

Stimulants and the Lung

Review of Literature

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Abstract Illicit stimulants, such as cocaine, amphetamine, and their derivatives (e.g., “ecstasy”), continue to exact heavy toll on health care in both developed and developing countries. The US Department of Health and Human Service reported over one million illicit drug-related emergency department visits in 2010, which was higher than any of the six previous years. Both inhaled and intravenous forms of these substances of abuse can result in a variety of acute and chronic injuries to practically every part of the respiratory tract, leading potentially to permanent morbidities as well as fatal consequences—including but not limited to nasal septum perforation, pulmonary hypertension, pneumothorax, pneumomediastinum, interstitial lung disease, alveolar hemorrhage, reactive airway disease, pulmonary edema, pulmonary granulomatosis, infections, foreign body aspiration, infections, bronchoconstriction, and thermal injuries. Stimulants are all rapidly absorbed substances that can also significantly alter the patient’s systemic acid–base balance and central nervous system, thereby leading to further respiratory compromise. Mounting evidence in the past decade has demonstrated that adulterants coinhaled with these substances (e.g., levamisole) and the metabolites of these substances (e.g., cocaethylene) are associated with specific forms of systemic and respiratory complications as well. Recent studies have also demonstrated the effects of

stimulants on autoimmune-mediated injuries of the respiratory tract, such as cocaine-induced midline destructive lesions. A persistent challenge to studies involving stimulant-associated respiratory toxidromes is the high prevalence of concomitant usage of various substances by drug abusers, including tobacco smoking. Now more than ever, health care providers must be familiar with the multitude of respiratory toxidromes as well as the diverse pathophysiology related to commonly abused stimulants to provide timely diagnosis and effective treatment.

Keywords Cocaine · Crack · Methamphetamine · Amphetamine · Cocaethylene · Methylenedioxymethamphetamine · MDMA · Ecstasy · Levamisole · Methylecgonidine · Inhaled stimulant · Pneumotoxicity · Midline destructive lesions · Pneumomediastinum · Pneumothorax · Pulmonary edema · Alveolar hemorrhage · BOOP · Foreign body · Pulmonary hypertension

Introduction

Substance abuse continues to be a major health care and socioeconomic problem in the USA and is increasing in developing countries. According to the United Nations report published in 2012, globally, 3.4–6.6 % of the population between ages 15 and 64 years used an illicit substance at least once in 2010 [1]. In terms of annual global prevalence in this age group, other than cannabis (2.6–5.0 %), amphetamine-type stimulants (ATS) besides ecstasy appear to be the most common drugs of abuse (0.3–1.2 %), followed closely by opioids (0.6–0.8 %) and cocaine (0.3–0.4 %). Methylenedioxymethamphetamine (MDMA or “ecstasy”) has a global prevalence of 0.2–0.6 %, similar to that of cocaine in this age group [2]. The rate of illicit drug use in the USA itself is alarming: according to the most recent

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National Survey on Drug Use and Health, in the year 2011, an estimated 22.5 million Americans over the age of 12 years were current or recent illicit drug users, comprising 8.7 % of this age group. Cocaine usage among those aged 12 years or older has decreased from 2.4 million in 2006 to 1.4 million in 2011, and methamphetamine usage has decreased from 731,000 in 2006 to 353,000 in 2010 but has then again increased to 439,000 in 2011 [1]. Despite the overall decrease in prevalence of stimulant abuse in the last 5 years, the detrimental effects associated with highly addictive stimulant drugs like cocaine and methamphetamine continue to take toll on our health care resources, as reflected by persistently high numbers of emergency department visits related to medical, psychiatric, and social consequences of cocaine abuse [3]. In fact, the US Department of Health and Human Service reported 1,171,024 illicit drug-related emergency department visits in 2010, which was higher than any of the six previous years [4]. Cocaine had the highest rate of involvement, being associated with 158 emergency room visits per 100,000 of the population [4].

The direct financial cost is difficult to measure. A series done by Baldwin and colleagues demonstrated that illicit drug-related intensive care unit (ICU) costs were 10 % of the total ICU costs [5]. A large retrospective study by de Wit and colleagues may offer an explanation. They compared 22,827 drug users with 1,196,048 controls and demonstrated that, independent of the medical diagnosis, illicit drug users were at an increased risk of requiring mechanical ventilation ($RR=1.50$, $p<0.0001$). More specifically, those who abused cocaine and amphetamines were found to have relative risks of 1.51 and 2.16 of needing mechanical ventilation, respectively ($p<0.0001$) [6]. The financial toll appears to be high for drug-exposed infants as well. A large study in the city of New York demonstrated that hospital costs until discharge were \$5,200 more for cocaine-exposed infants than unexposed infants ($p=0.003$), and importantly, fetal exposure to the inhaled form of cocaine (freebase or “crack” cocaine) was associated with a much larger increase in overall hospital costs compared to other forms of cocaine (\$6,735 vs. \$1,226, $p<0.05$) [7].

Studies on the effect of pulmonary diseases related to a specific substance of abuse are often confounded by the fact that the vast majority of cocaine users also inhale other substances of abuse such as tobacco and marijuana smoke. A study of 228 cocaine smokers revealed that 96 % of them had previous experience with marijuana, tobacco, or both; and after starting regular cocaine smoking, only 5 % of tobacco smokers decreased tobacco usage [8]. It is difficult but important to study inhaled substances as distinctly as possible.

Because of the large alveolar surface area exposed in inhaled air and large volume of pulmonary circulation, the lungs are directly subject to toxic effects of both intravenous and inhaled drugs of abuse [9]. This article aims to provide

an updated perspective on the short-term and long-term sequelae of stimulant abuse on the respiratory system, including the upper respiratory tract and the immune system.

Cocaine

Cocaine is an alkaloid derivative extracted in a paste from the leaves of *Erythroxylum coca* species, a plant of the Andean and Amazon regions in South America, where natives have been chewing these leaves for centuries. Currently, medical use of cocaine is limited, but early in this century, as many as 10 tons of cocaine were annually imported to the USA to be used in a multitude of over-the-counter medical products and elixirs, including a product called “Dr. Tucker’s Asthma Specific,” which contained 420 mg of cocaine per ounce for nasal application [10]. The Harrison Narcotics Act of 1914 banned nonprescription use of cocaine, which marked the end to the first cocaine epidemic in the USA. The second cocaine epidemic began in the 1970s with large-scale illegal importation and distribution [11]. Despite significant declines of the global cocaine market, the largest primarily illicit consumption continues to be that of the USA, responsible for 36 % of global consumption [2, 10].

When processed via solvent and alkaline extraction to form the “freebase” which has higher volatility and greater stability, cocaine can be smoked as “crack” cocaine. Smoking delivers the drug to the brain more quickly than snorting because the latter method relies on the absorption of the substance into the nasal bloodstream, where it travels through the venous system, the right heart, the lungs, the left heart, and eventually with oxygenated blood to the brain. Smoking substances of abuse has been a popular way of self-administration due to relative ease as well as the highly effective transport of the substances from the respiratory tract to the circulatory system. The rapidity of this delivery system has been suggested to underlie its addictive power. Smoked cocaine results in rapidly attained peak plasma levels about 5 min after beginning of smoking in a study, albeit with large variation in subjects [12]. The bioavailability after smoking was also variable, ranging from 32 to 77 % [12].

The pharmacologic mechanism of action of cocaine is complex. Cocaine significantly blocks neuronal catecholamine reuptake and, to a lesser extent, stimulates catecholamine release. It has moderate effects on central nervous system (CNS) serotonin release and reuptake blockade. Marked local anesthetic effects are seen with cocaine caused by its blockade of sodium channels. In addition, cocaine blocks potassium channels and may block some cellular membrane sodium calcium exchange mechanisms. A number of reviews have discussed the multitude of toxic effects from cocaine abuse, including our own [13–15]. In this updated review, we will continue to organize cocaine-induced pneumotoxicity according to the different domains

of the pathophysiology involved, including upper airway disease, reactive airway disease, and pulmonary hypertension.

Adulterants in the stimulants can contribute to their overall toxicity [16, 17], as exemplified by the effects of levamisole to be discussed in the succeeding sections. Alteration of toxicity can also occur when cocaine and amphetamine are taken with ethanol, which is the most common substance consumed with cocaine or amphetamine [18–20]. In the presence of ethanol, cocaine undergoes transesterification with ethanol instead of hydrolysis with water, and cocaethylene (ethylbenzoylecgonine) forms as shown in Fig. 1 [21, 22]. Cocaethylene has similar hemodynamic effects as cocaine on blood pressure and heart rate but has increased half-life [23, 24]. Cardiotoxicity of cocaethylene was demonstrated in a canine study, in which dogs given intravenous cocaethylene developed increased pulmonary artery wedge pressure as well as increased QTc prolongation [25]. In a rabbit study, respiratory arrest following cocaethylene injection into the vertebral artery lasted longer than that following cocaine injection [26]. Furthermore, elimination of cocaine is impaired in the presence of alcohol, and the “dual effect” of decreased cocaine catabolism and increased cocaethylene production may result in more prolonged and more significant toxicity [27].

Amphetamine-Type Stimulants

The global prevalence of amphetamine and methamphetamine was 0.3–1.3 % of people ages 15–64 years in 2009, and that of the ecstasy group (MDMA and its analogues) was 0.2–1.6 % [2]. There is a remarkable number of new users of MDMA in the USA every year [1].

Amphetamines were introduced into the USA in the 1930s as stimulants and as inhalers for asthma and nasal congestion [28]. Worldwide use of amphetamines increased during World War II. Following the war, large-scale amphetamine abuse was reported in Japan with the first reports of psychological addiction being noted. By the 1950s, amphetamines had replaced cocaine as the most common stimulant of abuse in the USA. This trend reversed again with cocaine's soaring popularity in the late 1970s. The cyclic nature of abuse repeated again in the mid-1990s in many communities in the USA. Methamphetamine has a long half-life and is highly addictive. It is easily synthesized from readily available precursors (such as pseudoephedrine), and major federal laws restricting precursor chemicals used in the synthesis of methamphetamine took place in response to the growing epidemic of abuse. From 1995 to 2008, methamphetamine

abuse increased in California in a pattern characteristic of drug epidemics, spreading through low-income Caucasian and Hispanic populations living outside of dense urban communities [29].

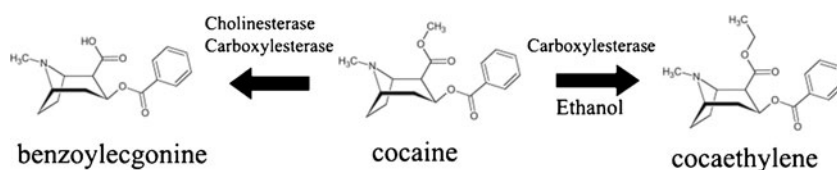
Analogous to “crack” cocaine, the nearly pure form of D-methamphetamine hydrochloride, called “ice” or “crystal meth,” is extremely toxic because of its purity and because it can be smoked [30, 31]. Because crystal meth has increased volatility, it has become very popular to inhale heated vapors of methamphetamine, which are capable of giving nearly the same “rush” as intravenous methamphetamine.

In addition, “designer” amphetamines have been abused widely in the USA as well. Examples include MDMA, methylenedioxymphetamine, 2,5-dimethoxy-4-methylamphetamine, and mephedrone (4-methylmethcathinone, marketed as bath salts). These amphetamine derivatives tend to have more hallucinogenic properties than the basic amphetamine molecule often because of a 3,4-methoxy substitution at the phenyl ring [32, 33]. While most people abuse MDMA for the predominant serotonin and dopaminergic feelings of euphoria, when patients present for medical attention it is typically due to the excessive sympathomimetic state typically seen in traditional amphetamine ingestions.

Similar to cocaine, amphetamines block neural catecholamine reuptake and release and also push significant amounts of neurotransmitter into the synaptic cleft. Moderate blockade of the reuptake and increased release of CNS serotonin and dopamine is also seen with amphetamines. Unlike cocaine, the amphetamines have no significant local anesthetic or sodium channel blockade effects, but they do inhibit monoamine oxidase activity [14, 31].

Methamphetamine has a much greater uptake, faster peak time, and slower clearance in the lungs compared to other organs [34]. In contrast, uptake of cocaine has been shown to be highest in the brain and lowest in the lungs using a similar method [35]. A recent study of 19 patients using positron emission tomography and [^{11}C]D-methamphetamine, prepared from D-amphetamine and [^{11}C]methyl iodide, to measure the whole body distribution of methamphetamine found that the liver and the lungs had the highest uptake, 23 and 22 %, respectively [34]. The injected [^{11}C]D-methamphetamine peaked in the lungs almost as fast as in the plasma, 55 s compared to 50 s; this rapid peaking was unlikely merely a reflection of pulmonary vascular perfusion since the lung had much greater peak concentration and much slower clearance of the compound than the arterial plasma. Furthermore, the authors demonstrated that [^{11}C]D-methamphetamine

Fig. 1 Transesterification of cocaine to cocaethylene in the presence of ethanol. Modified from [210]



accumulated at a markedly higher dose in the lungs of African Americans than that of Caucasians [34].

Illegal laboratories in the USA commonly produce methamphetamine through one of two methods, including a reduction of L-ephedrine or D-pseudoephedrine over red phosphorus with hydrochloric acid or a reduction of these compounds using liquid ammonia and lithium or sodium. These illicit manufacturing processes pose health risks to those living in or around meth labs as well as law enforcement officers and firefighters [36, 37]. Red phosphorus is highly flammable and can result in meth lab fires and subsequent smoke inhalation injury. Inhalation and skin absorption are the most common routes of exposure at meth labs. Corrosive chemicals and solvents, along with hydrogen cyanide and phosphine gases, have been found at these sites and can lead to respiratory and systemic toxicity [36, 38]. Phosphine gas inhalation can result in pulmonary edema and fatal respiratory consequences [36, 39, 40]. Ammonia inhalation can cause throat irritation, dyspnea, chest pain, and pulmonary edema. Inhalation of acids, bases, and solvents can cause pneumonitis. Inhalation of iodine causes mucus membrane irritation.

Symptoms of Presentation

Pulmonary symptoms are prevalent and diverse in those who inhale substances of abuse. These include wheezes, cough, hemoptysis, black (carbonaceous) sputum, chest pain, and shortness of breath. The carbonaceous secretions might be noticed upon sputum analysis or bronchoscopy but not necessarily by the patient [41]. The nonspecific nature of respiratory symptoms may be related to the diverse location and process of pulmonary pathology related to both cocaine and amphetamine. For instance, alveolar, bronchiolar, bronchial, interstitial, and vascular involvements have all been demonstrated histologically in users of crack cocaine [42, 43].

An earlier study of 137 cocaine-related emergency department visits found the chief presenting complaint to be chest pain in 15.3 % and dyspnea in 4.4 % of the patients, whereas the majority of patients presented with neuropsychiatric complaints [44]. Similar rates were reflected by another study [45]. Chest pain in particular could be a manifestation of toxic effects on the respiratory system, cardiovascular system, or an interaction between the two. For example, in addition to the direct vasoconstriction effect on coronary arteries, crack cocaine has been associated with higher carboxyhemoglobin (COHb) levels that may further decrease coronary artery oxygen delivery and, thus, presentation of acute chest pain (see the “[Metabolic and Acid–Base Disorders](#)” section).

Respiratory symptoms can present acutely or chronically. A Canadian study of 20 crack cocaine users revealed that 95 % reported at least one respiratory symptom in the past

week and that 68 % reported an improvement in their symptoms during the time of abstinence [46]. The clinical improvement was noticed as early as 1 day and as late as 3 months [46].

In a questionnaire study of 192 cocaine smokers admitted to the West Los Angeles Veterans Affairs Medical Center inpatient drug abuse treatment program and from participants in non-VA outpatient chemical dependency programs, the prevalence of acute cardiorespiratory symptoms was high [47]. Within 12 h of usage, 44 % of them experienced coughing of black sputum, 39 % experienced chest pain, and 5.7 % experienced hemoptysis. Of the smokers experiencing acute chest pain, 64 % reported a pleuritic nature, and one in six reported acute chest pain with >50 % frequency after smoking [47].

No recent studies documenting the rates of specific respiratory symptoms are available for inhaled ATS. However, our informal experience reflects that crack cocaine smokers are more likely to have respiratory complaints than are ice methamphetamine smokers. Both chest pain (9 %) and dyspnea (1 %) were reported as the major presenting symptoms to an emergency department in amphetamine toxic patients [48]. An estimated frequency of the toxic pulmonary effects related to the two major classes of stimulants is offered in Table 1, and proposed mechanisms are summarized in Table 2.

Upper Respiratory Tract Effects

Various upper airway complications have been reported with cocaine use. Alterations in sensory perception of smell, epistaxis, mucosal irritation, persistent sniffing, and sinus-related problems are consistently reported in cocaine users [49, 50]. Total nasal septal bony and cartilaginous vascular necrosis with subsequent saddle nose deformity and osteolytic sinusitis has been described in chronic cocaine snorters [51]. Other complications include epistaxis, anosmia, oropharyngeal necrosis, stomatitis, and palatal necrosis [52].

Because the nasal septum is particularly sensitive to the vasoconstrictor effects of cocaine and probably the amphetamines, nasal septal ulceration and perforation is not uncommon [53]. In the last decade, there has been a surge of interest in cocaine-induced midline destructive lesions (CIMDL), such as nasal septal perforation, in relationship to an autoimmune pathophysiology [54]. CIMDL can present as nasal obstruction, epistaxis, and/or facial pain; furthermore, depending on the extent of necrosis, patients may have dysphagia and nasal reflux from soft and hard palate perforations. Positive antineutrophil cytoplasmic antibody (ANCA) directed towards human neutrophil elastase (HNE) was found in a disproportionately large number of patients with CIMDL, as high as 84 % in a study, suggesting that CIMDL may be a result of necrotizing inflammation triggered by cocaine in a subset of patients with ANCA positivity [55].

Table 1 Respiratory complications associated with cocaine (C) and Amphetamine-type stimulants (A)

Complication	C	A
Barotrauma	+++	++
Pneumothorax		
Pneumopericardium		
Pneumomediastinum		
Pulmonary hypertension	+++	+++
Pulmonary hemorrhage/infarction	++	?
Diffuse alveolar hemorrhage	+	?
Chronic diffuse interstitial disease with fibrosis	+	?
Central nervous system effects	++	+
Respiratory depression		
Neurogenic pulmonary edema		
Postictal respiratory depression		
Abnormal neonatal hypoxic response		
Sudden infant death		
Bronchiolitis obliterans organizing pneumonia (BOOP)	+	?
Alveolar accumulation of carbonaceous material	++	+
Pleuritic chest pain	+++	+
Asthma exacerbation	++	?
Pulmonary edema	++	++
Noncardiogenic		
Cardiogenic		
Eosinophilic lung	++	?
Transient pulmonary infiltrates with peripheral eosinophilia	++	?
“Crack lung”, transient pulmonary infiltrates	++	?
Nasal septum perforation	++	?
Sinusitis	++	?
Epiglottitis	+	?
Bronchitis	+	+
Pulmonary granulomatosis	+	+
Cellulose granulomatosis of lung	+	+
Panlobular emphysema	?	+
Airway burn/tracheal stenosis	++	+

Adopted and modified with permission from reference [211]

+++ frequently seen or many case reports, ++ commonly reported, + reported as rare case, ? unknown

Although patients with CIMDL present with upper respiratory tract symptoms that could be clinically indistinguishable from those of granulomatosis with polyangiitis (GPA), which was formerly known as Wegner’s granulomatosis [56], CIMDL patients do not usually present with systemic symptoms of fever, malaise, arthralgia, or myalgia. Because of the lack of consistent histopathologic distinction, nasal biopsies are not a reliable way to discern GPA from CIMDL. However, almost all CIMDL patients have ANCA directed to HNE, in stark contrast to the reported prevalence of HNE-ANCA in only 0–20 % of those with GPA. The HNE-ANCA found in CIMDL has a perinuclear fluorescence pattern (p-ANCA), whereas GPA is associated mostly with ANCA with

Table 2 Proposed mechanisms of respiratory complications related to stimulant abuse

Syndrome	Proposed pathogenesis
Bronchospasm	Airway mucosal irritation
Hemoptysis	Mucosal ulceration
	Mucosal burn
	Bronchitis
	Pulmonary infarction
	Diffuse alveolar capillary injury
Cardiogenic pulmonary edema	Acute and chronic cardiomyopathy
	Myocardial ischemia
	Hypertensive crisis
	Diastolic dysfunction
	Arrhythmias
Noncardiogenic pulmonary edema	Alveolar epithelial and endothelial damage
	Sustained seizure activity
Pneumonia	Comorbidities, e.g., HIV and cirrhosis
	Impaired nitric oxide production by alveolar macrophages
	Impaired macrophage function in the presence of high pulmonary iron accumulation
	Agranulocytosis due to levamisole
	Positive pressure from “shotgunning”
Pulmonary septic embolism	Embolization of heart valve vegetations, foreign bodies, and infected thrombi
Granulomatous reaction and fibrosis	Immune reaction to foreign bodies from IV injection of crushed tablets
Pneumothorax and pneumomediastinum	Rupture of preexisting emphysematous blebs
	Cavitating septic emboli
	Violent coughing
	Deep inhalation followed by Valsalva maneuver and pursed lip exhalation
	Positive pressure from “shotgunning”
	Attempted vascular cannulation with “pocket shots” into the supraclavicular fossa
Hypersensitivity pneumonitis	Immunologic response to inhaled antigen
Ventilation–perfusion mismatch	Vasospasm

Modified from reference [165]

cytoplasmic pattern (c-ANCA) directed against proteinase 3 (PR3) targeting [55]. An important caveat is that about half of CIMDL patients may have coexisting PR3-ANCA as well. Although the p-ANCA found in CIMDL differs from that found in microscopic polyangiitis, the p-ANCA of the latter reacts mostly with myeloperoxidase but not to HNE. In short, patients with upper respiratory tract necrosis should undergo specific characterization of serum ANCA to help distinguish etiology, especially since CIMDL does not respond well to immunosuppressive therapy. Treatment is essentially based on cessation of cocaine with debridement

of necrotic tissues and administration of antibiotics if needed [57]. However, cessation of cocaine may be especially difficult for patients whose upper airway pain is alleviated by cocaine's topical analgesic effect, as seen in a patient with cocaine-induced oronasal fistulae whose cocaine cessation was associated with severe palatal discomfort [52]. Additional upper airway complications from both nasal application and smoking stimulants include bronchitis, epiglottitis, and sinusitis [58, 59]. Furthermore, complicated osteolytic sinusitis with optic nerve involvement has also been reported [60].

Frequent alterations in the gingivae and increased dental caries have been noted with routine and heavy cocaine use [61]. Hoarseness from smoking cocaine and vocal cord paralysis from neck injections of intravenous drugs, including cocaine, have been reported [51, 62]. Furthermore, development of bilateral laryngeal saccular cysts in a cocaine user who suffered acute airway obstruction and subsequently needed emergent tracheotomy has been described, highlighting the importance of endoscopic evaluation of cocaine users presenting with signs of laryngeal obstruction [63]. Cocaine has also been shown to directly inhibit the ability of tracheal submucosal glands to transport chloride ion secretion and fluid in a swine model, suggesting decreased respiratory tract mucus clearance function of cocaine abusers [64].

Methamphetamine abuse has been widely associated with severe dental caries known as “meth mouth” that present as black, rotting, and crumbling teeth in the characteristic buccal and anterior distribution. The underlying causes include poor oral hygiene, frequent craving of refined carbohydrates, increased oral cavity acidity, bruxism, severe xerostomia, as well as gastroesophageal regurgitation and emesis [65]. Among them, methamphetamine-induced xerostomia has received significant attention as an important cause of decay. It has been hypothesized to be due to central stimulation of alpha-2 receptors and resultant hyposalivation [66]. Although there is no direct study correlating methamphetamine-associated dental disease to respiratory diseases, there is evidence associating poor oral and dental health in general to lower respiratory infections, likely via aspiration events [67]. Laryngeal polyposis, laryngeal edema, and epithelial hyperplasia have been described in a 37-year-old male who suffered from sudden airway obstruction, but it was unclear whether the glottis pathology was linked to his chronic tobacco smoking or cocaine abuse [68].

Barotrauma-Related Injuries

Pneumomediastinum, Pneumothorax, and Pneumopericardium

Barotrauma and subsequent pulmonary consequences such as pneumomediastinum, pneumopericardium, and pneumothorax have been associated with cocaine, amphetamine, and

MDMA (“ecstasy”) usage in case reports [51, 69–75]. There have also been instances of MDMA-related epidural pneumatosis and retropharyngeal emphysema [76, 77]. Disruption of the alveolar structures allows air to dissect up fascial planes from these alveolar sources along a pulmonary vascular sheath into the mediastinum, pericardium, neck, or between the visceral and parietal surfaces of the lung, creating a pneumothorax. In a study of three university hospitals over a 6-year period, 17 adult cases of spontaneous pneumomediastinum were found. The presenting symptoms included chest pain in 47 %, dyspnea in 18 %, and throat discomfort in 18 % of these patients. Hamman’s sign or a pericardial crunch was heard in 52 % of these patients. Subcutaneous emphysema was found in 65 %, and a small pneumothorax was found in 11 % of these patients. Illicit inhalation of smoked drugs of abuse, including marijuana, cocaine, and phencyclidine, was reported in 76 % of these patients and 70 % had a history of using Valsalva maneuvers while smoking recreational drugs [78] (see Fig. 2a–c).

A review of 56 cases of MDMA-related pneumomediastinum between 1999 and 2004 concluded that the mechanism of barotrauma is mostly due to Valsalva maneuvers during periods of extreme physical exertion, such as “rave” parties that often last >24 h and typically involve ecstasy [79]. Likewise, a case of pneumomediastinum associated with MDMA abuse was thought to be related to ingestion of the ATS followed by several hours of sexual intercourse [80].

Crack cocaine and ice methamphetamine users aggressively inhale against a small pipe and have violent coughing episodes. In addition, they frequently and repeatedly smoke the stimulant to increase the intensity of euphoria. They often inhale deeply and perform a Valsalva maneuver prior to exhaling against pursed lips [81–83]. Although repetitive Valsalva maneuvers adopted by stimulant abusers in attempts to enhance the effects of their experience have been speculated to underlie the pathogenesis of barotrauma [71, 78], other causes of pneumomediastinum and pneumothoraces are possible. Perna and colleagues examined 47 cases and noted that consumption of cocaine coincided a few hours before the presentation of pneumomediastinum-related respiratory symptoms in 26 (55 %) of these cases [84]; the majority of these 26 patients (18 patients) had CT of the thorax that reveal signs of direct cocaine toxicity on the pulmonary parenchyma, such as multiple nodules, ground glass opacities, and smooth thickening of interlobular septa [84].

Furthermore, pneumothoraces in drug abusers can also be secondary to direct puncture of the mediastinum and chest structures when drug abusers with poor peripheral venous access attempt supraclavicular central venous access by performing “pocket shots” into the jugular or subclavian veins [85]. In addition, the practice of partner-aided mouth-to-mouth administration of inhaled substances of abuse (known as “shotgunning”)

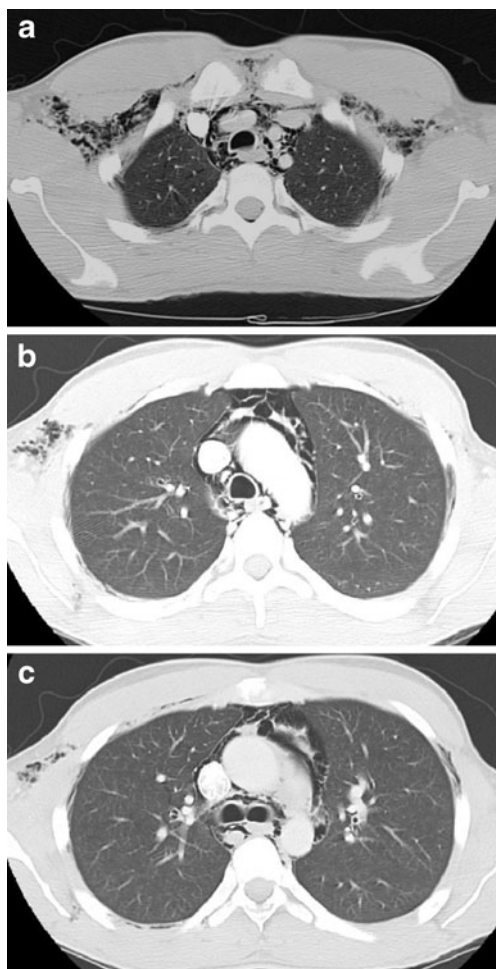


Fig. 2 Pneumomediastinum and subcutaneous emphysema in patient with methamphetamine abuse (courtesy of Dr. Elizabeth Moore, Department of Radiology, UC Davis Medical Center)

can precipitate barotrauma, likely from uncontrolled high-positive airway pressures, as demonstrated by one case of pneumomediastinum and another case of combined pneumothorax and pneumomediastinum [86, 87]. Statistically significant risk factors associated with “shotgunning” include age ≤ 35 , White race, crack cocaine use, alcohol intoxication, and high-risk sex; among them, crack cocaine has the highest odds ratio of 6.0 (95 % confidence interval of 3.0–12) [88].

The treatment of spontaneous pneumomediastinum is mostly supportive [78, 89]. However, Perna’s recent case series demonstrated that life-threatening outcomes may occur and require invasive modalities of treatment such as thoracotomy [85]. Pneumomediastinum cases associated with stimulant usage should be assessed carefully in the acute setting, and those demonstrating concerning clinical and radiographic changes should be considered for timely bronchoscopic evaluation to rule out airway injuries needing surgical intervention.

Effects on Asthma, Reactive Airway Disease, and Lung Function

Several case reports have suggested airway alterations consistent with asthma-like signs and symptoms after smoking “freebase” cocaine. Severe attacks of reversible airway disease in asthmatics or evidence of bronchospasm triggered by cocaine in nonasthmatics has been reported [90]. A series of six hospitalized patients ranging from 27 to 38 years of age was described by Rubin and Neugarten with severe or life-threatening exacerbations of asthma provoked by cocaine use, whose symptoms responded to standard bronchodilator and steroid therapy. However, three patients required intubation and mechanical ventilation [91]. As demonstrated by endobronchial biopsies, airway mucosal alterations in cocaine smokers include basal cell hyperplasia, stratification, and squamous cell metaplasia [92] (see Fig. 3).

Whether cocaine directly causes bronchoconstriction has been somewhat controversial. The relationship between stimulants and asthma may only be that of local airway irritation or it could be more direct in the pathophysiology of asthma. A crossover study involving measuring the specific airway conductance (SGaw) of 14 healthy, nonasthmatic current crack-smoking subjects between 24 and 48 years of age demonstrated that smoked cocaine base, but importantly not intravenous cocaine, led to acute bronchoconstriction with an onset within 3 min and a duration of at least 15 min [93]. A retrospective chart review of 166 adults admitted to an inner-city hospital with discharge diagnosis of “acute asthma exacerbation” demonstrated a 27.6 % prevalence of cocaine abuse [94]. Several studies have attempted to examine the effects of stimulants of abuse on lung function. These studies have been handicapped by their small size and by difficulties in controlling for simultaneous tobacco, marijuana, and other recreational drug abuse use in this patient population. The time after the last exposure to the stimulant is another potentially important variable that has been poorly controlled for in most of the current studies. While studying the relationship between chronic cocaine exposure and diffusing capacity (DL_{CO}), Kleerup and colleagues noted that, although a definitive relationship exists between regular tobacco smoking and decreased DL_{CO} , neither chronic nor acute exposure to cocaine inhalation significantly affected DL_{CO} [95].

When crack cocaine is heated, a significant amount of its product via pyrolysis, methylecgonidine (MEG), is produced. It has been shown *in vivo* that condensation aerosols of MEG base induce bronchoconstriction in a guinea pig model, as measured by specific airway conductance [96]. A follow-up study by another group of researchers, however, demonstrated *in vitro* in a guinea pig model that MEG actually antagonizes bronchoconstricting agents and produces airway smooth muscle relaxation instead [97].

Little has been published on the spirometric effects of the abuse of amphetamine, including the smoking of



Fig. 3 Airway inflammation, seen as peribronchovascular cuffing, in a cocaine abuser who presented with hemoptysis (courtesy of Dr. Elizabeth Moore, Department of Radiology, UC Davis Medical Center)

methamphetamine. Recent studies on a rat model of asthma by Oliveira and colleagues suggest that amphetamine decreases airway hyper-responsiveness [98, 99]. In 2011, they published an experiment demonstrating that, when allergic rats treated with a single dose of amphetamine at 1 mg/kg are subsequently challenged with ovalbumin 12 h later, there are signs of less intense pulmonary inflammation. Specifically, there were significant decreases in the number of leukocytes recovered in the bronchoalveolar lavage (BAL), decrease in cellular expression of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and macrophage-1 antigen (Mac-1), decrease in interleukin-4 production, decrease in pulmonary vascular permeability, and decrease in *in vitro* tracheal reactivity to methacholine—suggesting decreased airway hyper-responsiveness through immunomodulation [99]. In 2012, Oliveira and colleagues followed up with an experiment evaluating the effects of long-term (21-day) amphetamine on rat airways. They found that numerous inflammatory markers were increased, such as increased cellular expression of ICAM-1 and Mac-1; however, amphetamine-treated rat tracheal tissues still manifested decreased hyper-responsiveness to methacholine [98].

Amphetamine analogs like MDMA (ecstasy) appear to have unclear effects on airway reactivity. One asthma-related death has been reported with MDMA use [100], but an animal study by Stankevicius in 2012 demonstrated that MDMA actually decreased airway inflammation [101]. The role of contaminants in stimulants and their effects on lung function are difficult to study and to date have not been published.

Pulmonary Edema

Patients with cocaine toxicity often present with hypoxemia and respiratory failure. The chest radiographs demonstrate

classic diffuse pulmonary edema with perihilar, interstitial, and alveolar infiltrates, which resolve in survivors by 24 to 72 h [102]. Although numerous reports associated acute pulmonary edema to both acute and chronic uses of stimulants, no singular mechanism was isolated [103]. There has been evidence supportive of both cardiogenic and noncardiogenic pathology of stimulant-related pulmonary edema. Noncardiogenic acute pulmonary edema has been reported with intravenous, freebase smoking, passive or second-hand smoking, and nasal snorting of cocaine or amphetamine [104–108] (see Figs. 4 and 5).

Proposed mechanisms for stimulant-induced noncardiogenic pulmonary edema center on direct local cellular toxic effects, microvascular and endothelial effects, and the previously mentioned epithelial effects [109]. In a guinea pig model, Willets and colleagues noted that the lung lavage fluid of animals exposed to aerosols of MEG base, a major pyrolysis product of cocaine, contained blood, higher levels of protein, and higher levels of lactate dehydrogenase, supporting the theory of alveolar epithelial and endothelial damage in cocaine users [110]. However, Tashkin and colleagues have concluded from measurements of lung clearance of ^{99m}Tc -labeled diethylenetriamine pentaacetate in cocaine smokers that habitual smoking of cocaine has no effect on alveolar permeability and that alveolar epithelial permeability is more strongly associated with tobacco toxicity instead [111]. On the other hand, autopsy reports of patients dying from cocaine or amphetamine have noted pulmonary edema with simultaneous evidence of alveolar hemorrhage [112].

Potential cardiogenic causes of pulmonary edema associated with stimulants include acute and chronic cardiomyopathy. Wijetunga and colleagues retrospectively evaluated 1,640 patients admitted with diagnosis of cardiomyopathy and found 21 patients with methamphetamine abuse; among them, 19 (84 %) had echocardiographic findings consistent with dilated cardiomyopathy and ventricular dysfunction, and of the 6 patient who underwent cardiac catheterization, only 1 had evidence of coronary occlusion [113]. A relatively recent review of methamphetamine's cardiotoxicity by Kaye and colleagues pointed out that, although methamphetamine has been shown to have cardiotoxic effects in animals [114], the clinical importance of such effects in humans is unclear because of the difficulty in controlling for catecholamine levels in human subjects [115]. Similarly, cocaine and its metabolite in the presence of ethanol, cocaethylene, have been shown to lead to myocardial dysfunction (see the succeeding sections). Neurogenic pulmonary edema caused by sustained seizure activity can also be postulated as an indirect mechanism of noncardiogenic pulmonary edema [116, 117].

Since both cocaine and ATS, including ecstasy, could result in both cardiogenic and noncardiogenic pulmonary edema, efficient echocardiographic evaluation may be useful in guiding treatment. Whereas pulmonary edema related to acute heart failure may be treated with diuretics, inotropic

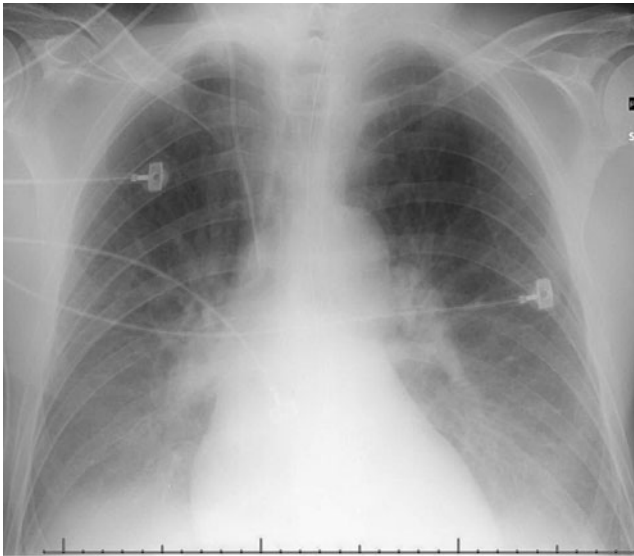


Fig. 4 Acute pulmonary edema in a patient suffering from cocaine intoxication (courtesy of Dr. Elizabeth Moore, Department of Radiology, UC Davis Medical Center)

agents, ventilation, and in severe cases intra-aortic balloon pump, noncardiogenic pulmonary edema is mostly treated supportively with ventilation alone [118].

Alveolar and Interstitial Diseases

Cocaine-induced pulmonary toxicity is common. In a study of 52 patients at autopsy that had positive toxicological findings for cocaine, interstitial pneumonitis and fibrosis was found in 38 % of them ($p \leq 0.01$) [112]. A variety of alveolar and interstitial processes have been associated with

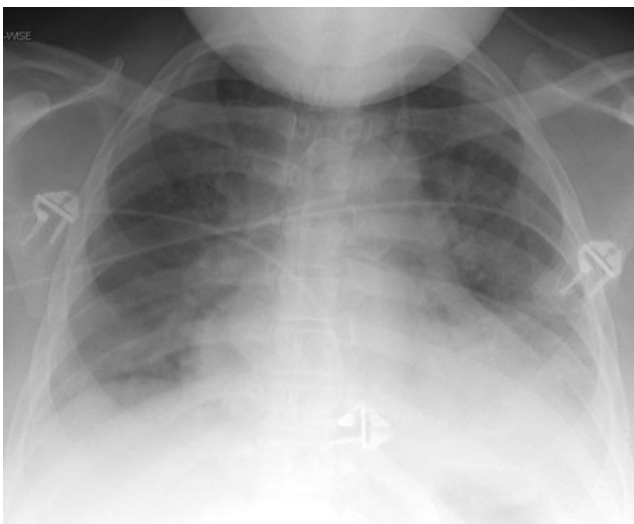


Fig. 5 Acute pulmonary edema in another patient suffering from cocaine intoxication (courtesy of Dr. Elizabeth Moore, Department of Radiology, UC Davis Medical Center)

stimulant abuse. The term “crack lung” has been used to define a syndrome associated with diffuse alveolar infiltrates without effusions, which occurs usually within 1–48 h after heavy cocaine smoking. In addition to the infiltrates, fever, hypoxemia, hemoptysis, pulmonary and peripheral eosinophilia, and IgE deposition in both lymphocytes and alveolar macrophages from lung biopsy specimens have been reported. Whether this syndrome progresses or resolves spontaneously and whether the alveolar process responds to immunosuppressive therapy are not clear [119, 120].

It is often challenging, if not impossible, to discern based on radiography alone whether the alveolar and interstitial infiltrates seen in a stimulant user with respiratory distress are related to a purely inflammatory process to the inhaled substances, a lower respiratory tract infection secondary to aspiration, a diffuse alveolar bleeding process (which often occurs subclinically in crack cocaine users according to Baldwin’s study) [121], cardiogenic pulmonary edema, or noncardiogenic pulmonary edema. Since cocaine abuse has been linked to all of these alveolar processes, the pathogenesis of “crack lung” is poorly defined. The radiographic location of the alveolar infiltrates has been described in all lung zones and varies from predominantly interstitial and perihilar opacities to predominantly alveolar and more peripheral opacities [122]. The nonspecific radiographic finding can be especially difficult to investigate in the setting of comorbidities, and this point is illustrated by a report of “crack lung” in a patient with non-Hodgkin lymphoma [123]. A variety of radiographic findings are listed in Table 3.

Eosinophilia has been reported as a sign of stimulant pneumotoxicity. In one case, a patient had both serum and BAL fluid with eosinophilia on two different occasions after inhaling crack cocaine, and a transbronchial biopsy demonstrated normal lung parenchyma with dense eosinophilic infiltrates in the bronchial wall. Treatment included corticosteroids with rapid improvement [124]. A similar case of migratory pulmonary infiltrates with marked serum eosinophilia and increased IgE levels in a heavy smoker of cocaine has been labeled Löffler’s syndrome [125]. It is unclear whether these cases represent a specific unique “crack lung” syndrome, a crack-induced Löffler’s syndrome, or simply variants of the acute pulmonary edema. As in all of these cases, it is unclear whether the burning of crack cocaine or that of its contaminants is the actual cause.

At least two cases of open lung biopsy-proven bronchiolitis obliterans with organizing pneumonia (BOOP) associated with smoking crack cocaine have been reported [102, 126]. Nonproductive cough and dyspnea were seen in both cases. One patient had fever and appeared to respond to corticosteroids without residual pulmonary symptoms [126]. The other patient was pregnant and progressed to respiratory failure and acute respiratory distress syndrome. She did not respond to

Table 3 Variety of radiographic features associated with cocaine abuse

Pneumothorax, pneumomediastinum, and pneumopericardium
Central bilateral alveolar infiltrates (e.g., cardiogenic edema, noncardiogenic edema)
Peripheral bilateral interstitial and alveolar infiltrates (e.g., pulmonary eosinophilia)
Focal pneumonitis and consolidation (e.g., aspiration, infection)
Multinodular opacities in vascular distribution (e.g., pulmonary septic embolism)
Foreign bodies
Interstitial opacities with diffuse multinodular pattern and areas of nodular coalescence into peribronchovascular conglomerate (e.g., talc granulomatosis)
Bilateral reticular opacities
“Crazy paving pattern”
Scattered ground glass opacities
Parahilar masses (e.g., silicotuberculosis)
Atelectasis
Peribronchial opacities (e.g., airway inflammation)
Upper lobe predominant emphysema
Prominent pulmonary vasculature (i.e., pulmonary hypertension)

corticosteroids and died on the 48th hospital day [102]. The rarity of these reports in view of the large number of regular crack cocaine users and the large number of irritant gases known to be capable of producing BOOP also makes proving a causative relationship between crack cocaine smoking and BOOP difficult [127].

Most chronic cocaine users do not suffer from alveolar or interstitial lung disease, and such differing susceptibilities may be due to genetic polymorphism. Wijnen and colleagues genotyped two patients who developed interstitial infiltrates after cocaine abuse and were able to associate their pulmonary susceptibility to cocaine toxicity to cytochrome P450 (CYP2C9 and CYP2C19) and vitamin K epoxide reductase complex 1 allelic variants of metabolic enzymes [128].

Co-inhalation of other compounds, such as impurities, often complicates investigating suspected pneumotoxicity from stimulant abuse. A report described three cases of “crack lung” that occurred after the three patients smoked cocaine from the same batch, with all of them demonstrating distinct perihilar and lower-zone interstitial infiltrates that resolved in 48 h. Since the crack cocaine came from the same source in these cases, adulterants introduced in the manufacturing process instead of the cocaine itself may have been responsible for causing the pulmonary infiltrates [129]. Similarly, exogenous lipoid pneumonia, which is typically associated with inhalation of lipid-laden material, was described recently in a patient who smoked crack cocaine that he deliberately mixed with petroleum jelly to conserve the quantity of cocaine for longer duration of usage [130].

Foreign Body Injury and Thermal Injury

Large amounts of particulate, smoke, and superheated gases are inhaled along with either crack cocaine or ice methamphetamine, causing a variety of thermal injury and inflammatory responses. Injurious foreign bodies include aspiration of the substance of abuse itself, the accompanying filler materials such as talc and starch, as well as the equipment used in administering the substance [131]. Thermal epiglottitis and thermal laryngopharyngeal injuries have been reported in numerous cases [132–134].

It is important to note that microscopic foreign body deposition can occur via both inhalation as well as intravenous injection. Intravenous injection of ground tablets of various illicit drugs, including amphetamines, has also been associated with pulmonary vascular granulomatosis, which can consequently develop into interstitial fibrosis and severe pulmonary hypertension [135, 136]. In one of the cases involving intravenously injected pulverized amphetamine tablets, high-dose prednisolone was given for the patient’s pulmonary granulomatosis and pulmonary hypertension, but there was no improvement in patient’s DL_{CO}, vital capacity, or respiratory symptoms [136]. Embolization of hypodermic needles or needle fragments has also been documented [137–139].

Incomplete burnt impurities may contribute to foreign substance deposition in the airways. As demonstrated in the case of a crack cocaine user who presented with cough and pulmonary infiltrates and was later found to have large amounts of carbonaceous materials and pigment-laden macrophages on his BAL, particulate matters from smoking substances of abuse can easily reach deep into the alveoli [41]. This may have resulted in observation of turbid gray or black BAL in cocaine smokers [140]. Extracellular carbonaceous materials can be seen in the BAL of these cocaine smokers, which is not observed with cigarette smoking according to a study by Greenebaum and colleagues [140]. Singh and colleagues even reported carbon-laden macrophages in the pleural fluid from two crack cocaine smokers [141].

The extent of pneumoconiosis-like fibrosis can be severe. A crack cocaine smoker who developed fatal pulmonary fibrosis that was refractory to treatment with high-dose corticosteroids and cyclophosphamide was found on lung biopsy to have numerous silica-laden macrophages in the pulmonary interstitium, primarily around vessels and airways [142]. As demonstrated in these cases, freebase cocaine may still be adulterated with insoluble substances like silica in the manufacturing and distribution processes. Cocaine sniffing has been associated with reports of cellulose and talc pulmonary granulomatosis as well [143, 144]. Diagnostically, the particle size of the foreign body on pulmonary biopsy specimen may provide histologic guidance in determining the route of foreign body deposition: a mean particle size of 3.7 µm was found in six cases of inhalation talcosis compared to a mean

size of 14.2 g in five cases of injection talcosis [145]. Figure 6 demonstrates possible granulomatosis in a patient with methamphetamine abuse.

The spectrum of foreign bodies causing respiratory tract injuries is diverse. Ludwig and colleagues introduced a case of upper airway burn from aspiration of a wire mesh screen used in smoking crack cocaine [146]. Aspiration of the crack pipe itself has also been reported [147]. Zaas and colleagues described a patient with an initial diagnosis of severe persistent asthma who actually suffered from tracheal obstruction by a large piece of crack cocaine after attempting to swallow a plastic bag containing the substance to avoid arrest [148]. Hypodermic needle aspiration and even necrotic nasal septum aspiration have also been reported with cocaine use [149, 150].

A case of crack cocaine-associated severe thermal injury to the conducting airways was thought to be due to either inhalation of heated gases or from airway ignition of the volatile solvents (e.g., ether) used in forming crack cocaine; the patient eventually developed tracheal stenosis that required tracheal reconstructive surgery [151]. The local anesthetic effects of crack cocaine may predispose to deep inhalation of foreign bodies and encourage airway thermal injuries.

Thermal injuries from methamphetamine manufacturing laboratories appear to result in greater mortality. Warner and colleagues found that burn patients under the influence of methamphetamine, such as those from meth labs, require twofold to threefold more volume of fluid resuscitation than that estimated by the Parkland formula [152]. In their series, methamphetamine-related burn patients with total body surface area >40 % had 100 % mortality, significantly higher than other burn patients. The authors suggested that the increased mortality may be a consequence of both inhaled chemical injury as well as direct methamphetamine toxicity [152].



Fig. 6 Innumerable, ill-defined pulmonary nodules with random distribution in a methamphetamine abuser. Diagnostic considerations include foreign body granulomatosis and granulomatous infections (courtesy of Dr. Elizabeth Moore, Department of Radiology, UC Davis Medical Center)

Hemoptysis and Alveolar Hemorrhage

Diffuse pulmonary alveolar hemorrhage with and more commonly without pulmonary infarction have been frequently seen with cocaine use [153, 154]. Most of the bleeding appears to occur asymptotically at the alveolar level. Baldwin and colleagues demonstrated that crack cocaine users without any clinical signs of hemoptysis or spirometric abnormality could have markedly elevated the percentage of hemosiderin-positive alveolar macrophages in their BAL, around 34 % of total cells, compared to <2 % in tobacco smokers or nonsmokers ($p < 0.05$). This remarkably elevated surrogate marker of alveolar bleeding suggests the likely high prevalence of chronic subclinical alveolar hemorrhage in crack cocaine users. The percentage of hemosiderin-laden macrophages also correlated somewhat with the level of endothelin-1 ($r = 0.64$, $p < 0.05$). However, it was unclear whether this vasoconstrictor was released from the alveolar capillary endothelial cells in response to bleeding or as a contributor to microvascular damage [121]. A study by Janjua and colleagues discovered that alveolar macrophages in the BAL of crack cocaine users contained about 5 times more iron than nonsmokers (25 vs. 5.5, $p < 0.01$). Furthermore, there appeared to be an additive effect of alveolar iron accumulation in subjects who used both crack cocaine and tobacco [155]. Features of BAL in cocaine abusers are listed in Table 4.

In the previously mentioned autopsy study comparing those with positive toxicological tests for cocaine to age-matched controls, acute pulmonary hemorrhage was seen in 58 % ($p \leq 0.01$) and chronic pulmonary hemorrhage was seen in 40 % ($p \leq 0.01$) of the autopsies of cocaine users [112]. Herculiani demonstrated in a mouse model that 2 months of crack cocaine inhalation results in extensive alveolar hemorrhage, as reflected by increased alveolar hemosiderin content [156].

Diffuse alveolar hemorrhage similar to that seen in Goodpasture syndrome was associated with crack cocaine abuse in one case [157]. A report associated the use of crack cocaine smoking to pulmonary infarction [158]. Incubation of whole blood with cocaine has demonstrated cocaine-induced activation of platelets, a thrombotic process that could contribute to the development of pulmonary infarction, in addition to cocaine's well-known vasoconstrictive effect [159]. Although a common differential diagnosis for hemoptysis is pulmonary embolism, an important confounder is that inhalation of cocaine can cause severe pulmonary vascular flow changes to the extent that V/Q scan can demonstrate perfusion defects indistinguishable from that seen in pulmonary embolism [160].

Metabolic and Acid–Base Disorders

Pertinent to the body's oxygen demands and ventilatory responses, acid–base disturbances and metabolic alterations

Table 4 Bronchoscopic features of cocaine abuse

Turbid and gray or black bronchoalveolar lavage
Carbonaceous materials are noted in the extracellular compartment
Foreign bodies
Endobronchial biopsies demonstrating airway mucosal changes such as stratification, squamous cell metaplasia, basal cell hyperplasia, and basement membrane thickening
Thermal epiglottitis
Thermal laryngopharyngeal inflammation
Hemosiderin-laden and iron-laden macrophages

secondary to the systemic effects of stimulant abuse could affect the respiratory system. In a small series of seven patients, Kales and colleagues noticed higher COHb levels in those who presented with cocaine-related chest pain, suggesting COHb as a potential contributor to cocaine-induced cardiotoxicity. This mechanism is in addition to increased myocardial demand from tachycardia and hypertension [161].

In a study of 156 cocaine-associated emergency department visits, the majority of patients had normal arterial pH measurements. However, acidic pH measurements (6.4–7.4) were seen in 33 % of the patients, with metabolic causes being twice as common as respiratory ones. Alkalemia (pH >7.45) was observed in 15 % of the patients and was mostly respiratory in origin [162]. Respiratory alkalosis was disproportionately associated with shortness of breath in cocaine abusers [162, 163]. A case report by Burchell described unexplained metabolic acidosis in a trauma patient who used methamphetamine; however, their retrospective case–control study demonstrated no significant differences in blood pH, vital signs, and outcomes between meth users and nonusers [164].

CNS disturbance from seizures and strokes could also lead to hypoventilation and secondary respiratory acidosis. Hypercapnic respiratory failure and respiratory acidosis may result from aforementioned stimulant-induced bronchospasm as well. Another mechanism is that metabolic acidosis from stimulant overdose could lead to respiratory muscle fatigue and secondarily respiratory acidosis [165]. The metabolic and acid–base disorders associated with stimulant abuse can be varied in presentation, interlinked in pathophysiology, and significant in severity. The clinician should promptly recognize and treat accordingly.

Pulmonary Vascular Disease

Stimulants have been associated directly and indirectly with the development of pulmonary hypertension. As early as 40 years ago, intravenous users of amphetamine were reported to have pulmonary artery foreign body granulomas, pulmonary artery muscular hypertrophy, and pulmonary artery

fibrous intimal proliferation consistent with pulmonary artery hypertension; the elevated pulmonary artery pressures also correlated with reduction in DL_{CO} [136].

Inhalation of cocaine has been weakly associated with the development of pulmonary hypertension as well [166]. Perinatal cocaine intoxication has been associated with persistent pulmonary hypertension in a neonate [167]. In an animal model, the vasoconstriction index was shown to be increased in the pulmonary arteries of the mice exposed to crack cocaine inhalation for 2 months [156]. Recently, Dhillon and colleagues demonstrated in vitro that cocaine has an additive effect to human immunodeficiency virus (HIV) infection in the development of pulmonary arteriopathy with proliferation of pulmonary smooth muscle cells and worsening of endothelial dysfunction [168]. In contrast, a study by Kleerup and Tashkin demonstrated that acute intravenous cocaine in habitual crack cocaine smokers did not cause short-term increases in pulmonary artery pressure [169].

Levamisole, a very common adulterant in crack cocaine, has also been implicated in the development of idiopathic pulmonary arterial hypertension (iPAH). Last year, a brief review on the subject was done by Karch and colleagues [170]. Their laboratory recently demonstrated in humans that levamisole gets converted to aminorex, an anorexigen previously sold in Europe that has been strongly linked to pulmonary hypertension in the 1960s [171]. The extremely high prevalence of levamisole in crack cocaine may be the underlying cause of pulmonary hypertension in those cases. The importance of aminorex as a substrate for serotonin transporters is discussed below.

More recently, a retrospective study by Chin and colleagues demonstrated that, among 97 patients with a diagnosis of iPAH, 28.9 % had a history of stimulant use (amphetamine, methamphetamine, or cocaine). Patients with iPAH were >10 times ($p<0.0001$) more likely to have used stimulants than patients with PAH and known risk factors, and they were 7.6 times ($p<0.0001$) more likely to have used stimulants than patients with chronic thromboembolic pulmonary hypertension [172]. These rates of stimulant use in iPAH patients were similar to those of fenfluramine use [172]. Because cocaine use alone without ATS was rare in this study, much stronger association was made with methamphetamine. Short of a formal case–control study, this is the best evidence available so far linking methamphetamine to pulmonary vascular disease.

Pulmonary hypertension has been reported to occur at a higher rate than baseline with medicinal use of amphetamine-like stimulant anorectic drugs including fenfluramine and dexfenfluramine [173–175]. The use of these anorectic drugs increased the risk of pulmonary hypertension with an odds ratio of 6.3 and, if the agents were used for more than 3-months, the odds ratio increased to 23 [176]. In these patients, additional risk factors for pulmonary hypertension included a family history of pulmonary hypertension, HIV infection,

cirrhosis, the use of cocaine, or the use of intravenous drugs. Direct vasoconstrictive effects of dexfenfluramine on pulmonary arteries have been demonstrated [177].

A sole cause has not been isolated. Some hypothesized mechanisms include endothelial injury, vasoconstrictive effects of stimulants, vasculitis response, and dysregulation of mediators of vascular tone. A study of 20 patients whose deaths were associated with cocaine smoking found that 20 % of the lungs showed evidence of pulmonary artery hypertension with pulmonary artery medial hypertrophy without foreign particle microembolization [178].

There has been a surge of interest in serotonin (5-hydroxytryptamine) mediated iPAH in patients exposed to methamphetamine. Dysfunctional handling of serotonin by platelets was first suggested as responsible for elevated plasma serotonin levels found in patients with iPAH [179]. Subsequently, hypoxia was shown to induce serotonin transporter expression in pulmonary artery smooth muscle cells [180]. Rothman and colleagues have identified that medications known to increase the risk of iPAH such as fenfluramine and aminorex share the common trait of serving as potent substrates for serotonin transporters, in contrast to drugs that have not been shown to increase the risk of iPAH [181]. They subsequently demonstrated that methamphetamine and MDMA (“ecstasy”) also function in vivo as a serotonin transporter substrate [182].

Recently, Liu and colleagues noted that the expressions of serotonin transporter and serotonin_{1B} receptor were both increased in the lungs and the pulmonary arteries of rats exposed to methamphetamine. They also noted that fluoxetine, an antidepressant that functions by inhibiting serotonin transporter, decreased pulmonary arterial remodeling by downregulating the expressions of aforementioned proteins in rats’ exposure to methamphetamine, suggesting fluoxetine as a potential therapeutic agent in meth abusers with iPAH [183].

Lastly, although fat embolism into the pulmonary vasculature has been associated with heat exposure, a Japanese study investigating the link between pulmonary fat emboli and pyrogenic compounds such as methamphetamine yielded no significant correlation [184].

Central Nervous System Respiratory Effects

Stimulants are generally associated with increased respiratory drive, but severe overdoses of stimulants of abuse have resulted in respiratory depression [26, 185, 186]. Several animal models have suggested that postictal respiratory depression or, in the absence of seizures, a direct respiratory depression from stimulants is possible [187–189].

As cocaine rapidly transfers across the placenta to the fetus, infants born to mothers who used cocaine are at higher risk of neonatal respiratory impairments [190]. Prenatal

cocaine exposure has been correlated with abnormal respiratory patterns in both humans and in animal models, including decreased ventilatory response to hypoxia and hypercapnia [191–194]. In a more recent murine study, the impairment in ventilatory response occurs primarily in hypoxia but not as much in hypercapnia [195]. The effect of prenatal exposure to cocaine appears to be worse than that to opioids; a prospective study of 32 cocaine-exposed and 18 methadone-exposed infants demonstrated that 5 cocaine-exposed infants but no opioid exposed infants had apnea of infancy [196]. Respiratory suppression and exaggerated respiratory dysrhythmia may result from increased endogenous opioid system activation content in the brain stem secondary to cocaine exposure instead, as demonstrated in a piglet model by Zhang and Moss [197].

Infections and Immunological Effects

Although increased alveolar and bronchiolar macrophage cell density has been shown to be elevated in animals exposed to crack cocaine [156], it has been demonstrated that the alveolar macrophages of cocaine smokers suffer from impaired production of nitric oxide, a crucial mediator of the innate immunity of the human lung [198]. This process may contribute significantly to the observation that cocaine users suffer from an increase in pulmonary infections.

As Janjua and colleagues noted, cocaine smokers consistently have about five times higher levels of alveolar macrophage iron and ferritin levels, which was suspected to be due to subclinical alveolar hemorrhage [155]. Since iron has been demonstrated to impair alveolar macrophage function, such as cytokine expression [199], the significant pulmonary iron accumulation, no matter the etiology, may contribute to the higher frequency of respiratory infection in crack cocaine users. It is unclear whether the high alveolar macrophage iron content relates to impairment in nitric oxide production.

A recent in vitro study demonstrated that, at pharmacologically relevant levels, methamphetamine suppresses rather than enhances influenza A virus replication in human lung epithelial cells, without enhancing antiviral interferon responses [200]. Cocaine usage also has been affiliated with multiple presentations of immunological derangement, including systemic vasculitis affecting large and small vessels. Specific syndromes that have been associated with cocaine include urticarial vasculitis, midline granulomatous disease, Churg–Strauss vasculitis, and GPA [157, 201]. A case associating Goodpasture syndrome with crack cocaine inhalation was reported in Spain, describing a young man who presented with life-threatening acute respiratory distress from diffuse alveolar hemorrhage [202].

Multiple studies have linked immunological derangement to levamisole, a common adulterant found in as much as over

70–80 % of street cocaine. Although used mostly as a veterinary deworming medication, because of its immunomodulatory activities, levamisole has also been used as a therapeutic against certain malignancies and inflammatory diseases. Multiple reports in the English literature have associated levamisole-contaminated cocaine to agranulocytosis and a characteristic cutaneous vasculopathy [203–206]. Although routine urine toxicology does not detect levamisole, bioanalytical methods such as gas chromatography have been developed and used in the identification of this common cocaine contaminant. A recent review suggested that high-performance liquid chromatography is preferred over gas chromatography in the clinical quantification of levamisole [207].

Smoking stimulants has been associated with pulmonary bacterial infection. Crack cocaine usage was shown to be an important risk factor for early readmission in patients with acquired immunodeficiency syndrome (AIDS) and pneumonia [208]. Perlman and colleagues evaluated whether the practice of inhaling smoke and then exhaling actively into another individual's mouth ("shotgunning") is associated with higher incidence of tuberculous infection, but no correlation was found [88]. A recent retrospective cohort study in French Guiana, however, found that crack cocaine usage was associated with higher incidence of AIDS and that crack cocaine inhalation is associated with greater incidence of disseminated histoplasmosis (hazard ratio [HR], 3.8), *Pneumocystis jirovecii* infection (HR, 5.0), bacterial pneumonia (HR, 10.6), esophageal candidiasis (HR, 7.5), cerebral toxoplasmosis (HR, 7.5), salmonellosis (HR, 12.1), and pulmonary tuberculosis (HR, 2.5) in HIV-infected individuals [209].

Conclusion

Stimulant abuse has taken heavy tolls on global health and economy. Cocaine and ATS, including MDMA, have been demonstrated in the last 40 years to be associated with a multitude of direct and indirect toxic effects on practically every part of the respiratory system—from the nasopharynx and oropharynx to the gas-exchanging units and pulmonary vasculature. Significant injuries to the respiratory system can result from both inhaled and intravenous forms of the substances of abuse. There is a high prevalence of concomitant usage of different substances in the majority of drug-abusing patients, and assigning risk in the context of simultaneous exposures to multiple toxic agents, including tobacco, requires large and rigorously controlled studies, which to date have not been done for stimulants of abuse. In the meantime, health care providers must be aware of the host of respiratory toxidromes-associated stimulant abuse in order to provide timely diagnosis and efficacious treatment.

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