Use of Overactive Bladder Medications in the Adult Population of the UK: A Cohort Study in the Clinical Practice Research Datalink

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BACKGROUND

- Mirabegron is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and urinary frequency; mirabegron was approved in 2012 in the United States and the European Union and is the first drug with this mechanism of action to enter the market.
- The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) requested a postapproval evaluation of cardiovascular safety; the FDA also required the evaluation of cancer risk.
- To prepare for a postmarketing safety assessment of cardiovascular and cancer risk associated with mirabegron use, we designed and implemented a study to describe drug-use patterns among users of antimuscarinic drugs commonly prescribed for the treatment of OAB, and incidence rates and ratios of cardiovascular and cancer outcomes. This study was part of a multicenter study, with data from the United States, Denmark, Sweden, and the United Kingdom (UK).
- Here we present the findings of the drug utilization component of the UK study, which is registered in the EU PAS Register.

OBJECTIVE

- To characterize users and use of darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium, which are common drugs to treat OAB.

METHODS

Study Population

- This cohort study was conducted with data from the UK Clinical Practice Research Datalink (CPRD) for patients newly exposed to darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium.
- Patients in the study had at least 12 months of continuous enrollment in the database, followed by a first (index) prescription for a study drug (i.e., the drug was not prescribed during the previous 12 months); patients were aged 18 years or older at the time of the index prescription. Patients with human immunodeficiency virus (HIV) or cancer diagnosis (except non–melanoma skin cancer) prior to the index prescription were excluded.
- The study period was January 2004 through December 2012. Follow-up started at the index prescription and ended at the earliest of the following: end of the study period, disenrollment, diagnosis of HIV or any cancer (except non–melanoma skin cancer), or death.

Data Sources

- For all practices data were obtained from general practice records in the CPRD for the entire study period.
- For the general practices that permit linkage, data were also collected as follows:
  - Hospital Episode Statistics (HES) data: until March 2012
  - Office for National Statistics (ONS) mortality data: until January 2012
  - National Cancer Data Repository (NCDR): until December 2010
- Drug use was ascertained from prescriptions issued by general practitioners.

Therapy Episodes

- Therapy episodes were created by concatenating consecutive prescriptions for the same drug into a single continuous episode, allowing for gaps ≤ 60 days, plus 7 days added to the end of the last prescription in the episode.
- The end of a therapy episode was defined by the end of treatment with a particular drug or a switch to or add-on of another OAB medication.
  - A switch in OAB therapy occurred when a patient stopped taking a given OAB medication and started taking a different OAB medication in an adjacent therapy episode. A switch could also occur if the patient was taking more than one OAB medication during a therapy episode and then stopped one or more of those drugs while continuing to take the other drug(s).
  - An add-on of OAB medication occurred when the patient started taking another OAB medication while continuing the current OAB therapy.
- Missing days of supply were imputed as the modal days' supply for all prescriptions of the same study drug, and strength with known days of supply in the study cohort.

Descriptive Analysis of Patterns of Drug Use

- Analyses were conducted of selected characteristics of the overall cohort, and the subsets were stratified by drug at cohort entry and by eligibility for linkage to the HES, ONS, and NCDR.
- Therapy episodes were described in terms of duration, changes in initial dose, reason why the therapy episode ended (drug add-on, drug switch, or lack of renewal of prescription), and drug switched to or added, if appropriate, and were stratified by drug.

RESULTS

Study Population

- The study cohort included 119,912 subjects; 70% were female (Table 1). The mean age at cohort entry was 62 years.
- The most common index prescriptions were for oxybutynin (34%), tolterodine (31%), and solifenacin (28%). The first prescriptions for oxybutynin, tolterodine, solifenacin, and trospium were in 2004, for darifenacin, in 2007; for fesoterodine, in 2008.
- About 50% of study patients had a recorded prior history of OAB (46% among those age ≥ 65 years, with overall range from 47% in users of oxybutynin to 58% in users of darifenacin).
- Overall, 55% of the study cohort was eligible for linkage to HES, ONS, and NCDR, and 43% were not eligible for linkage to either data source. Characteristics of groups based on eligibility for linkage were generally similar, including smoking and alcohol consumption, but patients from linkage-eligible practices had more use of oxybutynin and less use of fesoterodine (data not shown).

Therapy Episodes and Patterns of Drug Use

- Of 119,912 study patients, 73% were exposed to a single drug during follow-up. There were 245,800 total therapy episodes (28% oxybutynin, 27% solifenacin, 26% tolterodine, and 10% polytherapy) (data not shown).
- The duration of 119,912 index therapy episodes (i.e., therapy episode at cohort entry) varied across individual drugs (Table 2). The shortest mean (standard deviation [SD]) duration was 5.5 (10.9) months for oxybutynin, and the longest was 8.9 (14.4) months for darifenacin. For all individual drugs, most patients' index therapy episodes lasted between 1 and 3 months and comprised one or two prescriptions.
- In almost all index therapy episodes, dose did not change (87% of oxybutynin to 96% of tolterodine index therapy episodes).
- Of the 245,800 therapy episodes during follow-up, most ended because the drug was not renewed or refilled (89%-92% of therapy episodes of all individual drugs but darifenacin, for which the figure was 74%) (Figure 1). Solifenacin was the most common drug added to previous treatment or to which patients were switched.

Table 1. Characteristics of Study Population, Overall and by Stratified by Index Prescription

Variable	Overall (N = 119,912) n (%)		Oxybutynin (n = 40,651) n (%)		Tolterodine (n = 37,506) n (%)		Solifenacin (n = 33,120) n (%)		Trospium (n = 6,071) n (%)		Fesoterodine (n = 2,344) n (%)		Darifenacin (n = 151) n (%)	
Age in years at cohort entry														
Mean (SD)	62.4	(16.7)	62.8	(17.4)	62.8	(16.3)	61.3	(16.3)	64.1	(16.1)	60.1	(16.5)	65.3	(14.4)
18-44	19,233	(16.0)	6,785	(16.7)	5,616	(15.0)	5,560	(16.8)	814	(13.4)	431	(18.4)	16	(10.6)
45-54	18,411	(15.4)	5,804	(14.3)	5,622	(15.0)	5,693	(17.2)	819	(13.5)	439	(18.7)	21	(13.9)
55-64	23,951	(20.0)	7,610	(18.7)	7,766	(20.7)	6,839	(20.6)	1,230	(20.3)	458	(19.5)	30	(19.9)
65-74	25,429	(21.2)	8,355	(20.6)	8,118	(21.6)	6,989	(21.1)	1,395	(23.0)	512	(21.8)	43	(28.5)
75-84	23,612	(19.7)	8,429	(20.7)	7,583	(20.2)	5,880	(17.8)	1,303	(21.5)	378	(16.1)	32	(21.2)
85+	9,276	(7.7)	3,668	(9.0)	2,801	(7.5)	2,159	(6.5)	510	(8.4)	126	(5.4)	9	(6.0)
Female sex	83,734	(69.8)	27,515	(67.7)	25,740	(68.6)	24,476	(73.9)	4,203	(69.2)	1,642	(70.1)	106	(70.2)
OAB	59,502	(49.6)	18,937	(46.6)	18,666	(49.8)	17,273	(52.2)	3,232	(53.2)	1,267	(54.1)	87	(57.6)
Hypertension (diagnosis or treatment)	96,738	(80.7)	32,873	(80.9)	30,170	(80.4)	26,645	(80.4)	4,990	(82.2)	1,872	(79.9)	126	(83.4)
Diabetes (diagnosis or treatment)	13,495	(11.3)	4,711	(11.6)	3,862	(10.3)	3,864	(11.7)	734	(12.1)	300	(12.8)	16	(10.6)
Smoking														
Never	56,788	(47.4)	19,050	(46.9)	18,018	(48.0)	15,622	(47.2)	2,896	(47.7)	1,098	(46.8)	72	(47.7)
Former	42,229	(35.2)	14,448	(35.5)	12,702	(33.9)	12,043	(36.4)	2,093	(34.5)	871	(37.2)	52	(34.4)
Current	19,451	(16.2)	6,597	(16.2)	6,164	(16.4)	5,313	(16.0)	963	(15.9)	372	(15.9)	25	(16.6)
Unknown	1,444	(1.2)	556	(1.4)	622	(1.7)	142	(0.4)	119	(2.0)	3	(0.1)	2	(1.3)
Alcohol use[a]														
Nondrinker	16,289	(13.6)	5,607	(13.8)	4,973	(13.3)	4,455	(13.5)	839	(13.8)	372	(15.9)	33	(21.9)
Low-moderate intake	62,439	(52.1)	20,817	(51.2)	19,242	(51.3)	17,901	(54.0)	3,138	(51.7)	1,233	(52.6)	74	(49.0)
High-very high intake	22,008	(18.4)	7,496	(18.4)	6,881	(18.3)	6,128	(18.5)	1,069	(17.6)	389	(16.6)	29	(19.2)
Drinker unknown quantity	7,116	(5.9)	2,405	(5.9)	2,360	(6.3)	1,815	(5.5)	381	(6.3)	147	(6.3)	3	(2.0)
Unknown history of alcohol use	12,060	(10.1)	4,326	(10.6)	4,050	(10.8)	2,821	(8.5)	644	(10.6)	203	(8.7)	12	(7.9)
Alcoholism or alcohol-related diseases	3,506	(2.9)	1,261	(3.1)	1,010	(2.7)	967	(2.9)	172	(2.8)	87	(3.7)	6	(4.0)
History of disease														
AMI	4,810	(4.0)	1,723	(4.2)	1,539	(4.1)	1,179	(3.6)	270	(4.4)	87	(3.7)	9	(6.0)
Stroke	8,309	(6.9)	2,984	(7.3)	2,594	(6.9)	2,044	(6.2)	497	(8.2)	172	(7.3)	15	(9.9)
TIA	4,868	(4.1)	1,682	(4.1)	1,563	(4.2)	1,207	(3.6)	306	(5.0)	99	(4.2)	9	(6.0)
Coronary heart disease	15,541	(13.0)	5,309	(13.1)	4,964	(13.2)	4,034	(12.2)	915	(15.1)	285	(12.2)	25	(16.6)
Heart failure	3,869	(3.2)	1,438	(3.5)	1,259	(3.4)	863	(2.6)	234	(3.9)	64	(2.7)	9	(6.0)
Peripheral artery disease/peripheral vascular disease	8,392	(7.0)	2,951	(7.3)	2,567	(6.8)	2,228	(6.7)	480	(7.9)	149	(6.4)	11	(7.3)

AMI = acute myocardial infarction; TIA = transient ischemic attack.

[a] Alcohol use: categories based on recorded alcohol intake in electronic medical records (EMRs): nondrinker (specified by EMR), low-moderate intake (1-6 units/week), heavy-very heavy intake (7+ units/week), drinker unknown quantity (amount not specified), or unknown history of alcohol use (no EMRs for alcohol intake). The variable "alcohol-related diseases" includes all patients with related codes (e.g., ICD-10 code K70.3, Alcoholic cirrhosis of liver).

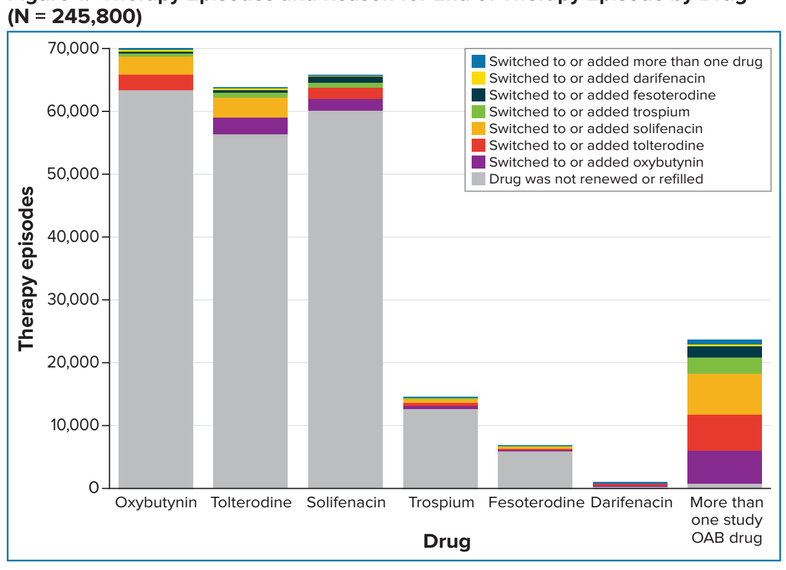
Note: Users of more than one study drug at cohort entry (n = 69) are included in overall counts but not in columns for individual drugs. Comorbidities were identified based on the presence of at least one code in available data sources prior to cohort entry. For smoking and alcohol use, more recent codes took precedence over older codes.

Table 2. Characteristics of Therapy Episodes at Cohort Entry

Characteristic	Oxybutynin (n = 39,994) n (%)		Tolterodine (n = 36,777) n (%)		Solifenacin (n = 31,856) n (%)		Trospium (n = 5,543) n (%)		Fesoterodine (n = 2,238) n (%)		Darifenacin (n = 140) n (%)		More Than One Study OAB Drug (n = 3,364) n (%)	
Duration of therapy episode														
Months, mean (SD)	5.5	(10.9)	8.4	(16.0)	7.5	(12.4)	6.7	(13.2)	5.7	(8.4)	8.9	(14.4)	1.4	(3.9)
< 1	3,779	(9.4)	1,769	(4.8)	1,412	(4.4)	404	(7.3)	126	(5.6)	18	(12.9)	1,782	(53.0)
≥ 1-≤ 3	24,052	(60.1)	20,730	(56.4)	16,894	(53.0)	3,133	(56.5)	1,260	(56.3)	56	(40.0)	1,378	(41.0)
> 3-≤ 6	4,401	(11.0)	4,488	(12.2)	4,421	(13.9)	694	(12.5)	311	(13.9)	19	(13.6)	130	(3.9)
> 6-≤ 9	1,943	(4.9)	2,106	(5.7)	2,073	(6.5)	349	(6.3)	130	(5.8)	12	(8.6)	27	(0.8)
> 9	5,819	(14.6)	7,684	(20.9)	7,056	(22.1)	963	(17.4)	411	(18.4)	35	(25.0)	47	(1.4)
Number of prescriptions during episode														
1	22,570	(56.4)	18,340	(49.9)	14,547	(45.7)	2,880	(52.0)	1,028	(45.9)	57	(40.7)	1,723	(51.2)
2	5,122	(12.8)	4,425	(12.0)	4,100	(12.9)	655	(11.8)	347	(15.5)	13	(9.3)	1,019	(30.3)
3	2,378	(5.9)	2,378	(6.5)	2,215	(7.0)	390	(7.0)	157	(7.0)	15	(10.7)	287	(8.5)
4	1,515	(3.8)	1,521	(4.1)	1,466	(4.6)	228	(4.1)	107	(4.8)	5	(3.6)	113	(3.4)
5+	8,409	(21.0)	10,113	(27.5)	9,528	(29.9)	1,390	(25.1)	599	(26.8)	50	(35.7)	222	(6.6)
Daily dose changed during therapy episode														
No change	34,814	(87.0)	35,294	(96.0)	27,088	(85.0)	5,395	(97.3)	1,928	(86.1)	123	(87.9)	3,101	(92.2)
Increased	4,056	(10.1)	947	(2.6)	4,586	(14.4)	74	(1.3)	291	(13.0)	17	(12.1)	194	(5.8)
Decreased	1,124	(2.8)	536	(1.5)	182	(0.6)	74	(1.3)	19	(0.8)	0	(0.0)	69	(2.1)
Prior exposure to a study drug	517	(1.3)	708	(1.9)	707	(2.2)	402	(7.3)	85	(3.8)	11	(7.9)	3,300	(98.1)

Note: Each study participant had only one initial therapy episode.

Figure 1. Therapy Episodes and Reason for End of Therapy Episode by Drug (N = 245,800)



DISCUSSION

Literature Review

- Our study updates findings from a study on use of antimuscarinic drugs to treat OAB in CPRD in years 1987 to 2004.[1]
- Results on duration of treatment are in general agreement, although OAB treatment patterns have changed, and two drugs that we studied (darifenacin and fesoterodine) became available after the previous study.
- Two studies conducted using the partially overlapping The Health Improvement Network (THIN) database also show the changing pattern of use of OAB treatment over time in the UK, with oxybutynin gradually replacing tolterodine, and with high discontinuation rates.[2,3]

Limitations

- Exposure information, including drug-use and treatment patterns, was derived from prescriptions issued by general practitioners, which the patient might not have filled and followed. In the UK, the general practitioner is the gatekeeper of patients' health care and is in charge of repeated prescriptions. First prescriptions issued by specialists would have been missed.
- Our definitions for therapy episodes were based on our clinical training and patient-matter knowledge but may not have captured the reality of drug treatments; for example, we found a relatively high percentage of treatment add-ons, which is surprising given that all study drugs have a shared (antimuscarinic) mechanism of action. Therefore, it is possible that some of the add-ons actually represent treatment switches.

CONCLUSIONS

In this study of 119,912 patients with prescriptions for antimuscarinic OAB medications, the majority of patients were female (70%), approximately 50% were aged 65 years and older, and most patients (73%) used a single drug during follow-up. The most commonly used OAB medications were oxybutynin (28% of therapy episodes), solifenacin (27%), and tolterodine (26%). Most episodes of use of OAB medications were of limited duration (≤ 6 months). The most commonly used OAB medications were oxybutynin (28% of therapy episodes), solifenacin (27%), and tolterodine (26%). Most episodes of use of OAB medications were of limited duration (≤ 6 months).

CONFLICT OF INTEREST STATEMENT

The authors 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.

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Abstracts From This Program Also Presented in This Conference

Fortuny J, Kaye JA, Margulis AV, Plana E, Calingaert B, Perez-Gutthann S, et al. Validity of cancer diagnoses in general practitioner medical records. Abstract #899. Poster Session C: Spotlight Session–Databases, Wednesday, 26 Aug, 8:00 AM-1:45 PM.

Kaye JA, Margulis AV, Plana E, Calingaert B, Perez-Gutthann S, Arana S. Cancer rates over time after initiation of overactive bladder drugs. Abstract #52. Oral presentation in session Those That Can Heal Can Harm; Those that Can Cure Can Kill, Monday, 24 Aug, 1:30 PM-3:00 PM.

Mortimer KM, Ezzy SM, Jessup JT, Gately RV, Seeger JD. Medical record validation of algorithms for acute myocardial infarction (AMI) within a United States (US) administrative claims database. Abstract #1007, Poster Session C: Methods, Wednesday, 26 Aug, 8:00 AM-1:45 PM

Mortimer KM, Ezzy SM, Jessup JT, Gately RV, Seeger JD. Medical record validation of algorithms for ten types of cancer within a United States (US) administrative claims database. Abstract #1016, Poster Session C: Methods, Wednesday, 26 Aug, 8:00 AM-1:45 PM

Mortimer KM, Ezzy SM, Jessup JT, Gately RV, Seeger JD. Revisions to published algorithms for stroke within a United States (US) administrative claims database. Abstract #1009, Poster Session C: Methods, Wednesday, 26 Aug, 8:00 AM-1:45 PM

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