

# Association Between Tamsulosin and Serious Ophthalmic Adverse Events in Older Men Following Cataract Surgery

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**B**ENIGN PROSTATIC HYPERPLASIA (BPH) affects nearly 3 out of 4 men by the age of 70 years.<sup>1,2</sup> Medical management of BPH is often preferred to surgical treatment because surgery increases the risk of impotence and incontinence. An effective and commonly prescribed medication for BPH is tamsulosin,<sup>3</sup> which accounted for more than \$1 billion in sales in 2007.<sup>4</sup>

Tamsulosin is believed to relieve symptoms of BPH by relaxing smooth muscle in the prostate and bladder neck through systemic blockade of  $\alpha_{1a}$ -adrenergic receptors. Because these receptors are present in dilator smooth muscle of the iris, tamsulosin may also impede mydriasis during surgery and lead to intraoperative floppy iris syndrome (IFIS).<sup>5-14</sup> In turn, IFIS may increase the risk of complications during cataract surgery. This association has prompted warnings regarding the risk of

See also p 2044 and Patient Page.

**Context** Both benign prostatic hyperplasia (BPH) and cataract formation are common in older men. The  $\alpha$ -adrenergic receptor blocker tamsulosin is frequently prescribed to treat BPH, and research suggests this drug may increase the intraoperative difficulty of cataract surgery. No studies have documented whether use of tamsulosin or other  $\alpha$ -blocker drug therapies affect the risk of serious postoperative adverse events.

**Objective** To assess the risk of adverse events following cataract surgery in older men prescribed tamsulosin or other  $\alpha$ -blocking drugs used to treat BPH.

**Design, Setting, and Patients** Nested case-control analysis of a population-based retrospective cohort study using linked health care databases from Ontario, Canada. We included all men aged 66 years or older who had cataract surgery between 2002 and 2007 (N=96 128).

**Main Outcome Measures** A composite of procedures signifying retinal detachment, lost lens or lens fragment, or endophthalmitis occurring within 14 days after cataract surgery. The risk of these adverse events was compared between men treated with tamsulosin or other  $\alpha$ -blockers and men with no exposure to these medications in the year prior to cataract surgery. We separately examined the association of drug exposure that was either recent (within the 14 days before surgery) or previous (15-365 days before surgery).

**Results** Overall, 3550 patients (3.7%) in the cohort had recent exposure to tamsulosin and 7426 patients (7.7%) had recent exposure to other  $\alpha$ -blockers. Two hundred eighty-four patients (0.3%) had an adverse event. We randomly matched 280 of the cases to 1102 controls according to their age, surgeon, and year of surgery. Adverse events were significantly more common among patients with recent tamsulosin exposure (7.5% vs 2.7%; adjusted odds ratio [OR], 2.33; 95% confidence interval [CI], 1.22-4.43) but were not associated with recent exposure to other  $\alpha$ -blockers (7.5% vs 8.0%; adjusted OR, 0.91; 95% CI, 0.54-1.54) or to previous exposure to either tamsulosin ( $\leq 1.8\%$  vs 1%; adjusted OR, 0.94; 95% CI, 0.27-3.34) or other  $\alpha$ -blockers (2.9% vs 2.1%; adjusted OR, 1.08; 95% CI, 0.47-2.48). This corresponds to an estimated number needed to harm (NNH) of 255 (95% CI, 99-1666).

**Conclusions** Exposure to tamsulosin within 14 days of cataract surgery was significantly associated with serious postoperative ophthalmic adverse events. There were no significant associations with exposure to other  $\alpha$ -blocker medications used to treat BPH.

JAMA. 2009;301(19):1991-1996

www.jama.com

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IFIS for patients taking tamsulosin and undergoing cataract surgery.<sup>15-17</sup> However, the warnings and noted precautions in reference materials focused only on the added intraoperative difficulty associated with tamsulosin and did not mention postoperative adverse events.<sup>18</sup>

Each year, approximately 5% of elderly US residents undergo cataract procedures.<sup>19</sup> Because 1% to 5% of male patients are taking tamsulosin at the time of surgery, a sizable proportion of patients may experience IFIS.<sup>12</sup> However, few studies have been large enough to assess the connection between tamsulosin exposure and postoperative complications. In addition, it is unclear whether proximity of therapy to the surgery is important or whether complications are equally likely with  $\alpha$ -blockers other than tamsulosin.<sup>7</sup>

Accordingly, we undertook a large, population-based analysis of postoperative adverse events experienced by patients who were prescribed tamsulosin or other  $\alpha$ -blockers at the time of cataract surgery. To assess specificity of effect, we also studied exposure to proton pump inhibitors—drugs for which an increased risk of adverse events would not be expected.

## METHODS

### Overview

We used several linked administrative databases and a nested case-control design to study serious ophthalmic adverse events experienced by Ontario residents who underwent cataract surgery between 2002 and 2007. Cases were those who experienced an adverse ophthalmic surgical outcome within 14 days of cataract surgery. Controls were selected from those patients who had cataract surgery but who had no such adverse event. The study protocol was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto. The analysis was performed at the Institute for Clinical Evaluative Sciences, which has statutory authority to conduct health services research without consent using anonymized administrative data.

### Data Sources

The province of Ontario has a universal health insurance program that covers all 12 million residents. Records from 3 health administrative databases were linked using encrypted unique identifiers. The Ontario Drug Benefit database contains highly accurate records of all outpatient prescriptions dispensed to patients aged 65 years or older.<sup>20,21</sup> The Ontario Health Insurance Plan database contains information on inpatient and outpatient physician services. This database has excellent reliability for surgical procedures.<sup>21</sup> The Ontario Registered Persons database contains demographic and vital status information on all residents. All 3 databases are virtually complete for the variables used in this research.<sup>21</sup>

### Cohort Identification

We used the Ontario Health Insurance Plan database to identify patients aged 66 years or older who had cataract surgery between April 1, 2002, and June 16, 2007. For those who had multiple procedures over the accrual period, we studied the first.

Because BPH was the only indication for tamsulosin for formulary coverage in Ontario and it is the only US Food and Drug Administration–labeled indication, women were excluded. We also excluded those who had other eye procedures in combination with their cataract surgery, those who had eye procedures other than cataract surgery in the preceding 5 years, those prescribed topical cyclosporine within 90 days of surgery, those who died within 14 days of surgery, and those who had a second cataract surgery within 14 days.

### Postoperative Adverse Events:

#### Case Ascertainment

Case patients had a physician service claim for any 1 of 4 procedures (vitrectomy, vitreous aspiration or injection, dislocated lens extraction, or air or fluid exchange) between 1 and 14 days after cataract surgery. Procedures occurring on the same day as the surgery were not included. These procedures were

a composite outcome for serious postoperative ophthalmic adverse events and served as indicators of retinal detachment, lost lens or lens fragment, and suspected endophthalmitis.<sup>22,23</sup> *Lost lens or lens fragment* was defined as any patient on whom the procedure for dislocated lens extraction was performed. *Retinal detachment* was defined as any patient on whom an air or fluid exchange was performed. *Suspected endophthalmitis* was defined as any patient on whom a vitrectomy or vitreous aspiration or injection was performed, which was not in tandem with a lost lens or lens fragment or air or fluid exchange. Outcomes were recorded regardless of who patients saw for their postoperative care.

### Selecting Controls

From the subgroup of patients who did not experience an adverse ophthalmic event, we selected up to 4 controls per case. Controls were randomly selected and matched to cases according to the patient's year of birth (within 3 years of case's birth), the surgeon who performed the cataract procedure, and the year the cataract surgery was performed (within 1 year of the case's surgery). This approach minimized bias due to patient age, surgeon volume and complication rates, and changes in surgical technique over time.<sup>22</sup>

### Assessing Exposure to $\alpha$ -Blockers

The drug exposure of primary interest was the relatively selective  $\alpha_{1a}$ -receptor blocker, tamsulosin. We also assessed exposure to other, less selective  $\alpha$ -blocking agents: alfuzosin, doxazosin, prazosin, and terazosin. All of these drugs were covered by the Ontario Drug Benefit Program during the period of study and were identified using specific drug identification numbers recorded on paid claims in the Ontario Drug Benefit Database. Alfuzosin, doxazosin, and terazosin all had indications for BPH. Doxazosin, prazosin, and terazosin all had indications for hypertension.

We created 3 mutually exclusive exposure groups: (1) the recent-exposure group were individuals whose most re-

cent prescription for an  $\alpha$ -blocker included the period of the 14 days before cataract surgery, incorporating a 20% grace period to accommodate nonadherence. This period was based on previous observations<sup>7,24</sup>; (2) the previous-exposure group were those who filled a prescription in the year prior to surgery but who did not qualify for the recent-exposure group (ie, those whose drug supply [plus a 20% grace period] ended between 15 and 365 days before cataract surgery); and (3) the no-exposure group were patients who had no exposure to an  $\alpha$ -blocking drug in the 365 days before surgery.

Because some patients received more than 1 study drug before surgery, we used a hierarchical approach to the exposures. We considered a recent exposure to a medication to be more important than a previous exposure, and exposure to tamsulosin (the drug of primary interest) to be more important than exposure to another  $\alpha$ -blocker. For example, a patient who satisfied the criteria for recent tamsulosin exposure could have a prior or overlapping prescription for another  $\alpha$ -blocker but would remain in the recent-tamsulosin category.

### Covariates

Our analysis adjusted for several potential confounders (TABLE 1). Individual-level income status was based on the Ontario Drug Benefit program's income test for prescription copayment. A count of the number of medications dispensed in the year prior to surgery was used as a validated measure of comorbidity.<sup>25</sup> Those prescribed an antidiabetic medication in the year before surgery were defined as having diabetes. We also adjusted for topical eye medications prescribed within 90 days of cataract surgery. These drugs were grouped according to indication or mechanism of action to avoid overfitting the statistical model.

### Statistical Analysis

We used descriptive statistics to characterize cases and controls. Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence

**Table 1.** Characteristics of Cases and Controls

Characteristics <sup>a</sup>	Patients	
	Case (n = 280)	Control (n = 1102)
Age, mean (SD), y	77.1 (6.6)	76.9 (6.3)
Diabetes, No. (%) <sup>b</sup>	79 (28.2)	232 (21.1)
Low income status, No. (%)	73 (26.1)	241 (21.9)
No. of drugs in previous y, mean (SD)	10.6 (6.1)	9.4 (5.5)
Topical eye treatment within 90 d, No. (%)	219 (78.2)	906 (82.2)
Anti-inflammatory, NSAIDs, and steroid-based	171 (61.1)	702 (63.7)
Antibiotics or antiviral treatment	35 (12.5)	139 (12.6)
Glaucoma treatment	42 (15)	128 (11.6)
Combination treatment with steroids and antibiotics, No. (%)	100 (35.7)	409 (37.1)

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

<sup>a</sup>Users of antiallergic and mydriatic drugs were not listed for confidentiality purposes because the cell sizes included fewer than 6 persons.

<sup>b</sup>Diabetes is defined as prescription for an antidiabetic medication in the year prior to surgery.

intervals (CIs) for the association between adverse events and the following: recent tamsulosin exposure, recent exposure to another  $\alpha$ -blocker, previous tamsulosin exposure, and previous exposure to another  $\alpha$ -blocker. All groups were compared with the reference group of no exposure. A multivariate model was fitted to adjust for potential confounding characteristics. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). For the study's case-control ratio of 4, independence in the probability of exposure among cases and controls, and a type I error probability of 0.05, our study had 88% power to reject the null hypothesis of an OR of 1 for a clinically significant unadjusted odds ratio of 2.5. This was based on a cataract surgery cohort of approximately 100 000 men, 3% taking tamsulosin at the time of surgery, and 0.3% experiencing a postoperative adverse event.<sup>12,22,26,27</sup> We used a 2-sided test of significance at the  $P < .05$  level.

### Test for Specificity

We assessed specificity of effect using proton pump inhibitors as a *tracer exposure*, an exposure for which we would not expect an association with serious ophthalmic adverse events from cataract surgery. Those analyses excluded patients who had any exposure to tamsulosin or another  $\alpha$ -blocker in the 365 days preceding cataract surgery.

### Estimate of Absolute Risk of Recent Tamsulosin Exposure

We calculated the event rate for our composite end point over the 5-year study period for all patients undergoing cataract surgery to estimate the absolute risk associated with recent tamsulosin exposure. We applied the estimated adjusted OR for recent tamsulosin exposure from the nested case-control analysis to the baseline event rate in the cohort to estimate the number needed to harm (NNH, for which,  $NNH = 100 \times [1/\text{absolute risk increase}]$ , and absolute risk increase = estimated absolute risk [OR  $\times$  baseline event rate] - baseline event rate).

### RESULTS

We identified 96 128 older men who had cataract surgery over the 5-year study period. There were 3550 patients (3.7%) who had recent exposure to tamsulosin and 1006 (1.1%) who had previous exposure to tamsulosin. There were 7426 patients (7.7%) who had recent exposure to other  $\alpha$ -blocking medications and 1683 (1.1%) who had previous exposure. We identified 284 case patients (0.3%) who experienced an adverse event in the 14 days after surgery. Of these 284 cases, 175 had a procedure for lost lens or lens fragment, 35 for retinal detachment, and 26 had both. One hundred had suspected endophthalmitis. Of the 284 cases, 280 were matched to 1102 control patients; more than 96% of cases

**Table 2.** Postoperative Adverse Outcomes for Patients Receiving  $\alpha$ -Blocker Medications<sup>a</sup>

Characteristic	No. (%) of Patients		Odds Ratio (95% Confidence Interval)	
	Case (n = 280)	Control (n = 1102)	Unadjusted	Adjusted <sup>b</sup>
	No use <sup>c</sup>	226 (80.7)	950 (86.2)	1 [Reference]
Recent exposure <sup>d</sup>				
Tamsulosin	21 (7.5)	30 (2.7)	2.92 (1.60-5.34)	2.33 (1.22-4.43)
Other $\alpha$ -blocker drugs <sup>e</sup>	21 (7.5)	88 (8.0)	1.00 (0.60-1.66)	0.91 (0.54-1.54)
Proton pump inhibitors <sup>f</sup>	26 (9.3)	126 (11.4)	0.84 (0.54-1.31)	0.73 (0.46-1.16)
Previous exposure <sup>g</sup>				
Tamsulosin	≤5 (≤1.8) <sup>a</sup>	11 (1.0)	1.42 (0.44-4.61)	0.94 (0.27-3.34)
Other $\alpha$ -blocker drugs <sup>e</sup>	8 (2.9)	23 (2.1)	1.35 (0.60-3.02)	1.08 (0.47-2.48)
Proton pump inhibitors <sup>f</sup>	11 (3.9)	42 (3.8)	1.04 (0.53-2.03)	0.91 (0.45-1.81)

<sup>a</sup>We are unable to display information on cell sizes less than 6.

<sup>b</sup>Adjusted for diabetes, low income status, number of drugs taken in the previous year, antibiotic or antiviral treatment, glaucoma treatment, anti-inflammatory treatment, combination treatment of steroids and antibiotics, mydriatics, and anti-allergy medication.

<sup>c</sup>The no-exposure group were patients who had no exposure to an  $\alpha$ -blocker in the 365 days before surgery.

<sup>d</sup>The recent exposure group comprised individuals whose most recent prescription for an  $\alpha$ -blocker ended within 14 days of cataract surgery, including a 20% grace period to accommodate nonadherence.

<sup>e</sup>Other drugs include alfuzosin, doxazosin, prazosin, or terazosin.

<sup>f</sup>Analysis for proton pump inhibitors excluded patients who had any exposure to tamsulosin or another  $\alpha$ -blocker in the 365 days preceding cataract surgery.

<sup>g</sup>Previous-exposure group were those who filled a prescription in the year prior to surgery but who did not qualify for the recent-exposure group (ie, those exposed with prescriptions ending between 15 and 365 days before cataract surgery).

were matched to 4 controls. The average age of cases and controls was 77 years, and both groups were dispensed an average of approximately 10 medications in the year preceding cataract surgery. Over one-fifth of the sample had diabetes and low-income status, respectively (Table 1).

In our primary analysis of adverse events following cataract surgery, 21 case patients (7.5%) and 30 control patients (2.7%) received tamsulosin in the 14 days before surgery. This resulted in an adjusted OR of 2.33 (95% CI, 1.22-4.43; TABLE 2) For patients prescribed other  $\alpha$ -blockers, 21 case patients (7.5%) and 88 control patients (8.0%) received the medication in the 14 days preceding surgery (adjusted OR, 0.91; 95% CI, 0.54-1.54).

Those who had previous exposure to tamsulosin were not at elevated risk for complications (≤5) case patients [≤1.8%] vs 11 control patients [1.0%]; adjusted OR, 0.94; 95% CI, 0.27-3.34). Previous exposure to other  $\alpha$ -blockers also was not associated with elevated risk (8 case patients [2.9%] vs 23 control patients [2.1%]; adjusted OR, 1.08; 95% CI, 0.47-2.48). For our test of specificity, neither recent nor previous exposure to proton pump inhibi-

tors was associated with increased risk for a postoperative adverse event (Table 2).

#### Estimated Absolute Risk of a Serious Postoperative Adverse Event

The baseline event rate for our composite outcome was 0.3%. Using this rate and the adjusted OR associated with recent tamsulosin exposure, the estimated number needed to harm was 255 (95% CI, 99-1666).

#### COMMENT

We included more than 96 000 older men who had cataract surgery over a 5-year period. We found that those who were recently dispensed tamsulosin had 2.3 times the risk of serious adverse events following cataract surgery. To our knowledge, this is the first study to link tamsulosin exposure to clinically important postoperative complications rather than to IFIS alone. We found no such association among patients prescribed other  $\alpha$ -blocking medications or among those previously exposed to tamsulosin. This finding is novel because it tested for a drug-procedure interaction and produced a population-based risk estimate.

Our findings are strengthened by the inclusion of consecutive surgeries, the population-based nature of the sample, and the negative finding within the tracer population of proton pump inhibitor users. Because the cataract surgery and adverse outcomes were linked regardless of what physician the patients saw postoperatively, cases were lost to follow-up only when patients sought postoperative care outside the province—an extremely infrequent occurrence. The case-control design is well-suited to this question because serious cataract surgical complications are rare, and nesting the analysis within a predefined cohort helped to identify suitable controls. Furthermore, matching according to age, surgeon, and year of surgery served to minimize bias.<sup>22</sup>

Our overall adverse event rate is comparable with those from other studies.<sup>28-32</sup> However, most studies examining the effect of tamsulosin have been small and have focused on the intermediate measure of IFIS.<sup>7,8,33</sup> Furthermore, few have studied the effect of timing of tamsulosin therapy or controlled for potential confounders, such as surgeon volume and ocular and disease comorbidity. Thus, our study contributes on several fronts.

Why did we find an effect with tamsulosin but not with other  $\alpha$ -blocking drugs? This may relate to differences in receptor affinity between tamsulosin and other related medications. It is believed that tamsulosin is more highly selective for  $\alpha_{1a}$ -adrenergic receptors than other  $\alpha$ -blocker drugs.<sup>14,34</sup> These particular receptors are present in bladder-neck smooth muscle and in the iris dilator muscle. Blockage of the iris dilator allows unopposed action of the parasympathetically innervated iris constrictor muscle and loss of iris tone, resulting in the clinical syndrome of IFIS.<sup>14,34</sup> In contrast, the design of the study and the hierarchical method of ascribing medication exposure precluded us from fully evaluating the effect of other  $\alpha$ -blocking drugs. In many cases, those prescribed tamsulosin were previously prescribed another  $\alpha$ -blocking drug so disentangling



gling an effect may be more complicated. Furthermore, the study may have been underpowered to detect a smaller estimated risk, despite the large sample size. Notably, the upper value of the 95% CI for the adjusted OR of 1.54 still includes a potentially clinically important effect. Indeed, some studies of IFIS have also implicated other  $\alpha$ -blocking drugs such as alfuzosin.<sup>5,11</sup>

Recent safety warnings about tamsulosin and increasing clinician awareness may lead to the practice of discontinuing tamsulosin prior to cataract surgery.<sup>7,15-17</sup> Our findings could not confirm whether this is an effective management strategy for several reasons. First, the adjusted OR associated with previous tamsulosin exposure was not statistically significant. However, our estimates may have had limited power to detect an effect because of the relatively small number of previous tamsulosin users. The CIs were wide and included values of clinically important higher and lower risk. Moreover, our methods could not reliably identify those individuals who were prescribed tamsulosin close to the time of surgery but who were instructed to not take the medication. Second, discontinuation of tamsulosin may not be a good clinical strategy because this can result in acute urinary retention, which also has significant morbidity and mortality risks.<sup>35</sup> This must be weighed against our estimated NNH of 255. Third, we could not determine whether replacing tamsulosin with another  $\alpha$ -blocking medication would change the risks related to surgery because IFIS can occur many months after stopping tamsulosin therapy.<sup>7,8,33,36</sup>

Our study has several important limitations. First, we used administrative health data, which lacks clinical information for detailed case-mix adjustment. Noting the difficulty of the cataract surgery using clinical records may explain some of the observed differences in patient outcomes.<sup>37</sup> However, our analysis did account for patient age, sex, and many potential confounders that could complicate cata-

ract surgery such as diabetes and other eye diseases.

Second, our claims data confirm only that prescriptions were filled; not whether the drugs were ingested. Third, although our study included 96 128 consecutive cataract surgeries, the small number of patients in our subgroup analyses may have limited power to detect significant effects. Fourth, many study patients were accrued after published evidence of an association between tamsulosin and IFIS.<sup>7</sup> We could not determine whether surgeons anticipated IFIS or used medical or surgical interventions such as iris expansion hooks, intracameral phenylephrine, or preoperative atropine.<sup>34,38,39</sup> Such interventions might reduce risks for complications. Furthermore, a knowledge of tamsulosin exposure might lead to closer postoperative scrutiny, thereby increasing the diagnosis of adverse events. However, our study period also included several years prior to the first description of IFIS in 2005, and data from this earlier era would not be subject to increased surveillance and ascertainment bias. Moreover, the adverse events we selected are usually dramatic, quickly present to medical attention, and require procedural interventions.

Fifth, we did not assess whether high doses of the individual  $\alpha$ -blocking drugs were associated with changes in risk. Again, these types of subgroup analyses would have limited power due to the low adverse event rates in cataract surgery. Sixth, we excluded adverse events occurring more than 2 weeks after surgery, which may underestimate the true adverse event rate. However, most such cases would usually present within this time frame.<sup>40</sup>

Seventh, our estimate of retinal detachment may be an underestimate because we captured retinal detachments repaired via vitrectomy and air or fluid exchange but not those repaired by scleral buckling. Similarly, our estimate of lost lens or lens fragment may be an underestimate because the procedure of dislocated lens extraction may not be performed if the lost

lens or lens fragment is not considered to compromise visual outcome. Eighth, our hierarchical approach to drug exposure assessment did not account for possible interaction or additive effects of  $\alpha$ -blocking medications. Ninth, since we did not measure IFIS directly, we are unable to definitively connect the adverse outcomes with IFIS. Tenth, our study was restricted to men older than 65 years. The findings may still pertain to younger individuals, although they may have a lower absolute risk of adverse events.<sup>23</sup>

Finally, because our data sources do not specify which eye underwent cataract surgery, it is possible that we captured postoperative complications occurring in the contralateral (nonoperative) eye. However, requiring such care within 2 weeks of surgery should be extraordinarily rare. Similarly, the procedures counted as adverse events can sometimes be unrelated to cataract surgery (eg, macular pathology from diabetes and macular degeneration). Still, it is unlikely that procedures for these conditions would be performed in the nonoperative or fellow eye within 2 weeks of cataract surgery. On balance, we believe it unlikely that any of these limitations would invalidate our principal finding of an increased risk of adverse events in patients dispensed tamsulosin in the weeks immediately preceding surgery.

Our finding that tamsulosin exposure is associated with an increased risk of postoperative complications concurs with prior studies of intraoperative adverse events. We believe that this is the first large study with an adequate study design to describe this effect and provide a population-based risk estimate (something that can only be done using population-based observational research). It is unclear whether drug discontinuation prior to surgery reduces this risk. Because the combination of cataract surgery and tamsulosin exposure is relatively common, patients should be properly appraised of the risks of drug therapy and preoperative systems should focus on the

identification of tamsulosin use by patients. In this way, surgeons can plan and prepare for a potentially more complicated procedure or refer to someone with more experience.

**Author Contributions:** Dr Bell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Bell, Hatch, Fischer, Paterson, Gill, Anderson, Rochon.

**Acquisition of data:** Bell, Cernat.

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**Drafting of the manuscript:** Bell, Hatch, Fischer, Paterson.

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**Study supervision:** Anderson, Rochon.

**Financial Disclosures:** Dr Hatch has been employed by the University of Toronto and the Toronto Western Hospital to coordinate clinical trials sponsored by Alcon and Novartis. Dr Fischer was last employed by Bayer Inc in 2004. No other authors have any potential or real conflicts of interest to declare. Dr Cernat performed the statistical analysis for this study and declares no conflicts of interest.

**Funding/Support:** This work was supported by Team Grant OTG-88591 from the Canadian Institutes of Health Research (CIHR) Institute of Nutrition, Metabolism, and Diabetes and by an Interdisciplinary Capacity Enhancement Grant, HOA-80075, from the CIHR Institute of Gender and Health and the CIHR Institute of Aging. Dr Bell is supported by a New Investigator Award from the CIHR Institute of Aging. This study was conducted at the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC).

**Role of the Sponsors:** The funding agencies had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

**Disclaimer:** The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

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