CHEST

Original Research

PULMONARY VASCULAR DISEASE

Selective Serotonin Reuptake Inhibitors and Pulmonary Arterial Hypertension

A Case-Control Study

Irfan A. Dhalla, MD; David N. Juurlink, MD, PhD; Tara Gomes, MHSc; John T. Granton, MD; Hong Zheng, MSc; and Muhammad M. Mamdani, PharmD, MPH

Background: **Animal and human studies suggest that selective serotonin reuptake inhibitors (SSRIs) might be useful for the prevention or treatment of pulmonary arterial hypertension.**
Methods: **We conducted a population-based, nested case-control study to explore the hypothesis that SSRIs might reduce the risk of pulmonary arterial hypertension. Cases were individuals who developed pulmonary arterial hypertension requiring pharmacologic treatment. For each case, we selected up to 10 matched control subjects. Exposure to SSRIs and non-SSRI antidepressants was ascertained using administrative data. The outcome of pulmonary arterial hypertension requiring pharmacologic therapy was defined as the receipt of a drug specific for the treatment of pulmonary arterial hypertension.**
Results: **In contrast to our hypothesis, and likely because of residual confounding, we found a positive association between SSRI use and pulmonary arterial hypertension (adjusted OR, 1.55; 95% CI, 1.13-2.13).**
Conclusions: **At conventional doses, SSRIs are not associated with a reduced risk of pulmonary arterial hypertension.** ***CHEST 2012; 141(2):348–353***

Abbreviations: SSRI = selective serotonin reuptake inhibitor

The pathophysiology of pulmonary arterial hypertension, a rare and often fatal disorder characterized by elevated pulmonary vascular resistance and remodeling of the pulmonary arterioles, remains incompletely understood.[1] Known risk factors include female sex, HIV infection,[2] connective tissue diseases (especially systemic sclerosis),[3] and exposure to fenfluramine and dexfenfluramine,[4] drugs previously marketed as appetite suppressants. Metabolites of these drugs stimulate serotonin receptor subtypes with varying affinity.[5] Several additional lines of evidence implicate serotonin, and in particular the serotonin transporter, in the pathophysiology of pulmonary arterial hypertension.[6] For example, serotonin induces smooth muscle cell proliferation in pulmonary arterioles, and polymorphisms of the serotonin transporter appear to be associated with pulmonary arterial hypertension.[7]

Limited evidence suggests that selective serotonin reuptake inhibitors (SSRIs), popular medications

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Affiliations: From the Department of Medicine (Drs Dhalla, Juurlink, and Granton), the Department of Health Policy, Management, and Evaluation (Drs Dhalla, Juurlink, and Mamdani), and the Leslie Dan Faculty of Pharmacy (Ms Gomes and Dr Mamdani), University of Toronto; the Department of Medicine (Dr Dhalla), and the Li Ka Shing Knowledge Institute (Dr Dhalla and Dr Mamdani), St. Michael's Hospital; the Institute for Clinical Evaluative Sciences (Drs Dhalla, Juurlink, and Mamdani; Mss Gomes and Zheng); the Sunnybrook Research Institute (Dr Juurlink); and the Division of Respirology (Dr Granton), University Health Network, Toronto, ON, Canada.
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Correspondence to: Irfan A. Dhalla, MD, Department of Medicine, St. Michael's Hospital, 30 Bond St, Toronto, ON, M5B 1W8, Canada; e-mail: dhallai@smh.ca

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primarily used to treat depression and anxiety, may prevent or ameliorate pulmonary arterial hypertension. In vitro, the proliferative effects of serotonin are inhibited in a dose-dependent fashion by fluoxetine and citalopram but not by serotonin receptor antagonists.[6,7] The development of monocrotaline-induced pulmonary arterial hypertension in rats has been shown to be prevented and reversed by fluoxetine.[8] In humans, one case-control study has suggested that exposure to SSRIs may be associated with a reduced risk of pulmonary arterial hypertension,[9] and two cohort studies have suggested that exposure to SSRIs may be associated with reduced mortality in individuals with pulmonary arterial hypertension.[9,10] Although the ClinicalTrials.gov registry lists at least two randomized controlled trials examining the use of SSRIs in patients with pulmonary arterial hypertension, results of these trials have not yet been published.[11,12] Furthermore, the anticipated sample size of the two studies (10 and 30 patients, respectively) suggests that the trials may produce indeterminate results.

Drugs that reduce the risk of pulmonary arterial hypertension would be useful for patients at high risk of developing the disease, such as those with systemic sclerosis or a genetic predisposition toward pulmonary arterial hypertension. Such drugs might also delay disease progression or even reverse the natural history of pulmonary arterial hypertension and would warrant careful study in adequately powered clinical trials. We, therefore, explored the hypotheses that the use of SSRIs might be associated with a reduced risk of pulmonary arterial hypertension.

Materials and Methods

Setting, Design, and Ethical Approval

We conducted a population-based, nested case-control study between January 1, 1998 and March 31, 2010, using health-care databases in Ontario, Canada. This study was approved by the research ethics board of the Sunnybrook Health Sciences Centre.

Data Sources

We examined data from the publicly funded drug programs in Ontario, Canada, which provide coverage to all Ontario residents aged 65 years or older, recipients of social assistance and disability support, as well as those whose drug costs are high relative to their household income.[13] We linked these records to the Ontario Health Insurance Plan database, which records physician billing claims, and the Registered Persons Database, which contains basic demographic information about every Ontario resident. These administrative databases were anonymously linked using encrypted health card numbers and have been widely used for clinical epidemiologic research.[14-17]

Identification of Cases and Control Subjects

Within the cohort of individuals who received at least one publicly funded prescription during the study period, we defined case patients as those who received at least one prescription for epoprostenol, sildenafil, bosentan, ambrisentan, or treprostinil in each of the two case-control studies. (Of note, sildenafil is available with two brand names in Canada, as Viagra for the treatment of erectile dysfunction and Revatio for the treatment of pulmonary arterial hypertension. Only Revatio was included in our study.) In Ontario, these drugs are publicly funded only for patients with World Health Organization group 1 pulmonary arterial hypertension. Pulmonary hypertension must be confirmed with right-sided heart catheterization, and secondary causes, such as left ventricular dysfunction, pulmonary embolism, COPD, or interstitial lung disease, must be excluded. Patients must also have symptoms consistent with New York Heart Association functional classes III or IV. During the period of our study, prior authorization after review by an independent physician consultant to the Ontario Ministry of Health and Long-Term Care was required for reimbursement of any of the pulmonary arterial hypertension drugs. The date of the first prescription for a pulmonary arterial hypertension drug served as the index date.

For each case, we randomly selected up to 10 control subjects from the general population of Ontario. To ensure continuous public drug plan eligibility over the exposure window, cases and control subjects were eligible only if they had filled a prescription for any drug in the 181 to 365 days prior to index date. Continuous eligibility is important because drugs used to treat pulmonary arterial hypertension are expensive, and eligibility for public drug coverage in Ontario can depend on the cost of prescription drugs as a proportion of income. Control subjects were randomly assigned index dates to match the distribution of index dates among cases and were then matched to cases based on age (within 2 years), sex, index date, and the drug program type (eg, seniors, social assistance, income-contingent eligibility, and so forth). Cases with no matched control subjects were excluded, and each potential control subject could only be matched to one case. The exposures of interest were SSRI use and non-SSRI antidepressant use in the 180 days prior to the index date (Table 1). We excluded individuals with prescriptions for both SSRI and non-SSRI antidepressants during the exposure window. Although we planned to exclude individuals who received fenfluramine at any time during the study period, there were no such individuals in the study population.

Statistical Analysis

We used standardized differences to compare baseline characteristics between cases and control subjects, with differences of < 0.1 taken to indicate good balance, and conditional logistic regression to estimate the OR for the association between drug

Table 1—*Exposure to Individual Antidepressants Among Cases and Control Subjects*

Exposure	Cases	Control Subjects
Any SSRI	60	381
Citalopram	23	160
Escitalopram	≤ 5[a]	12
Fluoxetine	7	31
Fluvoxamine	≤ 5[a]	14
Paroxetine	13	106
Sertraline	14	66

Individual exposures may exceed total class-level exposure because some individuals received more than one SSRI. SSRI = selective serotonin reuptake inhibitor.

[a]Cell sizes with ≤ 5 individuals are suppressed in accordance with institutional privacy regulations.

exposure and treated pulmonary arterial hypertension. Multivariable conditional logistic regression was used to adjust for potential confounding variables, including neighborhood socioeconomic status, HIV, the presence or absence of a visit to a rheumatologist in the year prior to the index date, and the presence or absence of a visit to a psychiatrist in the year prior to the index date. We also created a secondary model in which we adjusted for the number of physician visits in the year prior to the index date. All analyses were performed using SAS, version 9.2 (SAS Institute).

Results

We identified 460 eligible case patients and 4,539 eligible control subjects (Fig 1). Most case patients were women (n = 334, 72.6%), and the mean age at index date was 65.3 years (SD, 16.4 years). Case and control subjects were well matched with respect to age, sex, neighborhood socioeconomic status, and the type of public drug program (Table 2). As expected, case patients were more likely to have seen a psychiatrist or a rheumatologist in the year prior to the index date.

In contrast to our hypothesis, we found that SSRI use was associated with an increased risk of pulmonary arterial hypertension requiring pharmacologic treatment (Table 3). This association was only slightly attenuated by multivariate adjustment (adjusted OR, 1.55; 95% CI, 1.13-2.13) in our primary model. The most commonly used SSRI among the 60 exposed cases was citalopram (n = 23, 38%) (Table 1). Citalopram was also the most commonly used SSRI among the 381 exposed control subjects (n = 160, 42%). As expected, we did not find an association between non-SSRI antidepressant use and the risk of pulmonary arterial hypertension (adjusted OR, 1.08; 95% CI, 0.78-1.51).

Adjusting for the number of physician visits in a secondary model decreased the magnitude of the association between SSRI exposure and pulmonary arterial hypertension from 1.55 (95% CI, 1.13-2.13) to 1.23 (95% CI, 0.86-1.76). As expected, the number of physician visits was strongly associated with pulmonary arterial hypertension (eg, adjusted OR was 1.048 for each additional physician visit, with a 95% CI of 1.043-1.053).

Discussion

In a large population-based case-control study, we did not find evidence that treatment with SSRIs protects against the development of pulmonary arterial hypertension requiring pharmacologic treatment. Our finding of a positive association between SSRI use and the development of pulmonary arterial hypertension was unexpected. Although this raises the possibility that the use of SSRIs is a risk factor for pulmonary arterial hypertension, we suspect the finding is more likely to reflect confounding due to the high prevalence of psychologic disorders in patients with pulmonary arterial hypertension,[18-20] which we were unable to control for in our study. In other words, if more cases than control subjects were depressed, our study would have been biased toward the finding of an association between SSRI use and the development of pulmonary arterial hypertension. Given the high prevalence of depression in pulmonary arterial hypertension,[21] this scenario is entirely plausible.

Using data from the Surveillance of Pulmonary Hypertension in America (SOPHIA) registry, Shah et al[9] reported that SSRI use was associated with a reduced risk of pulmonary hypertension. There are at least two reasons that may explain the apparent difference in findings between our study and that of

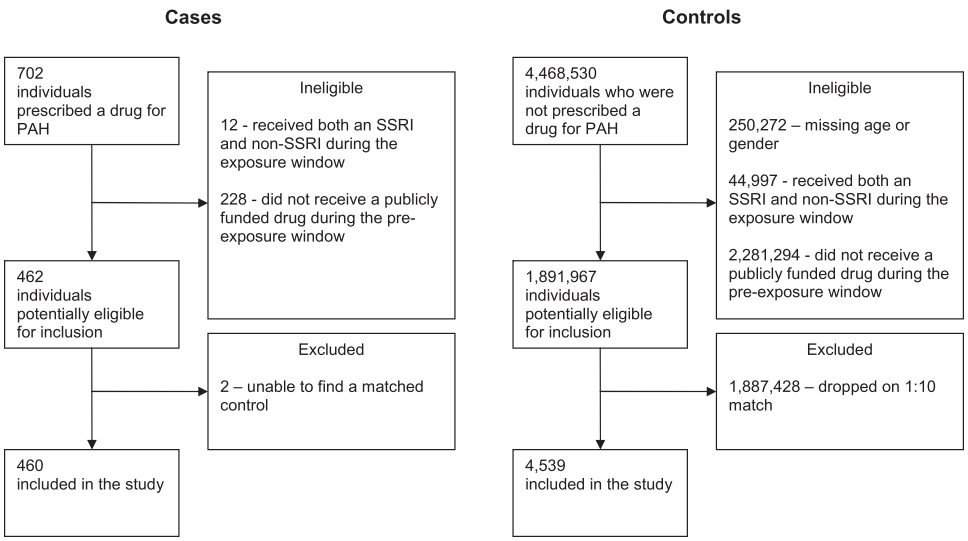

Figure 1. Identification of cases and control subjects. PAH = pulmonary arterial hypertension; SSRI = selective serotonin reuptake inhibitors.

Table 2—*Characteristics of Case Patients and Control Subjects*

Variable	Case Patients (n = 460)	Control Subjects (n = 4,539)	Standardized Difference
Age at index date; median (interquartile range)	70 (62-76)	70 (63-76)	.03
Female	334 (72.6)	3,290 (72.5)	0
Type of Ontario drug benefit program			
Seniors	320 (69.6)	3,200 (70.5)	.02
Disability or social assistance	87 (18.9)	867 (19.1)	0
Income-contingent program	29 (6.3)	277 (6.1)	.01
Home care	22 (4.8)	175 (3.9)	.05
Other	≤ 5[a]	20 (0.4)	0
Income quintile			
1 (lowest)	102 (22.2)	1,118 (24.6)	.06
2	98 (21.3)	973 (21.4)	0
3	90 (19.6)	869 (19.1)	.01
4	84 (18.3)	819 (18.0)	.01
5 (highest)	84 (18.3)	750 (16.5)	.05
Missing	≤ 5[a]	10 (0.2)	.04
HIV[b]	≤ 5[a]	≤ 5[a]	.09
Visit to a rheumatologist in the year before index date	134 (29.1)	283 (6.2)	.85
Visit to a psychiatrist in the year before index date	39 (8.5)	239 (5.3)	.14
Pulmonary artery hypertension drug at index		N/A	N/A
Bosentan	341 (74.1)		
Sildenafil	95 (20.7)		
Epoprostenol	20 (4.3)		
Ambrisentan	≤ 5[a]		
Treprostinil	≤ 5[a]		

Values are expressed as No. (%) unless otherwise indicated. N/A = not applicable.

[a]Cell sizes with ≤ 5 individuals are suppressed in accordance with institutional privacy regulations.

[b]Defined as receipt of antiretroviral therapy in the 180 d prior to the index date.

Shah et al.[9] First, the control subjects in the SOPHIA study were included because they were referred for possible pulmonary arterial hypertension and differed in important ways from the case patients. As the authors noted, control subjects may have had a higher incidence of depression-related somatization, leading to evaluation for pulmonary hypertension. If so, the increased prevalence of depression among control subjects relative to case patients may have biased the study toward finding that SSRIs protected against the development of pulmonary arterial hypertension. Second, when Shah et al[9] adjusted for potential confounders, the protective effect of SSRIs was diminished and the adjusted OR was not statistically significant ($P = .09$). Adjustment for unmeasured confounders might have attenuated the association even further. Although SSRIs have been associated with improved outcomes in two cohort studies,[9,10] these studies should be viewed as hypothesis-generating because of the possibility of unmeasured confounding. There are as yet no data from randomized controlled trials supporting the use of SSRIs in patients with pulmonary arterial hypertension.

Several limitations of our study merit emphasis. First, we used administrative data rather than clinical data to establish our case definition. The use of clinical data would likely have resulted in a more sensitive case definition than the one we used. However, our definition is likely to have a very high positive predictive value because independent clinical review was required for drug reimbursement. Because pulmonary arterial hypertension is rare,

Table 3—*Association Between Antidepressant Use and Incident Pulmonary Arterial Hypertension*

	No. (%) Exposed		OR (95% CI)	
Exposure Within 180 d of Index Date	Case Patients	Control Subjects	Univariate	Multivariate[a]
SSRI use	60 (13.0)	381 (8.4)	1.68 (1.25-2.25)	1.55 (1.13-2.13)
Non-SSRI antidepressant use[b]	50 (10.9)	434 (9.6)	1.23 (0.90-1.68)	1.08 (0.78-1.51)
No antidepressant use (reference)	350 (76.1)	3,724 (82.0)	1	1

See Table 1 legend for expansion of abbreviation.

[a]Adjusted for socioeconomic status, visit to a rheumatologist in the year before the index date, visit to a psychiatrist in the year before the index date (SSRI case control study only), and receipt of antiretrovirals in the 180 d before the index date.

[b]Potential non-SSRI exposures include amitriptyline, amoxapine, bupropion, clomipramine, desipramine, doxepin, imipramine, maprotiline, mirtazapine, moclobemide, nefazodone, nortriptyline, protriptyline, trazodone, trimipramine, venlafaxine.

very few of the control subjects in our study are likely to have had pulmonary arterial hypertension. Therefore, a specific but insensitive case definition is unlikely to result in significant bias. Second, we only considered medication exposure in the 180 days preceding the index date. It is possible that more remote SSRI use, perhaps over a longer period, might have reduced the likelihood of pulmonary arterial hypertension. However, because of the nature of the administrative data available to us, a longer exposure window would have reduced our ability to demonstrate a potential effect. Furthermore, the hemodynamic effects of serotonin in animal models and in vitro studies are not delayed. Similarly, the deleterious effects of fenfluramine were observed within a time frame similar to the one we used in our study.[4] Nevertheless, we are unable to exclude the possibility that SSRIs exert a protective effect over a longer time period. Similarly, because the cases had New York Heart Association class III or IV symptoms, we are also unable to exclude the possibility that SSRIs would prevent the development of asymptomatic or mildly symptomatic pulmonary arterial hypertension. Third, because public drug coverage in Ontario covers only some individuals under the age of 65 years, the age distribution of our study population is skewed in comparison with the age distribution of the pulmonary arterial hypertension population and also in comparison with the age distribution of the population studied by Shah et al.[9] However, as noted previously, our outcome definition is highly specific, and it is unlikely that any of the older case patients in our study did not have pulmonary arterial hypertension. Nevertheless, pulmonary arterial hypertension remains a heterogeneous group of conditions, and it is possible that SSRIs might have a preventive or therapeutic effect in younger patients or in another subgroup. Finally, we could not adjust for unmeasured confounders, including depression and anxiety, as well as risk factors for pulmonary arterial hypertension that are not yet elucidated or were unmeasured in our study (eg, genetic polymorphisms). We believe that confounding is likely to be the reason for the positive association between SSRI exposure and pulmonary arterial hypertension in our study.

In conclusion, we did not find a protective association between SSRI exposure and pulmonary arterial hypertension. If SSRIs do exert a protective effect, it is likely to be small, at least at doses currently used for depression, or to be restricted to a subset of the population.

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Dr Dhalla: contributed to the design of the study, the analysis and interpretation of the data, writing the first draft of the manuscript, and the final draft of the manuscript.
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Ms Gomes: contributed to the design of the study, the analysis and interpretation of the data, and the final draft of the manuscript.
Dr Granton: contributed to the design of the study, the analysis and interpretation of the data, and the final draft of the manuscript.
Ms Zheng: contributed to data analysis and the final draft of the manuscript.
Dr Mamdani: contributed to the design of the study, the analysis and interpretation of the data, and the final draft of the manuscript.
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