Original Contribution

Antipsychotics for the treatment of sympathomimetic toxicity: A systematic review ☆

Nicholas J. Connors, MD [a],*, Ahmed Alsakha, MD [b,h], Alexandre Larocque, MD [c,d], Robert S. Hoffman, MD [e], Tara Landry, MLIS [f], Sophie Gosselin, MD [b,c,g]

[a] Department of Emergency Medicine, Medical University of South Carolina, Charleston, SC, USA
[b] Department of Emergency Medicine, McGill University Health Centre, Montréal, Québec, Canada
[c] Centre Antipoison Du Québec, Montréal, Québec, Canada
[d] Department of Emergency Medicine, Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada
[e] Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, New York University School of Medicine, New York, NY, USA
[f] McGill University Library, Montréal, Québec, Canada
[g] Département d'urgence, Hôpital Charles-Lemoyne, Greenfield Park, Qc, Canada
[h] Department of Emergency Medicine, Cornwall Community Hospital, Cornwall, Ontario, Canada

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ABSTRACT

Objective: Benzodiazepines are often recommended first-line for management of cocaine and amphetamine toxicity while antipsychotic treatment is discouraged due to the potential for lowering seizure threshold, prolonging the QT interval, and decreasing heat dissipation. We performed a systematic review including animal and human studies to elucidate the efficacy and safety of antipsychotics in managing sympathomimetic toxicity specifically evaluating the effect of treatment on mortality, seizures, hyperthermia, and cardiovascular effects.

Methods: We searched MEDLINE, Embase, BIOSIS Previews, Web of Science, Scopus, CENTRAL and gray literature from inception to 31 May 2017 to answer: Can antipsychotics be used safely and effectively to treat cocaine or amphetamine toxicity? Citations were screened by title and abstract. Additional citations were identified with citation tracking. Data were extracted from full-texts.

Results: 6539 citations were identified; 250 full-text articles were assessed. Citation tracking identified 2336 citations; 155 full texts were reviewed. Seventy-three papers were included in this review. In 96 subjects with cocaine toxicity treated with an antipsychotic, there were three deaths, two cardiac arrests, two seizures, and one episode of hyperthermia. In 330 subjects with amphetamine toxicity treated with an antipsychotic, there were two episodes of coma and QT prolongation and one episode of each: hypotension, NMS, cardiac arrest, and death.

Conclusion: This systematic review represents an exhaustive compilation of the available evidence. There is neither a clear benefit of antipsychotics over benzodiazepines nor a definitive signal of harm noted. We encourage clinicians to adapt treatment based on specific circumstances and characteristics of their individual patients.

1. Introduction

Cocaine is one of the most common recreational substances used in the United States. According to the U.S. Substance Abuse and Mental Health Services Administration's 2015 National Survey on Drug Use and Health, there were 1.8 million active cocaine users, 1.6 million users of nonmedical stimulants, and 897,000 users of methamphetamine [1]. Of the 1,252,500 emergency department (ED) visits due to illicit drugs in 2011, 505,224 ED visits were due to cocaine alone (40.3%). Similarly, 182,338 ED visits (14.6%) were related to amphetamines and derivatives, including methamphetamine and MDMA [2]. Adverse effects of sympathomimetic drugs include: agitation, seizures, hypertension, tachycardia, hyperthermia, dysrhythmias, and sudden death [3-6].

The management of patients with sympathomimetic toxicity is challenging. Rapid sedation, hemodynamic stabilization, and

cooling are crucial early interventions in the management of these patients [7]. Pharmacological sedation options are limited to benzodiazepines, ketamine, and antipsychotic medications, though central alpha adrenergic antagonists and NMDA receptor antagonists are in the early stages of evaluation. It is sometimes difficult to know if an ED patient with acute agitation has sympathomimetic toxicity or an acute psychiatric illness.

Antipsychotics are used frequently for undifferentiated agitation. While quantifying use is nearly impossible, it is extremely common to see the use of haloperidol 5–10 mg IV or IM used for rapid sedation, among others. Paralytics and mechanical ventilation are generally considered a last resort and are usually reserved for severe symptoms such as hyperthermia or failure to control agitation. Benzodiazepines are considered by many to be the safest choice to treat sympathomimetic toxicity and, thus are often recommended as the first-line agent [8]. Some authors discourage using antipsychotics owing to the hypothesis that these medications lower seizure threshold, predispose to cardiac dysrhythmias, and decrease heat dissipation [9-11]. If true, these effects could worsen the clinical course of sympathomimetic toxicity and potentially increase mortality.

As sympathomimetic toxicity is a frequent clinical problem and as the optimal way to treat these patients remains partly based on expert opinion, we undertook this systematic review to evaluate the efficacy and safety of antipsychotics in managing sympathomimetic toxicity. We did not aim to address the use of ketamine or dexmedetomidine due to the significant lack of research into the use of these agents to treat sympathomimetic toxicity.

2. Methods

2.1. Search strategy

The following databases were searched from inception to 31 May, 2017 for relevant citations by an experienced librarian (T.L.): MEDLINE (via OvidSP; via PubMed); Embase Classic + Embase (via OvidSP); BIOSIS Previews (via OvidSP); Web of Science (via ThomsonReuters); Scopus (via Elsevier); CENTRAL (via Cochrane Library). The search strategy (Appendix 1) used key text words and relevant indexing to answer the following question: Can antipsychotics be used safely to treat cocaine or amphetamine toxicity? The full MEDLINE strategy was applied to all databases, with modifications to search terms as necessary. No language restrictions were applied. Further citations were identified in Web of Science and Scopus by carrying out searches for citations referencing the already included studies, as well as by examining their reference lists. Proceedings of the North American Congress of Clinical Toxicology were hand-searched from 2009 to 2017. Additionally, the gray literature was reviewed for references to relevant publications.

2.2. Outcomes measures

Significant clinical safety outcomes occurring as a result of treatment with antipsychotics in subjects with sympathomimetic toxicity were considered. The outcomes included in the present work were mortality, seizures, hyperthermia, and cardiovascular effects such as dysrhythmias, tachycardia and hypertension, as defined and reported by each study's authors. The reviewers also catalogued apparent adverse effects from treatment.

2.3. Study eligibility

Two investigators (A.A. and N.C.) initially evaluated the eligibility of citations and full-text articles; one author (AL) reviewed

excluded citations. All authors reviewed and agreed on full-text article inclusions. Full text articles were included if they respected the following criteria:

1. Study types: randomized controlled trials, non-randomized controlled trials, observational studies, case series, case reports, animal experimental studies, and data presented as abstracts in scientific meetings.
2. Study subjects: humans or animals poisoned with cocaine or amphetamines.
3. Intervention: antipsychotics used to mitigate the toxic effects of sympathomimetic drugs. Investigations utilizing chemicals without regulatory approval (investigative drugs) for humans use in the United States or Canada were excluded.

There was no restriction on language. All materials without original data were excluded. However, their references were reviewed to identify citations potentially missed by the previously described search strategy. In-vitro experiments or studies with clinically irrelevant outcomes in the ED such as place preference conditioning, behavioral changes, neuronal toxicity or cell death without clinical endpoints were also excluded.

2.4. Data extraction

One of two investigators (A.A. and N.C.) extracted data from each study on a standardized form agreed upon by all authors. For each of the included studies, the following data were collected: species of subjects and their numbers if available, study type, sympathomimetic, antipsychotic, benzodiazepine, and other study medications used with doses and routes of administration, outcomes measured including: mortality, seizures, hyperthermia, cardiovascular effects, and other relevant treatment effects. The GRADE approach was applied to the human studies. Two of the authors (S.G. and R.S.H.) reviewed all papers independently and discussed their findings to resolve conflicts, which were minimal. No kappa was calculated.

3. Results

The search strategy returned 6539 citations, (Medline via Ovid = 892, Embase = 4485, Biosis Previews = 367, Cochrane Library = 16, Medline via PubMed = 7, Scopus = 548, Web of Science = 155, PsycINFO = 69). The gray literature search yielded no additional reports. 5132 citations were screened after removing duplicates, of which 4882 were irrelevant and excluded by title alone. Articles were translated from Japanese, German, French, Bulgarian, Spanish and Dutch. Two hundred and fifty full-text articles were assessed for eligibility, of which 187 articles did not meet the inclusion criteria, leaving 63 studies. Citation tracking provided an additional 2336 citations after duplicates removal. Of these 2181 were excluded based on the title or abstract, 155 full texts were retrieved. A total of 74 papers met all criteria for inclusion, but there was very similar data between two [12,24]. Following a personal communication from one of the authors (N.C.) with the first author of these, it was clarified that the earlier study, published in 1997 is a subgroup of the later, published in 1998. For this analysis, only the later was included and the data were only counted once. Seventy-three papers were ultimately included in this review; 20 are human studies and described in the following text. Fifty-three animal studies are described in Supplemental material. Although all reviewed full text articles were translated, the included articles were all in English. Fig. 1 summarizes the study selection process.
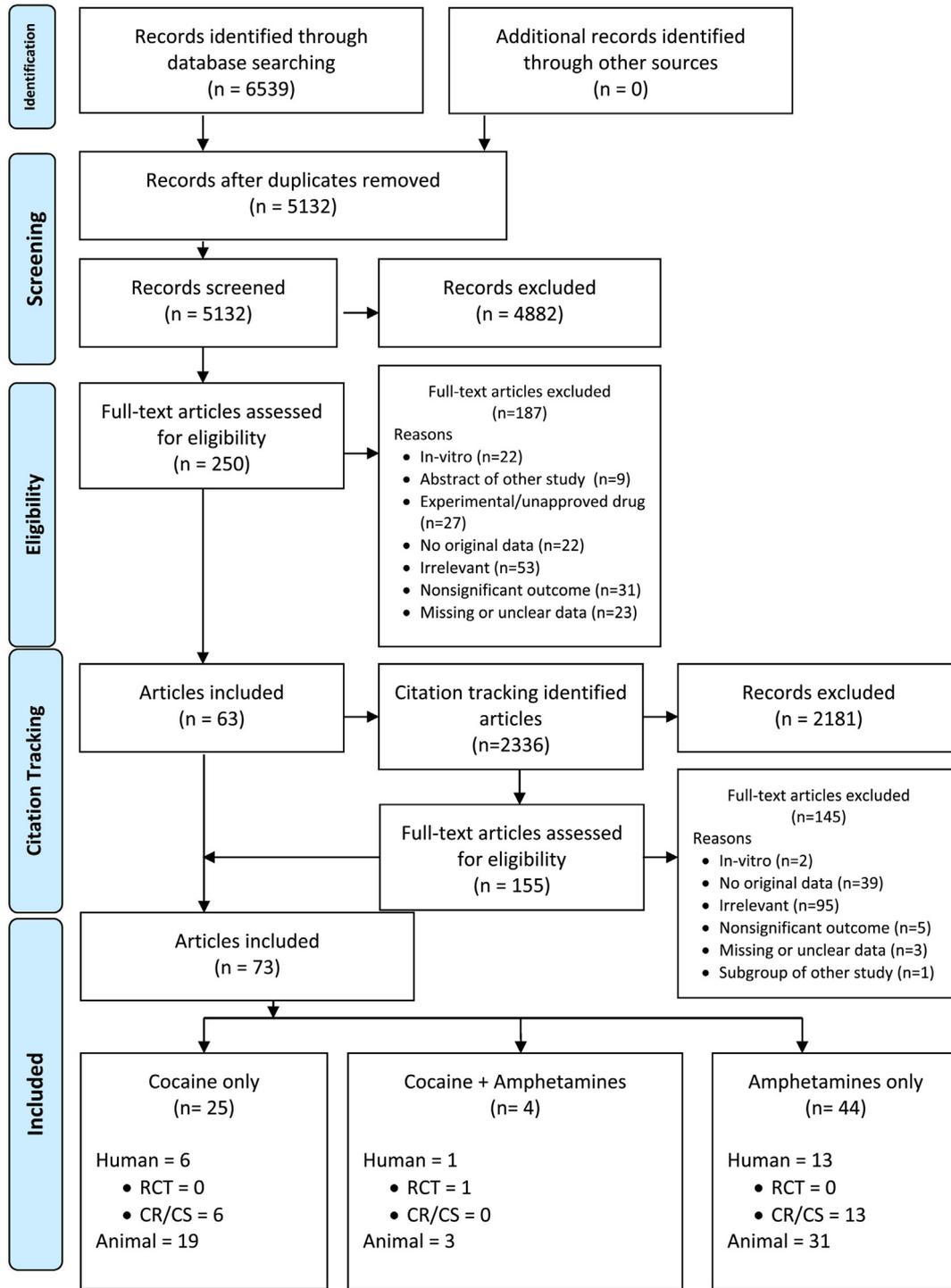
Fig. 1. Study selection access date May 31, 2017.

Twenty-five articles addressed cocaine alone, 44 articles addressed amphetamines alone, and 4 articles addressed cocaine and amphetamines together. The human data were not universally supported by confirmatory toxicologic confirmation, while the animal studies used pure drugs in precise doses. Heterogeneity was present in the animal amphetamine literature with studies addressing amphetamine (21), methamphetamine (7), methylenedioxymethamphetamine (MDMA) (4), methylenedioxyamphetamine (MDA) (3), and paramethoxyamphetamine (PMA) (2). Similar heterogeneity existed in the antipsychotic use for both cocaine and amphetamine toxicity with several different agents utilized at varying dosages. Haloperidol was the most common antipsychotic studied alone (27), followed by chlorpromazine (18), droperidol (7), ziprasidone (4), pimozide (3), olanzapine (2), clozapine (1) and quetiapine (1). An additional 13 papers studied multiple antipsychotics, with haloperidol most commonly investigated in 10 of them. There were 96 human subjects included in the articles dealing with cocaine toxicity and 330 in those with amphetamine toxicity. The adverse effects documented after antipsychotic administration include: hyperthermia (n = 1), hypotension

Articles included (n = 73)		
Human (n = 20) *1 studied both cocaine and amphetamine*	Cocaine + AP (n = 7) RCT: 1 Case Series: 3 Case Reports: 3 Total Patients (n = 96)	AE: Hyperthermia:1 Seizure: 2 Cardiac arrest: 2 Death: 3
	Amphetamines + AP (n = 14) RCT: 1 Case Series: 5 Case Reports: 8 Total Subjects (n = 330)	AE: Hypotension: 1 QT prolongation: 2 NMS:1 Coma:2 Cardiac arrest: 1 Death: 1
Animal (n = 53)	Cocaine (n = 22) Pretreatment - AP vs P: 15 Pretreatment - AP vs Bz: 4 Treatment: 3	Legend: AP, antipsychotic; AE, adverse events; RCT, randomized controlled trial; NMS, Neuroleptic Malignant Syndrome; P, placebo; Bz, benzodiazepine
	Amphetamines (n = 34) Pretreatment - AP vs P: 23 Pretreatment - AP vs Bz: 2 Treatment: 9	

Fig. 2. Article results summary with adverse effects.

(n = 1), Neuroleptic malignant syndrome (NMS) (n = 1), seizures (n = 2), QT prolongation (n = 2), coma (n = 2), cardiac arrest (n = 3), and death (n = 4) (Fig. 2).

3.1. Cocaine

3.1.1. Human data

Seven articles described the treatment of cocaine toxicity in humans (Table 1) [12-18]. In summary, there were several adverse events associated with antipsychotic administration. Droperidol was administered to 1 patient who suffered seizures and cardiac arrest, and another had seizures and hyperthemia. One patient developed asystolic cardiac arrest shortly after EMS-administered droperidol during transport and died. Haloperidol was administered to a patient who was found dead the next day and haloperidol and chlropromazine were given to a patient with unrecognized cocaine toxicity who died in the psychiatric ED. Low cocaine and metabolite concentrations were noted in a cohort of patients at autopsy who also had presence of an antipsychotic than those who had only evidence of cocaine.

3.1.1.1. Randomized trials.
A randomized controlled trial compared droperidol 2.5 mg IV for subjects ≤50 kg or 5 mg IV for subjects >50 kg to IV lorazepam 2 mg IV for subjects ≤50 kg, 4 mg IV for subjects >50 kg in agitated ED patients who used cocaine or methamphetamine. Twelve subjects with urine drug screens positive for cocaine (four of whom also had measurable serum ethanol concentrations) were treated with lorazepam while 16 (seven with concomitant ethanol intoxication) were treated with droperidol. There were no statistically significant differences in sedation 5 min after study drug administration, but those treated with droperidol were more likely to be sedated after 5 min and required less redosing than those treated with lorazepam. At 0 min the mean sedation scores (on a scale created by the authors with a lower score indicating greater sedation) were 5.3 and 5.6 in the lor-

azepam and droperidol groups respectively. At 5 min the mean sedation scores were 4.7 and 4.8, but over time, the differences became statistically significant between the lorazepam and droperidol groups with respective scores of 4.1 vs 2.8 at 10 min; 3.5 vs 2 at 15 min, 2.9 vs 1.6 at 30 min, and 2.5 vs 1.5 at 60 min. When sedation scores versus time were separated by cause of toxicity (cocaine vs methamphetamine), there was a similar increase in sedation with more rapid onset in those who had used cocaine and were treated with droperidol compared to lorazepam, but statistical analysis was not performed to determine the significance of these findings. One patient treated with droperidol developed an acute dystonic reaction, though it is not reported whether they had cocaine or amphetamine toxicity [12].

3.1.1.2. Uncontrolled observations.
A retrospective case series describes 64 patients who either admitted to using cocaine or had a urine drug screen positive for cocaine (20 of whom also had positive breath or serum ethanol concentrations), who were treated with IM or IV droperidol for agitation, anxiety, vomiting, or pain. Among these, a 39-year-old man was brought to the ED after ingesting multiple pieces of crack cocaine. He was treated with droperidol 5 mg IM and lorazepam 2 mg IM for sedation but eleven hours later he suffered a seizure and cardiac arrest. He was treated with cardioversion, antidysrhythmics, antiepileptics, multidose activated charcoal, and naloxone infusion. He was discharged seven days after presentation, neurologically intact. A 28-year-old woman with a urine drug screen positive for cocaine was brought to the ED by police with agitated delirium and a heart rate of 200/min. She was administered lorazepam 2 mg IM and, 12 min later, droperidol 5 mg IM. Nine minutes later she had a seizure. She was treated with antibiotics and phenytoin. She was discharged five days after presentation [13].

A case series describes five patients with oral ingestions of crack cocaine. The first ingested 28 nuggets and was found convulsing by police. She was given diazepam 10 mg IV, but suffered PEA arrest and was eventually declared brain dead after prolonged status epilepticus. Another adult patient became symptomatic and was treated with lorazepam 16 mg IV and haloperidol 5 mg IV. He was admitted and treated with an esmolol infusion and lorazepam 2–4 mg IV boluses and discharged without sequelae. A patient who was agitated after a cocaine ingestion was treated with a total lorazepam dose of 12 mg IV followed by labetalol, diphenhydramine, and esmolol and discharged without sequelae. Lorazepam 4 mg IV was used to treat another agitated patient after cocaine ingestion along with labetalol. The patient developed seizures and was treated with lorazepam 2 mg IV and midazolam 5 mg IV. He signed out of the hospital against medical advice and was lost to follow-up. Finally, a patient rapidly ingested poorly packaged cocaine to avoid prosecution and became agitated. He was treated with a total lorazepam dose of 10 mg IV and propranolol, then discharged home after 48 h [16].

Finally, a retrospective case series of cocaine-related deaths performed by a medical examiner reported lower cocaine and benzoylecgonine concentrations in patients who also had measurable concentrations of various antipsychotics compared to those without any measurable concentrations of antipsychotics, which included one case involving thioridazine [15].

3.1.1.3. Case reports.
The three case reports are summarized in Table 1 [14,17,18].

3.1.2. Animal data

Briefly, chlorpromazine pretreatment of dogs protected against mortality, compared to diazepam pretreatment, which resulted in 33% mortality 48–72 h after cocaine exposure. Chlorpromazine compared to placebo in pretreatment models in rats and guinea

Table 1
Human cocaine toxicity treated with antipsychotics

Citation and GRADE level of evidence	Subjects	Treatment	Results	Threats to validity
Randomized trials Richards JR et al., 1998 [12] Level LOW	Study of general agitated ED patients (n = 202), 28 of whom used cocaine.	Droperidol 2.5 mg IV for weight <50 kg, 5 mg IV for weight >50 kg vs. Lorazepam 2 mg IV for weight <50 kg, 4 mg IV for weight >50 kg	In 28 subjects with urine drug screen positive for cocaine, 11 of which were also positive for ethanol. Statistically significant increase in sedation in droperidol group compared to lorazepam after 5 min.	1. Definition of toxicity based on urine drug screen (−1 indirectness) 2. Non blinded (−1 lack of allocation concealment) 3. Weight "visually estimated" 4. Non validated sedation scale 5. Dose equivalency between lorazepam and droperidol not validated 6. See discrepancy with dosing below under methamphetamine as reported in Richards JR et al., 1997 [24] 7. Confounding of other drugs present (ethanol for one present in 33.3% of the lorazepam group vs 44% in the droperidol group) 8. Lorazepam not ideal comparator – proven slow onset compared with midazolam
Case series Merigian KS, 1994 [16] Level VERY LOW	Patients with oral cocaine ingestion (n = 5)	Patient 1: ingested 28 nuggets, convulsion, given diazepam 10 mg IV Patient 2: combative, violent, aggressive, given lorazepam 16 mg IV haloperidol 5 mg IV Patient 3: agitated, given lorazepam 12 mg IV Patient 4: agitation and Seizures. Given lorazepam; lorazepam 2 mg IV and midazolam 5 mg IV Patient 5: agitation, given lorazepam 10 mg	Patient 1: suffered PEA arrest. Brain dead after prolonged status epilepticus. Patient 2: discharged without sequelae. Patient 3: discharged without sequelae. Patient 4: he signed out of the hospital against medical advice. Patient 5: agitation. Discharged home after 48 h.	1. Uncontrolled data 2. Cocaine ingestion uncommon 3. Treatment confounded by multiple therapies – all patients given beta adrenergic antagonists, some received phenytoin, diphenhydramine and morphine 4. No confirmation of ingestion (indirectness)
Chase PB et al., 2002 [13] Level VERY LOW	Retrospective review of ED patients treated with droperidol (n = 2468)	Droperidol IM or IV	In 44 with cocaine exposures 2 subjects suffered seizures, 1 had hyperthermia, and 1 had cardiac arrest. Fourteen percent were admitted. In 20 patients with cocaine and alcohol exposures, 55% were admitted.	1. Uncontrolled data 2. Definition of toxicity unclear; history or urine drug screen positive
Molina K et al., 2011 [15] Retrospective Review Level VERY LOW	Patients with cocaine-related deaths		The concentration of cocaine and benzoylecgonine was less in those who also had measurable antipsychotic concentrations compared to those with only cocaine or benzoylecgonine.	1. Actual cause of death unclear. 2. Definition of "cocaine-related" is undefined. 3. 69% had at least one drug in addition to cocaine but only 12% had an antipsychotic plus cocaine. 4. Since percent of "dead on arrival" patients unknown, for some the antipsychotic was therapeutic prior to the cocaine use and not given as treatment for the toxicity.
Case reports Fishbain D et al., 1981 [14] Level VERY LOW	31 year old man, cocaine body packer	Chlorpromazine 50 mg IM × 2 Haloperidol 10 mg IM	The patient died 3.5 h after arrival to psychiatric ED, an unknown time from presentation or ingestion.	Anecdotal by definition
Klein C et al., 2000 [17] Level VERY LOW	38 year old woman, cocaine body packer	Diazepam 20 mg Haloperidol 10 mg	A seizure treated with phenytoin, then diazepam 20 mg and haloperidol 10 mg, increasingly paranoia. Transferred to psychiatry; found dead the next day. Autopsy: multiple intestinal broken packets containing cocaine	Anecdotal by definition
Cox RD et al., 2004 [18] Level VERY LOW	33 year old man with agitation	Droperidol 5 mg IM	Agitated and EMS gave droperidol. Apneic and asystolic after while in transport. Autopsy showed cocaine in blood and metabolites in urine	Anecdotal by definition

Table 2
Human amphetamine toxicity treated with antipsychotics

Citation	Subjects	Treatment	Results	Threats to validity
Randomized trials				
Richards JR et al., 1998 [12] Also reported in Richards JR et al., 1997 [24] Level LOW	Study of general agitated ED patients (n = 202), 146 of whom used methamphetamine	Droperidol 2.5 mg IV for weight <50 kg, 5 mg IV for weight >50 kg vs. lorazepam 2 mg IV for weight <50 kg, 4 mg IV for weight >50 kg	In 146 subjects with urine drug screen positive for methamphetamine, 59 of which were also positive for ethanol. Statistically significant increase in sedation in droperidol group compared to lorazepam after 5 min.	1. Definition of toxicity based on urine drug screen (−1 indirectness) 2. Non blinded (−1 lack of allocation concealment) 3. Weight "visually estimated" (indirectness) 4. Non validated sedation scale 5. Dose equivalency between lorazepam and droperidol not validated 6. Dosing listed as "suggestions" but left up to the clinicians decision 7. Confounding of other drugs present (ethanol for one) 8. Lorazepam not ideal comparator – proven slow onset compared with midazolam
Case series				
Espelin DE et al., 1968 [19] Level VERY LOW	Children aged 11–48 month old (n = 22) with toxicity due to: Methamphetamine (n = 2) Amphetamine (n = 5) Methamphetamine/phenobarbital (n = 8) Amphetamine/phenobarbital (n = 1) Phenmetrazine (n = 2) Detroamphetamine/Meprobamate (n = 1) Dextroamphetamine (n = 2) Carboxyphen/butabarbital (n = 1)	Varying doses (0.4 to 4.0 mg/kg) of chlorpromazine (n = 22) and 5/22 treated with barbiturates	Sedation occurred in all subjects. Two serious adverse effects. One child ingested a methamphetamine phenobarbital combination, was agitated and was treated with 1.2 mg/kg chlorpromazine IM. Then became unresponsive, apneic and pulseless which resolved with "chest pounding." They were discharged home without sequelae. Another became frankly comatose after 1.1 mg/kg chlorpromazine IM.	1. Retrospective 2. Uncontrolled data 3. No confirmation of ingestion 4. Chlorpromazine different from many antipsychotics with very potent alpha adrenergic antagonism (antihypertensive effect)
Derlet RW et al., 1989 [20] Level VERY LOW	127 adults with amphetamine toxicity	Haloperidol	6% (n = 8) of agitated patients were treated with haloperidol, 4% (n = 5) were treated with diazepam. Patients responded "equally well."	1. Retrospective 2. Uncontrolled data 3. Definition of toxicity is a positive urine drug screen 4. 21 cases had other drugs detected 5. Drug doses not specified
Calver L et al., 2013 [21] Level VERY LOW	Safety arm of a prospective study of the use of droperidol for agitation in 46 patients.	41 year old man with amphetamine toxicity treated with droperidol 20 mg IM 25 year old man taking methadone presents with amphetamine toxicity and is treated with droperidol 10 mg IM	QT prolongation 522 ms, 11 h post droperidol QT prolongation 512 ms up to 2.25 h post droperidol	1. Etiology of QT prolongation unclear because of time delay (case 1) and co-ingestion (case 2)
Guharoy R et al., 1999 [25] Level VERY LOW	Six adults with methamphetamine toxicity	Haloperidol, a benzodiazepine or both	One treated with haloperidol 6 mg and diazepam 10 mg; one treated with diazepam 50 mg and haloperidol 2 mg; one treated with haloperidol 4 mg; on treated with 40 mg diazepam and 4 mg lorazepam, one treated with 10 mg diazepam; on required no sedation. All did well.	1. Unclear how the cases were identified Uncontrolled data 2. Unclear rationale for doses of drugs given
Ruha AM et al., 2006 [26] Level VERY LOW	Retrospective review of children <13 years old with methamphetamine toxicity admitted to one ICU (n = 18)	All 18 received a benzodiazepine. Haloperidol (0.02–0.67 mg/kg) was also given in 12.	Clinical improvement without adverse effects reported in all	1. Retrospective 2. Uncontrolled data 3. Use of benzodiazepines in all patients confounds any assessment
Case reports				
Ginsberg MD et al., 1970 [22] Level VERY LOW	21 year old man with amphetamine toxicity	Chlorpromazine 100 mg subcutaneously	Ingestion of about 2 g amphetamine and became agitated, hyperthermic, tachycardic, and hypertensive. Post treatment became somnolent, obtunded and hypotensive. Blood pressure improved with IVF, Trendelenberg positioning. He developed AKI and	Anecdotal by definition

Table 2 (*continued*)

Citation	Subjects	Treatment	Results	Threats to validity
			required hemodialysis but improved over several days.	
Soong WJ et al., 1991 [23] Level VERY LOW	Two children with amphetamine toxicity	Case 1: 18 month old boy diazepam 10 mg, haloperidol 20 mg IV, and chloral hydrate, Case 2: 20 month old boy treated with diazepam 10 mg IV twice and haloperidol 20 mg IV	Slept for 20 h, and improved. Improvement in agitation	Anecdotal by definition
Gullatt R, 1957 [27] Level VERY LOW	21 month old boy with methamphetamine toxicity	Chlorpromazine 2.5 mg IV (two doses 9 h apart)	The child had rapid resolution of symptoms and survived without sequalae	Anecdotal by definition
Hall CD et al., 1973 [28] Level VERY LOW	26 year old man with methamphetamine toxicity	Chlorpromazine 50 mg IM	The patient presented agitated, hypertensive after complaining of severe headache. Post treatment became hemiplegic and evidence of intracranial hemorrhage was found on cerebral arteriography and confirmed on autopsy.	Anecdotal by definition
Gary NE et al., 1978 [29] Level VERY LOW	27 year old man with methamphetamine toxicity	Droperidol 2.5 mg/min IV infusion, Phenobarbital 120 mg IM initial treatment	Fifteen minutes after initiation of droperidol infusion (105 min after phenobarbital) pulse and BP improved.	Anecdotal by definition
Brown C et al., 1987 [30] Level VERY LOW	32 year old woman with MDMA toxicity	Haloperidol Gastric lavage, dextrose, diazepam, and naloxone. Drug doses not specified	The patient presented with agitation and hallucinations, was hyperthermic, tachycardic, hypotensive. She was intubated, After stabilization she was given haloperidol and diazepam for agitation. She was extubated and had no further complications.	1. Anecdotal by definition 2. No dose reported
Lehmann ED et al., 1995 [31] Level VERY LOW	36 year old man with MDMA toxicity	Chlorpromazine and diazepam given, dose not specified	The patient presented after seizing at a nightclub. He became hyperthermic and agitated. Sodium was 115 mmol/L. He developed rhabdomyolysis and recovered.	1. Anecdotal by definition 2. No dose reported
Russell T et al., 2012 [32] Level VERY LOW	20 year old woman with MDMA toxicity	Haloperidol, total 115 mg	NMS in a patient with ryanodine receptor mutation. Recovered without sequelae.	Anecdotal by definition

pigs protected against mortality. In a monkey model chlorpromazine treatment resulted in no mortality, while diazepam treatment resulted in 33% (n = 1). Due to species and model differences with the human clinical scenarios, the applicability of these finding to humans is questionable at best. See Supplemental text and tables for a detailed description of the animal data.

3.2. Amphetamines

3.2.1. Human data

In summary, there were several adverse events associated with antipsychotics. Chlorpromazine was associated with two episodes of coma, and one episode each of cardiac arrest, intracranial hemorrhage, hypotension, and death. Haloperidol, in a very high dose, was associated with NMS. Droperidol administration was associated with two episodes of QT prolongation. These findings are shown in Fig. 2.

3.2.1.1. Amphetamine.
3.2.1.1.1. Randomized trials. There are very few human studies on the effect of antipsychotics in patients with amphetamine toxicity. No randomized trials of the treatment for amphetamine toxicity were found. The data below are summarized in Table 2.

3.2.1.1.2. Uncontrolled observations. A case series of 22 children, aged from 11 to 48 months, describes exposures to various amphetamines, and amphetamine combination medications. Five of these children were initially treated with barbiturates for sym-

pathomimetic toxicity. All were administered chlorpromazine at varying doses to control symptoms. There was one case of apnea and pulselessness in a 23-month-old child who had ingested methamphetamine/phenobarbital and was given chlorpromazine 1.2 mg/kg intramuscularly. The child improved with "chest pounding" and was discharged without noted sequelae. Another child became "frankly comatose" after ingestion of a methamphetamine/phenobarbital combination and treatment with chlorpromazine 1.1 mg/kg intramuscularly [19]. Another case series from 1989 describes 127 adult patients with amphetamine toxicity. Six percent (n = 8) were treated with haloperidol and 4% (n = 5) were treated with diazepam for agitation. Patients responded "equally well" to both [20].

A 2013 case study on the effects of high-dose droperidol (normal dosage 2.5–5 mg IV or IM) for the treatment of aggressive ED patients reported two patients with QT prolongation. The first, a 41-year-old man with hallucinations due to amphetamines, had QT prolongation to 522 ms after 10 mg droperidol IM and a 25-year-old man on methadone with amphetamine toxicity and agitation had a QT of 512 ms after 20 mg droperidol IM (customary dosing: 2.5–5 mg IV/IM) [21].

3.2.1.1.3. Case reports. Two case reports are summarized in Table 2 [22,23].

3.2.1.2. Methamphetamine.
3.2.1.2.1. Randomized trials. A randomized controlled trial (previously described above with regards to cocaine-toxicity) compared

droperidol, 2.5 mg IV for patients ≤50 kg or 5 mg IV for patients >50 kg to IV lorazepam 2 mg IV for patients ≤50 kg or 4 mg IV for patients >50 kg for methamphetamine toxicity. Seventy-four patients with urine drug screens positive for methamphetamine (30 of whom also had serum ethanol concentrations) were treated with lorazepam while 72 (29 with serum ethanol concentrations) were treated with droperidol. There was statistically significant faster onset and greater sedation in all patients treated with droperidol compared to lorazepam. When sedation scores versus time were separated by cause of toxicity, there was similar increased sedation with more rapid onset in those who had used methamphetamine and treated with droperidol compared to lorazepam, but statistical analysis was not performed to determine the significance of these findings. One patient in the droperidol group developed an acute dystonic reaction. It was not stated whether this patient had evidence of amphetamine or cocaine use [12].

3.2.1.2.2. Uncontrolled observations. One case series reports six adults with methamphetamine toxicity, three of whom were treated with haloperidol for agitation and did well [25]. A more recent case series describes children, 4 months to 7 years old, with methamphetamine toxicity treated with benzodiazepines and haloperidol. Twelve children were administered haloperidol after all received a benzodiazepine. The haloperidol dose ranged from 0.02–0.67 mg/kg. There were no cases of QT prolongation, respiratory depression, or dystonic reactions [26].

3.2.1.2.3. Case reports. Three case reports are summarized in Table 2 [27-29].

3.2.1.3. Methylenedioxymethamphetamine (MDMA). No randomized trials of antipsychotics in MDMA toxicity were found. Three case reports are summarized in Table 2 [30-32].

3.2.2. Animal data

In summary, the animal data show chlorpromazine and haloperidol pretreatment resulted in decreased mortality compared to controls. In a rat model, haloperidol pretreatment reduced mortality compared to those pretreated with diazepam. Due to species and model differences with the human clinical scenarios, the applicability of these finding to humans is questionable at best. See Supplemental text and tables for a detailed description of the animal data.

4. Discussion

Abuse of amphetamines and cocaine is common resulting in many ED admissions for sympathomimetic toxicity and agitated delirium worldwide [33]. While EDs encounter a significant number of patients presenting with sympathomimetic toxicity, it is often unclear whether or not cocaine and or amphetamines are responsible due to the fact patients do not always know what they were supplied. Additionally, ED physicians encounter a fair number of patients who are agitated, and the differential diagnosis is extensive, including both toxicological and non-toxicological causes.

The ideal management of patients with acute agitation involves treatments that prevent significant complications such as seizures and hyperthermia in order to reduce mortality and morbidity but also, prevent harmful effects of the other possible etiologies. For decades, the notion that antipsychotic use could be detrimental for sympathomimetic toxicity was discussed in many forums yet, clinical experience and published case reports of successful use without harm continues. We undertook this systematic review to quantify the available literature on the topic and tried to gather evidence of either safety or harm to better inform clinical management.

Specifically, droperidol compared to lorazepam in cocaine and methamphetamine toxicity resulted in greater sedation and less frequent redosing, but also was likely responsible for one published case of dystonia [12]. Two other patients given droperidol exhibited complicated clinical courses [13]. One is a patient with ingestion of crack cocaine who suffered a cardiac arrest approximately 11 h after treatment with droperidol. While it is impossible to know the proximate cause, given the temporal delay, it seems most likely that this could be the result of chronic use and cocaine toxicity, rather than an adverse effect of the droperidol. The other patient with severe cocaine toxicity had a seizure 9 min after droperidol administration. The shorter delay makes it impossible to adjudicate the cause of the seizure between cocaine toxicity and a droperidol adverse effect. While others [14,17] report cocaine deaths after antipsychotic administration, all are cases of missed body packers and it is unclear if the causes of death are not more related to the massive amount of drug ingested. Finally, the one case that raises concerns describes an agitated patient who became asystolic shortly after treatment with droperidol [18]. It is unknown what underlying dysrhythmias were present pre-treatment. Animal data of cocaine toxicity suggests improved mortality with antipsychotics compared to benzodiazepines though the reported deaths were at least two days after exposure and potentially unrelated to cocaine exposure or treatment.

The published data for amphetamine toxicity is similarly limited; one author [21] reported two cases of QT prolongation after droperidol treatment, another [22] a patient who became obtunded and hypotensive after chlorpromazine 100 mg IV. Finally, one author [32] described a patient with MDMA toxicity, treated with haloperidol (115 mg) who subsequently developed NMS. Of note, this patient was found to possess a ryanodine receptor abnormality, raising the question of combined malignant hyperthermia with a massive dose of haloperidol that most clinicians would not administer.

Haloperidol, the most commonly used antipsychotic for acute agitation, and the most commonly studied antipyschotic in our sample of studies, has not been evaluated in any randomized controlled trial for the management of patients with cocaine or amphetamine toxicity [34]. Only case reports describe safe and effective use, though there are reports of adverse events associated with its use as well. Like droperidol, though, haloperidol is a first generation antipsychotic and has a warning for use due to QT prolongation. It does have less alpha$_1$ adrenergic and muscarinic antagonism than other typical antipsychotics though, which may make it somewhat safer for use in cocaine and amphetamine toxicity than other medications in its class [35].

Several limitations to our study exist. As with any systematic review, the evidence is prone to publications bias. However, the main findings of our work presented in this article reflect, in our opinion, the most comprehensive evidence collated from all possible sources. As a whole, the body of evidence is very heterogeneous, with many studies using different experimental models that cannot be merged into a formal meta-analysis. The choice of sympathomimetic, the dosing regimen, the type of antipsychotic used and the delay between sympathomimetic use and treatment differ greatly. Many animal experiments are also pretreatment models, which, while potentially useful to inform on the risk of individuals therapeutically treated with antipsychotics before using sympathomimetic, are not generalizable for the emergency clinician faced with an agitated patient. The human data are limited to low and very low quality of evidence suggesting a lack of certainty of true effects.

We were unable to establish a dose response curve for any antipsychotic treatment. The most common medication used was haloperidol followed by chlorpromazine. Doses used ranged from 0.25 mg/kg to 2 mg/kg in a number of different species. One cannot

directly extrapolate from doses given to animals to humans due to differences in species' drug metabolism. The administered dose varied significantly with many experiments done with the IP route, which is not something clinicians would consider in emergency settings.

5. Conclusion

This systematic review on the use of antipsychotics in sympathomimetic toxicity represents the most exhaustive compilation of the available evidence to date. Although the studies differ in their methodologies and several models are not generalizable to the human clinical poisoning scenarios, we did not identify a significant signal of harm within the published literature. While several major adverse events are noted in the literature, there are significant questions regarding causation for each. Also, while there is no recurrent evidence of safety issues, there is no more evidence of a significant benefit over benzodiazepines, especially at doses used in human medicine. Future studies should focus on establishing a benefit or non-inferiority of antipsychotics to benzodiazepines in the management of sympathomimetic toxicity in an ED population. Awaiting more robust data, we encourage clinicians to adapt their treatment based on the specific circumstances and characteristics of their individual patients rather than using a "one size fits all" strategy in order to balance the risks and benefits of any chosen therapy.

Disclosure

The authors have nothing to disclose.

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Author involvement

All authors contributed to the protocol and study planning. NC, AA and TL performed the search and article citations screen. AL resolved discrepancies. NC, AA, AL, RSH and SG analysed the included full text articles, summarized and wrote the manuscript.

Appendix 1

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily <1946 to Present>.
Search Strategy:
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1 exp Antipsychotic Agents/
2 Phenothiazines/
3 Butyrophenones/
4 Indoles/
5 Thioxanthenes/
6 Azepines/
7 Oxepins/
8 Benzamides/
9 Amides/
10 Benzoates/
11 exp Dopamine Antagonists/
12 (major adj3 (tranquilis* or tranquillis* or tranquiliz* or tranquilliz*)).tw,kf.
13 (butyrophen* or butyrofenon* or phenothiazin* or (indole* adj2 derivativ*) or indoles or thioxanthen* or azepin* or oxepin* or benzamide*).mp.
14 (antipsychotic* or anti-psychotic* or neuroleptic*).mp.
15 (azaperon* or r-1929 or r1929 or stresnil).mp.
16 (acetophenazin* or acephenazin*).mp.
17 (acepromazin* or acetopromazin* or vetranquil or acetylpromazin* or calmivet or acetazin* or plegicil).mp.
18 (aminosultoprid* or amisulprid* or amisulpirid* or dan2163 or dan-2163 or sertol or socian or solian).mp.
19 (benperidol or anquil or benperidolneuraxpharm or frenactil or glianimon).mp.
20 (ay23028 or ay-23028 or butaclamol).mp.
21 (butaperazin* or butyrylperazin* or megalectil or randolectil or randolectyl or repoise or riker-95 or tyrylen or ahr3000 or ahr-3000 or bayer-1362).mp.
22 (chlorpromazin* or thorazin* or largactil or chlorazin* or chlordelazin* or contomin or aminazin* or propaphenin or fenactil).mp.
23 (taractan or chlorprotixen* or chlorprothixen*).mp.
24 (cremin or clospipramin* or mosapramin* or y516 or y-516).mp.
25 (clozapin* or leponex or clozaril).mp.
26 (cyamemazin* or cyamepromazin* or cianactil or kyamepromazin* or fi6229 or fi-6229 or rp7204 or rp-7204 or tercian).mp.
27 (chlorproethazin* or neuriplege or rp4909 or rp-4909).mp.
28 (droperidol or dehydrobenzperidol or dehidrobenzperidol or droleptan or inapsin*).mp.
29 (etazolate or sq20009 or sq-20009).mp.
30 (fluanxol or flupentixol or flupenthixol or emergil).mp.
31 (fluphenazin* or lyogen or prolixin* or flufenazin*).mp.
32 (fluspirilen* or redeptin or spirodiflamin* or imap or kivat or fluspi).mp.
33 (haloperidol or Haldol).mp.
34 (flanapt* or hp873 or hp-873 or iloperidone or ilo522 or ilo-522 or zomaril).mp.
35 lithium.mp.
36 (loxapin* or loxipin* or cl71563 or cl-71563 or loxitane or cloxazepin* or oxilapin*).mp.
37 (lurasidone or latuda or mk3756 or mk-3756 or sm13496 or sm-13496 or smp13496 or smp-13496).mp.
38 (bunil or buronil or eunerpan or fg5111 or fg-5111 or flubuperone or melperon* or methylperon* or metylperon*).mp.
39 (mesoridazin* or serentil).mp.
40 (methiothepin* or metitepin*).mp.
41 (levopromazin* or tisercin* or tizercin* or methotrimeprazin* or levomepromazin* or levomeprazin or tizertsin).mp.
42 (moban or molindone).mp.
43 (moperon* or luvatren* or methylperidol* or methylperidol* or r1658 or r-1658).mp.
44 (hydroxyrisperidone or hydroxy-risperidone or invega or xeplion or r76477 or r-76477 or ro76477 or ro-76477 or ro92670 or ro-92670).mp.
45 (periciazin* or pericyazin* or properciazin* or propericiazin* or aolept or neulactil or neuleptil* or rp8909 or rp-8909 or skf20716 or skf-20716).mp.
46 (ondansetron or gr38032f or gr-38032f or sn307 or sn-307 or Zofran).mp.
47 (paliperidon* or invega or r76477 or r-76477 or ro76477 or ro-76477 or ro92670 or ro-92670 or xeplion).mp.
48 (r16341 or r-16341 or semap or penfluridol).mp.
49 (perazin* or taxilan).mp.
50 (pipotiazin* or pipothiazin* or piportil or rp19366 or (rp adj2 "19366")).mp.
51 (perfenazin* or trilafon or perphenazin* or chlorpiprazin*).mp.
52 (orap or antalon or pimozid* or r6238 or r-6238).mp.

53 (oxipertin* or oxypertin* or cl77328 or cl-77328 or forit or opertil or win18501* or win-18501*).mp.

54 (prochlorperazin* or Compazin*).mp.

55 (promazin* or sinophenin or sparin* or protactyl).mp.

56 (prothipendyl or prothipendil or protipendil or protipendyl or ay5603 or ay-5603 or azacon or d206 or d-206 or dominal or dominalforte or largophren or lg206 or lg-206 or phrenotropin or timovan or tolnate or tumovan).mp.

57 (racloprid* or flb-472 or flb472 or fla-870 or fla870 or flb472 or flb-472).mp.

58 (remoxiprid* or fla731 or fla-731).mp.

59 (serpivit* or vserp or v-serp or raunervil or rausedil or rausedyl or serpasil or raupasil or reserpin*).mp.

60 (Risperdal or Risperidal or r64766 or r-64766 or risperidone).mp.

61 (ritanserin* or r-55667 or r55667).mp.

62 (spiperone or spiroperone or spiroperidol).mp.

63 (sulpiride or sulperide or tepavil or lebopride or vertigomeresa or pontiride or ekilid or sulp or sulpor or dolmatil or digton or aiglonyl or guastil or sulpitil or meresa or synedil or deponerton or arminol or neogama or eglonyl or sulpivert or desisulpid or psicocen or dogmatil).mp.

64 (thiopropazat* or thipropazat* or artalan or dartal or dartalan or dartan or sc7105 or sc-7105).mp.

65 (melleretten or thioridazine or sonapax or thiozine or rideril or meleril or melleril or melleryl or mellaril or thioridazineneurazpharm or apothioridazine or melzine or aldazine).mp.

66 (thioproperazin* or thioperazin* or rp7843 or rp-7843).mp.

67 (thiothixene or tiotixene or navan or navane).mp.

68 (tiaprid* or flo-1347 or flo1347 or tiaprizal or equilium).mp.

69 (trifluperidol or trisedil).mp.

70 (siquil or triflupromazin* or trifluopromazin* or fluopromazin*).mp.

71 (trifluperazin* or trifluoperazin* or triftazin* or trifluoroperazin* or eskazin* or stelazin* or flupazin* or apotrifluoperazin* or terfluzin*).mp.

72 (zuclopenthixol or zuclopentixol or clopenthixol or cisordinol or sedanxol or dihydrochloride or di-hydrochloride or clopixol).mp.

73 ((amitriptyline adj2 perphenazine) or amperozide or aripiprazole or Asenapine or bromperidol or clothiapine or dapiprazole or dicarbine or dixyrazine or DN1417 or DN1417 or DuP-734 or Dup734 or ecopipam or fananserin or fencamfamine or fluanisone or fluperlapine or isofloxythepin or metylperon or nemonapride or olanzapine or perospirone or piflutixol or pipamperone or quetiapine or rimcazole or 22-1319 or Ro221319 or ro-221319 or sertindole or SR142801 or sr-142801 or stepholidine or sulforidazine or sultopride or tetrahydropalmatine or timiperone or veralipride or zetidoline or ziprasidone or zotepine).mp.

74 or/1-73

75 exp cocaine/

76 exp Amphetamines/

77 Sympathomimetics/

78 or/75-77

79 exp "Drug-Related Side Effects and Adverse Reactions"/

80 Drug Overdose/

81 Poisoning/

82 (to or po).fs.

83 (overdos* or over-dos* or OD or toxicit* or toxicosis or toxicoses or cardiotoxic* or intoxicat* or poison* or megados* or mega-dos*).tw,kf.

84 or/79-83

85 78 and 84

86 ((cocain* or crack) adj5 (overdos* or over-dos* or OD or toxicit* or toxicosis or toxicoses or cardiotoxic* or intoxicat* or poison* or megados* or mega-dos*)).tw,kf.

87 (sympathomimetic* adj5 (overdos* or over-dos* or OD or toxicit* or toxicosis or toxicoses or cardiotoxic* or intoxicat* or poison* or megados* or mega-dos*)).tw,kf.

88 ((Adipex-P or AdipexP or Amfetamin* or amphetamin* or Avipron or Benzfetamin* or Benzphetamin* or Centramina or Chloramphetamin* or chloroamphetamin* or Chlorphentermin* or Curban or Deoxyephedrin* or desoxyphedrin* or Desopimon or Desoxyn or Desoxynorephedrin or Dexamfetamin* or Dexamphetamin* or Dexedrin* or dextroamfetamin* or dextroamphetamin* or DextroStat or Didrex or Duromine or Ecstacy or Ecstasy or Fenamin* or Hydroxyamfetamin* or Hydroxyamphetamin* or Hydroxyphenylisopropylamin* or Ly123362 or Ly-123362 or Ly-121860 or Ly121860 or iodine-123 or iodoamfetamin* or iodoamphetamin* or Iofetamin* or Iophetamin* or Ionamin* or Levoamfetamin* or Levoamphetamin* or Madrine or MDMA or Metamfetamin* or methamfetamin* or Metamphetamin* or methamphetamin* or Mephentermin* or methylamfetamin* or methylamphetamin* or Methylenedioxyamfetamin* or Methylenedioxyamphetamin* or Methyltyramin* or Mydrial or Norpholedrin or Oxyamfetamin* or Oxyamphetamin* or Oxydess or Paredrin* or Phenamin* or Phenopromin* or Phentermin* or Pre-Sate or Thyramin* or crystal meth*) adj5 (overdos* or over-dos* or OD or toxicit* or toxicosis or toxicoses or cardiotoxic* or intoxicat* or poison* or megados* or mega-dos*)).tw,kf.

89 or/85-88

90 74 and 89

91 limit 90 to (comment or editorial or letter)

92 90 not 91

93 remove duplicates from 92

Appendix 2. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2019.01.001.

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