Temporal trends and drug exposures in pulmonary hypertension: An American experience

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Background Reports have linked anorexigen intake to an increased risk of pulmonary arterial hypertension (PAH). With the rise in anorexigen use in the latter half of the last decade, we established a surveillance network within the United States to monitor temporal trends in the number of reported cases of PAH. We also studied whether use of anorexigens and other drugs differed among patients with pulmonary hypertension of different etiologies.

Methods Newly diagnosed subjects (N = 1335) at 13 tertiary pulmonary hypertension centers were enrolled between January 1998 and June 2001. Patient-reported medication use was obtained by a telephone interview. Patients were classified as to the type of pulmonary hypertension. Poisson regression models were fitted to monthly case counts, and logistic regression methods were used to assess the association between type of pulmonary hypertension and medication use.

Results The average monthly number of reported cases of PAH and other categories of pulmonary hypertension did not change over the study period. Fenfluramine or dexfenfluramine use during the 5 years before the time of the interview was preferentially associated with PAH. Fenfluramine/dexfenfluramine use was particularly common in cases referred but found not to have pulmonary hypertension.

Conclusions No epidemic of anorexigen-related PAH was evident during the study period. As persons who had taken fenfluramine or dexfenfluramine were particularly likely to be referred for evaluation of pulmonary hypertension, it is unlikely that the failure to detect an anorexigen-induced rise in primary pulmonary hypertension was because of underascertainment. The association between fenfluramine derivatives and PAH is consistent with the risk elevations previously reported. (Am Heart J 2006;152:521-6.)

Widespread use of the anorexigen aminorex fumarate (Menocil) in Switzerland, Austria, and Germany in the late 1960s led to an outbreak of primary pulmonary hypertension (PPH).[1] In the 1980s and 1990s, case reports and case series suggested that anorexigen fenfluramine was also associated with the development of PPH.[2] A case control study in Europe established an association between anorexigens, principally fenfluramine derivatives, and PPH, which increased with duration of use.[3] A registry study in the United States found that patients with PPH had used fenfluramines more commonly than patients with secondary pulmo-

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Conflicts of interest: Dr Constantine is an employee of Wyeth-Ayerst, and Dr Strom has served as a consultant to Wyeth-Ayerst.

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Table I. Characteristics of the study population

Variable	PPH (n = 346), %	SPH-Thrombo (n = 219), %	SPH-Other (n = 468), %	PH-Unclassified (n = 147), %	No-PH (n = 155), %	Total (N = 1335), %
Age (y)						
18-34	20.8	13.2	12.4	15.0	15.5	15.4
35-54	51.2	43.4	48.7	51.7	54.2	49.4
≥55	28.0	43.4	38.9	33.3	30.3	35.2
Gender						
Male	18.8	48.0	27.8	21.1	11.0	26.1
Female	81.2	52.0	72.2	78.9	89.0	73.9
Race/Ethnicity						
White, non-Hispanic	81.5	79.9	75.0	81.0	81.9	79.0
NYHA class						
I	1.5	0.0	0.4	0.7	12.9	2.0
II	18.3	10.8	16.6	19.6	53.6	20.4
III	70.8	81.1	68.4	67.1	32.1	67.1
IV	9.4	8.0	14.6	12.6	1.4	10.5
BMI (kg/m^2)						
≥30.0	41.9	33.0	27.3	43.0	48.3	36.2

nary hypertension (PH).[4] Following concerns that valvular heart disease might be associated with use of the anorexigen combination fenfluramine-phentermine,[5] the manufacturer of fenfluramine and dexfenfluramine withdrew these products from the US market in September 1997.

At the time of the product withdrawal, our group was organizing a prospective surveillance of PPH in the United States, the purpose of which would be to detect important changes in the national incidence of PPH, characterize patients with primary and noncardiac secondary PH, and detect associations with a variety of drugs, including anorexigens. With the participation of major PH treatment centers in the United States, the Surveillance of Pulmonary Hypertension in America (SOPHIA) working group was established. The SOPHIA registry extended previous work on PPH[4,6] by including both primary and secondary hypertension cases and analyzing information on patient history, potential risk factors, and clinical characteristics abstracted from medical records and collected during a telephone interview. Although this was not an incidence study, the surveillance was sufficiently inclusive to detect important increases in the incidence of PH.

Methods

This work was supported by Wyeth-Ayerst through a contract with the Harvard School of Public Health. The Scientific Steering Committee had complete control over design, execution, analysis, and reporting. Furthermore, the terms of support guaranteed a full right of publication of the results to the Harvard School of Public Health.

The SOPHIA network consisted initially of 15 centers. Two were unable to implement study procedures and dropped out of the collaboration. For each patient referred for evaluation of PH not due to left-sided heart disease, the centers completed a patient screening form and submitted patient contact information to the data-coordinating center (DCC) for those subjects who signed an informed consent. The DCC collected information on potential risk factors for PH through a telephone interview. The centers submitted clinical data. The Scientific Steering Committee oversaw the creation of the study protocol, which was approved by the institutional review board of each center, the DCC, and the Harvard School of Public Health.

Patients

Investigators screened patients for eligibility at the time of their first visit to a SOPHIA center. Eleven of the centers began enrolling cases in January 1998. Two additional centers joined in September 1999. Enrollment closed on June 30, 2001. Subjects were residents of the United States aged 18 years or older whose objective evidence of PH included a right heart catheterization at a SOPHIA center, with measurement of right-sided hemodynamics, including pulmonary arterial pressure, cardiac output, and pulmonary capillary wedge pressure. Patients thought to have PH secondary to left heart disease of any kind were not enrolled. A diagnosis committee classified each subject into one of the following categories: PPH—currently considered category 1 in the revised clinical classification of the Third World Symposium on Pulmonary Hypertension, Venice 2003[7]; secondary PH due to left heart disease—currently considered Venice category 2; secondary PH due to chronic thromboembolic disease (SPH-Thrombo)—currently considered Venice category 4; secondary PH due to a cause other than left heart disease and thromboembolic disease (SPH-Other)—currently considered Venice categories 3 and 5; or not PH (No-PH). For a small number of PH cases, there was insufficient information to distinguish between primary and secondary PH (PH-Unclassified). The diagnosis committee members did not know the medications or other potential risk factors reported by the subject during the telephone interview,

and they signed out a case assignment only after coming to unanimous agreement. Subsequent analysis omitted subjects with left heart disease (secondary PH due to left heart disease) and subjects whose mean pulmonary capillary wedge pressure was above 15 mm Hg.

Exposure to prescription and over-the-counter drugs

Telephone interviewers asked subjects the names and duration of use of appetite suppressants, antidepressants, and amphetamines they had taken during the 5 years before the interview. After responding to these questions, the subject was asked to review a card that had been sent to them before the interview, which contained photographs and names of prescription medications as well as common herbal and over-the-counter (OTC) appetite suppressants and antidepressants, and to identify any products that they took but had failed to mention before.

Statistical methods

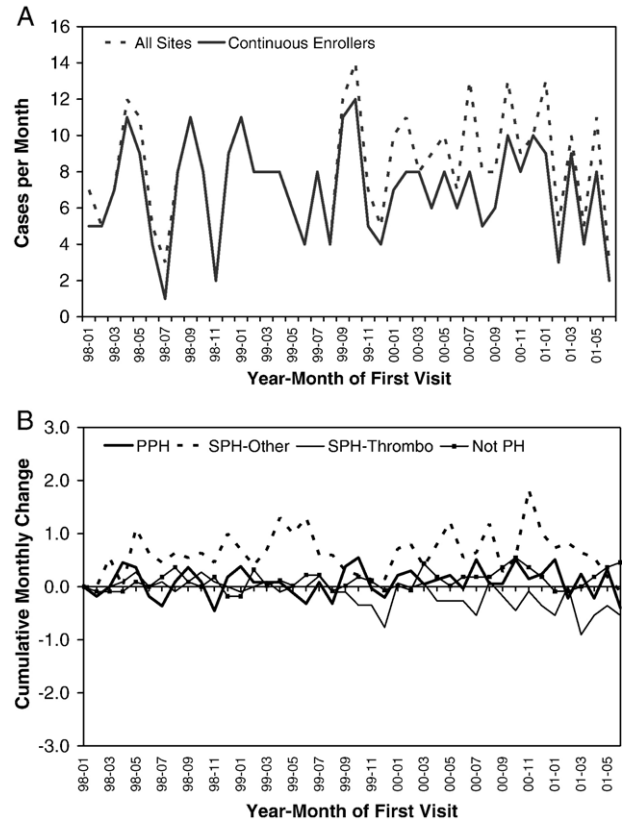
The monthly number of cases for each type of PH formed the basis for temporal trend analysis. Poisson regression models based on the monthly center-specific case counts were used to estimate time trends and conduct statistical tests of significance. Models were fit using the generalized estimating equations approach for repeated Poisson outcomes using an autoregressive correlation matrix.[8] The SAS software (PROC GENMOD) was used in the analysis.[9] Polytomous logistic regression models permitted analysis of the relationship between PH and medication use, yielding an odds ratio and a 95% confidence interval (95% CI). The SPH-Thrombo and SPH-Other were each taken as the comparison groups for exposures in PPH patients. All multivariable models included terms for gender, age, race/ethnicity, and center.

Results

There were 2915 patients potentially eligible to participate and 2361 (81.0%) who consented. There were 1555 (65.9%) patients who had a right heart catheterization performed at the SOPHIA center, and 1551 (99.7%) who had sufficient information available for review by the diagnosis committee. The diagnosis committee categorized 93 patients (6%) as having left heart disease based on clinical indications; these and an additional 123 patients (8%) with mean pulmonary capillary wedge pressures above 15 mm Hg were excluded from the analyses. The accrual and trend analyses reflect the remaining 1335 subjects. The 1189 (89.1%) subjects who completed the telephone interview provided information for the analysis of medication use.

As shown in Table I, there were 346 subjects with PPH, 219 subjects with SPH-Thrombo, 468 subjects with SPH-Other, 147 subjects with PH-Unclassified, and 155 subjects with No-PH. PPH subjects were younger and more likely to be female than subjects in the SPH groups. The distribution across the New York Heart Association (NYHA) functional classes was generally similar for the different PH groups, although the SPH-Thrombo group had a higher percentage of subjects in the NYHA class III or IV. The No-PH group differed from the PPH and SPH groups by being more likely to be female, to be in NYHA class I or II, and to have a body mass index (BMI) greater than 30.0. Figure 1 shows the number of cases of PPH reported by SOPHIA centers and the average within-center cumulative change for the 3 types of PH and the No-PH group. The number of new cases of PH (both PPH and SPH) was essentially constant throughout the study period. Poisson regres-

Figure 1



Accrual for cases of PPH and cumulative monthly change for each type of PH. The number of cases of PPH reported by all centers each month showed a slight increase in the later months of the study (panel **A**), primarily because of the change in center participation. Panel **B** shows the cumulative within-center change, a measure that is not affected by shifts over time in participation. This index is derived by calculating for each center the cumulative change in monthly counts of newly diagnosed cases, and averaging this number over each month's participating centers, and adding the monthly average change to the summed changes from all previous months. The index is set at 0.0 for the start of the study (January 1998); a rising cumulative change corresponds to increasing numbers of cases, and if there were no centers added to or removed from the collaboration, would give exactly the average number of cases in each month minus the average number of cases in January 1998.

Table II. Number and percentage of subjects reporting medication use during the 5 years before the interview and the adjusted odds ratios for the risk of PPH

	n (%)					Adjusted odds ratio (95% CI)*	
Medication	**PPH (n = 321)**	**SPH-Thrombo (n = 187)**	**SPH-Other (n = 405)**	**PH-Unclassified (n = 133)**	**No-PH (n = 143)**	**SPH-Thrombo as Control**	**SPH-Other as Control**
OTC antiobesity agents	14 (4.4)	2 (1.1)	5 (1.2)	7 (5.3)	2 (1.4)	5.3 (1.0-28.4)	3.0 (1.1-8.7)
Dexfenfluramine	16 (5.0)	3 (1.6)	6 (1.5)	7 (5.3)	23 (16.1)	4.3 (1.1-16.3)	2.8 (1.1-7.5)
Fenfluramine	35 (10.9)	4 (2.1)	14 (3.5)	24 (18.0)	41 (28.7)	10.2 (3.3-31.0)	2.6 (1.3-5.0)
Dexfenfluramine or fenfluramine	45 (14.0)	6 (3.2)	18 (4.4)	25 (18.8)	51 (35.7)	8.8 (3.4-22.6)	2.7 (1.5-4.9)
Phentermine	38 (11.8)	9 (4.8)	15 (3.7)	20 (15.0)	40 (28.0)	3.5 (1.5-8.0)	2.7 (1.4-5.1)
Any adrenergics for systemic use—antiobesity	60 (18.7)	13 (7.0)	26 (6.4)	31 (23.3)	55 (38.5)	4.8 (2.4-9.9)	2.7 (1.6-4.5)
Any nonselective monoamine reuptake inhibitor	25 (7.8)	17 (9.1)	42 (10.4)	9 (6.8)	26 (18.2)	0.7 (0.3-1.5)	0.6 (0.4-1.1)
Any selective serotonin reuptake inhibitor	80 (24.9)	32 (17.1)	97 (24.0)	28 (21.1)	49 (34.3)	1.3 (0.8-2.2)	0.9 (0.6-1.3)
Any other antidepressant	31 (9.7)	6 (3.2)	30 (7.4)	9 (6.8)	13 (9.1)	2.5 (0.9-6.5)	1.2 (0.7-2.0)
Any anxiolytic	19 (5.9)	11 (5.9)	12 (3.0)	4 (3.0)	5 (3.5)	1.2 (0.5-3.0)	2.0 (0.9-4.2)
Any herbal preparations	22 (6.9)	5 (2.7)	17 (4.2)	6 (4.5)	11 (7.7)	3.8 (1.2-11.6)	1.6 (0.8-3.0)

*Odds ratios are adjusted for age, gender, race/ethnicity, and site.

sion models fit to the monthly counts of each type of PH yielded the same result.

Table II displays medications reported by at least 10 of the 1189 subjects who completed the telephone interview in response to the question about antidepressants or appetite suppressants during the 5 years before the time of the interview. (Note that the responses included anxiolytics and herbal preparations.) More PPH subjects (18.7%) than SPH subjects (7.0% and 6.4% for SPH-Thrombo and SPH-Other, respectively) reported the use of an antiobesity agent.

The No-PH group, however, had the largest percentage of anorexigen users (38.5%). The percentages reporting antidepressant use among the PH groups are generally similar, although the No-PH group had the largest percentage of subjects reporting use of nonselective monoamine reuptake inhibitors and selective serotonin reuptake inhibitors. No single amphetamine or class of amphetamines was reported by 10 or more subjects. Based on very small numbers of reported users, the percentages for amphetamine use were similar across PH groups (data not shown).

Covariate-adjusted odds ratios and CIs for the medications and medication groups listed in Table II are in the 2 rightmost columns. Odds ratios for exposures in primary as opposed to nonthrombotic secondary PH were between 2.0 and 3.0 for several individual anorexigens and for the antiobesity medication class and were consistently greater when SPH-Thrombo served as the comparison group. There were no antidepressants strongly associated with PPH as opposed to either comparator, with the exception of a marginal association with the other antidepressants medication class. The association between PPH and OTC diet pills containing phenylpropanolamine and between PPH and herbal preparations (primarily St. John's Wort) was similar to that seen with anorexigens when SPH-Thrombo was used as the comparison group and also elevated when compared with SPH-Other (Table III).

Table III. Adjusted odds ratios for PPH and appetite suppressant use—additional models

	Adjusted odds ratio (95% CI)*	
Appetite suppressants taken during the 5 y before the interview	**SPH-Thrombo as control**	**SPH-Other as control**
Model 1		
Fenfluramines†	19.4 (4.6-81.7)	2.1 (0.9-4.7)
Phentermine	0.4 (0.1-1.3)	1.5 (0.6-3.7)
Model 2		
Fenfluramines†	8.6 (3.3-22.1)	2.7 (1.5-4.8)
OTC antiobesity agents	5.2 (0.9-29.3)	2.7 (1.0-7.8)
Model 3		
Fenfluramines†	8.7 (3.4-22.2)	2.7 (1.5-4.9)
Other appetite suppressants	1.0 (0.2-5.7)	1.6 (0.5-4.9)
Model 4		
Fenfluramines†	8.3 (3.2-21.2)	2.7 (1.5-4.9)
St. John's Wort	3.6 (1.0-13.0)	1.6 (0.8-3.1)
Model 5		
OTC antiobesity agents	4.8 (0.9-26.2)	3.0 (1.0-8.4)
St. John's Wort	4.2 (1.2-14.6)	1.5 (0.8-3.0)

*Adjusted odds ratio from logistic regression with age, gender, race/ethnicity, and site as covariates in addition to indicated appetite suppressants.
†Fenfluramine or dexfenfluramine.

Discussion

Although concern for cardiac valve disease dominated public discussion of the withdrawal of the fenfluramines from the US market in September 1997, there was a parallel speculation that fenfluramine use would dramatically raise the incidence of PPH. SOPHIA was to be an early warning system for such an increase. The withdrawal of fenfluramines before the first patient entered SOPHIA meant that the network could identify only the later consequences, if there were any, of fenfluramine use. From January 1998 to June 2001, there was no overall increase in the monthly counts of new PPH cases in the referral centers. As in International Primary Pulmonary Hypertension Study (IPPHS)[3] and Surveillance of North American Pulmonary Hypertension (SNAP),[4] however, fenfluramine and dexfenfluramine were associated with PPH. Use of OTC diet pills also emerged in association with PPH and deserves further scrutiny.

Apart from a small number of people who declined to have their data included, the study included all patients referred to the centers for a suspicion of PPH based on one or more tests. However, all noninvasive tests provide mere suggestions or estimates of the presence of PH, whereas a cardiac catheterization provides a definitive diagnosis. Almost 12% of the referred patients who were registered had mean pulmonary artery pressures below 25 mm Hg at rest. The finding of a large group without PH, among referred patients whose noninvasive tests suggested PH, highlights the importance of retaining cardiac catheterization as the definitive test for the diagnosis.

The SOPHIA investigators are experienced clinicians in major referral centers. The demands for careful documentation were high, and the diagnosis committee, which provided consistency in evaluation and classification, reviewed all cases. The interviews were monitored and checked. Patients received visual aids for identification of medications. Thus, we believe that the rigor of our methods led to a highly accurate data for analysis. The incidence of diagnosed PPH in the United States is not likely to have changed appreciably during the 42 months of case accrual. This conclusion rests on 3 key considerations. First, the case ascertainment, although not population-based, was both sensitive and comprehensive. In 2001, centers participating in SOPHIA accounted for 70% of all US patients taking epoprostenol, the only approved specific therapy for PPH at the time (S Rich, personal communication from Gentiva Health Services). Second, ascertainment was specific because of the high level of documentation demanded by SOPHIA diagnosis committee and the familiarity with those standards brought about by the rotating participation of each center investigator on the diagnosis committee. Specificity means that the inclusion of noncases is not likely to have obscured true variations in the occurrence of PPH. Finally, artifacts of case ascertainment should have accentuated, not blunted, the appearance of an epidemic. The high rate of anorexigen use in referred patients later determined not to have PH (the No-PH group) confirms that there was a high level of diagnostic suspicion in anorexigen users; hence, any anorexigen-induced epidemic should have been readily apparent.

For the reasons outlined above, we believe that case ascertainment was reasonably complete; nonetheless, some relevant cases must have been missed. SOPHIA centers will not have seen many cases, certainly including ones in whom the correct diagnosis was never entertained. Moreover, a normal resting pulmonary artery pressure does not necessarily exclude pulmonary vasculopathy nor does an elevated wedge pressure. There was, however, no practical way to drop these criteria without flooding the registry with cases with other (or absent) pathology.

The increased use of fenfluramine and dexfenfluramine in PPH patients is consistent with the findings of both the International Primary Pulmonary Hypertension Study (IPPHS) and Surveillance of North American Pulmonary Hypertension (SNAP) studies. The SOPHIA results taken alone, however, do not establish a causal association between fenfluramine use and PPH, nor was it the study's intent to demonstrate such an association because of irresolvable questions about ascertainment bias. Nevertheless, SOPHIA's design incorporated many safeguards against ascertainment or interview bias. The preplanned use of comparators sharing the symptoms and initial diagnostic findings of PPH (ie, those diagnosed with secondary PH) should have removed much of the effect of differential referral patterns. The diagnosis committee assigned the final classification only after registration and interview of the patient, so that knowledge of diagnosis could not have affected recall of drug use. Conversely, the diagnosis committee was unaware of the results of the patient interview, and so could not have incorporated exposure into its evaluations.

Our focus for this analysis was on the occurrence and frequency of recent drug use as collected by patient-reported data. We were not able to validate drug usage through medical charts or pharmacy records. Therefore, we felt the analysis for this manuscript should be restricted to a broad measure of drug use and that classifying subjects according to whether they used a drug during the 5 years before the interview would be the most valid indicator. Accordingly, we are unable to address what role duration or extent of use may play.

The use of other secondary PH as a comparator could lead to an understatement of the association between fenfluramines and PPH. If the fenfluramines were to accelerate or potentiate an underlying or preexisting pathological process, the use of fenfluramines would be higher in that secondary PH population, and the com-

parative extent of the association between fenfluramines and the PPH population would understate the situation. The absence of a detectable increase in the occurrence of PPH is not inconsistent with the simultaneous finding that anorexigens were associated with PPH. Fewer than 20% of the PPH cases were associated with any adrenergic agent for the treatment of obesity, and any effects of such agents on the overall incidence may well have been beyond the resolving capacity of this registry.

The findings were robust over numerous analytic and procedural variations. For example, adding current BMI or the BMI from the 5 years before the interview as a covariate in the regression models did not meaningfully affect the results, nor did including the originally excluded cases of left heart disease in the SPH group. Alternative methods for defining anorexigen use patterns (eg, separating single drug users from multiple drug users) all yielded similar results.

The OTC diet pills reported by subjects were believed to be of the type known to contain phenylpropanolamine as one of their active ingredients, although it should be noted that OTC reports were not aided by the picture cards used to aid in the recall of prescription drugs. The association between PPH and antiobesity agents containing phenylpropanolamine use has not previously been described. Referral bias, which requires that the referring physician have knowledge of the association in question, cannot account for a novel drug-disease correlation.

Furthermore, there was no excess use of these products reported by the No-PH group. Phenylpropanolamine is a sympathomimetic amine that was formerly a component of some cold medications and was found in higher doses in some OTC anorexigens. Theoretically, it could act as a pulmonary vasoconstrictor, affect pulmonary uptake and metabolism, or potentiate an underlying predisposition to PH. In 2000, Kernan and colleagues[10] described an increased risk of hemorrhagic stroke with phenylpropanolamine ingestion.

The SOPHIA registry is the first large multicenter study of a PH population in the United States since the PPH registry of the 1980s. In addition to PPH patients, it includes carefully categorized populations of secondary PH. SOPHIA will enable further study of survival, clinical parameters, and the effects of therapy in a population diagnosed and treated according to modern standards. An epidemic of anorexigen-related PPH was not evident during the SOPHIA study period, which began 3 months after the fenfluramines were withdrawn from the market. The use of fenfluramine derivatives, however, was associated with PPH in many cases, which is consistent with prior studies. The excess of fenfluramine users in the No-PH group strongly suggests a referral bias, in which fenfluramine-exposed individuals are more likely than others to have been sent to a SOPHIA center for evaluation. The associations with St. John's Wort and OTC diet pills, which contained phenylpropanolamine, were new and unexpected findings.

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Appendix A

The following study coordinators and managers participated in the SOPHIA study: D. Camanga, Harbor-UCLA Medical Center; T. Housten-Harris, University of Maryland and Johns Hopkins University; A. Krichman, Duke University Medical Center; C. List, Rush-Presbyterian-St. Luke's Medical Center; C. Mason, Westat; W. Mason, Vanderbilt University Medical Center; D. McIntyre, University of California, San Diego Medical Center; M. Panella, Rush-Presbyterian-St. Luke's Medical Center; H. Purl, Baylor College of Medicine; L. Rayl, University of Pittsburgh Medical Center; P. Shechter, Harvard School of Public Health; M. Smith, University of Alabama at Birmingham; M. Therrien, Westat; S. Tointon, Mayo Clinic; K. Wynne, University of Colorado Health Science Center; A. Yoney, Columbia University College of Physicians and Surgeons.