

Review of the Ongoing Story of Appetite Suppressants, Serotonin Pathway, and Pulmonary Vascular Disease



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Obesity is pandemic in the Western Hemisphere, especially in the United States (US) and is associated with morbidity and mortality. Recent data show that a large proportion of the US population is at least overweight and almost 2 in 5 Americans are obese. This ongoing trend of increasing obesity rates has led to a thriving market for anorexigens. Despite the health benefits of weight loss, several anorexigens had devastating side effects including pulmonary vascular disease which manifests as the clinical syndrome of pulmonary arterial hypertension (PAH). PAH is an incurable and fatal disease and is characterized by vascular constriction, hypertrophy, and proliferation that over time lead to right-sided cardiac failure. Over the past few decades, several weight loss medications have been associated with the development of PAH, possibly caused by an increase in systemic serotonin levels, resulting in vasoconstriction of the pulmonary arteries and initiating a cascade of pathologic vascular remodeling leading to vascular fibrosis. Once sufficient evidence for the association of these drugs with PAH or other related pathologies was found, many were removed from the market. However, there are other appetite suppressants still currently on the market (whether Food and Drug Administration–approved or “dietary supplements”) that have to some extent similar mechanisms of action to those associated with PAH but lack robust enough data to prove or disprove an association. The serotonin pathway seems to be repeatedly implicated. In conclusion, given that PAH is a progressive and debilitating disease, it is important to highlight possible risk factors that could be avoided. © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2016;117:1691–1696)

Obesity is a rising global epidemic associated with many fatal conditions, with high rates in North America.¹ The worldwide prevalence of obesity has nearly doubled from 1980 to 2013. Mortality rates increase as body mass index increases. Pharmacotherapy may be recommended as an adjunct weight loss intervention.² However, some of the efficacious weight loss medications were later found to cause devastating side effects and were taken off the market,^{3–5} which led to an ongoing controversy about the long-term safety of many currently available anorexigens. The serotonin (5-hydroxytryptamine, 5-HT) pathway has been repeatedly implicated in anorexigen-associated pulmonary vascular disease (PVD). We will briefly review in this study the pathophysiology of PVD and focus on the serotonin pathway. We do this as we tie together the potential for anorexigen-induced heart valvulopathy with PVD; both share similar serotonin mechanisms (including having both the receptors and the transmembrane transporters), and both are known side effects of anorexigens.

Pulmonary Arterial Hypertension

Pulmonary hypertension (PH) is a hemodynamic state associated with progressive and fatal diseases. The World

Health Organization (WHO) has classified PH into 5 major categories based on etiologic and pathophysiological groupings. The first group is pulmonary arterial hypertension (PAH), known as WHO group 1 PH (idiopathic, heritable, drug/toxin induced, or associated with conditions such as connective tissue diseases, portal hypertension, or human immunodeficiency virus). The other 4 WHO groups of PH are left heart-, lung-, chronic thromboembolic-, and “miscellaneous” disease–associated PH.

There was a surge of drug-associated PAH in the 1960s related to the anorexigen aminorex fumarate, which prompted the first World Symposium on PH in 1973. Current guidelines classify drug-associated PAH into 4 categories⁶ (Table 1).

The pathophysiology of PAH is complex but is known to at least involve endothelial cells, smooth muscle cells, and fibroblast dysfunction although many other cell types have also been implicated. The involved molecular derangements impair production of vasodilators including nitric oxide and prostacyclin and increase the production of vasoconstrictors and proinflammatory molecules such as endothelin-1, serotonin, and thromboxane-A.⁷ Systemic increase of serotonin in PAH is believed to be in the pathobiologic pathway of developing PAH that may act as a growth factor for pulmonary artery smooth muscle cells (PASCs).⁸ These aberrant changes increase vascular tone and promote pathologic vascular remodeling, hypertrophy, in-situ thrombosis, platelets aggregation, and disruptive proliferation of the pulmonary arteries.

Despite significant advances in the therapeutic options for PAH,⁹ PAH continues to be an incurable and devastating

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See page 1695 for disclosure information.

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Table 1
Drugs and strength of association with pulmonary arterial hypertension

Likelihood of Association	Drugs
Definite	Aminorex
	Fenfluramine
	Dexfenfluramine
	Benfluorex
Likely	In-utero exposure to SSRI's
	Amphetamines/methamphetamines
	L-tryptophan
	Dasatinib
Possible	Cocaine
	Phenylpropanolamine
	St. John's wort
	Other chemotherapeutic agents
Unlikely	Interferon alpha and beta
	Cigarette smoking, oral contraceptives, estrogens

SSRIs = selective serotonin reuptake inhibitors.

disease. The estimated median survival of PAH without specific pulmonary vasodilators is about 2.8 years,¹⁰ and even with currently available therapies, patients with PAH still have a shortened life span.⁹

Implicated Pathways Associated With PVD: The Serotonin System “Common Denominator”

Serotonin is a potent vasoconstrictor. It mediates proliferation of the PSMCs and fibroblasts, migration of the PSMC, aggregation of platelets, and matrix deposition by fibroblasts (Figure 1). Although the association with PAH has been well established (including in animal data), none of the currently approved medications to treat PAH directly target the serotonin pathway.^{11,12} Despite this established association, the serotonin pathway is complex and its full association with PVD is not fully understood.

The serotonin system has 4 main components: membrane receptor, serotonin transporter (SERT), synthesis of serotonin (through tryptophan hydroxylase-1), and downstream effector molecules.^{12,13} SERTs are Na⁺/Cl⁻ membrane transporters, which belong to the same transporter family as noradrenaline receptors. SERTs are present in neural, endothelial, and smooth muscle cells, which tie together the major effect (appetite suppression) and side effects of anorexigens (PVD and cardiac valvular disease; Figure 2). SERT gene polymorphism is associated with idiopathic PAH.¹⁴

Receptors 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} are the 3 subtypes of the 5-HT₂ receptors that mediate the physiological functions of serotonin. The 5-HT_{2B} receptors have the strongest association with valvular heart disease and PH. The 5-HT_{2C} receptors are located in the central nervous system and have similar amino acid sequence homology to 5-HT_{2A}.

Some of the downstream effector molecules and signaling pathways involve reactive oxygen species, Rho Kinase, and many other kinases and growth factors. There seems to be a synergistic effect of serotonin with other vasoconstrictors¹¹ such as endothelin-1, noradrenaline, and

thromboxane-A which are known PAH pathologic molecules. Abnormalities in the homeostasis of the serotonin system are believed to be “second hits” that patients with bone morphogenetic protein receptor type-2 mutation for example require for the development of PAH.

Anorexigens

Although many anorexigens believed to cause PAH have been withdrawn from the market (Table 2), a strong causal relation with PAH was never conclusively established. Several other weight loss medications are still currently approved by the US Food and Drug Administration (FDA; Table 3).

Aminorex fumarate: In the 1960s, aminorex fumarate was an appetite suppressant that was particularly popular in Europe for its efficacy in weight loss. However, as mentioned previously, the use of aminorex led to a surge in the incidence of PAH. Because of this outbreak, it was subsequently removed from the market in 1972.

Aminorex fumarate is structurally similar to epinephrine and acts as a central stimulant. Median exposure to time of onset of PAH was estimated between 3 weeks and 1 year. If discontinued early, regression of PAH was often seen. The partial, if not complete, resolution of PAH after drug cessation is consistent with our more recent experience with non-anorexigens-associated PAH, such as dasatinib-associated PAH.

Fenfluramines/fen-phen: Structurally related compounds were developed in the 1980s, the most popular of which was “Fen-phen” or fenfluramine-phentermine. Fenfluramine was FDA approved for the use as an appetite suppressant but was commonly combined with phentermine to enhance its weight loss effects. Fenfluramine (and aminorex) is a sympathomimetic amine that is a SERT substrate and an indirect serotonergic agonist.

Fenfluramine promotes the rapid release of serotonin, inhibits its reuptake, and may have receptor-agonist activity.⁴ Phentermine is a noradrenergic agent and derivative of amphetamine, whose main action is to stimulate norepinephrine release but also interferes with serotonin clearance.⁴ The International Primary Pulmonary Hypertension Study, a multicenter case control study, showed a strong association between fenfluramines and PAH, with the risk of PAH increasing with duration of use.^{15,16}

However, it was not until 1997 that fenfluramines were removed from worldwide use.³ This followed the discovery of their association with valvular heart disease (both left- and right-sided heart valves).^{4,17} Seventy-seven percent of patients were symptomatic from their new valvular disease, and 24% required valve replacement surgery.¹⁷

The mechanism of fenfluramines causing valvular disease is hypothesized to involve serotonin, and this is in part extrapolated from data known about patients with malignant carcinoid syndrome. These patients have very high levels of circulating serotonin and often develop fibrodysplasia that primarily involves the valvular endocardium.¹⁸ Studies have also found that there are SERTs on heart valves that have a high affinity for fenfluramines, strengthening the evidence for this association.


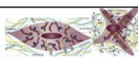




Effect of Serotonin on PASMCs 	↑ proliferation / apoptosis resistance ↑ migration ↑ vasoconstriction
Effect of Serotonin on fibroblasts 	↑ proliferation ↑ matrix deposition / fibrosis 
Effect of Serotonin on platelets 	↑ aggregation 
Effect of Serotonin on progenitor cells 	↑ proliferation, activity, influx, & migration of progenitor cells

Figure 1. Effect of serotonin on select cells in the pathophysiology of PVD.

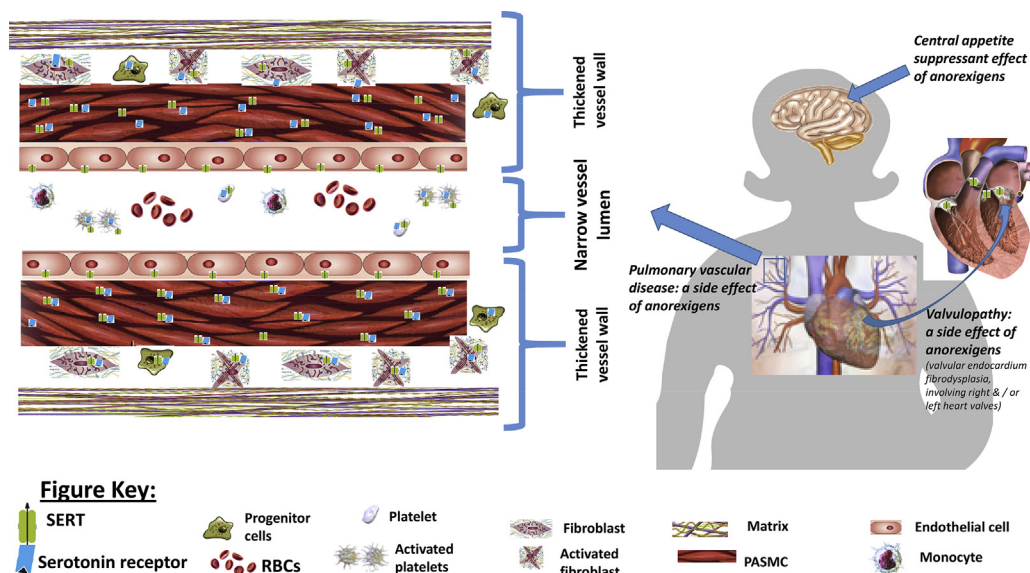


Figure 2. Relevant sites of serotonin actions causing appetite suppression centrally and heart valvulopathy and PVD. Relevant select sites of action of serotonin (brain, heart valves, and pulmonary vasculature) on the *right side* of the figure, and a schematic cross section of a pulmonary arteriole on the *left side*. The serotonin (produced in the endothelial cells) has transmembrane receptors (SR) and membrane transporters (SERT) on the PASMCs, fibroblasts, and platelets, among other targets. The progenitor cells also have serotonin receptors. RBCs = red blood cells.

The exact mechanism by which fen-phen and similar drugs increase PAH risk is also not well understood; however, serotonin is again implicated. It is hypothesized that the increased serotonin blood levels results in pulmonary arteries vasoconstriction, chronic stimulation for increased pulmonary blood pressure, and resultant hypertrophy of arterial smooth muscle (Figure 1). As noted previously for their association with valvular disease, studies found that these drugs affect SERTs.¹⁹ Studies also suggest that there are more SERTs in human lungs than in the human brain, suggesting that the lungs, and specifically the pulmonary vasculature, are likely major sites of action for these drugs.²⁰ Based on this, the 3 major relevant sites of action of the drugs targeting the serotonin pathway are the central nervous system, pulmonary vasculature, and cardiac valves (Figure 2), which would explain the effect and side effects of these drugs, respectively.

Exposure to fenfluramines for as little as few weeks is associated with PAH.¹⁵ Furthermore, PAH may not manifest until many years after drug discontinuation.

Benfluorex: Benfluorex is a benzoate ester that shares similar structural and pharmacologic characteristics with

fenfluramine derivatives. Its active and common metabolite is norfenfluramine, which is also a metabolite of fenfluramines with a similar chemical structure to amphetamines.²¹ Benfluorex was approved for the use in patients with hypertriglyceridemia or obese diabetics, however, was frequently used off-label as an anorexigen. It was not until much larger studies were done that a strong association between benfluorex and valvular heart disease could be identified.⁵ Again, serotonin was implicated and studies found that the metabolite norfenfluramine had a high affinity for the SERTs on heart valves.²² For this reason, it was withdrawn from the market⁵ although questions about its PVD association still remain.²³

Supplements

In addition to FDA approved medications, there have also been over-the-counter weight loss supplements implicated in PAH pathogenesis. For example, Ephedra is a herbal preparation used in several weight loss supplements, including Herbalife and Hydroxycut.²⁴ It is a naturally occurring chemical stimulant, a member of the class of ephedrine alkaloids which are amphetamine-like

Table 2
Weight loss drugs removed from market

Generic drug name	Mechanism of Action	Years on the market	Year removed from market
Fenfluramine	Serotonin-reuptake inhibitor	24	1997
Sibutramine	Serotonin-reuptake inhibitor	13	2010
Dexfenfluramine	Serotonin-reuptake inhibitor	1	1997
Aminorex fumarate	Central stimulant, indirect serotonin agonist (24)	10	1972
Benfluorex	Serotonin-reuptake inhibitor	33	2009
Chlorphentermine	Adrenergic agent, serotonin-reuptake inhibitor	7	1969

compounds. In the 1990s, concerns about the safety of ephedra-containing products were raised. In 1997, the Department of Health and Human Services in the US evaluated all dietary supplements containing ephedrine alkaloids and found many adverse effects including a case of PAH. Subsequently, ephedra adverse reactions were found to include sudden cardiac death, myocardial infarction, and stroke,²⁵ leading to FDA banning in 2004. Of note, Hydroxycut was reformulated without ephedra and remarketed for public use in 2004. In 2009, the new formulation of Hydroxycut was again recalled because of the development of serious liver problems in some patients.²⁴ As of 2010, Hydroxycut was back on the market to be removed again in 2015 for concerns about liver toxicity.

The exact mechanism linking ephedrine alkaloids to PAH has not been well defined, but their vasoconstrictive adrenergic effect on cerebral arteries was implicated in cases of stroke,²⁵ which in theory could be extrapolated to pulmonary arteries and the development of PAH. It should be noted that any process or molecule that generates chronic vasoconstriction can result in irreversible pathologic remodeling and the vasculopathy may persist even if the original vasoconstrictor stimulus is removed.

One important concern regarding supplements is that they are not regulated by the FDA. FDA-approved drugs cannot enter the market until there is sufficient evidence that they are safe and effective, whereas supplements become available without significant restrictions and are removed from the market only after significant harm is shown which usually is incidentally found. There is no standardization or quality control of supplements, and the ingredients dosage can vary widely between brands and lots.

Although, St John's wort is not an anorexigen, its effect on modulating serotonin, norepinephrine, and dopamine levels at least in part by inhibiting their reuptake, is likely the origin of St John's wort's association with PVD (Table 1).

Tying it All Together With the Currently Available Anorexigens

Although a clear association between the currently available anorexigens and PAH is not established, their

mechanisms of action are in many aspects similar to other drugs with documented harm. Their potential PAH link is concerning. Based on our expanding but still relatively limited understanding of PAH pathophysiology, serotonin receptor agonists have a potentially high risk to be associated with PAH. Lorcaserin for example is a serotonin receptor agonist that is currently approved for short-term use for weight loss (Table 3). It acts on the hypothalamus with selective affinity for the 5-HT_{2C} receptor, less so for the 5-HT_{2A} and 5-HT_{2B} serotonin receptors.

Based on the Behavioral modification and Lorcaserin for Overweight and Obesity Management trial,²⁶ the lorcaserin's package insert does not warn of an increased risk of valvular disease.²⁷ It is important to note that about 50% of the patients in this trial did not finish the study. Although the development of PH was not explicitly listed as a prespecified safety outcome, the data on the pulmonary artery systolic pressure were prospectively measured per the study protocol. (In our opinion, all trials of medications that may interact with the serotonin pathway should have PH as a clear prespecified safety outcome.) Some have raised concerns about an elevated odds ratio of 1.4 for developing possible PH^{27,28} despite a statistically insignificant association (p value of 0.16), in view of the clinical implications for such a progressive and fatal disease and especially in the setting of inadequate sample size to tighten the CI for such a possible association with a relatively rare complication. There is still possible association with mitral regurgitation.²⁸

Given that lorcaserin's mechanism of action is similar to some extent to fenfluramines, the association with valvulopathy is plausible. Similar to other serotonin receptor agonists, lorcaserin may similarly act to cause valvular fibrosis although this association was not evident in the trial (see challenges section in the following).

The currently available sympathomimetic agents (Table 3) are structurally similar to amphetamines, which are risk factors for PAH based on case reports and their pharmacologic similarities to fenfluramine.²¹ A large retrospective study that investigated amphetamines and their role in the development of PAH found that patients with idiopathic PAH were 10 times more likely to have used stimulants than those with PAH associated with other risk factors.²⁹ These drugs act predominantly on norepinephrine and dopamine transporters, with less effect on SERTs. Serotonin and norepinephrine both have vasoconstrictive and growth modulating effects on smooth muscle cells,^{21,29} suggesting a potential link to PAH.

In addition, chlorphentermine, a chlorinated phentermine analogue, was found to inhibit serotonin uptake in rodents, similar to fenfluramines.²⁰ Aminorex is also a central stimulant that was later found to have indirect action on SERTs.¹³ This suggests there is a role of serotonin in these medications that has not yet been identified.

The association between in-utero exposure to selective serotonin reuptake inhibitors (SSRIs) and persistent PH of the newborn, as well as concerns raised by some (not validated as of yet) about the association between SSRIs and PAH³⁰ strongly support the need to further explore the serotonin pathway in the PVD pathogenesis. The risk of developing PH after in-utero exposure was independent of the specific SSRI used and without a dose-response

Table 3
Currently available weight loss medications

Drug Class	Generic Drug Names	Mechanism of Action	Year of Approval	Approval indication
Disrupt fat absorption	Orlistat	Pancreatic and gastric lipase inhibitor	1999	Chronic use
Serotonin agonists	Lorcaserin	Serotonin 5-HT _{2C} receptor agonist	2012	Chronic use
Sympatho-mimetics	Phentermine	Norepinephrine-releasing agent	1960s	Short-term use
	Diethylpropion	Norepinephrine-releasing agent + GABA receptor modulator	1960s	Short-term use
Antidepressants	Phendimetrazine	Norepinephrine-releasing agent	1979	Short-term use
	Benzphetamine	Norepinephrine-releasing agent	1982	Short-term use
	Phentermine-topiramate	Norepinephrine-releasing agent	2012	Chronic use
	Bupropion-naltrexone	Norepinephrine and Dopamine reuptake inhibitor + opioid antagonist	2014	Chronic use
Hypoglycemics	Liraglutide	Glucagon-Like-Peptide-1 agonist	2014	Chronic use

relation, which may suggest a noncausal relation. Although both SSRIs and anorexigens ultimately increase the downstream effects of serotonin, the way this effect is induced is different: SSRIs inhibits the reuptake of serotonin and thus increases the availability of already secreted serotonin, whereas anorexigens may do this through many different ways including, for example, direct agonist effect on the 5-HT receptors. The relevance of this difference is not understood. Having limited evidence that SSRI may actually have protective effects on the pulmonary vasculature in some animal models highlights the complex serotonin-PVD relation.

Challenges to Identify PVD Risks

The incidence of developing PAH even with a drug known to cause the condition is quite low. One study found that 0.2% of those who used aminorex fumarate went on to develop PAH, with the incidence increasing with amount and duration of drug taken. This highlights the rarity of drug-associated PAH and thus the need for a large number of patients to be on the drug before an association is confirmed.

In addition, as noted in cases with fenfluramine, symptoms of PAH were found up to 8 years after the use of fenfluramine, even longer in our own experience, and it was on the market for 24 years before sufficient evidence was found linking it to PAH. More time may be needed for these associations to reveal themselves. Although the phase 3 trials of these anorexigens did not show an association with PAH, this association cannot be confidently ruled out.

Although there is no easy solution to detect the association between a newly approved drug, be it anorexigenic or otherwise, and its rare potential complication of PVD, an active collaboration between registries, international regulatory agencies, and patient-driven PAH advocacy groups would facilitate early recognition and hopefully earlier removal of any offending agent from the market. In addition, a thorough history must be taken of all medications and supplements a patient may have taken to make the appropriate diagnosis. Many patients do not consider supplements or herbs as medications, so detailed and specific history taking is warranted.

Disclosures

The authors have no conflicts of interest to disclose.

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