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Review

Treatment of toxicity from amphetamines, related derivatives, and analogues: A systematic clinical review☆

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ABSTRACT

Background: Overdose of amphetamine, related derivatives, and analogues (ARDA) continues to be a serious worldwide health problem. Patients frequently present to the hospital and require treatment for agitation, psychosis, and hyperadrenegic symptoms leading to pathologic sequelae and mortality.
Objective: To review the pharmacologic treatment of agitation, psychosis, and the hyperadrenergic state resulting from ARDA toxicity.
Methods: MEDLINE, PsycINFO, and the Cochrane Library were searched from inception to September 2014. Articles on pharmacologic treatment of ARDA-induced agitation, psychosis, and hyperadrenergic symptoms were selected. Evidence was graded using Oxford CEBM. Treatment recommendations were compared to current ACCF/AHA guidelines.
Results: The search resulted in 6082 articles with 81 eligible treatment involving 835 human subjects. There were 6 high-quality studies supporting the use of antipsychotics and benzodiazepines for control of agitation and psychosis. There were several case reports detailing the successful use of dexmedetomidine for this indication. There were 9 high-quality studies reporting the overall safety and efficacy of β-blockers for control of hypertension and tachycardia associated with ARDA. There were 3 high-quality studies of calcium channel blockers. There were 2 level I studies of α-blockers and a small number of case reports for nitric oxide-mediated vasodilators.
Conclusions: High-quality evidence for pharmacologic treatment of overdose from ARDA is limited but can help guide management of acute agitation, psychosis, tachycardia, and hypertension. The use of butyrophenone and later-generation antipsychotics, benzodiazepines, and β-blockers is recommended based on existing evidence. Future randomized prospective trials are needed to evaluate new agents and further define treatment of these patients.

Contents

☆ Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

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1. Introduction

The accidental or intentional overdose and abuse of over-the-counter, prescribed, and illicit amphetamine, its related derivatives, and analogues (ARDA) such as ephedrine, pseudoephedrine, methylphenidate, lisdexamfetamine, methamphetamine, cathinone ("khat") and derivatives ("bath salts"), and 3,4-methylenedioxy-N-methylamphetamine (MDMA or "ecstasy") is a growing problem. Based on the most recent United Nations World Drug Report (2012), there are an estimated 50 million ongoing users worldwide, which surpasses heroin and cocaine use combined. This does not include frequent use of naturally occurring compounds such as cathinone from the khat plant (*Catha edulis*) used in the horn of Africa and Middle East, and ephedrine and pseudoephedrine from *Ephedra sinica*, which are commonly ingested by inhabitants of East Asia.

In the United States, there were greater than 150,000 emergency department visits for toxicity from ARDA in 2011 based on data from the Substance Abuse and Mental Health Services Administration (SAMHSA, 2011). The Drug Enforcement Agency estimates there were 439,000 past-month methamphetamine users in 2011 (USDOJ, 2013). The number of first-time methamphetamine users ages 12 and older was 133,000 in 2011, which represents an increase from 97,000 in 2008 (SAMHSA, 2012). In 2011, 11% of children 4–17 years old (6.4 million) had at some point in their lives been diagnosed with attention deficit hyperactivity disorder (ADHD), and 3.5 million were taking ADHD medication (Visser et al., 2014). Illicit use of these prescribed medications among young adults without ADHD and of designer synthetic cathinones such as "bath salts" is also an increasing problem (Garnier et al., 2010; Lakhan and Kirchgessner, 2012; Wood, 2013). Over-the-counter decongestants and herbal products targeting weight loss may contain pseudoephedrine, ephedrine, and phenylpropanolamine and have been associated with morbidity and mortality even when taken at correct dosage (Gunn et al., 2001).

These patients frequently present to the emergency department for acute care and consume hospital resources at a higher than normal rate, including emergency, psychiatric, trauma, intensive care unit, and telemetry services (Cloutier et al., 2013; Hendrickson et al., 2008; Richards et al., 1999a; Swanson et al., 2007). Furthermore, they are rarely forthcoming about their illicit drug use, and treating clinicians must consider a wide spectrum of diagnoses during the initial face-to-face evaluation, such as acute psychosis, thyrotoxicosis, sepsis, pheochromocytoma, anticholinergic toxicity, alcohol, benzodiazepine and opioid withdrawals, serotonin and neuroleptic malignant syndromes, and intracranial hemorrhage. Debate exists regarding the best "antidote" and method of treating acute intoxication or overdose. Therefore inconsistencies may occur among different physicians, specialties, and regional hospitals in their approach to the ARDA-intoxicated patient.

Amphetamine, its related derivatives, and analogues increase concentrations of norepinephrine, dopamine, and serotonin through multiple mechanisms and are amphipathic molecules which can cross the blood–brain barrier and placenta (Panenka et al., 2013). Blockade of plasmalemmal and vesicular transporters results in elevated levels of monoamines in the cytoplasm and synapse, respectively, and also cause reverse transport of cytoplasmic monoamines across the cell membrane of the presynaptic neuron into the synaptic space. These drugs also disrupt vesicular storage of monoamines and inhibit the degradative enzymes monoamine oxidase A and B. The net effect is a precipitous rise in central nervous system (CNS) and serum catecholamines with sudden and unpredictable increase in heart rate (HR), systolic (SBP), and diastolic blood pressure (DBP; Fleckenstein et al., 2007). All ARDA have this potential hyperadrenergic effect, but with varying degrees based on the specific ARDA, route of administration, patient tolerance, and pharmacogenetics (de la Torre et al., 2012). Patients abusing ARDA may have serious consequences from this hyperadrenergic state.

Control of agitation and the hyperadrenergic state are top priorities to prevent acute coronary syndrome (ACS), stroke, pulmonary hypertension, acute heart and renal failure, and fetal/maternal morbidity and mortality (Ali et al., 2011; Bingham et al., 1998; Davis and Swalwell, 1994; Hawley et al., 2013; Johnson and Berenson, 1991; Kaye et al., 2007; Richards et al., 1999b; Stewart and Meeker, 1997; Sutamtewagul et al., 2014; Thompson, 2008; Turnipseed et al., 2003; Westover et al., 2007; Won et al., 2013). The half-lives of ARDA are several hours and vary with route of administration, increasing the potential for pathologic sequelae (Mendelson et al., 2006). The purpose of this review is to determine the current best evidence for treatment of (1) agitation/psychosis, and (2) the hyperadrenergic state caused by toxicity from ARDA, and any treatment-related adverse events.

2. Methods

All human trials, case series, or case reports of pharmacologic treatment of ARDA-related agitation, psychosis, and

hyperadrenergic symptoms (hypertension, tachycardia) were considered in the literature search. Data was abstracted systematically from an extensive query of MEDLINE, PsycINFO, and the Cochrane Library from inception to September 20, 2014. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed (Supplement 1[1]). Non-English language publications were included and translated when necessary. Our final search strategy included free-text words (TW) and controlled vocabulary terms using medical subject headings (MeSH) for these topics, their synonyms, abbreviations, and alternate spellings. The specific search strategy is detailed in Supplement 2.[2]

Additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL), and the Database of Abstracts of Reviews of Effects (DARE) were made. References in each selected publication were also carefully hand screened for any additional reports having relevance. In the development of specific treatment recommendations, all references are cited in appropriate context. A gray literature search was also performed using OpenGrey, Google, Google Scholar. A meaningful meta-analysis was not possible due to the wide variety of pharmacologic treatments, protocols, study durations, and ARDA. Therefore, we analyzed the data in a qualitative manner.

3. Results

The search resulted in 6082 articles, of which 6001 were not relevant and excluded (Fig. 1). There were no prior systematic reviews regarding this topic. The gray literature search yielded no additional reports. A total of 81 treatment publications involving 835 human subjects were included (Tables 1 and 2). Because of the small number of high-quality (levels I, II) eligible studies, case series and case reports detailing treatments and outcomes were also included and discussed when appropriate. Articles were graded using the Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence (Oxford CEBM, 2011). The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) evidence-based guidelines were compared for treatment recommendations, and for each treatment option, classification of recommendation (I, IIa, IIb, or III) and level of evidence (A, B, or C) are reported (Supplement 3[3]).

3.1. Treatment of agitation and psychosis

A summary of clinical studies, case series, and case reports is detailed in Table 1. For the 47 papers reviewed, there were 506 subjects and 43 adverse events.

3.1.1. Antipsychotics. Agitation and psychosis are frequently observed in patients with acute ARDA toxicity and may appear concomitantly. While a state of agitation is easily recognized by the initial treating clinician, psychosis may be more subtle. Fortunately, treatment for both behavioral symptoms is the same. The CNS dopaminergic receptor antagonist haloperidol and droperidol (first generation butyrophenones), ziprasidone, olanzapine, risperidone, and aripiprazole (later generation) represent the most commonly used agents for control of agitation and psychosis. All generations of antipsychotics may result in varying degrees of QT interval prolongation, akathisia, dystonia, and neuroleptic malignant syndrome (NMS). Later generation atypical antipsychotics are associated with fewer extrapyramidal side effects, reflecting differences in the pharmacodynamics of limbic versus striatal dopamine-2 and serotonin 2A receptor antagonism, as well as anticholinergic properties (Haddad and Dursun, 2008). Haloperidol and ziprasidone have the highest risk of QT interval prolongation, and aripiprazole has the lowest risk (Beach et al., 2013; Chung and Chua, 2011). The authors of a Cochrane review identified one high-quality (level I) trial of olanzapine and haloperidol from 2005 (Shoptaw et al., 2009). From this study Leelahanaj et al. (2005) reported both drugs mitigated amphetamine-induced psychosis in 58 subjects, but there were ten with extrapyramidal side effects in the haloperidol subgroup. Since then there have been three level I trials published. Sulaiman et al. (2013) compared aripiprazole to placebo and determined it to be superior for psychotic symptom control. Farnia et al. (2014) compared aripiprazole to risperidone and reported greater control of positive psychotic symptoms with risperidone. The authors of the most recent level I trial compared haloperidol and quetiapine for methamphetamine-induced psychosis and found both to be equally effective in controlling symptoms (Verachai et al., 2014). More extrapyramidal events occurred with haloperidol ($n = 5$) than quetiapine ($n = 1$). In the only randomized prospective study of acute methamphetamine toxicity in the emergency department, Richards et al. (1997) compared intravenous (IV) lorazepam to droperidol for control of agitation in 146 patients. Both drugs were effective at controlling agitation, but droperidol resulted in faster time to sedation and lorazepam required repeat dosing to achieve sedation. There was one dystonic reaction in the droperidol subgroup. In a study of schizophrenic patients receiving amphetamine, Angrist et al. (2001) noted haloperidol treatment had the added effect of lowering SBP and DBP.

There were 5 case series and 18 case reports documenting successful treatment of ARDA-related agitation and psychosis with antipsychotics (Table 1). There was one case series and one case report in which adverse outcomes from antipsychotic use are detailed. Two male adolescents illicitly taking methamphetamine were treated with both zuclopenthixol, a thioxanthene antipsychotic, and haloperidol and subsequently developed rigidity without hyperthermia concerning for mild NMS which resolved over time (Henderson, 2011). The author suggested dopamine depletion from methamphetamine use combined with dopaminergic antagonism may have provoked this adverse state. A case report from the Netherlands detailed a 20-year-old female with cocaine and amphetamine toxicity who was profoundly dehydrated and received droperidol for agitation (Koerselman and Goslinga, 1987). Hours later she developed circulatory collapse requiring 6 L of IV crystalloid for reversal. The authors recommended droperidol be withheld until adequate rehydration has been achieved. The final adverse event was a dystonic reaction in a chronic amphetamine user who received aripiprazole and was resolved with administration of benztropine (Shen, 2008).

3.1.2. Benzodiazepines. Benzodiazepine receptor agonists such as lorazepam, diazepam, and midazolam enhance the inhibitory effects of γ-aminobutyric acid (GABA). Over-sedation and respiratory depression are a risk of large and repeated doses of benzodiazepines (Forster et al., 1980). Paradoxical agitation is another potential adverse effect (Short et al., 1987). As previously discussed, there was one high quality study comparing lorazepam to droperidol for agitation from methamphetamine (Richards et al., 1997). There were 6 case series and 12 case reports of successful use of benzodiazepines for control of agitation but not psychosis (Table 1). Three adverse outcomes with benzodiazepine use were reported. All were associated with failure to achieve adequate

[1] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[2] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.
[3] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

Table 1
Summary of evidence for treatment of overdose of amphetamines: agitation and psychosis.

Source	Type of study/trial	Stimulant[a]	Treatment	Level of evidence[b]	No. of Sbjects	Adverse events	Summary
Leelahanaj et al., 2005	Prospective randomized double-blind controlled	Amphetamine	Olanzapine Haloperidol	I	58	10	Both drugs reduced psychosis ($P < 0.001$), haloperidol had extrapyramidal side effects
Sulaiman et al., 2013	Prospective randomized double-blind controlled	Methamphetamine	Aripiprazole	I	37	0	Aripiprazole superior to placebo for psychotic symptom control ($P < 0.05$)
Farnia et al., 2014	Prospective randomized double-blind controlled	Amphetamine	Aripiprazole Risperidone	I	45	0	Risperidone had greater effect on positive psychotic symptoms ($P < 0.05$)
Verachai et al., 2014	Prospective randomized double-blind controlled	Methamphetamine	Haloperidol Quetiapine	I	80	25	Both drugs equally effective for psychosis, haloperidol had more extrapyramidal side effects
Richards et al., 1997	Prospective randomized	Methamphetamine	Droperidol Lorazepam	II	146	1	Droperidol superior to lorazepam for prolonged sedation ($P < 0.05$), single dystonic reaction
Angrist et al., 2001	Prospective controlled	Amphetamine	Haloperidol	II	18	0	Haloperidol reduced SBP, DBP ($P < 0.0001$)
Espelin and Done, 1968	Case series	Amphetamine	Chlorpromazine	IV	22	0	Agitation effectively controlled by chlorpromazine
Angrist et al., 1974	Case series	Amphetamine	Haloperidol	IV	8	0	Haloperidol effectively controlled psychosis
Ruha and Yarema, 2006	Case series	Methamphetamine	Benzodiazepines	IV	18	0	Pediatric patients, no adverse events, 12 had combination therapy with effective sedation
Tobias, 2010	Case series	MDMA	Dexmedetomidine	IV	3	0	Control of agitation with dexmedetomidine
Wood et al., 2010a	Case series	Mephedrone	Benzodiazepines	IV	7	0	3 of 7 required benzodiazepines for sedation
Wood et al., 2011	Case series	Mephedrone	Benzodiazepines	IV	15	0	3 of 15 required benzodiazepines for sedation
Henderson, 2011	Case series	Methamphetamine	Zuclopenthixol Haloperidol	IV	2	2	Possible mild NMS after antipsychotic treatment
Penders et al., 2012	Case series	Bath salts (unspecified)	Haloperidol	IV	3	0	Control of agitation with haloperidol (1 patient)
Wood et al., 2012	Case series	D2PM	Diazepam Lorazepam	IV	5	0	3 of 5 required benzodiazepines for sedation
Ford et al., 2012	Case series	Lisdexamfetamine Amphetamine	Haloperidol	IV	2	0	Resolution of chorea after haloperidol
Kasick et al., 2012	Case series	Mephedrone	Lorazepam, Haloperidol Risperidone	IV	2	0	Resolution of psychosis after lorazepam, haloperidol and risperidone
Imam et al., 2013	Case series	Bath salts (unspecified)	Benzodiazepines	IV	6	0	2 of 5 required benzodiazepines for sedation
Perry and Juhl, 1977	Case report	Amphetamine	Haloperidol	V	1	0	Resolution of psychosis with haloperidol
Gary and Saidi, 1978	Case report	Methamphetamine	Droperidol	V	1	0	Control of agitation and decreased HR, SBP, DBP after droperidol
Koerselman and Goslinga, 1987	Case report	Amphetamine Cocaine	Droperidol	V	1	1	Shock hours after droperidol, extreme dehydration
Uday et al., 1988	Case report	Mephentermine	Haloperidol	V	1	0	Resolution of psychosis with haloperidol
Misra and Kofoed, 1997	Case report	Methamphetamine	Risperidone	V	1	0	Resolution of psychosis with risperidone
Jha and Fourie, 1999	Case report	Amphetamine	Risperidone	V	1	0	Control of psychosis with risperidone
Misra et al., 2000	Case report	Methamphetamine	Olanzapine	V	1	0	Control of psychosis with olanzapine
Alevizos, 2003	Case report	Pseudoephedrine	Haloperidol	V	1	0	Resolution of psychosis with haloperidol

Caldicott et al., 2003	Case report	PMA	Midazolam	V	1	1	Failed sedation after midazolam, intubated
Dore and Sweeting, 2006	Case report	Methamphetamine	Quetiapine	V	1	0	Control of psychosis with quetiapine
Lidder et al., 2008	Case report	D2PM	Diazepam	V	1	0	Control of agitation with diazepam
Shen, 2008	Case report	Amphetamine	Aripiprazole	V	1	1	Dystonia from aripiprazole use that resolved with benztropine
Kiely et al., 2009	Case report	Methamphetamine	Lorazepam	V	1	1	Death from fatal ingestion, multiple doses lorazepam failed to achieve sedation
Machado et al., 2010	Case report	Methylphenidate	Chlorpromazine	V	1	0	Chorea resolved after chlorpromazine
Wood et al., 2010b	Case report	Mephedrone	Lorazepam	V	1	0	Resolution of anxiety, tachycardia and HTN after lorazepam
Bajaj et al., 2010	Case report	Mephedrone	Olanzapine	V	1	0	Resolution of psychosis after olanzapine
Urban et al., 2011	Case report	Mephedrone	Olanzapine	V	1	0	Resolution of psychosis after olanzapine
Lusthof et al., 2011	Case report	Mephedrone	Midazolam	V	1	1	Mephedrone-related extreme agitation and death, midazolam not causative
Thornton et al., 2012	Case report	MDPV Flephedrone	Droperidol Lorazepam	V	1	0	Resolution of psychosis with droperidol and lorazepam
Akingbola and Singh, 2012	Case report	Lisdexamfetamine	Dexmedetomidine	V	1	0	Control of agitation with dexmedetomidine
Joksovic et al., 2013	Case report	Bath salts (unspecified)	Haloperidol Lorazepam	V	1	0	Control of agitation with haloperidol and lorazepam
Bagdure et al., 2013	Case report	Methylphenidate	Dexmedetomidine	V	1	0	Control of agitation with dexmedetomidine
Marti et al., 2013	Case report	Methylphenidate	Lorazepam	V	1	0	Control of agitation with lorazepam
Mangewala et al., 2013	Case report	Bath salts (unspecified)	Olanzapine Lorazepam	V	1	0	Control of agitation with olanzapine and lorazepam
Chan et al., 2013	Case report	6-APB	Diazepam	V	1	0	Control of agitation with diazepam
Gehlawat et al., 2013	Case report	Mephentermine	Olanzapine	V	1	0	Resolution of psychosis with olanzapine
Sutamtewagul et al., 2014	Case report	Bath salts (unspecified)	Haloperidol Lorazepam	V	1	0	Control of agitation with haloperidol and lorazepam
Yeh et al., 2014	Case report	Amphetamine	Aripiprazole	V	1	0	Delusional behavior mitigated by aripiprazole
Lee et al., 2014	Case report	Methiopropamine	Diazepam	V	1	0	Control of agitation with diazepam
			Total		506	43	

Abbreviations: MDMA, 3,4-methylenedioxy-N-methylamphetamine; MDPV, 3,4-methylenedioxypyrovalerone; DOB, 4-bromo-2,5-dimethoxyamphetamine; D2PM, diphenylprolinol; PMA, p-methoxyamphetamine; 6-APB, 6-(2-aminopropyl)benzofuran; NE, norepinephrine; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; *T*, temperature; HTN, hypertension; PVR, peripheral vascular resistance; MI, myocardial infarction; NMS, neuroleptic malignant syndrome.

[a] Includes amphetamine derivatives, precursors, or analogues with similar pharmacology not normally found *in vivo*.

[b] Evidence was graded using the Oxford Centre for Evidence-Based Medicine levels of evidence for treatment recommendations[31] (I = properly powered and conducted randomized clinical trial, systematic review, or meta-analysis; II = well-designed controlled trial without randomization; prospective comparative cohort; III = case–control studies, retrospective cohort studies; IV = case series with or without intervention, cross-sectional studies; V = opinion of authorities, case reports).

Table 2
Summary of evidence for treatment of overdose of amphetamines: hyperadrenergic state.

Source	Type of study/trial	Stimulant[a]	Treatment	Level of evidence[b]	No. of subjects	Adverse events	Summary
O'Connell and Gross, 1990	Prospective randomized double-blind crossover	Phenylpropanolamine	Metoprolol Atenolol Propranolol	I	7	0	Peak SBP and DBP, not baseline, slightly higher after single dose phenylpropanolamine ($P<0.05$)
O'Connell and Gross, 1991	Prospective randomized double-blind crossover	Phenylpropanolamine	Metoprolol Atenolol Propranolol	I	7	0	Peak SBP and DBP, not baseline, slightly higher after multiple doses of phenylpropanolamine ($P<0.05$)
Hassan et al., 2005	Prospective randomized double-blind crossover	Cathinone	Atenolol Indoramin	I	63	0	Atenolol, not indoramin, reduced HR and SBP ($P<0.05$)
Hysek et al., 2012a	Prospective randomized double-blind crossover	MDMA	Carvedilol	I	16	0	Carvedilol reduced HR, SBP, and T ($P<0.001$)
Hysek et al., 2012b	Prospective randomized double-blind crossover	MDMA	Clonidine	I	16	0	Clonidine reduced SBP, DBP, but not HR ($P<0.001$)
Hysek et al., 2013	Prospective randomized double-blind crossover	MDMA	Doxazosin	I	16	0	Prazosin decreased MAP, increased HR ($P<0.05$)
Nurnberger et al., 1984	Prospective controlled	Dextroamphetamine	Propranolol	II	12	0	Propranolol inhibited pressor response and plasma ME ($P<0.05$)
Pentel et al., 1985	Prospective controlled double-blind	Phenylpropanolamine	Propranolol	II	6	0	Propranolol reduced SBP, DBP, and HR after phenylpropanolamine ($P<0.05$)
Goldberg et al., 1989	Prospective controlled	Ephedrine	Labetalol	II	60	0	5 anesthesia patients pre-treated with ephedrine developed HTN resolved by labetalol
Fabian and Silverstone, 1997	Prospective crossover	Dextroamphetamine	Diltiazem	II	10	0	Diltiazem reduced SBP, DBP ($P<0.002$)
Mores et al., 1999	Prospective controlled single-blind	Pseudoephedrine	Propranolol Atenolol	II	29	0	Both β-blockers decreased SBP and HR after pseudoephedrine, not DBP ($P<0.05$)
Johnson et al., 2000	Prospective crossover	Methamphetamine	Isradipine	II	18	0	Isradipine reduced SBP, DBP, but increased HR ($P<0.05$)
Johnson et al., 2005	Prospective crossover	Methamphetamine Cocaine	Isradipine	II	31	0	Isradipine reduced SBP, DBP, but increased HR ($P<0.05$)
Hysek et al., 2010	Prospective crossover	MDMA	Pindolol	II	16	0	Pindolol reduced HR but not MAP ($P<0.05$)
Silverman and Turner, 1991	Case series	Methamphetamine	Tolazoline	IV	3	0	Improved perfusion after tolazoline
Burkhart, 1992	Case series	Ephedrine Pseudoephedrine	Propranolol	IV	2	0	Resolution of HTN emergency after propranolol
Duvernoy, 1969	Case report	Phenylpropanolamine	Phentolamine	V	1	0	Phentolamine reduced SBP and DBP after phenylpropanolamine-induced HTN emergency
Rosen, 1981	Case report	Pseudoephedrine	Nitroglycerin	V	1	0	Resolution of chest pain and ST-depression after nitroglycerin
Hamer and Phelps, 1981	Case report	Phenteramine	Tolazoline	V	1	0	Tolazoline resolved vasospasm
Weesner et al., 1982	Case report	Phenylpropanolamine	Propranolol	V	1	0	Propranol normalized HR after phenypropanolamine

Bowen et al., 1983	Case report	DOB	Phenoxybenzamine Tolazoline Nitroprusside	V	1	0	Both α-blockers failed to fully alleviate vasospasm. nitroprusside rescue required
Mariani, 1986	Case report	Pseudoephedrine	Labetalol	V	1	0	Resolution of HTN emergency after labetalol
Bal et al., 1989	Case report	p-Methylamphetamine N,p-dimethylamphetamine	Practolol	V	1	1	Acute elevation of blood pressure after practolol
Wiener et al., 1990	Case report	Pseudoephedrine	Nitroglycerin	V	1	0	Resolution of chest pain and ST-elevation after nitroglycerin
Heyman et al., 1991	Case report	Pseudoephedrine Ephedrine	Nifedipine	V	1	0	Resolution of HTN emergency after nifedipine
Ragland et al., 1993	Case report	Amphetamine	Propranolol	V	1	1	Chest pain and ST-elevation after propranolol given 6 days post-ingestion
Derreza et al., 1997	Case report	Pseudoephedrine	Metoprolol	V	1	0	Ventricular tachycardia after nitroglycerin, metoprolol given after spontaneous resolution
Zahn et al., 1999	Case report	Ephedrine	Nitroprusside	V	1	0	Resolution of HTN emergency after nitroprusside
Sakuragi et al., 2004	Case report	Ephedrine	Propranolol	V	1	0	Propranolol reduced SBP, DBP, and HR after high-dose intravenous ephedrine
Manini et al., 2005	Case report	Pseudoephedrine	Metoprolol	V	1	0	Resolution of chest pain and ST-elevation after nitroglycerin and metoprolol
Grześk et al., 2004	Case report	Pseudoephedrine	Atenolol	V	1	1	Pseudoephedrine-induced chest pain for >19 h did not respond to atenolol
Gedevanishvili et al., 2004	Case report	Ephedrine	Nitroglycerin	V	1	0	Resolution of chest pain and ST-elevation after nitroglycerin
Bassi and Rittoo, 2005	Case report	MDMA	Nitroglycerin				Resolution of chest pain and ST-depression after nitroglycerin
Akay and Ozdemir, 2008	Case report	Pseudoephedrine	Metoprolol	V	1	0	Resolution of tachycardia and ST-elevation after metoprolol
			Total		329	3	

Abbreviations: MDMA, 3,4-methylenedioxy-N-methylamphetamine; MDPV, 3,4-methylenedioxypyrovalerone; DOB, 4-bromo-2,5-dimethoxyamphetamine; D2PM, diphenylprolinol; PMA, p-methoxyamphetamine; 6-APB, 6-(2-aminopropyl)benzofuran; NE, norepinephrine; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; *T*, temperature; HTN, hypertension; PVR, peripheral vascular resistance; MI, myocardial infarction; NMS, neuroleptic malignant syndrome.

[a] Includes amphetamine derivatives, precursors, or analogues with similar pharmacology not normally found *in vivo*.

[b] Evidence was graded using the Oxford Centre for Evidence-Based Medicine levels of evidence for treatment recommendations[31] (I = properly powered and conducted randomized clinical trial, systematic review, or meta-analysis; II = well-designed controlled trial without randomization; prospective comparative cohort; III = case–control studies, retrospective cohort studies; IV = case series with or without intervention, cross-sectional studies; V = opinion of authorities, case reports).

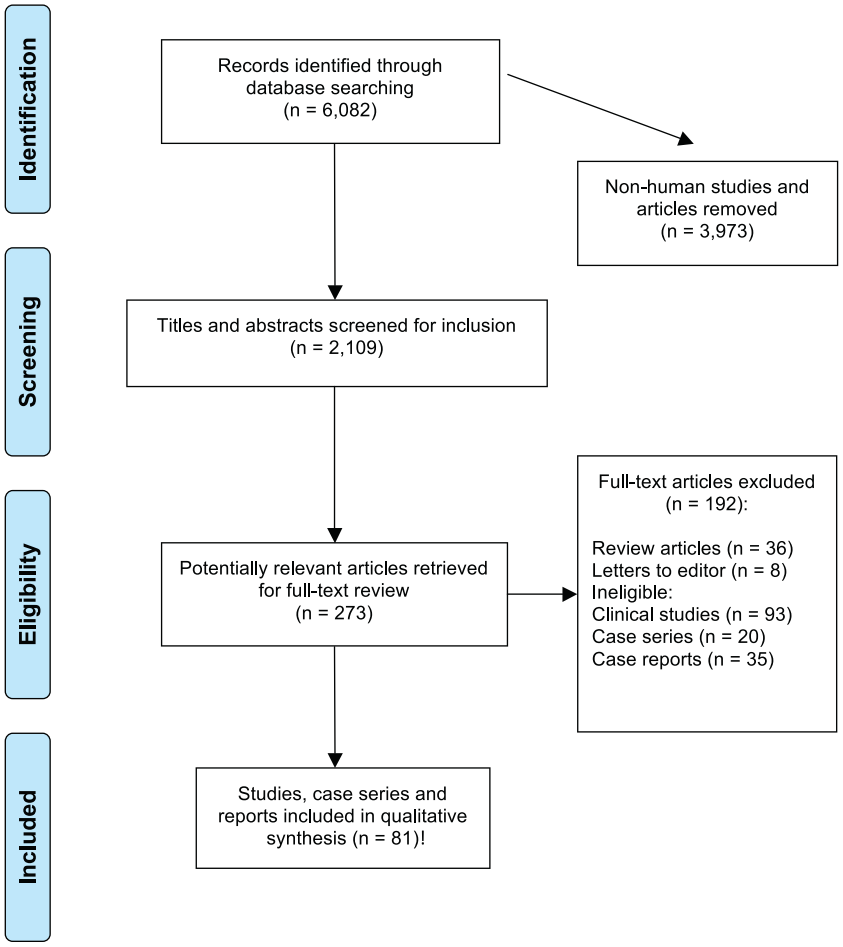

Fig. 1. Flow of reports identified in the published literature through the systematic review process.
From: Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., The PRISMA Group, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS. Med 6(6), e1000097. http://dx.doi.org/10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

sedation, with two deaths from massive ARDA overdose and one patient requiring intubation for chemical restraint (Caldicott et al., 2003; Kiely et al., 2009; Lusthof et al., 2011).

3.1.3. Dexmedetomidine. Dexmedetomidine is a α2-adrenoceptor agonist with inhibitory effects on CNS sympathetic outflow, producing sedation, analgesia, and no respiratory depression (Wujtewicz et al., 2013). Besides being a powerful sedative, dexmedetomidine has the added benefit of sympatholysis to counteract the cardiovascular and CNS overstimulation from ARDA. Based on one case series and two case reports, dexmedetomidine has been successfully used to control agitation in adult and pediatric patients with toxicity from ARDA with no adverse effects, but there were no randomized high-quality clinical trials for this indication published as of September 2014 (Akingbola and Singh, 2012; Bagdure et al., 2013; Tobias, 2010).

3.1.4. Ketamine, propofol, and "ketofol". There were no trials or case reports of ketamine or propofol for treatment of ARDA-induced agitation and psychosis. Ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist, has been used successfully for control of generalized agitation in a small number of reports (Burnett et al., 2012; Le Cong et al., 2012; Roberts and Geeting, 2001). Normally used for procedural sedation, ketamine produces dissociative anesthesia and a trancelike cataleptic state while protecting airway reflexes and respiratory drive. Difficulties in using ketamine include emergence agitation and catecholamine surge after administration, which may be problematic in ARDA-toxic patients.

Propofol is a unique sedative with several mechanisms of action, including potentiation of GABA receptor activity, inhibition of NMDA receptors, alteration of serotonin levels in the area postrema, and possible modulation of the endocannabinoid system (Kotani et al., 2008). It has been effectively used alone and in combination with ketamine ("ketofol") for control of generalized agitation in a small number of case reports (Alletag et al., 2012; Andolfatto et al., 2012; Ting and Chatterjee, 2008). The main disadvantages of using propofol for control of agitation are the need for continuous infusion by the treating clinician, who may be required to remain at the bedside, and the potential for profound respiratory depression requiring supplemental oxygen and emergency airway intervention.

3.2. Treatment of the hyperadrenergic state

A summary of clinical studies, case series, and case reports is detailed in Table 2. For the 34 papers reviewed, there were 329 subjects and 3 adverse events.

3.2.1. Beta-blockers. The majority of published research regarding treatment of hyperadrenergic symptoms from ARDA involves the use of β-adrenoceptor antagonists (β-blockers) in animal models, human trials, and case reports. There were 14 high-quality (levels I, II) human studies. Hassan et al. (2005) reported atenolol, a

selective β1-blocker, but not indoramin, an α1-adrenoceptor antagonist (α1-blocker), lowered SBP and HR in khat (cathinone) chewers. Hysek et al. (2012a) showed carvedilol, a non-selective β- and α1-blocker, attenuated MDMA-induced increase in HR, SBP, DBP, and body temperature. The authors postulated the reduction of temperature was a result of carvedilol's α1- and β3-adrenoceptor blocking properties, leading to vasodilation and heat dissipation.

In a study of healthy adults receiving IV dextroamphetamine, Nurnberger et al. (1984) demonstrated propranolol, a non-selective β-blocker, attenuated increases in HR and SBP. In another study of anesthesia patients receiving ephedrine for hypotension who then became hypertensive as a result, the authors reported resolution of hypertension with the non-selective β- and α1-blocker labetalol (Goldberg et al., 1989). The interaction of the methamphetamine precursor pseudoephedrine (a common decongestant), and β-blockers was evaluated in a prospective study in which propranolol and atenolol decreased SBP and HR, but not DBP (Mores et al., 1999). Another study by Hysek et al. (2010) found that pindolol, a non-selective β-blocker with intrinsic sympathomimetic activity, reduced HR but not mean arterial pressure after MDMA.

Pentel et al. (1985) showed propranolol given to normotensive subjects before and after 75 mg phenylpropanolamine (a decongestant and anorexiant banned in the United States, Canada, and India) decreased SBP, DBP, cardiac output, and systemic vascular resistance. In contrast, O'Connell and Gross (1990, 1991) reported patients already taking propranolol, metoprolol, a selective β1-blocker, or atenolol for hypertension had higher peak SBP and DBP blood pressure after 25 mg phenylpropanolamine versus placebo administration in single and multiple doses. For both studies the increases were modest, with peak SBP averaging 8 mm Hg higher and DBP 4.9 mm Hg higher than placebo in the single-dose study. For the multiple-dose study peak SBP ranged from 3 to 22 mm Hg and DBP 0 to 16 mm Hg higher compared to placebo. These measurements were taken on the first and last days of the study period. This effect may reflect the predominant α- versus β-mediated properties of phenylpropanolamine in the setting of non-selective β- (propranolol) or selective β1-adrenoceptor blockade (metoprolol, atenolol) (Flavahan, 2005).

There were several case series and reports of successful use of β-blockers for ARDA-induced hyperadrenergic symptoms (Table 2). There was one adverse event possibly attributed to β-blocker use discovered during our literature search (Bal et al., 1989). A 40-year-old male inhaled a powder mixture of p-methylamphetamine and N,p-dimethylamphetamine and received IV practolol, a non-specific β-blocker no longer marketed, for HR 150 beats per minute and BP 200/120 mm Hg. His BP increased to 240/160 mm Hg and HR dropped to 115 beats per minute after practolol. There was no deleterious outcome, and after several hours his vital signs normalized without further treatment. Delayed absorption and metabolism of these rarely encountered ARDA compounds to active metabolites could have resulted in the noted increase in BP. The authors of this case report recommended labetalol as a more appropriate choice for this patient.

Two case reports were identified in which β-blockers in the presence of ARDA were implicated in acute coronary vasoconstriction. Detailed analysis of these cases show otherwise. In the first case, a 37-year old female was admitted for chest pain with ST-elevation after intravenous amphetamine use (Ragland et al., 1993). Her echocardiogram on day two was notable for severe cardiomyopathy and low ejection fraction. She received two doses of propranolol 6 days after admission and again developed chest pain and ST-elevation that resolved with nitroglycerin and discontinuation of propranolol. Her coronary catheterization at time of discharge was normal. It is doubtful this represents an adverse amphetamine/β-blocker interaction as she would have metabolized the drug fully by day 6. She returned 4 weeks later with chest pain and shortness of breath and died of cardiogenic shock. The second case involved a 19-year old male with heavy smoking history who developed chest pain after taking higher than recommended doses of pseudoephedrine (Grześk et al., 2004). He waited 19 h before seeking medical attention, and his chest pain and ST-elevation resolved with nitroglycerin, acetylsalicylic acid, heparin, and the cardioselective β-blocker atenolol. Several hours after admission his chest pain and ST-elevation returned and again resolved with increasing dose of nitroglycerin. His coronary angiogram was normal. As with the previous case, it is doubtful the recurrence of the patient's chest pain was a result of an adverse pseudoephedrine/β-blocker interaction as there was no temporal association with atenolol and the near-complete metabolism of pseudoephedrine should have occurred by 24 h.

3.2.2. Calcium channel blockers. Compared to β-blockers, much less has been published regarding the use of calcium channel blockers for toxicity from ARDA in either animal or human subjects. There were three level II evidence studies published. In 10 healthy human subjects who were pretreated with oral diltiazem and then given oral dextroamphetamine, Fabian and Silverstone (1997) showed diltiazem significantly prevented rise in SBP and DBP. Johnson et al. (2000) reported isradipine, a dihydropyridine-class calcium channel antagonist, reduced methamphetamine-induced rise in SBP and DBP. However, this beneficial effect was offset by a reflex increase in HR. This same research group confirmed this result again in a later study using both methamphetamine and cocaine for induction of hypertension and tachycardia (Johnson et al., 2005). This finding has also been confirmed in a prospective study involving only cocaine (Negus et al., 1994). There was one case report in which nifedipine was successfully used to resolve a pseudoephedrine- and ephedrine-precipitated hypertensive emergency (Heyman et al., 1991).

3.2.3. Alpha-blockers and agonists. There were two high-quality human studies of α1-blockers and one study of a α2-agonist for treatment of hyperadrenergic symptoms from ARDA. One study was discussed in the previous section (Hassan et al., 2005). Hysek et al. (2012b, 2013) reported in two separate studies that doxazosin, an α-blocker and clonidine, an α2-agonist, mitigated MDMA-induced increases in mean arterial pressure. However, doxazosin caused a reflex increase in HR, while clonidine had no effect on HR. There was one case series in which the non-specific α-blocker tolazoline was used to improve perfusion after intra-arterial amphetamine injection (Silverman and Turner, 1991). There were two case reports of peripheral arterial vasospasm from ARDA in which the α-blockers tolazoline and phenoxybenzamine were used (Bowen et al., 1983; Hamer and Phelps, 1981). One treatment was successful, and the other patient failed both α-blockers and required nitroprusside rescue. In an early case report from 1969, the non-specific α-blocker phentolamine successfully resolved a hypertensive emergency induced by phenylpropanolamine (Duvernoy, 1969). As the evidence is limited for specific α-blocker treatment with ARDA, it is worth noting a prospective study in which intracoronary phentolamine reversed cocaine-induced coronary artery vasoconstriction and hypertension, but not HR (Lange et al., 1989). The α2-agonist dexmedetomidine was previously discussed (Akingbola and Singh, 2012; Bagdure et al., 2013).

3.2.4. Nitric oxide-mediated vasodilators. There were no high-quality human studies of the nitric oxide-mediated vasodilators nitroglycerin or nitroprusside for treatment of toxicity from ARDA. There were two case reports of successful treatment of limb ischemia and hypertensive emergency from ARDA using

nitroprusside (Bowen et al., 1983; Zahn et al., 1999). There were 4 case reports detailing the resolution of ARDA-induced chest pain and ST-segment changes with nitroglycerin (Akay and Ozdemir, 2008; Gedevanishvili et al., 2004; Rosen, 1981; Wiener et al., 1990). In contrast, high-quality studies do exist for cocaine. Nitroglycerin is helpful in cocaine-induced chest pain and ACS, but does not mitigate tachycardia (Baumann et al., 2000; Brogan et al., 1991; Honderick et al., 2003). Jacobsen et al. (1997) reported nitroprusside reduced cocaine-induced hypertension but also increased sympathetic discharge nearly 3 times above baseline.

3.2.5. Benzodiazepines. There were no high-quality studies of benzodiazepines for treatment of ARDA-associated hyperadrenergic state. Two level I studies of cocaine-induced chest pain compared benzodiazepines to nitroglycerin, with dual therapy having advantage over single therapy in one study (Honderick et al., 2003). In the other trial there was no difference between dual versus single agent therapy (Baumann et al., 2000). There is one case report of mephedrone toxicity with resolution of tachycardia and hypertension using lorazepam (Wood et al., 2010b). There is a theoretical disadvantage of benzodiazepine use for this indication secondary to intrinsic positive inotropic effects which are not widely known (Starcevic and Sicaja, 2007).

4. Discussion

As of September 2014, there were no published evidence-based systematic reviews regarding pharmacologic treatment of agitation, psychosis, and hyperadrenergic symptoms from ARDA. For control of agitation and psychosis from ARDA, butyrophenones and later-generation antipsychotics are a reasonable choice, with the understanding extrapyramidal side effects may occur. There were 287 patients receiving antipsychotics and 15 adverse extrapyramidal identified in this review. A position statement from the American Association for Emergency Psychiatry recommends antipsychotics for first-line treatment of generalized agitation without an obvious reversible medical cause (Wilson et al., 2012).

In general, benzodiazepines are commonly used to treat agitation from stimulant abuse. In a series of 409 "bath salt" cases from a regional poison center, over half were agitated and tachycardic, with 46% receiving benzodiazepines (Murphy et al., 2013). The prehospital use of benzodiazepines has been recommended by consensus in a prior review of methylphenidate toxicity (Scharman et al., 2007). A potential disadvantage of benzodiazepines is the possibility of under-sedation, which occurred in 3 cases identified in this review. The adverse effects of over-sedation with respiratory depression and paradoxical agitation were not encountered. As far as other sedatives to control ARDA-induced agitation and psychosis, further studies are needed to determine the efficacy of dexmedetomidine, ketamine, propofol, and "ketofol" for this indication.

For the ARDA-induced hyperadrenergic state, treatment with β-blockers is a reasonable choice. The concept of "unopposed α-stimulation" after β-blockade in patients with hyperadrenergic states from cocaine abuse is controversial, but far less is known with regard to ARDA (Freeman and Feldman, 2008; Leikin, 1999; Mariani, 2008; Page et al., 2007). There were 9 high-quality clinical studies, 10 case series/reports, with 227 total subjects involving the use of β-blockers with concomitant ARDA, and one putative case of "unopposed α-stimulation." This proportion loosely suggests an incidence rate of only 0.4%. If, however, there is a theoretical or real risk of "unopposed α-stimulation" in the setting of toxicity from ARDA, then treatment with the combined β- and α-blockers labetalol or carvedilol is a logical choice. The use of labetalol for treatment of cocaine- and methamphetamine-associated chest pain has been included by the ACCF/AHA in their most recent 2012 guidelines (Supplement 3[4]) as Class IIb-C (Anderson et al., 2013). Some theories regarding this phenomenon have been proposed. Increasing levels of dopamine and norepinephrine induced by cocaine and ARDA activate α1-adrenoceptors causing arterial constriction, while non-specific β-blockade inhibits compensatory β2-mediated vasodilation (Schurr et al., 2014). Another alternative theory is based on the Frank–Starling principle, in which decreases in heart rate from β-blockers results in increased end diastolic pressure and fiber length thus increasing ventricular contraction and blood pressure (Freeman and Feldman, 2008). It is interesting that "unopposed α-stimulation" is not routinely observed in other hyperadrenergic conditions in which non-specific β-blockers are routinely used, such as thyrotoxicosis.

Calcium channel blockers are a reasonable choice to treat ARDA-induced hypertension, but not necessarily tachycardia. However the number of studies is small. The dihydropyridine-class calcium channel blockers such as nifedipine and amlodipine are more likely to result in reflex tachycardia compared to the benzothiazepine- and phenylalkylamine-class agents such as diltiazem and verapamil (Olson, 2013). The current ACCF/AHA guidelines include recommendations for IV or oral calcium channel blockers as Class I-C in the setting of chest pain with ST-segment changes, and Class IIa-C for chest pain without ST-segment changes. Alpha-blockers and clonidine may improve hypertension and vasospasm but not tachycardia, and neither is included in the ACCF/AHA guidelines. Nitroglycerin is recommended as ACCF/AHA Class I-C for treatment of cocaine and ARDA-associated chest pain but should be given with the recognition it may result in reflex tachycardia. Nitroprusside may ameliorate peripheral arterial vasospasm and hypertension, but no clinical studies exist at present. Dexmedetomidine may be effective for both agitation and hyperadrenergic symptoms, but no clinical trials specific to ARDA have been published yet. Benzodiazepines may be useful in ARDA-precipitated chest pain alone or in combination with nitroglycerin, although this is based on cocaine studies as none exist for ARDA.

4.1. Limitations

Our systematic review has potential limitations. There are no large-scale randomized, multi-center, double-blind studies regarding the acute treatment of ARDA toxicity. Therefore, any bias associated with the design or conduct of the included studies could have influenced the results of our systematic review. The overall number of patients is small. Publication bias is a concern, and it is possible that not all adverse events during treatment have been reported. In anticipation of this, we used a comprehensive search strategy and a low inclusion threshold of all published and unpublished reports. We also included case series and case reports to be as comprehensive as possible regarding any potential adverse drug reactions with ARDA.

4.2. Conclusion

Intoxication with ARDA has potentially serious effects on the CNS resulting in agitation and psychosis, and on the adrenergic system with sympathetic overstimulation. Prospective studies of the treatment of CNS and cardiovascular toxicity from ARDA with antipsychotics, benzodiazepines, β- and α-blockers, clonidine, calcium channel blockers, nitric oxide-mediated vasodilators, dexmedetomidine, and other sedatives such as ketamine and propofol are critically needed to guide therapeutic

[4] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

recommendations with the goal of increasing patient safety and reducing length of stay. Until such studies are completed, we recommend utilizing the data summarized in this review. This includes use of butyrophenone and later-generation antipsychotics, benzodiazepines, and labetalol as dictated by the clinical symptoms.

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Contributors

All authors (JRR, TEA, RWD, RAL, KRO, BZH) were involved in the conception and design of the work; JRR, TEA, RWD, BZH were involved in the acquisition and analysis of data; all authors interpreted the data; JRR, TEA, RWD, BZH wrote the manuscript; all authors revised the manuscript critically for important intellectual content and provided final approval of the version to be published.

Conflict of interest

No conflict declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2015.01.040.

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