

# Stimulants and Pulmonary Arterial Hypertension: An Update

Ramon L. Ramirez III, MD

*Department of Medicine  
Stanford University School of Medicine  
Stanford, CA*

Vinicio De Jesus Perez, MD

*Division of Pulmonary and Critical Care  
Medicine  
Stanford University School of Medicine  
Vera Moulton Wall Center for Pulmonary  
Vascular Disease  
Stanford, CA*

Roham T. Zamanian, MD

*Division of Pulmonary and Critical Care  
Medicine  
Stanford University School of Medicine  
Vera Moulton Wall Center for Pulmonary  
Vascular Disease  
Stanford, CA*

The connection between stimulants and pulmonary arterial hypertension (PAH) was first made apparent in the 1960s during an outbreak associated with anorexigen (amphetamine-like appetite suppressants) use. Since then, a total of 16 drugs and toxins have been linked to PAH (ie, drug and toxin-associated PAH [DT-APAH]), including illicit stimulants like methamphetamine. Recently, basic science research and novel genomic studies have started to shed light on possible pathologic and genetic mechanisms implicated in disease development, namely loss of function variants in genes involved in drug detoxification. This review will discuss the history and current state of knowledge regarding stimulants and their association with PAH. It will also discuss clinical management of patients with DT-APAH. Lastly, it will highlight the importance of ongoing research efforts to identify susceptibility factors implicated in DT-APAH and the need for increased pharmacovigilance and awareness to identify new drugs that may be risk factors for PAH. Ultimately, this may be our best strategy to improve clinical outcomes and prevent deadly future outbreaks of DT-APAH.

Pulmonary arterial hypertension (PAH) is characterized by progressive dyspnea, right heart failure, and unless treated, premature death. Pathologically, it is defined by severe small vessel loss and obstructive vasculopathy, which causes elevated pulmonary artery pressures. Historically, the pathology of PAH was first reported by the German physician Romberg in 1891 in postmortem cadaver studies. In the following years, PAH remained a relatively uncommon “orphan” disease with only a few cases being reported on a yearly basis; however, all this would change in the 1960s when a surge of new cases of PAH were being reported in association with anorexigen (amphetamine-like appetite suppressants) use in Germany, Austria, and Switzerland.<sup>1</sup>

To date many different drugs and toxins have been identified as risk factors for PAH. These drugs and toxins are classified as “definite,” “likely,” and “possible” risk factors according to the strength of evidence linking them and PAH development<sup>2</sup>; of note, this classi-

fication will be updated as a result of the 2018 World Symposium on Pulmonary Hypertension in Nice, France. Among these drugs and toxins are stimulants such as anorexigens, methamphetamine, and cocaine. They also include chemotherapeutic agents such as dasatinib,<sup>3</sup> medical therapies such as interferon,<sup>4</sup> and even the widely available herbal supplement St. John's wort.<sup>2</sup> Recent studies have established certain stimulants as definite risk factors for PAH. We are also starting to slowly unravel the molecular mechanisms and genetic underpinnings implicated in disease development. This review will focus on highly prevalent stimulants and their association with PAH.

## STIMULANT EPIDEMIOLOGY/ CLINICAL SIGNIFICANCE

The effects of a growing (meth)amphetamine, cocaine, and MDMA abuse crisis have been felt on a global scale. In 2015, there were 37 million amphetamine and prescription stimulant users, 22 million ecstasy (MDMA) users, and 17 million

cocaine past-year users. A 2017 United Nations Office on Drugs and Crime (UNODC) report states that, after opioids, amphetamines are the second most abused drug in the world. Among the amphetamines, methamphetamine has become a formidable public health concern with an expanding market in East and Southeast Asia, where some reports indicate it may be the most commonly abused drug.<sup>5</sup> In 2015, people receiving treatment for methamphetamine use accounted for the largest share of people being treated for drug use in the majority of countries and territories in East and Southeast Asia. There is also evidence that methamphetamine use is increasing in other regions of the world, particularly Australia (Oceania).<sup>5</sup>

The global markets for cocaine and MDMA are smaller than for methamphetamine but still pose a significant threat. Following several years of decline, there are indications that the cocaine market is expanding worldwide, particularly in North America and Europe. The UNODC reports an increase in drug overdose cases involving cocaine in the United States between 2012 and 2015. The National Institutes of Health (NIH) Drug Abuse Warning Network

Key Words—drugs and toxins, pulmonary arterial hypertension, stimulants

Correspondence: Ramon.Ramirez@Stanford.edu

Disclosure: The authors have no relevant personal financial relationships to disclose.

(DAWN) report states that in 2011, cocaine was the most commonly involved illicit drug in emergency department visits.<sup>6</sup>

The European market for ecstasy seems to be expanding while use in the United States seems stable.<sup>5</sup> Ecstasy is now available in 3 major forms: tablets with little or no MDMA (and a high content of adulterants), tablets with an extremely high content of high-purity MDMA, and powder/crystal forms. Ecstasy tablets with high MDMA content are of particular concern in Europe, where law enforcement entities have discovered industrial-scale MDMA manufacturing facilities.<sup>5</sup>

## ANOREXIGENS

The first stimulant historically implicated in the development of PAH (which was referred to as primary pulmonary hypertension [PPH] before 1998)<sup>7</sup> was aminorex fumarate, an amphetamine derivate used in parts of Europe in the 1960s to promote weight loss. Aminorex works by suppressing appetite at the level of the central nervous system and by promoting catabolism of fat stores.<sup>8</sup> Only 2 years after its introduction on the market, reports began to surface of patients developing PAH at an alarming rate. The fact that 60% of the patients diagnosed with PAH had a history of aminorex use allowed physicians and scientists to establish a temporal relationship between aminorex and PAH. This form of drug-induced PAH carried a dismal prognosis, and 50% of patients had perished from right heart failure within 10 years of the start of the epidemic. These patients were found to have precapillary PH with typical plexiform arteriopathy on histological examination. These reports of PAH led to the withdrawal of aminorex in 1972, and a subsequent decrease in the number of new PAH cases reported.<sup>9</sup>

This tragic epidemic sparked interest in PAH and subsequently led to the first World Health Organization (WHO) conference in 1973 to discuss the current state of knowledge regarding pulmonary hypertension (PH), to develop nomenclature and a classification system, and to attempt to understand

this increasingly prevalent and largely fatal disease.<sup>10</sup>

Not long after the aminorex epidemic in Europe, another amphetamine derivate was introduced into the market for weight loss. Similar to aminorex, fenfluramine (which was marketed alone and often in combination with phentermine, in a compound known commonly as “fen-phen”) had serotonergic properties that mediated its weight loss effects. The first case of fenfluramine-associated PAH was reported in 1981.<sup>11</sup> Subsequently, in 1992, the International Primary Pulmonary Hypertension Study (IPPHS) found that the use of anorexic drugs, such as fenfluramine, was associated with an odds ratio of 6.3 of having PPH; the odds ratio was even higher if anorexic substances had been used for greater than 3 months.<sup>12</sup> In the years following this initial study, 2 more studies would confirm a strong association between fenfluramine and PAH.<sup>13,14</sup> During this time there was also evidence mounting that these drugs were associated with cardiac valvular lesions similar to those seen in carcinoid syndrome (a syndrome of serotonin excess). This association was presumed due to fenfluramine's increased serotonergic properties.<sup>15</sup> Fenfluramine was withdrawn from the market shortly after the publication of these reports due to its association with valvular heart disease.

Yet another amphetamine derivate appetite suppressant drug, benfluorex—which had a similar chemical structure to fenfluramine (both also share a common active metabolite)—was introduced in the market labeled as an antidiabetic and weight loss agent. Because it was primarily marketed as an antidiabetic medication, it was able to bypass the scrutiny associated with anorexigen drug use. Following the publication of several studies, benfluorex was finally established as a “definite” risk factor for PAH and also withdrawn from the market in Europe in 2009.<sup>16,17</sup>

## METHAMPHETAMINE

Methamphetamine stimulates the central nervous system by promoting the release of serotonin, dopamine, and norepinephrine.<sup>18</sup> This produces its desired effects, which include increased energy,

focus, euphoria, and decreased appetite. Methamphetamine has been associated with toxicity in multiple organ systems including cardiomyopathy, hypertension, cerebrovascular accidents, and psychosis.<sup>19</sup> Initial suspicion of an association between methamphetamine and PAH was first reported by Schaiberger et al in 1993. They published the case of a truck driver who was a long-term user of “crank” methamphetamine (crank is a common nickname for methamphetamine) who developed severe PAH. After an exhaustive diagnostic evaluation to identify an alternate cause, the authors concluded that the development of PAH was likely secondary to methamphetamine use. This association was reasonable given the similar chemical structure of methamphetamine and aminorex.<sup>20</sup> In 2006, Chin et al conducted the first known retrospective cohort study investigating methamphetamine use and the risk of PAH. They evaluated rates of stimulant use (stimulants were defined as methamphetamine, cocaine, or amphetamines) in 340 patients and found that a history of stimulant use was present in 28.9% of patients with a diagnosis of “idiopathic PAH” (IPAH) compared to only 3.8% of patients with a diagnosis of PAH and known risk factors and only 4.3% of patients with chronic thromboembolic pulmonary hypertension (CTEPH). Patients with IPAH were approximately 10 times more likely to have a history of stimulant use than patients with PAH and known risk factors, and almost 8 times more likely than patients with CTEPH, after adjustment for age. Not surprisingly, these ratios were similar to those found in studies of fenfluramine use. Interestingly, of the 3 stimulants studied in the cohort, methamphetamine was the most common stimulant used alone; cocaine was rarely used alone.<sup>21</sup>

In the first prospective cohort study looking at patients with methamphetamine-associated PAH (Meth-APAH), we recently published our findings comparing the clinical presentation, outcomes, and disease characteristics of patients with Meth-APAH—which was defined as PAH in the setting of significant (meth)amphetamine exposure, characterized as more than 3 episodes of

use reported per week for greater than 3 months or a positive urine toxicology screen—to those with IPAH.<sup>22</sup> We prospectively followed 90 Meth-APAH and 97 IPAH patients who presented to the Stanford Adult Pulmonary Hypertension program between 2003 and 2015. These patients underwent cardiac echocardiography, pulmonary function testing, chest imaging, and right heart catheterization. Lung pathology from autopsies of Meth-APAH patients showed characteristic vascular changes similar to those seen in IPAH, including plexiform angiomatoid lesions with slit-like vascular channels within the arterial lumen, as well as veno-occlusive disease. Interestingly, despite these common histologic changes, we found that Meth-APAH presents with a more severe phenotype of clinical disease. We found that Meth-APAH was more common in men and the most common route of administration was smoking/inhalation. Kaplan-Meier analysis showed a 5-year and 10-year survival of 47.2% and 25% respectively in Meth-APAH vs 64.5% and 45.7% in IPAH. Meth-APAH patients had worse hemodynamic measurements including higher right atrial pressures, lower stroke volume index, and more dilated, dysfunctional right ventricles when compared to patients with IPAH. Even after accounting for possible confounding variables such as age and lower socioeconomic status (SES), Meth-APAH was associated with an increased risk of heart failure, transplantation, and death. Additionally, there were treatment challenges encountered in the management of Meth-APAH patients. The clinical teams were reluctant to treat Meth-APAH patients with IV (intravenous)/SQ (subcutaneous) prostacyclin analogs given concerns regarding appropriate central line and skin site care, safety, and adherence. Subcutaneous and intravenous prostacyclin administration requires active patient engagement, adherence with the medical plan, as well as appropriate and consistent mixing and self-administration of the prostacyclin analog via a relatively complex pump device. However, despite this fact, multivariable analysis demonstrated that these factors did not explain the worse outcomes in

Meth-APAH. In addition, data obtained from a large statewide hospital database demonstrated that hospitalized methamphetamine users had a 2.6-fold increase risk of carrying an International Classification of Diseases (ICD)-coded diagnosis of PAH compared to nonusers.

Methamphetamine can be smoked, inhaled (vaporized), ingested orally, injected, and even snorted. Studies have shown that the route of administration of methamphetamine varies greatly by geographic location, gender, and even sexual orientation. In California, most users smoke or inhale vaporized methamphetamine. However, women are more likely to inhale or ingest the pill form rather than inject the drug.<sup>23</sup> A study in San Francisco reported that identifying as homosexual was predictive of more primary substance use (including methamphetamine) via smoking over the reference category of oral administration.<sup>24</sup> Other studies have found that IV methamphetamine users tend to be older, unemployed, possess less than a high school education, and live in rural areas.<sup>25</sup> An important aspect of our work will be to determine the precise implication route of administration plays in the development of methamphetamine cardiopulmonary toxicity.

Another recent retrospective study looking at methamphetamine-induced PH and methamphetamine-induced cardiomyopathy showed similar hemodynamic characteristics in their methamphetamine-induced PH cohort, including higher right ventricular systolic pressure (RVSP), more dilated atrial chambers, and more significantly reduced right ventricular systolic function when compared to the methamphetamine-induced cardiomyopathy and control cohorts. While this study was based on echocardiographic diagnosis of PH, and several patients in their methamphetamine-induced PAH cohort had elevated pulmonary capillary wedge pressures (PCWP), the authors report that methamphetamine-induced PH patients had increased morbidity and mortality when compared to methamphetamine users without PH. Interestingly, the mortality rate at 20 months was higher in the methamphetamine-in-

duced PH cohort than in the methamphetamine-induced cardiomyopathy cohort (18% vs 15.2% respectively). In this study the only risk factor associated with methamphetamine-induced PH development was female sex.<sup>26</sup>

Results of these studies may help upgrade the status of methamphetamine from a “likely” to “definite” risk factor for PAH, as was recently discussed at the 2018 World Symposium on Pulmonary Hypertension in Nice, France.

The true underlying mechanisms of Meth-APAH are currently unknown; however, several theories have been proposed. A study by Volkow et al used radiolabeled methamphetamine to demonstrate that uptake was highest in the lungs, a phenomenon which may explain the high degree of pulmonary toxicity seen with methamphetamine use.<sup>27</sup> Several molecular mechanisms have been proposed in the pathogenesis of Meth-APAH. Serotonin is a neurotransmitter known for its actions on mood regulation and appetite. Dysregulated serotonin metabolism has been implicated in the pathogenesis of anorexigen-induced PAH<sup>28</sup>; however, it may also play a role in the development of Meth-APAH. Studies have shown that in monocrotaline-treated rat models, methamphetamine administration promoted severe vascular remodeling that was associated with increased levels of the 5HT<sub>1B</sub> receptor subtype and the serotonin transporter (5HTT). It is important to mention that in this study, fluoxetine, a serotonin inhibitor, was capable of attenuating the pathologic vascular remodeling seen in these rats. This raised the possibility that selective serotonin reuptake inhibitors (SSRIs) could be used as pharmacologic treatment for Meth-APAH.<sup>29</sup> However, there is a study demonstrating the use of SSRIs in humans with PAH does not seem to be protective once the disease has been diagnosed.<sup>30</sup> In addition, another study has shown that rats with a loss of function mutation in 5HTT were not protected from PAH when exposed to a vascular endothelial growth factor (VEGF) inhibitor, Sugen 5614 (VEGF is needed for normal pulmonary endothelial cell homeostasis), indicating that dysregulated serotonin metabolism



is not the only pathologic mechanism involved in pulmonary vascular remodeling).<sup>31</sup>

Using whole exome sequencing, we have recently shown that carboxylesterase 1 (CES1), a gene involved in drug metabolism that codes for an enzyme involved in the detoxification of several drugs including methamphetamine, amphetamine, methylphenidate, heroin, and cocaine, expression was found to be predominantly expressed in healthy but not Meth-APAH patients. Reduction of CES1 increases methamphetamine-induced apoptosis through the generation of harmful reactive oxygen species (ROS) and deranged autophagy responses in cells (autophagy is a stress-related response by cells to allow repair).<sup>32</sup> Whether pharmacologic agents that restore levels of CES1 can be used as therapy for Meth-APAH patients remains to be determined.

## COCAINE

Cocaine is a popular stimulant drug that produces its desired effects by inhibiting the reuptake of dopamine, norepinephrine, and serotonin, resulting in euphoria, increased energy and libido, and decreased appetite.<sup>33</sup> Soon after its introduction in the late 1800s, reports appeared regarding its medical complications. In the early 1900s, US law banned its nonprescription use. In the 1980s, another epidemic would break out in the United States with the introduction of “crack” cocaine.<sup>34</sup> Crack cocaine is considered to be the most addictive form of cocaine potentially due to the fact that smoking the drug produces its intended effects within seconds. Cocaine has been associated with multiorgan toxicity including cardiovascular, pulmonary, and central nervous system effects. Known cardiac toxicity includes coronary vasospasm, myocardial ischemia, aortic dissection, and hypertension.<sup>33,35</sup> Lung manifestations of cocaine are also well described and include alveolar hemorrhage (described as part of a syndrome known as “crack lung,” which also involves an eosinophilic hypersensitivity response), decreased diffusion of carbon monoxide ( $D_LCO$ ), barotrauma, pneumothorax, and PAH.<sup>36</sup> Initial reports of an association between

cocaine and PAH were related to foreign body embolization of adulterants used to “cut” cocaine such as talc, cornstarch, or microcrystalline cellulose. These foreign bodies were shown to produce local granulomatous inflammatory responses in the pulmonary vasculature, which resulted in increased pulmonary pressures.<sup>37</sup> However, there is evidence that increased pulmonary artery pressures occurred in patients despite the absence of these foreign bodies. In a study examining the histopathology of 20 deaths due to cocaine intoxication, 4 of the 20 were found to have evidence of pulmonary artery medial hypertrophy in the absence of foreign body embolization, suggesting a cocaine-specific factor in the development of PAH.<sup>38</sup> One study by Collazo et al demonstrated that cocaine produced an acute reversible form of PAH, in the absence of left ventricular dysfunction, that improved after cocaine discontinuation.<sup>39</sup> Additionally, levamisole (an anti-helminthic medication), a common adulterant in cocaine preparations, can be metabolized to aminorex in the human body.<sup>40</sup> However, despite these numerous reports, the evidence definitively linking cocaine to PAH is mixed, which explains its status as a “possible” risk factor for PAH.

## OTHER STIMULANTS

MDMA, or 3,4-methylenedioxymethamphetamine—commonly referred to as “ecstasy”—is a popular designer amphetamine derivative commonly used by younger individuals recreationally and in “rave” music culture. Serious medical complications linked to MDMA use include hyperthermia, cardiac arrhythmias, liver failure, serotonin syndrome, and hyponatremia.<sup>41</sup> MDMA binds to the serotonin transporter (SERT) on platelets and increases circulating levels of 5HT 2- to 7-fold above baseline in a dose-dependent manner.<sup>42</sup> This association is relevant given the role of altered serotonin biology in other forms of stimulant-induced PAH. Another study demonstrated that binding of MDMA activates the serotonin receptor 5HT<sub>2B</sub> in a manner identical to drugs proven to cause valvular heart disease and PAH, such as fenfluramine.<sup>43</sup> Binding of this receptor induced mitogenesis in

in vitro human heart valve interstitial cells that results in lesions identical to those found in carcinoid syndrome. The authors conclude that given the similar pharmacokinetic profile, MDMA may have potential as a risk factor for PAH. At this time, more dedicated studies are needed to characterize the true degree of risk between MDMA and the development of PAH.

Mazindol is a nonamphetamine central nervous system stimulant and appetite-suppressant drug that exerts most of its pharmacologic effects through dopamine and norepinephrine reuptake inhibition. It has been used for the treatment of narcolepsy and obesity. A single case of PAH has been reported with mazindol therapy. In this case, symptoms temporarily resolved with discontinuation of the drug; unfortunately this was subsequently followed by severe dyspnea and a diagnosis of PAH.<sup>44</sup> Despite this single case report, PAH was not reported in a large trial of patients being treated with mazindol for drug-resistant narcolepsy.<sup>45</sup> There is also evidence to suggest that mazindol is a much weaker 5HT<sub>2B</sub> receptor modulator than other anorectic agents known to cause PAH.<sup>46</sup>

Phenylpropanolamine is a synthetic sympathomimetic that was marketed as an over-the-counter antiobesity drug. The Study of Pulmonary Hypertension in America (SOPHIA) found a significantly increased risk of developing PAH with exposure to phenylpropanolamine.<sup>14</sup> In addition, there has been a case report of a young boy frequently prescribed the cold remedy Dimetapp, which contains phenylpropanolamine, for his upper respiratory tract infections. He developed severe PAH and perished. The authors of the study emphasized that, in addition to the SOPHIA results, this case report further strengthened the association between phenylpropanolamine and PAH.<sup>47</sup> Phenylpropanolamine was withdrawn from the market in 2000 due to concerns regarding hemorrhagic stroke risk.<sup>48</sup>

Cathinone, an amphetamine-like stimulant found in khat leaves, has been used worldwide for recreational and religious reasons. A crystalline form of cathinone has been nicknamed “bath

salts” due to its appearance. Bath salts have been featured recently in the media due to their dramatic and frightening effects in users. Cathinone use has been linked to cardiac toxicity including myocardial infarction and dilated cardiomyopathy.<sup>49</sup> Cathinones can also modulate serotonin metabolism, a pathway that has been implicated in other forms of stimulant-induced PAH.<sup>50</sup> One study found that cathinones induced dyspnea and pulmonary edema in subjects<sup>51</sup>; however, despite its amphetamine-like chemical structure and pharmacokinetics, there has not yet been a clear link to PAH.

## CLINICAL RELEVANCE AND FUTURE DIRECTIONS

The clinical management of patients with stimulant-induced PAH can be challenging. In our practice, we emphasize the importance of taking thorough current and past drug use histories in addition to obtaining random and routine drug screening for patients with PAH. Continuous drug screening is important as we know that several stimulants, such as methamphetamine, have high recurrence rates.<sup>52</sup> Certain stimulants such as methamphetamine are still routinely prescribed for disorders such as attention-deficit/hyperactivity disorder (ADHD) and obesity; therefore, it is crucial to routinely screen patients on these therapies for early signs of PAH. As the current iatrogenic opioid epidemic has shown us, we must be cautious when prescribing stimulants for medical conditions to avoid precipitating another life-threatening iatrogenic drug epidemic.

From a therapeutic standpoint, the treatment of stimulant-induced PAH is similar to the standard guideline-based care for patients with other forms of PAH. Our recently published prospective study with Meth-APAH clearly showed that therapy selection in these patients can be challenging and further complicated by social factors, such as a clinician reluctance to use IV therapies (due to risk of IV line misuse). Our study also showed that in general, fewer of these patients had a positive vasodilator response to inhaled nitric oxide and a poorer prognosis.

An evolving area of research is determining whether prescription amphetamine-based substances such as methylphenidate or amphetamine salts—which are prescribed for ADHD but commonly abused by many young individuals to increase mental focus and productivity—are also associated with an increased risk of PAH. Thus far, studies have shown that these prescription amphetamine derivative medications have minimal effects on plasma 5-HT levels and serotonin transporter (5HTT) activity, likely due to variability in serotonin transporter selectivity.<sup>53-55</sup> This is in stark contrast to the massive doses of methamphetamine the body receives when it is smoked, inhaled, and exposed to the brain and periphery.<sup>56</sup> There is, however, at least one case report in which an adolescent developed PAH after using oral methylphenidate; interestingly, pulmonary artery pressures normalized with cessation of treatment.<sup>57</sup> Further in-depth studies are needed to elucidate the connection, if any, between prescription amphetamine derivatives and PAH.

## CONCLUSION

A variety of potentially harmful stimulants are being increasingly abused worldwide. There are well recognized cardiac and central nervous system complications associated with stimulant use, and current data have shown a more definite connection between certain stimulants and PAH. Newer studies have shown that methamphetamine is associated with a progressive, more deadly form of PAH. Active research efforts are ongoing to understand the molecular mechanisms and genetic factors responsible for the pathogenesis of this disease. Thus far, a few promising candidate genes involved in drug detoxification and protection from oxidative stress have been identified. Future studies using precision medicine tools such as gene sequencing and bioinformatics are needed to identify which susceptibility factors increase the risk of PAH in stimulant users, as we know that only a small percentage develop phenotypic disease. Most importantly, we must make a concerted effort to increase pharmacovigilance by practicing

physicians and promote close communication between drug regulatory agencies, national PH networks, and PAH patient associations as ultimately prevention may be our best strategy to combat this deadly drug-induced form of PAH.

## References

1. Follath F, Burkart F, Schweizer W. Drug-induced pulmonary hypertension? *Br Med J*. 1971;1(5743):265-266.
2. Galie N, Humbert M, Vachiery JL, et al; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67-119.
3. Montani D, Bergot E, Günther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation*. 2012;125(17):2128-2137.
4. Savale L, Sattler C, Günther S, et al. Pulmonary arterial hypertension in patients treated with interferon. *Eur Respir J*. 2014;44(6):1627-1634.
5. United Nations Office on Drugs and Crime, *World Drug Report 2017* (ISBN: 978-92-1-148291-1, eISBN: 978-92-1-060623-3, United Nations publication, Sales No. E.17.XI.6).
6. Substance Abuse and Mental Health Services Administration, *Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits*. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.
7. Fishman AP. Primary pulmonary arterial hypertension: a look back. *J Am Coll Cardiol*. 2004;43(12 Suppl S):2S-4S.
8. Rothman RB, Baumann MH. Therapeutic and adverse actions of serotonin transporter substrates. *Pharmacol Ther*. 2002;95(1):73-88.
9. Montani D, Seferian A, Savale L, Simonneau G, Humbert M. Drug-induced pulmonary arterial hypertension: a recent outbreak. *Eur Respir Rev*. 2013;22(129):244-250.
10. Hatano S, Strasser T. Primary pulmonary hypertension: report on a WHO meeting, Geneva, 15-17 October 1973. World Health Organization. Geneva, Switzerland; 1975.
11. Douglas JG, Munro JF, Kitchin AH, Muir AL, Proudfoot AT. Pulmonary hypertension and fenfluramine. *Br Med J (Clin Res Ed)*. 1981;283(6296):881-883.
12. Abenham L, Moride Y, Brenot F, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med*. 1996;335(9):609-616.

13. Rich S, Rubin L, Walker AM, Schneeweiss S, Abenham L. Anorexigens and pulmonary hypertension in the United States: results from the surveillance of North American pulmonary hypertension. *Chest*. 2000;117(3):870-874.
14. Walker AM, Langleben D, Korelitz JJ, et al. Temporal trends and drug exposures in pulmonary hypertension: an American experience. *Am Heart J*. 2006;152(3):521-526.
15. Connolly HM, Cray JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997;337(9):581-588.
16. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34-D41.
17. Savale L, Chamaus MC, Cottin V, et al. Pulmonary hypertension associated with benflurox exposure. *Eur Respir J*. 2012;40(5):1164-1172.
18. Kish SJ. Pharmacologic mechanisms of crystal meth. *CMAJ*. 2008;178(13):1679-1682.
19. Albertson TE, Derlet RW, Van Hoozen BE. Methamphetamine and the expanding complications of amphetamines. *West J Med*. 1999;170(4):214-219.
20. Schaiberger PH, Kennedy TC, Miller FC, Gal J, Petty TL. Pulmonary hypertension associated with long-term inhalation of "crank" methamphetamine. *Chest*. 1993;104(2):614-616.
21. Chin KM, Channick RN, Rubin LJ. Is methamphetamine use associated with idiopathic pulmonary arterial hypertension? *Chest*. 2006;130(6):1657-1663.
22. Zamanian RT, Hedlin H, Greuenwald P, et al. Features and Outcomes of Methamphetamine Associated Pulmonary Arterial Hypertension. *Am J Respir Crit Care Med*. 2018;197(6):788-800.
23. Center for Substance Abuse Treatment. Epidemiology and Treatment of Methamphetamine Abuse in California: A Regional Report. National Evaluation Data and Technical Assistance Center. February 1998.
24. Flentje A, Heck NC, Sorensen JL. Substance use among lesbian, gay, and bisexual clients entering substance abuse treatment: Comparisons to heterosexual clients. *J Consult Clin Psychol*. 2015;83(2):325-334.
25. Novak SP, Kral AH. Comparing injection and non-injection routes of administration for heroin, methamphetamine, and cocaine users in the United States. *J Addict Dis*. 2011;30(3):248-257.
26. Zhao SX, Kwong C, Swaminathan A, Gohil A, Crawford MH. Clinical Characteristics and Outcome of Methamphetamine-Associated Pulmonary Arterial Hypertension and Dilated Cardiomyopathy. *JACC Heart Fail*. 2018;6(3):209-218.
27. Volkow ND, Fowler JS, Wang GJ, et al. Distribution and pharmacokinetics of methamphetamine in the human body: clinical implications. *PLoS One*. 2010;5(12):e15269.
28. Eddahibi S, Adnot S. Anorexigen-induced pulmonary hypertension and the serotonin (5-HT) hypothesis: lessons for the future in pathogenesis. *Respir Res*. 2002;3:9.
29. Liu M, Wang Y, Wang HM, et al. Fluoxetine attenuates chronic methamphetamine-induced pulmonary arterial remodelling: possible involvement of serotonin transporter and serotonin 1B receptor. *Basic Clin Pharmacol Toxicol*. 2013;112(2):77-82.
30. Sadoughi A, Roberts KE, Preston IR, et al. Use of selective serotonin reuptake inhibitors and outcomes in pulmonary arterial hypertension. *Chest*. 2013;144(2):531-541.
31. de Raaf MA, Kroeze Y, Middelma A, et al. Serotonin transporter is not required for the development of severe pulmonary hypertension in the Sugan hypoxia rat model. *Am J Physiol Lung Cell Mol Physiol*. 2015;309(10):L1164-L1173.
32. Orcholski ME, Khurshudyan A, Shamskhou EA, et al. Reduced carboxylesterase 1 is associated with endothelial injury in methamphetamine-induced pulmonary arterial hypertension. *Am J Physiol Lung Cell Mol Physiol*. 2017;313(2):L252-L266.
33. Ciccarone D. Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy. *Prim Care*. 2011;38(1):41-58.
34. Albertson TE, Walby WF, Derlet RW. Stimulant-induced pulmonary toxicity. *Chest*. 1995;108(4):1140-1149.
35. Rezkalla SH, Kloner RA. Cocaine-induced acute myocardial infarction. *Clin Med Res*. 2007;5(3):172-176.
36. Restrepo CS, Carrillo JA, Martinez S, Ojeda P, Rivera AL, Hatta A. Pulmonary complications from cocaine and cocaine-based substances: imaging manifestations. *Radiographics*. 2007;27(4):941-956.
37. Yakel DL, Jr, Eisenberg MJ. Pulmonary artery hypertension in chronic intravenous cocaine users. *Am Heart J*. 1995;130(2):398-399.
38. Murray RJ, Smialek JE, Golle M, Albin RJ. Pulmonary artery medial hypertrophy in cocaine users without foreign particle microembolization. *Chest*. 1989;96(5):1050-1053.
39. Collazos J, Martinez E, Fernandez A, Mayo J. Acute, reversible pulmonary hypertension associated with cocaine use. *Respir Med*. 1996;90(3):171-174.
40. Hofmaier T, Luf A, Seddik A, et al. Amine-orex, a metabolite of the cocaine adulterant levamisole, exerts amphetamine like actions at monoamine transporters. *Neurochem Int*. 2014;73:32-41.
41. Hall AP, Henry JA. Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management. *Br J Anaesth*. 2006;96(6):678-685.
42. Yubero-Lahoz S, Ayestas MA, Jr, Blough BE, et al. Effects of MDMA and related analogs on plasma 5-HT: relevance to 5-HT transporters in blood and brain. *Eur J Pharmacol*. 2012;674(2-3):337-344.
43. Setola V, Hufeisen SJ, Grande-Allen KJ, et al. 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. *Mol Pharmacol*. 2003;63(6):1223-1229.
44. Hagiwara M, Tsuchida A, Hyakkoku M, et al. Delayed onset of pulmonary hypertension associated with an appetite suppressant, mazindol: a case report. *Jpn Circ J*. 2000;64(3):218-221.
45. Nittur N, Konofal E, Dauvilliers Y, et al. Mazindol in narcolepsy and idiopathic and symptomatic hypersomnia refractory to stimulants: a long-term chart review. *Sleep Med*. 2013;14(1):30-36.
46. Konofal E, Benzoud C, Delclaux C, Lecendreu M, Hussey E. Mazindol: a risk factor for pulmonary arterial hypertension? *Sleep Med*. 2017;34:168-169.
47. Barst RJ, Abenham L. Fatal pulmonary arterial hypertension associated with phenylpropanolamine exposure. *Heart*. 2004;90(7):e42.
48. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med*. 2000;343(25):1826-1832.
49. Al-Motarreb A, Al-Habori M, Broadley KJ. Khat chewing, cardiovascular diseases and other internal medical problems: the current situation and directions for future research. *J Ethnopharmacol*. 2010;132(3):540-548.
50. Prosser JM, Nelson LS. The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol*. 2012;8(1):33-42.
51. Bentur Y, Bloom-Krasik A, Raikhlin-Eisenkraft B. Illicit cathinone ("Hagigat") poisoning. *Clin Toxicol (Phila)*. 2008;46(3):206-210.
52. Brecht ML, Herbeck D. Time to relapse following treatment for methamphetamine use: a long-term perspective on patterns and predictors. *Drug Alcohol Depend*. 2014;139:18-25.
53. Zolkowska D, Rothman RB, Baumann MH. Amphetamine analogs increase plasma serotonin: implications for cardiac and pulmonary disease. *J Pharmacol Exp Ther*. 2006;318(2):604-610.
54. Rothman RB, Baumann MH. Therapeutic potential of monoamine transporter substrates. *Curr Top Med Chem*. 2006;6(17):1845-1859.
55. Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology*. 2002;27(5):699-711.
56. Rothman RB, Baumann MH. Methamphetamine and idiopathic pulmonary arterial hypertension: role of the serotonin transporter. *Chest*. 2007;132(4):1412-1413.
57. Karaman MG, Atalay F, Tufan AE, Erdogan A. Pulmonary arterial hypertension in an adolescent treated with methylphenidate. *J Child Adolesc Psychopharmacol*. 2010;20(3):229-231.