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

References
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 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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**TABLE 1** Characteristics of study populations

<table>
<thead>
<tr>
<th>C by group</th>
<th>Effective</th>
<th>Sex ratio</th>
<th>Age years</th>
<th>Age at time of diagnosis years</th>
<th>PAH form</th>
<th>Drug or toxin-induced</th>
<th>Heritable with BMPR2 mutation</th>
<th>Heritable without BMPR2 mutation</th>
<th>PVOD</th>
</tr>
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<tbody>
<tr>
<td>PAH</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>C=1</td>
<td>8 (8.1)</td>
<td>0.6</td>
<td>71.0 [20.2–84.6]</td>
<td>59.4 [16.3–81.9]</td>
<td>5 [6.2]</td>
<td>1 [12.5]</td>
<td>1 [12.5]</td>
<td>0</td>
<td>1 [12.5]</td>
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<tr>
<td>Controls</td>
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<td></td>
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<tr>
<td>Total</td>
<td>58</td>
<td>1</td>
<td>52.3 [27.3–82.8]</td>
<td></td>
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<td></td>
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<tr>
<td>C=0</td>
<td>12 (20.7)</td>
<td>1</td>
<td>65.3 [31.4–82.8]</td>
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<td></td>
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</tr>
<tr>
<td>C=1</td>
<td>6 (10.3)</td>
<td>5</td>
<td>53.9 [30.6–73.5]</td>
<td></td>
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<td></td>
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<tr>
<td>C=2–10</td>
<td>26 (44.8)</td>
<td>0.5</td>
<td>49.3 [27.3–77.3]</td>
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<tr>
<td>C&gt;10</td>
<td>14 (24.1)</td>
<td>1.8</td>
<td>50.2 [30.6–68.0]</td>
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</tbody>
</table>

Data are presented as n, n (%) or median (range). BMPR2: bone morphogenetic protein receptor type II, PVOD: pulmonary veno-occlusive disease.
Pulmonary tumour thrombotic microangiopathy: unclassifiable pulmonary hypertension?

To the Editor:

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure ≥25 mmHg, and can be associated with multiple conditions. The diagnostic strategy and treatment of PH is heavily reliant on accurately classifying patients [1]. We recently identified two patients presenting with rapidly fatal PH of unknown aetiology, who were subsequently diagnosed at post mortem with pulmonary tumour thrombotic microangiopathy (PTTM). This is a rare, albeit likely under-diagnosed cause of PH, characterised by a remodelling pulmonary vasculopathy rather than simple tumoral obstruction. At present, it is unclear where PTTM fits within the current classification system.

Case 1 was a 58-year-old male smoker who presented with a short history of progressive breathlessness. Initial imaging at his local hospital was suggestive of an interstitial lung process with associated PH, and he was transferred to our hospital for further assessment. Computerised tomography (CT)-pulmonary angiography (PA) excluded pulmonary embolism, and high-resolution cuts revealed widespread ground glass changes and interlobular septal thickening, consistent with interstitial and airspace oedema, rather than an interstitial lung process (figure 1a). Echocardiography revealed a moderately hypertrophic right ventricle with reduced longitudinal systolic function and an estimated right ventricular systolic pressure (RVSP) of 68 mmHg. The left ventricle was hypertrophic with good systolic function. Subsequent right and left heart catheterisation confirmed increased pulmonary vascular resistance (5.2 Wood units), with a

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