ORIGINAL RESEARCH

The relationship of SSRI and SNRI usage with interstitial lung disease and bronchiectasis in an elderly population: a case–control study

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Background: The association between interstitial lung disease (ILD) and selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors (SSRI/SNRI) has been previously described in published case reports. However, its prevalence may be more common than expected. We examined the association between SSRI/SNRI usage and presence of ILD and or bronchiectasis (ILD/B) in an elderly population.

Methods: We conducted a retrospective case series and case–control study involving all 296 eligible elderly patients in one primary care geriatric practice in Victoria, BC, Canada. Cases required the presence of ILD/B on computed tomography (CT) or chest X-ray (CXR). Cases were excluded if they had other causes for ILD/B on CXR or CT such as exposure to known pneumotoxic drugs, metastatic cancer, rheumatoid lung disease, sarcoidosis, previous pulmonary tuberculosis, or pneumoconiosis. Data were abstracted from the patients' medical record. The exposure variable was standardized cumulative person-month (p-m) dose of SSRI/SNRI. The study was approved by the Clinical Research Ethics Board of University of British Columbia with a waiver of informed consent.

Results: A total of 12 cases and 273 controls were identified. Their mean ages were 89.0 and 88.7 years, respectively (p=0.862). A total of 10/12 cases and 99/273 controls were exposed to SSRI/SNRI. The odds ratio was 8.79, 95% confidence interval 2.40–32.23 (p=0.001). The median p-m exposure to SSRI/SNRI was 110.0 months for cases and 29.5 for controls (p=0.003).

Conclusion: SSRIs and SNRIs were significantly associated with the risk of ILD/B in this elderly population. Because of their widespread usage, further studies should be done to validate these findings. Prescribers should cautiously monitor patients for development of insidious pulmonary symptoms when these drugs are used.

Keywords: SSRI, SNRI, antidepressant, interstitial lung disease, aging, geriatric psychiatry

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Introduction

Prescription drug use is increasing in all adult age groups in the USA,[1] and antidepressants (ADs) are the third most commonly prescribed medications.[1,2] It is estimated that 17% of the USA population aged >60 years takes an AD[1] and that 89% of elderly people aged ≥65 years in general practices in the UK with a diagnosis of depression have been given at least one prescription for an AD.[3] Furthermore, 60% of people take ADs for ≥2 years and 14% are on ADs for ≥10 years.[2] The mean duration of AD use for elderly people in the UK study was 364 days.[3] The prevalence of AD usage has increased to 46.2% for residents of American nursing homes.[4] The overall prevalence of AD usage increased by 400% in the USA between 1988–1994 and 2005–2008.[2]

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are the most commonly prescribed ADs because of their lower side effect profile compared to older drugs such as tricyclic antidepressants (TCADs).[3,4] However, a UK study documented an increased total mortality in elderly SSRI users compared to TCADs and non-users of ADs.[3]

SSRIs and SNRIs are listed as sources of interstitial lung disease (ILD) and airway pathology on the Pneumotox website (www.pneumotox.com), which tracks drug-induced lung diseases. There have been case reports linking SSRIs and SNRIs to asthma,[5] bronchiolitis,[6] eosinophilic pneumonia,[7–11] pneumonitis,[12,13] granulomatous pneumonia,[14] diffuse alveolar damage[15] and pulmonary scarring,[16] and pneumonitis with cardiomyopathy.[13,17] Studies have shown that the prevalence of ILD is more common than thought[18,19] and that mortality from ILD is increasing.[20,21] A Danish study showed that the incidence was increasing in the general population and was highest in the elderly group.[22] A recent study of the Framingham cohort has shown that interstitial lung abnormalities (ILA) were not uncommon and 6% of all participants showed progressive ILA on serial high-resolution computerized tomography (HRCT) scanning over a 6-year period with reduced lung capacity, reduced exercise tolerance, and higher mortality.[23] We report a case series and case–control study examining the association between SSRI and SNRI usage and ILD and/or bronchiectasis (ILD/B) on chest X-ray (CXR) and computed tomography (CT) scans in an elderly population.

Methods
Study design
The study was a retrospective chart review with case–control analyses.

Study population
The study included all 296 elderly people in a primary care home-based geriatric practice.[24] This practice model includes a team that provides primary medical care to frail elderly people living in the community. The team includes a clinical care manager, physician, nurse, physiotherapist, and rehabilitation/exercise aide. Eligibility criteria included age 70 years or older, not living in a nursing home, difficulty accessing usual medical care, and having a frailty syndrome (eg, mobility problems or cognitive impairment) and/or complex multiple comorbidities/polypharmacy. Patients are followed up until they die or move to a nursing home.

A minority continue to be followed up in a few selected nursing homes in Victoria.

Patients were active members of the practice as of February 1, 2016 when data were abstracted. A total of 144 (50.3%) people were living in houses or apartments, 108 (37.8%) living in retirement homes or assisted living facilities, and 34 (11.9%) living in nursing homes. The median length of stay (LOS) in the practice was 27 months (range 1–146 months).

Data sources
The electronic medical record was audited for age, sex, estimated glomerular filtration rate (eGFR), type and duration of AD usage, smoking status, Clinical Frailty Scale (CFS),[25] and CXR and CT reports.

Case definition
Cases required radiological evidence (RE) of ILD/B on CXR or CT. RE was defined as the reported presence of fibrosis, scarring, interstitial lung changes, or bronchiectasis. Reports of isolated atelectasis, pleural plaques, asbestosis, and acute pneumonia were not counted as cases. CXRs and CT scans were performed as part of usual care and ordered if patients had symptoms and clinical disease but not for the purposes of this study. A total of 173/286 (60.1%) participants had CXRs and 31/286 (10.8%) had CT scans. CXRs and CTs were reported by radiologists as part of routine clinical care and blinded to AD usage.

Exclusion criteria
Cases were excluded if they had potentially confounding factors that could cause ILD/B. Eleven cases (3.9% of total) were excluded for the following reasons: metastatic cancer (n=2), silicosis/asbestosis (n=3), old pulmonary tuberculosis (TB) (n=3), brainstem stroke with severe dysphagia and chronic aspiration (n=1), and pneumotoxic drugs, methotrexate (n=2) or hydralazine (n=1). Six excluded cases were exposed to SSRI/SNRI and five were not. None of the cases were on chronic nitrofurantoin and amiodarone or had chest radiation. Cases 1, 5, and 9 (Table 1) used an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker but did not experience chronic cough. They were not excluded from the analyses.

AD usage
Each individual patient's chart was audited for the following ADs using both generic and trade names: venlafaxine, duloxetine, citalopram, escitalopram, sertraline, fluoxetine,

Table 1 Cases

Case	Age, years	Sex	Smoking history	Primary symptoms	CXR	CT	p-m exposure	Estimated latency*	Drug	Impact after stopping
1	93	F	Yes	Fatigue, dyspnea	Diffuse pulmonary fibrosis	Central bronchiectasis and scarring	128	78	Venlafaxine	Improvement
2	90	F	Yes	Fatigue	No lung disease	Bilateral peripheral sub-pleural reticular opacity consistent with pulmonary fibrosis	287	72	Venlafaxine, paroxetine	Not stopped
3	92	F	No	Cough, mucous, dyspnea, wheeze	Chronic changes are again noted in both lung apices and left lower lobe Consolidation	Cylindrical bronchiectasis, ground glass opacities, fine and coarse reticulations nodularity	376	19	Duloxetine, venlafaxine	Improvement
4	75	M	Yes	Fatigue	No lung disease	Parenchymal scarring in lower lobes and pleural thickening	72	54	Duloxetine, citalopram	Not stopped
5	90	F	Yes	Dyspnea, fatigue	Left basilar scarring	Not available	161	37	Venlafaxine, duloxetine, escitalopram	Not stopped
6	91	F	No	Dyspnea, fatigue	Bilateral interstitial markings in bases suggestive of interstitial lung disease	Not available	92	11	Duloxetine	Not stopped
7	88	F	Yes	Cough, mucous, dyspnea, wheeze	Bilateral coarse peripheral reticular interstitial opacities in lower lobes	Bilateral idiopathic pulmonary fibrosis with honeycombing patchy airspace consolidation, bronchiectasis in left lung base	531	109	Fluoxetine	Improvement
8	93	F	Yes	Cough, mucous, dyspnea	Left basilar scarring/ atelectasis	Chronic bronchial wall thickening, bilateral lower lobe bronchiectasis with inflammatory changes	33	19	Paroxetine	Improvement
9	91	M	No	Fatigue	Extensive interstitial markings consistent with pulmonary fibrosis	None available	26	8	Paroxetine	No change
10	85	M	Yes	Fatigue, cough, wheeze	Scarring left lung base	None available	84	35	Sertraline	Not stopped
11	86	F	Yes	Cough, fatigue, dyspnea	Extensive bilateral reticular interstitial opacity worse in periphery and lower lung zones consistent with pulmonary fibrosis	Interstitial changes in lung peripheries of upper and lower lobes, pulmonary fibrosis, honeycombing in both bases	0	Not applicable	None	Not applicable
12	85	F	Yes	Cough	None available	Peripheral fibrosis, honeycombing, traction bronchiectasis	0	Not applicable	None	Not applicable

Note: *Months between initial exposure and first radiological abnormality.
Abbreviations: CXR, chest X-ray; CT, computed tomography; p-m, person-month; F, female; M, male.

fluvoxamine, paroxetine, mirtazapine, amitriptyline, nortriptyline, and bupropion. SSRI/SNRI exposure was standardized to 10 mg of citalopram equivalents using the following equivalents based on usual clinical practice: a) 10 mg citalopram; b) 5 mg escitalopram; c) 25 mg sertraline; d) 10 mg fluoxetine; e) 10 mg paroxetine; f) 15 mg duloxetine; and g) 37.5 mg venlafaxine.

Start dates and stop dates for each SSRI/SNRI used by a patient were used to calculate person-months (p-ms) of exposure to an equivalent dose of 10 mg of citalopram.

The total exposure was summed and included all the different SSRI/SNRIs used during the study period. We did not have access to start dates for patients who were on an AD at the time of entering the practice. Because >60% of people are on ADs for more than 2 years,[2] we conservatively estimated that they were on these drugs for 12 months at their current dose before they entered the practice.

Other confounding factors

Charts were audited for dementia or other neurological problems that may cause dysphagia, aspiration, and ILD. Dementia was defined as cognitive impairment that affected daily function. Other neurological problems without dementia included neurodegenerative diseases (eg, multiple sclerosis and Parkinson's disease), strokes, and head/brain injuries with chronic deficits. There were 103 people who had dementia and 41 people who had other central nervous system (CNS) problems without dementia. These were combined into one variable called "neurological problems".

Statistical analyses

Means, standard deviations, and two-sided t-tests were used for continuous data. The p-m exposure to SSRI/SNRI was skewed with unequal variance. Therefore, Mann-Whitney U test was used to compare median doses of exposure between cases and controls. Chi-square tests with Yates corrections were used to compare proportions. Fisher's exact test was used if there were <5 observations. Odds ratios were calculated, and Mantel-Haenszel test was used to calculate 95% confidence intervals (95% CI).

Multiple logistic regression was used to test the association between age, GFR, smoking status, neurological problems, p-m exposure, and being a case.

Ascertainment bias was estimated by comparing the frequency of CXR and CT testing in cases and controls. Multiple linear regression was used to test the association between the number of CXRs and CTs and case status, SSRI/SNRI exposure, and LOS (in months).

Statistical analyses were done using the Number Cruncher Statistical System V.10 (NCSS)™ (Kaysville, UT, USA).

Ethics

The study was approved by the Clinical Research Ethics Board of University of British Columbia (H16-00656) with a waiver of informed consent. Consent was waived because this study was part of an audit, conformed to standards for minimal risk research and did not affect patient safety or clinical care. To protect patient confidentiality, personal identifiers were removed from spreadsheets used for data analyses and all reports. Signed informed consent to publish was obtained from the daughter of the reported index case because the woman was deceased.

Results

Index case report

The index case was a 92-year-old woman. She quit smoking at the age of 57 years. There was no history of cardiac or lung disease. In June 2010, she insidiously developed fatigue and dyspnea with exertion. She had bilateral coarse crackles to mid-lungs, normal jugular venous pressure (JVP), blood pressure (BP), heart rate (HR), and minimal pedal edema. Room air oxygen saturations were 88% at rest and dropped to 85% with walking. There was no cough or infection. BNP was elevated to 927 ng/L (normal <100), CXR showed mild pulmonary edema, and troponin t was normal. She was given oral furosemide with some improvement in her dyspnea but no change in her severe fatigue. She was seen by a respirologist who identified a restrictive lung disease on pulmonary function tests. HRCT showed apical scarring and central bronchiectasis. Echocardiogram showed pulmonary artery pressure of 58 mmHg and left ventricular ejection fraction of 60%. Continuous O_2 was started.

On December 22, 2014, she was found to be depressed. She had been on venlafaxine 37.5 mg OD since May 2004. Venlafaxine was increased to 75 mg OD. On December 23, 2014, there was a severe deterioration in her mobility, fatigue, and breathlessness. There was no cough, fever, or symptoms of acute infection. O_2 saturation was 87% on 2 L/m, dropping to 80% with walking. There were bilateral coarse crackles throughout her lungs. Other clinical findings included: JVP 3 cm, HR 68, BP 102/68 mmHg, and +1 edema. CXR was reported as cardiomegaly with diffuse pulmonary fibrosis. BNP was 1,741 ng/L. She refused to undergo CT. Diuresis with furosemide did not improve her symptoms nor oxygen saturations. Her medications were reviewed and venlafaxine was discontinued because of previous case reports linking it to ILD.

After discontinuing venlafaxine, there was a significant improvement in her dyspnea, fatigue, mobility, and oxygen saturation. The crackles from her lungs had largely cleared except for her bases. By February 19, 2015, she was back to baseline function.

Case series

The index case led us to review all patients in our practice with symptomatic lung disease who were also using SSRI/

SNRIs. Table 1 shows the characteristics and radiological reports for all the people who met the case definition. Five cases had severe symptomatic lung disease (cases 1 [index case], 3, 7, 8, and 9) and were taken off their SSRI/SNRI. Four of the five cases showed significant improvement in cough, mucous production, dyspnea, and wheezing with cessation of what were previously thought to be exacerbations of bronchiectasis and chronic bronchitis. Four of the five cases relapsed with depressive symptoms and had to be put on the non-SSRI/SNRI ADs bupropion and mirtazapine. The estimated median latency between first known exposure to SSRI/SNRIs and presences of abnormalities on CXR and CT was 36 months.

Case–control study

Table 2 compares characteristics between cases and controls. The mean ages of cases and controls were 89.0 and 88.7 years, respectively (p=0.862). For cases and controls, respectively, there were no significant differences between the proportions who were females (75% vs 72.9%) and ever-smoked (75% vs 50.2%) mean eGFR (53.3 vs 59.1 mL/min/1.73 m^2), median CFS (6 vs 6), and presence of neurological problems (41.7% vs 50.9%). There were 10 of 12 (83.3%) cases who used an SSRI/SNRI at any time while in the practice, compared to 99 of 273 (36.3%) controls (p=0.002). The Mantel-Haenszel odds ratio was 8.79, 95% CI 2.40–32.2 (p=0.001). For SSRI/SNRI users, the median cumulative dose was significantly higher for cases (110.0 p-m) compared to controls (29.5 p-m, p=0.003).

Table 2 Comparison of cases and controls

	Cases	Controls	*p*-value
Number	12	273	
Age, years – mean (SD)	89.0 (5.0)	88.7 (6.4)	0.862
Female – n (%)	9 (75.0)	199 (72.9)	0.871
Ever smoked – n (%)	9 (75.0)	122 (50.2)	0.138
eGFR, mL/min/1.73 m^2 – mean (SD)	53.3 (18.4)	59.1 (18.7)	0.315
Clinical Frailty Scale – median	6	6	0.950
Neurological problems*	5 (41.7)	139 (50.9)	0.569
Chest X-ray – n (%)	11 (91.7)	161 (59.0)	0.031
Chest X-ray – median	2.5	1	0.003
CT chest – n (%)	8 (66.7)	23 (8.4)	0.000
CT chest – median	1	0	0.000
SSRI/SNRI ever used – n (%)	10 (83.3)	99 (36.3)	0.002
SSRI/SNRI person-month exposure for users only – median	110.0	29.5	0.003

Note: *Neurological problems included the presence of either dementia, neurodegenerative disease, stroke, or brain injury without dementia.
Abbreviations: SD, standard deviation; n, number; eGFR, estimated glomerular filtration rate; CT, computed tomography; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor.

Table 3 Frequency of exposure by type of antidepressant for all patients in the study

	Number	%
Citalopram	35	12.2
Escitalopram	18	6.3
Sertraline	7	2.5
Paroxetine	5	1.8
Fluoxetine	1	0.4
Venlafaxine	35	12.2
Duloxetine	17	5.9
Mirtazapine	39	13.6
Bupropion	22	7.7
Amitriptyline	3	1.0
Nortriptyline	2	0.7
Total	184	

Table 3 shows the frequency of exposure by the type of AD prescribed. There were 23.2% of people exposed to SSRIs, 18.1% to SNRIs, 13.6% to mirtazapine, 7.7% to bupropion, and 2.0% to tricyclic ADs.

The possibility of confounding was tested by examining exposure to SSRI/SNRIs in people with neurological problems. There were 144 people who had neurological problems of whom 65 (45.1%) were exposed to SSRI/SNRIs compared to 44 of 141 (31.2%) of the people without these conditions (p=0.022). The Mantel-Haenszel odds ratio was 1.8, 95% CI 1.1–2.9, p=0.016. For SSRI/SNRI users, the median cumulative dose was 39 p-m for people with neurological problems compared to 25 p-m for people without these conditions (p=0.453). Only cumulative dose of SSRI/SNRIs was significantly associated with being a case (p=0.001) in a multiple logistic regression model that also included neurological problems, smoking, eGFR, and age.

Ascertainment bias was assessed by comparing CT and CXR testing between cases and controls, as well as between SSRI/SNRI exposed and non-exposed. Table 2 shows that cases had significantly more CT and CXR tests compared to controls. Bivariate analysis showed the number of CXRs and CTs were significantly correlated with being a case, practice LOS, cumulative dose of SSRI/SNRI and being exposed to an SSRI/SNRI. Multiple linear regression showed that only being a case was associated with the number of CTs (p<0.000), and both being a case (p=0.002) and LOS (p<0.000) were associated with the number of CXRs. Cumulative dose and SSRI exposure were no longer significantly associated with testing in these models.

Discussion

This study demonstrates a significant association between using an SSRI/SNRI and development of ILD/B. The

strength of association (odds ratio 8.79) and difference in median exposure between cases and controls is suggestive that this may be a true association. It appears that the association is not restricted to one drug but may be due to a class effect.

It is estimated that 11% of the American population >11 years old are taking ADs.[2] Despite this level of exposure in the population, there have only been rare published case reports of drug-induced ILD/B in the non-geriatric population. It is likely that younger populations have greater lung reserve and may need to be on SSRIs/SNRIs for a significantly longer period of time to develop symptomatic disease. Our patient population is a frail elderly group with multiple comorbidities and a high level of SSRI/SNRI exposure, which may leave them more vulnerable to development of ILD/B. In an elderly population, it would be easy to miss the association between drug exposure and pulmonary disease due to the high prevalence of non-specific symptoms such as fatigue, cough, dyspnea, and reduced diagnostic intensity. Other factors that may lead to missing this association include: increased prevalence of cognitive impairment affecting reporting of symptoms; fragmentation of care between family doctors and specialists; higher frequency of pulmonary comorbidities with lower lung reserves; and long latency from the time of exposure until the onset of symptomatic disease. Factors that may increase the risk of drug-induced ILD/B in this population include reduced drug clearance from lower GFRs as well as the higher prevalence of polypharmacy with increased risk of drug interaction and accumulation.

Most published case reports of SSRI/SNRI-induced lung damage describe people with severe respiratory problems, most of whom improved clinically and radiologically after withdrawing these drugs. Our cases had a more indolent and chronic presentation and only showed partial improvement in clinical symptoms after withdrawing these drugs. The lack of complete resolution may be due to prolonged exposure with permanent fibrosis in the lungs.

Drugs may cause lung injury by a multitude of non-specific direct cytotoxic mechanisms and oxidative damage to alveoli, bronchioles, and capillaries as well as via immune mediation.[26,27] Fluoxetine has been shown to cause ILD in an animal model.[28] Genetic factors including polymorphisms in MUC5B promoter[23] may lead to increased susceptibility to lung damage. Similarly, polymorphisms in cytochrome P450 may also lead to variable drug accumulation.[29]

Our findings suggest that at the very least, prescribers should reassess rationale for treating people with mild depression and anxiety. Considerations should be given to using alternative effective treatments such as cognitive behavior therapy. Also, consideration should be given to using the lowest possible dose of AD and to limit the duration of treatment. Nevertheless, we recommend caution and close monitoring following tapering and cessation of ADs as most of our patients relapsed and needed alternative medications to treat relapse of their depression and anxiety.

Strengths and limitations of this study

Because of the retrospective design, we were unable to demonstrate a temporal association between exposure to drugs and development of ILD/B. Similarly, one must be cautious interpreting the median latency (36 months) from the time of exposure to SSRI/SNRIs to the development of abnormalities on CXR or CT because testing was not done at regular intervals. However, four of our five most severely affected cases clinically improved with withdrawal of these drugs. It is possible that this may have been spontaneous improvement. However, a number of the case reports demonstrated development of disease after exposure, radiological and clinical improvement with withdrawal of the drug,[10–14,16] and worsening with rechallenge.[15]

Only 60% of patients in the study had CXR reports in their charts and 10% had CT imaging, which could lead to ascertainment bias. Analyses demonstrated a low probability of an ascertainment bias for radiological imaging.

It is not possible to measure the incident risk of developing ILD/B because of the retrospective nature of this study. Nevertheless, 10 of 109 (9.2%) patients who had been exposed to SSRIs/SNRIs during this study period met the case definition for ILD/B. Even if we restricted the case definition to half of the group with the most severe clinical and CT findings, this prevalence would not be considered rare. It is possible that the true risk may be higher as people who had longer exposure or more severe reactions may have died or moved to nursing homes, creating a selection bias of survivors.

Our estimation of 1 year of exposure for people who came into the practice on an SSRI/SNRI may have underestimated exposure, as many elderly people are on these drugs for years.[2,3] It is possible that there was some confounding factors and that insidious chronic lung disease led to a higher risk of depressive symptoms and need for AD medications. However, this would not explain symptomatic improvement after withdrawing SSRIs/SNRIs, in our patients, and many of the published reports.

People with neurological problems and dementia have a higher risk of chronic dysphagia/aspiration pneumonitis as well as depression. We tried to control for this potential confounder. Multivariate analysis showed that only cumulative dose of SSRI/SNRIs but not neurological problems was associated with the risk of ILD/B. The small number of cases makes it difficult to control for all possible confounders as well as increases the risk of a type II statistical error.

The strengths of this study include use of all patients, use of patient-level clinical data, validated case definition by independent, blinded radiologists, and actual SSRI/SNRI exposure. The index case had a Naranjo algorithm[30] score of seven, indicating that venlafaxine probably caused this adverse drug reaction. We were also able to control for some of the known confounding causes of ILD/B.

Conclusion

Both the incidence of ILD and the usage of SSRIs/SNRIs in the general population are increasing. This study shows a significant association between SSRI/SNRI usage and development of ILD/B in an elderly population. It does not prove cause and effect. Because of the public health implications, future studies are needed to validate these findings.

Acknowledgments

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Data sharing

The anonymized dataset is available from the corresponding author upon reasonable request.

Disclosure

The authors report no conflicts of interest in this work.

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