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LETTER

Nasal decongestant exposure in patients with pulmonary arterial hypertension: a pilot study

To the Editor:

In the scientific and medical community, it is recognised that exposure to certain drugs could promote the development of pulmonary arterial hypertension (PAH). These drugs, with a "class effect" (amphetamine-like) or not (dasatinib), are prescribed for serious (dasatinib, interferons) or moderate (benfluorex) pathologies and do not induce PAH in all patients [1–9]. As a result, assessment of drug history exposure from PAH patients has become essential for providing optimal disease management [10].

Nasal decongestants are a class of drugs used by nasal or oral route for symptomatic treatment of nasal obstruction. Some of them have a chemical structure similar to amphetamine, as had been observed for fenfluramine derivatives [11]. According to the French national agency for medicines and health products safety, the mean annual sales of nasal decongestants between 2008 and 2011 in France were respectively (all specialties combined): 17.5 million boxes per year for systemic/oral and 19.3 million of units per year for nasal decongestants. Despite the fact that nasal decongestants are largely used, these drugs are not trivial and induce rare but serious cardiovascular or neurological side effects [12]. Phenylpropanolamine, also known as norephedrine, is a drug of the phenethylamine chemical class with a structure similar to amphetamine [13]. Phenylpropanolamine was used as a stimulant, nasal decongestant, and also as an anorectic agent. The study of pulmonary hypertension in America (SOPHIA) carried out between 1998 and 2001, found that over-the-counter appetite suppressants pills containing phenylpropanolamine were a risk factor for developing PAH [14]. In addition, an overdose-related fatal case of PAH in a child treated for a cold with a high dose of phenylpropanolamine was reported in 2004 [15]. Due to the rare but serious side effects, phenylpropanolamine was withdrawn from the US market in 2000. In Europe, phenylpropanolamine was withdrawn in France in 2001 but was still marketed in several countries such as Belgium or Switzerland. Despite this fact, other molecules similar to phenylpropanolamine such as ephedrine or pseudoephedrine are still commercialised in several medications. The majority of these therapies are easily available (over-the-counter) and are often used for self-medication. To date, no specific research on the impact of nasal decongestants exposure on the development of PAH has been performed, probably in part due to trivialisation of these treatments. However, given the reported adverse events associated with these drugs and their vasoconstrictor property, assessment of nasal decongestants exposure in PAH patients was needed.

Our study was conducted from December 15, 2012 to July 30, 2013, in the French pulmonary hypertension referral centre, with ethics committee approval (Comité d'Evaluation des Protocoles de Recherche Observationnelle de la Société Française de Pneumologie; ref: CEPRO 2013-009). We retrospectively collected nasal decongestant exposure data from patients before their PAH diagnosis and compared them with nasal decongestant exposure in a control group. The study cohorts consisted of a group of patients suffering from idiopathic, heritable or drug-induced PAH and a control group consisting of people accompanying the included patients (family member or home help person). The control group was used as the reference to determine the normal frequency of nasal decongestant exposure in the population from which the PAH cases were derived. In order to collect data on drug-exposure in PAH patients and their accompaniers, a systematic validated questionnaire was performed by a pharmacist specialised in PAH. In order to cross-check drug exposure information obtained from the interview, and/or collect potential additional data, the general practitioner and the pharmacist of each subject were also contacted. During the patient's interview, nasal decongestant exposure before PAH diagnosis as well as other suspected drugs potentially promoting PAH were assessed. As the assessment was about the period before the PAH diagnosis, none of patients received any specific treatment for PAH, which could promote nasal congestion. For the control population, nasal decongestant exposure was assessed until the date of the interview.

As the collected information about vasoconstrictor nasal decongestant exposure was semi-qualitative ("2 times a year", "3 or 4 times"), an accurate estimation of exposure duration was unrealisable. Therefore, for each subject, nasal decongestant exposure was translated as an estimated number of treatment periods ("C"), using

a specific scale performed for the study. This tool has allowed a classification of each subject according to consumption categories respecting the principle of never overestimating an exposure.

A total of 99 exposure assessments were obtained in PAH patients and 58 in the control group. 68 women and 31 men were interviewed in the PAH group, whereas 29 women and 29 men in the control group. The median ages were 56.2 years in PAH patients and 52.3 years in controls ($p>0.05$). The median (range) time from PAH diagnosis to study interview was 3.8 years (0–22). At least one health professional (the general practitioner and/or the pharmacist) of each subject was successfully contacted (additional data obtained) for 64.6% of patients and 96.6% of controls. A history of nasal decongestants exposure ($C\geqslant1$) was found in 70.7% of PAH patients and 79.3% of controls ($p>0.05$). In PAH patients previously exposed to nasal decongestants, 29.3% presented another PAH drug exposure risk factor, such as a previous use of amphetamine, appetite suppressant, cocaine, dasatinib and/or interferon. In PAH patients with exposure to nasal decongestant of $C\geqslant2$ courses, the characteristics of the population are different with a lower median age at diagnosis and an increased female:male sex ratio. This trend is confirmed in PAH patients with an exposure to nasal decongestant of $C>10$ courses (table 1). However, these observations should be interpreted with caution. Foremost, the analysis does not seem to show any other drug or toxic risk factors more commonly associated. In addition, differences in the age of diagnosis and sex ratio might to be explained by different consumption behaviours between generations, by different memory capacities or by sampling fluctuations. Similarly, the lower age of diagnosis could also be explained by the scientific advances, particularly in genetic research of PAH. Among subjects with an exposure to nasal decongestants of $C\geqslant2$ courses, the most reported agent was oral pseudoephedrine which exists in more than 10 different decongestive therapies. The other drugs often reported were nasal naphazolin, nasal oxymetazolin, nasal tuaminoheptan and oral phenylpropanolamine.

Our study showed there was no significant difference of nasal decongestants exposure between PAH patients and their accompanying persons. This specific research of nasal decongestants exposure allowed us to highlight the high level of exposure in PAH patients and accompaniers confirming the large consumption of these drugs in the general population in France. While no significant difference has been reported, further studies will be required with larger numbers of patients to answer this question fully. PAH has a complex pathophysiology and it is possible that nasal decongestants could be one of several risk factors for PAH, which when combined lead to the development of the disease. For example it has been suggested that patients with mutations in *BMPR2* (bone morphogenetic protein receptor type II) develop PAH after a shorter exposure to fenfluramine than people without the mutation [16]. In our study, the low number of patients with *BMPR2* mutation does not allow an analysis of this hypothesis. Our study has other limitations. Firstly, there was a low number of control subjects included. This observation is due to the choice of a methodology based on matched control group to avoid an environment bias. Unfortunately some control candidates were unavailable or refused to participate. Secondly, the assessment of nasal decongestant exposure was limited by recall bias where some patients were interviewed many years after the diagnosis of PAH. Moreover, nasal decongestants are very common and are found in various drugs. The use of supplemental information from the general practitioners and pharmacists reduces this bias. Finally, there was a lack of specific research on cardiopulmonary diseases and specific

TABLE 1 Characteristics of study populations

C by group	Effective	Sex ratio female:male	Age years	Age at time of diagnosis years	PAH form				
					Idiopathic	Drug or toxin-induced	Heritable with *BMPR2* mutation	Heritable without *BMPR2* mutation	PVOD
PAH									
Total	99	2.2	56.2 (20.2–84.6)	50.6 (16.3–81.9)	50 (50.5)	15 (15.2)	16 (16.2)	5 (5.0)	13 (13.1)
C=0	29 (29.3)	1.4	66.0 (24.6–80.8)	58.7 (16.3–79.1)	12 (41.4)	6 (20.7)	4 (13.8)	0	7 (24.1)
C=1	8 (8.1)	0.6	71.0 (20.2–84.6)	59.4 (16.3–81.9)	5 (62.5)	1 (12.5)	1 (12.5)	0	1 (12.5)
C=2–10	39 (39.4)	2.9	53.4 (20.9–75.3)	41.1 (19.9–73.9)	18 (46.2)	6 (17.9)	8 (20.5)	3 (3.7)	4 (7.7)
C>10	23 (23.2)	4.8	42.1 (21.7–71.0)	38.2 (21.6–69.4)	15 (65.2)	2 (8.7)	3 (13.1)	2 (8.7)	1 (4.3)
Controls									
Total	58	1	52.3 (27.3–82.8)						
C = 0	12 (20.7)	1	65.3 (31.4–82.8)						
C=1	6 (10.3)	5	53.9 (30.6–73.5)						
C=2–10	26 (44.8)	0.5	49.3 (27.3–77.3)						
C>10	14 (24.1)	1.8	50.2 (30.0–68.0)						

Data are presented as n, n (%) or median (range). *BMPR2*: bone morphogenetic protein receptor type II; PVOD: pulmonary veno-occlusive disease.

treatments potentially leading to nasal congestion in the control group. These limitations had been taken into account. Thus, the extension study was now limited to patients with a PAH diagnosed within 2 years to avoid recall bias, and control group is asked about diseases and treatments exposure.

In conclusion, this study allowed the implementation of a data collection methodology in our centre. Assessment of drug exposure prior PAH diagnosis could highlight precious information for the future in terms of signal detection (other suspected drugs or specific characteristics of patients associated with specific drug exposure in) as well as strengthening the drug monitoring system in the French pulmonary hypertension referral centre.

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More studies are needed to measure nasal decongestant exposure in patients with pulmonary arterial hypertension. http://ow.ly/OFxs8

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