved. In methamphetamine-related episodes, compared to non-drug-related episodes, the patients were younger (median age 28 compared to 39), were more likely to be male (67% compared to 51%) and were less likely to have a history of psychosis (23% compared to 44%).

Bousman *et al*. (2015) assessed symptoms in a cohort of 40 methamphetamine dependent individuals with a history of psychotic symptoms. A history of dependence on other drugs, and of mental health disorders was common in the cohort. Chen *et al*. (2003) found that methamphetamine users with a lifetime diagnosis of psychosis, compared to users without a diagnosis of psychosis, were younger at first use of methamphetamine, used larger amounts, had significantly higher mean score on the Premorbid Schizoid and Schizotypal Traits, and higher rates of major depressive disorder, alcohol dependence and antisocial personality disorder. A family history of psychiatric disorders is also a risk factor for the development and duration of psychosis (C.-K. Chen et al., 2005; Glasner-Edwards & Mooney, 2014).

In general, patients with schizophrenia are more vulnerable to the effects of amphetamine, but the response is heterogeneous. It is known from imaging studies that amphetamine-induced striatal dopamine release is significantly higher in schizophrenic patients than in healthy controls, and dopamine release is correlated with amphetamine-induced increases in psychosis. Recent research suggests that deficits in gamma-aminobutyric acid is likely to be a factor underlying the variability in vulnerability to amphetamines (Ahn et al., 2015).

Hides *et al*. (Hides et al., 2015) interviewed a cohort of 198 methamphetamine users (61% male) who were accessing needle and syringe programs in three Australian cities. They found that 51% met DSM-IV criteria for a lifetime psychotic disorder, with 80% of these considered to be substance-induced and 20% were considered primary psychotic disorders. Those with a younger age of onset of weekly methamphetamine use were at increased risk of a lifetime substance-induced psychotic disorder. A current psychotic disorder was found in 39%. The severity of persistent psychotic symptoms may also be related to earlier and longer exposure to stimulants (Lichlyter, Purdon, & Tibbo, 2011).

4.2 Prognosis of amphetamine-induced psychosis

Most drug-induced psychoses resolve within a few days, with 8-27% being reported to persist for more than one month (Vallersnes et al., 2016).

Resolution of psychotic symptoms with cessation of stimulant use is one of the criteria used to differentiate substance-induced psychosis from a primary psychotic disorder such as schizophrenia (Bramness et al., 2012; Glasner-Edwards & Mooney, 2014). However, a subpopulation develops rapid recurrences of psychotic episodes with low doses of methamphetamine (Bramness et al.,

2012; Glasner-Edwards & Mooney, 2014), and some develop chronic psychosis (C. Chen et al., 2003) even after a long-term cessation of stimulant use (Akiyama, Saito, & Shimoda, 2011; Ali et al., 2010; Kittirattanapaiboon et al., 2010).

Stress, use of other substances, and sleep deprivation may also be factors in the recurrence of psychosis in some people (Dore & Sweeting, 2006; Glasner-Edwards & Mooney, 2014). Sensitization to methamphetamine psychosis due to the neurotoxic effects of methamphetamine has also been suggested as a factor (Cruickshank & Dyer, 2009).

In a cohort study, Lecomte *et al*. (Lecomte et al., 2013) followed 295 people who used methamphetamine, and were seeking psychiatric services for psychotic symptoms. Study participants were assessed at baseline and then monthly. Persistent psychotic symptoms were observed in 30% of the sample. Those with persistent psychosis were significantly older, had more severe psychotic symptoms, longer duration of methamphetamine use, had more antisocial personality traits, and had more sustained depressive symptoms.

Sara *et al*. (2014) used hospital records to identify a cohort of 7269 persons (aged 15-29 years) with a first psychosis admission, other than schizotypal disorder or organic psychosis, in a defined period. Episodes where the person was admitted and discharged on the same day were excluded. At admission 66% of the cohort was male, 30% had a comorbid cannabis disorder and 16% a comorbid stimulant disorder. The most common diagnoses at first admission were schizophrenia or delusional disorders (36%) and drug-induced psychosis (22%); 16% had prior admissions for mental health or substance-related problems but without a psychosis diagnosis. Within 2 years 37% were readmitted for psychosis (with 45% of readmissions occurring within 90 days). The highest rate of readmission (42%) was for people with an index diagnosis of schizophrenia. Cannabis disorders at index admission were associated with a greater risk of readmission (HR=1.15, 95% CI 1.06-1.25), but cannabis disorders prior to the index admission were not (HR=1.11, 95% CI 0.97-1.26). However, baseline stimulant disorders were unrelated to risk of readmission, but people with an admission with stimulant disorders prior to their index admission had a higher risk of readmission (HR=1.30, 95% CI 1.11-1.51). The readmission rate was highest for those with an ongoing drug problem (66%), intermediate for those with no drug problem (50%) and lowest for the group that ceased drug use (40%).

Medhus *et al*. (Medhus et al., 2015) identified a sample of 28 individuals hospitalised in Norway for amphetamine-induced psychosis and reviewed their hospital records after six years. In that 6-year period, 7 had died and 9 had moved from the area. Four of the remaining 12 were diagnosed with schizophrenia. The sample is too small to draw meaningful conclusions on risk factors for the development of schizophrenia.

5. Post-acute care

Debate about the association, differentiation and etiology of methamphetamine psychosis and primary psychosis is ongoing. No matter what the association, as noted by Glasner-Edwards and Mooney (2014), the possibility of chronic or recurrent psychosis in those who have experienced an episode of methamphetamine psychosis points to the need for post-acute care encompassing monitoring and pharmacological management of acute symptoms if needed, as well as interventions to address methamphetamine use.

For people who are at low to moderate risk of harm from their methamphetamine use, an assessment with feedback aimed at providing insight into their substance use and possible harms can be sufficient to promote reduction in methamphetamine use (Humeniuk et al., 2012). The

experience of psychosis can be distressing, and the timely provision of assessment and brief intervention can take advantage of this to promote behavioural change.

For people whose methamphetamine use is placing them at high risk of harms, including dependence, a brief intervention is insufficient to promote behavioural change. The focus of assessment and brief intervention in this group is to encourage entry into structured treatment. This section provides a brief overview of evidence on structured treatments for methamphetamine use.

5.1 Management of methamphetamine withdrawal

Abrupt cessation of repeated methamphetamine use leads to a withdrawal syndrome consisting of depressed mood, anxiety and sleep disturbance. Acute withdrawal lasts typically for 7-10 days, and residual symptoms associated with neurotoxicity may persist for several months (Cruickshank & Dyer, 2009).

Depressive and psychotic symptoms accompany acute withdrawal from methamphetamine but usually resolve in around a week. Craving is also present and lasts at least 5 weeks (Zorick et al., 2010).

Generally withdrawal is not life threatening or physically risky, but strong cravings, feelings of fatigue and low mood, and disturbed sleep patterns make it difficult for most people to complete. Reassurance and support are important components of withdrawal management, along with medications to relieve the symptoms of withdrawal (such as benzodiazepines to help with sleep). Most people can successfully manage their own withdrawal in the community with support from family, friends or a general practitioner, but some people will have greater need for support.

No medication has been demonstrated to be effective in alleviating amphetamine withdrawal (Shoptaw, Kao, Heinzerling, & Ling, 2009). The mainstay of withdrawal treatment is supportive care and symptomatic medications[3].

Antidepressants have been used to counter some of the acute effects of amphetamine withdrawal. Mirtazapine is used at Drug and Alcohol Services South Australia and has resulted in some improvement in symptoms.

Short-term use of benzodiazepines (diazepam 5 to 10mg QID PRN) and antipsychotics (olanzapine 2.5-5mg BD PRN) for symptom control of irritability and agitation can be helpful, particularly in the inpatient setting. Care should be taken to limit access to large quantities of medications and to avoid development of benzodiazepine dependence. These medications should be prescribed for a maximum of seven to 10 days.

Modafinil is also used at Drug and Alcohol Services South Australia for treatment of somnolence associated with acute amphetamine withdrawal and has been demonstrated to result in some improvement in symptoms, but this is not an approved medication for amphetamine withdrawal treatment.

5.2 Structured treatment for amphetamine use

There are currently no medications that counteract the specific effects of methamphetamine or that prolong abstinence from and reduce the abuse of methamphetamine by an individual addicted to

[3] Drug and Alcohol Services South Australia, information on methamphetamine withdrawal. http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+topics/substance+misuse+and+dependence/substance+withdrawal+management/amphetamine+withdrawal+management. Last accessed 23 May 2017.

the drug (Perez-Mana, Castells, Torrens, Capella, & Farre, 2013). There is ongoing research in Australia and internationally into medications for substitution treatment of amphetamine dependence, but at present there are no pharmacotherapies of proven effectiveness to assist with withdrawal, craving, or relapse prevention in people who are dependent on amphetamine-type stimulants.

The mainstay of treatment for amphetamine dependence is psychosocial therapies (Minozzi, Saulle, De Crescenzo, & Amato, 2016), including cognitive behavioural therapy, motivational interviewing, and contingency management. Residential rehabilitation is appropriate for those who have been more severely affected by their substance use.

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Appendix: Search strategies

Medline (via Ovid Online)

1. exp Perceptual Disorders/
2. exp Emergency Medical Services/
3. Crisis Intervention/
4. Emergency Service, Hospital/
5. Psychomotor Agitation/
6. Aggression/
7. Drug Overdose/co, th [Complications, Therapy]
8. Psychoses, Substance-Induced
9. exp "Anesthesia and Analgesia"/
10. Ketamine/
11. Haloperidol/
12. Droperidol/
13. Antipsychotic Agents/
14. Benzodiazepines/
15. 1 or 5 or 6 or 7 or 8
16. 2 or 3 or 4
17. 9 or 10 or 11 or 12 or 13 or 14
18. 15 and 16 and 17

(150 records retrieved 16/9/2016)

PsycINFO (via Ovid Online)

1. Psychosis/
2. aggressive behaviour/
3. perceptual disturbances/ or perceptual distortion/
4. exp Drug Overdoses/
5. exp Agitation/
6. exp Emergency Services/
7. exp Crisis Intervention/
8. exp Psychiatric Hospitalization/
9. exp SEDATIVES/
10. exp KETAMINE/
11. exp HALOPERIDOL/
12. exp Neuroleptic Drugs/
13. Droperidol.mp
14. exp BENZODIAZEPINES/
15. 1 or 2 or 3 or 4 or 5
16. 6 or 7 or 8
17. 9 or 10 or 11 or 12 or 13 or 14
18. 15 and 16 and 17

(63 records retrieved 16/9/2016)