# Selective Serotonin Reuptake Inhibitors and the Risk of Cataracts

## *A Nested Case-Control Study*

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***Objective:*** Older-generation antidepressants have been associated with increasing the risk of cataracts. Although animal studies have alluded to a potential link between selective serotonin reuptake inhibitors (SSRIs) and the development of cataracts, no large population based-study has addressed this potential association. This study sought to quantify the risk of cataracts with SSRIs by conducting a pharmacoepidemiologic study using the linked administrative databases in the province of Quebec, Canada.

***Design:*** Nested case-control study.

***Participants:*** A cohort of subjects who had received a coronary revascularization procedure from 1995 through 2004 in the province of Quebec, Canada.

***Methods:*** Using an administrative data set, a case-control study was conducted within a cohort of Quebec residents who had received a coronary revascularization procedure from 1995 through 2004. Cases were defined as those with the first diagnosis of a cataract diagnosed by an ophthalmologist. For each case, 10 controls were selected and matched to the cases by index date, age, and cohort entry. Crude and adjusted rate ratios (RRs) and corresponding confidence intervals (CIs) were computed for current use of SSRIs. Rate ratios were adjusted for gender, corticosteroid use, statins, high blood pressure, antihypertensives, and antidiabetics.

***Main Outcome Measures:*** First International Classification for Disease (Ninth Revision) code for a cataract diagnosed by an ophthalmologist.

***Results:*** Eighteen thousand seven hundred eighty-four cases and 187 840 controls met our study inclusion criteria. The adjusted RR for cataracts among current users of SSRIs was 1.15 (95% CI, 1.08–1.23). The risk of cataracts was highest with fluvoxamine (RR, 1.39; 95% CI, 1.07–1.80), followed by venlafaxine (RR, 1.33; 95% CI, 1.14–1.55) and paroxetine for cataract surgery (RR, 1.23; 95% CI, 1.05–1.45). The average time to diagnosis of cataracts while on SSRI therapy was 656 days.

***Conclusions:*** A possible association was found between current exposure to SSRIs, especially fluvoxamine and venlafaxine, and a future diagnosis of cataracts. The possibility that this observation may be the result of the effect of smoking, which could not be controlled for in the study, cannot be excluded. Future studies are needed to confirm this association in other populations.

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Cataracts are the leading cause of blindness in the world. In recent years, numerous studies have focused on the potential risk of prescription drugs and their catarogenic properties. It is now accepted that oral and inhaled steroids[1] increase the risk of cataracts. A recent study has linked $\beta$-blocker use to the development of cataracts.[2] The role of antidepressants in the development of the disease is less clear. Amitriptyline has been associated with an increase in the risk of cortical cataracts in the Beaver Dam Eye Study.[3] However, the risk of cataracts with the newer-generation antidepressants is less clear.

Selective serotonin reuptake inhibitors (SSRIs) are one of the most prescribed classes of medication in the United States and the third most prescribed class in the world.[4] Some of the nonpsychiatric adverse events associated with long-term SSRI use include gastrointestinal bleeding[5] and fractures.[6] However, the risk of ocular adverse events with SSRIs is less clear. Serotonin receptors have been identified in the lens of animal models.[7] Animal studies have shown that serotonin can increase lens opacity and can lead to development of cataracts.[8] To date, no population based-study has addressed a possible association between SSRI use and risk of cataracts. Given the widespread use of SSRIs, a potential risk of cataracts with these drugs warrants evaluation. Therefore, the objective of this study was to investigate any association between cataracts and exposure to SSRIs in a population of Quebec seniors by conducting a pharmacoepidemiologic study.

## Patients and Methods

The linked administrative databases of the health insurance of the province of Quebec in Canada were used as the main source of data for this study. Briefly, the databases capture health-related information for all residents of Quebec who are 65 years or older



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and are part of the universal health care plan offered by the province of Quebec, Canada. The specific data for this study included: (1) the beneficiary database, which captures information on sociodemographic data and dates of coverage and is managed by the Régie de l'Assurance-Maladie du Québec; (2) the prescription drugs database, which captures prescription drug information (drug name, strength, quantity, day supply) on all prescription drugs covered by the provincial formulary for all residents 65 years or older; (3) the hospitalizations database, which contains information for all hospitalizations, including date of admission and discharge, a primary diagnosis, and up to 15 secondary diagnoses coded using the International Classification of Diseases, 9th and 10th revisions. The databases were validated previously[9,10] and were used in pharmacoepidemiologic studies, including those addressing the risk of inhaled corticosteroids and risk of cataracts.[1] Approval for access to the study data was provided by the ethics board of Québec (Commission d'accès à l'information du Québec) and the Royal Victoria Hospital, McGill University.

## Study Population and Design

A nested case-control study (a case-control study within a previously defined cohort with a history of cardiovascular disease[11]) was conducted. All residents of Quebec 65 years or older who had undergone a coronary revascularization procedure between 1995 and 2004 were followed up from the date of their first procedure until the earliest of: (1) diagnosis of cataracts; (2) end of study period; (3) date of death; or (4) end of health care coverage.

## Selection of Cases and Controls

In the primary analysis, cases included all cohort members with a physician diagnosis for cataracts (International Classification of Diseases, 9th revision, code 366). To increase specificity, only cases that were diagnosed by an ophthalmologist were included. As a secondary analysis, cases were restricted to those with a hospital admission for day care (outpatient) surgery for cataracts. The date of the first diagnosis was taken as the index date. A similar definition was used previously by other pharmacoepidemiologic studies evaluating risk of cataracts and corticosteroids.[1]

A density-sampling method of selecting controls that allows for the close approximation of the rate ratio (RR) to the odds ratio was used.[12] Controls were eligible if they satisfied the following criteria: (1) each control had to have been followed up at least as long as the time of the index date of the case and hence was at risk of a cataract developing and (2) controls were matched to the cases within 1 year of birth date. From the pool of eligible controls, 10 controls were selected randomly and were matched to the cases by age (±1 year) and cohort entry (±30 days).

## Statistical Analysis

Descriptive statistics were used to explore data demographics. Available SSRIs included citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. The risk of venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI), was also assessed with respect to cataracts. All SSRIs and venlafaxine prescriptions were identified 1 year before the index date. Current users were defined as those who had received an SSRI or a venlafaxine prescription within 30 day of the index date. Past users were defined as have having received a prescription more than 30 days from the index date. The mean number of days of SSRI use also was computed from the first SSRI prescription after cohort entry to the index date. Conditional logistic regression was used to compute adjusted RR, controlling for potential confounders including gender, oral corticosteroids as well as other forms of corticosteroids (topical, inhaled, intranasal, and other injectable forms of corticosteroids), hypertension, antihypertensive drugs, antidiabetic drugs, and statins.

Table 1. Characteristics of All Community Diagnosed Cataracts and Corresponding Controls

| Characteristics | Cases | Controls | P Value |
|---|---|---|---|
| No. | 18 784 | 187 840 | |
| Age (yrs) | 73.0±8.1 | 72.8±7.9 | 0.06 |
| Follow-up (yrs) | 2.8±2.2 | 2.8±2.2 | NA |
| Female gender (%) | 40.7 | 33.4 | 0.0001 |
| Oral hypoglycemics (%) | 21.1 | 17.0 | 0.0001 |
| Blood pressure (%) | 30.4 | 28.5 | 0.0001 |
| Antihypertensives (%) | 78.0 | 76.0 | 0.0071 |
| Statins (%) | 48.3 | 47.3 | 0.01 |
| Oral corticosteroids (%) | 8.5 | 6.3 | 0.0001 |
| Other corticosteroids* (%) | 25.8 | 17.6 | 0.0001 |

NA = not available due to matching.
*Topical, inhaled, intranasal, and other injectable forms of corticosteroids.

# Results

In the primary analysis, 18 784 cases and 187 840 controls met the study inclusion criteria (Table 1). As shown in previous studies,[13] women had a higher risk of cataracts developing (Table 2). Similarly, use of antidiabetics or corticosteroids and a history of hypertension also was associated with an increase in the risk of cataracts (Table 2). In the primary analysis, the adjusted RR for cataracts among current users of SSRIs was 1.15 (95% confidence interval [CI], 1.08–1.23). Past users did not pose a risk (RR, 1.06; 95% CI, 0.97–1.17). The risk of cataracts was the highest for fluvoxamine (RR, 1.39; 95% CI, 1.07–1.80), followed by venlafaxine (RR, 1.33; 95% CI, 1.14–1.55). The average time for the diagnosis of cataracts while receiving SSRI therapy was 656 days for the first analysis and 690 days for the second analysis. The results for the secondary analysis with cases restricted to outpatient surgical cases generally were concordant with the first analysis, with the exception of paroxetine, which also was associated with cataracts (RR, 1.23; 95% CI, 1.05–1.45; Table 3).

# Discussion

This study showed for the first time that SSRIs use may be associated with an increase in the risk of cataracts. The risk was similar for all community-diagnosed cataracts as well as those cases diagnosed in the outpatient clinics. In this study, fluvoxamine, venlafaxine, and paroxetine had the highest risk of cataracts. Although citalopram, fluoxetine, and sertraline did not show a statistically significant increase in the risk of cataracts, our study may have lacked adequate power to assess the risk of cataracts with all individual antidepressants. This may suggest the importance of selectivity of serotonin receptors in the formation of cataracts. Whether the catarogenic effects of SSRIs are a class effect or are limited to specific agents must be investigated further.

Recent animal studies have shown the importance of the role of serotonin in different areas of the eye.[7] Serotonin has

Table 2. Rate Ratios and 95% Confidence Intervals for Selective Serotonin Reuptake Inhibitor Use and Incidence of Community Diagnosed Cataracts

| | Cases 18 784 | Controls 187 840 | Crude Rate Ratio | Adjusted Rate Ratio* | 95% Confidence Interval |
|---|---|---|---|---|---|
| No SSRI use (%) | 91.5 | 93.2 | 1.00 | 1.00 | Reference |
| Female gender (%) | 40.7 | 33.4 | | 1.33 | 1.29–1.39 |
| Oral hypoglycemics (%) | 21.1 | 17.0 | | 1.27 | 1.23–1.32 |
| Blood pressure (%) | 30.4 | 28.5 | | 1.06 | 1.02–1.09 |
| Statins (%) | 48.3 | 47.3 | | 1.00 | 0.97–1.03 |
| Oral corticosteroids (%) | 8.5 | 6.3 | | 1.14 | 1.07–1.20 |
| Other corticosteroids (%) | 25.8 | 17.6 | | 1.56 | 1.50–1.62 |
| Antihypertensive drugs (%) | 78.2 | 76.3 | | 1.05 | 0.98–1.03 |
| **SSRI** | | | | | |
| Any current use | 5.7 | 4.4 | 1.32 | 1.15 | 1.08–1.23 |
| Any past use | 2.8 (%) | 2.4 (%) | 1.19 | 1.06 | 0.97–1.17 |
| Citalopram | | | | | |
| Any current use | 1.1 (%) | 0.9 (%) | 1.30 | 1.13 | 0.98–1.31 |
| Any past use | 0.7 (%) | 0.5 (%) | 1.32 | 1.17 | 0.97–1.41 |
| Fluoxetine | | | | | |
| Any current use | 0.3 (%) | 0.3 (%) | 1.24 | 1.13 | 0.86–1.49 |
| Any past use | 0.3 (%) | 0.2 (%) | 1.31 | 1.13 | 0.83–1.52 |
| Fluvoxamine | | | | | |
| Any current use | 0.4 (%) | 0.2 (%) | 1.57 | 1.39 | 1.07–1.80 |
| Any past use | 0.2 (%) | 0.2 (%) | 1.06 | 0.96 | 0.69–1.32 |
| Paroxetine | | | | | |
| Any current use | 1.7 (%) | 1.4 (%) | 1.25 | 1.07 | 0.96–1.21 |
| Any past use | 1.0 (%) | 0.9 (%) | 1.10 | 0.98 | 0.84–1.14 |
| Sertraline | | | | | |
| Any current use | 1.2 (%) | 1.0 (%) | 1.17 | 1.06 | 0.92–1.22 |
| Any past use | 1.0 (%) | 0.90 (%) | 1.31 | 1.19 | 1.01–1.41 |
| Venlafaxine | | | | | |
| Any current use | 1.0 (%) | 0.7 (%) | 1.50 | 1.33 | 1.14–1.55 |
| Any past use | 0.5 (%) | 0.4 (%) | 1.18 | 1.06 | 0.85–1.33 |

SSRI = selective serotonin reuptake inhibitor.
*Rate ratios adjusted for gender, hypertension, antihypertensives, antidiabetics, statins, and all forms of corticosteroids.

been shown to play a crucial role in lens transparency.[14] Serotonin receptors have been identified in the lens of animal models. Boerrigter at al[8] were one of the first groups who showed the catarogenic potential of serotonin in the rat model. The authors observed opacification of the lens and formation of cortical cataracts after injection of 1% solution of serotonin. One postulated mechanism is the interference of serotonin with the lens metabolism through compromised ciliary body and anterior chamber.[8]

Fluvoxamine is a relatively older SSRI mainly used in the treatment of depression and anxiety and may have a lower risk of sexual dysfunction than other SSRIs.[15] Venlafaxine is a dual SNRI and mainly is used for the treatment of depression, anxiety disorders, and panic disorders and has gained popularity in off-label indications such as migraine prophylaxis, diabetic neuropathy, and treatment of hot flashes in postmenopausal women. In 2007, venlafaxine was the twelfth most prescribed medication in the United States, with an estimated 17 million prescriptions written for the drug.[16] There have been reports of cataracts with venlafaxine in the premarketing clinical trials of the drug, although the true risk of this event had not been quantified (CPS).[17] The increase in the risk of cataracts with venlafaxine may be related to the drug's dual mechanism of action. Unlike SSRIs, SNRIs upregulate concentration of both serotonin and norepinephrine. In light of the presence of $\beta$ receptors in the lens and of the catarogenic properties of catecholamines,[18] venlafaxine may increase the risk of cataracts more than other SSRI antidepressants. However, the degree by which venlafaxine may increase the risk of cataracts compared with other SSRIs must be verified in future studies.

The annual number of prescriptions for antidepressants in the United States has surpassed that of antihypertensives.[19] It is estimated that up to 10% of United States residents are receiving an antidepressant,[19] mainly SSRIs and SNRIs, with estimated annual sales of $12 billion.[20] Similarly, the incidence of cataracts worldwide also is increasing. The population attributable risk (PAR) is the percent of the incidence of a disease in the population (exposed and unexposed) that is the result of exposure and represents the percent of disease incidence that would be eliminated if exposure were eliminated. The PAR is calculated using the population prevalent exposure ($p$) and the exposure relative risk (PAR = $[p(r-1]/(1+p[r-1])$. Using a relative risk of 1.15 for SSRI users, a PAR of 1.5%, and a 10% prevalence of SSRI use in the United States, roughly 22000 cases of cataracts may be avoided secondary to SSRI use in the United States every year.

Table 3. Rate Ratios and 95% Confidence Intervals for Selective Serotonin Reuptake Inhibitor Use and Incidence of Cataracts in Surgical Outpatient Clinics

| | Cases 9346 | Controls 9346 | Crude Rate Ratio | Adjusted Rate Ratio* | 95% Confidence Interval |
|---|---|---|---|---|---|
| No SSRI use (%) | 92.6 | 94.3 | 1.00 | 1.00 | Reference |
| SSRI use (%) | | | | | |
| Any current use | 4.8 | 3.6 | 1.37 | 1.15 | 1.04–1.28 |
| Any past use | 2.6 | 2.1 | 1.22 | 1.05 | 0.92–1.21 |
| Citalopram (%) | | | | | |
| Any current use | 1.1 | 0.9 | 1.28 | 1.10 | 0.89–1.36 |
| Any past use | 0.7 | 0.5 | 1.28 | 1.11 | 0.85–1.47 |
| Fluoxetine (%) | | | | | |
| Any current use | 0.3 | 0.3 | 1.15 | 0.96 | 0.65–1.43 |
| Any past use | 0.3 | 0.2 | 1.31 | 1.12 | 0.71–1.77 |
| Fluvoxamine (%) | | | | | |
| Any current use | 0.4 | 0.2 | 1.81 | 1.51 | 1.07–2.13 |
| Any past use | 0.2 | 0.2 | 0.84 | 0.70 | 0.43–1.13 |
| Paroxetine (%) | | | | | |
| Any current use | 1.7 | 1.4 | 1.48 | 1.23 | 1.05–1.45 |
| Any past use | 1.0 | 0.9 | 1.17 | 0.99 | 0.79–1.23 |
| Sertraline (%) | | | | | |
| Any current use | 1.2 | 1.0 | 1.22 | 1.05 | 0.86–1.28 |
| Any past use | 1.0 | 0.9 | 1.26 | 1.11 | 0.84–1.40 |
| Venlafaxine (%) | | | | | |
| Any current use | 1.0 | 0.7 | 1.54 | 1.34 | 1.07–1.67 |
| Any past use | 0.5 | 0.4 | 1.19 | 1.09 | 0.77–1.93 |

SSRI = selective serotonin reuptake inhibitor.
*Rate ratios adjusted for gender, hypertension, antihypertensives, antidiabetics, statins, and all forms of corticosteroids.

The strength of this study is the large sample size and the detailed prescription drug information that allowed us to look at the time of onset of cataracts with SSRIs, as well as the risk of cataracts with individual SSRIs. As with all administrative databases, this study is subject to limitations. Cataract diagnosis was assessed only using International Classification of Diseases, 9th revision, codes, which may not necessarily confirm cataract surgery. Also, information for a more detailed work-up for cataract diagnosis was not available. Because of the nature of the data, it was not possible to adjust for all the risk factors for cataracts and potential confounders, including smoking history. Also, because cataracts may take a few years to develop, it is possible for a subject to have undiagnosed cataracts. However, a potential bias from this effect would depend on the prevalence of undiagnosed subjects as well as the exposure status to SSRIs.

The results of this study suggest a possible association between SSRI use and an increase in the risk of cataracts, especially with fluvoxamine and venlafaxine. The possibility that this observation may be the result of the effect of smoking, which could not be controlled for in this study, cannot be excluded.

## References


1. Ernst P, Baltzan M, Deschênes J, Suissa S. Low-dose inhaled and nasal corticosteroid use and the risk of cataracts. Eur Respir J 2006;27:1168–74.
2. Kanthan GL, Wang JJ, Rochtchina E, Mitchell P. Use of antihypertensive medications and topical beta-blockers and the long-term incidence of cataract and cataract surgery. Br J Ophthalmol 2009;93:1210–4.
3. Klein BE, Klein R, Lee KE, Danforth LG. Drug use and five-year incidence of age-related cataracts: the Beaver Dam Eye Study. Ophthalmology 2001;108:1670–4.
4. Ludwig J, Marcotte DE, Norberg K. Anti-depressants and suicide. J Health Econ 2009;28:659–76.
5. van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. BMJ 2001;323:655–8.
6. Ginzburg R, Rosero E. Risk of fractures with selective serotonin-reuptake inhibitors or tricyclic antidepressants. Ann Pharmacother 2009;43:98–103.
7. Costagliola C, Parmeggiani, Sebastiani A. SSRIs and intraocular pressure modifications: evidence, therapeutic implications and possible mechanisms. CNS Drugs 2004;18:475–84.
8. Boerrigter RM, Siertsema JV, Kema IP. Serotonin (5-HT) and the rat's eye: some pilot studies. Doc Ophthalmol 1992;82:141–50.
9. Levy AR, Tamblyn RM, Fitchett D, et al. Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. Can J Cardiol 1999;15:1277–82.
10. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 1995;48:999–1009.
11. Mancini GB, Etminan M, Zhang B, et al. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. J Am Coll Cardiol 2006;47:2554–60.
12. Essebag V, Genest J Jr, Suissa S, Pilote L. The nested case-control study in cardiology. Am Heart J 2003;146:581–90.
13. McCarty CA, Mukesh BN, Fu CL, Taylor HR. The epidemiology of cataract in Australia. Am J Ophthalmol 1999;128:446–65.
14. Vivekanandan S, Lou MF. Evidence for the presence of phosphoinositide cycle and its involvement in cellular signal transduction in the rabbit lens. Curr Eye Res 1989;8:101–11.
15. Westenberg HG, Sandner C. Tolerability and safety of fluvoxamine and other antidepressants. Int J Clin Pract 2006;60:482–91.
16. DrugTopics. Top 200 brand drugs by unit in 2007. February 18, 2008. Available at: http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/072008/491207/article.pdf. Accessed September 15, 2009.
17. Venlafaxine. In: Repchinsky C, ed-in-chief. CPS 2009: Compendium of Pharmaceuticals and Specialties. 44th ed. Ottawa, Canada: Canadian Pharmaceutical Assoc.; 2009:787–97.
18. Weinstock M, Scott JD. Effect of various agents on drug-induced opacities of the lens. Exp Eye Res 1967;6:368–75. javascript:PopUpMenu2_Set(Menu6060548).
19. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. Arch Gen Psychiatry 2009;66:848–56.
20. IMS reports 11.5 percent dollar growth in '03 U.S. prescription sales [press release]. Fairfield, CT: IMS Health; February 15, 2004. Available at: http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=77c91d3be7a29110VgnVCM10000071812ca2RCRD&vgnextchannel=41a67900b55a5110VgnVCM10000071812ca2RCRD&vgnextfmt=default. Accessed November 20, 2009.

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