Anorexigen-Associated Pulmonary Arterial Hypertension and the Serotonin Hypothesis: A Story Worth Telling

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Diet pills such as aminorex, fenfluramine, and dexfenfluramine have been strongly associated with the development of pulmonary arterial hypertension (PAH). Other drugs ostensibly related in function have also been implicated as "likely" associated, including amphetamine, methamphetamine, and the serotonin precursor L-tryptophan. Serotonin signaling is thought to be a mediator of diet pill–associated PAH, and it is also thought to potentially play a significant role in PAH in general. In this article, we review the evidence supporting the serotonin hypothesis in PAH in both contexts, and the potential concerns related to selective serotonin reuptake inhibitors and other medications acting on serotonin signaling pathways.

SEROTONIN HYPOTHESIS

The serotonin hypothesis of pulmonary arterial hypertension (PAH) was first proposed in the 1990s after small studies in primary pulmonary hypertension (PH) found increased plasma serotonin levels and abnormal platelet serotonin storage.[1,2] (Throughout this review, primary PH [PPH] is used when it was used in the original manuscripts; in most cases this refers to what is now called idiopathic PAH [IPAH], although in some studies drug/toxin-associated PAH was also included under this term.)

The serotonin hypothesis gained popularity after case-control studies suggested an association between anorexigens and PPH. Several serotonin-related mechanisms were suggested to explain this association.[3-6] First, anorexigens increase free serotonin levels, activating serotonin receptors and causing pulmonary artery vasoconstriction and pulmonary artery smooth muscle cell proliferation. Also, norfenfluramine, a fenfluramine metabolite, has direct activity on the serotonin 2B receptor.[7] Finally, internalization of the drug via the serotonin transporter may disrupt internal serotonin storage and promote pulmonary artery smooth muscle cell (PASMC) proliferation.

The serotonin story was not without controversy, however. A few studies questioned the role for serotonin signaling in the association between fenfluramine and PAH, because serotonin levels were *lower* after chronic fenfluramine exposure in animals. However, subsequent more careful measurements described a 2- to 4-fold increase in serotonin levels.[8,9] The authors of these studies suggested that the prior results were due to difficulty in preventing serotonin release during blood handling and a real reduction in intracellular serotonin stores after long-term exposure. (Of note, similar issues may have contributed to subsequent variability in free serotonin levels in studies of PAH in patients as well.[10])

Over the years, the serotonin hypothesis has been revised and expanded, but remains generally intact (Figure 1). Modern work has emphasized the importance of local serotonin production and signaling,[11] the serotonin 1B receptor (vs other serotonin receptor subtypes),[12] and interactions between estrogen pathways and serotonin signaling.[13]

CLINICAL STUDIES FOCUSED ON SEROTONIN SIGNALING

A number of medications targeting serotonin receptors have been investigated in clinical studies in patients with PAH, with disappointing results thus far. This includes hemodynamic studies of serotonin 2A and serotonin 2A/2B receptor antagonists (Table 1). Subsequent studies suggest that the

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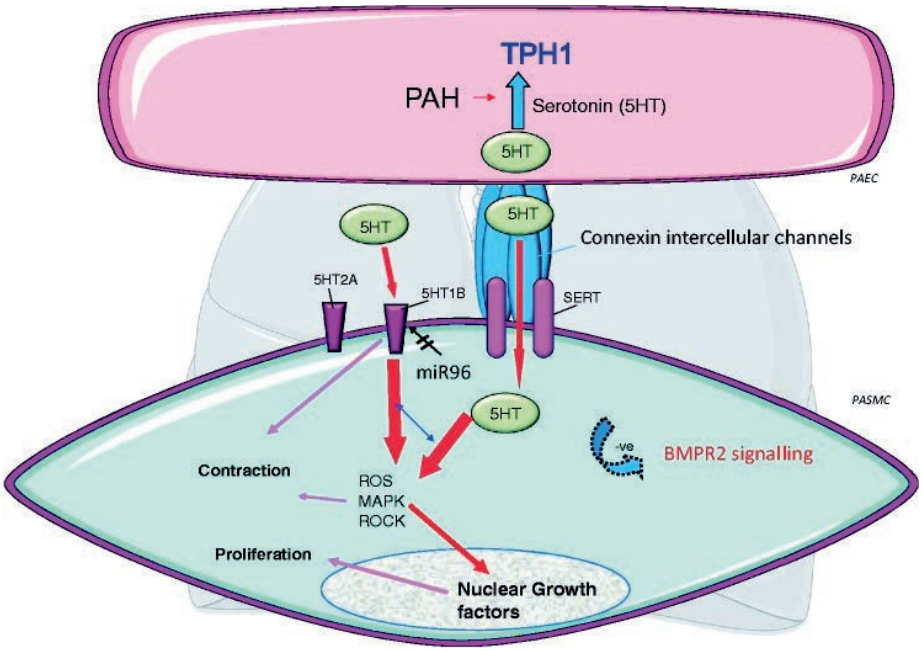

Figure 1: Serotonin synthesis via tryptophan hydroxylase 1 (TPH1) is increased in pulmonary artery endothelial cells (PAECs) from rodent models of PH (inset showing a small pulmonary artery from a control and hypoxic rat with TPH1 staining in the PAECs) and patients with PAH. Serotonin can act in a paracrine fashion on underlying PASMCs, facilitated by myoendothelial gap junctions (connexin intercellular channels). Serotonin can enter the PASMC via the serotonin transporter (SERT) or activate serotonin receptors. The important receptor in the human pulmonary arterial smooth muscle cell (PASMC) is the 5-HT1B receptor, regulated by microRNA96 (miR96) such that it is upregulated (by decreased miR96 expression) in female PAH patient PASMCs. 5-HT1B activation and SERT activity cooperate to induce PASMC contraction and proliferation via increased reactive oxygen species (ROS) and activation of downstream signaling pathways such as MAPK and rho-kinase (ROCK). These can also facilitate nuclear growth factors such as GATA-4. Increased serotonin can facilitate a pulmonary hypertensive phenotype in BMPR2-/+ mice via decreased BMPR2 signaling. Reprinted with permission [Creative Commons CC BY license] from MacLean MR. The serotonin hypothesis in pulmonary hypertension revisited: targets for novel therapies (2017 Grover Conference Series). *Pulm Circ*. First published February 22, 2018.

Table 1. Hemodynamic Studies of Medications Acting on Serotonin Signaling in Humans

	Target	Patient Population	Results
Ketanserin[59]	5-HT2A receptor antagonist	PAH	PVR fell 12% vs baseline ($P<0.001$); SVR fell 16.5% ($P<0.001$) Acute hemodynamics only
Terguride (abstract)[60]	5-HT2A/2B receptor antagonist	PAH	No change in PVR vs placebo (16 weeks, terguride vs placebo: -0.5 Wood units, $P=$NS)
Fluoxetine (abstract)[17]	Serotonin transporter reuptake inhibitor (SSRI)	PAH	No change in PVR vs baseline (12-24 weeks)
Sumatriptan[61]	5-HT1B/D receptor agonist	Healthy controls	mPAP increased 58% acutely (from 16 mm Hg to 26 mm Hg)

serotonin 1B receptor is more important in pulmonary vasoconstriction in human lungs,[14] but clinical studies are lacking. The serotonin transporter has also been considered a potential therapeutic target, based on both in vitro human and animal studies and in animal models of PH due to monocrotaline or hypoxia.[15,16] We recently completed a small open-label study of fluoxetine in PAH (N=10), and found no significant hemodynamic improvement or worsening over 12 to 24 weeks.[17] Other researchers in this field have suggested that a more effective strategy could be to target both serotonin receptors and the serotonin transporter at the same time.[14,18] Combined 5-HT1B receptor/serotonin transporter antagonists are effective in preventing and reversing experimental PAH and at reducing serotonin-induced proliferation of PASMCs derived from IPAH patients. However, it remains to be seen whether the combination of 5-HT1B receptor/serotonin transporter antagonists will have similar effects in clinical studies.

STIMULANTS: SEROTONIN VS OTHER MECHANISMS OF ACTION

Most prescription and illicit stimulants as well as the diet pills aminorex, fenfluramine, and dexfenfluramine act as monoamine transporter substrates. They bind to and are internalized by various cell surface transporters including serotonin, norepinephrine, and dopamine. Cocaine, the major exception, is a monoamine transporter reuptake inhibitor. Transporter selectivity varies considerably. All 3 diet pills act as serotonin transporter substrates. Methamphetamine, and to a lesser extent amphetamine, also have activity at the serotonin transporter; this has been suggested as a likely contributor to methamphetamine-associated PAH.[19]

On the other hand, many other stimulants including phenylpropanolamine, methylphenidate, and phentermine have little or no serotonin activity. Norepinephrine receptor activation can also promote pulmonary vasoconstriction and vascular remodeling; as such, an adrenergic hypothesis of PAH has also been proposed.[20] It should be noted,

however, that evidence to support an association with these medications is relatively weak. Only phenylpropanolamine, found to be associated with PPH in one case-control study,[21] has even been considered "possibly associated" in prior consensus documents.[22]

In contrast, phentermine was included in 2 case-control studies, neither of which found an association,[6,21] and only case reports have described phentermine-[23] and methylphenidate-associated PAH.[24] Some researchers have also argued that these case reports likely represented IPAH rather than drug-associated PAH, given the widespread use of these medications and small number of reports.[25] Further studies will be needed to address these possible associations.

For the illicit stimulants, a number of other mechanisms could also contribute, as described in more detail in the Stimulants and PAH article in this issue by Ramirez et al. In addition to mechanisms related to the primary (intended) drug, contaminants and adulterants must also be considered. Some illicit drug users inject or inhale crushed tablets, and the talc used as a filler and lubricant for the pills may result in foreign body granulomas in the lung parenchyma or vasculature, contributing to PH.[26,27] Another potential contributor has been described with regard to levamisole, an adulterant commonly found in cocaine. Levamisole is an antihelminthic agent used to "cut" cocaine, presumably because it is both relatively inexpensive and has some stimulant properties of its own. However, levamisole is associated with a number of serious adverse reactions, and, most notably, is also metabolized to aminorex. This adulteration could contribute to a resurgence of aminorex-induced PH.[28]

It also remains unclear why some patients develop PAH after anorexigen exposure, but most do not. One hypothesis is that the anorexigens may serve as a "second hit" in patients who have a genetic predisposition to develop PAH. Indeed, patients with anorexigen-induced PAH are more likely to harbor BMPR2 mutations (9%).[29] Moreover, serotonin increases susceptibility to PH in BMPR-deficient mice.[30]

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND PAH: TO PRESCRIBE OR NOT IN PAH?

Selective serotonin reuptake inhibitors (SSRIs) block the reuptake of serotonin and cause increases in circulating serotonin levels as well as alterations in serotonin signaling in the central nervous system. This has raised questions about whether SSRIs could lead to serotonin-mediated pulmonary vasoconstriction. However, circulating levels appear to return to baseline during long-term administration.[8]

Interestingly, the association between SSRIs and PH also appears to be different for newborns vs adults. A rat model showed that prenatal exposure to fluoxetine induces fetal PH.[31] Furthermore, epidemiology studies reveal that risk for persistent pulmonary hypertension of the newborn (PPHN) is increased in neonates whose mothers report SSRI exposure.[32] Although variability has been reported for this finding,[33-35] meta-analyses and larger well-designed population studies have convincingly shown a small but statistically significant increased risk of PPHN with SSRI use late in pregnancy (after 20 weeks' gestation).[36,37]

In contrast to the neonatal studies, SSRI use has not been clearly linked with the development of PAH in adult studies. Four studies have investigated antidepressant use in PAH (all antidepressants combined or specifically SSRIs). Three utilized a traditional case-control methodology, none of which found a positive association between antidepressant or SSRI use and PAH. In fact, SSRI use was numerically lower in PPH patients compared with controls (P=NS or not reported in all three).[6,21,38,39] A fourth study using an administrative dataset found a significant association with SSRI exposure (OR 1.6, 95% CI 1.1 to 2.1), but the authors themselves suspected residual confounding may have accounted for their findings.[40] A separate concern regarding the validity of this finding is that the accuracy of the PAH diagnosis code in database studies is often poor.[41]

Outcomes among PAH patients who are subsequently treated with an SSRI have also been investigated. These studies had mixed results, with improved outcomes in 2 studies,[39,42] similar outcomes vs untreated patients in one study, and worse outcomes for the SSRI-treated patients in a fourth study.[40,43] Finally, animal studies have found a protective effect in both monocrotaline- and chronic hypoxia–induced PH in adult rats and mice.[44,45]

Given the absence of randomized controlled clinical trials of SSRIs in PAH, a firm conclusion is not currently possible. So practically, what recommendations can be made with regard to SSRI use in PAH? Unfortunately in adult PAH patients, depression is very common (25% prevalence) and SSRIs are considered a first-line medication for treatment of major depression.[46] Although consensus statements are lacking, our current practice is to consider use of an SSRI for moderate or severe depression in PAH patients in whom they are otherwise indicated. For pregnant women, stronger evidence of harm has been suggested. Nevertheless, consensus documents from the American College of Obstetricians and Gynecologists (ACOG) currently note that "untreated maternal depression is associated with increased rates of adverse outcomes (eg, premature birth, low birth weight, fetal growth restrictions, postnatal complications), especially when depression occurs in the late second to early third trimester." They recommend the initiation or continuation of SSRIs in the setting of past or current moderate or severe depression.[47] Thus while we express caution, benefits of treatment may in many cases outweigh the risks of untreated depression. Further studies are required in this area.

ANOREXIGENS AND PAH: REVIEW/NEWER AGENTS

As much of the world continues to struggle with the obesity epidemic, anorexigens continue to be prescribed to aid weight loss, generally in combination with lifestyle approaches. Medications for obesity have a long history of controversy. Between the 1940s and the 1970s, amphetamines were commonly prescribed for weight loss. With recognition of the potentially addictive nature of amphetamines, the Bureau of Narcotics and Dangerous Drugs (the forerunner to today's Drug Enforcement Agen-

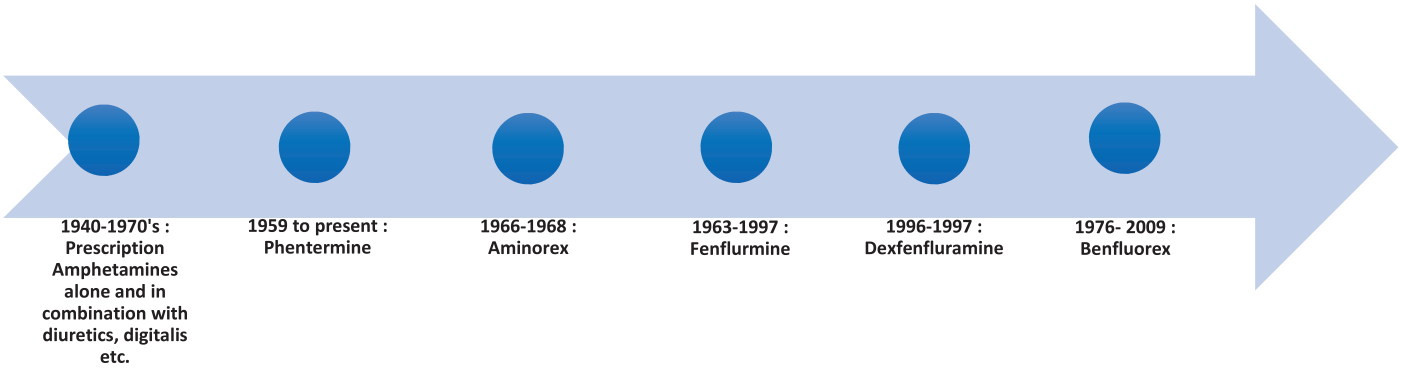

Figure 2: Timeline of anorexigens associated with PAH.

cy) imposed more restrictions on their prescription, and a shift in prescribing patterns toward alternative agents began.[48] Fenfluramine and dexfenfluramine subsequently became the most commonly prescribed diet pills, prescribed alone and in combination with phentermine until their withdrawal from the market in 1997. Finally, benfluorex, which is molecularly similar to fenfluramine, was introduced in 1976 for the treatment of diabetes and metabolic syndrome. Although withdrawn from several European markets due to a suspected association with valvular heart disease, it remained available in France until 2009, when additional studies found an association with both valvular heart disease and PAH; an estimated 300,000 patients were exposed annually.[49-53] Figure 2 shows a timeline of anorexigen approvals.

Newer Agents

Among the diet pills shown in the timeline in Figure 2, only phentermine remains available by prescription for this indication. However, a number of other newer anorectic agents and combinations of agents are currently available. This includes orlistat (pancreatic lipase inhibitor), liraglutide (glucagon-like peptide agonist), lorcaserin (5-HT2C agonist), bupropion-naltrexone, and phentermine in combination with topiramate. None have been significantly associated with PH, and one study of liraglutide found that it could prevent and reverse monocrotaline-induced PAH in rats.[54]

Lorcaserin, as a 5-HT2C agonist, has been of particular interest to the PH community because it interacts with a serotonin receptor. In 2 randomized control trials including 3182 patients and 4008 patients treated for one year, no increase in cardiac valvulopathy or PH was seen in association with lorcaserin use.[55,56] The size and duration of newer anorexigen studies has been mandated by the Food and Drug Administration, with goals of allowing assessment of both longer-term efficacy as well as adverse effects.[57]

In contrast to the large studies described above, a larger study investigating the combination drug naltrexone-buproprion was terminated early related to premature disclosure of results from an interim analysis. Although no cardiovascular safety concerns were raised and no association with the development of PAH was found, completed long-term studies are lacking.[58]

CONCLUSION

Anorectic agents like aminorex, fenfluramine, and benfluorex are strongly associated with development of PAH, while evidence in support of methamphetamine, amphetamine, and cocaine is growing. Current evidence suggests that alteration in the serotonin pathway by these drugs may play a major role in development of PAH. Since most exposed individuals do not develop PAH, genetic susceptibility and other factors are thought to play an important role.

Serotonin receptors and transporters have also been considered as potential therapeutic targets. Studies so far have been disappointing, but a number of additional serotonin pathway targets exist. Potential future considerations include inhibition of serotonin synthesis, antagonists to the serotonin 1B receptor (vs antagonists to the serotonin 2A and 2B receptors), and targeting one or more serotonin receptors while also blocking the serotonin transporter.[14]

References

1. Herve P, Drouet L, Dosquet C, et al. Primary pulmonary hypertension in a patient with a familial platelet storage pool disease: role of serotonin. *Am J Med*. 1990;89(1):117-120.
2. Herve P, Launay JM, Scrobohaci ML, et al. Increased plasma serotonin in primary pulmonary hypertension. *Am J Med*. 1995;99(3):249-254.
3. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997;337(9):581-588.
4. Souza R, Humbert M, Sztrymf B, et al. Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. *Eur Respir J*. 2008;31(2):343-348.
5. Abenhaim L, Moride Y, Brenot F, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med*. 1996;335(9):609-616.
6. Rich S, Rubin L, Walker AM, Schneeweiss S, Abenhaim L. Anorexigens and pulmonary hypertension in the United States: results from the surveillance of North American pulmonary hypertension. *Chest*. 2000;117(3):870-874.
7. Hong Z, Olschewski A, Reeve HL, Nelson DP, Hong F, Weir EK. Nordexfenfluramine causes more severe pulmonary vasoconstriction than dexfenfluramine. *Am J Physiol Lung Cell Mol Physiol*. 2004;286(3):L531-L538.
8. Zolkowska D, Baumann MH, Rothman RB. Chronic fenfluramine administration increases plasma serotonin (5-hydroxytryptamine) to nontoxic levels. *J Pharmacol Exp Ther*. 2008;324(2):791-797.

9. Zolkowska D, Rothman RB, Baumann MH. Amphetamine analogs increase plasma serotonin: implications for cardiac and pulmonary disease. *J Pharmacol Exp Ther*. 2006;318(2):604-610.
10. Lederer DJ, Horn EM, Rosenzweig EB, et al. Plasma serotonin levels are normal in pulmonary arterial hypertension. *Pulm Pharmacol Ther*. 2008;21(1):112-114.
11. Eddahibi S, Guignabert C, Barlier-Mur AM, et al. Cross talk between endothelial and smooth muscle cells in pulmonary hypertension: critical role for serotonin-induced smooth muscle hyperplasia. *Circulation*. 2006;113(15):1857-1864.
12. Morecroft I, Heeley RP, Prentice HM, Kirk A, MacLean MR. 5-hydroxytryptamine receptors mediating contraction in human small muscular pulmonary arteries: importance of the 5-HT1B receptor. *Br J Pharmacol*. 1999;128(3):730-734.
13. Wallace E, Morrell NW, Yang XD, et al. A Sex-Specific MicroRNA-96/5-Hydroxytryptamine 1B Axis Influences Development of Pulmonary Hypertension. *Am J Respir Crit Care Med*. 2015;191(12):1432-1442.
14. MacLean MMR. The serotonin hypothesis in pulmonary hypertension revisited: targets for novel therapies (2017 Grover Conference Series). *Pulm Circ*. 2018;8(2):2045894018759125.
15. MacLean MR, Deuchar GA, Hicks MN, et al. Overexpression of the 5-hydroxytryptamine transporter gene: effect on pulmonary hemodynamics and hypoxia-induced pulmonary hypertension. *Circulation*. 2004;109(17):2150-2155.
16. Morecroft I, Loughlin L, Nilsen M, et al. Functional interactions between 5-hydroxytryptamine receptors and the serotonin transporter in pulmonary arteries. *J Pharmacol Exp Ther*. 2005;313(2):539-548.
17. Sodimu A, Bartolome S, Igenoza O, Chin KM. Hemodynamic effects of fluoxetine in pulmonary arterial hypertension (PAH) - an open label pilot study. *Am J Respir Crit Care Med*. 2018;197:A5701.
18. Morecroft I, Pang L, Baranowska M, et al. In vivo effects of a combined 5-HT1B receptor/SERT antagonist in experimental pulmonary hypertension. *Cardiovasc Res*. 2010;85(3):593-603.
19. Rothman RB, Baumann MH. Methamphetamine and idiopathic pulmonary arterial hypertension: role of the serotonin transporter. *Chest*. 2007;132(4):1412-1413.
20. Salvi SS. Alpha1-adrenergic hypothesis for pulmonary hypertension. *Chest*. 1999;115(6):1708-1719.
21. Walker AM, Langleben D, Korelitz JJ, et al. Temporal trends and drug exposures in pulmonary hypertension: an American experience. *Am Heart J*. 2006;152(3):521-526.
22. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34-D41.
23. Bang WD, Kim JY, Yu HT, et al. Pulmonary hypertension associated with use of phentermine. *Yonsei Med J*. 2010;51(6):971-973.
24. Karaman MG, Atalay F, Tufan AE, Erdogan A. Pulmonary arterial hypertension in an adolescent treated with methylphenidate. *J Child Adolesc Psychopharmacol*. 2010;20(3):229-231.
25. Hendricks EJ, Rothman RB. RE: Pulmonary hypertension associated with use of phentermine? *Yonsei Med J*. 2011;52(5):869-870.
26. Robertson CH Jr, Reynolds RC, Wilson JE 3rd. Pulmonary hypertension and foreign body granulomas in intravenous drug abusers. Documentation by cardiac catheterization and lung biopsy. *Am J Med*. 1976;61(5):657-664.
27. Arnett EN, Battle WE, Russo JV, Roberts WC. Intravenous injection of talc-containing drugs intended for oral use. A cause of pulmonary granulomatosis and pulmonary hypertension. *Am J Med*. 1976;60(5):711-718.
28. Karch SB, Mari F, Bartolini V, Bertol E. Aminorex poisoning in cocaine abusers. *Int J Cardiol*. 2012;158(3):344-346.
29. Humbert M, Deng Z, Simonneau G, et al. BMPR2 germline mutations in pulmonary hypertension associated with fenfluramine derivatives. *Eur Respir J*. 2002;20(3):518-523.
30. Long L, MacLean MR, Jeffery TK, et al. Serotonin increases susceptibility to pulmonary hypertension in BMPR2-deficient mice. *Circ Res*. 2006;98(6):818-827.
31. Fornaro E, Li D, Pan J, Belik J. Prenatal exposure to fluoxetine induces fetal pulmonary hypertension in the rat. *Am J Respir Crit Care Med*. 2007;176(10):1035-1040.
32. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med*. 2006;354(6):579-587.
33. Andrade SE, McPhillips H, Loren D, et al. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Saf*. 2009;18(3):246-252.
34. Wilson KL, Zelig CM, Harvey JP, Cunningham BS, Dolinsky BM, Napolitano PG. Persistent pulmonary hypertension of the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors. *Am J Perinatol*. 2011;28(1):19-24.
35. Wichman CL, Moore KM, Lang TR, St Sauver JL, Heise RH Jr, Watson WJ. Congenital heart disease associated with selective serotonin reuptake inhibitor use during pregnancy. *Mayo Clin Proc*. 2009;84(1):23-27.
36. Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. *BMJ*. 2012;344:d8012.
37. Huybrechts KF, Bateman BT, Palmsten K, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. *JAMA*. 2015;313(21):2142-2151.
38. Louis WJ. Primary pulmonary hypertension and anorectic drugs. *N Engl J Med*. 1999;340(6):480-482.
39. Shah SJ, Gombert-Maitland M, Thenappan T, Rich S. Selective serotonin reuptake inhibitors and the incidence and outcome of pulmonary hypertension. *Chest*. 2009;136(3):694-700.
40. Dhalla IA, Juurlink DN, Gomes T, Granton JT, Zheng H, Mamdani MM. Selective serotonin reuptake inhibitors and pulmonary arterial hypertension: a case-control study. *Chest*. 2012;141(2):348-353.
41. Link J, Glazer C, Torres F, Chin K. International Classification of Diseases coding changes lead to profound declines in reported idiopathic pulmonary arterial hypertension mortality and hospitalizations: implications for database studies. *Chest*. 2011;139(3):497-504.
42. Kawut SM, Horn EM, Berekashvili KK, et al. Selective serotonin reuptake inhibitor use and outcomes in pulmonary arterial hypertension. *Pulm Pharmacol Ther*. 2006;19(5):370-374.
43. Sadoughi A, Roberts KE, Preston IR, et al. Use of selective serotonin reuptake inhibitors and outcomes in pulmonary arterial hypertension. *Chest*. 2013;144(2):531-541.
44. Guignabert C, Raffestin B, Benferhat R, et al. Serotonin transporter inhibition prevents and reverses monocrotaline-induced pulmonary hypertension in rats. *Circulation*. 2005;111(21):2812-2819.
45. Marcos E, Adnot S, Pham MH, et al. Serotonin transporter inhibitors protect against hypoxic pulmonary hypertension. *Am J Respir Crit Care Med*. 2003;168(4):487-493.
46. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest*. 2010;137(2):376-387.
47. ACOG Committee on Practice Bulletins–Obstetrics. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. *Obstet Gynecol*. 2008;111(4):1001-1020.
48. Rasmussen N. America's first amphetamine epidemic 1929-1971: a quantitative and qualitative retrospective with implications for the present. *Am J Public Health*. 2008;98(6):974-985.
49. Savale L, Chaumais MC, Cottin V, et al. Pulmonary hypertension associated with benfluorex exposure. *Eur Respir J*. 2012;40(5):1164-1172.
50. Boutet K, Frachon I, Jobic Y, et al. Fenfluramine-like cardiovascular side-effects of benfluorex. *Eur Respir J*. 2009;33(3):684-688.
51. Frachon I, Etienne Y, Jobic Y, Le Gal G, Humbert M, Leroyer C. Benfluorex and unexplained valvular heart disease: a case-control study. *PLoS One*. 2010;5(4):e10128.

52. Rafel Ribera J, Casanas Munoz R, Anguera Ferrando N, Batalla Sahun N, CaStro Cels A, Pujadas Capmany R. [Valvular heart disease associated with benfluorex]. *Rev Esp Cardiol*. 2003;56(2):215-216.
53. Noize P, Sauer M, Bruneval P, et al. Valvular heart disease in a patient taking benfluorex. *Fundam Clin Pharmacol*. 2006;20(6):577-578.
54. Lee MY, Tsai KB, Hsu JH, Shin SJ, Wu JR, Yeh JL. Liraglutide prevents and reverses monocrotaline-induced pulmonary arterial hypertension by suppressing ET-1 and enhancing eNOS/sGC/PKG pathways. *Sci Rep*. 2016;6:31788.
55. Fidler MC, Sanchez M, Raether B, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab*. 2011;96(10):3067-3077.
56. Smith SR, Weissman NJ, Anderson CM, et al; Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med*. 2010;363(3):245-256.
57. Krentz AJ, Fujioka K, Hompesch M. Evolution of pharmacological obesity treatments: focus on adverse side-effect profiles. *Diabetes Obes Metab*. 2016;18(6):558-570.
58. Nissen SE, Wolski KE, Prcela L, et al. Effect of Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients With Cardiovascular Risk Factors: A Randomized Clinical Trial. *JAMA*. 2016;315(10):990-1004.
59. McGoon MD, Vlietstra RE. Acute hemodynamic response to the S2-serotonergic receptor antagonist, ketanserin, in patients with primary pulmonary hypertension. *Int J Cardiol*. 1987;14(3):303-309.
60. Ghofrani HA, Al-Hiti H, Vonk-Noordgraaf A, et al. Proof-of-concept study to investigate the efficacy, hemodynamics and tolerability of terguride vs. placebo in subjects with pulmonary arterial hypertension: results of a double-blind, randomized, prospective phase IIa study. *Am J Respir Crit Care Med*. 2012;185:A2496.
61. MacIntyre PD, Bhargava B, Hogg KJ, Gemmill JD, Hillis WS. Effect of subcutaneous sumatriptan, a selective 5HT1 agonist, on the systemic, pulmonary, and coronary circulation. *Circulation*. 1993;87(2):401-405.
62. Blanpain C, Le Poul E, Parma J, et al. Serotonin 5-HT(2B) receptor loss of function mutation in a patient with fenfluramine-associated primary pulmonary hypertension. *Cardiovasc Res*. 2003;60(3):518-528.