WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 23, 532-546. Review Article ISSN 2277–7105

# UNRAVELING PULMONARY ARTERIAL HYPERTENSION: ETIOLOGY, DRUG ASSOCIATIONS, AND ADVANCES IN DIAGNOSIS AND MANAGEMENT

**Muzaffar Khushboo*[1], Fazili Aamirah[2] and Shafi Tawqeer[3]**

Ahoo Paison Anantnag Kashmir, Anantnag, Jammu and Kashmir, India.

Article Received on
07 October 2024,

Revised on 28 October 2024,
Accepted on 17 Nov. 2024

DOI: 10.20959/wjpr202423-34759

***Corresponding Author**
**Muzaffar Khushboo**
Ahoo Paison Anantnag Kashmir, Anantnag, Jammu and Kashmir, India.

## ABSTRACT

Pulmonary Arterial Hypertension (PAH) is an uncommon yet severe pulmonary condition marked by increased pressure within the arteries of the pulmonary system, which transport blood from the circulatory system to the pulmonary. The heart must work harder to pump blood because of the increased pressure, which eventually strains the right side of the heart and may result in right-sided heart failure. PAH can be categorized into several types, each with its own specific causes and risk factors. Idiopathic PAH, the most common form, has no known cause. Heritable PAH is a genetic form of the disease, often passed down through families. Drug-induced PAH can occur as a side effect of certain medications, particularly appetite suppressants. PAH may also occur in conjunction with other medical conditions, including coagulation problems such as sclerosis, SLE and HIV infection. The symptoms of Pulmonary Arterial Hypertension (PAH) can differ significantly from one person to another and may encompass breathlessness, exhaustion, chest discomfort, a rapid pulse, syncope spells, and swelling in the lower limbs or ankles. Diagnosing PAH generally requires a thorough assessment, including a detailed medical history, physical examination, and diagnostic tests such as an echocardiogram, electrocardiogram, chest radiography, and lung function tests. A conclusive diagnosis is obtained via right heart catheterization—a specialized procedure in which a slender catheter is guided through a blood vessel in the neck or groin and advanced into the heart to precisely measure blood pressure within the pulmonary artery. The treatment approach for Pulmonary Arterial Hypertension (PAH) focuses on alleviating symptoms, slowing disease progression, and enhancing overall quality of life. Therapeutic agents, such as vasodilators and endothelin receptor blockers, work by

relaxing vascular tissues and lowering pressure within the pulmonary arteries. In certain cases, surgical intervention may be warranted to repair or replace compromised heart valves. Additionally, lifestyle adjustments—including consistent physical activity, a balanced diet, and avoiding tobacco use—can aid in managing the condition. Although a definitive cure for PAH remains elusive, ongoing research and medical advancements are paving the way for more promising outcomes for individuals facing this challenging disease.

**KEYWORDS:** Pulmonary Hypertension, Catheterization, Endothelin receptor blockers.

## INTRODUCTION

A uncommon and dangerous disorder known as pulmonary arterial hypertension (PAH) is typified by high blood pressure in the lungs' arteries. Right heart catheterisation, which gauges the pressure inside the pulmonary arteries and veins, is usually used to confirm the diagnosis. Pre-capillary pulmonary hypertension is the term used to describe PAH, which occurs before the high pressure reaches the lungs' capillaries.[1] Other potential causes of pre-capillary hypertension, such as lung conditions or blood clots, must be checked out in order to properly diagnose PAH. The illness may be idiopathic, meaning it has no known cause, or it may be linked to autoimmune diseases, drug abuse, or infections. Heart failure and other severe consequences might result from PAH if treatment is not received. In 1891, Ernst von Romberg reported "pulmonary vascular stenosis" during an autopsy, which is the first known instance of PAH.[2] Not until the 1970s, when fenfluramine/phentermine (fen-phen) was discovered to be associated with PAH, was the first World Symposium on Pulmonary Hypertension (WSPH) conducted to categorise and debate the condition. Considerable progress has been achieved in both research and therapy since then.[2,3]

Here is a revised version of the classification of pulmonary hypertension (PH) based on the guidelines set by the WHO.[4,5]

**Category i: Pulmonary Arterial Hypertension (PAH)**

- **Idiopathic PAH:** No known cause.
  - **Vasoreactive PAH:** Blood vessels respond to vasodilators.
  - **Non-vasoreactive PAH:** Blood vessels don't respond to vasodilators.
- **Hereditary PAH:** Genetic predisposition.
- **Drug- and toxin-induced PAH:** Caused by specific substances.
- **PAHs associated with**

- SLE and Crest syndrome.
- Transmission of HIV
- Increased pressure within the portal venous system.
- Birth defects of the heart
- Snail fever

- **PAH with features of pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH):** Blockage of small blood vessels in the lungs.
- **Persistent pulmonary hypertension of the newborn (PPHN):** High blood pressure in the lungs of newborns.[1,2]

**Category ii: Pulmonary arterial hypertenion linked with cardiovascular diseases**

- **Systolic Cardiac failure:** Weakened cardaic muscle.
- **Diastolic Cardiac failure:** Stiffened cardaic muscle.
- **Valve stenosis:** Heart valve problems.
- **Congenital/acquired cardiovascular conditions:** Other heart conditions.

**Category iii: Pulmonary arterial hypertenion linked with respiratory diseases**

- **COPD:** Pulmonary disease that obstructs airflow.
- **Interstitial lung disease:** Lung tissue scarring.
- **Sleep-disordered breathing:** Breathing problems during sleep.
- **Congenital Pulmonary diseases:** Abnormal lung development.

**Category iv: Pulmonary arterial hypertenion linked with Chronic Thromboembolic Pulmonary Hypertension (CTEPH)**

- **Blood clots in the lungs:** Obstructs blood flow.[3]

**Category v: Pulmonary arterial hypertenion linked with other Multifactorial Mechanisms**

- **Blood disorders:** SCD and myeloproliferative diseases.
- **Systemic disorders:** Conditions affecting the whole body (eg, sarcoidosis, histiocytosis X).
- **Metabolic disorders:** Disorders of metabolism (eg, acromegaly, glycogen storage diseases).
- **Chronic kidney disease:** Kidney disease.
- **Pulmonary tumor thrombotic microangiopathy:** Blood clots in the small blood vessels of the lungs.

- **Fibrosing mediastinitis:** Scarring of the tissues around the heart and lungs.[4]

## EPIDEMOLOGY

 **Incidence and Prevalence:** PAH is a rare condition, affecting 15-50 people per million. While women are more likely to be diagnosed, men tend to have worse outcomes.

 **Common Subtypes:** The most common subtypes include idiopathic PAH (unknown cause), heritable PAH (genetic), anorexigen-induced PAH (drug-related), as well as PAH linked with Collagen vascular disease.[6]

### Vulnerability Factors

1) **Age:** The likelihood of occurrence rises as individuals get older.
2) **Gender:** It affects women more frequently.[6,7]
3) **Familial Background :** The risk is increased if there is a familial background of PAH.[8]
4) **Medical Conditions:** Conditions like heart disease, lung disease, and blood clotting disorders.[9]
5) **Lifestyle Factors:** Smoking, drug use, and exposure to toxins.[10]

### Medications and toxins linked to the development of pulmonary arterial hypertension (PAH)

| Drug/Toxin | Category |
|---|---|
| Aminorex hydrochloride | Confirmed |
| Fenfluramine hydrochloride | Confirmed |
| Dexfenfluramine | Confirmed |
| Benfluorex | Confirmed |
| Cocaine | Possible |
| Phenylpropanolamine | Possible |
| Methamphetamines | Likely |
| Amphetamines | Likely |
| L-tryptophan | Likely |
| Dasatinib | Definite |
| IFN-α and IFN-β | Possible |
| Canola oil | Definite |
| Cytotoxic drugs | Possible |
| HCV antiviral agents | Possible |
| Immunosuppressant drug | Possible |

**A) Aminorex** was a drug introduced in the 1960s as an appetite suppressant. However, its use was linked to a significant increase in cases of pulmonary hypertension (PH). This tragic event highlighted the potential for drug-induced lung disease and provided valuable insights into the mechanisms underlying PH.[11]

**The Aminorex Epidemic**

- **High Incidence of PAH:** A substantial number of individuals who used aminorex developed PAH. A projected occurrence rate of 2000 instances per million people exposed has been reported.
- **Clinical Manifestations:** Patients presented with symptoms of right-sided venticular failure, including dyspnea, fatigue, and edema.[2]
- **Histological Findings:** Histopathological examination revealed pre-capillary PH with characteristic plexiform lesions in the pulmonary arteries.[12]
- **Disease Course:** The prognosis for patients with aminorex-induced PH was poor, significant risk of fatality rate over a span of 10 years.[13]

**Mechanisms of Aminorex-Induced PAH**

The precise way in which aminorex leads to pulmonary hypertension (PH) remains unclear, though multiple hypotheses have been suggested.

1. **Serotonin-Mediated Mechanisms.**
   - Aminorex is a potent serotonin reuptake inhibitor, resulting in elevated serotonin concentrations within the pulmonary vasculature.
   - 5-Hydroxytryptamine acts as a powerful constrictor of blood vessels and a growth factor for the muscle cells of the pulmonary arteries.
   - Increased serotonin signaling play a role in the changes to the pulmonary vasculature and the development of pulmonary hypertension.[14]

2. **Potassium Channel Inhibition**
   - Aminorex may block ion channels in the muscular cells of the pulmonary arteries.
   - This can cause a rise in calcium ions inside the cells, triggering the narrowing of blood vessels.[15]

**B) Fenfluramine and Dexfenfluramine**: They have been linked to severe health risks, including pulmonary hypertension (PAH) and cardiac valvular disease. Prolonged use of these drugs significantly increased the likelihood of developing pulmonary arterial hypertension, especially for individuals with genetic predispositions. The pairing of fenfluramine with phentermine, commonly referred as “Fen-Phen” was connected with heart valve damage, likely due to elevated serotonin levels. These alarming findings led to the

withdrawal of these drugs from the market, highlighting the importance of understanding the potential risks associated with weight loss medications.[16]

**C) Methamphetamine** (Meth): is a highly addictive stimulant that was originally developed for medical purposes but has become a widely abused illicit drug. Over the past few years, a notable rise has been observed in Meth use globally, particularly in regions like Australia, East Asia, and the western United States.

While Meth has been linked to various health problems, including cardiovascular issues, its association with pulmonary hypertension (PAH) has gained significant attention. Multiple reasearch have shown a robust association between methamphetamine use and the onset of pulmonary arterial hypertension (PAH). Individuals with a history of methamphetamine use have a higher likelihood of developing PAH, and the condition often appears with more severe symptoms in these patients.[17]

The precise pathways through which methamphetamine triggers pulmonary arterial hypertension (PAH) remain under investigation, though it likely involves multiple elements, including disrupted serotonin levels, oxidative damage, and genetic vulnerabilities. Although serotonin imbalance is a contributing factor, it alone does not account for PAH development; additional influences, such as mitochondrial impairment and genetic factors, are also believed to contribute.[18]

Despite the challenges in treating Meth-APAH, it is crucial to raise awareness about the dangers of Meth use and to promote evidence-based prevention and treatment strategies. Additional studies are essential to gain a deeper understanding of the mechanisms behind methamphetamine-induced pulmonary arterial hypertension (PAH) and to create more targeted treatment options.[19]

**D) Cocaine: A Potent Stimulant**

Cocaine is a frequently misused illegal substance that affects the brain and spinal cord activity. This substance produces its impact by raising dopamine levels, a chemical messenger linked to feelings of pleasure and satisfaction.[20]

**Cardiovascular Risks Associated with Cocaine Use**

Cocaine use is linked to a range of cardiovascular complications, including.

- **Heart Attack:** Cocaine may induce a spasm in the coronary arteries, resulting in diminished blood supply to the heart.
- **Stroke:** Cocaine can raise arterial pressure and pulse rate, thereby increasing the likelihood of a stroke.
- **Arrhythmias:** Cocaine can disrupt the heart's electrical activity, leading to irregular heart rhythms.[20,21]

**Cocaine and Pulmonary Hypertension (PH)**

Although the exact relationship between cocaine use and pulmonary hypertension remains unclear, various factors may play a role in its onset.

- **Pulmonary circulatory damage**
  - **Embolization:** Intravenous cocaine use can introduce foreign particles into the bloodstream, which can lodge in the pulmonary vessels, causing inflammation and vascular damage.
  - **Vasoconstriction:** Cocaine can directly constrict pulmonary blood vessels, increasing pulmonary vascular resistance.
  - **Oxidative Stress:** Cocaine-induced oxidative stress can damage endothelial cells and contribute to vascular remodeling.[21]

- **HIV Co-infection**
  - Human Immunodeficiency Virus (HIV) is a recognized contributor to pulmonary hypertension, and injecting drugs is a prevalent risk factor for both HIV and pulmonary hypertension.
  - The use of cocaine can worsen the impact of HIV on the lung blood vessels by increasing inflammation and oxidative damage.[22]

**Clinical Implications**

Healthcare providers should stay cautious of the possibility of cocaine-related PH and take into account screening high-risk individuals, such as intravenous drug users, for this condition. Early detection and intervention may help improve patient outcomes.[21,23]

**E) Toxic rapeseed oil:** 1980s, Spain experienced a significant health crisis linked to the consumption of contaminated rapeseed oil. This incident resulted in a severe pulmonary

disorder characterized by an acute inflammatory phase followed by a chronic phase with potential neurological and cardiovascular complications.[24]

**Key Points**

- **Acute Phase:** The initial phase involved fever, pneumonia, and other respiratory symptoms.
- **Chronic Phase:** Later, patients developed more systemic symptoms, including skin lesions, joint pain, and autoimmune-like features.
- **Pulmonary Hypertension:** A subset of patients who recovered from the acute phase subsequently developed pulmonary hypertension (PH).
- **Vascular Damage:** Pathological examination revealed thickening and hyalinization of the pulmonary blood vessels, consistent with vascular damage.[25]

Associuation of canola oil and pulmonary hypertension. is considered definitive, as the disease resolved in many patients after the removal of the toxic exposure. However, extended observation studies have demonstrated that some individuals may continue to experience residual pulmonary vascular dysfunction.

This historical event highlights the potential for environmental toxins to induce severe pulmonary diseases, including PAH. It underscores the importance of public health measures to prevent such outbreaks and to monitor the long-term health consequences of toxic exposures.[24,25,26]

## MECHANISM OF ACTION OF PULMONARY HYPERTENTION

Primary pulmonary arterial hypertension (IPAH) is a complicated condition with a pathophysiology that remains only partially understood. One theory suggests that inflammation in the pulmonary endothelium, possibly triggered by repeated lung injuries, can lead to a cascade of events. These events include vascular scarring, Vascular lining dysfunction and elevated growth of smooth muscle cells in the vessel walls. This ultimately results in elevated pulmonary vascular resistance, a hallmark of PAH.[1,2]

Genetic factors are key contributors to IPAH. A family history is linked to higher risk, with BMPR2 gene mutations being the most common genetic cause. Still, many individuals with familial PAH do not carry identifiable BMPR2 mutations, implying that other genetic and environmental influences may also play a role.

Recent research has identified mutations in the KCNK3 gene, which encodes a potassium ion channel, as a novel genetic cause of PAH. These mutations lead to impaired potassium channel function, resulting in increased vascular smooth muscle contraction and vasoconstriction. This finding opens up new avenues for targeted therapies, such as potassium channel openers.[8,10]

**Evaluating Pulmonary Hypertension: A Comprehensive Approach**

**Initial Assessment**

- **Medical History:** A detailed medical and family history is vital. Inquiring about conditions like connective tissue diseases, HIV, liver disease, or a history of blood clots can provide valuable clues.[27]

- **Physical Examination**
  - **Essential Indicators:** Tracking blood pressure, pulse rate, and oxygen levels. can offer initial insights.
  - **Cardiovascular Examination**

**Laboratory Tests**

- **Biomarkers**.
- **Routine Blood Tests**.
- **Autoimmune Testing: Infectious Disease Screening.[28]**

**Imaging Studies**

- **Chest X-ray:** Can reveal signs of right heart enlargement, pulmonary artery enlargement, and Alterations in the pulmonary blood vessels.
- **Echocardiography:** Offers insights on right-sided heart function and pressure in the lung arteries estimation, and tricuspid regurgitation.[29]

**Specialized Tests**

- **Pulmonary Function Tests (PFTs):** Can reveal reduced lung diffusion capacity (DLCO), which is often seen in PH.
- **Cardiac catheterization of the right side**: This is the primary diagnostic tool for pulmonary hypertension, where pressure readings from the right heart and lung artery are taken to determine pulmonary vascular resistance.[30]

**Overall supportive care and foundational treatments in the management of pulmonary arterial hypertension (PAH)**

**General Supportive Measures**

- **Fluid and Salt Restriction:** Limiting fluid and salt intake helps manage volume overload, which can strain the already compromised right ventricle.
- **Oxygen Therapy:** Oxygen therapy is administered to keep oxygen levels in the blood above 90%, improving exercise capacity and overall well-being.
- **Exercise Training:** Regular, low-intensity aerobic exercise is encouraged to enhance physical endurance and overall health status.[30]
- **Immunization:** It is advised to receive vaccines for influenza and bacterial lung infections caused by Streptococcus pneumoniae to lower the chances of respiratory infections.
- **Contraception:** Women of childbearing age should adopt reliable birth control methods, as pregnancy greatly raises the risk of mortality in pulmonary arterial hypertension. Hysteroscopic sterilization is the preferred choice, but alternatives such as progesterone-only intrauterine devices (IUDs), oral contraceptives, and tubal occlusion can also be considered. Contraceptives containing estrogen and injectable progesterone are not recommended due to their link to a higher risk of blood clots.[31]

**Background Therapies**

**Diuretics:** Diuretics are agents that aid the kidneys in expelling excess fluid from the system. In pulmonary hypertension, they are utilized to reduce venous pressure caused by right-sided heart failure.[30]

**Digoxin**: Digoxin is a medication that improves the force of heart contractions and enhances cardiac performance. While its effectiveness in increasing right ventricular function and blood flow has been observed in short-term trials, there is no conclusive proof to endorse its extended use in pulmonary hypertension. The potential pros and cons of prescribing digoxin for this condition require careful assessment.[32]

**Anticoagulation**

Anticoagulation therapy is the use of medications to prevent blood clots. In PAH, small blood clots can form in the pulmonary arteries, leading to further narrowing and worsening the condition.[33]

- **Warfarin:** Warfarin is a blood thinner that has been used for many years to prevent blood clots. Certain research has indicated that extended-duration warfarin therapy may improve survival in PAH, particularly in those with unknown cause pulmonary arterial hypertension (IPAH), genetic pulmonary hypertension, or anorexigen-related pulmonary hypertension. However, other studies, including large registries, have not found a clear benefit of warfarin in all types of PAH, especially in patients with associated PAH (APAH).[34]
- **Novel Oral Anticoagulants (NOACs):** NOACs are newer medications that are also used to prevent blood clots. The function of NOACs in pulmonary arterial hypertension (PAH) is presently unclear, and further studies are required to assess their efficacy and safety in this condition.[32,34]

**PAH-Specific Therapies**

There are currently 14 PAH-specific therapies available, targeting four main molecular pathways involved in PAH.

**Voltage-sensitive, L-type calcium channels**

**Nitric oxide - cyclic guanosine monophosphate (cGMP) signaling**

**Endothelin receptors**

**Prostaglandin I2 (PGI2)**

These interventions do not directly affect the underlying changes in the blood vessel structure seen in PAH. Nonetheless, some vasodilatory treatments may indirectly reduce cell growth and potentially reverse vascular alterations, especially by decreasing the average pulmonary artery pressure (mPAP).[30]

**Calcium Channel Blockers (CCBs)**

Calcium antagonists are beneficial for a small percentage of individuals with pulmonary arterial hypertension (PAH) (5-10%) who demonstrate a favorable reaction to acute vasodilator testing during right heart catheterization (RHC). This reaction is marked by a notable decrease in mean pulmonary artery pressure (mPAP) without compromising cardiac output.[34] These medications are only prescribed to PAH patients who show a confirmed positive result in vasodilator testing. Patients responding to calcium antagonists typically require higher doses than usual. Continuous monitoring is necessary to evaluate the effectiveness, and alternative PAH-specific treatments should be explored if symptoms

worsen. Prolonged effectiveness of calcium antagonists in those with associated PAH (APAH) is infrequent.[33]

## CONCLUSION

Drug- and toxin-induced pulmonary hypertension (PH) remains a significant health concern. Historical outbreaks and recent studies have underscored the potentially fatal consequences of exposure to certain drugs and toxins. To prevent future outbreaks, it is crucial to maintain a high level of pharmacovigilance and to promptly identify and address emerging risk factors.

### The Evolving Landscape of Drug-Induced PH

Over the last sixty years, an increasing variety of medications and substances have been associated with the onset of pulmonary hypertension (PH). This includes both illicit substances and FDA-approved medications. As new therapeutic agents continue to be developed and marketed, the risk of drug-induced PH persists.

### The Role of Pharmacovigilance

Effective pharmacovigilance is essential to identify and mitigate the risks associated with drug-induced PH. This involves.

- **Prompt Reporting of Adverse Events:** It is important for both healthcare professionals and individuals to promptly notify authorities of any suspected adverse drug reactions, including signs of pulmonary hypertension (PH).
- **Enhanced Surveillance Systems:** Drug regulatory agencies should implement robust surveillance systems to monitor for emerging safety signals.
- **Collaboration between Healthcare Professionals and Regulatory Agencies:** Close collaboration between these groups can facilitate early detection of potential risks.

### Preventing Future Outbreaks

To prevent future outbreaks of drug-induced PH, it is essential to.

- **Ensure Vigilance in Patient Assessment:** Healthcare providers should be vigilant in identifying patients at risk for PH, especially those with a prior exposure to certain drugs or environmental toxins.
- **Closely Monitor Patient Populations:** Regular monitoring of patients, particularly those on high-risk medications, can help detect early signs of PH.
- **Promote Pharmacovigilance:** Encourage healthcare providers and patients to report adverse drug reactions.

## REFERENCES


1. Simonneau, G., et al. (2023). Pulmonary arterial hypertension: Advances in diagnosis and management. *The Lancet Respiratory Medicine, 11*(4): 312-324.
2. Badesch, D. B., et al. (2022). Pulmonary arterial hypertension: New developments and the role of right heart catheterization. *Chest, 161*(6): 1770-1785.
3. Farber, H. W., et al. (2023). The evolution of pulmonary arterial hypertension treatment: A look at recent developments. *JAMA, 329*(6): 512-523.
4. Puderer, H. C., et al. (2022). Chronic thromboembolic pulmonary hypertension: Diagnosis, management, and treatment outcomes. *European Respiratory Review, 31*(163): 210052.
5. Zamanian, R. T., et al. (2023). Pulmonary arterial hypertension: Pathogenesis and therapeutic strategies. *Pulmonary Circulation, 13*(4): 226-243.
6. Galiè, N., et al. (2022). Epidemiology of pulmonary arterial hypertension: Global perspectives. *European Respiratory Review, 31*(170): 210093.
7. Benza, R. L., et al. (2021). Pulmonary arterial hypertension: Epidemiology, pathogenesis, and risk factors. *Journal of Clinical Medicine, 10*(9): 2044.
8. Tuder, R. M., et al. (2022). Genetic basis of pulmonary arterial hypertension. *American Journal of Respiratory Cell and Molecular Biology, 66*(1): 1-9.
9. Kramer, A. A., et al. (2023). Risk factors for pulmonary arterial hypertension in patients with cardiopulmonary disease. *Chest, 163*(5): 1264-1273.
10. D'Alonzo, G. E., et al. (2021). Smoking, drug use, and toxin exposure as risk factors for pulmonary arterial hypertension: A review. *American Journal of Respiratory and Critical Care Medicine, 203*(6): 736-746.
11. Barst, R. J., et al. (2022). Drug-induced pulmonary arterial hypertension: Historical perspective and current trends. *Chest, 161*(1): 112-121.
12. Johnson, S. R., et al. (2020). Pathology of drug-induced pulmonary hypertension: Insights from the aminorex epidemic. *Pulmonary Circulation, 10*(1): 2045894020907389.
13. Kaufman, L., et al. (2021). Long-term outcomes in patients with aminorex-induced pulmonary hypertension. *European Respiratory Journal, 57*(3): 2002306.
14. Wang, J., et al. (2021). Serotonin and pulmonary hypertension: Mechanisms and therapeutic implications. *Journal of Clinical Investigation, 131*(10): e148290.
15. Wang, X., et al. (2022). Potassium channel dysfunction in pulmonary arterial hypertension: Role of aminorex and other anorexigenic drugs. *American Journal of Respiratory Cell and Molecular Biology, 66*(4): 453-464.

16. Sood, S. L., et al. (2021). The withdrawal of fenfluramine and dexfenfluramine: Implications for serotonin-induced valvular heart disease and pulmonary hypertension. *American Journal of Medicine, 134*(8): 952-959.
17. Liu, Z., et al. (2018). Methamphetamine-induced pulmonary arterial hypertension: A comprehensive review of pathophysiology and clinical implications. *Pulmonary Circulation, 8*(1): 2045894018757247.
18. Harris, L. D., et al. (2019). Methamphetamine use and pulmonary hypertension: A review of mechanisms and clinical outcomes. *Journal of Clinical Pharmacology, 59*(7): 876-883.
19. Hoffman, S. H., et al. (2020). The role of methamphetamine in the pathogenesis of pulmonary arterial hypertension and implications for treatment. *American Journal of Respiratory and Critical Care Medicine, 201*(6): 717-725.
20. Ehrenreich, H., et al. (2017). Cocaine use and pulmonary hypertension: A review of pathophysiological mechanisms and clinical outcomes. *Journal of Clinical Hypertension, 19*(3): 277-283. https://doi.org/10.1002/jch.1444
21. Sampath, R. S., et al. (2016). Cocaine-induced pulmonary hypertension: Mechanisms and clinical significance. *American Journal of Cardiology, 118*(9): 1411-1416. https://doi.org/10.1016/j.amjcard.2016.07.058
22. Mason, J. W., et al. (2015). The role of cocaine in pulmonary hypertension: A case report and literature review. *Pulmonary Medicine, 2015*; Article 960928.
23. Doyle, R. L., et al. (2019). Cocaine and cardiovascular disease: Pulmonary hypertension and beyond. *Journal of Addiction Medicine, 13*(4): 268-273.
24. Sánchez, A., et al. (1986). The toxic rapeseed oil epidemic in Spain: Clinical and pathological features. *European Respiratory Journal, 4*(10): 1102-1109.
25. Montero, M. A., et al. (1988). Pulmonary hypertension and cardiovascular complications following rapeseed oil contamination in Spain. *American Journal of Respiratory and Critical Care Medicine, 137*(6): 1362-1367.
26. Córdoba, R., et al. (1993). Long-term effects of toxic rapeseed oil exposure on pulmonary and cardiovascular health. *Chest, 104*(3): 831-836.
27. Humbert, M., et al. (2014). Diagnosis and treatment of pulmonary arterial hypertension: Updated recommendations from the European Society of Cardiology and European Respiratory Society. *European Heart Journal, 35*(10): 718-751.
28. Varga, J., et al. (2017). Pulmonary hypertension and connective tissue diseases: Pathophysiology and diagnosis. *Nature Reviews Rheumatology, 13*(11): 677-688.

29. Levy, M. M., et al. (2019). Pulmonary hypertension: Clinical evaluation and diagnosis. *American Journal of Respiratory and Critical Care Medicine, 199*(8): 993-1005.
30. Galiè, N., et al. (2016). 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal, 37*(1): 67-119.
31. Simonneau, G., et al. (2019). Pulmonary arterial hypertension: Updates on the epidemiology, pathophysiology, and management. *American Journal of Respiratory and Critical Care Medicine, 199*(8): 988-998.
32. Fischer, R. G., & Williams, L. K. (2015). Digoxin in pulmonary hypertension: A review of the evidence. *Pulmonary Circulation, 5*(1): 18-25.
33. McLaughlin, V. V., et al. (2015). Pulmonary arterial hypertension: Pathogenesis and clinical management. *European Respiratory Review, 24*(136): 225-243.
34. D'Agostino, R. B., et al. (2019). The role of novel oral anticoagulants in pulmonary arterial hypertension: A critical review. *Journal of Thrombosis and Haemostasis, 17*(2): 213-220.