

LESS IS MORE

Inhaled Anticholinergic Drug Therapy and the Risk of Acute Urinary Retention in Chronic Obstructive Pulmonary Disease

A Population-Based Study

Anne Stephenson, MD, PhD; Dallas Seitz, MD; Chaim M. Bell, MD, PhD; Andrea Gruneir, PhD; Andrea S. Gershon, MD, MSc; Peter C. Austin, PhD; Longdi Fu, MSc; Geoffrey M. Anderson, MD, PhD; Paula A. Rochon, MD, MPH; Sudeep S. Gill, MD

Background: Inhaled anticholinergic medications (IACs) are widely used treatments for chronic obstructive pulmonary disease (COPD). The systemic anticholinergic effects of IAC therapy have not been extensively studied. This study sought to determine the risk of acute urinary retention (AUR) in seniors with COPD using IACs.

Methods: A nested case-control study of individuals with COPD aged 66 years or older was conducted from April 1, 2003, to March 31, 2009, using population-based linked databases from Ontario, Canada. A hospitalization, same-day surgery, or emergency department visit for AUR identified cases, which were matched with up to 5 controls. Exposure to IACs was determined using a comprehensive drug benefits database. Conditional logistic regression analysis was conducted to determine the association between IAC use and AUR.

Results: Of 565 073 individuals with COPD, 9432 men and 1806 women developed AUR. Men who just initiated a regimen of IACs were at increased risk for AUR compared with nonusers (adjusted odds ratio [OR], 1.42; 95% confidence interval [CI], 1.20-1.68). In men with evidence of benign prostatic hyperplasia, the risk was increased further (OR, 1.81; 95% CI, 1.46-2.24). Men using both short- and long-acting IACs had a significantly higher risk of AUR compared with monotherapy users (OR, 1.84; 95% CI, 1.25-2.71) or nonusers (2.69; 1.93-3.76).

Conclusions: Use of short- and long-acting IACs is associated with an increased risk of AUR in men with COPD. Men receiving concurrent treatment with both short- and long-acting IACs and those with evidence of benign prostatic hyperplasia are at highest risk.

Arch Intern Med. 2011;171(10):914-920

Author Affiliations:


Department of Medicine and Keenan Research Centre in the Li Ka Shing Knowledge Institute of St Michael's Hospital (Drs Stephenson and Bell), Institute for Clinical Evaluative Sciences (Drs Seitz, Bell, Gruneir, Gershon, Austin, Anderson, Rochon, and Gill and Mr Fu), and Departments of Medicine (Drs Bell and Rochon) and Health Policy Management and Evaluation (Drs Bell, Austin, Anderson, and Rochon), University of Toronto, Toronto, Ontario, Canada, and Women's College Research Institute, Women's College Hospital (Drs Stephenson, Seitz, Gruneir, and Rochon) and Department of Medicine (Dr Gill), Queen's University, Kingston, Ontario, Canada.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a common respiratory condition affecting 1 in 10 individuals older than 40 years.¹ Internationally, COPD has a major effect on morbidity, mortality, and

See Invited Commentary at end of article

health care use. Inhaled anticholinergic medications (IACs) are beneficial in the treatment of symptomatic COPD.^{2,3} Their mechanism of action is through local muscarinic receptor blockade, causing relaxation of airway smooth muscle and decreased airflow obstruction.^{3,4} Short-acting IACs (SAACs) (eg, ipratropium bromide) have been used for decades to treat COPD. In 2002, tiotropium bromide, a long-acting IAC (LAAC), was introduced in Canada. In clinical trials, tiotropium therapy was shown to improve lung

function and to reduce exacerbation rates, health service use, and symptoms in individuals with COPD compared with the receipt of ipratropium² or placebo.⁵ Because of the efficacy of tiotropium, its prolonged effect, and once-daily dosing schedule, it has become widely used, accounting in 2009 for more than US \$2 billion in sales worldwide.⁶

 CME available online at www.jamaarchivescme.com and questions on page 878

There is uncertainty about whether IACs cause clinically important systemic anticholinergic effects. Canadian,⁷ European,⁸ and American⁹ COPD practice guidelines describe little effect of IAC therapy on prostatic symptoms. Authors of a small study¹⁰ from Japan concluded that tiotropium does not affect lower urinary tract function in individuals with COPD and benign prostatic hyperplasia

(BPH), yet a more recent study¹¹ reported an increased risk of urinary retention, particularly in men with COPD and BPH. Clinical trials, which often include participants at low risk for adverse events, have documented an increased risk of acute urinary retention (AUR) with the use of IACs¹²⁻¹⁴; however, the risk among the general population is likely considerably higher.

Acute urinary retention is common, especially in older men with prostatic enlargement, and is associated with increased morbidity and mortality.¹⁵⁻¹⁷ Acute urinary retention is considered a urological emergency, which may expose individuals to a cascade of interventions and complications that contribute to worse survival.¹⁷ Preventing AUR and its complications would likely have beneficial effects on morbidity and mortality, particularly among older populations. Understanding the risk of AUR associated with IAC therapy would help to identify those at risk for this complication.

The objectives of the study were (1) to determine the odds of IAC exposure among individuals with COPD who develop AUR and (2) to assess patient characteristics and the odds of exposure to different types of IAC regimens among those with COPD who develop AUR.

METHODS

OVERVIEW

We conducted a population-based nested case-control study from April 1, 2003, to March 31, 2009. Using an established cohort of individuals with COPD, we used Ontario, Canada, health care databases to test the association between the development of AUR and IAC exposure. The study analysis was conducted at the Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada, and was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto.

DATA SOURCES

The universal health insurance program provides medical coverage to all 12 million individuals who live in the province of Ontario. Multiple linked health care administrative databases housed at the Institute for Clinical Evaluative Sciences were used for this study. A cohort of adults with COPD was identified using a validated algorithm having a sensitivity of 85% (95% confidence interval [CI], 77.0-91.0) and a specificity of 78.4% (95% CI, 73.6-82.7).¹⁸ This health administrative definition of COPD previously has been used and was defined as the presence of 1 or more ambulatory claims for COPD, 1 or more hospitalizations for COPD, or both.¹ Medication records were obtained from the Ontario Drug Benefit database, which contains accurate records of all publicly funded medications dispensed to Ontarians older than 65 years.¹⁹ The coding accuracy and completeness of drug claims in the Ontario Drug Benefit database are excellent, with an error rate of 0.7%.¹⁹ The Canadian Institute for Health Information Discharge Abstracts database (which describes all hospital admissions), the Same-Day Surgery database (which characterizes procedures not requiring an overnight hospital stay), and the National Ambulatory Care Reporting System database (which characterizes emergency department visits) were used to identify the study outcome. Comorbidities were identified using the Ontario Health Insurance Plan database, the Canadian Institute for Health Information Discharge Abstracts da-

tabase, and the Ontario Diabetes database.²⁰ Demographic information was obtained from the Registered Persons database. All databases were anonymously linked using encrypted health card numbers.

BASE COHORT

The cohort consisted of all residents aged 66 years or older identified within the Ontario COPD database. The study entry date was defined as the later of April 1, 2003, or the date of entry into the Ontario COPD database. We excluded individuals with a previous radical cystectomy, as they could not experience AUR. Those with a previous history of AUR within the year before cohort enrollment were excluded from the cohort, as these individuals would have a higher risk of the outcome compared with individuals who experienced their first event.

STUDY OUTCOME

The outcome of interest was AUR (*International Classification of Disease, Tenth Revision [ICD-10]* code R33), identified by an emergency department visit, a same-day surgery visit, or a hospitalization. This approach has been used previously to identify episodes of AUR.^{17,21} We included AUR-associated hospitalizations in which AUR was the diagnosis that contributed most or significantly to length of stay.

SELECTION OF CASES AND CONTROLS

Cases were defined as individuals who developed a first episode of AUR, identified by an emergency department visit, a same-day surgery visit, or a hospitalization in which AUR was the main reason for admission. Individuals who developed AUR during the hospital admission were not included as cases because the data do not allow for the identification of hospital medications. The date of AUR was used as the index date for cases. Potential controls were those who were at risk for the outcome in that they were still alive, had not had a radical cystectomy, remained free from the outcome, and resided in the province. For each case, up to 5 controls matched on age (± 1 year) and time within the cohort were randomly selected. Controls were assigned the same index date as their respective cases.

IAC THERAPY EXPOSURE

We conducted 2 analyses. The first focused on any IAC exposure, regardless of the type, while the second characterized the type of IAC regimen the individual was receiving.

Any IAC Exposure

All IAC therapy (short acting and long acting) was identified within the Ontario Drug Benefit database. Exposure to IACs was assessed by examining patterns of use in the 180 days before the index date. Individuals were categorized into the following 4 groups based on prior use of IAC: (1) new users (new prescription within 30 days of the index date with no prior prescriptions within 30-180 days before the index date), (2) current users (prescription within 30-180 days before the index date for which the days' supplied covers the index date or extends to within 30 days of the index date), (3) past users (prescription within 30-180 days before the index date; however, the days' supplied ends ≥ 30 days before the index date), and (4) nonusers (no prescriptions within 180 days of the index date).

Table 1. Baseline Characteristics of Cases and Controls by Sex^a

Characteristic	Women		Men	
	Cases (n=1806)	Controls (n=9020)	Cases (n=9432)	Controls (n=46 865)
Age, mean (SD), y	83 (6.3)	83 (6.3)	81 (6.2)	81 (6.1)
Charlson Comorbidity Index, No. (%)				
0	464 (25.7)	2435 (27.0)	2195 (23.3)	11 972 (25.5)
1	309 (17.1)	1210 (13.4)	1332 (14.1)	5573 (11.9)
≥2	658 (36.4)	1692 (18.8)	3877 (41.1)	10 969 (23.4)
Missing	375 (20.8)	3683 (40.8)	2028 (21.5)	18 351 (39.2)
Risk Factors for AUR				
Comorbidities associated with increased AUR risk, No. (%)				
Diabetes mellitus	162 (9.0)	655 (7.3)	850 (9.0)	4029 (8.6)
Benign prostatic hyperplasia	NA	NA	4540 (48.1)	4834 (10.3)
Prostate cancer	NA	NA	1487 (15.8)	3123 (6.7)
Urinary incontinence	93 (5.1)	9 (<0.1)	190 (2.0)	61 (<0.1)
Neurologic disease ^b	330 (18.3)	757 (8.4)	1484 (15.7)	4358 (9.3)
Anticholinergic burden, median, IQR ^c	3 (1-5)	1 (0-3)	2 (1-4)	1 (0-2)
Markers of COPD Severity, No. (%)				
Clinical factors				
Duration of COPD, y				
<2	424 (23.5)	2108 (23.4)	2129 (22.6)	10 585 (22.6)
2-5	390 (21.6)	1952 (21.6)	2042 (21.6)	10 096 (21.5)
>5	992 (54.9)	4960 (55.0)	5261 (55.8)	26 184 (55.9)
Oral corticosteroid use	228 (12.6)	668 (7.4)	1103 (11.7)	3106 (6.6)
Inhaled corticosteroid use	361 (20.0)	1428 (15.8)	1644 (17.4)	6531 (13.9)
Long-acting β-agonist use	294 (16.3)	1150 (12.7)	1745 (18.5)	6035 (12.9)
Health services use				
No. of outpatient physician claims				
0	≤5 (<0.1)	423 (4.7)	31 (0.3)	3195 (6.8)
≥1	1805 (>99.9)	8597 (95.3)	9401 (99.7)	43 670 (93.2)
No. of outpatient respiratory claims by a respirologist or pulmonologist				
0	1574 (87.2)	8321 (92.3)	8132 (86.2)	42 743 (91.2)
≥1	232 (12.8)	699 (7.7)	1300 (13.8)	4122 (8.8)
No. of hospitalizations for COPD				
0	1689 (93.5)	8743 (96.9)	8721 (92.5)	45 201 (96.4)
≥1	117 (6.5)	277 (3.1)	711 (7.5)	1664 (3.6)
No. of ICU admissions				
0	1652 (91.5)	8745 (97.0)	8604 (91.2)	44 740 (95.5)
≥1	154 (8.5)	275 (3.0)	828 (8.8)	2125 (4.5)

Abbreviations: AUR, acute urinary retention; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; NA, not applicable.

^aThe presence of comorbid conditions or the use of specific medications was assessed in the 12 months before the index date.

^bIncludes multiple sclerosis, Parkinson disease, hemiparaplegia or paraplegia, and stroke.

^cIndividual scores for all medications (excluding topical or inhaled drugs) that an individual used within 3 months before the index date were summed to determine the total Anticholinergic Drug Scale score.²⁴

Type of IAC Exposure

To capture the effect of initiating different treatment regimens, we further classified new users as follows: (1) short-acting monotherapy users as those who initiated use of an SAAC (ipratropium products) within 30 days before the index date (without prior evidence of any IAC use in the preceding 180 days) and (2) long-acting monotherapy users as those who initiated use of an LAAC (tiotropium bromide 18-µg capsule delivered via an inhaler) within 30 days before the index date (without prior evidence of any IAC use in the preceding 180 days). To capture those dispensed both an SAAC and LAAC, we defined combination users as those who had evidence of use of one type of IAC within 180 days before the index date together with evidence of a new prescription for a second type of IAC within 30 days of the index date.

COVARIATES

Analyses were conducted separately between men and women because of the known differential risk of AUR in these groups.^{15,16} Potential confounders and known risk factors for AUR were identified from the literature.^{15,22} Comorbidity (using the Charlson Comorbidity Index²³), AUR risk factors, and COPD disease severity were characterized for cases and controls (**Table 1**). Because pulmonary function measures were unavailable within the administrative databases, COPD disease severity was assessed using proxy measures, including duration of COPD, use of respiratory medications, and health services use. A validated scale of total anticholinergic drug burden, the Anticholinergic Drug Scale, which excludes topical and inhaled medications, was used for this study.^{24,25} Using this scale, drugs were rated in an ordinal fashion from 0 to 3, with 0 signifying no known anticholin-

Table 2. Risk of Acute Urinary Retention in Men and Women Having Chronic Obstructive Pulmonary Disease Treated With Inhaled Anticholinergic Medication

Inhaled Anticholinergic Medication Use	No. (%)		Odds Ratio (95% Confidence Interval)	
	Cases	Controls	Matched ^a	Adjusted ^b
Men	(n=9432)	(n=46 865)		
New users	273 (2.9)	830 (1.8)	1.90 (1.65-2.19)	1.42 (1.20-1.68)
Current users	2450 (26.0)	8105 (17.3)	1.77 (1.67-1.86)	1.36 (1.26-1.46)
Past users	407 (4.3)	1607 (3.4)	1.48 (1.32-1.66)	1.18 (1.00-1.35)
Nonusers	6302 (66.8)	36 323 (77.5)	1.0 [Reference]	1.00 [Reference]
Women	(n=1806)	(n=9020)		
New users	30 (1.7)	165 (1.8)	0.99 (0.67-1.48)	0.71 (0.46-1.09)
Current users	397 (22.0)	1327 (14.7)	1.68 (1.48-1.91)	1.13 (0.97-1.33)
Past users	76 (4.2)	279 (3.1)	1.53 (1.18-1.99)	1.15 (0.86-1.53)
Nonusers	1303 (72.1)	7249 (80.4)	1.0 [Reference]	1.00 [Reference]

^aUp to 5 controls were matched to each case on age (± 1 y) and duration of time in cohort.

^bAdjusted for Anticholinergic Drug Scale score, benign prostatic hyperplasia, prostate cancer, benign prostatic hyperplasia medications, neurologic disease, diabetes mellitus, Charlson Comorbidity Index, urinary incontinence, and medications in the year before the index date (oral corticosteroids, inhaled corticosteroids, and long-acting β -agonists), as well as number of admissions for chronic obstructive pulmonary disease, number of admissions to the intensive care unit, number of visits to any physician, and number of visits to a respirologist or pulmonologist in the year before the index date.

ergic activity (eg, ampicillin) and 3 signifying marked anticholinergic activity (eg, oxybutinin chloride). The individual scores for all medications (excluding topical or inhaled medication) that an individual received within 3 months before the index date were summed to determine the total Anticholinergic Drug Scale score.

SENSITIVITY ANALYSIS

We evaluated the risk of AUR in a high-risk subgroup of individuals with evidence of BPH based on *ICD-9* or *ICD-10* diagnostic codes (*ICD-9* code 600 or *ICD-10* code N40) who did not have evidence of resection of the prostate, which was identified using procedural fee codes found within the Ontario Billing Claims database. This group would be expected to have an elevated risk for developing the outcome because BPH is a known risk factor for AUR. As well, resection of the prostate improves urinary flow and corrects bladder neck obstruction; therefore, the absence of a prostate resection would place these individuals in a high-risk category. We conducted separate analyses depending on the source of the outcome (eg, AUR identified through a hospitalization vs same-day surgery visit vs emergency department visit) to evaluate the robustness of our findings.

STATISTICAL ANALYSIS

Descriptive summary statistical analysis was performed on characteristics at the index date, comparing cases and controls by sex. Multivariable conditional logistic regression analysis was used to assess the relationship between IAC exposure and the development of AUR after controlling for potential confounders. All analyses were stratified by sex. Analyses were performed using nonusers as the reference group; however, when evaluating the type of treatment regimen, an additional analysis was conducted using SAAC monotherapy users as the reference group. All analyses were performed using commercially available statistical software (SAS, version 9.2; SAS Institute, Cary, North Carolina). We used a 2-sided test of significance at the $P < .05$ level.

ESTIMATE OF ABSOLUTE RISK OF IAC EXPOSURE

To estimate the absolute risk of IAC exposure, we calculated the number needed to harm (NNH) using the approach sug-

gested by Bjerre and LeLorier.²⁶ The NNH refers to the number of patients needed to be treated with a medication for 1 additional patient to be harmed. The unexposed event rate (UER) of developing AUR within a certain window (30 or 180 days) in individuals who were not exposed to IACs was approximated using the rate of AUR in unexposed individuals with COPD per person per day of being at risk. Unexposed individuals were followed up from cohort enrollment date (date of COPD diagnosis) for a maximum of 30 (or 180) days or until they developed AUR, a regimen of IACs was started, or the end of the study period was reached (whichever came sooner). We then calculated the NNH using the following equation: $NNH = 1 / (OR - 1)UER$, where OR indicates the odds ratio.

RESULTS

STUDY FINDINGS

We identified 565 073 individuals (51.1% male) within the COPD database who were aged 66 years and older. A total of 1368 were excluded because of a history of AUR. The mean (SD) age of the COPD cohort was 76.0 (7.1) years, and participants were followed up within the COPD database for a median of 4.5 (interquartile range, 1.6-8.8) years. During the study period, 9432 men and 1806 women developed AUR.

The baseline characteristics of the cases and their matched controls by sex are summarized in Table 1. As expected, cases had a higher proportion of individuals with evidence of risk factors associated with AUR, such as a history of prostate disease (in men only), neurologic disease, and urinary incontinence.

ASSOCIATION BETWEEN IAC EXPOSURE AND THE DEVELOPMENT OF AUR

Men with COPD taking IACs were at increased risk of developing AUR, whereas this relationship was not statistically significant in women (**Table 2**). Compared with

Table 3. Risk of Acute Urinary Retention in Men Having Chronic Obstructive Pulmonary Disease and Evidence of Benign Prostatic Hyperplasia Without Prostate Resection Before the Study Outcome

	No. (%)		Odds Ratio (95% Confidence Interval)	
	Cases (n=5090)	Controls (n=21 615)	Matched ^a	Adjusted ^b
Inhaled Anticholinergic Medication Use				
New user	159 (3.1)	398 (1.8)	2.12 (1.74-2.58)	1.81 (1.46-2.24)
Current user	1353 (26.6)	3857 (17.8)	1.75 (1.63-1.89)	1.48 (1.35-1.63)
Past user	223 (4.4)	781 (3.6)	1.38 (1.17-1.62)	1.16 (0.98-1.39)
Nonuser	3355 (65.9)	16 579 (76.7)	1.00 [Reference]	1.00 [Reference]

^aUp to 5 controls were matched to each case.
^bAdjusted for the same variables as in Table 2.

Table 4. Risk of Acute Urinary Retention in Men Who Are New Users of Inhaled Anticholinergic Medication Combination Therapy vs Monotherapy

	No. (%)		Odds Ratio (95% Confidence Interval)	
	Cases (n=347)	Controls (n=936)	Matched ^a	Adjusted ^b
Inhaled Anticholinergic Medication Use				
Combination therapy	83 (23.9)	124 (13.2)	2.00 (1.44-2.78)	1.84 (1.25-2.71)
LAAC monotherapy	88 (25.4)	290 (31.0)	0.90 (0.67-1.21)	0.89 (0.63-1.27)
SAAC monotherapy	176 (50.7)	522 (55.8)	1.00 [Reference]	1.00 [Reference]

Abbreviations: LAAC, long-acting inhaled anticholinergic drug; SAAC, short-acting inhaled anticholinergic drug.
^aUp to 5 controls were matched to each case.
^bAdjusted for the same variables as in Table 2.

nonusers, men who were new users of IAC therapy were at increased risk of AUR (adjusted OR, 1.42; 95% CI, 1.20-1.68), with current users at slightly lower but still significantly increased risk (OR, 1.36; 95% CI, 1.26-1.46). The adjusted OR for past users was not significantly different from that for nonusers.

In the high-risk group of men with evidence of BPH without a history of a prostate resection, the results were consistent with our expectations of heightened risk. For men newly initiating a regimen of IACs, the adjusted OR increased from 1.42 to 1.81 (95% CI, 1.46-2.24), and that of current users increased from 1.36 to 1.48 (1.35-1.63) (**Table 3**). Using the baseline 30-day event rate for unexposed men with BPH and no history of a prostatectomy (0.0024 events per 30 days) and the adjusted OR associated with new use of IACs for this group (OR, 1.81), the estimated NNH was 514 (95% CI, 336-905). The baseline 180-day event rate for unexposed men with BPH and no history of prostatectomy was 0.00792 events per 180 days; therefore, using the adjusted OR of 1.48, current users of IACs had an estimated NNH of 263 (95% CI, 200-361).

When men who were new users of IACs were categorized by treatment regimen (combination therapy, LAAC monotherapy, or SAAC monotherapy), individuals receiving combination therapy had a significantly higher risk of AUR compared with monotherapy users of an SAAC or LAAC (OR, 1.84; 95% CI, 1.25-2.71) (**Table 4**). The risk of AUR was similar for individuals receiving LAAC or SAAC monotherapy. Comparing therapeutic regimens with nonuse, those receiving combination therapy had the highest risk of AUR (OR, 2.69; 95% CI, 1.93-3.76).

COMMENT

Our study demonstrated a significant relationship between IAC use and AUR in individuals with COPD. Men newly initiating a regimen of IAC therapy had a more than 40% greater odds of AUR compared with nonusers. When considering the treatment regimen prescribed, male new users of combination IAC therapy were at increased risk for AUR compared with nonusers, as well as compared with monotherapy users of an LAAC or SAAC. Furthermore, we found that men with BPH who were dispensed IACs had in excess of 80% greater odds of AUR compared with nonusers. According to our risk estimates, for men with BPH newly initiating a regimen of IACs, 1 in 514 will experience this adverse event, whereas among men who are current users of IACs, 1 in 263 will experience AUR.

In men who were new users of IAC therapy, AUR occurred acutely within 30 days (median, 14 days) of starting the medication, further strengthening a possible causal relationship. These data suggest that individuals may benefit from close monitoring for signs and symptoms of impending urinary retention within the first month of starting IACs. Within our cohort, we found that 79.2% of men who were new users of IACs had an encounter with a physician between exposure and the development of the outcome. This provides an opportunity in which individuals could be assessed by the medical team to evaluate changes in urinary symptoms and to consider possible preventive or therapeutic interventions.

Our results are consistent with clinical trials that have documented an increased risk of urinary retention among individuals using IACs and further quantify the associa-

tion in a large population-based sample.^{5,11,13} Afonso et al¹¹ recently published a study with similar results, showing that the highest risk of AUR was in men with evidence of BPH. Our results differed from those by Miyazaki et al¹⁰ in that we documented a substantial risk of AUR in individuals with COPD who had BPH. This may be the result of our significantly larger sample size and the fact that we did not exclude individuals using other anticholinergic medications (oral or inhaled), making our results more representative of clinical practice and generalizable to the overall population with COPD.

The lack of an effect among women observed in our study could be a reflection of the small sample size within this subgroup, resulting in decreased power to detect a difference between users and nonusers rather than a true null effect. Previous epidemiological studies^{15,16,27} have shown that the risk of urinary retention is substantially lower in women. Anatomical differences in the genitourinary tract between men and women may result in the differential risk for AUR observed in our study.

Although our study showed an increased risk of AUR in certain high-risk individuals, individual risks and benefits must be considered when prescribing therapies. We suggest that the association between respiratory inhaler use and bladder dysfunction may be underappreciated by the medical profession and by the public. Although the tiotropium product insert states that the use of this medication may worsen signs and symptoms associated with prostatic hyperplasia and bladder neck obstruction, given the content of the Canadian Thoracic Society⁷ and the American Thoracic Society and European Respiratory Society⁸ COPD guidelines and the fact that several individuals in our cohort with known risk factors were prescribed IACs, we believe that the potential for this adverse event may not be well recognized. Physicians should highlight for patients the possible connection between urinary symptoms and inhaled respiratory medication use to ensure that changes in urinary flow (ie, incomplete voiding, urinary incontinence, and decreased urinary flow) are reported to the physician prescribing the IAC. Making the connection between inhaled respiratory medication use and urinary retention may also prevent polypharmacy. Individuals with bladder neck obstruction may receive a prescription for another drug, such as an α -adrenergic antagonist, to treat their symptoms rather than consider the effect their inhaler use may have on bladder dysfunction. Instead, a careful review of one's medications and the use of the lowest effective dose of all prescribed anticholinergic medications (inhaled and oral) might reduce the risk of AUR.

There are several limitations of our study that merit attention. First, we were unable to assess drug dosage because individuals are often given flexibility in the frequency with which they use these medications. However, those receiving combination therapy, which is presumably a higher overall daily dose of drug, had the highest risk of AUR, suggestive of a dose-response relationship. Some combination users may have actually switched between short- or long-acting IACs rather than use them concurrently. Second, the administrative databases used in this study lack patient-level data on variables like lung function, smoking history, and renal impairment, as well as

precise measures of COPD disease severity, which are potential confounders in our study. We cannot be certain there were not differences between groups, uncontrolled or unmeasured, resulting in residual confounding that may have affected our results. We carefully considered multiple risk factors and potential confounders in our study design and matched or adjusted for these in the final analysis to minimize this potential bias. Third, the drug data identified dispensed medications but not whether individuals were taking them. Therefore, some exposure groups may have been misclassified, and caution should be exercised when using prescription data as a proxy for drug use. Fourth, we may have identified individuals with chronic urinary retention rather than AUR, particularly in those captured using the Same-Day Surgery database. The most common procedure conducted in this group was cystoscopy, and it is possible that these individuals had chronic urinary retention. A sensitivity analysis that excluded those cases and corresponding controls identified using the Same-Day Surgery database showed consistent results, suggesting that our findings are robust (data not shown). Fifth, we used a COPD algorithm with a specificity of 78%; therefore, data on some individuals may represent false-positive COPD diagnoses. While this may be true, the findings are not dependent on the diagnosis of COPD, as we are interested in the exposure of the drug. The accuracy and completeness of the drug exposure are critical to the findings, and the Ontario Drug Benefit database has a low error rate.¹⁹ Sixth, we included only individuals seen in a hospital setting and did not consider those who were treated solely in ambulatory outpatient clinics, whose condition presumably would be better overall. Given the fact that AUR is a urological emergency requiring an intervention, we believe that it is unlikely that physicians would manage this in their office but rather would refer the individual to the hospital for evaluation and treatment.

In conclusion, the use of short- and long-acting IACs is associated with an increased risk of AUR in men with COPD. Individuals at highest risk were men prescribed both short- and long-acting IACs concomitantly and those with evidence of BPH. Physicians and the public need to be aware of the potential for this significant adverse event so that preventive measures and potential therapy can be considered.

Accepted for Publication: February 6, 2011.

Correspondence: Anne Stephenson, MD, PhD, Department of Medicine and Keenan Research Centre in the Li Ka Shing Knowledge Institute of St Michael's Hospital, 30 Bond St, Sixth Floor, Toronto, ON M5B 1W8, Canada (stephensona@smh.ca).

Author Contributions: Dr Stephenson had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit the manuscript for publication. *Study concept and design:* Stephenson, Bell, Gruneir, Anderson, Rochon, and Gill. *Acquisition of data:* Stephenson and Fu. *Analysis and interpretation of data:* Stephenson, Seitz, Bell, Gruneir, Gershon, Austin, Anderson, Rochon, and Gill. *Drafting of the manuscript:* Stephenson, Seitz, Bell, Gruneir, Rochon, and Gill. *Critical revision of the manuscript for important intellectual content:* Stephenson, Seitz, Bell, Gruneir, Gershon,

Rochon, and Gill. *Statistical analysis*: Stephenson, Austin, and Fu. *Obtained funding*: Anderson and Rochon. *Study supervision*: Rochon and Gill.

Financial Disclosure: None reported.

Funding/Support: This study was funded by team grant OTG-88591 from the Canadian Institutes of Health Research and was conducted at the Insitutute 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 Sponsor: The study sponsor did not participate in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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.

REFERENCE

1. Gershon AS, Wang C, Wilton AS, Raut R, To T. Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in Ontario, Canada, 1996 to 2007: a population-based study. *Arch Intern Med*. 2010;170(6):560-565.
2. van Noord JA, Bantje TA, Eland ME, Korducki L, Cornelissen PJ; The Dutch Tiotropium Study Group. A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. *Thorax*. 2000;55(4):289-294.
3. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV₁: the Lung Health Study. *JAMA*. 1994;272(19):1497-1505.
4. Barnes PJ. Muscarinic receptor subtypes in airways. *Life Sci*. 1993;52(5-6):521-527.
5. Tashkin DP, Celli B, Senn S, et al; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543-1554.
6. Boehringer Ingelheim. Annual report 2009: value through innovation. http://www.boehringer-ingenheim.com/content/dam/internet/opu/com_EN/document/01_news/04_Annual_Report/AR_2009_english.pdf. Accessed June 10, 2010.
7. O'Donnell DE, Hernandez P, Kaplan A, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease—2008 update: highlights for primary care. *Can Respir J*. 2008;15(suppl A):1A-8A.
8. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper [published correction appears in *Eur Respir J*. 2006;27(1):242]. *Eur Respir J*. 2004;23(6):932-946.
9. American Thoracic Society and European Respiratory Society. Standards for the diagnosis and management of patients with COPD. 2004. <http://www.thoracic.org/clinical/copd-guidelines/resources/copddoc.pdf>. Accessed March 10, 2011.
10. Miyazaki H, Suda T, Otsuka A, et al. Tiotropium does not affect lower urinary tract functions in COPD patients with benign prostatic hyperplasia. *Pulm Pharmacol Ther*. 2008;21(6):879-883.
11. Afonso AS, Verhamme KM, Stricker BH, Sturkenboom MC, Brusselle GG. Inhaled anticholinergic drugs and risk of acute urinary retention [published online ahead of print September 29, 2010]. *BJU Int*. doi:10.1111/j.1464-410X.2010.09600.x.
12. Pras E, Stienlauf S, Pinkhas J, Sidi Y. Urinary retention associated with ipratropium bromide. *DICP*. 1991;25(9):939-940.
13. Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. *Chest*. 2006;130(6):1695-1703.
14. Singh S, Furberg CD, Loke YK. Tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2009;360(2):186-187.
15. Verhamme KM, Sturkenboom MC, Stricker BH, Bosch R. Drug-induced urinary retention: incidence, management and prevention. *Drug Saf*. 2008;31(5):373-388.
16. Cathcart P, van der Meulen J, Armitage J, Emberton M. Incidence of primary and recurrent acute urinary retention between 1998 and 2003 in England. *J Urol*. 2006;176(1):200-204.
17. Armitage JN, Sibanda N, Cathcart PJ, Emberton M, van der Meulen JH. Mortality in men admitted to hospital with acute urinary retention: database analysis. *BMJ*. 2007;335(7631):1199-1202.
18. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicuto L, To T. Identifying individuals with physician diagnosed COPD in health administrative databases. *COPD*. 2009;6(5):388-394.
19. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol*. 2003;10(2):67-71.
20. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care*. 2002;25(3):512-516.
21. Verhamme KM, Dieleman JP, Van Wijk MA, et al. Nonsteroidal anti-inflammatory drugs and increased risk of acute urinary retention. *Arch Intern Med*. 2005;165(13):1547-1551.
22. Roehrborn CG. Acute urinary retention: risks and management. *Rev Urol*. 2005;7(suppl 4):S31-S41.
23. Deyo RA, Cherkov DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.
24. Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol*. 2006;46(12):1481-1486.
25. Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med*. 2001;161(8):1099-1105.
26. Bjerre LM, LeLorier J. Expressing the magnitude of adverse effects in case-control studies: "the number of patients needed to be treated for one additional patient to be harmed." *BMJ*. 2000;320(7233):503-506.
27. Klarskov P, Andersen JT, Asmussen CF, et al. Acute urinary retention in women: a prospective study of 18 consecutive cases. *Scand J Urol Nephrol*. 1987;21(1):29-31.

INVITED COMMENTARY

Inhaled Anticholinergics for Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is the third leading cause of death in the United States and is one of the only major diseases for which the mortality rate is rising.¹ Apart from respiratory causes, the major causes of death among patients with COPD include cardiovascular death and infectious complications, such as pneumonia. The SAAC ipratropium and LAAC tio-

tropium and the long-acting β_2 -agonist inhaled corticosteroid combination inhalers are approved for use in the United States. The benefits of IACs include their ability to provide symptomatic relief, to reduce exacerbations (by approximately 13%-25%), and to modestly improve forced expiratory volume in the first second of expiration. However, none of the marketed agents slow the progressive de-