The use of antidepressants and the risk of idiopathic pulmonary arterial hypertension

Benjamin D Fox BM BS [1,2,3], Laurent Azoulay PhD [1,4], Sophie Dell'Aniello MSc [1], David Langleben MD [2], Francesco Lapi PharmD PhD [1,5], Jacques Benisty MD [1], Samy Suissa PhD [1]

1. Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Canada
2. Center for Pulmonary Vascular Diseases, Division of Cardiology, Jewish General Hospital, Montreal, Canada
3. Department of Medicine, Tel Aviv University, Israel
4. Department of Oncology, McGill University, Montreal Canada
5. Department of Preclinical and Clinical Pharmacology, University of Florence (Florence, Italy); Agency for Healthcare Services of Tuscany (Florence, Italy)

Running title: Anti-depressants and Pulmonary Arterial Hypertension
Word Count: 2496

Correspondence:
Dr. Samy Suissa
Centre for Clinical Epidemiology
Lady Davis Institute, Jewish General Hospital
3755 Côte-Sainte-Catherine, H-461
Montreal, Quebec, Canada, H3T 1E2
Tel: 514.340.8222; Fax: 514.340.7510
Email: samy.suissa@mcgill.ca

Abbreviations:

5HT, 5-hydroxytryptamine (serotonin)

BMI, Body Mass Index

CPRD, Clinical Practice Research Datalink

HES, Hospital Episodes Statistics Database

IPAH, Idiopathic Pulmonary Arterial Hypertension

NSAID, non-steroidal anti-inflammatory drugs

PAH, Pulmonary Arterial Hypertension

SERT, serotonin transporter

SSRI, Selective Serotonin Reuptake Inhibitors

RR, Rate Ratio

ABSTRACT

Background: Serotonin has been implicated in the development of idiopathic pulmonary arterial hypertension (IPAH). Drugs modulating serotonin pathways, including anti-depressants, have been associated with the incidence of IPAH, with conflicting reports as to the direction of the effect. We aimed to determine whether antidepressant exposure is associated with the incidence of IPAH.

Methods: A nested case-control study was conducted using the United Kingdom Clinical Practice Research Datalink and the Hospital Episodes Statistics repository between January 1, 1988 and September 30, 2011. Incident cases of IPAH were identified and matched to all controls in case's risk set on age, sex, general practice, and date of registration with the practice. Rate ratios (RRs) and 95% confidence intervals (CIs) were estimated for the use of antidepressants on the risk of IPAH, with an 18-month lag period prior to the diagnosis.

Results: 195 IPAH cases were identified (incidence 3.84/million/year). Use of any antidepressant was associated with 67% increased risk of IPAH (RR: 1.67, 95% CI: 1.17–2.37). The rate of IPAH was similar across antidepressant classes, whether with Selective Serotonin Reuptake Inhibitors [SSRIs] (RR: 1.67, 95% CI: 1.09–2.57) or non-SSRI antidepressants (RR: 1.66, 95% CI: 1.07–2.59). In sensitivity and exploratory analyses, no change in risk was observed with different lag times, serotonin transporter affinities, or durations of exposure.

Conclusions: The use of antidepressants was associated with a significantly increased risk of developing IPAH. However, the consistency of this risk across all antidepressants and absence of a dose-response relationship suggests a non-causal association.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare but fatal disease of the lung blood vessels.[1] Several anorexigen medications have been strongly associated with the development of PAH, including aminorex, fenfluramine and dexfenfluramine.[1, 2] Anorexigens stimulate serotonin (5HT) release from the gastrointestinal tract and platelets, increase 5HT uptake into pulmonary artery smooth muscle cells through the serotonin transporter (SERT), and also act as a direct 5HT agonist at cell surface receptors.[3] 5HT promotes pulmonary artery smooth muscle cell contraction and proliferation. Animal and in-vitro models of PAH have generally supported this 'serotonin hypothesis' of PAH.[3] Inhibition of the SERT molecule is therefore a potential target for prevention or treatment of PAH.

Many antidepressants block SERT, notably the selective serotonin reuptake inhibitors (SSRIs).[4] In a case-control study of patients referred to a pulmonary hypertension center, use of SSRIs was associated with a trend towards a decreased risk of pulmonary hypertension (odds ratio [OR]: 0.71, 95% confidence interval [CI]: 0.48-1.06) and a decreased risk of death (hazard ratio: 0.35, 95% CI: 0.14-0.88).[5] In contrast, in a large case-control study, the use of SSRIs was associated with a 55% increased risk of developing PAH (OR, 1.55; 95%CI: 1.13-2.13).[6] In the Multi-Ethic Study of Atherosclerosis – Right Ventricle study of 4114 healthy subjects, exposure to SSRIs was associated with a small but measurable increase in right ventricular mass, consistent with increased right ventricular afterload.[7] Data from the REVEAL registry demonstrated increased likelihood of poor outcomes in PAH patients treated with SSRIs.[8]

In view of the conflicting data surrounding the potential role of antidepressants in the pathogenesis of PAH, we performed a population-based study using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD) and the Hospital Episodes Statistics (HES)

repository. The objective was to assess whether the use of antidepressants modulating the 5-HT pathway are associated with the incidence of developing PAH. The manuscript was drafted with reference to the STROBE guidelines.[9]

METHODS

Data sources

This study was carried out using two databases from the UK, the CPRD, previously known as the General Practice Research Database, and the HES. The CPRD is the world's largest computerized database of longitudinal records from primary care, covering more than 12 million people in more than 650 general practices.[10] The CPRD is representative of the UK population, both in terms of the geographic distribution of the general practices and the age and sex distributions of patients.[11] Participating general practitioners have been trained to record medical information, demographic data, body mass index, smoking and alcohol use, medical diagnoses, procedures, and deaths. The Read code classification is used for medical diagnoses and procedures. Prescriptions are automatically recorded based on the UK Prescription Pricing Authority Dictionary. CPRD data for diagnoses and medications have been validated.[12, 13, 14]

The HES repository contains dates of hospital admissions, primary and secondary diagnoses (coded using the ICD-10 classification), and related procedures (coded using the Office of Population Censuses and Surveys classification of interventions and procedures, v. 4).

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Committee of the Jewish General Hospital, Montreal, Canada.

Study population

The source population of this study consisted of all patients present in the CPRD between January 1, 1988 and September 30, 2011. Cohort entry was defined as the latest of the following events: January 1, 1988, date of a patient's 12th birthday, date of current registration, or date of the 'up-to-standard' designation of a patient's general practice. Patients were excluded if they were not from an up-to-standard practice, had less than one year of medical history information, were diagnosed with a condition related to excessive alcohol use, or aortic/mitral valvular disease at any time prior to cohort entry. Patients meeting these criteria were followed until a first-ever diagnosis of PAH, diagnosis of a condition related to excessive alcohol use or valve disease, death from any cause, end of registration with the general practice, or end of the study period (September 30, 2011), whichever came first.

Case-control selection

We identified all potential incident cases of idiopathic PAH (IPAH) in either the CPRD (Read codes: G41y000, G410.00, 7Q01300, 7Q01200, 7Q01100, 7Q01000, G42..11, G41z.00, G41..00) or HES database (ICD-10 code I27.0). As a second step, a physician with extensive experience of PAH (BDF) examined the entire computerized medical record of each potential case and allocated the patient to a diagnostic category (idiopathic PAH, PAH associated with other conditions, and no PAH) **according to clinical judgment**. The physician was blinded to the patients' age, sex, and antidepressant drug exposure. The computerized medical record included codes for PAH-associated diseases (e.g., connective tissue diseases, congenital heart lesions, portal hypertension, HIV infection), therapeutic procedures associated with PAH (e.g. right heart catheterization, insertion of hickman catheter), as well as those with diagnoses of cardiac and respiratory diseases associated with

pulmonary hypertension but not PAH (e.g. pulmonary thromboembolism or sarcoidosis). Prescriptions for PAH-specific vasodilators (sildenafil, bosentan, ambrisentan, sitaxsentan, epopoprostenol, treprostenil, iloprost), drugs frequently prescribed to patients with PAH (e.g. vitamin K antagonists, diltiazem, nifedipine, amlodipine) and other cardiovascular or respiratory medications were also included in the reviewed medical records. A **pseudo-**random sample of 200 cases was examined by a second physician (JB) who was blinded to the diagnosis of the first physician. The kappa statistic for agreement between the two physicians for the sample was 0.68 **representing substantial agreement**.**[15]** The index date was defined as the date of the first-ever diagnosis of IPAH.

All controls were selected from the same CPRD/HES cohort. Given the rarity of the outcome and to maximize statistical power, we selected all controls in the case's risk set, after matching on age (± 5 years), sex, general practice, and current registration date in the practice (± 1 year). By definition, all controls were alive, never diagnosed with IPAH at the time of the index date, and registered with the general practice when matched to a case, and thus had equal duration of medical history information at the index date.

Exposure assessment

For all cases and matched controls, we obtained information on antidepressants received between cohort entry and index date. We did not include exposures received in the 18-month time window immediately prior to index date to account for the insidious nature of PAH, which results in a lag between onset of symptoms and clinical diagnosis, and to minimize protopathic bias (i.e. depressive symptoms related to IPAH onset leading to antidepressant prescription before the PAH is diagnosed).**[16]** All classes of antidepressants were considered: tricyclics, SSRIs, monoamine-oxidase inhibitors, other monoamine reuptake

inhibitors and other miscellaneous classes. Given the uncertainties related to the length of the lag period, we conducted sensitivity analyses varying the lag period to 0, 12, 24, 36, 48 and 60 months.

In secondary analyses, exposure to antidepressant was categorized into three different ways. In the first two, we assessed whether different drug affinity (K_D) for both serotonin and noradrenaline transporters were associated with the incidence of IPAH.[4] For the third analysis, we assessed whether cumulative duration of use of antidepressants was associated with the incidence of IPAH. Cumulative duration was calculated by summing the durations of all antidepressant prescriptions received between cohort entry and index date.

Statistical analysis

We conducted a nested case-control analysis. We used this approach because of the time varying nature of the exposure, the size of the cohort, and the long duration of follow-up.[17] This technique is computationally efficient, while producing ORs that are unbiased estimators of incidence rate ratios (RRs) with little or no loss in precision.[17, 18, 19]

Descriptive statistics were used to summarize the characteristics of the cases and matched controls. We also calculated crude incidence rates of IPAH, along with 95% CIs based on the Poisson distribution. Conditional logistic regression was used to estimate the RRs with 95% CIs of incident IPAH associated with the use of antidepressants.

In addition age, sex, general practice, and year of current registration or ‘up-to-standard’ designation in the general practice on which the logistic regression models were conditioned, we adjusted for the following potential confounders measured between cohort entry and 18 months before index date: obesity (BMI>30 kg/m^2), smoking (ever versus never), and in the year prior to the lagged period, the use of antihypertensives, anti-parkinsonian drugs,

antipsychotics, inhaled corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, and narcotic analgesics. All statistical tests were two-tailed.

RESULTS

Overall, a total of 9644 patients with a diagnostic code consistent with PAH were identified. After initially excluding patients with a PAH diagnosis outside of the study period, pediatric cases, prevalent PAH or patients diagnosed with alcohol-related disorders or valve disease prior to PAH diagnosis, there remained 3192 potential PAH cases (Figure 1). After excluding cases with a history of cardiac or pulmonary disease, and PAH-associated conditions, the final IPAH cases consisted of 195 patients, generating an incidence rate of 3.84 (95% CI: 3.34 - 4.42) per million per year.

Table 1 presents the characteristics of the cases and matched controls. The mean age at index date for both cases and controls was 61.6 years (standard deviation: 16.5) and 67% were females. Compared to controls, cases were more likely to have been obese, and to have used inhaled corticosteroids and antihypertensives (Table 1).

Table 2 presents the results of the primary analysis based on an 18-month lag before the index date. Overall, the use of any antidepressant was associated with a 67% increased risk of IPAH (RR: 1.67, 95% CI: 1.17–2.37) (Table 2). The rate of IPAH was similar between SSRIs (RR: 1.67, 95% CI 1.09–2.57) and non-SSRI antidepressants (RR: 1.66, 95% CI 1.07–2.59). In the sensitivity analysis which varied the lag period before the index date (Table 3 and Figure 2), the risk of developing IPAH remained relatively consistent (Figure 2).

Table 4 presents the results of the secondary analyses. Overall, antidepressants categorized as high and intermediate-low affinity for the serotonin or noradrenaline transporter yielded similar RRs for IPAH. Furthermore, there was no effect of cumulative duration of antidepressant use on the risk of IPAH.

DISCUSSION

The results of this population-based study indicate that the use of antidepressants was associated with an increased risk of IPAH. However, the association was not specific to the antidepressant class, potency, or by cumulative duration of use. Such consistent results suggest a non-causal association between the use of antidepressants and the risk of IPAH.

To date, the few studies investigating the association between the use of antidepressants and the incidence of PAH have produced conflicting results.[5, 6] One initial report suggested that SSRIs may be protective against the development of PAH, **although this study was based on a case series of patients referred to a specialist center and as such may have been biased**.[5] Subsequently, a case-control study of PAH patients from Ontario, Canada showed an increased risk of PAH in patients exposed to SSRIs, but not with non-SSRI antidepressants.[6] However, **both of these studies**, the use of antidepressants was measured at any time prior to the date of the event, including the period immediately before the event during when the disease process has already begun. Depressive symptoms are prevalent in PAH patients, raising the concern of *protopathic bias*, where the initiation of a drug may have been influenced by the initial signs or symptoms of the outcome of interest **(i.e. IPAH) rather than the drug itself**.[**16**, 19, 20, 21] Indeed, we believe that the risk of IPAH associated with inhaled corticosteroid use in our study is most likely a protopathic bias reflecting empirical treatment of dyspnea with asthma medications. If the use of antidepressants were truly associated with an increased risk of PAH, it would have been expected that the risk would increase with longer lag periods, since exposure would precede the initiation of the first symptoms. In our study, varying the lag period was not associated with a substantial change in the point estimates. Moreover, it would have been expected that exposure to higher potency inhibitors of the SERT or longer cumulative exposure would

confer a higher IPAH risk. The absence of these effects in our study likely points to a non-causal association between antidepressants and the incidence of IPAH, suggesting that patients with depressive symptoms may be at increased risk of IPAH, independently from their exposure to antidepressants. Indeed, it may be that depression and IPAH share a common genetic dysregulation in 5HT signalling predisposing to both conditions.[23]

This study also has some limitations. Case ascertainment was difficult due to the manner in which IPAH was recorded in the database. It is possible that some cases were missed if they were never recorded in either the CPRD or HES databases, although our incidence rate of 3.84/million per year is concordant with what has been previously reported elsewhere.[24, 25, 26] The relatively high rates of obesity in our cohort are also consistent with prior reports.[27] Our cohort had slightly higher rates of anti-hypertensive medication use than has been previously reported, although we note that our cases were slightly older and would therefore be more likely to require such medications.[24] The rarity of IPAH combined with the difficulty of case designation lead to a relatively small cohort of cases and this would tend to bias our results towards the null-hypothesis. The CPRD uses outdated nomenclature (PPH – primary pulmonary hypertension) which was superseded at the Evian consensus conference in 1998 with the current term idiopathic pulmonary arterial hypertension. In addition, awareness of the nuances of pulmonary hypertension diagnosis amongst non-specialists is likely to be low such that coding any patient with any form of pulmonary hypertension as ’PPH’ may seem reasonable. In the present cohort only 3.3% of patients coded by their general practitioner as having PPH were judged by to have IPAH by a PAH specialist. Another limitation in the case ascertainment was that the CPRD/HES do not capture prescriptions written by hospital physicians, which may have increased the likelihood of rejecting a true case. We believe therefore that our case diagnosis was specific but not

necessarily sensitive. We did not have patient-level physiological data to confirm each case, which is a limitation common to many studies with this type of design.[6, 28] A sample of cases was reviewed by a second physician whose classification of patients was in **substantial** agreement with the first. It should also be emphasized that our cohort was an *idiopathic* PAH population, where all secondary or associated causes of pulmonary hypertension had been excluded. The previous studies included either all patients with pulmonary hypertension of any cause (including cardiac and pulmonary disease), or all patients with PAH without exclusion of associated diseases.[5, 6] Our risk estimates should therefore be considered the most accurate to date.

In conclusion, in this study, the use of antidepressants, including SSRIs, was associated with an increased risk of IPAH. However, the absence of a differential association between the different types of antidepressants and by cumulative duration suggest a non-causal association, and that perhaps the indication of use of these drugs may itself be associated with an increased risk of IPAH.

Acknowledgements

We acknowledge Diane Gaudreau for her administrative assistance.

Funding

This study was funded by the Canadian Institutes of Health Research. Dr Samy Suissa is the recipient of the James McGill Chair. The funding sources had no role in the design, analysis, and interpretation of the results, and thus the authors were independent from the funding source.

Conflicts of Interest:

None of the authors have a conflict of interest with the contents of this article.

Author Contributions

BDF conceived and designed the study, analyzed and interpreted the data, drafted the manuscript and gave final approval for publication.

LA designed the study, analyzed and interpreted the data, drafted the manuscript and gave final approval for publication.

SD'A designed the study, analyzed and interpreted the data, drafted the manuscript and gave final approval for publication.

DL designed the study, reviewed the manuscript for important intellectual content and gave final approval for publication.

FL interpreted the data, reviewed the manuscript for important intellectual content and gave final approval for publication.

JB designed the study, analyzed and interpreted the data, reviewed the manuscript for important intellectual content and gave final approval for publication.

SS designed the study, interpreted the data, reviewed the manuscript for important intellectual content and gave final approval for publication. SS is the guarantor of the manuscript.

References

[1] McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation* 2009;119:2250–2294.

[2] Abenhaim L, Moride Y, Brenot F, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;335:609–616.

[3] Adnot S. The Serotonin System as a Theraputic Target in Pulmonary Hypertension. In: Yuan JXJ, Garcia JGN, West JB et al, Eds. *Textbook of Pulmonary Vascular Disease*. Springer, 2011;1501–1507.

[4] Tatsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol* 1997;340:249–258.

[5] Shah SJ, Gomberg-Maitland M, Thenappan T, Rich S. Selective serotonin reuptake inhibitors and the incidence and outcome of pulmonary hypertension. *Chest* 2009;136:694–700.

[6] Dhalla IA, Juurlink DN, Gomes T, Granton JT, Zheng H, Mamdani MM. Selective serotonin reuptake inhibitors and pulmonary arterial hypertension: a case-control study. *Chest* 2012;141:348–353.

[7] Ventetuolo CE, Barr RG, Bluemke DA, et al. Selective serotonin reuptake inhibitor use is associated with right ventricular structure and function: the MESA-right ventricle study.

PLoS One 2012;7:e30480.

[8] Sadoughi A, Roberts KE, Preston IR, Lai GP, McCollister DH, Farber HW, Hill NS. Use of selective serotonin reuptake inhibitors and outcomes in pulmonary arterial hypertension. Chest. 2013;144:531-41.

[9] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies. *BMJ* 2007;335:806-8

[10] Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997;350:1097–1099.

[11] Rodríguez LAG, Gutthann SP. Use of the UK General Practice Research Database for pharmacoepidemiology. *Br J Clin Pharmacol* 1998;45:419–425.

[12] Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. *Pharmacotherapy* 2003;23:686–689.

[13] Lawrenson R, Todd JC, Leydon GM, Williams TJ, Farmer RD. Validation of the diagnosis of venous thromboembolism in general practice database studies. *Br J Clin Pharmacol* 2000;49:591–596.

[14] Lawrenson R, Williams T, Farmer R. Clinical information for research; the use of general practice databases. *J Public Health Med* 1999;21:299–304.

[15] Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33:159-74.

[16] Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. *Am J Med*. 1980;68:255-58.

[17] Suissa S. Novel Approaches to Pharmacoepidemiology Study Design and Statistical Analysis. In: Strom BL, ed. *Pharmacoepidemiology*. Chichester, UK:Wiley, 2007:811–29.

[18] Essebag V, Platt RW, Abrahamowicz M, Pilote L. Comparison of nested case-control and survival analysis methodologies for analysis of time-dependent exposure. *BMC Med Res* Methodol 2005;5:5.

[19] Essebag V, Genest J, Suissa S, Pilote L. The nested case-control study in cardiology. *Am Heart J* 2003;146:581–590.

[20] McCollister DH, Beutz M, McLaughlin V, et al. Depressive symptoms in pulmonary arterial hypertension: prevalence and association with functional status. *Psychosomatics* 2010;51:339–339.e8.

[21] Looper KJ, Pierre A, Dunkley DM, Sigal JJ, Langleben D. Depressive symptoms in relation to physical functioning in pulmonary hypertension. *J Psychosom Res* 2009;66:221–225.

[22] Löwe B, Gräfe K, Ufer C, et al. Anxiety and depression in patients with pulmonary hypertension. *Psychosom Med* 2004;66:831–836.

[23] Cao H, Gu H, Qiu W, et al. Association study of serotonin transporter gene polymorphisms and ventricular septal defects related possible pulmonary arterial hypertension in Chinese population. *Clin Exp Hypertens* 2009;31:605–614.

[24] Ling Y, Johnson MK, Kiely DG, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. *Am J Respir Crit Care Med* 2012;186:790–796.

[25] Escribano-Subias P, Blanco I, López-Meseguer M, et al. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. *Eur Respir J* 2012;40:596–603.

[26] Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006;173:1023–1030.

[27] Burger CD, Foreman AJ, Miller DP, Safford RE, McGoon MD, Badesch DB. Comparison of body habitus in patients with pulmonary arterial hypertension enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management with normative values from the National Health and Nutrition Examination Survey. *Mayo Clin Proc* 2011;86:105–112.

[28] Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax*. 2013;68:1029-36.

Figure legends:

Figure 1: Case Identification Flowchart.

Figure 2: Risk of developing Idiopathic Pulmonary Arterial Hypertension, at different lag times between exposure to anti-depressants and disease diagnosis. Size of the point estimate is proportional to sample size.

Table 1: Characteristics of cases and matched controls

Characteristic	IPAH Cases n=195	Controls n=61,926	Crude RR (95% CI)
Age, mean (SD)	61.6 (16.5)	61.2 (16.5)	Matching variable
Female, n (%)	131 (67.2)	38,037 (67.2)	Matching variable
Years follow-up ; Mean (SD)	8.4 (5.5)	8.4 (5.5)	Matching variable
Body mass index, n (%)			
<30 kg/m^2	63 (32.3)	21,953 (37.5)	1.00 (reference)
≥30 kg/m^2	42 (21.5)	7,628 (12.7)	2.01 (1.35 - 3.00)
Missing	90 (46.2)	32,345 (49.8)	0.97 (0.64 - 1.47)
Smoking status, n (%)			
Never	60 (30.8)	17,919 (30.0)	1.00 (reference)
Ever	63 (32.3)	15,882 (28.2)	1.13 (0.78 - 1.63)
Missing	72 (36.9)	28,125 (41.8)	0.66 (0.41 - 1.08)
Prescription drugs, n (%)			
Antihypertensives	93 (47.7)	16,732 (30.6)	2.82 (1.99 - 4.02)
Antiparkinsons	1 (0.5)	222 (0.5)	1.13 (0.16 - 8.19)
Antipsychotics	7 (3.6)	1,914 (3.5)	1.02 (0.47 - 2.19)
Inhaled corticosteroids	29 (14.9)	3,783 (6.7)	2.49 (1.65 - 3.74)
NSAIDs	35 (17.9)	9,089 (15.4)	1.22 (0.83 - 1.78)
Oral corticosteroids	13 (6.7)	1,959 (3.5)	2.01 (1.13 - 3.57)
Narcotic analgesics	51 (26.2)	10,060 (18.0)	1.73 (1.22 - 2.44)

Abbreviations: IPAH Idiopathic Pulmonary Arterial Hypertension; NSAID non-steroidal anti-inflammatory drugs.

The percentages in controls were weighted by the inverse of the number of controls in each matched set.

Table 2: Crude odds ratios and adjusted rate ratios of IPAH associated with the use of antidepressants

Use of antidepressants	IPAH Cases n=195	Controls n=61,926	Crude RR	Adjusted RR (95% CI)*
No use, n (%)	136 (69.7)	50,653 (81.8)	1.00	1.00 (reference)
Use, n (%)	59 (30.3)	11,273 (18.2)	1.98	1.67 (1.17 - 2.37)
SSRIs	31 (15.9)	5,885 (9.5)	2.01	1.67 (1.09 - 2.57)
Non-SSRIs	28 (14.4)	5,388 (8.7)	1.96	1.66 (1.07 - 2.59)

Abbreviations: IPAH, idiopathic pulmonary arterial hypertension; SSRI, selective serotonin reuptake inhibitors.

*Adjusted for smoking status, obesity, and use of antihypertensives, antiparkinsonians, antipsychotics, inhaled corticosteroids, NSAIDs, oral corticosteroids, and narcotic analgesics.

Table 3: Sensitivity Analyses – varying lag times from 0 to 60 months.

Use of antidepressants	IPAH Cases n=195	Controls n=61,926	Crude RR	Adjusted RR (95% CI)
No lag				
No use, n (%)	123 (63.1)	48,223 (77.9)	1.00	1.00 (Reference)
Use, n (%)	72 (36.9)	13,703 (22.1)	2.07	1.56 (1.12 - 2.16)
12-month Lag				
No use, n (%)	134 (68.7)	49,937 (80.6)	1.00	1.00 (Reference)
Use, n (%)	61 (31.3)	11,989 (19.4)	1.90	1.52 (1.07 - 2.15)
24-month lag				
No use, n (%)	141 (72.3)	51442 (83.1)	1.00	1.00 (Reference)
Use, n (%)	4 (27.7)	10484 (16.9)	1.94	1.62 (1.13 - 2.32)
36-month lag				
No use	148 (75.9)	52877 (85.4)	1.00	1.00 (Reference)
Ever use	47 (24.1)	9049 (14.6)	1.96	1.62 (1.10 - 2.38)
48-month lag				
No use	158 (81.0)	54137 (87.4)	1.00	1.00 (Reference)
Ever use	37 (19.0)	7789 (12.6)	1.74	1.41 (0.93 - 2.14)
60-month lag				
No use	164 (84.1)	55373 (89.4)	1.00	1.00 (Reference)
Ever use	31 (15.9)	6553 (10.6)	1.73	1.43 (0.91 - 2.25)

Abbreviations: IPAH Idiopathic pulmonary hypertension; RR Rate Ratio

*Adjusted for smoking status, obesity, and use of antihypertensives, antiparkinsonians, antipsychotics, inhaled corticosteroids, NSAIDs, oral corticosteroids, and narcotic analgesics.

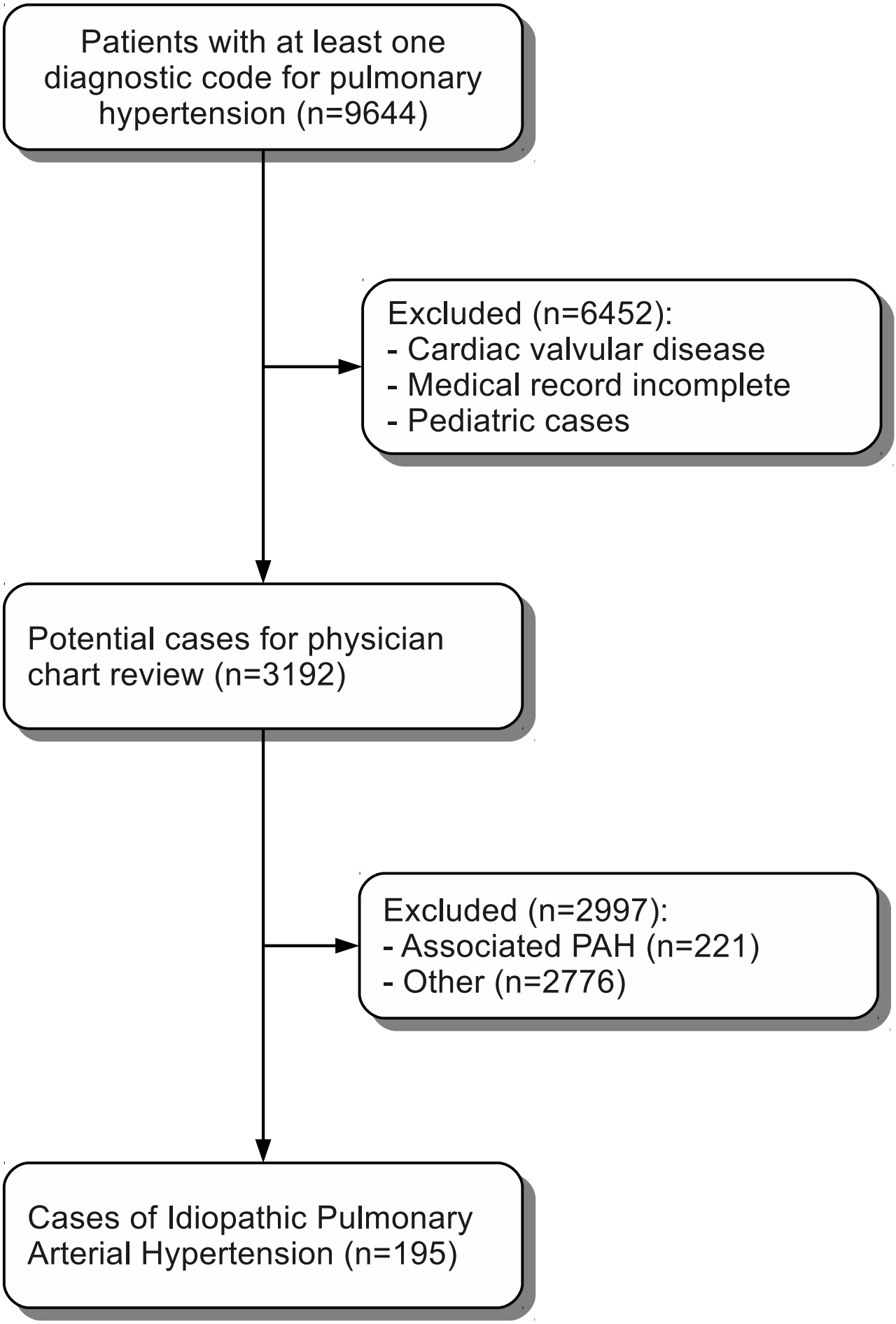
Table 4: Effect of drug receptor affinities and cumulative duration of antidepressant use on the incidence of IPAH

	IPAH Cases n=195	Controls n=61,926	Crude RR	Adjusted RR (95% CI)*
K_D for inhibition of 5HT transporter				
High, n (%)	21 (10.8)	4,666 (7.5)	1.76	1.46 (0.89 - 2.40)
Low/intermediate, n (%)	38 (19.5)	6,607 (10.7)	2.13	1.80 (1.21 - 2.69)
K_D for inhibition of NA transporter				
High, n (%)	42 (21.5)	7850 (12.7)	2.09	1.72 (1.16 – 2.55)
Low/intermediate, n (%)	17 (8.7)	3423 (5.5)	1.78	1.57 (0.92 – 2.67)
Cumulative duration of use of SSRIs				
<1 year, n (%)	15 (7.7)	3,184 (5.1)	1.82	1.62 (0.92 - 2.84)
≥1 year, n (%)	16 (8.2)	2,701 (4.4)	2.22	1.73 (0.99 - 3.02)

Abbreviations: 5HT Serotonin; AD antidepressants; K_D Dissociation Constant; IPAH Idiopathic Pulmonary Arterial Hypertension; NA Noradrenaline; SSRI Selective Serotonin Reuptake Inhibitors.

*Adjusted for smoking status, obesity, use of antihypertensive anti-parkinsonians, antipsychotics, inhaled corticosteroids, NSAIDs oral corticosteroids and narcotic analgesics.

Figure 1


Patients with at least one diagnostic code for pulmonary hypertension (n=9644)
Excluded (n=6452):
- Cardiac valvular disease
- Medical record incomplete
- Pediatric cases
Potential cases for physician chart review (n=3192)
Excluded (n=2997):
- Associated PAH (n=221)
- Other (n=2776)
Cases of Idiopathic Pulmonary Arterial Hypertension (n=195)

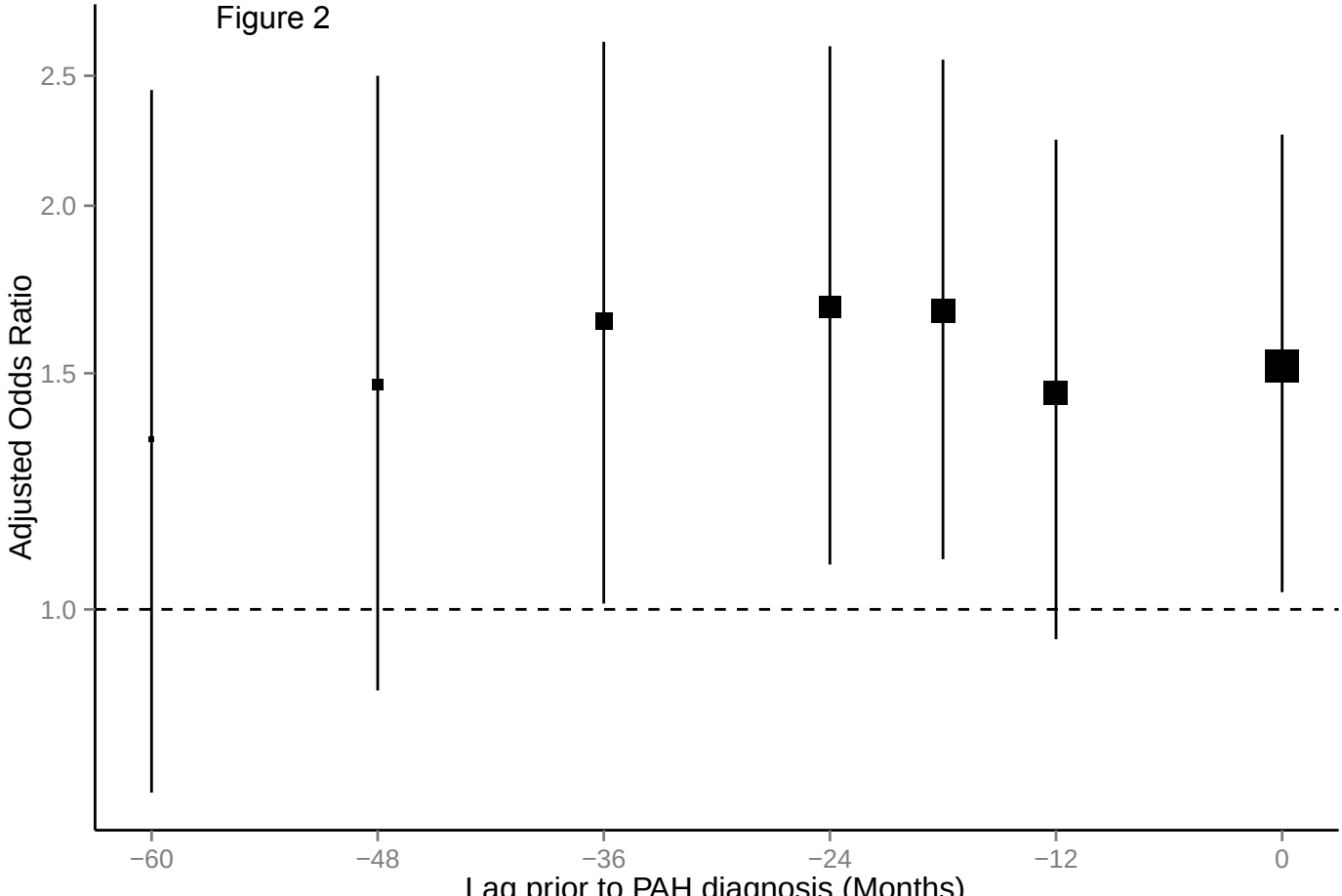


Figure 2
2.5
2.0
1.5
1.0
Adjusted Odds Ratio
−60
−48
−36
−24
−12
0
Lag prior to PAH diagnosis (Months)