Elevated Bladder and Prostate Cancer Rates Following Initiation of OAB Medication: Findings From the Danish Registries, 2004-2012

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CONFLICT OF INTEREST

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BACKGROUND

- Overactive bladder (OAB) is defined as urgency, with or without urge incontinence; it is usually experienced with frequency and nocturia.
- Symptoms reported by patients with undiagnosed genitourinary cancers, including prostate cancer and bladder cancer, may be confused with symptoms of OAB.
- Cancer risks associated with the use of individual drugs to treat OAB are not known.

OBJECTIVE

- To estimate the incidence rates (IRs) of genitourinary cancers and other common cancers in initiators of antimuscarinic OAB drugs in the Danish national registries, overall and stratified by time since first prescription.

METHODS

Study Design and Population

- A nationwide retrospective cohort study of new users of darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium in years 2004-2012, aged ≥ 18 years, with no history of cancer before entry
- Follow-up ended with cancer diagnosis, death, disenrollment, or end of study

Drug Exposure

- Ever use was defined as having filled at least one ambulatory prescription for any OAB medication, according to the Danish National Prescription Registry

Outcomes

- 10 most commonly occurring malignancies (excluding nonmelanoma skin cancer): bladder, breast (female), colon and rectum, lung and bronchus, melanoma of skin, non-Hodgkin lymphoma, kidney and renal pelvis, pancreas, prostate, corpus uteri
- Incident cases ascertained from the Danish Cancer Registry

Statistical Analyses

- Estimated age-and-sex standardized IRs per 1,000 person-years and 95% confidence intervals (CIs), overall and by categories of months since cohort entry for each study cancer (two sex-specific composite cancer endpoints and the individual cancers)

RESULTS

- Cohort of 72,917 patients, 60% women, mean age at entry of 66 years (Table 1)
- Follow-up: 259,072 person-years
- Study cancers: 3,475 patients (1,832 men, 1,643 women)
- Most frequent study cancers: prostate (881; 25.4% of study cancers), breast (658; 18.9%), lung (534; 15.4%), colorectal (434; 12.5%), bladder (369; 10.6%)
- Overall study cancer standardized IRs (95% CI): 6.2 per 1,000 person-years (6.0-6.5) in men and 4.6 (4.4-4.9) in women
- Minimal variation in cancer IRs was observed across OAB drug used (Table 2)
- Bladder cancer standardized IR (95% CI) (Figure 1): highest for < 6 months since cohort entry (19. [1.6-2.3]), lower for 6 to < 12 months since cohort entry (0.5 [0.4-0.7]) and thereafter
- Prostate cancer standardized IR (95% CI) (Figure 1): highest for < 6 months since cohort entry (7.2 [6.5-8.1]), lower for 6 to < 12 months since cohort entry (2.7 [2.2-3.2]) and thereafter
- Other cancer IRs did not show this effect of time since cohort entry

DISCUSSION

Limitations

- Adjustment for potential confounders is limited in the estimates we present. Although we did not see important differences across users of the study medications, more complete adjustment is planned for the next phase of this study.
- We relied on dispensed prescriptions for drug utilization. We do not expect noncompliance or unrecorded use to be substantial or to affect one study drug more than others.

Strengths

- The nationwide Danish registers cover the entire Danish population.
  - This is especially important for the Danish Cancer Registry, which is critical for ascertainment of the cancer outcomes in this study.
  - The use of census data allowed for tracking of all patients and accounted for migration in or out of the population.
- We compared users of different OAB medications rather than users and nonusers, thus reducing confounding by design.
  - These comparative safety results are the most relevant information for clinicians who need to treat patients with OAB.

Context

- These findings are in line with the results of a study in the United Kingdom conducted with the same common protocol presented at ICPE in 2015,[1] and a study in Sweden, presented at this conference.[2]

CONCLUSIONS

- Protopathic bias (reverse causation) and/or detection bias are plausible explanations for higher IRs of bladder and prostate cancers in the first 6 months after starting OAB drug treatment.
- These findings are in line with results from other studies and must be considered in etiologic studies of OAB drugs and cancer risk.

Table 1. Patient Characteristics at Cohort Entry by OAB Antimuscarinic Drug Received at Cohort Entry

Patient Characteristic	OAB Antimuscarinic Drug Received at Cohort Entry, n (%)						
	Darifenacin (n = 2,698)	Fesoterodine (n = 5,749)	Oxybutynin (n = 740)	Solifenacin (n = 30,792)	Tolterodine (n = 23,776)	Trospium (n = 9,105)	Multiple Drugs (n = 57)
Age at cohort entry (years)							
Median (interquartile range)	69 (59-78)	67 (56-76)	66 (55-76)	68 (57-77)	69 (58-78)	68 (56-77)	60 (41-71)
18-54	504 (18.7)	1,339 (23.3)	175 (23.6)	6,415 (20.8)	4,498 (18.9)	2,066 (22.7)	25 (43.9)
55-64	523 (19.4)	1,155 (20.1)	158 (21.4)	6,200 (20.1)	4,719 (19.8)	1,786 (19.6)	10 (17.5)
65-74	712 (26.4)	1,660 (28.9)	201 (27.2)	8,304 (27.0)	6,194 (26.1)	2,386 (26.2)	11 (19.3)
75-84	671 (24.9)	1,143 (19.9)	147 (19.9)	6,984 (22.7)	5,903 (24.8)	2,047 (22.5)	10 (17.5)
85+	288 (10.7)	452 (7.9)	59 (8.0)	2,889 (9.4)	2,462 (10.4)	820 (9.0)	1 (1.8)
Female	**1,768 (65.5)**	**3,407 (59.3)**	**597 (80.7)**	**18,353 (59.6)**	**13,812 (58.1)**	**5,466 (60.0)**	**31 (54.4)**
Comorbidity							
Ever smoking	246 (9.1)	666 (11.6)	72 (9.7)	3,437 (11.2)	2,347 (9.9)	937 (10.3)	5 (8.8)
Obesity	176 (6.5)	548 (9.5)	64 (8.6)	2,215 (7.2)	1,327 (5.6)	624 (6.9)	3 (5.3)
Hypertension	561 (20.8)	1,416 (24.6)	175 (23.6)	6,974 (22.6)	5,012 (21.1)	1,903 (20.9)	10 (17.5)
Diabetes	207 (7.7)	500 (8.7)	55 (7.4)	2,413 (7.8)	1,881 (7.9)	713 (7.8)	4 (7.0)
Hormone-replacement therapy	1,237 (45.8)	2,286 (39.8)	449 (60.7)	11,931 (38.7)	8,370 (35.2)	3,522 (38.7)	19 (33.3)

Note: Information on comorbidities is based on ambulatory dispensed prescriptions from the Danish Prescription Registry and diagnoses in the Danish National Registry of patients, using all available information prior to the cohort entry.

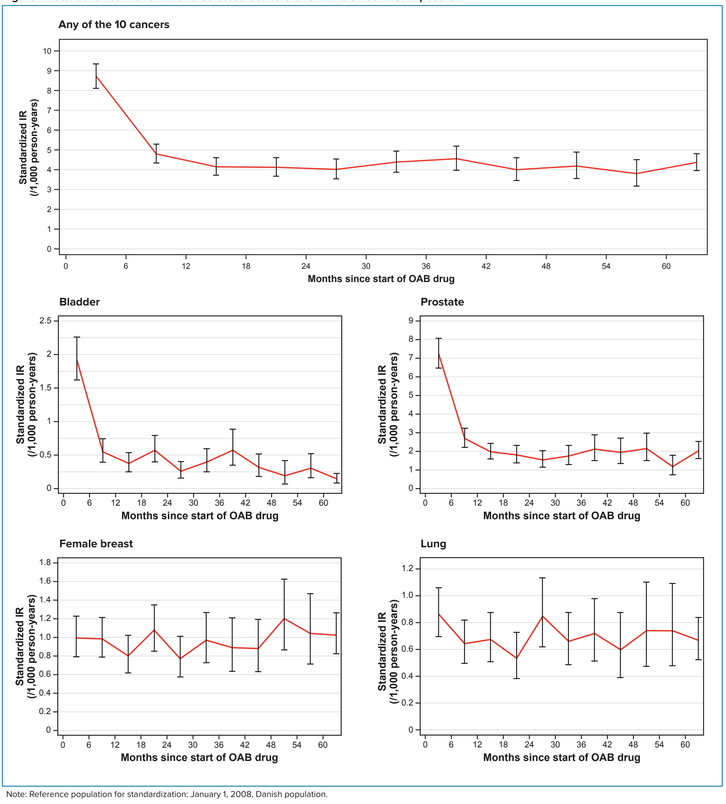
Table 2. Standardized IRs (95% CI) for Individual Cancer Types, by Sex and OAB Medication

(Blue shading indicates the smallest point estimate for individual drugs in the row; green shading indicates the largest.)

Cancer Type	Standardized IR (95% CI)						
	Any OAB Drug	Darifenacin	Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium
Any study cancer							
Women	4.6 (4.4-4.9)	4.8 (4.0-5.7)	5.3 (4.5-6.2)	4.8 (3.8-6.0)	4.8 (4.5-5.2)	4.6 (4.3-4.9)	4.8 (4.3-5.4)
Men	6.2 (6.0-6.5)	6.8 (5.5-8.3)	6.8 (5.7-7.9)	7.2 (5.1-10.0)	6.4 (6.0-6.9)	5.9 (5.5-6.3)	6.7 (6.0-7.5)
Bladder							
Women	0.3 (0.2-0.3)	0.5 (0.3-0.9)	0.5 (0.3-0.8)	0.3 (0.1-0.6)	0.3 (0.2-0.4)	0.3 (0.2-0.3)	0.3 (0.2-0.5)
Men	1.0 (0.9-1.1)	1.0 (0.6-1.7)	1.3 (0.9-1.9)	2.6 (1.2-4.7)	1.4 (1.2-1.6)	0.9 (0.7-1.1)	0.8 (0.6-1.1)
Breast							
Women	2.1 (1.9-2.2)	2.3 (1.8-3.0)	3.2 (2.6-3.9)	2.8 (2.0-3.8)	2.3 (2.1-2.6)	2.2 (1.9-2.4)	2.5 (2.1-2.9)
Colorectal							
Women	0.6 (0.5-0.6)	0.7 (0.4-1.0)	1.0 (0.7-1.4)	0.6 (0.3-1.1)	0.6 (0.5-0.8)	0.6 (0.5-0.7)	0.7 (0.5-0.9)
Men	0.7 (0.6-0.8)	0.5 (0.3-1.0)	1.4 (0.9-2.0)	0.8 (0.3-1.7)	0.7 (0.6-0.9)	0.8 (0.6-0.9)	0.8 (0.6-1.2)
Kidney/renal pelvis							
Women	0.1 (0.1-0.2)	0.2 (0.1-0.5)	0.2 (0.1-0.5)	0.1 (0.0-0.5)	0.2 (0.1-0.3)	0.1 (0.1-0.2)	0.1 (0.0-0.2)
Men	0.1 (0.1-0.2)	0.0 (0.0-0.2)	0.2 (0.1-0.4)	0.3 (0.0-1.1)	0.2 (0.1-0.3)	0.1 (0.1-0.2)	0.1 (0.1-0.3)
Lung/bronchus							
Women	0.7 (0.6-0.8)	0.6 (0.4-1.0)	1.1 (0.8-1.6)	1.1 (0.6-1.7)	0.7 (0.6-0.9)	0.8 (0.6-0.9)	0.7 (0.5-1.0)
Men	0.9 (0.8-1.0)	1.5 (0.9-2.3)	1.3 (0.9-1.8)	1.0 (0.5-2.1)	0.9 (0.8-1.1)	0.7 (0.6-0.9)	0.8 (0.6-1.0)
Melanoma							
Women	0.3 (0.2-0.4)	0.4 (0.2-0.8)	0.5 (0.3-0.9)	0.3 (0.1-0.7)	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.4 (0.2-0.6)
Men	0.3 (0.2-0.4)	0.1 (0.0-0.4)	0.4 (0.2-0.7)	0.7 (0.1-2.5)	0.3 (0.2-0.4)	0.4 (0.3-0.5)	0.5 (0.3-0.8)
Non-Hodgkin lymphoma							
Women	0.1 (0.1-0.2)	0.1 (0.0-0.3)	0.2 (0.1-0.5)	0.1 (0.0-0.4)	0.2 (0.1-0.2)	0.1 (0.0-0.1)	0.1 (0.1-0.3)
Men	0.1 (0.1-0.2)	0.1 (0.0-0.4)	0.2 (0.1-0.5)	1.1 (0.0-6.0)	0.2 (0.1-0.3)	0.2 (0.1-0.2)	0.3 (0.1-0.5)
Pancreas							
Women	0.2 (0.1-0.2)	0.1 (0.0-0.2)	0.1 (0.0-0.3)	0.3 (0.1-0.6)	0.2 (0.2-0.3)	0.2 (0.1-0.2)	0.3 (0.1-0.4)
Men	0.2 (0.2-0.3)	0.1 (0.0-0.4)	0.3 (0.1-0.6)	0 (0.0-1.8)	0.2 (0.2-0.3)	0.2 (0.1-0.2)	0.4 (0.2-0.7)
Prostate							
Men	2.9 (2.7-3.1)	4.4 (3.3-5.7)	6.3 (5.2-7.4)	3.4 (2.1-5.1)	3.4 (3.1-3.7)	3.1 (2.8-3.4)	3.9 (3.3-4.5)
Uterus							
Women	0.3 (0.2-0.4)	0.3 (0.1-0.6)	0.3 (0.1-0.5)	0.4 (0.1-0.7)	0.4 (0.3-0.5)	0.3 (0.2-0.4)	0.2 (0.1-0.3)

Note: Reference population for standardization: January 1, 2008, Danish population.

Figure 1. Standardized IRs for All and Selected Cancers Over Time Since First Exposure



Note: Reference population for standardization: January 1, 2008, Danish population.

ABSTRACTS FROM THIS PROGRAM ALSO PRESENTED IN THIS CONFERENCE

Arana A, et al. **Do individual antimuscarinic drugs to treat overactive bladder have different cardiovascular risks? A UK CPRD cohort study.** Abstract #920. Poster Session C: Safety & Effectiveness - GU & Hormones, Sunday, 28 August 2016, 8:00 AM-1:45 PM.

Fortuny J, et al. **Evaluation of free-text comments to validate common cancer diagnoses in the UK CPRD.** Abstract #91. Poster Session A: Spotlight Session-Databases, Friday, 26 August 2016, 8:00 AM-6:00 PM.

Hallas J, et al. **Incidence of cardiovascular events in new users of overactive bladder medications in Denmark.** Abstract #848. Oral presentation in session CV Adverse Events: Affairs of the Heart, Sunday, 28 August 2016, 3:15 PM-4:45 PM.

Linder M, et al. **Cancer risk in users of antimuscarinic drugs for overactive bladder: a cohort study in the Swedish national registers.** Abstract #919. Poster Session C: Safety & Effectiveness - GU & Hormones, Sunday, 28 August 2016, 8:00 AM-1:45 PM.

Linder M, et al. **Cardiovascular risk in users of antimuscarinic drugs for overactive bladder: a cohort study in the Swedish national registers.** Abstract #849. Oral presentation in session CV Adverse Events: Affairs of the Heart, Sunday, 28 August 2016, 3:15 PM-4:45 PM.

Margulis AV, et al. **Patterns of use of antimuscarinic drugs to treat overactive bladder in Denmark, Sweden, and the United Kingdom.** Abstract #1126. Poster Session C: DUR - Trends in GU and Hormones, Sunday, 28 August 2016, 8:00 AM-1:45 PM.

Margulis AV, et al. **Validation of cardiovascular events and covariates in CPRD GOLD using questionnaires to general practitioners.** Abstract #437. Oral presentation in session Identification and Validation of Outcomes, Saturday, 27 August 2016, 8:00 AM-9:30 AM.

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2. Linder M, Margulis AV, Anveden-Berglind I, Bahmanyar S, Bui C, Atsma WJ, et al. Cancer risk in users of antimuscarinic drugs for overactive bladder: a cohort study in the Swedish National Registers. Presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management; August 25-28, 2016. Dublin, Ireland.

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