Appetite suppressants and pulmonary hypertension

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Introductory article

Appetite-suppressant drugs and the risk of primary pulmonary hypertension

L Abenhaim, Y Moride, B Brenot, S Rich, J Binichou, X Kurz, T Higenbottam, C Oakley, E Wouters, M Aubier, G Simonneau, B Begaud for the International Primary Pulmonary Hypertension Study Group

Background. Recently in France, primary pulmonary hypertension developed in a cluster of patients exposed to derivatives of fenfluramine in appetite suppressants (anorexic agents), which are used for weight control. We investigated the potential role of anorexic agents and other suspected risk factors for primary pulmonary hypertension. Methods. In a case-control study, we assessed 95 patients with primary pulmonary hypertension from 35 centers in France, Belgium, the United Kingdom, and the Netherlands and 355 controls recruited from general practices and matched to the patients' sex and age. Results. The use of anorexic drugs (mainly derivatives of fenfluramine) was associated with an increased risk of primary pulmonary hypertension (odds ratio with any anorexic-drug use, 6.3; 95 percent confidence interval, 3.0 to 13.2). For the use of anorexic agents in the preceding year, the odds ratio was 10.1 (95 percent confidence interval, 3.4 to 29.9). When anorexic drugs were used for a total of more than three months, the odds ratio was 23.1 (95 percent confidence interval, 6.9 to 77.7). We also confirmed an association with several previously identified risk factors: a family history of pulmonary hypertension, infection with the human immunodeficiency virus, cirrhosis, and use of cocaine or intravenous drugs. Conclusions. The use of anorexic drugs was associated with the development of primary pulmonary hypertension. Active surveillance for this disease should be considered, particularly since the use of anorexic drugs is expected to increase in the near future.

Primary pulmonary hypertension (PPH), also called unexplained pulmonary hypertension, is a rare disease with at least three different recognised histological presentations,1 of which the so-called plexogenic arteriopathy is the most commonly encountered. The disease occurs with a predominance in young women, but incidence peaks have been noted also in children and in a geriatric population.2 PPH is clinically characterised by non-specific symptoms of dyspnoea or cough and therefore is quite often initially misdiagnosed. Occasionally the first clinical presentation is with signs of right heart failure. The median survival after diagnosis of PPH has been estimated to be 2.8 years.3 Thus, in many patients the disease takes a rapidly progressive very malignant course. In recent years associations of plexogenic pulmonary arteriopathy have been found with portal hypertension4,5 and with AIDS.6 U till 1993 when Brenot and co-workers7 published their observations entitled Primary pulmonary hypertension and fenfluramine/norepinephrine, the historical context of appetite depressants and their possible role as pulmonary hypertension-inducing drugs had been nearly forgotten. This was particularly apparent in a number of contemporary reviews of pulmonary artery hypertension where the potential aetiological role of anorexigenes was not mentioned.8,9 The introductory article10 reminds us that there is a recognised association between the intake of certain appetite-suppressant drugs and the development of PPH.11 As stated, PPH is a rare disease and its incidence in any population group where an unusually high prevalence has been established – for example, in patients with liver cirrhosis and portal hypertension or patients with AIDS – is still rather small. The most likely explanation is a low prevalence of a pulmonary hypertension gene or of a constellation of genetic factors. Given such a low prevalence of genetic predisposition, any trigger or expression factor will raise the number of patients with PPH to only a small extent. The introductory article by Abenhaim et al describes the first prospective study which attempts to estimate the relative risk for the development of PPH from anorexigen use. Prior to this multinational European study there had
been isolated case reports which strongly indicated that
anorexigen intake can be associated causally with PPH:
usually such association can be claimed when a patient
develops unexplained pulmonary hypertension in close
temporal relation to anorexigen use and when no other
drugs are involved. Analysis of the data collected for
the primary pulmonary hypertension registry of the US
National Institutes of Health showed that 5% of the
patients with PPH had a history of anorexigen use, and
Brenot et al. found that, among their 125 cases of PPH,
14% had a history of anorexigen use (25% of all their
female patients). Based on these data, it is not likely
that anorexigen use is currently the overwhelming cause
of PPH, but if anorexigen use continues to increase, it
is likely to become an increasingly important cause
of PPH.

For the prospective International Primary Pulmonary
Hypertension Study (IPPHS) Group, 35 centres in
France, Belgium, the Netherlands, and the UK agreed
to participate and to report cases of PPH diagnosed
between September 1992 and September 1994. A total
of 95 patients with PPH were identified, 64 of whom
had been reported by French centres. Definite use
of anorexigen had been reported by 30 of the 95 patients
with PPH but by only 26 of 355 controls. Although
the study was international in design, the data largely
represented the French experience. Perhaps the most
striking finding of the IPPHS was that roughly 12% of
the patients with PPH had taken anorexigens for 12
months or longer (compared with 0.6% in the control
group).

Anorexigens and PPH: the historical context
Several medical centres in Switzerland, Austria, and
Germany registered an increased incidence of severe
pulmonary hypertension beginning in 1967, roughly
18 months after the anorexigen Mencol (aminorex fumarate) had been released in these three countries; by 1970 150 cases of PPH associated with anorexigen usage had been reported. The 1985 review by Gurtner concluded that altogether 582 cases of anorexigen-induced PPH had been reported. The early experience
with this epidemic in Vienna (fig. 1) illustrates the latency
period between the time of introduction of the drug
and the time when an increased incidence of PPH was
recognised (the drug had been released in December
1965). Although the drug was taken off the market in
November 1968, cases of anorexigen-induced PPH were diagnosed for several years thereafter. Symptoms consistent with PPH occurred 9–14 months after the start of the anorexigen treatment, approximately one per 1000 aminorex users developed
PPH, and the lesions of anorexigen-induced PPH were
histologically indistinguishable from those recognised
in sporadic cases of PPH. Since the aminorex epidemic, sporadic cases of PPH related to the use of fenfluramine or phentermine have been reported.

Anorexigen-associated pulmonary hypertension:
the pharmacological context
The exact pathogenetic events leading to the mani-
festation of PPH are still unknown. It appears, however,
that for the anorexigen-associated cases of PPH, 5-
hydroxytryptamine (5-HT, serotonin) might be a com-
mon denominator. Figure 2 shows the structures of
some of the anorexigens, including aminorex, and also
the frequently used antidepressant agents such as ser-
traline hydrochloride and fluoxetine hydrochloride. All
of these agents release 5-HT from storage sites or inhibit
uptake of 5-HT. Gahl and coworkers found no increase in levels
of metabolites of 5-HT in the urine of patients with
aminorex-induced PPH. However, these measurements
were conducted many months after the anorexigen intake.
Moreover, the hypothesis of a 5-HT paradigm may be justified at the present time.

Herve and coworkers reported the case history of a
patient with PPH and a platelet storage disorder and,
more recently, described the plasma 5-HT levels in
patients with PPH. Of great interest is their finding
that, in their patients with PPH (some of whom had
taken anorexigen), there was an increase in plasma 5-
HT levels and an increased release of 5-HT from
the platelets. Moreover, this increase in plasma levels of
5-

![Figure 1](https://example.com/figure1.png)  
Figure 1: Graph showing the increase in the incidence of primary pulmonary hypertension (particularly in women) with a latency period following introduction of the drug. The drug was taken off the market in November 1968. Reproduced with permission from reference 15.

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<th>History of drug-induced primary pulmonary hypertension (PPH)</th>
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<th>Date</th>
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<td>December 1965</td>
<td>Gurtner (1968)</td>
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<td>Gahl (1970)</td>
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Table of dates and studies related to the historical context of drug-induced primary pulmonary hypertension.
Appetite suppressants and pulmonary hypertension

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<td>Phentermine hydrochloride</td>
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<td>Amphetamine</td>
<td>Sertraline hydrochloride</td>
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<td>Aminorex</td>
<td>Fluoxetine hydrochloride</td>
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Figure 2. Chemical structures of 5-hydroxytryptamine (5-HT, serotonin) and 5-HT-releasing appetite suppressants or antidepressants.

HT persisted in those patients who had received lung transplantation. If this finding of raised levels of 5-HT in patients with PPH can be confirmed in other populations with PPH, it would be tempting to speculate that agents which alter the metabolism of 5-HT could be trigger factors for PPH (figs 3 and 4). It is clear from experimental data that 5-HT does, indeed, cause pulmonary vasoconstriction and produces both hyperplasia and hypertrophy of isolated cultured pulmonary artery smooth muscle cells. This proliferative effect of 5-HT is apparently transduced through the 5-HT2 receptor. However, the relationship between alteration in 5-HT metabolism and PPH is probably more complex, as evidenced by the absence of reports of a relationship between the chronic intake of antidepressants such as fluoxetine hydrochloride (a very widely used drug) and PPH. However, in our centre we have recently diagnosed PPH in a woman who had not taken anorexigens but had been treated for her depression with sertraline hydrochloride (unpublished observation).

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Figure 3. Scheme depicting the confluence of a presently ill described genetic disposition and trigger factors in the development of primary pulmonary hypertension. It is clear that the trigger factors are of a vastly varied nature, including high blood flow or increased shear stress, viral infections, and anorexigens.

Figure 4. Scheme depicting a hypothetical sequence of events involving appetite suppressants which alter the metabolism of 5-hydroxytryptamine (5-HT) or affect release of 5-HT from platelets and mast cells. In susceptible individuals – that is, those with a genetic disposition – increased levels of 5-HT could both alter pulmonary vascular tone and also affect pulmonary vascular cell growth.
LEARNING POINTS

- Appetite suppressants which affect the release or uptake of 5-HT (serotonin) may be trigger factors for primary pulmonary hypertension (PPH) in a genetically susceptible segment of the general population.

- Primary pulmonary hypertension is a generally fatal disease of young women, a group more likely to take appetite suppressants than men.

- There may or may not be an association between obesity itself and the development of PPH but PPH does occur in non-morbidly obese users of appetite suppressants.

- Development of dyspnoea, fatigue and cough in anorexigen users (particularly when these symptoms occur in spite of weight loss) is a reason for alarm and should trigger investigation for pulmonary hypertension.

Anorexigen-associated pulmonary hypertension and obesity: risk-benefit ratio

It should be clear from the above that anorexigen can cause pulmonary hypertension. It should also be appreciated that many patients are looking for a pharmacological solution to their obesity problem. In the USA dieting and weight management are a multimillion dollar industry. Hundreds of new diet pill clinics have opened during the last year. Presently we have no good understanding of the relationship between body weight and pulmonary hypertension – apart from the well known association of the obesity/hyperventilation/polythymia syndrome and pulmonary hypertension.

Gurtner, summarising his experience of 71 patients with presumed anorexigen-induced PPH, found that 50% of the patients had used aminorex while being only mildly overweight (110% of ideal body weight). While anywhere from 400 to 1000 additional new cases of PPH were opened during the last year. Presently we have no good understanding of the association of obesity and pulmonary hypertension. It should be clear from the above that anorexigen users are less likely to achieve their weight loss goal and they need to continue the drug to maintain their weight loss [M 1996].

All this is worrisome when one considers that the pharmaceutical industry does not generally screen new compounds for their potential to cause pulmonary hypertension. By contrast, drugs do not usually reach the market if they raise the systemic blood pressure. Given the uncertainty of currently available “diet pills” to cause successful long term weight loss [34 35] and the risk of developing a lethal disease, the risk-benefit ratio could be considered unacceptable high. The introductory article has lessened previous uncertainty and, as the number of anorexigen users in the USA approaches 20 million, we may soon witness a much greater incidence of PPH in that country as in Europe.

References:

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