**Intravenous Midazolam-Droperidol Combination, Droperidol or Olanzapine Monotherapy
for Methamphetamine-related Acute Agitation: Subgroup Analysis of a Randomised
Controlled Trial**

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All authors conceived and designed the study, and contributed to the ethics committee application. DT obtained the research funding. ST, CY and DK prepared the study packs. DT and CY supervised the study overall. JCK, JK and GP supervised the study at their respective

sites. CY, JCK, JK and GP were responsible for all staff education. CY managed collation of the data and entry into the study database. CY, DT and JK undertook the data analysis. All authors contributed to interpretation of the results, drafting and revision of the manuscript and take responsibility for the paper as a whole.

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ABSTRACT

Aim

To examine the efficacy and safety of (1) midazolam-droperidol vs droperidol and (2) midazolam-droperidol vs olanzapine for methamphetamine-related acute agitation.

Design and setting

A multi-centre, randomised, double-blind, controlled, clinical trial was conducted in two Australian emergency departments, between October 2014 and September 2015.

Participants

Three hundred and sixty-one patients, aged 18-65 years, requiring intravenous medication sedation for acute agitation were enrolled. We report the results of a sub-group of 92 methamphetamine-affected patients.

Intervention and comparator

Patients were randomly assigned to receive either an intravenous bolus of midazolam 5 mg-droperidol 5 mg combined, droperidol 10 mg or olanzapine 10 mg. Two additional doses were administered, if required: midazolam 5mg, droperidol 5mg or olanzapine 5mg, respectively.

Measurements

The primary outcome was the proportion of patients adequately sedated at ten minutes. Odds ratios with 95% confidence intervals (ORs, 95%CI) were estimated.

Findings

The baseline characteristics of patients in the three groups were similar. At 10 minutes, significantly more patients in the midazolam-droperidol group [29/34 (85.3%)] were adequately sedated compared with the droperidol group [14/30 (46.7%), OR 6.63 (2.02-21.78)] or with the olanzapine

group [14/28 (50.0%), OR 5.80 (1.74-19.33)]. The number of patients who experienced an adverse event (AE) in the midazolam-droperidol, droperidol and olanzapine groups was 7/34, 2/30 and 6/28, respectively. The most common AE was oxygen desaturation.

Conclusion

A midazolam-droperidol combination appears to provide more rapid sedation of patients with methamphetamine-related acute agitation than droperidol or olanzapine alone.

Trial registration

ACTRN12614000980639

Key words

Methamphetamine, sedation, droperidol, midazolam, olanzapine, emergency care, psychomotor agitation

INTRODUCTION

Amphetamine-type stimulants, including methamphetamine, are used by 14-56 million people worldwide.¹ As the number of people requiring treatment for methamphetamine use is also increasing, the drug's related harms have become a focus of public health.¹⁻⁴ In the United States (U.S.), Australia and Canada, the increased availability of high purity and relatively inexpensive methamphetamine has raised concerns among ambulance services and emergency departments (EDs).⁴⁻⁸

Emergency department staff are experiencing high levels of aggression and violence as a result of increased methamphetamine use in the population.⁶ Although clinical guidelines recommend benzodiazepines alone (i.e. lorazepam, diazepam) to manage methamphetamine-related agitation,^{9, 10} there is limited clinical trial data to support this recommendation. The absence of such evidence has posed further safety risks for the patient, hospital staff and community members.¹¹

Methamphetamine-related agitation may arise from direct stimulant effects of the drug, often compounded by sleep deprivation, hallucinations and delusions.^{12, 13} Rapid sedation provides a humane alternative to mechanical restraint, and allows clinicians to re-assess the patient after the acute effects of methamphetamine have worn off.

Antipsychotic medications (e.g. droperidol or olanzapine), as monotherapy or in combination with benzodiazepines, have been commonly used in the ED to sedate patients with undifferentiated acute

agitation.¹⁴⁻¹⁷ However, few studies have reported sedation outcomes in methamphetamine-affected patients.

A recent double-blind, randomised, controlled trial (RCT) concluded that a midazolam-droperidol combination is superior to droperidol or olanzapine monotherapy for sedation of the acutely agitated ED patient.¹⁸ Notably, approximately one quarter of the patients enrolled were methamphetamine affected. The applicability of these findings in methamphetamine-affected patients is unknown. The present study examined the efficacy and safety of the midazolam-droperidol combination compared to droperidol or olanzapine monotherapy, in the subgroup of methamphetamine-affected patients enrolled in the RCT.

METHODS

Study Design, Setting and Participants

The RCT design has been reported elsewhere.¹⁸ Briefly, it was a multi-centre, randomised, double-blind, controlled clinical trial undertaken in the EDs of two metropolitan, tertiary referral, Australian hospital EDs with annual censuses of 45,000 and 70,000 adult patients. Patients were enrolled between October 2014 and August 2015, inclusive. The RCT was registered on the Australian and New Zealand Clinical Trial Registry, (ACTRN12607000591459).

Three hundred and sixty-one patients, aged 18 to 65 years (inclusive), requiring intravenous medication sedation for acute agitation were recruited.¹⁸ A subgroup of methamphetamine-affected patients were examined in this study. Patients were identified by self-report of methamphetamine use or from collateral reports from accompanying persons (e.g. police, ambulance officers).

Ethics approval

Human Research Ethics Committees (HRECs) at the Melbourne Health and Monash University approved the RCT. Due to agitation, informed consent was not possible and waiver of consent was granted.

Interventions

Patients were randomised to receive an intravenous bolus of midazolam 5mg-droperidol 5mg combination, droperidol 10mg only or olanzapine 10mg only. Two additional doses were administered, if required: midazolam 5mg, droperidol 5mg or olanzapine 5mg, respectively. Doses

were determined from clinical practice and previous trials.^{14, 15} The midazolam-droperidol combination was identical to that of Chan et al.¹⁴

If adequate sedation was not achieved 5 minutes after two additional doses, the doctor could administer additional, open label, sedative medication(s) at his/her discretion. Observations of heart rate, blood pressure and oxygen saturation were recorded as routine ED care. Electrocardiograms (ECGs) were recorded within 30 minutes post-sedation if permitted by the patient's condition.

Main Outcome Measures

The primary outcome was the proportion of patients adequately sedated at 10 minutes after the initial dose administration. Adequate sedation was defined as a score ≤ 2 based on a 6-point, validated Acute Arousal Scale¹⁹ (5=highly aroused, violent toward self, others, or property; 4=highly aroused and possibly distressed or fearful; 3=moderately aroused, agitated, more vocal, unreasonable, or hostile; 2=mildly aroused, pacing, willing to talk reasonably; 1=settled, minimal agitation; 0=asleep).

Secondary outcomes included time to adequate sedation, the need for additional doses, open label sedative medication to achieve adequate sedation, the ECG QTc interval and AEs.

Statistical Analysis

An *a priori* sample size calculation was not undertaken for this sub-study. However, a *post hoc* power calculation indicated that it had power of 0.87 and 0.75 to demonstrate a statistically significant difference in proportions of patients adequately sedated at 10 minutes between the

midazolam-droperidol group and the droperidol and olanzapine groups, respectively (alpha 0.05, 2-sided).

Simple logistic regression was used to identify potential patient characteristics associated with the primary outcome. The primary outcome was compared using χ^2 test and simple logistic regression. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. The median times to adequate sedation were compared using the Wilcoxon rank-sum test and the 95%CI for the difference in medians were calculated using the *cendif* module. As this study was not powered to compare AE rates, AE data are reported descriptively. Analyses were performed using StataCorp. 2015. (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) The level of significance was 0.05.

RESULTS

A total of 92 patients from the RCT¹⁸ were included in this sub-study and were distributed approximately equally across each study group (Figure 1). Seventy-three (73/92) patients required mechanical restraint for a median (interquartile range [IQR]) duration of 2.0 (0.13-4.25) hours. Security assistance was essential in all of these cases, and a median (IQR) duration of 33 (23-55) minutes of security staff time was required until the behavioural control was achieved. No patient characteristic was associated with the primary outcome (Table 1).

At 10 minutes after the initial dose of study medication, over one third more patients in the midazolam-droperidol group were adequately sedated compared to the droperidol and olanzapine groups. The median time to sedation for the midazolam-droperidol group was significantly shorter than both the droperidol and olanzapine groups (Table 2).

Forty-five (45/92) patients were adequately sedated with the initial dose of study medication and 26/45 of these patients had been administered the midazolam 5mg-droperidol 5mg combination (Table 3). Of the 13/92 patients who required open label sedative medications, in addition to both additional doses of the study medication, only one patient was from the midazolam-droperidol group.

Baseline systolic blood pressure (SBP) and heart rate were recorded in 41/92 patients. Thirty (30/41) patients presented with elevated SBP and 15/41 patients presented with a heart rate > 100 beats per minute. The highest recorded baseline SBP and heart rate for any patient was 186 mmHg and 137

beats per minute, respectively. The mean SBP and heart rate decreased significantly at 60 minutes after adequate sedation was achieved.

An ECG was obtained within 30 minutes of the first dose in 77/92 patients: midazolam-droperidol 31/34, droperidol 25/30 and olanzapine 21/28. The median (range) QTc intervals (msec) of the three groups were similar: 460 (350-504), 447 (339-493) and 441 (313-513), respectively.

Seven, two and six patients experienced an AE in the midazolam-droperidol, droperidol and olanzapine groups, respectively (Table 4). The most common AE was oxygen desaturation and all cases were resolved within a minute without adverse clinical outcomes. ED length of stay and patient disposition are reported in Table 5.

DISCUSSION

Patients intoxicated with methamphetamine commonly present with psychotic episodes featuring agitation and paranoid delusions.²⁰ These patients have been reported to be more agitated and violent than patients with other illicit drug intoxication.²¹ This study affirms the perception that management of methamphetamine-related agitation is labour intensive, as the majority of these patients required lengthy attendance of security and clinical staff. A safe and effective protocol is urgently needed to minimise the burden of methamphetamine-related agitation in EDs.

In this study, the intravenous midazolam-droperidol combination was more efficacious than the droperidol or olanzapine monotherapy in achieving rapid and adequate sedation. Anecdotally, high doses of sedative medications are frequently required to manage methamphetamine-related agitation. However, compared to the droperidol and olanzapine groups, most of the patients in the midazolam-droperidol group were adequately sedated with only the initial dose of midazolam 5mg and droperidol 5mg.

The AE profiles of the three regimens appeared to be similar, although respiratory events were slightly more common in the midazolam-droperidol group. The risk of benzodiazepines in causing respiratory events is well documented.^{14-16, 22, 23} Importantly, all respiratory events in this study were easily managed with no clinical consequence. Among the 77 patients who had ECGs done within 30 minutes after sedation, only two in the midazolam-droperidol group and one patient in the olanzapine group had a borderline QTc prolongation. However, no case required intervention or cardioversion. Dose-dependent QTc prolongation following droperidol administration has been

described.²⁴⁻²⁷ ECGs are not routinely obtained in the ED especially when patients are agitated. In this study, it is not known whether the borderline QTc prolongations were pre-existing conditions or medication-related.

Methamphetamine causes cardiovascular complications similar to cocaine, and places heavy demands upon the cardiovascular system by increasing heart rate and blood pressure.¹³ Previous studies have recommended benzodiazepines as the first line treatment for cardiac toxicity associated with psychostimulant use.²⁸ In this study, the midazolam-droperidol appeared to exert some benefit in reducing the SBP and heart rate. Importantly, no incidents of hypotension were reported.

High dose benzodiazepine (e.g. midazolam) is often used to manage this patient group,^{22, 29} despite significant safety concerns.^{15, 16, 22} An observational study reported that high dose midazolam with frequent dosing (midazolam in 10mg increments, intramuscularly or intravenously, at 10 minutes intervals, up to 40mg) was not superior to normal dose, specifically in patients who had developed tolerance to benzodiazepines.²² As such, the midazolam-droperidol combination is potentially a safer and more efficacious option for patients who have pre-existing tolerance to benzodiazepines.

Only one ED RCT has investigated the efficacy of intravenous droperidol and lorazepam in managing acute methamphetamine toxicity.³⁰ In that U.S.-based trial, patients in the droperidol group were sedated with a mean (SD) dose of 5.2 (1.1) mg. Notably, the patients in our droperidol group required nearly triple the dose of droperidol to be adequately sedated. Since the U.S. trial was conducted two decades ago, the purity of illicit methamphetamine has increased.⁵ The difference

observed may indicate a higher magnitude of harmful neurotoxicity effect caused by the shift in use from the low-purity powder methamphetamine to high purity crystal.

We found that more than one half of the methamphetamine-affected patients required referral to emergency psychiatric services. This is consistent with previous studies that report a high prevalence of psychiatric co-morbidity among people who use methamphetamine.^{31, 32} This observation suggests a potential role of the midazolam-droperidol combination in the psychiatric setting for management of acute agitation in patients with concurrent methamphetamine use. Further research is required to provide definitive evidence.

Although this is the first study to provide evidence of superior efficacy of the midazolam-droperidol combination for methamphetamine-related agitation in the ED, there are important methodological limitations.

The major limitation is that it is a sub-study of a larger trial, with the usual methodological concerns of such an analysis (i.e. reduced power to detect an overall treatment effect). However, our *post hoc* power analyses indicated that the study was well powered, and the ORs of the proportions of patients sedated at 10 minutes indicate a clear difference between the groups. The 95% CI of these ORs, however, were wide and a larger trial is recommended to provide a more precise estimate of the clinical effect.

As patients in this study were only enrolled at two Australian EDs, the external validity may be questionable. However, our patients demonstrated similar characteristics to previous studies of

patients with methamphetamine-related ED visits.^{21, 22, 29, 33} These patients were predominantly male, the majority arrived with police attendance, and a high proportion of them had a history of illicit drug abuse.

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CONCLUSION

This study demonstrates that the intravenous midazolam-droperidol combination is superior to either intravenous droperidol or olanzapine monotherapy for the management of methamphetamine-related acute agitation in the ED. These findings contribute to the limited published evidence in an area that consumes considerable emergency services resource. Given that methamphetamine users are usually transported to the ED in an agitated state, more research is needed to develop an evidence-based protocol for management of methamphetamine-related agitation.

Figure 1. Patient Flow (Modified CONSORT flow diagram)

Table 1. Patient characteristics

	midazolam- droperidol n=34	droperidol n=30	olanzapine n=28
Age, years, mean (95%CI)	32 (29-35)	33 (29-36)	32 (28-35)
Male, n (%)	24 (70.6)	21 (70.0)	22 (78.6)
ATS category, n (%)			
1 (to be seen immediately)	2 (5.9)	1 (3.3)	4 (14.3)
2 (to be seen within 10 minutes)	12 (35.3)	14 (46.7)	14 (50.0)
3 (to be seen within 30 minutes)	19 (55.9)	13 (43.3)	10 (35.7)
4 (to be seen within 60 minutes)	1 (2.9)	2 (6.7)	0 (0.0)
5 (to be seen within 120 minutes)	0 (0.0)	0 (0.0)	0 (0.0)
Time of Triage, n (%)			
00:00-06:59	5 (14.7)	8 (26.7)	6 (21.4)
07:00-12:59	8 (23.5)	11 (36.7)	4 (14.3)
13:00-18:59	12 (35.3)	7 (23.3)	9 (32.1)
19:00-23:59	9 (26.5)	4 (13.3)	9 (32.1)

ICD-10 category, n (%)			
Mental illness	10 (29.4)	4 (13.3)	7 (25.0)
Intoxication (drugs and/or alcohol)	24 (70.6)	24 (80.0)	20 (71.4)
Organic illness	0 (0.0)	2 (6.7)	1 (3.6)
Past psychiatric history, n (%)			
Past psychiatric history, n (%)	16 (47.1)	10 (33.3)	11 (39.3)
Illicit drug abuse history, n (%)			
Illicit drug abuse history, n (%)	29 (85.3)	23 (76.7)	25 (89.3)
Polydrug abuse history, n (%)			
Polydrug abuse history, n (%)	4 (11.8)	6 (20.0)	7 (25.0)
Co-ingestion at time of presentation, n (%)			
Marijuana	2 (5.9)	3 (10.0)	5 (17.9)
Heroin	2 (5.9)	2 (6.7)	2 (7.1)
GHB	1 (2.9)	0 (0.0)	0 (0.0)
Ecstasy	0 (0.0)	1 (3.3)	1 (3.6)
Alcohol	8 (23.5)	7 (23.3)	7 (25.0)
Total duration of security attendance, minutes, median, IQR			
Total duration of security attendance, minutes, median, IQR	29 (20-47)	41 (29-61)	33 (22-58.5)

Need for mechanical restraint, n (%)	27 (79.4)	26 (86.7)	20 (71.4)
Sedatives prior enrolment,* n (%)	9 (26.5)	7 (23.3)	6 (21.4)
intramuscular midazolam	0 (0.0)	3 (10.0)	1 (3.6)
oral diazepam	7 (20.6)	3 (10.0)	1 (3.6)
oral olanzapine	7 (20.6)	1 (3.3)	5 (17.9)
Police attendance on arrival, n (%)	28 (82.4)	20 (66.7)	23 (82.1)
Mode of arrival, n (%)			
Ambulance	15 (44.1)	17 (56.7)	11 (39.3)
Police	18 (52.9)	9 (30.0)	15 (53.6)
Other [†]	1 (2.9)	4 (13.3)	2 (7.1)
Referral made to EMH services, n (%)	24 (70.6)	18 (60.0)	19 (67.9)
ED visit in the past 12 months, n (%)			
No previous visit	19 (55.9)	18 (60.0)	15 (53.6)
1-4 visits	12 (35.3)	11 (36.7)	13 (46.4)
>4 visits	3 (8.8)	1 (3.3)	0 (0.0)

ATS=Australasian Triage Scale; ICD-10=International Classification of Diseases; GHB=Gamma Hydroxybutyrate;
 IQR=Interquartile range; EMH= Emergency Mental Health

*Sedatives prior enrolment included those administered in the out-of-hospital care setting (i.e. administered by ambulance officers) or in the ED. Patients may have more than one medication.

†Other modes of transport include private travel (i.e. self, family, or friends).

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Table 2. Proportion of patients sedated at specific time points after first dose administration and median times to adequate sedation

	midazolam - droperidol (n=34)	droperidol (n=30)	olanzapine (n=28)	midazolam- droperidol vs. droperidol OR, 95% CIs	midazolam- droperidol vs. olanzapine OR, 95% CIs
Proportion sedated, n (%)					
at 5 minutes	20 (58.8)	5 (16.7)	8 (28.6)	7.14 (2.2-23.21)	3.57 (1.23- 10.38)
at 10 minutes	29 (85.3)	14 (46.7)	14 (50.0)	6.63 (2.02- 21.78)	5.80 (1.74- 19.33)
at 15 minutes	32 (94.1)	17 (56.7)	21 (75.0)	12.24 (2.47- 60.64)	5.33 (1.01- 28.19)
at 30 minutes	33 (97.1)	26 (86.7)	23 (82.1)	5.08 (0.54- 48.21)	7.17 (0.79- 65.53)
at 60 minutes	33 (97.1)	30 (100.0)	27 (96.4)	-	1.22 (0.07- 20.47)
				Difference in medians, 95% CIs	Difference in medians, 95% CIs
Time to adequate	5.0 (2.0-	11.5 (6.0-	10.5 (5.0-	6.5 (3-13)	5.5 (2-9)

sedation, median 10.0) 22.3) 17.3)
(IQR), min

IQR=interquartile range

Table 3. The need for additional parenteral sedative medication

	midazolam- droperidol (n=34)	droperidol (n=30)	olanzapine (n=28)
Need for additional doses, n (%)			
1 additional dose	6 (17.6)	9 (30.0)	8 (28.6)
2 additional doses	2 (5.9)	11 (36.7)	11 (39.3)
Need for open label sedative medications to achieve adequate sedation, n (%)	1 (2.9)	4 (13.3)	8 (28.6)
Mean dose (SD), mg	6.5 (3) [†]	15 (4)	15 (4)

[†] mean dose for midazolam; all patients in the midazolam-droperidol combination group received a fixed dose of droperidol 5mg

Table 4. Reported adverse events

(Patients may have experienced more than 1 event)

	midazolam- droperidol (n=34)	droperidol (n=30)	olanzapine (n=28)
Number of patients with reported events, n (%)	7 (20.6)	2 (6.7)	6 (21.4)
Oxygen desaturation (SaO ₂ <90%)	5 (14.7)	2 (6.7)	4 (14.3)
Airway obstruction*	4 (11.8)	1 (3.3)	0 (0.0)
Bradycardia (SBP<80 mmHg)	0 (0.0)	0 (0.0)	1 (3.6)
Prolonged QTc [†] (QTc >500ms)	2 (5.9)	0 (0.0)	1 (3.6)

SaO₂=Oxygen saturation; SBP= Systolic Blood Pressure

* All cases were partial obstruction and resolved promptly following the airway intervention (i.e. chin lift or with insertion of airway adjuncts.

[†]Two patients in the midazolam-droperidol combination group had a QTc (msec) of 501 and 504, respectively. One patient in the olanzapine group had a QTc of 513 msec.

Table 5. ED length of stay and patient disposition

	midazolam- droperidol (n=34)	droperidol (n=30)	olanzapine (n=28)
ED LOS, hours median, (IQR)	11.92 (5.35-14.6)	9.42 (6.7-12.88)	11.73 (7.28-16.83)
Patient Disposition, n (%)			
home	19 (55.9)	18 (60.0)	17 (60.7)
ED short stay	4 (11.8)	3 (10.0)	1 (3.6)
psychiatry ward	8 (23.5)	4 (13.3)	6 (21.4)
medical ward	1 (2.9)	3 (10.0)	0 (0.0)
other institution psychiatry ward	0 (0.0)	1 (3.3)	0 (0.0)
correctional facility	1 (2.9)	1 (3.3)	2 (7.1)
absconded	1 (2.9)	0 (0.0)	2 (7.1)

LOS length of stay; IQR interquartile range

REFERENCES

1. Vearrier D, Greenberg MI, Miller SN, Okaneku JT, Haggerty DA. Methamphetamine: History, Pathophysiology, Adverse Health Effects, Current Trends, and Hazards Associated with the Clandestine Manufacture of Methamphetamine. *Dis Mon.* 2012;**58**(2):38-89.
2. United Nations Office on Drugs and Crime. World Drug Report 2015: United Nations Publication: Sales No. E.15.XI.6; 2015. Available from: http://www.unodc.org/documents/wdr2015/World_Drug_Report_2015.pdf. (Last accessed Aug 2016)
3. Chomchai C, Chomchai S. Global patterns of methamphetamine use. *Curr Opin Psychiatry.* 2015;**28**(4):269-274.
4. EMCDDA. European Drug Report 2015. Trends and Developments. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2015. Available from: <http://www.emcdda.europa.eu/system/files/publications/974/TDAT15001ENN.pdf>. (Last accessed 3/1/2017)
5. Scott N, Caulkins JP, Ritter A, Quinn C, Dietze P. High-frequency drug purity and price series as tools for explaining drug trends and harms in Victoria, Australia. *Addiction.* 2015;**110**(1):120-128.
6. Westmore T, Van Vught J, Thomson N, Griffiths P, J R. Impacts of methamphetamine in Victoria: a community assessment Melbourne, Australia.: Penington Institute; 2014. Available from: <http://www.penington.org.au/wp-content/uploads/2014/09/Impacts-of-methamphetamine-in-Victoria-Community-Assessment-Penington-Institute.pdf>. (Last accessed Aug 2016)
7. Cloutier RL, Hendrickson RG, Fu R, Blake B. Methamphetamine-related Psychiatric Visits to an Urban Academic Emergency Department: An Observational Study. *The Journal of Emergency Medicine.* 2013;**45**(1):136-142.
8. Marshall BDL, Grafstein E, Buxton JA, Qi J, Wood E, Shoveller JA, et al. Frequent methamphetamine injection predicts emergency department utilization among street-involved youth. *Public Health.* 2012;**126**(1):47-53.
9. Wilson MP, Pepper D, Currier GW, Holloman GH, Feifel D. The Psychopharmacology of Agitation: Consensus Statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup. *West J Emerg Med.* 2012;**13**(1):26-34.
10. Abdilrahim D, Bowden JO. Guidance on the Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances. London: Novel Psychoactive Treatment UK Network (NEPTUNE); 2015. Available from: <http://neptune-clinical-guidance.co.uk/wp-content/uploads/2015/03/NEPTUNE-Guidance-March-2015.pdf>. (Last accessed 3/1/2017)
11. Fulde GWO, Forster SL. The impact of amphetamine-type stimulants on emergency services. *Current Opinion in Psychiatry.* 2015;**28**(4):275-279.
12. Cruickshank CC, Dyer KR. A review of the clinical pharmacology of methamphetamine. *Addiction.* 2009;**104**(7):1085-1099.
13. Darke S, Kaye S, McKetin R, Duflou J. Major physical and psychological harms of methamphetamine use. *Drug Alcohol Rev.* 2008;**27**(3):253-262.
14. Chan EW, Taylor DM, Knott JC, Phillips GA, Castle DJ, Kong DC. Intravenous droperidol or olanzapine as an adjunct to midazolam for the acutely agitated patient: a multicenter,

- randomized, double-blind, placebo-controlled clinical trial. *Ann Emerg Med.* 2013;**61**(1):72-81.
15. Knott JC, Taylor DM, Castle DJ. Randomized Clinical Trial Comparing Intravenous Midazolam and Droperidol for Sedation of the Acutely Agitated Patient in the Emergency Department. *Ann Emerg Med.* 2006;**47**(1):61-67.
 16. Isbister GK, Calver LA, Page CB, Stokes B, Bryant JL, Downes MA. Randomized Controlled Trial of Intramuscular Droperidol Versus Midazolam for Violence and Acute Behavioral Disturbance: The DORM Study. *Ann Emerg Med.* 2010;**56**(4):392-401.
 17. Battaglia J, Moss S, Rush J, Kang J, Mendoza R, Leedom L, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med.* 1997;**15**(4):335-340.
 18. Taylor DM, Yap CY, Knott JC, Taylor SE, Phillips GA, Karro J, et al. Intravenous Midazolam-Droperidol (Combination), Droperidol (Only) or Olanzapine (Only) for the Acutely Agitated Patient: A Multi-Centred, Randomised, Double-Blind, Triple-Dummy, Clinical Trial. *Ann Emerg Med.* 2016;
<http://dx.doi.org/10.1016/j.annemergmed.2016.07.033>
 19. Castle D, Daniel J, Knott J, Fielding J, Goh J, Singh B. Development of Clinical Guidelines for the Pharmacological Management of Behavioural Disturbance and Aggression in People with Psychosis. *Australasian Psychiatry.* 2005;**13**(3):247-252.
 20. Grant KM, LeVan TD, Wells SM, Li M, Stoltenberg SF, Gendelman HE, et al. Methamphetamine-Associated Psychosis. *J Neuroimmune Pharmacol.* 2012;**7**(1):113-139.
 21. Bunting PJ, Fulde GW, Forster SL. Comparison of crystalline methamphetamine ("ice") users and other patients with toxicology-related problems presenting to a hospital emergency department. *Med J Aust.* 2007;**187**(10):564-566.
 22. Spain D, Crilly J, Whyte I, Jenner L, Carr V, Baker A. Safety and effectiveness of high-dose midazolam for severe behavioural disturbance in an emergency department with suspected psychostimulant-affected patients. *Emerg Med Australas.* 2008;**20**(2):112-120.
 23. Martel M, Sterzinger A, Miner J, Clinton J, Biros M. Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Acad Emerg Med.* 2005;**12**(12):1167-1172.
 24. Perkins J, Ho JD, Vilke GM, DeMers G. American Academy of Emergency Medicine Position Statement: Safety of Droperidol Use in the Emergency Department. *The Journal of Emergency Medicine.* 2015;**49**(1):91-97.
 25. Calver L, Isbister GK. High dose droperidol and QT prolongation: analysis of continuous 12-lead recordings. *Br J Clin Pharmacol.* 2014;**77**(5):880-886.
 26. Lischke V, Behne M, Doelken P, Schledt U, Probst S, Vettermann J. Droperidol causes a dose-dependent prolongation of the QT interval. *Anesth Analg.* 1994;**79**(5):983-986.
 27. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SHL. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *The Lancet.* 2000;**355**(9209):1048-1052.
 28. Jenner L, Spain D, Whyte I, Baker A, Carr VJ, Crilly J. Management of patients with psychostimulant toxicity: Guidelines for emergency departments. Canberra: Australian Government Department of Health and Ageing; 2006. Available from:
[http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/content/9DFC79ECB850641ECA2571F40016229F/\\$File/emergency-book.pdf](http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/content/9DFC79ECB850641ECA2571F40016229F/$File/emergency-book.pdf). (Last accessed Aug 2016)

29. Gray SD, Fatovich DM, McCoubrie DL, Daly FF. Amphetamine-related presentations to an inner-city tertiary emergency department: a prospective evaluation. *Med J Aust*. 2007;**186**(7):336-339.
30. Richards JR, Derlet RW, Duncan DR. Methamphetamine toxicity: treatment with a benzodiazepine versus a butyrophenone. *Eur J Emerg Med*. 1997;**4**(3):130-135.
31. Alarcon Manchego P, Knott J, Graudins A, Bartley B, Mitra B. Management of mental health patients in Victorian emergency departments: A 10 year follow-up study. *Emerg Med Australas*. 2015;**27**(6):529-536.
32. Sara G, Burgess P, Harris M, Malhi GS, Whiteford H, Hall W. Stimulant use disorders: Characteristics and comorbidity in an Australian population sample. *Aust N Z J Psychiatry*. 2012;**46**(12):1173-1181.
33. Pasic J, Russo JE, Ries RK, Roy-Byrne PP. Methamphetamine users in the psychiatric emergency services: a case-control study. *Am J Drug Alcohol Abuse*. 2007;**33**(5):675-686.

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