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Sympathomimetic Toxidromes and Other Pharmacological Causes of Acute Hypertension

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Abstract

Purpose of Review Acute drug-induced hypertension, sympathomimetic toxicity, and other hyperadrenergic states can be caused by both xenobiotic toxicity and withdrawal. This manuscript is a selective review of the recent literature regarding pharmacologic causes of hypertensive emergencies and other hyperadrenergic states.

Recent Findings We will discuss designer stimulants, alpha$_2$ and baclofen agonist withdrawal, and the clinical entity known as posterior reversible encephalopathy syndrome (PRES). Additionally, we examine the controversial "unopposed alpha" phenomenon which may result from use of beta-adrenergic antagonist in the presence of stimulant toxicity.

Summary These topics encompass clinical situations and disease entities that are increasingly encountered and are often either unanticipated or under-recognized.

Keywords Sympathomimetic toxidrome · Acute hypertension · Alpha$_2$ agonist withdrawal · Baclofen withdrawal · Unopposed alpha phenomenon · Posterior reversible leukencephalopathy syndrome

Background

Acute hypertension and hyperadrenergic states are common medical emergencies. Rapid and accurate identification of the underlying causes optimizes treatment and improves patient outcomes. The changing disease prevalence of certain conditions is making unfamiliar causes of acute hypertension and hyperadrenergic states more common. The types and amounts of xenobiotics employed in clinical practice today are influenced by increasing age in population, prevalence of chronic pain conditions, opioid dependence, drug abuse, and neoplastic conditions. Thus, adverse effects from these "trending" xenobiotics are expected to become more commonplace. This review will focus on increasingly common drug-induced causes of acute hypertension and hyperadrenergic

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states, including the newest designer recreational stimulants, alpha$_2$ and baclofen agonist withdrawal, and the clinical entity known as posterior reversible encephalopathy syndrome (PRES). Additionally, we will review literature regarding beta-blocker therapy in cocaine and stimulant users.

The sympathomimetic toxidrome is a group of clinical signs and symptoms caused by activation of the sympathetic division of the autonomic nervous system. Signs and symptoms may vary significantly based on an agent's individual pharmacokinetic and pharmacodynamic profile, and classically have characteristic effects on each organ system (see Table 1). Severe hyperthermia portends a poor outcome. Sedative-hypnotic withdrawal can be indistinguishable from sympathomimetic toxicity and can manifest all the aforementioned many of the signs and symptoms seen in Table 1.

While acute hypertension is part of the sympathomimetic toxidrome, it has multiple other pharmacologic causes. Mechanisms underlying the blood pressure response include, but are not limited to, activation of the renin-aldosterone-angiotensin system, peripheral alpha-adrenergic stimulation, central alpha$_2$ receptor antagonism, central alpha$_2$ agonist withdrawal, nicotinic receptor agonism, sedative-hypnotic withdrawal (GABA-A and B), mineralocorticoid excess, prostaglandin inhibition, smooth muscle calcium signaling, and nitric oxide inhibition or sequestration. Similarly, any

Table 1 End-organ effects of the sympathomimetic toxidrome

Cardiovascular	Neurologic	Psychiatric	Other
Hypertension	Altered mental status	Anxiety	Diaphoresis
Tachycardia	Nystagmus	Hyperarousal states	Dehydration
Myocardial ischemia/infarction	Tremors	Insomnia	Hyponatremia
Tachydysrhythmias	Bruxism	Agitation	Rhabdomyolysis
Arterial dissections	Stroke	Hallucinations	Disseminated intravascular coagulation
Vasospasm	Intracranial hemorrhage	Paranoia/psychosis	
Stress-induced cardiomyopathy	Posterior reversible encephalopathy syndrome	Delusions	ARDS
Myocarditis		Repetitive stereotypic movements	Acute kidney injury
	Seizures	Reinforcing behaviors	Hyperthermia
			Inhibits GI motility

xenobiotic that affects the absorption, distribution, metabolism, or elimination of drugs that work via the same mechanisms, can also induce acute hypertension. End-organs regularly injured by acute hypertension include the brain, heart, eyes, kidneys, and lungs.

Newer Synthetic "Designer" Stimulants

Designer Stimulants

The newest generation of synthetic "designer" stimulant, hallucinogenic, and/or entactogenic xenobiotics are classified into four main categories based on their structures: phenethylamines, piperazines, piperadines, and tryptamines. Recreational use of these substances has increased in recent years. This is likely due to increased availability, affordability, and purity. They may be perceived as both legal to possess and more likely to produce sought-after effects [1••]. The Internet allows for discreet sale and distribution, and a safe place to set up forums for users to share their thoughts, tips, experiences, and advice on use of these drugs.

Basic structures of the designer drugs are demonstrated in Fig. 1.

Phenethylamines, piperazine, piperadines, and tryptamines have various effects on and affinities for the norepinephrine, dopamine, and serotonin systems. In general, stimulants cause biogenic amine release, inhibit reuptake, and inhibit monoamine oxidase. The newest hallucinogens tend to be direct serotonin receptor agonists and the newest entactogens cause serotonin release. Manipulation of various parts of each basic chemical structure can change the molecule's ability to cross membranes, stimulate or inhibit receptors, resist enzymatic degradation, and affect cellular transporters [2–8]. Many of these changes result in functional and physiologic changes reflecting a structure-function relationship. For example, oxidation of an amphetamine's ß-carbon to α ketone, creates the cathinone molecule, increasing the chemical's polarity and decreasing

its penetration of the central nervous system (CNS). This modification leads to higher dosing and more profound peripheral effects including end-organ effects. Another example is addition of dihydrofuran or difuran rings to the phenyl group. These
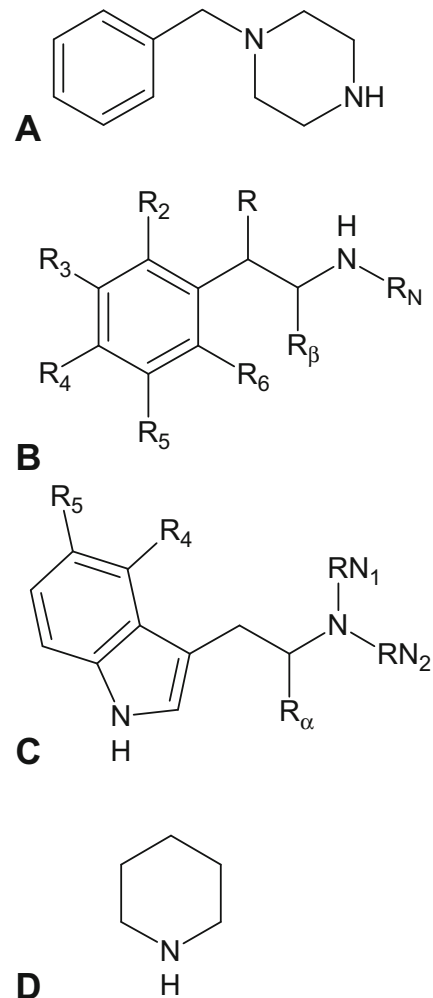

Fig. 1 Basic chemical structures of the piperazines (**a**), phenethylamines (**b**) tryptamines (**c**), and piperidine (**d**). Reprinted with permission from [1••]

additions not only give the molecule the appearance of an insect but also create a chemical with potent 5HT2$_a$ and alpha-adrenergic properties [7]. An example of this is Bromo-DragonFLY (See figure 3 from Hill et al.).

Phenethylamines

Phenethylamines form the basic backbone for a very large class of sympathomimetics seen in Fig. 1 [1••]. These agents predominantly cause hyperadrenergic states with various degrees of serotonin toxicity that are correlated with structural modifications. The ring-substituted phenethylamines 2C- and D-series (methoxylated 2 and 5 positions of the benzene ring) are direct serotonin receptor activators with comparatively less stimulant effects. The benzyl derivatives of this group became popular as NBOMe and other offshoots. Halogenated derivatives strengthen the hallucinogenic potential [6]. Beta-ketonated phenethylamines form the cathinone group which earned the sobriquet "bath salts". A further derivative of ß-ketonated substituted methylene diophyphenethylamines include ethylone, MDPV and agents such as αPVP known as "Gravel" and "Flakka". Neurologic effects include agitation, aggression, paranoia, hallucinations, confusion, anxiety, bruxism, delusions, tremors, hyperreflexia and seizures. Cardiovascular effects include hypertension, tachycardia, chest pain, and myocarditis. Reports of severe vasoconstriction suggest that the D-series and benzodifurans ("FLY" and "DragonFLY") have relatively stronger vascular effects than other phenethylamines [7, 9–12]. Some ring-substituted phenethylamines (paramethoxyamphetamine and 4-methyltrioamphetamine) are particularly deadly. Aptly named "Death" and "Flatliner," respectively, exposed patients frequently succumb to severe hyperthermia [13, 14]. Other effects of phenethylamines include renal failure, hyperthermia, hyponatremia, dehydration, exertional compartment syndrome and acidosis [15].

Figure 2 is taken from [1••].

Piperazines

Piperazines (benzylpiperazine and phenylpiperazines) are another class of stimulant xenobiotics causing a sympathomimetic toxidrome. 1-benzylpiperazine (BZP), an antihelminth, achieved international notoriety in the recent past but its use has fallen. Metabolic acidosis, prolonged QT, seizures, hyponatremia, psychosis, multiorgan failure, and death are reported with benzylpiperazine use [16–19]. Phenylpiperazines appears to be relatively less toxic, yet are known to cause dysphoria, confusion, headache, dissociation, agitation, anxiety, and vomiting [20].

Piperidines

Piperidines are structurally related to methylphenidate and causes a hyperadrenergic state, which may be complicated by

extreme and prolonged psychotic reactions [21]. Other effects include hypertension, rhabdomyolysis, dystonia, tachycardia, tachypnea, euphoria, diaphoresis, bruxism, agitation, hallucinations, insomnia, and leukocytosis [21, 22].

Tryptamines

Tryptamines are serotonergic and have less effect on norepinephrine and dopaminergic systems. These are the classic hallucinogenic amphetamines that appeared during the 1960s and include DMT, methoxyDMT (foxy-methoxy) and LSD [1••]. Clinical effects of tryptamines are primarily hallucinogenic rather than stimulant or entactogenic. Patients may present with hyperadrenergic features including hypertension, tachycardia, chest pain, and mydriasis. Death is possible and is caused by hyperthermia, coma, and hallucinations leading to life-threatening behaviors.

Management Considerations for Synthetic "Designer" Drugs

General management is contingent on meticulous supportive care. The major cause of morbidity and mortality is hyperthermia which should be aggressively diagnosed and managed with direct cooling measures since intoxicated patients with hyperthermia have worse outcomes [23, 24•]. Antipyretics, act by reducing PGE$_2$ concentrations in the hypothalamus and will have no effect on thermogenesis from sympathomimetics. Hyperthermia should be treated by reducing any macro- or micromuscular hyperactivity through sedation and possibly paralysis in addition to active cooling measures. Succinylcholine competes with cocaine for plasma cholinesterase and may prolong effects, thus is relatively contraindicated. Hypertension should be treated if it is the cause of end-organ damage. Drug-induced hypertension often responds to sedation with benzodiazepines. If end-organ toxicity due to hypertension still persists, other pharmacological therapies may be considered. Choice of agent should be dependent on the organ affected. For example, ischemic chest pain or pulmonary edema should be managed with nitroglycerin [25]. Intracranial hemorrhage should be managed with nicardipine and potentially nimodipine for vasospasm.

Personal Insights and Observations

The diagnosis of "synthetic designer drug intoxication" is frequently used for undifferentiated agitated delirium. Unfortunately, a diagnosis applied in the ED and is frequently carried through to discharge whether it is appropriate or not. Once a patient is given a diagnosis, it may cause premature closure of other investigations and anchoring on the diagnosis. It is important to keep a broad differential diagnosis for these
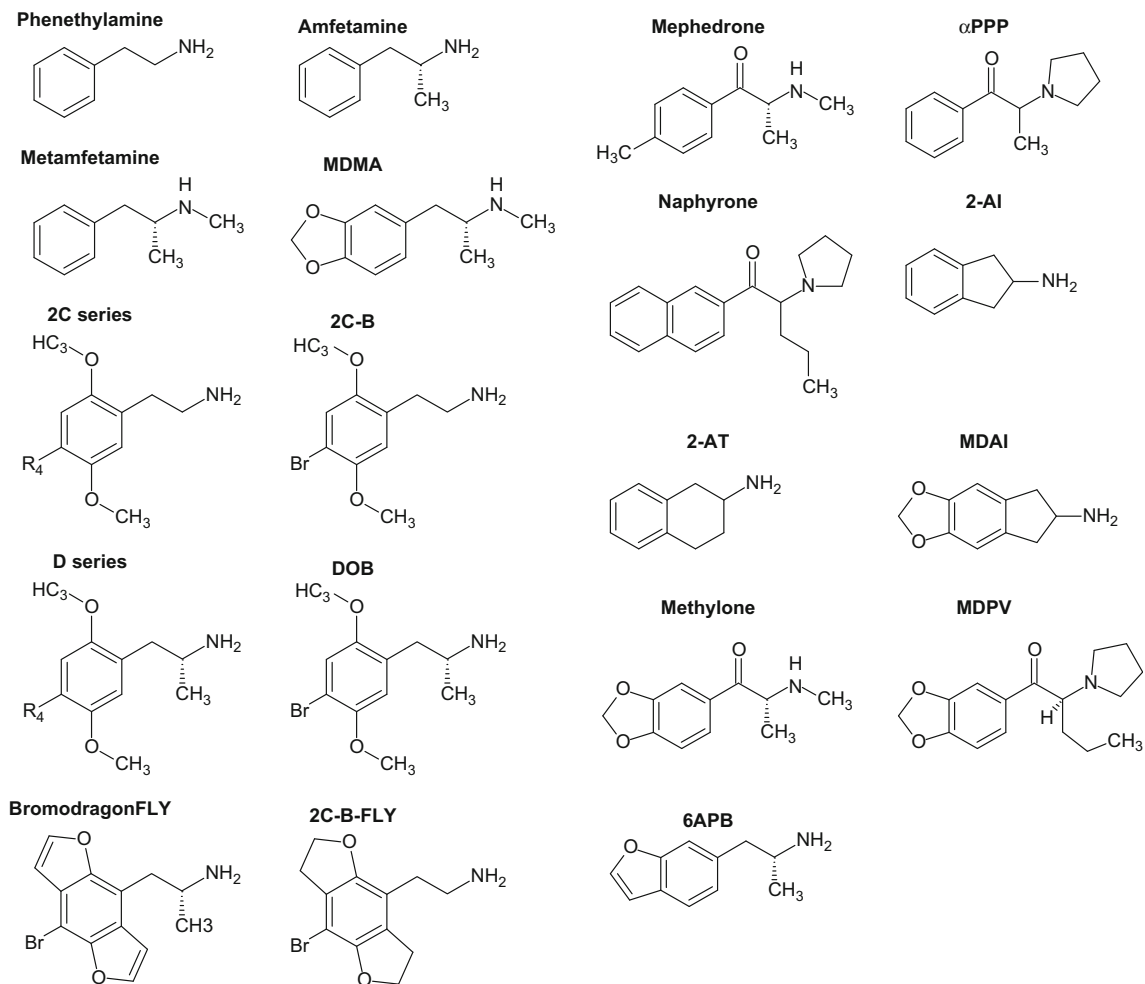
Fig. 2 Skeletal formulae for phenethylamines (note all are presented as the d stereoisomer irrespective of activity for ease of comparison). Reprinted with permission from [1••]

patients as many have a number of comorbidities. Table 2 lists a number of missed diagnoses that have been erroneously attributed to synthetic designer drug intoxication.

Alpha₂ Agonist Withdrawal

Alpha (α)$_2$–adrenergic agonists and imidazolines are commonly prescribed medications with a number of medical and non-medical uses. Over-the-counter imidazolines cause topical vasoconstriction and are used for nasal congestion and eye redness. Clonidine, guanfacine, tizanidine, and dexmedetomidine find use in the treatment of hypertension, opioid withdrawal, attention deficit/hyperactivity disorder, muscle spasms, sedative-hypnotic withdrawal, and procedural sedation. CNS stimulation of α_2–adrenergic and imidazoline receptors (IR) inhibit the release of norepinephrine, epinephrine, dopamine, serotonin, and gamma-butyric acid (GABA). In the spinal cord, alpha$_2$ receptor stimulation has an analgesic effect [26]. Peripherally, alpha$_2$ receptor stimulation in the sympathetic terminal decreases norepinephrine release. This inhibition of sympathetic outflow is often termed "sympatholysis".

Table 2 Synthetic designer stimulant toxicity mimics

Meningitis
Infectious/Autoimmune Encephalitis
Baclofen/GHB withdrawal (oral or intrathecal)
Status epilepticus (convulsive or nonconvulsive)
Posterior reversible encephalopathy syndrome (PRES)
Alpha$_2$ agonist withdrawal (oral or intrathecal)
Alpha$_2$ antagonist toxicity
Mercury toxicity
Pheochromocytoma
Anticholingeric toxicity
Sedative-hypnotic and ethanol withdrawal
Neuroleptic malignant syndrome, serotonin syndrome
Strychnine toxicity
Thyroid storm
Methylxanthine toxicity

Physiologic dependence can result from short-term use of α_2 agonists. Abrupt cessation of clonidine with its subsequent hyperadrenergic withdrawal state is well known [27–30]. Withdrawal symptoms include marked blood pressure elevation (i.e., "rebound hypertension"), tachycardia, diaphoresis, abdominal pain, headache, increased arousal, irritability, anxiety, and agitation. Reported life-threatening complications include myocardial infarction, pulmonary edema, ventricular tachycardia, and vertebral artery dissection [31–34]. A similar withdrawal syndrome can be seen for any of the other α_2 agents including guanfacine, tizanidine, and dexmedetomidine.

Intrathecal, epidural, and topical clonidine administration is used for controlling chronic pain syndromes. Severe and refractory hyperadrenergic states occur if drug delivery is abruptly interrupted [35, 36]. For example, Lee and colleagues described the case of a 47-year-old man whose intrathecal pump malfunctioned leading to hypertension, new left-bundle branch block, pulmonary edema requiring non-invasive ventilatory support, and stress-induced cardiomyopathy. The patient was treated with intravenous infusions and boluses of clonidine, nitroglycerin, and diazepam but still required 4 days in the intensive care unit [36].

Dexmedetomidine is FDA-approved for sedation of the "initially intubated and mechanically intubated patient" or "non-intubated patients prior to and/or during surgical and other procedures" (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021038s021lbl.pdf). Once the patent expired in 2013, dexmedetomidine use increased to include off-label indications such as sedative hypnotic withdrawal, ventilator weaning, and opioid withdrawal. Although not a common complication of prolonged sedation [37, 38•], dexmedetomidine withdrawal does occur and is an increasingly recognized issue. Despite manufacturer recommendations to limit its use to less than 24 h, prolonged use occurs [37, 38•] and increases the likelihood for physiologic dependence and subsequent withdrawal [39, 40].

Treatment of Alpha₂ Agonist Withdrawal

Treatment of alpha₂ agonist withdrawal syndrome focuses on identifying and reversing end-organ damage or dysfunction caused by the elevated blood pressure. The best therapy is to "give back" the drug causing the withdrawal and then slowly taper it off over several days [41]. Early administration of clonidine or a similar agent improves blood pressure for both acute clonidine and dexmedetomidine withdrawal. Substitution of a longer acting oral agent (oral or transcutaneous clonidine for dexmedetomidine infusion) is a frequently used option to wean off a short-acting agent once control has been achieved [39, 42–44]. Alternatively, dexmedetomidine has been successfully used for acute clonidine withdrawal and can be considered when a rapidly acting titratable agent is needed [45]. The hypertension encountered with clonidine withdrawal may be refractory to standard doses of certain antihypertensive medications, including nitroglycerin, nicardipine, and certain beta-blockers. Additional antihypertensive therapy should be chosen based on end organs affected, as discussed previously.

Personal Insights and Observations

Emergency practitioners who treat patient populations where hypertension is prevalent and poorly controlled frequently encounter markedly elevated blood pressure. A substantial portion of these emergencies may result from medication withdrawal, most frequently clonidine. If alpha₂ agonist withdrawal is suspected, administering the patient's usual dose and allowing time for the medication to work should help to more adequately control blood pressure. Additional doses of clonidine or similar agents may be required, however keep in mind that large doses of clonidine are associated with sedation and apnea. As noted, when clinically appropriate, benzodiazepines can be quite effective to control symptoms of agitation, and reduce blood pressure.

Baclofen Withdrawal

Baclofen and gamma hydroxybutyrate are agonists at the GABA-B receptor. GABA-B receptors are G protein-coupled and are located both pre- and postsynaptically. Presynaptic GABA-B receptors prevent Ca^{2+} influx and as a result, provide feedback inhibition. Postsynaptic receptors increase K^+ efflux and inhibit signal transduction. Interestingly, baclofen can cause seizures in both overdose and withdrawal. In overdose, presynaptic stimulation prevents release of inhibitory neurotransmitters. In withdrawal, there is loss of postsynaptic tonic inhibition resulting in a lack of inhibitory tone.

Baclofen withdrawal can be clinically indistinguishable from a sympathomimetic toxidrome, serotonin syndrome, or other GABAergic withdrawal syndromes. Similar to alpha₂ agonist intrathecal pumps, intrathecal baclofen pump malfunction can lead to life-threatening overdose and withdrawal states. In withdrawal, hypertension, tachycardia, stress cardiomyopathy, diaphoresis, spasticity, dystonia, seizures, fever, anxiety, delirium, rhabdomyolysis, DIC and death are reported [46–49, 50••, 51, 52]. Accidental intrathecal overdose can cause seizures, coma, and hemodynamic instability, and it may be difficult to differentiate overdose from withdrawal. If intrathecal overdose is suspected, the airway should be secured, the pump should be emptied immediately through the percutaneous port, and CSF drug aspiration should be considered after consultation with the prescribing clinician [50••]. Good supportive care is the backbone of treatment for both overdose and withdrawal. In withdrawal states, oral baclofen, intravenous benzodiazepines,

propofol, and dexmedetomidine are reasonable options for symptom control [50••, 53, 54].

Personal Insights and Observations

Chronic pain is common and, in the setting of the current opioid crisis, providers will increasingly look for opioid-sparing options. Some of these options may include "muscle relaxers" such as tizanidine or baclofen orally and/or intrathecally. Most patients do not list intrathecal pump medication as part of their medication list and may be unaware of what the pump is infusing. The only clue to intrathecal overdose or withdrawal may be the characteristic scar and lump on physical examination. This is a reminder to consider non-traditional medication administration. Unless the clinician specifically asks about this medication or performs a comprehensive physical exam, it is an easily missed diagnosis.

Classic Drugs of Abuse

Cocaine, amphetamines, and amphetamine derivatives have historically been the most widely consumed illegal stimulants in the USA and their clinical effects and associated hyperadrenergic toxidromes are well known. Because these substances cause disease by overstimulation of the adrenergic system (among others), a logical therapeutic approach would be to block the overstimulated receptors causing the disease state. However, animal studies and a few case reports demonstrated the potential for harm with this method, and the putative mechanism was termed the "phenomena of unopposed alpha stimulation." An oversimplified view of the pathophysiology underlying the "unopposed alpha phenomena" generally involves the administration of a nonselective beta-adrenergic antagonist to an individual in a hyperadrenergic state. The vasodilatory effects of the beta$_2$ adrenergic stimulation by the agent is lost or "blocked" in the systemic and coronary circulation. In turn, the body is unable to counteract the opposing vasoconstricting effect of postsynaptic alpha$_1$ and alpha$_2$ agonism that persists. Thus, the alpha agonism is "unopposed" and can lead to profound hypertension and coronary ischemia.

Though the "unopposed alpha" phenomenon is a common teaching and feared adverse drug event, it is based on a few case reports, animal models, and small prospective studies. Recent publications have questioned the quality of the evidence that serves as the foundation for this claim [55•, 56•, 57•, 58•, 59•, 60•, 61•, 62••]. Richards et al. performed the most recent review of the literature regarding the "unopposed alpha" phenomenon and the reader is referred to its table of contents and summary of literature and evidence grade [62••].

Table 3 summarizes the studies and cases of cocaine use and beta-blockers and includes descriptions of the adverse

outcomes in each reference [62••]. Adverse outcomes were documented in only 7 of 2124 patients and included increased coronary vascular resistance with decreased coronary blood flow, attenuated increases in heart rate and blood pressure, myocardial infarction, worsened pulmonary edema, and cardiac arrest. Notably, these instances were rare, inconsistent, and difficult to differentiate from the adverse effects of cocaine itself. Of note, there were no adverse events attributed to the unopposed alpha phenomenon when combined alpha/beta antagonists were used (i.e., labetalol and carvedilol).

There are also case reports showing potential beneficial effects of beta bockers in acute sympathomimetic intoxication. These include improvement of blood pressure with IV propranolol and labetalol in the setting of intentional overdose of pseudoephedrine and ephedrine, improvement of injury pattern on ECG with administration of metoprolol in the setting of pseudoephedrine toxicity, and lower heart rates with no change in blood pressure when MDMA users were pretreated with pindolol [63–66]. Larger, retrospective studies report beta-adrenergic antagonist therapy either does not cause harm or may even show benefit. A retrospective review of 307 admitted patients with cocaine present on their urine drug screens reported that the 60 who received beta-blockers had a lower risk of myocardial infarction than those who did not receive beta-blockers [67•]. Hoskins et al. analyzed patients with acute coronary syndrome and urine drug screen positive for cocaine treated with either labetalol or diltiazem showed that subjects who received labetalol had lower serum inflammatory markers when compared to the diltiazem group and both groups had decreases in blood pressure [68]. A study by Ibrahim et al., evaluated patients presenting with chest pain and positive cocaine urine drug screens with elevated troponins. Subjects were administered either beta1-selective or mixed α_1/beta-blockers and the investigators found no association with higher troponin levels in either group. No cases of hypertensive urgency were identified in any patient that received beta-blockers [69•]. Finally, a study by Rangel et al. found that patients with cocaine-associated chest pain discharged on a beta-blocker had a lower risk for cardiovascular death [70•].

Reviews have concluded that while the evidence of harm remains limited, the use of selective beta-blockers to control *acute* chest pain and hypertension as a first-line therapy is not recommended. Other effective agents that do not carry the same potential risks exist and the appropriate comparison studies do not exist [59•]. Schurr et al. sums up the inconsistencies in the evidence: "current literature is limited but suggests that beta-adrenergic antagonists are harmful. Although case reports support a detrimental effect of beta-adrenergic antagonists, the anecdotal data are inconsistent, and the conclusions from case studies are overruled by larger studies". [61•].

Table 3 Studies and cases involving cocaine use and beta-blockers to date

Author (s) year	Type of study/trial	β-blocker	Level of evidence[a]	No. of subjects	Adverse events	Summary
Lange et al.[25] 1990	Prospective. randomized. Double-blind. Controlled	Propranolol	I	10	1	Ineacoronary propranolol increased coronary vascular resistance, decreased coronary sinus blood flow
Vongpatanasin et al.[44] 1999	Prospecdve. randomized. Double-blind, controlled	Propranolol	I	II	0	Propranolol prevented increases in heart rate
Sofuoglu et al.[45] 2000	Prospective. randomized. Double-blind. Crossover	Carnadthal	I	12	0	Carvedilol prevented increases in blood pressure and heart rate
Sofuoglu et al.[41] 2000	Prospective. randomized. Double-blind. Crossover	Labetalol	I	12	0	Labetalol prevented increases in blood pressure and heart rate
Vongpatanasin et al.[47] 2004	Prospective. randomized. Double-blind, controlled	Propranolol	I	24	0	Heart rate increase was attenuated by propranolol
Orr and Jones[48] 1968	Prospective cohort	Propranolol	II	60	0	Propranolol pretreatment decreased heart rate; posttreatment decreased blood pressure, dysrhythmias
Sand et al.[27] 1991	Prospective cohort	Esmolol, labetalol	II	7	3	Inconsistent response to esmolol: rescue with labetalol and nifedipine in 2 cases
Boehrer et al.[26] 1993	Prospective. controlled	Labetalol	II	9	0	Labetalol reduced heart rate, blood pressure; no effect on coronary artery cross-sectional area
Hoskins et al.[49] 2010	Prospective cohort	Labetalol	II	30	0	Diltiazem and labetalol decreased blood pressure, heart rate
Brody et al.[50] 1990	Retrospective	Labetalol	III	18	0	Eighteen of the 233 cocaine required treatment. no adverse effects reported
Dattilo et al.[51] 2008	Retrospective	Metoprola atenolol labetalol, prepranolol, carvediol	III	60	0	β-Blockers associated with decreased incidence of myocardial infarction
Mohamad et al.[52] 2008	Retrospective	β-blockers (unspecified)	III	364	0	β-Blockers associated with higher incidence of myocardial infarction
Rangel et al.[53] 2010	Retrospective	Metoprolol, atenolol, labetalol, propranol, carvedilol	III	151	0	β-blocker use associated with greater reduction in blood pressure and death
Ibrahim et al.[54] 2013	Retrospective	Metoprolol, atenolol, labetalol, carvedilol	III	162	0	β-blockers did not change incidence of troponin elevation
Fanari et al.[55] 2014	Retrospective	Metoprolol. atenolol, labetalol, carvedilol	III	164	0	No difference in outcomes with β-blockers
Gupta et al.[56] 2014	Retrospective	β-blockers (unspecified)	III	600	0	Majority of cocaine-positive patients with myocardial infarction received β-blockers
Chibungu et al.[57] 2016	Retrospective	β-blockers (unspecified)	III	378	0	Thirty-one percent of cocaine-induced myocardial infarction treated with β-blockers
Reppolt et al.[58] 1977	Case series	Propranolol	IV	5	0	Resolution of hypertension. Tachycardia after propranol

Table 3 (continued)

Author(s) year	Type of study/trial	β-blocker	Level of evidence[a]	No. of subjects	Adverse events	Summary
Meyers[59] 1980	Case series	Propranolol	IV	2	0	Resolution of tachycardia, dysrhythmia after propranolol
Rigs and Weibley[60] 1990	Case series	Propranolol	IV	4	0	Control of ventricular tachycardia after propranolol
Minor et al.[61] 1991	Case series	Metoprolol	IV	3	0	Successful treatment of myocardial infarction in patients with normal coronary arteries
Merigian et al.[62] 1994	Case series	Esmolol propranolol, labetalol	IV	5	0	Successful use of β-blockers for cocaine toxicity
Nicholson and Rogers[63] 1995	Case series	Labetalol	IV	3	0	Resolution of tachycardia, hypertension, dysrhythmia after labetalol
Gay[64] 1976	Case report	Propranolol	V	1	0	Resolution of tachycardia, hypertension after propranolol
Rappolt et al.[65] 1976	Case report	Propranolol	V	1	0	Resolution of hypertension, tachycardia after propranolol
Roppolt et al.[66] 1978	Case report	Propranolol	V	1	0	Resolution of hypertension, tachycardia after propranolol
Jonsson et al.[67] 1983	Case report	Propranolol	V	1	0	Resolution of dysrhythmia, tachycardia after propranolol
el-Din and Mostoh[68] 1985	Case report	Labetalol	V	1	0	Resolution of dysrhythmia, hypertension after topical intranasal cocaine
Ramoska and Sacchetti[14] 1985	Case report	Propranolol	V	1	1	Hypertension worsened after propranolol, resolution with nitroprusside
Dusenberry and Marian[69] 1987	Case report	Labetalol	V	1	0	Resolution of hypertension, tachycardia after labetalol
Ascher et al.[70] 1988	Case report	Metoprolol	V	1	0	Pen myocardial infarction treatment
Gay and Loper[71] 1988	Case report	Labetalol	V	1	0	Labetalol resolved hypertension, tachycardia
Burton et al.[72] 1989	Case report	Propranolol	V	1	0	Propranolol resolved hypertension, tachycardia in cocaine dependent hyperthyroid patient
Pollan and Tadjiechy[73] 1989	Case report	Esmolol	V	1	0	Esmolol resolved hypertension, tachycardia advent after failure with nitroglycerin and digoxin
Samuels et al.[74] 1991	Case report	Labetalol	V	1	0	Labetalol resolved hypertension, tachycardia
Merigian[75] 1993	Case report	Propranolol. esmolol	V	1	0	Resolution of tachycardia, dysrythmia with propranolol esmolol
Malbrain et al.[76] 1994	Case report	Labetalol	V	1	0	Labetalol resolved hypertension. Tachycardia
Singh et al.[77] 1994	Case report	Labetalol	V	1	0	Hypotension and pulmonary edema during general anesthesia, phenylephrine

Table 3 (continued)

Author (s) year	Type of study/trial	β-blocker	Level of evidence[a]	No. of subjects	Adverse events	Summary
Williams et al. [78] 1996	Case report	Esmolol	V	1	0	Esmolol resolved hypertension, tachycardia. Dysrhythmia after preoperative intranasal cocaine
Inyang et al. [79] 1999	Case report	Labetalol	V	1	0	Failure of nitroglycerin, morphine, labetalol to mitigate chest pain, myocardial infarction
Laffey et al. [80] 1999	Case report	Esmolol	V	1	0	Resolution of tachycardia after esmolol
Missouri et al. [81] 2001	Case report	Metoprolol	V	1	0	Successful treatment of unstable angina
Ortega-Casnicer et al. [82] 2001	Case report	Labetalol	V	1	0	Ventricular tachycardia and ST-elevation resolved with both medications
Erwin and Deliargyris [83] 2002	Case report	Metoprolol	V	1	0	Worsening hypertension and pulmonary edema after multiple medications given
Megarbane et al. [84] 2004	Case report	Labetalol	V	1	0	Hypertension. tachycardia resolved after labetalol
Fareed et al. [28] 2007	Case report	Metoprolol	V	1	1	Diazepam, nitroglycerin faded to resolve tachycardia; cardiac arrest after metoprolol
Feldhendler et al. [85] 2007	Case report	Esmolol	V	1	0	Successful treatment of cocaine-induced aortic dissection
Izquierdo Gómez et al. [29] 2009	Case report	Propranolol	V	1	1	Propranolol worsened chest pain, ST-elevation
Javed et al. [86] 2011	Case report	Labetalol, esmolol	V	1	0	Dexmedetomidine resolved hypertension, tachycardia after failure of other attempted medications
Martinez-Quintana et al. [87] 2013	Case report	Propranolol	V	1	0	Resolution of hypertension tachycardia with combined treatment including propranolol
Öcal et al. [88] 2015	Case report	Carvedilol	V	1	0	Resolution of tachycardia with carvedilol
Richards et al. [89] 2016	Case report	Labertalol	V	1	0	Resolution of tachycardia. Hypertension with labetalol
Richards et al. [90] 2016	Case report	Labertalol	V	1	0	Resolution of tachycardia. Hypertension with labetalol
	Total			2124	7	

Summary of studies regarding cocaine and beta-blockers from [62••]

[a] Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence. 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; and V—opinion of authorities, case reports [91]

Management

General management of patients presenting with cocaine and amphetamine associated cardiovascular effects involves decreasing the hyperadrenergic state and agitation with benzodiazepines, as well as controlling blood pressure with nitrates and/or calcium channel blockers. A few prospective studies have been performed attempting to define the optimal treatment regimen. The combination of lorazepam with nitroglycerin versus nitroglycerin alone in one study was more effective in reducing chest pain [71••]. However, another reported that in patients with cocaine-associated acute coronary syndrome treated with nitroglycerin, diazepam, or both, did not demonstrate any difference with regard to therapy in terms of chest pain, and other hemodynamic and cardiac profiles [72•]. A systematic literature review performed by Richards et al. also graded the evidence for management of cocaine cardiovascular toxicity with regards benzodiazepines, calcium channel blockers, nitric-oxide-mediated vasodilators, alpha-blockers, alpha2 agonists, and beta-blockers [62••].

Personal Insights and Observations

The documented adverse effects and outcomes of patients administered beta-adrenergic antagonists suggest the possibility of harm; however, these observations are rare and inconsistent. In vivo cardiac catheterization studies demonstrate the potential for coronary vasoconstriction but are difficult to generalize, while larger studies of beta-blockers in cocaine users demonstrate benefit. Unfortunately, it is easy to remember case stories rather than study results, and the practice of medicine based on dramatic case reports often supersedes more robust and reliable data. That being said, it is entirely possible that selective beta blockade is harmful as suggested by case reports when patients are *acutely* toxic. The larger studies may or may not include or capture the acutely toxic patients with their inclusion criteria. Much of this is a non-issue. Alternative non-stigmatized medications exist and are effectively employed to stabilize the acutely hyperadrenergic patient.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) or reversible posterior leukoencephalopathy syndrome (RPLS), first described in 1996, seems to be associated with certain xenobiotics [73]. PRES is characterized by a reversible constellation of findings and symptoms including headache, hypertension, altered mental status, seizures, vision loss, and posterior leukoencephalopathy seen on imaging [73, 74, 75••, 76, 77]. Blood pressure elevations are usually critically high, with a mean of 199/104 mmHg in one case series [74]. Risk factors include autoimmune disease, renal failure, and hypertension. PRES has occurred in the aftermath of sympathomimetic toxicity but more commonly associated with immunosuppressant agents and chemotherapy medications [77–80, 81•, 82].

There are multiple yet unproven theories regarding the pathogenesis of PRES, and the extent to which xenobiotics play a causal role remains unclear [76]. The "vasogenic" theory involves a rapid increase in systemic vascular resistance that overwhelms cerebral autoregulation resulting in hyperperfusion, increased hydrostatic pressure, and capillary leak with vasogenic edema. The "cytotoxic" theory purports the xenobiotics used in chemotherapy and immunomodulatory therapy cause endothelial dysfunction and cerebral edema. The "neuropeptide theory" argues vasoconstrictors such as endothelin-1, prostacyclin, and thromboxane A_2 induce vasospasm, ischemia, and subsequent edema. The "immunogenic theory" posits T cell activation and cytokine release to cause increased cellular permeability.

Treatment of PRES

Recommended treatment for PRES includes blood pressure control as well as discontinuation of any associated medications. Seizures should be rapidly halted and may require anti-epileptic medications. Although there are no studies on blood pressure control and its effect on resolution of PRES, hypertension treatment is generally thought to be important. In severe hypertension, reducing pressure by 25% in the first hours is reasonable. There is no specific agent preferred in PRES. Patients tend to have a good prognosis when treated quickly and 75–90% of patients have complete recoveries [75••].

Personal Inights and Observations

PRES is another disease process in which a high degree of suspicion is needed to make the diagnosis. Once seizure activity is controlled and subsequent catecholamine surge, patients may have persistent hypertension. It is often unclear how aggressive one should be with blood pressure control in this situation. On the one hand, rapid lowering of blood pressure may result in watershed infarct but on the other, as in the case of PRES, more aggressive control may be warranted. Rapid and emergent access to MRI to help confirm the diagnosis may not be available in all institutions. Regardless, the diagnosis should be entertained in the setting of patients with hypertension, seizures, and/or altered mental status and an unremarkable head CT after immunomodulator or chemotherapeutic use.

Conclusions

Xenobiotic-induced hypertension and hyperadrenergic states are common medical emergencies. Optimal treatment

is predicated by the underlying etiology of these states. Designer stimulants will continue to cause toxicity in both predictable and unpredictable ways each time an "untested" compound becomes available. The increasing prevalence of chronic pain syndromes and use of opioid-sparing therapies (e.g. baclofen and intrathecal medication delivery devices) will put an increasing number of patients at risk for life-threatening withdrawal phenomena either due to medication noncompliance or device malfunction. Diagnosis requires a high index of suspicion. The "unopposed alpha" phenomenon is rare and based on low level evidence. While evidence for harm exists, other studies suggest treatment efficacy and overall benefit when beta-blockers are administered to stimulant users. Regardless, other effective options exist to treat acute stimulant-induced cardiovascular toxicity. Finally, the pathophysiologic underpinnings of PRES remain poorly understood; however, the clinical presentation, associated xenobiotics and risk factors are well established.

Compliance with Ethical Standards

Conflict of Interest   The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

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