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Review article

Drug- and toxin-induced pulmonary arterial hypertension: Current state of the literature

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ABSTRACT

Drug- and toxin-induced pulmonary arterial hypertension (PAH) is an increasingly important sub-group of group 1 pulmonary hypertension (PH). In the last 60 years, we have seen the rise and fall of numerous prescription and illicit agents that have caused severe and deadly outbreaks of PAH. Currently, drugs and toxins are classified into "possible" and "definite" risk factors for PAH. While the exact mechanisms and pathogenesis of drug- and toxin-induced PAH are currently unknown, novel clinical and basic science studies are beginning to unravel the biologic factors and genetic underpinnings responsible for disease development. The clinical management of affected patients can be challenging as it is often difficult to identify patients early and demonstrate causality between drugs and PAH. Given the recent trends in drug utilization and defrontmattervelopment, it is highly likely that we will continue to identify new agents capable of causing pulmonary vascular disease. We must keep a high index of suspicion in order to identify patients and new compounds deemed definite or likely risk factors for PAH. Practicing pharmacovigilance, raising awareness, and working in tandem with PH patient associations and drug regulatory agencies may ultimately be our most effective strategy in preventing the next deadly outbreak of drug- and toxin-induced PAH.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a life-threatening disease which is characterized by a mean pulmonary artery pressure of greater than 20 mmHg, right ventricular dysfunction, and if left untreated, eventual death. The pathology of the disease, defined by obstructive vasculopathy and severe small vessel loss, was first described by the German physician Ernst Von Romberg in 1891, who saw the now well-recognized and classic pathologic changes in the lungs of cadavers during autopsy cases[1]. In the decades after its discovery, "primary" pulmonary hypertension (PH) remained a relatively rare and orphan disease, with only a handful of cases being reported each year. However, all of this would change in the 1960s when a marked increase in the number of cases of PH was noted in association with aminorex fumarate (Trade name: *Menocil*), an amphetamine-like anorexigen (i.e., appetite suppressant) that was marketed for weight loss in Austria, Switzerland, and Germany[2,3]. This deadly epidemic would catapult PH into the international limelight and prompt the first World Health Organization (WHO) World Symposium of PH in 1973 to discuss the current state of knowledge and devise a clinical classification scheme for PH. The results of this symposium would form the basis for future diagnostic and therapeutic approaches in treating the disease.

Since the aminorex epidemic, many other drugs and toxins have been recognized as risk factors for PAH. To date, there are more than 18 drugs and toxins that have been identified as risk factors for PAH. These drugs are classified according to their risk of causing PAH. Previously, they were classified into "definite", "likely", and "possible" risk factors for PAH[4]. In 2019, as the result of an update from the task force at the 6th World Symposium on PH, the classification scheme was simplified to "definite" and "possible" risk factors for PAH[5]. These drugs include appetite suppressant agents, such as the historically relevant aminorex fumarate, illicit agents such as methamphetamine, and more recently even FDA-approved agents used for therapeutic purposes such as dasatinib and interferon. Other chemicals used in industry, such as toxic rapeseed oil, and certain common dietary supplements are also included.

Throughout the years, new agents continue to be added to the list of drugs associated with PAH. As we will discuss, some of these agents are FDA-approved therapies for a number of medical conditions. This underscores the importance of post-marketing surveillance and monitoring for newly approved therapeutic agents. Although the exact mechanisms responsible for disease development are currently unknown, recent research efforts have identified some of the molecular mechanisms and genetic underpinnings of the pathogenesis of the disease. Interestingly, the clinical presentation, hemodynamic profile, and pathologic changes in idiopathic PAH (IPAH) and drug- and toxin-induced PAH are indistinguishable, which further highlights the importance of collecting thorough illicit drug and medication history from all patients.

In this review, we will discuss the current state of knowledge regarding drugs and toxins recognized as "definite" and "possible" risk factors for PAH according to the most recent clinical classification of PH. We will also discuss the evolving evidence linking other agents to PAH and the importance of practicing pharmacovigilance, raising physician awareness, and working collaboratively with the public sector to prevent the next deadly PAH epidemic (Table 1).

AMINOREX FUMARATE

The first agent to be implicated as a risk factor for the development of PAH was aminorex fumarate. Only 2 years after the release of the drug, physicians began to notice a

Table 1 Updated classification of drugs and toxins associated with PAH. Retrieved from: Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *The European respiratory journal.* 2019;53(1).

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	L-tryptophan
Benfluorex	St John's Wort
Methamphetamines	Amphetamines
Dasatinib	Interferon alpha and beta
Toxic rapeseed oil	Alkylating agents
	Bosutinib
	Direct-acting antiviral agents against hepatitis C virus
	Leflunomide
	Indirubin

sudden 10–20-fold increase in the incidence of PAH compared to the 12 years prior to the epidemic[2]. Among patients taking aminorex, the observed rate of pulmonary hypertension was estimated at 2000 cases per million exposed, translating to an odds ratio of greater than 1000[6,7]. Several case series were published which demonstrated that nearly 60% of the patients diagnosed with PAH had been using the drug aminorex fumarate prior to their symptoms developing. These studies also noted that most of these patients did not have other known risk factors of PAH. This temporal and geographical association between the rise in cases of PAH and aminorex fumarate use allowed physicians to identify the relationship between the development of PAH and exposure to the weight loss drug.

These case series, and the mounting evidence of the causality of aminorex in the sudden rise in PAH cases, led to the withdrawal of the agent in 1972. As expected, the sales curve of the drug closely followed the incidence rate of PAH[3]. Unfortunately, patients exposed to aminorex who developed PAH had a dismal prognosis. Nearly 50% of these patients died within 10 years of their diagnosis due to complications of right heart failure. Histologically, these patients were found to have pre-capillary PH with typical plexiform arterial lesions. Fortunately, for some patients (12 of 20), the disease did regress after drug withdrawal, indicating that there was some degree of reversibility in the disease course. Interestingly, 50% of the patients affected weighed only 10% more than their ideal weight, and there were four times as many women than men[8].

Aminorex fumarate has potent stimulant properties due to its ability to release catecholamines. In terms of its appetite suppressant properties, aminorex acts by suppressing appetite at the level of the central nervous system by increasing levels of serotonin, norepinephrine, and dopamine[9,10]. Similar to other amphetamines, it also increases basal metabolic rate and energy expenditure, which also contribute to its weight loss effects. Aminorex is known to act as a strong serotonin uptake inhibitor that interacts directly with the serotonin transporter (SERT or 5HTT), located on pulmonary artery smooth muscle cells[11]. Serotonin has been demonstrated to stimulate the growth and proliferation of pulmonary arterial smooth muscle cells[12]. Occlusion of the small pulmonary arterioles by smooth muscle cells contributes to PAH disease development and is one potential mechanism for aminorex-induced PAH. However, there is data which has refuted the "serotonin hypothesis" as the sole mechanism for PAH development

in individuals exposed to anorexigens[13]. There is also data to support the view that aminorex and other anorexigens may inhibit potassium channels, which then leads to direct vasoconstriction due to derangements in intracellular calcium levels[14,15].

The aminorex epidemic highlighted several important concepts. First, that oral dietary drugs could lead to pulmonary vascular lesions in the small muscular pulmonary arteries and arterioles (this was termed "dietary pulmonary hypertension")[16]. Second, among all patients exposed to aminorex, only about 2% developed PAH, suggesting a genetic predisposition to developing the disease. Indeed, when animals were fed aminorex, they did not develop PAH, highlighting the interplay of various factors implicated in disease development[8].

FENFLURAMINES

Several decades after the aminorex epidemic, reports of pulmonary hypertension associated with the anorectic drug fenfluramine (trade name: *Pondimin*) appeared in the European literature[17,18]. Fenfluramine and dexfenfluramine (trade name: *Redux*; dexfenfluramine is an enantiomer of fenfluramine; fenfluramine was withdrawn fairly early in its course due to its lack of specificity and links to causing depression)[8,19] are both agents in the phenylethylamine class that have similar pharmacokinetic and structural similarities to amphetamine.

In 1993, a study by Brenot et al began to link fenfluramine exposure to pulmonary hypertension[20]. In 1996, the International Primary Pulmonary Hypertension Study (IPPHS) was published. It was a case control epidemiological study conducted in five European countries over 2 years. This report found that use of anorexigens, such as fenfluramine and dexfenfluramine, was associated with a 10-fold increased risk of developing PAH if the drugs were used in the preceding year (HR 10.1; 95% CI [3.4–29.9]), the risk was even higher if the drugs were used for greater than 3 months (HR 6.3; 95% CI [3.0–13.2], with any definite anorexic-drug use, and HR 23.1; 95% CI [6.9–77.7], if anorexigens were used >3 months)[21]. Despite these frightening results, the FDA approved the medication for weight loss in the United States. Tragically, the editorial which accompanied the New England Journal of Medicine article noted that, "the possible risk of pulmonary hypertension associated with dexfenfluramine is small and appears to be outweighed by benefits (from treating obesity) when the drug is used appropriately"[22]. It is important to note that the efficacy of the drug was not very robust, with many patients averaging a sustained weight loss of only 10% compared to 6% in control subject[8].

Another study by Rich et al in 2000, also confirmed a link between fenfluramine derivatives and PAH. The study was a prospective surveillance study of 579 patients with primary PH (PPH) and secondary PH (defined as PH from secondary causes such as COPD, sleep apnea, pulmonary embolism, etc) in North America. The authors of this study found that fenfluramine use for greater than 6 months had a preferential association with PPH as compared to secondary PH with an adjusted OR of 7.5 (95% CI [1.7–32.4]). The association was stronger with longer duration of use and was more pronounced in recent users than in remote users[23]. Interestingly, the study noted an unexpectedly high number of patients with SPH that had also used anorexigens (11.4%), raising the possibility that the fenfluramine derivatives could precipitate PH in patients with pre-existing risk factors for the disease.

During this time, fenfluramine was also marketed with another amphetamine like agent, phentermine, in a combination colloquially called "Fen/Phen". A report by

Connolly et al in 1997 began to identify a potential link between fenfluramine-phentermine and the development of cardiac valvular lesions[24]. The mechanism behind this phenomenon was thought to be related to increased levels of serotonin. It was identified that the cardiac lesions in patients taking "Fen/Phen" were similar to those caused by metastatic carcinoid tumors, a disease characterized by serotonin excess[25].

In 1997, shortly after the publication of these reports, fenfluramine and dexfenfluramine were withdrawn from the market. In 2002, a study by Humbert et al showed that patients who developed PAH secondary to fenfluramine exposure may be carriers of bone morphogenetic protein receptor type 2 (BMPR2) mutations (a familial gene mutation known to be associated with an increased risk of PAH). Interestingly, patients carrying a BMPR2 mutation had significantly lower duration of exposure to fenfluramine than non-carriers prior to developing PAH[26]. The authors postulated that BMPR2 mutations could combine with fenfluramine exposure to greatly increase the risk of developing severe PAH.

BENFLUOREX

Benfluorex hydrochloride (Trade name: *Mediator*) is an anorexic agent similar in structure to the fenfluramines that were originally marketed in 1976 in France as anti-diabetic and lipid lowering agents. The common metabolite of the fenfluramines and benfluorex is norfenfluramine, which itself has a chemical structure similar to amphetamine[27]. Given the pharmacological and molecular similarities between the fenfluramines and benfluorex, one would expect the agents to have similar toxicity profiles. However, when benfluorex was re-introduced in France in 1997, it was marketed as an anti-diabetic agent used for the treatment of metabolic syndrome. Because of this clever marketing strategy, benfluorex was not subject to the same restrictions or scrutiny as the fenfluramine derivatives, and remained on the market in France until 2009 (it had been removed from other European countries a few years prior to 2009)[28].

The first case of benfluorex-induced PAH was reported in 1999 by the French Reference Center of Pulmonary Hypertension to the French pharmacovigilance authorities[29]. Shortly after this report, several other cases of PAH and valvular heart disease were reported in association with benfluorex use. In 2006, there was a dramatic increase in the number of cases of benfluorex associated PAH being reported. One postulated theory was that this was due to a sharp increase in the sales of benfluorex due to the recent withdrawal of the other popular anorexic agents and increased demand. Approximately two thirds of the total sales of benfluorex in France were recorded from 2000 to 2009. The French National Fund of health insurance reported that 200,000 to 300,000 patients were exposed to benfluorex, and about 7 million boxes of the product were sold during these years[27].

Two case series were published in 2009 and 2012 which described an association between benfluorex exposure and the development of PAH and valvulopathy. The first was a study by Boutet et al, which reported five cases of severe PAH and one case of valvular heart disease occurring in patients exposed to benfluorex[29]. Shortly thereafter, Savale et al, described 85 patients with PAH associated with benfluorex exposure. 70 of these patients had confirmed pre-capillary PAH. The median duration of exposure was 30 months, 33% of all patients also had prior exposure to the fenfluramine derivatives, and 30% of patients with pre-capillary PAH also had an additional risk factor for PH identified. A quarter of patients in this series showed co-existing PH and cardiac valve involvement[27]. Due to increasing evidence that benfluorex served as a risk factor for the development of PH and valvular heart disease, in 2010 benfluorex was finally withdrawn

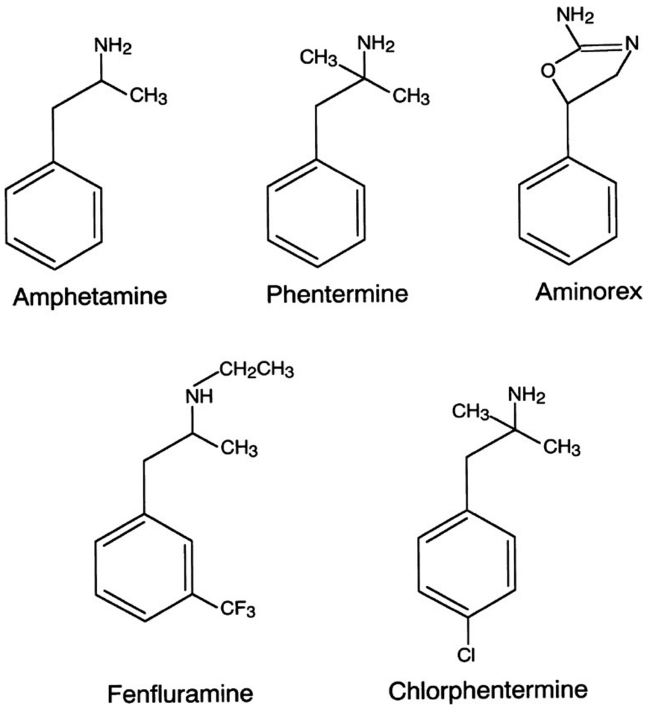

Figure 1. Chemical structure of amphetamine-derived anorexigens. Retrieved from: Orcholski ME, Khurshudyan A, Shamskhou EA, et al. Reduced carboxylesterase 1 is associated with endothelial injury in methamphetamine-induced pulmonary arterial hypertension. *American journal of physiology Lung cellular and molecular physiology.* 2017;313(2):L252-l266.

from the French market amidst some controversy and scandal in the French medical community[28] (Figure 1).

METHAMPHETAMINE

Methamphetamine (Meth) was originally developed from Ephedrine in the 1880s and used as a treatment for narcolepsy, asthma, and obesity. Historically, it was used by soldiers during World War II in order to promote alertness and wakefulness during combat situations[30]. Meth is a highly addictive and potent stimulant whose mechanism involves the release of serotonin, norepinephrine, and dopamine in the central nervous system. Recently, there has been a massive global increase in the illicit usage of Meth. The manufacture of illicit amphetamine-type stimulants continues to be dominated by Meth. Recent reports are highlighting the increased use of Meth around the world in regions such as Australia (Oceania) and East and Southeast Asia[31]. The western United States has also been recognized as a "hot spot" for Meth activity. From 1983 to 2008 the incidence of Meth abuse and dependence presenting to hospitals in California increased 13-fold. Between 1999 and 2008, Meth usage increased exponentially at a rate of 17% per year[32]. Historically, Meth abuse has been known to be associated with an increased risk of cardiomyopathy and stroke[33,34]; however, it was only recently that a definite association between Meth and PAH was confirmed.

The first reported case of methamphetamine associated PAH (Meth-APAH) was reported in 1993 by Schaiberger et al. The authors reported the case of a truck driver who was a long-term user of "crank" methamphetamine ("crank" is a commonly used nickname used for Meth) and subsequently went on to develop severe PAH. An exhaustive diagnostic evaluation was undertaken but alternative etiologies failed to

be identified. The authors concluded that the development of PAH was most likely secondary to Meth use. This association was reasonable given that Meth shares a similar chemical structure to aminorex fumarate, a previously known risk factor for PAH[35]. In 2006, a retrospective cohort study performed by Chin et al was published examining the association between stimulants, including Meth, and PAH. In this study, the authors were able to show that a history of stimulant use (stimulants were defined as cocaine, methamphetamine, or amphetamine) was found in 28.9% of patients with a diagnosis of "idiopathic PAH" 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 eight times more likely than patients with CTEPH (after adjustment for age). Of the three stimulants studied, Meth was most commonly used alone[36].

The first prospective cohort study conducted to examine the relationship between Meth and PAH was conducted by our group in 2017[37]. We compared the clinical presentation, disease characteristics, and outcomes of patients with Meth-APAH. We followed 187 patients between the years 2003 and 2015 with a diagnosis of Meth-APAH or IPAH. Meth-APAH was defined as greater than 3 episodes of Meth use per week for greater than 3 months, active use was defined by a positive urine toxicology screen. 90 Meth-APAH patients and 97 IPAH patients were included in the study. Patients in the study underwent echocardiography, pulmonary function testing, right heart catheterization (RHC), and chest imaging. Lung pathology was obtained from patients with Meth-APAH, and these samples demonstrated characteristic vascular changes including plexiform angiomatoid vascular lesions, identical to those seen in IPAH (veno-occlusive disease was also noted on pathology).

Despite the histologic similarities, we found that Meth-APAH presented with a more severe phenotype of clinical disease. Our findings demonstrated that Meth-APAH was more common in men and the most common form of administration was through smoking or inhalation (Meth can also be ingested, injected intravenously, or snorted). Kaplan-Meier analysis demonstrated 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 also had worse hemodynamic values such as higher right atrial pressures, lower stroke volume index, and more dilated, dysfunctional right ventricles, as compared to IPAH patients. Even after accounting for confounding factors such as age and lower socioeconomic status, Meth-APAH was still statistically significantly associated with a higher risk of heart failure, transplantation, and mortality.

Furthermore, in this study we analyzed data obtained from a large California statewide hospital database and found that hospitalized methamphetamine users had a 2.6-fold increased risk of carrying an International Classification of Diseases (ICD)-coded diagnosis of PAH when compared to non-methamphetamine users. Data from this study appeared to show that Meth-APAH presents with worse hemodynamics than dasatinib-induced PAH[38]. On the basis of these studies and mounting scientific and clinical evidence, Meth is now considered a definite risk factor in the most recent clinical classification of pulmonary hypertension in 2019[5].

Treatment challenges are routinely encountered during the management of patients with Meth-APAH. For instance, the use of long term indwelling intravenous catheters could serve as a conduit for Meth administration. In our study we found that

treatment teams were more reluctant to start intravenous (IV) or subcutaneous prostacyclin analog therapies on patients with Meth-APAH as compared to those with IPAH. Subcutaneous and IV prostacyclin administration require active engagement from the patient, adherence with the medical treatment plan, a certain degree of trust, and confidence that the patient can safely and consistently mix and self-administer these therapies through a relatively complex pump device. However, despite this fact, multivariable analysis demonstrated that these factors did not explain the worst outcomes in Meth-APAH patients.

The pathologic mechanisms of how Meth exposure causes PAH is unclear. Anatomically, the lungs appear to be a primary target for Meth related injury. A PET study conducted by Volkow et al, demonstrated that the highest whole organ uptake of radiolabeled Meth occurred in the lungs[39]. This fact may further underscore why the pulmonary vasculature is particularly susceptible to Meth exposure and its deleterious effects. Meth is chemically and pharmacologically similar to the previously mentioned anorexic agents (aminorex, the fenfluramines, and benfluorex) which are known to be risk factors for PAH. The previously described anorexic agents were proposed to promote the development of PAH, at least in part, by their actions on serotonin regulation. These agents all act to increase circulating levels of serotonin, which can act as a growth factor for pulmonary smooth muscle cells[40]. This dysregulated growth can lead to arterial luminal narrowing and increased pulmonary pressures. A study conducted using monocrotaline treated rat models of PAH demonstrated that the administration of Meth promoted severe vascular remodeling in the pulmonary arteries that was associated with increased levels of the $5HT_{1B}$ surface receptor subtype and the serotonin transporter (5HTT or SERT)[41]. Interestingly, in this study, Fluoxetine, a competitive inhibitor of the serotonin transporter, was capable of attenuating the vascular remodeling seen in the rats. This observation raised the possibility that selective serotonin re-uptake inhibitors (SSRIs) could be used as therapeutic agents in PAH. However, later studies conducted in humans demonstrated that SSRIs are not effective in the treatment of PAH once the disease is diagnosed[42].

It is important to note that serotonin dysregulation alone does not fully explain the pathogenesis of Meth-APAH. There have been several studies that show conflicting evidence regarding serotonin's proposed role in disease development. A study conducted using rat models which harbored a loss of function mutation in the serotonin transporter (a protein that has been implicated in the development of Meth-APAH) were not protected from PAH, indicating that serotonin signaling is not the only factor responsible for triggering pulmonary vascular remodeling[43]. Meth exposure can damage pulmonary endothelial cells through the generation of toxic reactive oxygen species (ROS) and through the promotion of mitochondrial dysfunction[44]. Since only a small subset of patients exposed to Meth will go on to develop phenotypic PAH disease, it has been proposed that Meth-APAH develops in susceptible patients as part of a "two-hit" phenomenon involving the interaction of genetic and environmental factors.

Recent work by our group has begun to shed light on potential candidate genes implicated in the development of Meth-APAH. We used whole exome sequencing to identify gene variants with a potential role in the pathogenesis of Meth-APAH. We identified a gene, carboxylesterase 1 (CES1), that is involved in drug metabolism and codes for an enzyme required in the detoxification of several illicit drugs including amphetamines, cocaine, and heroin. Using immunofluorescence techniques, we found

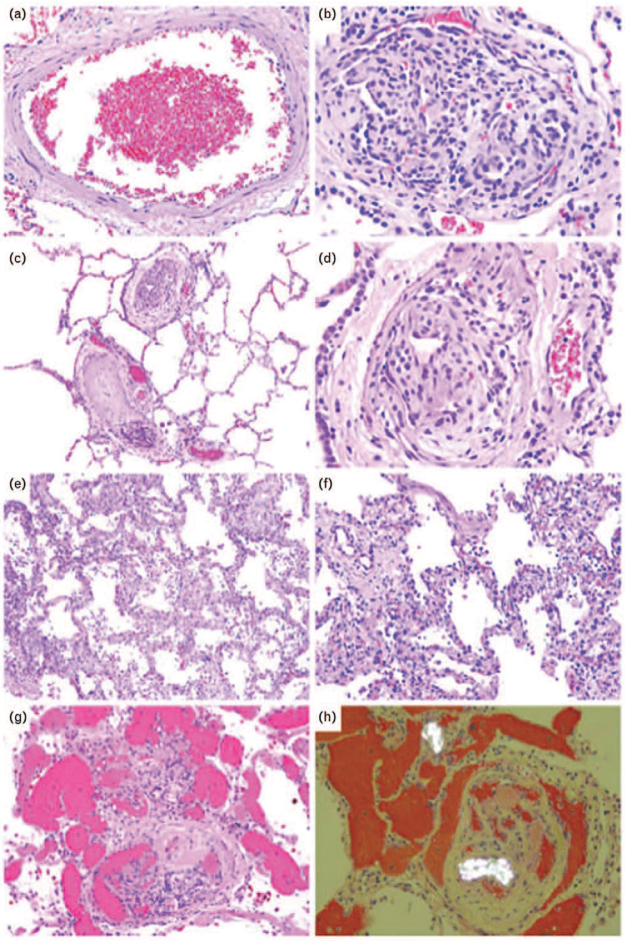

Figure 2. Histopathology of Meth-APAH and IPAH. Panel A: normal muscular pulmonary artery. Panel B: plexiform lesion in patient with IPAH who underwent lung transplantation. Panel C: plexiform arteriopathy in Meth-APAH involving muscular artery. Panel D: high-power magnification showing proliferation of slit-like vascular channels within artery. Panel E: pulmonary microvasculopathy in Meth-APAH. Panel F: high-power magnification showing proliferation of capillaries within the pulmonary interstitium. Panel G: angiomatoid lesion in Meth-APAH composed of dilated, thin-walled vascular spaces surrounding a plexiform lesion. Panel H: the patient in panel G also exhibited scattered intravascular collections of microcrystalline cellulose (a fillercommonly used to "cut" amphetamines), causing an intimal proliferative response within the muscular artery. IPAH, idiopathic pulmonary arterial hypertension; Meth-APAH, methamphetamine-associated pulmonary arterial hypertension. Retrieved from: Zamanian RT, Hedlin H, Greuenwald P, et al. Features and Outcomes of Methamphetamine Associated Pulmonary Arterial Hypertension. *American journal of respiratory and critical care medicine*. 2017.

that in explanted lung tissue, CES1 was markedly reduced in the lungs of Meth-APAH patients as compared to healthy patient samples. CES1 is an important factor in the cell regulation of ROS through cellular autophagy, a process by which cells degrade and recycle damaged cytoplasmic components in an effort to cope with cellular stress and restore homeostasis. Based on our findings, it appears that CES1 deficiency may result in greater Meth-induced pulmonary endothelial cell apoptosis and death which may lead to small vessel loss and PAH[45]. In addition, other studies have suggested that Meth exposure in the setting of hypoxia (a known risk factor for PAH) can also lead to greater DNA damage and increase the risk of PAH[44] (Figure 2) (Figure 3).

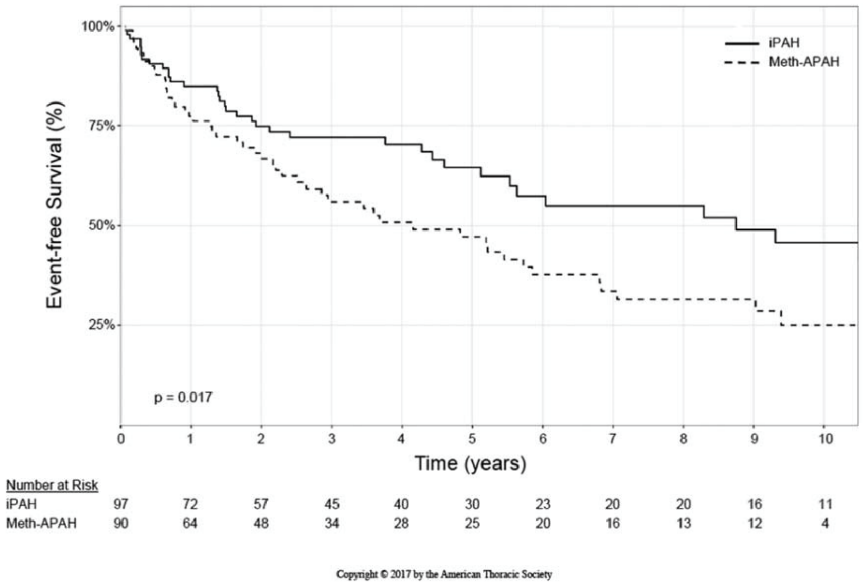

Figure 3. Kaplan-Meier plot comparing event-free survival in Meth-APAH patients vs. iPAH patients. Kaplan-Meier estimated event-free survival demonstrates worse outcomes for patients presenting with Meth-APAH (dashed line) as compared to those with iPAH (solid line). iPAH, idiopathic pulmonary arterial hypertension; Meth-APAH, methamphetamine associated pulmonary arterial hypertension. Retrieved from: Zamanian RT, Hedlin H, Greuenwald P, et al. Features and Outcomes of Methamphetamine Associated Pulmonary Arterial Hypertension. *American journal of respiratory and critical care medicine.* 2017.

PRESCRIPTION AMPHETAMINE-BASED STIMULANTS

Many of the offending agents implicated in the development of drug-induced PAH are derivatives of amphetamine such as the anorexic agents (aminorex, fenfluramine/dexfenfluramine, benfluorex) and methamphetamine. Given their molecular and pharmacological similarities, there has been growing interest in establishing if there is a link between prescription amphetamine-based stimulants (PABS) and PAH.

PABS, such as methylphenidate (Trade name: *Ritalin*), dextroamphetamine salt preparations (Trade name: *Adderall*) and lisdexamfetamine (Trade name: *Vyvanse*), were recently scrutinized due to case reports of their use leading to an increased risk of stroke, myocardial infarction, and sudden cardiac death[46,47]. The FDA launched an investigation in 2006 and several studies were published examining this relationship[48,49].

Although the studies did not find a clear link between PABS and an increased risk for these cardio- and neurovascular outcomes, some still harbor concern over their safety[46]. PABS were originally designed for the treatment of attention deficit/hyperactivity disorder (ADHD), but recently their therapeutic applications have been expanding. ADHD was originally considered a disease of childhood, but there are new data to suggest that there is an increasing prevalence and incidence of ADHD in adult patients[50]. In addition, PABS are now being used for many other off-label indications such as the treatment of depression[51], obesity[52,53], and narcolepsy[54]. There is also a worrisome recent trend among high school and college students who are abusing these drugs for academic enhancement. Some of these agents have been referred to "study drugs"[55,56]. Research attempting to further characterize the link between PABS, and PAH is currently ongoing. This research is significant given the public health implications of prescription drugs that are currently used by millions of people on a daily basis.

TYROSINE KINASE INHIBITORS

The tyrosine kinase inhibitors (TKI) are pharmacologic agents used for the treatment of chronic myelogenous leukemia (CML)[57], as well as other hematologic disorders such as acute lymphoblastic leukemia[58], systemic mastocytosis[59], non-small cell lung carcinoma[60], among others. The family of approved TKIs for the treatment of CML that target the BCR-ABL kinase includes dasatinib, imatinib, nilotinib, bosutinib and ponatinib[57]. Dasatinib is an oral second-generation TKI approved for first- or second-line treatment of CML and Philadelphia chromosome-positive acute lymphoblastic leukemia[61–63]. Dasatinib is associated with higher rates of cytogenic remission than imatinib[64], and it is also associated with a stronger inhibition of not only BCR-ABL kinase activity, but other tyrosine kinases and different protein kinase families, as compared to imatinib[65]. The difference in target activity and selectiveness between dasatinib and imatinib could explain the difference not only in effectiveness but also on the safety profile between these drugs[66–68].

Different case series have reported an association between dasatinib and PAH[38,69]. Smaller case series have also reported an association with bosutinib[70,71] and ponatinib[72]. Of interest, while imatinib and nilotinib are used more frequently than dasatinib, no definite cases of PH have been reported, a difference that will be further explained in the following sections[67].

Using data from the French registry, several cases of PH in patients using dasatinib have been reported[38,67]. Furthermore, using data from an international pharmacologic database surveillance, 41 cases of dasatinib-induced pulmonary arterial hypertension were reported as well[69]. As such, PAH is a recognized complication of treatment with dasatinib, with an estimated incidence of 0.45% in chronically treated patients[38]. Cases of PAH associated with dasatinib usually improve after discontinuation of the offending agent[38,69]. A study based on the French registry reported clinical and hemodynamic data in 19 patients, both at the time of diagnosis and at follow-up, after discontinuation of dasatinib (median of 24 months)[67]. Following discontinuation of dasatinib, there were improvements in functional class (while 76% patients were functional class III/IV at the time of diagnosis, only 10% of cases where functional class III at follow-up), as well as improvements in six-minute walking distance (from a median of 306 m at baseline, to a median of 430 m at follow-up). At follow-up, 7 out of 19 patients (37%) had persistent elevations in pulmonary vascular resistance. Of note, only 11 patients received therapy for PAH, either with pulmonary vasodilators or calcium channel blockers. In line with other reports, these findings were suggestive that dasatinib can induce irreversible pulmonary vascular dysfunction and remodeling[67,69]. The histopathology on a patient with dasatinib-induced PAH revealed medial hypertrophy, intimal thickening and plexiform lesions[73].

As mentioned above, no clear association between imatinib and the development of PAH has been described. Imatinib has a more specific target for tyrosine kinases than dasatinib, as it can be seen in Figure 4. The widespread inhibition profile of dasatinib (as well as bosutinib or ponatinib) include inhibition of receptor and non-receptor tyrosine kinases, and other types of protein kinases, such as the platelet-derived growth factor SRC; this wider inhibition profile is not seen with imatinib or nilotinib[65,74]. SRC kinases are important modulators in vascular regulation, vascular bed integrity, vasodilation and vascular proliferation[75]. Furthermore, SRC and other tyrosine kinases have been shown to be involved in the pathogenesis of PAH[76]. In fact, inhibition of SRC by dasatinib resulted in pulmonary vasoconstriction and increased pulmonary vascular resistance[77]. This led to

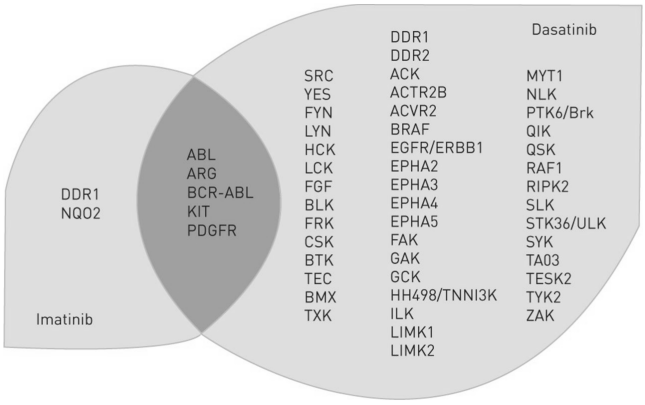

Figure 4. Comparison of kinase inhibition profiles for imatinib and dasatinib. Retrieved from: Weatherald J, Chaumais MC, Savale L, et al. Long-term outcomes of dasatinib-induced pulmonary arterial hypertension: a population-based study. *The European respiratory journal.* 2017;50(1).

investigational studies using imatinib as a therapeutic agent in PAH[78,79]. While a clinical trial of imatinib in patients with PAH led to improvements in six-minute walking distance (primary end-point of the study), it was also associated with a higher incidence of serious side effects, such as subdural hematomas, and a high discontinuation rate[79,80]. Other TKIs that have been studied as potential therapeutic agents include sorafenib[81], nintedanib[82] and erlotinib[83], with mixed results.

Dasatinib can also affect the vascular bed in mechanisms independent of SRC inhibition[68]. Dasatinib can cause dose-dependent endothelial dysfunction, injury and apoptosis in the pulmonary circulation. Patients with CML treated with dasatinib had higher markers of endothelial injury (such as soluble ICAM-1, soluble VCAM-1 and soluble E-selectin), as compared to patients treated with imatinib, treatment-naïve patients and healthy controls[84] (Figure 4).

Given the cumulative evidence from different multicenter case series regarding the use of dasatinib with the development of PH, dasatinib is now considered to have a definite association with PAH[5]. The association of other TKIs with PH is less clear. A small single center study reported echocardiographic findings suggestive of PH in 6 out of 27 patients treated with lapatinib (3 cases confirmed with right heart catheterization)[85]. There are case reports of clinical worsening of PH after switching dasatinib to bosutinib[71,86]and to ponatinib[72]. As such, the association of PH and other TKIs such as ponatinib and bosutinib is considered possible[5].

TOXIC RAPESEED OIL

In 1981, an outbreak of an acute febrile pulmonary disorder was identified in Spain, associated with the use of food oils contaminated with high amounts of rapeseed oil[87]. The disease had a phasic nature, with an early phase associated with fever and pneumonitis, followed by the development of eosinophilia and the late development of a neuromuscular disorder[88]. The epidemic was thought to be related to the clandestine distribution and consumption of adulterated food oils containing rapeseed oil, especially among lower to middle class populations, due to its lower cost (as compared to olive oil)[89]. While the disease had an initial presentation characteristic of a pneumonitis, late manifestations suggestive of an immunologic basis were also reported, such as cutaneous lesions similar to scleroderma, sicca syndrome, elevations in antinuclear antibodies and vasculitis changes noted in pathologic samples[88,89].

After the identification of this outbreak, and the posterior warning of the Spanish government against the consumption of the suspected oil, the number of cases of pneumonitis significantly decreased[88,89]. Between 1 to 4 months after the acute phase, a case series of patients with manifestations suggestive of PH was reported[90]. The authors reported the echocardiographic findings in 38 patients, and hemodynamic data in 11 patients. Patients had a range of mean pulmonary pressures of 27–55 mmHg, all with pulmonary artery wedge pressures below 15 mmHg. Follow-up data in 6 patients showed interval improvement in pulmonary hemodynamics after a period of 6 months. Autopsy in one of the cases revealed thickening and hyalinization of the media of small and medium-sized vessels, subintimal edema and mononuclear cell infiltration.

The development of PH during an outbreak of rapeseed oil exposure, and the interval improvement after removal of the offending agent led to classify the link between toxic rapeseed oil consumption and PH as a definite association[5]. While no additional cases have been reported since then, follow-up studies in patients exposed to rapeseed oil have demonstrated abnormal hemodynamic responses during exercise in a minority of them, suggestive of pulmonary vascular disease[91,92].

COCAINE

Cocaine is among the most commonly used illicit recreational drugs worldwide[93]. The United Nations Office on Drugs and Crime reported an increase in the number of cases of drug overdose related to cocaine use in the United States between 2012 and 2015[94]. In 2011, cocaine was the illicit drug most commonly involved in emergency department visits[95]. Cocaine produces its positive stimulant effect due to enhancement of brain dopamine activity[96], especially in the cortico-mesolimbic dopamine reward circuit[97]. Different reports of cardiopulmonary toxicity related to cocaine use have been reported, such as myocardial ischemia, coronary spasm, hypertensive crisis, as well as alveolar hemorrhage, pneumothorax, among others[98,99].

The association between cocaine use and the development of PH included case reports in intravenous users, where it was suggested that embolization of adulterants such as talc or microcrystalline cellulose could trigger a local inflammatory response in the pulmonary circulation, with the resultant elevations in pulmonary vascular resistance and pulmonary pressures[100]. Another study reported the histopathologic findings of 20 patients that died due to cocaine intoxication (6 intravenous users and 4 with mixed route use). Pulmonary vascular abnormalities were noted in 4 cases, with medial hypertrophy of the small and medium-sized pulmonary arteries, in the absence of foreign particle embolization[101].

Infection with the human immunodeficiency virus (HIV) is a known risk factor for pulmonary arterial hypertension[4,102,103]. The association between HIV infections and PH is more prevalent among intravenous drug users[104]. Studies in animals with HIV infection and cocaine exposure have revealed markers of pulmonary vascular remodeling and smooth muscle dysfunction[105]. For example, cocaine and the HIV protein Trans-activator of transcription decreased bone morphogenetic protein receptor expression in human pulmonary arterial smooth muscle cells, leading to enhanced proliferation of pulmonary smooth muscle cells[106]. Given the small number of case series suggesting an association between cocaine and PH, the causality association is less clear, and as such, it is considered as possible in the recent report[5].

PHENYLPROPANOLAMINE

Phenylpropanolamine, also known as norephedrine, is a synthetic sympathomimetic amine commonly found in over-the-counter appetite suppressants, common cold and cough remedies, as well as nasal decongestants[107]. While the association between PH and appetite suppressants such as aminorex was well recognized, the association with other anorexigens was less clear by the early 2000s[21,23]. A prospective surveillance of patients with newly diagnosed PH between 1998 and 2001 was performed at different tertiary referral centers in the United States, which included telephone interviews regarding the use of appetite suppressants, antidepressants and amphetamines within the 5 years prior to diagnosis[108]. The surveillance also used visual aids such as photographs for identification of medications, to assist with recollection data. This study, known as the SOPHIA study (Surveillance of Pulmonary Hypertension in America) found an increased association between PAH and the use of over-the-counter appetite suppressants containing phenylpropanolamine. The reported adjusted odds ratio was 4.8, although with a wide 95% confidence interval (0.9–26.2). There was an additional case report of a child with chronic use of over-the-counter phenylpropanolamine who died of severe PH; the autopsy revealed changes of vascular remodeling[109]. Phenylpropanolamine was withdrawn from the market due to its association with hemorrhagic strokes[110]. The association between phenylpropanolamine and PH is described as possible[5].

L-TRYPTOPHAN

Between July and December of 1989 an epidemic known as the eosinophilia-myalgia syndrome developed in the United States[111,112]. The syndrome typically progressed from a prodrome of myalgia and fatigue with peripheral eosinophilia, to the posterior development of neurologic symptoms and scleroderma-like skin changes[113]. Over 1500 cases of people affected by the disease were reported to the Center for Disease Control and Prevention[114,115]. The development of the eosinophilia-myalgia syndrome was associated to the use of products containing the essential amino acid L-tryptophan, with a median exposure of 6 months[113]. L-tryptophan was an agent used for the treatment of insomnia, depression and obesity at that time[116]. After the recall of over-the-counter preparations of L-tryptophan, the number of new cases fell dramatically[111].

The clinical history of the disease was that of an early phase with myalgias and fatigue, followed within several weeks by cough and dyspnea. Some patients will have later manifestations of neuromuscular symptoms and changes similar to scleroderma. Pulmonary symptoms developed by the third week of illness, with development of interstitial lung disease and PH in a minority of patients[113,116]. The reported cases of PH were mostly in patients with evidence of interstitial lung disease, and the histopathology revealed small vessels surrounded by a lymphocytic infiltrate, with involvement of the media and intima layers in some cases, as well as medial hypertrophy. In one small case series, there was no evidence of plexiform lesions in affected individuals[116]. While the presence of respiratory symptoms was relatively frequent, the incidence of PH was rare[115]. Based on two population-based case series, the frequency of PH in affected individuals by the eosinophilia-myalgia syndrome ranged from 0 out of 21 cases[117] to 3 out of 47 cases[113].

Although L-tryptophan was implicated as the etiologic agent of this disease, epidemiologic studies revealed that microcontaminants such as 1,1′-ethylidenebis(tryptophan) and 3-(phenylamino)alanine were the responsible

agents, rather than L-tryptophan itself. Many similarities between the eosinophilia-myalgia syndrome and the toxic rapeseed oil syndrome were identified[113,115], such as the history of toxic exposure, the development of myalgias, eosinophilia and fatigue, as well as the incidence of autoimmune-like symptoms such as scleroderma-like skin changes. In addition, it's been suggested that the 3-(phenylamino)alanine (found in L-tryptophan) and the 3-phenylamino-1,2-propanediol (found in some samples of rapeseed oil), could be interconverted biologically[115,118]. Despite these similarities, while the incidence of PH was relatively larger in the cases of exposure to toxic rapeseed oil, it was infrequent in cases of L-tryptophan exposure[113,115,119]. As such, the association between L-tryptophan and PH was described only as possible, in the most recent classification[5].

ST. JOHN'S WORT

St. John's wort is a plant from the genus Hypericum, with a complex spectrum of bioactive compounds, and is one of the most commonly used herbal remedies and supplements in the world[120]. St. John's wort is an over-the-counter supplement that has been used as an adjuvant for the treatment of major depression[121], as well as an aid for weight loss and treatment of obesity[122]. As previously described in the phenylpropanolamine section, the SOPHIA study was a prospective surveillance of patients with newly diagnosed PH at different centers in the United States, regarding the use of appetite suppressants, antidepressants and amphetamines within the 5 years prior to diagnosis[108]. The surveillance showed an increased adjusted odds ratio of 4.2 (95% confidence interval 1.2–14.6) for St. John's wort use and PH, similar to that seen with other anorexigens. As a result of this report, St. John's wort has been listed as a likely drug to induce PH since the earlier versions of the ESR/ERS guidelines[4,123], although there are no additional reports or cases in the literature regarding this association. As such, the association between St. John's wort use and the development of PH is currently considered as possible[5].

INTERFERON ALPHA AND BETA

Interferons continue to be considered as drugs having a 'possible' association with PAH per the updated hemodynamic and clinical classification of PH guidelines[5]. Interferons are a group of signaling proteins naturally produced in human cells and are manufactured using recombinant DNA technology. The majority of the data linking interferons to drug- and toxin-induced PAH comes from the French registry. Interferons are therapeutic options in several diseases including use of IFN-β in multiple myeloma, IFN-α for chronic hepatitis C and IFN-γ for chronic granulomatous disorder as well as certain solid organ tumors[124].

The use of IFN-α and IFN-β has been linked to PAH through numerous past case series and, more recently, through retrospective cohort reviews. The 2014 French PH registry reported 48 patients who developed PAH after starting IFN-α therapy. It is difficult to directly correlate the two as many of these patients had concomitant liver disease and/or HIV, both of which are independently associated with the development of PAH. These patients developed disease approximately 3 years after drug initiation that was largely irreversible with drug discontinuation[125].

That being said, in individuals with known pulmonary hypertension, treatment with IFN-α can cause a transient increase in pulmonary vascular resistance (PVR) when measured during IFN treatment that tended to resolve post-treatment[126]. Regarding IFN-β, Savale et al note that PAH secondary to this drug has a female predominance (13/13 in all reviewed case studies) and an onset about 10 years following initial

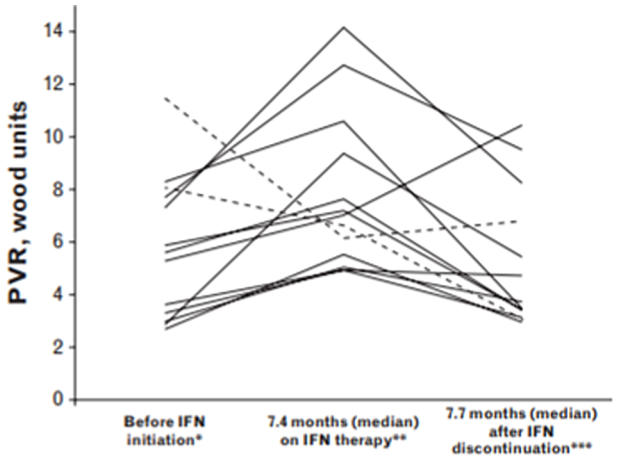

Figure 5. In this letter, the authors highlights the temporal and clinical arguments suggesting a causal link between interferon exposure and pulmonary arterial hypertension. Retrieved from: Savale L, Chaumais MC, Sitbon O, Humbert M. Pulmonary arterial hypertension in patients treated with interferon. *Eur Respir J* 2015; 46:1851–1853.

treatment. The PH was reversible in about half of cases with IFN discontinuation and pulmonary vasodilator therapy, however it was not reversible in three cases and two short term follow up deaths were observed. Histopathological findings described by authors were similar to those observed in idiopathic PAH with a marked inflammatory component[124] (Figure 5).

ALKYLATING AGENTS

Commonly used alkylating agents like bleomycin, carmustine, cyclophosphamide and mitomycin C have been linked to the development of pulmonary veno-occlusive disease (PVOD). PVOD is a disease of the pulmonary venous system that results in pulmonary venous hypertension, a poor response to traditional pulmonary vasodilators and a poor prognosis. The connection between alkylating agents and PVOD was first made in 1983 when a case report of a woman treated with bleomycin and mitomycin C suffered right heart failure and was found to have changes consistent with PVOD on autopsy[127].

Since then, numerous papers have documented the connection between chemotherapeutics and pulmonary hypertension. In 2015, seven cases of mitomycin-induced PVOD diagnosed based on clinical findings were identified in the French registry[128]. Within the group the majority of patients were female, more than half received concurrent 5-fluorouracil chemotherapy, and most were being treated for anal squamous cell carcinoma. All patients had significant symptom limitation (despite PH therapies in several) and 4 of 7 died during the observation period, prompting the authors to recommend that clinicians maintain a high suspicion for PVOD in patients who are currently or have previously received alkylating agent therapies, specifically mitomycin C.

When numerous classes of anti-cancer therapies were tested in mice, rabbits and rats, animals who received alkylating agents were significantly more likely to develop histopathologic changes consistent with PVOD compared to other drug classes tested[129]. It was hypothesized in this paper that DNA crosslinking may inhibit cell proliferation and thereby limit the repair capacity of endothelial cells in the lungs specifically given the lack of detoxifying agents in this organ. Additionally, lower levels of certain antioxidant enzymes in the lungs including glutathione (GSH) and glucose-6-phosphate

dehydrogenase (G6PD) suggests that pulmonary toxicity secondary to cyclophosphamide may be mediated by oxidative damage.

SOFOSBUVIR

Sofosbuvir is an oral nucleotide analog that inhibits HCV polymerase and results in rapid suppression of HCV replication[130]. Sofosbuvir cures 85% of patients infected with hepatitis C and is far more effective than previous therapies. Its FDA approval followed two phase 3 trials published in the New England Journal in 2013[131,132]. Renard et al reported some of the first cases of increased pulmonary pressures while on sofosbuvir. Notably, of the three cases reviewed, one had portal hypertension, two had concurrent HIV infection and one of the HIV infected individuals carried a previous diagnosis of PAH, suggesting that all had other risk factors for PAH before receiving sofosbuvir. The authors note that after receiving sofosbuvir these three patients experienced a rapid clinical decline secondary to increased pulmonary pressures and decreased cardiac output. In each case the clinical decline followed periods of relative clinical stability. Two of three patients experienced clinical improvement with sofosbuvir cessation[130]. Little other published evidence exists to support the connection of sofosbuvir to PH. The pathophysiologic mechanism of sofosbuvir-induced PH is unknown.

DIRECT-ACTING ANTIVIRAL AGENTS AGAINST HEPATITIS C VIRUS

In response to the Renard article mentioned above, Savale et al reviewed all cases of PAH in the French registry who had previously received any form of direct acting antiviral (DAA) for HCV (including sofosbuvir, simeprevir and daclatasvir). They found that, of the 16 patients identified, 13 carried a preceding diagnosis of PAH secondary to portopulmonary hypertension (PoPH) or HIV infection and that these patients did not develop new or worsening PH. However, three patients were identified who developed PAH after combined DAA therapy who had previously been asymptomatic. Two of these three were found to have evidence of portal hypertension while one did not. Of the one who did not, the PH resolved months after completing therapy. PVR dramatically improved with cessation of DAA agents and addition of pulmonary vasodilators in the other two individuals[133]. A potential mechanistic cause for PH in patients treated with DAA is unclear.

LEFLUNOMIDE

Leflunomide is a pyrimidine synthesis inhibitor that works as a disease-modifying antirheumatic drug used mainly in rheumatoid arthritis (RA) and psoriatic arthritis (PA). It has been associated with several cases of PAH published in case reports and case series. The first published report of leflunomide-induced pulmonary hypertension was diagnosed by echocardiography and demonstrated significant symptomatic and echocardiographic improvement following leflunomide discontinuation[134]. The second, a case in Argentina, was published in 2011 and described a 28-year-old woman who developed new respiratory symptoms and severe pre-capillary PH (mPAP 63mmHg) while taking leflunomide. The symptoms, elevated pulmonary pressures and right ventricular dysfunction seemed to completely resolve one year after cessation of leflunomide and initiation of PH specific therapy. While the patient had a diagnosis of RA, the disease was not considered to be active per serology testing at the time of PH diagnosis[135].

Four more cases of potential leflunomide-induced PAH were reported by a French group in 2017. Two of these patients had RA, one had PA and one had an undiagnosed

arthritis. Of the reported cases, pre-capillary PH was confirmed in all patients (mPAP 35–48) and the pulmonary pressures improved in all patients at 2–4 month follow up after discontinuation of drug. Three of the four were found to have improvement in their PA pressures with addition of PAH therapies while one of the RA cases improved with discontinuation of leflunomide and washout with cholestyramine alone[136]. A potential pathophysiologic mechanism of PH-induced by leflunomide is unknown.

INDIRUBIN (CHINESE HERB *QING-DAI*)

Indirubin, a red isomer of indigo, is the active ingredient of *indigo naturalis* in the traditional Chinese medicinal formulation Danggui Longhui Wan . The first documented case of natural indigo-induced pulmonary hypertension was a 58-year-old female with ulcerative colitis that developed progressive dyspnea after taking the drug for two years. Lymphocyte testing for an allergy to natural indigo was positive. The patient's PA pressures did not improve after therapy discontinuation[137]. More recently, a case report was published documenting a more convincing course of pre-capillary PH that developed in an individual taking the Chinese herbal medicine Qing-Dai (of which indirubin is a component) and resolved when the drug was discontinued. In this case, the patient had normal echo findings before starting the medicine; after starting the medication, the patient demonstrated increased RV strain on EKG and echo as well as an elevated BNP. Pre-capillary PH was diagnosed via RHC which prompted cessation of the medication. Subsequently, the patient experienced complete resolution of PH on repeat RHC after three months of PH triple therapy. Notably, the PH did not recur at five-month follow up after stopping the PAH medicines. Interestingly, the PH in this individual was not identified until 18 months after starting Qing-Dai therapy but resolved within weeks to months of stopping[138].

KHAT

Khat is a native tree that grows in the Arabian Peninsula and East Africa. When chewed, its leaves release a number of alkaloids, including cathinone, cathine and norephedrine[139]. Cathinone in particular has central nervous system stimulation properties that are similar to amphetamine, producing euphoria and increased alertness in its users. Khat use is an established risk factor for systemic hypertension[140], acute myocardial infarction (AMI)[141] and dilated cardiomyopathy[142]. The mechanism by which khat use contributes to AMI appears to be coronary vasospasm and not coronary artery disease (CAD). Cathinone has also been observed to produce coronary vasoconstriction[143,144], which has led to the hypothesis that khat users have worse in-hospital outcomes after AMI than do non-khat users with CAD[145]. More generally, khat use has been linked to a variety of other serious findings, including pulmonary edema and intracerebral hemorrhage[146].

Synthetic cathinones, also known as "bath salts," have become more popular in the United States in recent years. In addition to their amphetamine-like properties, they may also modulate serotonin[147], which has been implicated in the pathogenesis of PAH. Despite these associations, there is currently no evidence that khat or bath salts directly cause or are associated with pulmonary arterial hypertension.

LEVAMISOLE

Levamisole is an antihelminthic, adjuvant chemotherapeutic and immunomodulating medication that has been used as an adulterant in cocaine[148]. Levamisole has been

found in 40–80% of bulk cocaine samples[149], with some samples containing roughly 10% levamisole by weight[150]. Levamisole has also been shown to block norepinephrine, dopamine and serotonin uptake, albeit at much lower potency than cocaine[151]. Interestingly, studies in horses show that levamisole is metabolized to aminorex[152], which has a well-established link to pulmonary arterial hypertension. There is one case report of possible PAH in a cocaine user who was known to have ingested cocaine containing levamisole[153]; however there are a number of confounders present in this case. While there is a strong rationale behind the levamisole-aminorex-PAH connection, more research is needed to establish whether there is a causal link with PH.

MAZINDOL

Mazindol is a non-amphetamine central nervous system stimulant that has been used as an appetite suppressant, and as treatment for attention deficit disorder and narcolepsy[154]. Despite having properties similar to other anorexigens, it is more closely related to tricyclic antidepressants than to fenfluramines and amphetamines[155]. The mechanism of mazindol is incompletely understood, but it is thought to work through inhibition of re-uptake of norepinephrine, dopamine and serotonin[156]. Despite similarities to other compounds known to be associated with PAH, there is only one published case report that suggest a link between mazindol and delayed onset PAH[157]. In a large trial of 139 patients treated with mazindol for narcolepsy for an average of 30 months, there were no reports of PAH[158].

MDMA (ECSTASY)

3,4-methylenedioxymethamphetamine (MDMA), also known as ecstasy, is a popular street drug used for its euphoric effects. MDMA has well-described severe side effects that include tachycardia, hyperthermia, rhabdomyolysis, serotonin syndrome and hyponatremia, and has been linked to sudden death[159]. The mechanism of MDMA involves both the release and inhibition of the reuptake of serotonin, dopamine and norepinephrine in the central nervous system. There is some data to suggest that MDMA induces prolonged mitogenic responses in human valvular interstitial cells via activation of the serotonin $5HT_{2B}$ receptor in a manner that is identical to drugs known to cause PAH, such as fenfluramine[160]. Despite this, there are currently no case reports or other studies that suggest that MDMA directly causes PAH.

CLINICAL RELEVANCE AND FUTURE DIRECTIONS

The clinical management of drug- and toxin-induced PAH patients can be challenging. In our practice we emphasize taking thorough drug use and exposure histories in patients with a diagnosis of PAH in order to identify potential offending agents. We also advocate for frequent urine drug- and toxin screening in this patient population. We monitor patients closely for signs and symptoms of PAH if they have been exposed to an agent known or suspected to increase the risk of developing PAH. Given the rarity of the disease and the difficulty in proving that drugs and toxins have casually led to PAH, the clinician's index of suspicion must remain high in order to identify patients at risk early, stop the offending agent, and prevent severe disease progression.

At present, drug- and toxin-induced PAH is thought to require a combination of genetic and environmental factors in order to produce clinical disease. This "two-hit" hypothesis is reasonable given that only a very small subset of patients exposed to these drugs and toxins will go on to develop phenotypic disease. Novel research efforts

are identifying new candidate genes which may be implicated in the pathogenesis of drug- and toxin-induced PAH, however more studies using precision medicine tools such as gene sequencing, exosome analysis, and bioinformatics are needed in order to further advance our understanding of genetic factors which render patients susceptible to developing PAH in the setting of drug- and toxin exposure. Future research studies must also focus on delineating drug- and toxin dose and exposure thresholds which confer an increased risk of PAH, as we know that some agents have a dose dependent effect on their risk of PAH[21]. Historically, it has been difficult to study how drugs and toxins affect the pulmonary vasculature as animal models do not seem to faithfully replicate important features of human forms of PAH, which may be due to animal models lacking human specific genetic factors. Improvements and refinement in PAH animal models and research techniques are warranted in order to further our understanding of PAH pathobiology.

CONCLUSION

Drug- and toxin-induced PAH remains an important and ever-growing sub-group of group 1 PH. As historical outbreaks and recent studies have demonstrated, PAH secondary to drugs and toxins can be deadly, and outbreaks have the potential to affect many individuals and cause significant morbidity and mortality. It is important to reiterate that these outbreaks are preventable, and it is paramount that physicians and the public continue to practice pharmacovigilance in order to prevent the next epidemic of drug- and toxin-induced PAH. In the last 60 years, numerous drugs and compounds have been implicated in the development of PAH. Many of these agents are illicit agents however, in recent years many prescription FDA approved agents to treat disease have been identified as risk factors as well. It is highly likely that with the development of new therapeutic agents and an ever-growing market for illicit recreational substances, that more agents will continue to be identified as risk factors for PAH. As novel pharmacologic agents continue to be developed and approved for a wide variety of therapeutic uses, we must practice caution and closely monitor our patients for signs and symptoms of PAH. We must also work closely with drug regulatory agencies, national PH networks, and PAH patient associations in order to identify new agents which may be risk factors for PAH. Currently, in the United States, the FDA (Food and Drug Administration) provides a passive system for individuals to report adverse events and toxicities associated with drugs. This system however relies on a voluntary reporting of events and does not mandate individuals to report potentially dangerous drug toxicities. Refinement of this system may be warranted in order to improve our ability to identify early warning signals for drugs which may lead to an increased risk of PAH.

As physicians, we must keep a high index of suspicion for drug- and toxin-induced PAH, closely monitor our patient populations for signs and symptoms, and practice pharmacovigilance in order to prevent the next deadly epidemic of PAH, as ultimately prevention may be our best strategy to combat this severe and often fatal disease.

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