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## Selective Serotonin Reuptake Inhibitor Use and Increased Risk of Cataract Surgery: A Population-Based, Case-Control Study

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### Abstract

**Purpose**—To investigate whether selective serotonin reuptake inhibitor use is associated with an increased risk of cataract surgery.

**Design**—Population-based, case-control study

**Methods**—Setting: Olmsted County, Minnesota. Patient Population: Eligible patients were county residents in the Rochester Epidemiology Project. Cases included 6,024 county residents aged 50+ years who underwent first-eye cataract surgery between January 1, 2004 and December 31, 2011. Controls included 6,024 residents who never had cataract surgery and were matched to cases by age, sex, and date of surgery. Logistic regression models were used to compute odds ratios for differences in selective serotonin reuptake inhibitor use between cases and controls, and to adjust for confounding variables. Observation Procedure: Rochester Epidemiology Project databases were used to assess cataract surgery and selective serotonin reuptake inhibitor treatment. Main Outcome Measure: Selective serotonin reuptake inhibitor use.

**Results**—In the cataract surgery cohort of 6,024 residents, 1,024 (17%) were selective serotonin reuptake inhibitor users compared to 788 (13%) in the matched cohort of 6,024 residents never having cataract surgery ( $P<0.001$ ). Selective serotonin reuptake inhibitor use of 1 or more years was associated with an increased risk of cataract surgery (OR=1.36; 95% CI, 1.23 – 1.51;  $P<0.001$ ). The associations were similar in women (OR=1.37; 95% CI, 1.22-1.55;  $P<0.001$ ) and men (OR=1.34; 95% CI, 1.12-1.61;  $P=0.002$ ). The risk of cataract surgery was highest with citalopram use (OR=1.53, 95% CI, 1.33-1.77;  $P<0.001$ ).

**Conclusion**—Selective serotonin reuptake inhibitor use of 1 or more years in people aged 50+ years is associated with an increased risk of cataract surgery.

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## Introduction

Cataract surgery rates in the U.S. have increased at least 2.5 fold over the last 20 years,<sup>1,2</sup> and similar increases have been reported in other developed countries throughout the world.<sup>3,4</sup> Additionally, cataract surgery rates have increased at a rate faster than can be explained by aging demographics alone, and the rate of increase has accelerated for women.<sup>1</sup>

Many prescription drugs have been associated with cataract formation, including oral and inhaled corticosteroids, statins, and *B*-blockers.<sup>5-7</sup> Recently, a population-based Canadian study suggested an association between the use of selective serotonin reuptake inhibitors and the diagnosis of cataract.<sup>8</sup> Although the role of serotonin in lens metabolism is unclear, serotonin receptors have been identified in the crystalline lens of animal models,<sup>9</sup> and increased serotonin levels have been shown to cause lens opacities in rats.<sup>10</sup>

It is estimated that 1 in 4 women over the age of 50 years, and approximately 10% of all U.S. residents receive an antidepressant, mainly selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors.<sup>11,12</sup> Given the increasing use of antidepressant medications in the last decade,<sup>13</sup> an association between selective serotonin reuptake inhibitor use and an increased risk of cataract surgery would be useful information and warrants further evaluation. Therefore, the purpose of our population-based, case-control study was to investigate an association between selective serotonin reuptake inhibitor use and incident cases of first-eye cataract surgery within a defined American population by using the resources of the Rochester Epidemiology Project.

## Methods

### Data Sources

A population-based, case control study was conducted. All aspects of the study were prospectively approved by Mayo Clinic and Olmsted Medical Center institutional review boards. Data were obtained by using the resources of the Rochester Epidemiology Project, a medical records linkage system that has linked and archived the medical records, medical diagnoses, surgical interventions, and demographic information of virtually all persons residing in Olmsted County, Minnesota (2010 total county population = 144,248).<sup>14-16</sup> The characteristics of the Olmsted County population are very similar to Minnesota and the Upper Midwest, although compared to the entire U.S., Olmsted County is less ethnically diverse, more educated, and wealthier.<sup>14</sup> Virtually all of the medical care for this relatively isolated, semi-urban county is provided by the Mayo Clinic and its 2 affiliated hospitals, Olmsted Medical Center and its affiliated hospital, and the Rochester Family Medicine Clinic. Only a small proportion of the population (approximately 2%) does not allow any of their medical records to be used for research.<sup>14</sup>

To enumerate the population, the medical records are linked across different health care providers to create a list of unique subjects. Then, residency criteria and imputations are applied to describe the residency status of residents over time. As a result, the Rochester

Epidemiology Project provides a data-retrieval system for a complete description of virtually all sources of medical care used by the Olmsted County population over time.<sup>14-16</sup>

### Ascertainment of Cases and Controls

Cases included a population-based cataract surgery cohort of 6,024 Olmsted County residents aged 50 years and older who underwent incident first-eye cataract surgery between January 1, 2004 and December 31, 2011. Cases were retrospectively identified by using the *International Classification of Diseases, 9<sup>th</sup> Revision* (ICD-9) procedure codes 13.1, 13.11, 13.2/9, 13.3, 13.41, 13.42, 13.43, 13.51, 13.59/9, 13.69/9, 13.71 and *Current Procedural Terminology* (CPT) procedure codes 66982, 66983, or 66984 for cataract surgery. Included were first-eye cataract surgeries performed by phacoemulsification, extracapsular cataract extraction, intracapsular cataract extraction, lens aspiration, and pars plana lensectomy as a primary procedure or as a combined procedure with penetrating keratoplasty, trabeculectomy, or glaucoma shunt procedure. Pars plana lensectomy when combined with a vitreoretinal procedure to improve surgical visualization and cataract extraction in the surgical management of ocular trauma were excluded. A previous REP manual record review of the codes used to identify cases verified case over-ascertainment of less than 1% when using the codes listed above.<sup>17</sup>

Controls included a cohort of 6,024 county residents who never had cataract surgery and who were matched to cases by sex, age ( $\pm 1$  year), and date of cataract surgery ( $\pm 30$  days). Olmsted County residence at the time of surgery was verified for cases and controls using previously validated procedures.<sup>14-16</sup>

### Drug Prescription Records

The Rochester Epidemiology Project prescription drug database captured all drug information (drug name, strength, quantity, day supply) on all outpatient drug prescriptions obtained from Mayo Clinic and Olmsted Medical Center and written for Olmsted county residents in the cases and controls between January 1, 2003 and December 31, 2011. Since 2003, both institutions have used proprietary electronic prescription systems in their office and hospital outpatient settings. Electronic prescriptions were retrieved from the proprietary systems and converted into RxNorm codes. Prescriptions were then grouped using the National Drug File – Reference Terminology (NDF-RT).<sup>18</sup> Available SSRIs included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline. Venlafaxine and duloxetine, serotonin norepinephrine reuptake inhibitors were also assessed.

An event was defined as the identification of a selective serotonin reuptake inhibitor user and serotonin norepinephrine reuptake inhibitor user who was continuously prescribed medication for 1 year or longer before the cataract surgery date (cases) or index date (controls).

### Statistical Analysis

Differences in selective serotonin reuptake inhibitor use and serotonin norepinephrine reuptake inhibitor use between cases and controls were compared by calculations using logistic regression models. The estimated odds ratios and the associated 95% confidence

intervals from these models were used to summarize the relationships. The models were also used to adjust for potential confounding variables that are risk factors for cataract formation including diabetes and oral corticosteroid use. We do not have county-specific data for smoking status or self-reported exposure to second hand smoke and these could not be analyzed. A *P* value of less than 0.05 was considered to be statistically significant.

## Results

During the study period 2004 through 2011 there were 6,024 residents in the primary cataract surgery cohort (cases) and 6,024 residents in the age-, sex, and date of surgery-matched cohort without cataract surgery (controls). After matching, there was no difference between cases and controls in age ( $74 \pm 9$  years) and gender (40% men, 60% women). Diabetes was present in 538 (9%) of the 6,024 cases, and this was significantly higher when compared to diabetes in controls (444, 7%;  $P < 0.001$ ). Oral corticosteroids were used in 360 (6%) of the 6,024 of the cases, and this was significantly higher when compared to controls (236, 4%;  $P < 0.001$ )

Table 1 shows that selective serotonin reuptake inhibitor use was greater among residents with cataract surgery (17%) compared to matched controls who did not have cataract surgery (13%,  $P < 0.001$ ). Selective serotonin reuptake inhibitor use of 1 or more years was associated with an increased risk of cataract surgery (OR=1.36; 95% CI, 1.23-1.51;  $P < 0.001$ ) in residents of 50+ years of age (Table 1); the association was similar for women (OR=1.37; 95% CI, 1.22-1.55;  $P < 0.001$ ) and men (OR=1.34; 95% CI, 1.12-1.61;  $P = 0.002$ ; Table 2). Diabetes (OR=1.23; 95% CI, 1.08-1.41;  $P = 0.002$ ) and oral corticosteroid use (OR=1.56 95% CI, 1.32-1.84;  $P < 0.001$ ) were significantly associated with an increased risk of cataract surgery. After adjusting for diabetes and oral corticosteroid use, selective serotonin reuptake inhibitor use was still associated with a higher risk of cataract surgery ( $P < 0.001$ ).

Serotonin norepinephrine reuptake inhibitor use was greater among residents with cataract surgery (3.3%) compared to matched controls who did not have cataract surgery (2.4%; Table 3). Serotonin norepinephrine reuptake inhibitor use of 1 year or more was associated with an increased risk of cataract surgery (OR=1.37; 95% CI, 1.11-1.70;  $P = 0.004$ ). The association was significant for women (OR 1.36; 95% CI, 1.07-1.74;  $P = 0.01$ ), but did not reach statistical significance in men (OR 1.42; 95% CI 0.88-2.29;  $P = 0.15$ ). The observed difference remained significant after adjusting for oral corticosteroid use and diabetes.

## Discussion

The Rochester Epidemiology Project is unique in that it allows complete capture of outpatient prescription data and medical and surgical information within the defined American population of Olmsted County, Minnesota. Using these resources, our population-based study showed that selective serotonin reuptake inhibitor use of 1 year or more was associated with a significantly increased risk of cataract surgery in residents aged 50+ years. Within the selective serotonin reuptake inhibitor class, citalopram use had the highest risk of cataract surgery.

Our findings confirm an earlier Canadian study that first reported an association between exposure to selective serotonin reuptake inhibitors and an increased risk of cataract formation.<sup>8</sup> The cohort of subjects in this Canadian study was limited to patients over the age of 65 years who had received a coronary revascularization procedure. By contrast, our cohorts included all residents aged 50 years or more and who were part of a well-defined general community. Residents aged 50-64 years comprise 19% of all cataract surgeries<sup>1</sup> and are the highest users of selective serotonin reuptake inhibitors.<sup>12</sup>

Selective serotonin reuptake inhibitors block the absorption (reuptake) of the neurotransmitter, serotonin, leading to higher serotonin levels. It is believed that a serotonin deficiency plays a role in depression. It is estimated that approximately 10% of U.S. residents are receiving an antidepressant, mainly selective serotonin reuptake inhibitors, making antidepressants the third most commonly prescribed class of medication in the U.S.<sup>11,13</sup> In our study population of Olmsted County, antidepressants are the second most prescribed drug group (13%), particularly in women aged 50-64 years (26%).<sup>12</sup> Nationally, the prevalence of antidepressant use has risen 63% between 1999 and 2010.<sup>13</sup> The increase in antidepressant use has been positively associated with a decrease in the use of psychotherapy.<sup>11</sup> However, many antidepressants are prescribed to patients who do not have a psychiatric diagnosis,<sup>19</sup> and are prescribed by general medical providers rather than psychiatrists.<sup>13,20</sup> Concurrent with the recent rise in selective serotonin reuptake inhibitor prescription rates, we observed accelerated growth in incident cataract surgery in women between 2005 and 2012 when compared to an earlier 7-year period (1998-2004).<sup>1</sup> A possible association between increased selective serotonin reuptake inhibitor use and rising rates of cataract surgery in women is unclear, but may warrant further study.

Why selective serotonin reuptake inhibitors would be associated with cataracts and cataract surgery is unclear. Serotonin receptors are found in the lens of animal models,<sup>9</sup> and serotonin has been shown to be important in lens transparency.<sup>10, 21</sup> Although our data was adjusted for some cataract risk factors such as diabetes and oral corticosteroid use, patients treated with antidepressants have a higher prevalence of various persistent general medical conditions,<sup>22</sup> of which some may increase the risk of cataract formation. Finally, patients who begin SSRIs for treatment of depression and milder forms of mood and anxiety disorders may find that their change in mood encourages them to live more carefully and take health precautions, such as seeking surgical attention for previously tolerated vision difficulties.

Similar to Etminan,<sup>8</sup> we also found an association between the use of serotonin norepinephrine reuptake inhibitors, which up regulate the concentrations of serotonin and norepinephrine, and an increased risk of cataract surgery. Although this association was statistically significant, the clinical meaningfulness may be minimal as the difference in serotonin norepinephrine reuptake inhibitor use between the two groups was <1%, and these medications were used by a very small proportion of the cohorts. Nevertheless, catecholamines such as norepinephrine, have catarogenic properties, and premarketing clinical trials suggest an association between cataracts and venlafaxine.<sup>23</sup>

The strengths of our study include being conducted under the auspices of the Rochester Epidemiology Project, which has a 50-year history of robust epidemiologic studies.<sup>14-16</sup> Complete enumeration of the cases of cataract surgery is possible as virtually all county residents have surgery at sites for which REP has complete data capture.<sup>14,16</sup> All residents' medication prescription data, regardless of insurance status, are included, providing a complete picture of prescribing patterns in our county. Finally, our study avoids patient inclusion bias and recall bias, which are common confounders in series that are not population based.

Some limitations should be addressed to aid in the interpretation of the data. First, our prescription-based study is unable to confirm if patients purchased and actually used the prescribed selective serotonin reuptake inhibitors. Although this is a common limitation of studies relying on prescription data, the pattern of selective serotonin reuptake inhibitor prescriptions in our population may not reflect the pattern of actual medication use. Nevertheless, the ability to link prescription data with diagnoses and with clinical details in the electronic medical records of all medical and surgical providers in Olmsted County is a unique strength of the Rochester Epidemiology Project. Second, our study assessed cataract surgery rather than actual cataract formation. When studying selective serotonin reuptake inhibitor use and risk of cataract, Etminan and colleagues,<sup>8</sup> however, found that when their analysis was restricted to cataract surgery, the results were concordant to those restricted to cataract formation. Third, drug formularies and prescribing patterns vary across health care practices and may influence the choice of specific medication within the SSRI drug class. Consequently, our findings for the selective serotonin reuptake inhibitor class in general may be more applicable to other populations than the specific drugs within this class. Fourth, there may be differences in medical accessibility for cataract surgery between antidepressant users and non-users. However, in Olmsted County more than 90% of all older adults are seen at least once at Rochester Epidemiology Project sites within a 1 year period.<sup>15</sup>

Similar to Etminan and coworkers,<sup>8</sup> smoking and exposure to secondhand smoke could not be controlled for in this study. Smoking is a well-known risk factor for cataract formation with a prevalence 14.9% in Minnesota in 2010.<sup>24</sup> Secondhand smoke exposure has negative effects that are nearly as large as those with active smoking.<sup>25</sup> Consequently, our results could be the result of the effects of smoking and secondhand smoke exposure or other unidentified confounders.

In summary, our population-based, case-control study confirms the earlier findings of Etminan and coworkers<sup>8</sup> that selective serotonin reuptake inhibitor use of 1 year or longer is associated with an increased risk of cataract surgery for both men and women. The highest risk was found in users of citalopram. The possibility that the observed recent increases in selective serotonin reuptake inhibitor use is contributing to accelerated growth of incident cataract surgery in our population, especially for women, cannot be excluded.

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**Table 1**  
**Use of selective serotonin re-uptake inhibitors among Olmsted County residents**  
**(2004-2011) and the risk of cataract surgery**

Variable	Cataract Surgery, n (%)		Univariate OR (95% CI)	P Value
	Yes (n=6024)	No (n=6024)		
No SSRI use	5000 (83)	5236 (87)	-	-
Any SSRI use	1024 (17)	788 (13)	1.36 (1.23-1.51)	<0.001
<b>Individual SSRI</b>				
Citalopram	486	326	1.53(1.33-1.77)	<0.001
Sertraline	283	225	1.27(1.06-1.52)	0.009
Paroxetine	173	142	1.22(0.98-1.53)	0.08
Fluoxetine	175	148	1.19(0.95-1.48)	0.13
Escitalopram	83	72	1.16(0.84-1.59)	0.37
Fluvoxamine	4	1	3.97(0.45-35.27)	0.22

SSRI = selective serotonin reuptake inhibitor; OR = odds ratio; CI = confidence interval

**Table 2**  
**Use of selective serotonin reuptake inhibitors among women and men in Olmsted County (2004–2011) and the risk of cataract surgery**

SSRI use	Women			Men		
	Cataract Surgery, n (%)	OR (95% CI)	P	Cataract Surgery, n (%)	OR (95% CI)	P
	Yes (n=3623)	No (n=3623)		Yes (n=2401)	No (n=2401)	
No	2893 (80)	3061 (85)	-	2107 (91)	2175 (88)	-
Yes	730 (20)	562 (15)	1.37 (1.22-1.55)	294 (9)	226 (12)	1.34 (1.12-1.61)

SSRI = selective serotonin reuptake inhibitor; OR = odds ratio; CI = confidence interval

**Table 3**  
**Use of serotonin norepinephrine reuptake inhibitors among Olmsted County residents**  
**(2004-2011) and the risk of cataract surgery**

Variable	Cataract Surgery, n (%)		Univariate OR (95%CI)	P Value
	Yes (n=6024)	No (n=6024)		
No SNRI use	5824 (97)	5877 (98)	-	-
Any SNRI use	200 (3)	147 (2)	1.37 (1.11-1.70)	0.004
<b>Individual SNRI</b>				
Duloxetine	40	22	1.82(1.08-3.07)	0.02
Venlafaxine	170	129	1.32(1.05-1.67)	0.02

SNRI = serotonin norepinephrine reuptake inhibitor; OR =odds ratio; CI = confidence interval

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