Drugs induced pulmonary arterial hypertension

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Summary

Pulmonary arterial hypertension (PAH) is a rare disorder characterized by progressive obliteration of the pulmonary microvasculature, resulting in elevated pulmonary vascular resistance and premature death. According to the current classification, PAH can be associated with exposure to certain drugs or toxins, particularly appetite suppressant drugs, such as aminorex, fenfluramine derivatives and benfluorex. These drugs have been confirmed to be risk factors for PAH and were withdrawn from the market. The supposed mechanism is an increase in serotonin levels, which was demonstrated to act as a growth factor for the pulmonary arterial smooth muscle cells. Amphetamines, phentermine and mazindol were less frequently used but are also considered as possible risk factors for PAH. Dasatinib, a dual Src/Abl kinase inhibitor, used in the treatment of chronic myelogenous leukaemia was associated with cases of severe PAH, in part reversible after its withdrawal. Recently several studies raised the potential endothelial dysfunction that could be induced by interferon, and few cases of PAH have been reported with interferon therapy. Other possible risk factors for PAH include: nasal decongestants, like phenylpropanolamine, dietary supplement – L-Tryptophan, selective serotonin reuptake inhibitors, pergolide and other drugs that could act on 5HT2B receptors. Interestingly, PAH remains a rare complication of these drugs, suggesting possible individual susceptibility and further studies are needed to identify patients at risk of drugs induced PAH.
Pulmonary arterial hypertension (PAH) is a rare disease defined by an elevated mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, which leads to an increase in pulmonary vascular resistance, right cardiac failure and subsequently to death [1]. In the current classification of pulmonary hypertension (table I), PAH is defined as “group 1” and can be idiopathic, heritable or associated with different conditions, including connective tissue disease, congenital heart disease, HIV infection, portal hypertension but also exposure to toxins/drugs [2]. All these subgroups of PAH share common alterations in the signalling pathways and broadly similar histological findings, i.e. intense remodelling of non-muscularized pulmonary arteries [2]. The first “outbreak” of PAH occurred in 1965 in Switzerland, Germany and Austria and has been associated with an anorectic intake, aminorex [3,4]. After that, improvement in medical awareness and the diagnosis of the disease allowed the identification of additional drugs associated with an increased risk for the development of PAH. In the European Respiratory Society/European Society of Cardiology guidelines for diagnosis and treatment of PH, drugs and toxins are classified upon their risk of inducing PH on four categories (table II):

- **definite**: aminorex, fenfluramine, dexfenfluramine or benfluorex;
- **possible**: cocaine, phenylpropanolamine, chemotherapeutic agents or selective serotonin reuptake inhibitors (SSRI);
- **likely**: amphetamines/methamphetamines or L-tryptophan and;
- **unlikely**: cigarette smoking, oral contraceptives or estrogen [5].

The current knowledge and recent advances on drug-induced PAH will be discussed below.

**Anorexigen-associated PAH**

Appetite suppressant drugs have been the first well-established risk factors for the development of PAH [6,7]. First of all, aminorex, then, fenfluramine derivatives and more recently benfluorex have been used in the treatment of obesity, and were associated with PAH. Fenfluramine derivatives, like aminorex are potent serotonin (5-HT) uptake inhibitors and they interact directly with the 5-HT transporter [8]. In PAH, elevated levels of 5-HT may act as a growth factor for pulmonary artery smooth muscle cells, thus, contributing to the development of the disease [9–11].

**Aminorex**

In 1967, only 2 years after the introduction of the anorexigen drug aminorex on the market in Switzerland, West Germany and Austria, an epidemic of PAH was observed [4]. During this period, nearly 60% of the diagnosed patients had history of aminorex intake that allowed the recognition of temporal and geographic relationships between the use of the drug and PAH development. Patients had pre-capillary PH with plexogenic arteriopathy being found on histological examinations [2,4,12]. The outcome was severe: 10 years after the epidemic, half of the patients have died, usually of right heart failure [4].

**Fenfluramine and derivatives**

In the 1980s, several case reports suggested a possible relationship between the use of fenfluramine derivatives and PAH [13]. In the 1990s, an initial retrospective study found a possible role of fenfluramine derivatives as risk factors for the development of PAH [14]. The results of the International Primary Pulmonary Hypertension Study (IPPHS) conclusively demonstrated a strong association between PAH and the use of anorexic drugs (mainly derivatives of fenfluramine) [15]. In a French study, Simonneau et al. reported the characteristics of 62 patients with fenfluramine-induced PAH (61 women) [7]. The interval between the onset of dyspnea and that of drug intake was 49 ± 68 months. The majority of patients used fenfluramine derivatives for at least 3 months: about half of the patients used dexfenfluramine alone, 27% used fenfluramine in association with amphetamines, 11% used fenfluramine alone and 8% used both drugs [7]. When compared with sex-matched PAH patients non-exposed to fenfluramine, patients with fenfluramine-induced PAH had the same clinical presentation at diagnosis, comparable hemodynamics, were treated with the same available drugs and had broadly similar prognosis (50% overall survival at 3 years) [7]. By contrast, fenfluramine-induced PAH group was characterized by a higher age and BMI and a lower proportion of patients with an acute vasodilator response [7]. More recently, Sousa et al. showed that patients with fenfluramine-induced PAH might be carriers of bone morphogenetic protein receptor type 2 (BMPR2) mutations, in a similar proportion (22.5%) that was reported in sporadic PAH [16]. Interestingly, patients carrying a BMPR2 mutation had a significantly lower duration of exposure to fenfluramine than patients without any mutation [16]. The median survival was 6.4 years, without significant difference between fenfluramine-induced PAH and a control group of idiopathic and heritable PAH patients. Duration of fenfluramine exposure showed no relation to survival [16]. Fenfluramine derivatives were banned from commercial use in 1997.

In conclusion, fenfluramine-induced PAH patients share clinical, functional, hemodynamic and genetic features with idiopathic PAH patients, as well as similar overall survival rates. These observations suggest that fenfluramine derivatives may act as a trigger for PAH without influencing its clinical course [7,16].

**Benfluorex**

Benfluorex is a benzoate ester that shares similar structural and pharmacological characteristics with fenfluramine derivatives [17]. The active and common metabolite of each of these
molecules is norfenfluramine, which itself has a chemical structure similar to that of the amphetamines. The commercial product was marketed since 1976 as a treatment of diabetes and the metabolic syndrome and mainly prescribed in France (5 millions of exposed patients). Benfluorex was not marketed as an anorexigen and therefore, it could escape the restrictions imposed in late 1990s after the proven association between fenfluramine derivatives and PAH or cardiac valvular diseases. In 2009, a series of cases reported by Frachon et al. provided evidence of possible cardiotoxic effects of benfluorex [18]. In addition, a case-control study demonstrated that benfluorex is associated with valvular heart diseases, and premature deaths [19]. Between 1998 and 2011, the French PAH Network reported 85 cases of pulmonary hypertension associated with benfluorex exposure, 70 patients having PAH [20]. The median delay between initiation of benfluorex exposure and diagnosis of PAH was 108 months and the median duration of exposure was 30 months. Interestingly, a third of the patients had prior exposure to fenfluramine derivatives and an additional risk factor for PAH was identified in 20 out of the 70 PAH patients. About 25% of the patients showed coexisting PAH and mild-to-moderate valvular heart disease. The authors conclude that giving the known toxic effects of fenfluramine derivatives that have the same active metabolite as benfluorex, this later drug is a trigger of PAH [20].

Amphetamines

Amphetamine, methamphetamine, and cocaine are considered to be risk factors for PAH based on case reports and pharmacologic similarities to fenfluramine [2,21–24]. The large

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<thead>
<tr>
<th>Table I</th>
<th>Updated clinical classification of pulmonary hypertension (Dana Point, 2008)</th>
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<tr>
<td>Group 1. Pulmonary arterial hypertension (PAH)</td>
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<tr>
<td>- Idiopathic</td>
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<td>- Heritable</td>
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<td>- BMPR2</td>
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<td>- ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)</td>
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<tr>
<td>- Unknown</td>
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<tr>
<td>Drug- and toxin-induced</td>
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<tr>
<td>Associated with:</td>
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<td>Connective tissue diseases</td>
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<td>HIV infection</td>
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<td>Portal hypertension</td>
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<td>Congenital heart diseases</td>
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<td>Schistosomiasis</td>
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<td>Chronic hemolytic anemia</td>
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<td>Persistent pulmonary hypertension of the newborn</td>
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<td>Group 2. Pulmonary hypertension due to left heart disease</td>
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<tr>
<td>- Systolic dysfunction</td>
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<td>- Diastolic dysfunction</td>
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<td>- Valvular disease</td>
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<td>Group 3. Pulmonary hypertension due to lung diseases and/or hypoxia</td>
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<tr>
<td>- Chronic obstructive pulmonary disease</td>
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<td>- Interstitial lung disease</td>
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<tr>
<td>- Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
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<tr>
<td>- Sleep-disordered breathing</td>
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<tr>
<td>- Alveolar hypoventilation disorders</td>
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<td>- Chronic exposure to high altitude</td>
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<td>- Developmental abnormalities</td>
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<td>Group 4. Chronic thromboembolic pulmonary hypertension (CTEPH)</td>
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<td>Group 5. PH with unclear multifactorial mechanisms</td>
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<tr>
<td>- Hematologic disorders: myeloproliferative disorders splenectomy</td>
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<tr>
<td>- Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis</td>
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<td>- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders</td>
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<tr>
<td>- Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis</td>
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Source: From Simonneau et al. [2].

<table>
<thead>
<tr>
<th>Table II</th>
<th>Risk factors for and associated conditions of PAH</th>
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<tbody>
<tr>
<td>Definite</td>
<td>Possible</td>
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<tr>
<td>Aminorex</td>
<td>Cocaine</td>
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<tr>
<td>Fenfluramine</td>
<td>Phenylpropanolamine</td>
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<tr>
<td>Dexfenfluramine</td>
<td>St. John’s Wort</td>
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<tr>
<td>Toxic rapeseed oil</td>
<td>Chemotherapeutic agents</td>
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<tr>
<td>Benfluorex</td>
<td>Selective serotonin reuptake inhibitors</td>
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<tr>
<td>Dasatinib</td>
<td>Pergolide</td>
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<tr>
<td>Likely</td>
<td>Unlikely</td>
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<tr>
<td>Amphetamines</td>
<td>Oral Contraceptives</td>
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<tr>
<td>L-tryptophan</td>
<td>Estrogen</td>
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<tr>
<td>Methamphetamines</td>
<td>Cigarette smoking</td>
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Source: Adapted from Galie et al. [5].

molecules is norfenfluramine, which itself has a chemical structure similar to that of the amphetamines. The commercial product was marketed since 1976 as a treatment of diabetes and the metabolic syndrome and mainly prescribed in France (5 millions of exposed patients). Benfluorex was not marketed as an anorexigen and therefore, it could escape the restrictions imposed in late 1990s after the proven association between fenfluramine derivatives and PAH or cardiac valvular diseases. In 2009, a series of cases reported by Frachon et al. provided evidence of possible cardiotoxic effects of benfluorex [18]. In addition, a case-control study demonstrated that benfluorex is associated with valvular heart diseases, and premature deaths [19]. Between 1998 and 2011, the French PAH Network reported 85 cases of pulmonary hypertension associated with benfluorex exposure, 70 patients having PAH [20]. The median delay between initiation of benfluorex exposure and diagnosis of PAH was 108 months and the median duration of exposure was 30 months. Interestingly, a third of the patients had prior exposure to fenfluramine derivatives and an additional risk factor for PAH was identified in 20 out of the 70 PAH patients. About 25% of the patients showed coexisting PAH and mild-to-moderate valvular heart disease. The authors conclude that giving the known toxic effects of fenfluramine derivatives that have the same active metabolite as benfluorex, this later drug is a trigger of PAH [20].

Amphetamines

Amphetamine, methamphetamine, and cocaine are considered to be risk factors for PAH based on case reports and pharmacologic similarities to fenfluramine [2,21–24]. The lar-
gest retrospective study on amphetamines and their role in the development of PAH was performed by Chin et al. between 2002 and 2004 (University of California, San Diego) [25]. The authors analyzed the proportion of stimulants used (amphetamine, methamphetamine, or cocaine) in 340 patients with idiopathic PAH, CTEPH or PAH associated with other risk factors. A history of stimulant use was found in 28.9% of the patients with a diagnosis of idiopathic PAH, compared with 3.8% of the patients with PAH and a known risk factor, and 4.3% of the patients with CTEPH [9]. After adjustment for differences in age, patients with idiopathic PAH were about 10 times more likely to have used stimulants than patients with PAH associated with other risk factors, and eight times more than patients with CTEPH [8]. Another interesting finding of the study is the high rates of stimulant use in patients with HIV infection and as the mechanisms behind this particular form of PAH are still unclear the use of stimulant substances might play a role [25]. Methamphetamine and amphetamine act more potently on noradrenalin and dopamine transporters and have a minor activity on the serotonin transporter [26]. Nevertheless, both serotonin and noradrenalin have vasoconstrictive and growth modulating effects on smooth muscle cells, suggesting a possible implication of methamphetamine and amphetamine in the development of PAH [26–28].

Mazindol

Mazindol is an amphetamine-like appetite suppressant and stimulant agent used in the treatment of narcolepsy and obesity. It has been recently reported as a possible cause of partially reversible PAH [31]. However, in a larger series of 139 patients treated with mazindol, no case of PAH has been reported, however, only 45 patients underwent cardiac echography [32]. Because of its mechanism, periodic cardiovascular examinations should be proposed to patients treated with mazindol.

Dasatinib induced PAH

Tyrosin kinase inhibitors (TKI), and particularly imatinib, revolutionized the treatment of chronic myelogenous leukaemia (CML) [33]. It has been clearly demonstrated that platelet derived growth factor (PDGF) pathway is involved in the development of animal model of pulmonary hypertension and in human PAH [34]. Interestingly, imatinib, a TKI that could block PDGF receptor, has been discussed as a potential treatment for PAH. Dasatinib is a TKI with markedly higher affinity for BCR/ABL kinase in comparison with imatinib (approximately 300-fold) and it inhibits a large number of kinases, including the Src family kinases. Dasatinib is approved as a second line treatment in imatinib resistant CML and recent data suggested that dasatinib might have higher efficacy in newly diagnosed CML than imatinib [35,36]. In this context, it came as a paradox that cases of PAH were reported with the use of dasatinib [37–39]. Recently, we published a series of nine cases of dasatinib-induced PAH from the French National Network of PH [40]. These patients were characterized by a female predominance in the cohort. By contrast with anorexigen-associated PAH, all cases occurred during treatment with dasatinib. Median delay between initiation of dasatinib and PAH diagnosis was 34 months. At diagnosis, most patients had severe clinical, functional and hemodynamic impairment, some of them requiring vasoactive drugs and management in intensive care unit. Clinical and functional improvements were usually observed after dasatinib discontinuation, but some patients required specific PAH treatment. Indeed, the majority of patients failed to demonstrate complete hemodynamic recovery and two patients died at follow-up. No predictive factor (including clinical co-morbidities or BMPR2 genetic status) of dasatinib related-toxicity was detected in this study. Authors estimated the lowest incidence of PH in patients exposed to dasatinib at 0.45%. Interestingly, all patients have previously received imatinib before dasatinib and six patients have received nilotinib after dasatinib discontinuation without PAH recurrence [40]. This suggests that pulmonary vascular toxicity induced by dasatinib is probably molecule-related and not class-related. There are many hypotheses behind this phenomenon and no clear answer up to this date. One of them is that by inhibiting Src, which plays a critical role in smooth muscle cell proliferation and vasoconstriction, dasatinib alters the proliferation/antiproliferation equilibrium at the endothelial and pulmonary arterial smooth muscle level [41]. In addition, all the other molecular targets specific to dasatinib might be implicated and further research must be done to understand the exact mechanisms. In conclusion, large inhibition spectrum and lack of specificity of TKIs may be responsible for unexpected toxicities, even at the pulmonary vascular level.
Interferon associated PAH

The interferons (IFNs) comprise an evolutionary conserved family of secreted proteins that participate as extracellular messengers in a wide variety of responses, including antiviral, antiproliferative and immunomodulatory and developmental activities that act to maintain homeostasis and in-host defence [42,43]. IFNs are classified as helical cytokines and are categorized as type I or type II, according to their physical and functional characteristics. Type I IFNs include \( \alpha \) (leukocyte), \( \beta \) (fibroblast), \( \tau \) and \( \sigma \) subtypes that are likely to be diverged from a common ancestral gene [44].

IFN\( \alpha \)

IFN\( \alpha \) has been used extensively in the treatment of viral hepatitis, but also in hematologic, nephrologic, and dermatologic malignancies. Association of IFN\( \alpha \) and ribavirin has been considered to be the current standard of care for hepatitis C in the last decade [45,46]. Side effects associated with interferon therapy have been reported, including transient flu-like symptoms to serious effects, such as cardiac arrhythmias, cardiomyopathy, renal and liver failure, polyneuropathy, and myelosuppression. Several pulmonary side effects have been reported, including asthma exacerbation, pleural effusion, sarcoidosis, cryptogenic organising pneumonia, bilateral pulmonary infiltrates [47]. Dhillon et al. presented four cases of PAH occurring in patients treated with IFN\( \alpha \) for hepatitis C infection [48]. Three of them were non-cirrhotic and two patients were post-liver transplant with uncomplicated post-surgical course. Portopulmonary hypertension and other causes of pulmonary hypertension had been systematically ruled out. Although most of the side effects disappear 24 months after IFN\( \alpha \) discontinuation, in this four cases, PAH was not reversible [48]. As experimental investigations in sheep showed that IFN\( \alpha \) can stimulate the thromboxane cascade which resulted in transient PAH [49], the authors suggest as potential mechanisms the acceleration of a previously subclinical phenomenon caused by other factors, such as human herpes virus 8, hepatitis C virus itself, or a previously unrecognized genetic predisposition.

IFN\( \beta \)

IFN\( \beta \) is an extracellular protein mediator of host defence and homeostasis. IFN\( \beta \) has well-established direct antiviral, antiproliferative and immunomodulatory properties. Recombinant IFN\( \beta \) is approved for the treatment of relapsing – remitting multiple sclerosis [50]. Up to date, there are two cases of patients with multiple sclerosis that developed possible PAH after IFN\( \beta \) therapy [51,52]. In conclusion, therapies with IFN\( \alpha \) and \( \beta \) may be associated with an increased risk for the development of PH and future studies are needed to evaluate their full impact on pulmonary hemodynamics.

Suspected drugs associated with PAH

L-tryptophan

Tryptophan is one of the 22 standard amino acids and an essential amino acid in the human diet. In the 1990s, the eosinophilia-myalgia syndrome was epidemiologically associated with ingestion of \( \text{L-tryptophan} \)-containing preparations (LTCP) [53]. PH may develop in people who ingest LTCP and usually, it is a component of the eosinophilia-myalgia syndrome. However in literature, some patients had neither eosinophilia nor myalgia. In some patients, the PH regressed after withdrawal of the LTCP and the administration of oral steroids, but in others it persisted. Open lung biopsy specimens, when performed, showed extensive arteriopathy compatible with other forms of PAH [54]. Analysis of case-associated lots of LTCP has revealed several chemical impurities, which would be responsible for the development of the syndrome [55]. More recently, consumption of large doses of tryptophan was proven to induce production of metabolites, some of which may interfere with normal histamine degradation [56].

Phenylpropanolamine

Phenylpropanolamine (PPA), also known as the stereoisomers norephedrine and norpseudoephedrine, is a psychoactive drug of the phenethylamine and amphetamine chemical classes, which is used as a stimulant, decongestant, and anorectic agent. The commercial drug Dimetapp (Pfizer, United States) was removed from the market in 2000 due to the risk of haemorrhagic stroke but was re-released after with pseudoephedrine replacing the PPA. The study of pulmonary hypertension in America (SOPHIA) found that over-the-counter appetite suppressants pills containing PPA where a risk factor for developing PAH [57]. There is also a case report of a 7.5-year-old boy with a history of chronic upper airways obstruction treated on multiple occasions by nasal decongestants containing PPA who died of severe PAH. Other possible PAH causes had been ruled out and at necropsy pulmonary vascular changes and endarteritis consistent with severe PAH were found [58]. The big problem with nasal decongestants containing norephedrine and norpseudoephedrine, two potent vasoconstrictors is their wide availability without medical prescription and therefore, they represent a big risk factor for PH in the general population.

Pergolide

Pergolide was an ergot-derived dopamine agonist prescribed mainly in Parkinson’s disease and restless leg syndrome. It was withdrawn by the FDA from the US market in 2007 after it was proven to induce valvulopathies [59]. In literature, there is one case of pre-capillary PH associated with pergolide use although probably, they were not diagnosed due to the difficulties in performing RHC to the particular population that used the drug [60].
Selective serotonin reuptake inhibitors

In the 21st century, more and more people suffer from depression and nowadays selective serotonin reuptake inhibitors (SSRI) represent the treatment of choice. Pregnancy is considered to be a period of high stress for women and therefore antidepressants are not discontinued. Persistent PH of the newborn (PPHN) is defined as the failure of the normal circulatory transition that occurs after birth and it is associated with substantial infant mortality and morbidity [61]. Two studies show consistent data regarding the association between PPHN and SSRI use in late pregnancy [62,63]. In the first study published by Chambers et al. from a total of 377 women, whose offspring developed PPHN, 14 had been using SSRI after the 20th week of gestation [62]. A larger study from the five Scandinavian countries analysed a total of 1.6 million infants born after gestational week 33. Around 30,000 women had used SSRIs during pregnancy and 11,014 had been dispensed an SSRI later than gestational week 20. Exposure to SSRIs in late pregnancy was associated with an increased risk of PPHN: 33 of 11,014 exposed infants (absolute risk 3 per 1000 live-born infants compared with the background risk of PPHN: 33 of 11,014 exposed infants (absolute risk 3 per 1000)). The increased risks of PPHN for each of the specific SSRIs (sertraline, citalopram, paroxetine, and fluoxetine) were of similar magnitude. Filling a prescription with SSRIs before gestational week 8 yielded slightly increased risks with an adjusted odds ratio of 1.4 [63]. In conclusion, there is a risk of PPHN with the use of SSRIs, especially in late pregnancy and therefore, this class of antidepressants must be avoided in pregnant women.

Conclusion

At the beginning of the 21st century, drug associated PAH remains a clinical problem. After worldwide alerts, many drugs that were found responsible for inducing a higher risk for PAH have been withdrawn from the market and more recently and by surprise, dasatinib, a TKI was found to be associated with a higher risk for PAH and cardiovascular warnings have been issued ever since. Even so, clearly stating that a certain drug is associated with a higher risk for PAH is a very difficult task because PAH remains a rare disease and the altered pulmonary hemodynamic represent a rare side effect for all suspected drugs. The French model of crosslink interactions between the national drug regulatory agencies, the national PAH network and the PAH patients association represent a possible solution for detecting new potential drugs capable of inducing PAH and for launching global alerts if necessary.

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