Do Individual Antimuscarinic Drugs to Treat Overactive Bladder Have Different Cardiovascular Risks? A UK CPRD Cohort Study

Alejandro Arana,[1] Cristina Varas-Lorenzo,[1] Lisa J. McQuay,[2] Ryan Ziemiecki,[2] Christine L. Bui,[2] Alicia W. Gilsenan,[2] Kenneth J. Rothman,[3] Willem J. Atsma,[4] Kwame Appenteng,[5] Billy Franks,[4] Stefan de Vogel,[4] Milbhor D'Silva,[5] Andrea V. Margulis,[1] Susana Perez-Gutthann[1]

[1]RTI Health Solutions, Barcelona, Spain; [2]RTI Health Solutions, Research Triangle Park, NC, United States; [3]RTI Health Solutions, Waltham, MA, United States; [4]Astellas Pharma Europe BV, Leiden, The Netherlands; [5]Astellas Inc. Northbrook, IL, United States

CONFLICT OF INTEREST

A. Arana, L. McQuay, R. Ziemiecki, C. Bui, A. Gilsenan, K.J. Rothman, A. Margulis, and S. Perez-Gutthann are full-time employees of RTI Health Solutions, which received funding from Astellas Pharma Global Development, Inc. to conduct this study. The contract between RTI Health Solutions and the sponsor includes independent publication rights. RTI conducts work for government, public, and private organizations, including pharmaceutical companies. C. Varas-Lorenzo is a former employee of RTI Health Solutions.

W.J. Atsma, K. Appenteng, B. Franks, S. de Vogel, and M. D'Silva are employees of Astellas Pharma Global Development.

BACKGROUND

- Overactive bladder (OAB) is defined as urgency, with or without urge incontinence; it is usually experienced with frequency and nocturia.[1]
- Until recently, antimuscarinic drugs were the only class of drugs approved for the pharmacologic treatment of OAB. These drugs block muscarinic receptors at the neuromuscular junction and prevent acetylcholine-mediated bladder contraction.[2]
- Muscarinic receptors are present throughout the body, and blocking these receptors could affect cardiac function, especially among elderly patients with OAB, who are likely to have cardiovascular (CV) comorbidities and risk factors.
- Adverse cardiac effects associated with antimuscarinic drug use include an increase in heart rate and QT interval prolongation.[3]
- The comparative CV safety of antimuscarinic drugs used to treat OAB is currently unknown.

OBJECTIVE

- To assess the extent to which the risk of acute myocardial infarction (AMI), stroke, CV mortality, major adverse CV events (MACE), and all-cause mortality differed by antimuscarinic OAB drug use, in the context of a larger postapproval safety study requested by the health authorities for mirabegron (a beta-3 adrenergic agonist indicated for the treatment of symptomatic OAB).

METHODS

- **Study cohort:** new users of oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine, aged ≥ 18 years, in the Clinical Practice Research Datalink (CPRD), 2004 to 2012
- **End of follow-up:** study endpoint, cancer, HIV, disenrollment, or end of study
- **Exposure:** ascertained from general practitioner prescriptions
- **Study endpoints:** AMI (out-of-hospital coronary heart disease [CHD] deaths), stroke, CV mortality (CHD death and cerebrovascular disease death), composite endpoint (MACE) (nonfatal AMI, nonfatal stroke, and CV mortality), and all-cause mortality
  - Outcomes and covariates ascertained by medical records and questionnaires completed by general practitioners
- **Incidence rates (IRs) and incidence rate ratios (IRRs):** estimated crude and age-sex–standardized IRs per 1,000 person-years and propensity score–adjusted IRRs compared with current use of any other OAB drug
  - Estimated propensity score through logistic regression, using patients who experienced single exposure to corresponding OAB medications at cohort entry
  - Adjusted for age at cohort entry, sex, calendar year at cohort entry, and comorbidities and exposure to medications identified
  - Trimmed approximately 1% of extreme values in each tail; grouped patients into propensity score strata defined by deciles of the propensity score distribution in "unexposed" (patients in the comparison group)
  - Stratified and aggregated IRRs estimated in propensity-score analyses using the Mantel-Haenszel approach

CONCLUSIONS

- It has been reported that patients with OAB have a higher prevalence of CV comorbidities than persons without such a diagnosis.[5]
  - In our study, the distribution of CV risk factors was relatively similar across users of different OAB drugs, with the possible exception of darifenacin (which had very low use).
- We found elevated IRRs for different CV endpoints for oxybutynin and tolterodine and lower IRRs for solifenacin.
  - The IRRs presented compare current use of a medication with current use of any other OAB drug.
  - We recognize that the lack of a fixed referent group makes IRR estimates for single medications not directly comparable; this approach was selected to align with a wider research program.
  - In our study population, we were able to conduct analysis with a single fixed comparator (tolterodine), and results were in the same direction.

REFERENCES

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al.; Standardisation Sub-Committee of the International Continence Society. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2003;61(1):37-49.
2. Robinson D, Cardozo L. Antimuscarinic drugs to treat overactive bladder. BMJ. 2012;344:e2130.
3. Rosa GM, Bauckneht M, Scala C, Tafi E, Leone Roberti Maggiore U, Ferrero S, et al. Cardiovascular effects of antimuscarinic agents in overactive bladder. Expert Opin Drug Safety. 2013;12(6):815-27.
4. Dobson AJ, Kuulasmaa K, Eberle E, Scherer J. Confidence intervals for weighted sums of Poisson parameters. Stat Med. 1991 Mar;10(3):457-62.
5. Hubeaux K, Deffieux X, Raibaut P, Le Breton F, Jousse M, Amarenco G. Evidence for autonomic nervous system dysfunction in females with idiopathic overactive bladder syndrome. Neurourol Urodyn. 2011 Nov;30(8):1467-72.

CONTACT INFORMATION

Alejandro Arana, MD, MPH, MSc, FISPE
Director, Epidemiology

RTI Health Solutions
Trav. Gracia 56, Atico 1
08006 Barcelona, Spain

Phone: +34.93.362.2805
Fax: +34.93.414.2610
E-mail: aarana@rti.org

ABSTRACTS FROM THIS PROGRAM ALSO PRESENTED IN THIS CONFERENCE

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. **Elevated bladder and prostate cancer rates following initiation of QAB medication: findings from the Danish registries, 2008-2012.** Abstract #918. Poster Session C: Safety & Effectiveness - GU & Hormones, Sunday, 28 August 2016, 8:00 AM-1:45 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.

RESULTS

Patient Characteristics at Cohort Entry (Table 1)

- **Study cohort:** 119,912 new users of OAB drugs: mean age, 62 years; 70% female; mean follow-up, 3.3 years (range, 1 day to 9 years); of all index therapy episodes: 33% oxybutynin, 31% tolterodine, 27% solifenacin
- **Prior recorded diagnosis for OAB (based on Read codes):** about 50% of the study cohort, from 47% in users of oxybutynin to 58% in users of darifenacin

Incidence Rates

- **Standardized IR for any OAB drug (95% confidence interval [CI]):** 4.9 (4.5-5.3) for AMI, 6.0 (5.6-6.4) for stroke, 4.5 (4.2-4.9) for CV mortality, 12.2 (11.6-12.8) for MACE, 19.9 (19.1-20.6) for all-cause mortality (Table 2)

Incidence Rate Ratios

- **IRRs for CV endpoints:** generally approximately 1 for individual antimuscarinic OAB drugs, except for oxybutynin and solifenacin (Figure 1)

Table 1. Characteristics of Exposed Patients, by Index OAB Drug(s)[a] at Study Cohort Entry

	Index OAB Drug					
	Oxybutynin	Tolterodine	Darifenacin	Solifenacin	Trospium	Fesoterodine
Variable	n = 40,651	n = 37,506	n = 151	n = 33,120	n = 6,071	n = 2,344
Mean (SD) age at cohort entry, years	62.8 (17.4)	62.8 (16.3)	65.3 (14.4)	61.3 (16.3)	64.1 (16.1)	60.1 (16.5)
Age range in years at cohort entry, %						
18-24	2.4	1.4	n/a	1.8	1.3	2.1
25-34	4.7	3.9	n/a	4.0	3.4	5.0
35-44	9.6	9.7	8.6	11.0	8.8	11.3
45-54	14.3	15.0	13.9	17.2	13.5	18.7
55-64	18.7	20.7	19.9	20.6	20.3	19.5
65-74	20.6	21.6	28.5	21.1	23.0	21.8
75-84	20.7	20.2	21.2	17.8	21.5	16.1
85+	9.0	7.5	6.0	6.5	8.4	5.4
Sex, %						
Male	32.3	31.4	29.8	26.1	30.8	29.9
Female	67.7	68.6	70.2	73.9	69.2	70.1
Calendar year at cohort entry, %						
2004	10.1	18.4		0.5	23.6	
2005	9.3	17.3		3.9	18.5	
2006	9.5	15.0		5.8	13.4	
2007	10.3	13.2	21.9	8.2	9.0	
2008	9.9	10.6	29.1	11.4	6.7	2.4
2009	10.7	8.6	13.9	15.2	5.5	16.9
2010	11.5	7.0	n/a	16.9	6.3	24.1
2011	13.8	5.5	12.6	18.5	7.6	28.9
2012	14.9	4.4	19.9	19.5	9.4	27.7
Index of multiple deprivation, %						
1	21.0	24.2	27.2	22.0	21.3	20.6
2	20.3	19.9	19.2	21.1	21.5	22.2
3	20.5	20.1	17.9	19.5	21.8	17.6
4	21.6	19.4	21.9	20.0	17.3	22.8
5	16.6	16.4	13.9	17.3	18.1	16.8
OAB,[b] %	46.6	49.8	57.6	52.2	53.2	54.1
Hypertension diagnosis codes or medications, %	80.9	80.4	83.4	80.4	82.2	79.9
Diabetes diagnosis codes or medications, %	11.6	10.3	10.6	11.7	12.1	12.8
Smoking, %						
Never	46.9	48.0	47.7	47.2	47.7	46.8
Former	35.5	33.9	34.4	36.4	34.5	37.2
Current	16.2	16.4	16.6	16.0	15.9	15.9
Unknown history	1.4	1.7	n/a	0.4	2.0	n/a
Alcohol use, %						
Nondrinker	13.8	13.3	21.9	13.5	13.8	15.9
Low-moderate intake	51.2	51.3	49.0	54.0	51.7	52.6
High-very high intake	18.4	18.3	19.2	18.5	17.6	16.6
Drinker unknown quantity	5.9	6.3	2.0	5.5	6.3	6.3
Unknown history	10.6	10.8	7.9	8.5	10.6	8.7
Alcoholism or alcohol-related diseases	3.1	2.7	4.0	2.9	2.8	3.7
History of AMI, %	4.2	4.1	6.0	3.6	4.4	3.7
History of stroke, %	7.3	6.9	9.9	6.2	8.2	7.3
History of transient ischemic attack, %	4.1	4.2	6.0	3.6	5.0	4.2
History of CHD, %	13.1	13.2	16.6	12.2	15.1	12.2
History of heart failure, %	3.5	3.4	6.0	2.6	3.9	2.7
History of peripheral artery disease/ peripheral vascular disease, %	7.3	6.8	7.3	6.7	7.9	6.4
Menopause (females only), %	22.0	24.0	24.5	24.8	25.7	25.0
Health services utilization, mean (SD)						
Outpatient visits	10.8 (9.6)	10.7 (9.5)	12.3 (11.0)	10.6 (8.9)	11.5 (9.8)	10.8 (8.5)
Hospitalizations	0.5 (1.4)	0.5 (1.2)	1.0 (1.7)	0.6 (1.2)	0.6 (1.2)	0.7 (1.3)

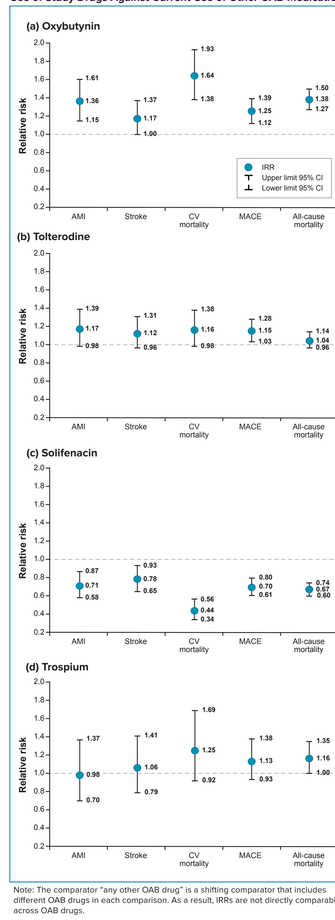
n/a = not applicable; SD = standard deviation.
[a] Includes all patients with a qualifying index prescription.
[b] OAB diagnosis per Read codes.

Table 2. Standardized IRs (per 1,000 Person-Years) for CV Outcomes, by Current Exposure

Current Exposure	Standardized IR[a]	95% CI[b]
AMI, with current exposure to		
Any OAB drug	4.90	4.53-5.29
Oxybutynin	5.94	5.16-6.80
Tolterodine	5.01	4.39-5.68
Darifenacin	2.45	0.06-13.67
Solifenacin	4.00	3.41-4.67
Trospium	5.58	4.11-7.39
Fesoterodine	3.95	2.08-6.79
Stroke, with current exposure to		
Any OAB drug	6.00	5.60-6.43
Oxybutynin	6.76	5.94-7.65
Tolterodine	6.34	5.63-7.10
Darifenacin	5.11	1.01-15.06
Solifenacin	5.12	4.45-5.87
Trospium	6.54	4.94-8.49
Fesoterodine	3.47	1.71-6.23
CV mortality, with current exposure to		
Any OAB drug	4.53	4.18-4.90
Oxybutynin	6.37	5.59-7.24
Tolterodine	4.71	4.13-5.36
Darifenacin	4.70	0.50-17.16
Solifenacin	2.43	1.98-2.96
Trospium	5.79	4.33-7.59
Fesoterodine	3.24	1.54-5.97
MACE, with current exposure to		
Any OAB drug	12.19	11.61-12.80
Oxybutynin	14.32	13.10-15.62
Tolterodine	12.63	11.63-13.69
Darifenacin	12.31	4.32-27.16
Solifenacin	9.82	8.88-10.84
Trospium	14.52	12.07-17.31
Fesoterodine	8.47	5.55-12.36
All-cause mortality, with current exposure to		
Any OAB drug	19.87	19.13-20.63
Oxybutynin	25.61	24.00-27.30
Tolterodine	19.21	18.00-20.49
Darifenacin	16.31	6.13-34.38
Solifenacin	15.37	14.18-16.64
Trospium	23.42	20.35-26.82
Fesoterodine	11.85	8.21-16.54

[a] Overall, results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.
[b] CIs for the standardized IRs were calculated using the methods described in Dobson et al., 1991.[4]

Figure 1. Propensity Score–Stratified Analysis Comparing Current Use of Study Drugs Against Current Use of Other OAB Medications



Note: The comparator "any other OAB drug" is a shifting comparator that includes different OAB drugs in each comparison. As a result, IRRs are not directly comparable across OAB drugs.