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European Association of Urology

Platinum Priority – Incontinence
Editorial by XXX on pp. x–y of this issue

Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice

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Article info

Article history:
Accepted January 20, 2017

Associate Editor:
Christian Gratzke

Keywords:
Adherence
Antimuscarinics
Mirabegron
Observational
Overactive bladder
Persistence

Abstract

Background: Persistence with antimuscarinic therapy in overactive bladder (OAB) is poor, but may be different for mirabegron, a β_3-adrenoceptor agonist with a different adverse event profile.
Objective: To compare persistence and adherence with mirabegron versus tolterodine extended release (ER) and other antimuscarinics in routine clinical practice over a 12-mo period.
Design, setting, and participants: Retrospective, longitudinal, observational study of anonymised data from the UK Clinical Practice Research Datalink GOLD database. Eligibility: age $\geq$18 yr, $\geq$1 prescription for target OAB drug (between May 1, 2013 and June 29, 2014), and 12-mo continuous enrolment before and after the index prescription date.
Interventions: Mirabegron, darifenacin, fesoterodine, flavoxate, oxybutynin ER or immediate-release (IR), propiverine, solifenacin, tolterodine ER or IR, and trospium chloride.
Outcome measurements and statistical analysis: The primary endpoint was persistence (time to discontinuation). Secondary endpoints included 12-mo persistence rates and adherence (assessed using medication possession ratio, MPR). Cox proportional-hazards regression models and logistic regression models adjusted for potential confounding factors were used to compare cohorts. Analyses were repeated after 1:1 matching.
Results and limitations: The study population included 21 996 eligible patients. In the unmatched analysis, the median time-to-discontinuation was significantly longer for mirabegron (169 d, interquartile range [IQR] 41–not reached) compared to tolterodine ER (56 d, IQR 28–254; adjusted hazard ratio [HR] 1.55, 95% confidence interval 1.41–1.71; $p < 0.0001$) and other antimuscarinics (range 30–78 d; adjusted HR range 1.24–2.26, $p < 0.0001$ for all comparisons). The 12-mo persistence rates and MPR were also significantly greater with mirabegron than with all the antimuscarinics. Limitations include the retrospective design, use of prescription records to estimate outcomes, and inability to capture reasons for discontinuation.
Conclusions: Persistence and adherence were statistically significantly greater with mirabegron than with tolterodine ER and other antimuscarinics prescribed for OAB in the UK.
Patient summary: This study assessed persistence and adherence (or compliance) with medications prescribed for OAB in a large UK population. We found that patients prescribed mirabegron remained on treatment for longer and showed greater adherence than those prescribed traditional antimuscarinics.

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http://dx.doi.org/10.1016/j.eururo.2017.01.037
0302-2838/

Please cite this article in press as: Chapple CR, et al. Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice. Eur Urol (2017), http://dx.doi.org/10.1016/j.eururo.2017.01.037

1. Introduction

Overactive bladder (OAB) is a complex of lower urinary tract storage symptoms characterised by urgency, with or without urgency incontinence, and often accompanied by frequency and nocturia in the absence of proven infection or other pathology [1]. The condition is common, affecting an estimated 12% of adults [2].

In the UK, pharmacotherapy is used to manage OAB symptoms if lifestyle, behavioural, and conservative measures fail [3,4]. Antimuscarinics are the mainstay of pharmacotherapy for OAB. However, systemic blockade of muscarinic receptors leads to common, bothersome class-related adverse events such as dry mouth, constipation, and headache [5]. Mirabegron, a selective β_3-adrenoceptor agonist, is an alternative treatment option with established efficacy in patients with OAB [6–8]. Overall rates of treatment-emergent adverse events for mirabegron are similar to those observed for antimuscarinics [9], but the risk of dry mouth and constipation is significantly lower for mirabegron [10].

Persistence (time from initiation to discontinuation of therapy [11]) and adherence (extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen [11]) with oral antimuscarinics are recognised as among the lowest for medications used for common chronic conditions [12] and fall rapidly after treatment initiation [13]. Depending on the antimuscarinic prescribed, 65–86% of patients discontinue therapy after 1 yr [14]. Real-world data, mainly from retrospective medical claims databases, suggest that treatment persistence with mirabegron may be greater than for antimuscarinics in OAB [15–17].

The objective of this study was to compare treatment persistence and adherence for mirabegron compared to tolterodine extended-release (ER) over a 12-mo period, consistent with a previous long-term comparative study [18], and with other antimuscarinics in UK clinical practice. Our study was based on prescription records from a large primary and secondary care database in the UK, Clinical Practice Research Datalink (CPRD). One other UK-specific comparative study of persistence for mirabegron versus antimuscarinics is ongoing, but has only been presented in preliminary form to date [19,20]. As well as evaluating persistence in the total study population, we also looked at specific predefined subgroups of interest (ie, treatment-naïve, treatment experienced and elderly patients) and applied matching to control for key baseline characteristics.

2. Patients and methods

2.1. Study design and data source

This was a retrospective, longitudinal, observational, cohort study of patients who received a prescription for a target OAB medication in UK clinical practice. The primary objective was to compare persistence on treatment between mirabegron and tolterodine ER. Secondary objectives included comparing persistence and adherence between mirabegron and other antimuscarinics, and to describe patient characteristics that affected persistence and adherence.

Anonymised data were taken from the CPRD GOLD, a large, nationally representative, primary care research database that collates medical records from 674 general practices across the UK. It includes data for approximately 4.4 million active patients (ie, alive, currently registered) who meet database quality criteria [21].

Approval for the study protocol was obtained from the CPRD Independent Scientific Advisory Committee (protocol 16_097R; approval date July 6, 2016). The study was conducted in compliance with national and European Union requirements ensuring the rights of participants in noninterventional studies.

2.2. Study population

Adults aged ≥18 yr with at least one prescription for a target drug issued between May 1, 2013 and June 29, 2014 (selection period) were eligible (Supplementary Fig. 1). The selection period was based on the availability of mirabegron (approved in Europe in January 2013) and to allow at least 12-mo patient follow-up before analysis of the database. The target drugs were mirabegron, darifenacin, fesoterodine, flavoxate, oxybutynin ER or immediate-release (IR), propiverine, solifenacin, tolterodine ER or IR, and trospium chloride. The first prescription date for a target drug initiated during the selection period was defined as the index date, and the drug was designated the index drug. Only patients with a new prescription were included; patients with a prescription for the index drug in the 12 mo before the index date were excluded. Patients were required to have at least 12 mo of continuous enrolment in CPRD before (pre-index period) and after (post-index period) the index date. Prescriptions for combination therapy with two target drugs at the index date or a 5α-reductase inhibitor (suggestive of benign prostatic hyperplasia due to an enlarged prostate) during follow-up were not permitted.

2.3. Endpoints

Persistence on treatment was assessed using two endpoints: median time to discontinuation (primary endpoint) and the persistence rate at 12 mo. Adherence was also assessed using two endpoints: medication possession ratio (MPR) at 12 mo and adherence rate at 12 mo. Definitions of the endpoints are provided in Supplementary Table 1.

2.4. Statistical analysis

Analyses included all patients meeting the inclusion criteria. Analyses were also stratified according to the following prespecified subcohorts at index date: treatment-naïve (no prescription for any target drug during the pre-index period); treatment-experienced (prescription for at least one non-index target drug during the pre-index period); and elderly patients (≥65 yr).

Time to discontinuation was calculated using Kaplan-Meier survival analysis, and differences between cohorts were assessed via log-rank test; hazard ratios (HRs) are reported for comparisons between mirabegron (reference) and antimuscarinics. Patients were censored if they reached the end of follow-up without discontinuation. Cox proportional-hazards regression models, adjusted for potential confounding factors (gender, age, Charlson index, treatment status, hypertension, polypharmacy), were used to compare cohorts (expressed as HR and 95% confidence interval [CI]). For the primary analysis, OAB treatment was defined as discontinued if the maximum allowable gap duration (MAGD) was at least 1.5 times the intended duration of the most recent prescription. Sensitivity analyses were conducted using a MAGD ratio of 2 and fixed definitions of 30, 45, 60, and 90 d. Logistic regression models, adjusted for potential confounding factors, were used to compare 12-mo persistence rates between cohorts (expressed as odds ratio [OR] and 95% CI). Proportions of persistent and adherent patients

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Table 1 – Baseline characteristics

Characteristic	Mirabegron (*n* = 1203)	Tolterodine ER (*n* = 1561)	Darifenacin (*n* = 126)	Fesoterodine (*n* = 1287)	Flavoxate (*n* = 144)	Oxybutynin ER (*n* = 1144)	Oxybutynin IR (*n* = 5779)	Propiverine (*n* = 95)	Solifenacin (*n* = 8191)	Tolterodine IR (*n* = 1523)	Trospium chloride (*n* = 943)	All patients (*N* = 21 966)
Gender, *n* (%)												
Male	293 (24)	563 (36)*	37 (29)	333 (26)	68 (47)	359 (31)	1748 (30)	22 (23)	2372 (29)	440 (29)	278 (29)	6513 (30)
Female	910 (76)	998 (64)	89 (71)	954 (74)	76 (53)	785 (69)	4031 (70)	73 (77)	5819 (71)	1083 (71)	665 (71)	15483 (70)
Age, years												
Mean (SD)	64.1 (14.8)	64.6 (16.1)	63.5 (14.9)	63.3 (15.8)	64.6 (16.7)	61.6 (17.5)	63.4 (17.0)	66.3 (14.3)	63.8 (16.2)	66.4 (15.2)	66.3 (15.8)	63.94 (16.3)
Range	19.0–95.0	19.0–99.0	28.0–94.0	18.0–96.0	19.0–98.0	18.0–99.0	18.0–102.0	37.0–92.0	18.0–106.0	18.0–96.0	18.0–97.0	18.0–106.0
Age group, *n* (%)												
<65 yr	542 (45)	685 (44)	60 (48)	623 (48)	68 (47)	596 (52)	2685 (46)	41 (43)	3816 (47)	615 (40)	372 (39)	10103 (46)
≥65 yr	661 (55)	876 (56)	66 (52)	664 (52)	76 (53)	548 (48)	3094 (54)	54 (57)	4375 (53)	908 (60)	571 (61)	11893 (54)
Treatment status, *n* (%)												
Naïve	476 (40)	1150 (74)*	73 (58)	799 (62)	111 (77)	907 (79)	5233 (91)	46 (48)	7021 (86)	990 (65)	549 (58)	17355 (79)
Experienced	727 (60)	411 (26)	53 (42)	488 (38)	33 (23)	237 (21)	546 (9.4)	49 (52)	1170 (14)	533 (35)	394 (42)	4641 (21)
CCI												
Mean (SD)	0.38 (0.78)	0.35 (0.78)	0.41 (0.87)	0.40 (0.88)	0.47 (0.79)	0.36 (0.78)	0.38 (0.83)	0.44 (0.92)	0.38 (0.84)	0.36 (0.77)	0.38 (0.80)	0.38 (0.82)
Range	0.0–6.0	0.0–5.0	0.0–7.0	0.0–8.0	0.0–3.0	0.0–6.0	0.0–8.0	0.0–4.0	0.0–8.0	0.0–5.0	0.0–7.0	0.0–8.0
Hypertension, *n* (%)												
No	1021 (85)	1316 (84)	111 (88)	1070 (83)	113 (78)	979 (86)	4865 (84)	74 (78)	6844 (84)	1270 (83)	795 (84)	18458 (84)
Yes	182 (15)	245 (16)	15 (12)	217 (17)	31 (22)	165 (14)	914 (16)	21 (22)	1347 (16)	253 (17)	148 (16)	3538 (16)
Polypharmacy, *n* (%)												
0	113 (9.4)	172 (11)*	16 (13)	120 (9.3)	15 (10)	122 (11)	630 (11)	6 (6.3)	811 (9.9)	135 (8.9)	77 (8.2)	2217 (10)
1–3	329 (27)	515 (33)	36 (29)	424 (33)	28 (19)	365 (32)	1936 (34)	24 (25)	2680 (33)	484 (32)	259 (27)	7080 (32)
4–5	218 (18)	263 (17)	22 (17)	227 (18)	17 (12)	182 (16)	1055 (18)	15 (16)	1514 (18)	262 (17)	170 (18)	3945 (18)
6–8	245 (20)	321 (21)	29 (23)	253 (20)	34 (24)	215 (19)	1031 (18)	23 (24)	1612 (20)	291 (19)	213 (23)	4267 (19)
>8	298 (25)	290 (19)	23 (18)	263 (20)	50 (35)	260 (23)	1127 (20)	27 (28)	1574 (19)	351 (23)	224 (24)	4487 (20)

CCI = Charlson comorbidity index; ER = extended release; IR = immediate release; SD = standard deviation.
* $p < 0.05$ versus mirabegron.

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were compared between cohorts using Fisher's exact test or a χ^2 test, depending on the sample size.

Patients in the mirabegron cohort were randomly matched (1:1) to patients in each of the other target drug cohorts based on sex, age (<65 or ≥65 yr), Charlson comorbidity index score [22,23], and treatment status (naïve or experienced) using a greedy algorithm. All analyses were repeated in matched populations.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

Between May 1, 2013 and June 29, 2014, 69 002 patients with at least one prescription for a target OAB drug were identified. A total of 47 006 (68%) patients were excluded (Fig. 1), so 21 996 (32%) patients constituted the study population. Solifenacin was the most commonly prescribed drug (n = 8191, 37%), followed by oxybutynin IR (n = 5779, 26%). Other target drugs each accounted for less than 10% of the study population, including mirabegron (5.5%). All patients were followed for 12 mo.

Patient demographics and characteristics at baseline are presented in Table 1. Compared to tolterodine ER, a significantly higher proportion of patients prescribed mirabegron were female (76% vs 64%), treatment-experienced (60% vs 26%), and receiving more than eight coexisting medications at the index date (25% vs 19%).

3.1. Mirabegron versus tolterodine ER

3.1.1. Unmatched analysis

Persistence was statistically significantly greater with mirabegron than with tolterodine ER (Table 2). The median time to discontinuation with mirabegron was 169 d (interquartile range [IQR] 41–not reached) compared to 56 d (IQR, 28–254) with tolterodine ER (adjusted HR 1.55, 95% CI 1.41–1.71; $p < 0.0001$; Fig. 2A). Persistence at 12 mo was also significantly greater for mirabegron (38%) than for tolterodine ER (20%; adjusted OR 0.48, 95% CI 0.40–0.58; $p < 0.0001$). Both persistence endpoints were significantly greater with mirabegron than with tolterodine ER in all predefined subcohorts (treatment-naïve, treatment-experienced, and ≥65 yr; $p < 0.0001$ for all comparisons; Table 2). Mean MPR was significantly greater with mirabegron than with tolterodine ER in all patients, and in the treatment-naïve and ≥65-yr-old subcohorts ($p < 0.0001$ all comparisons; Table 2).

Treatment discontinuation was significantly more likely in treatment-naïve patients ($p < 0.0001$), whereas age, sex, comorbidities, hypertension, and coexistent medications did not affect persistence (Table 3).

3.1.2. Matched analysis

Matched patient baseline characteristics are presented in Supplementary Table 2. Time to discontinuation and 12-mo

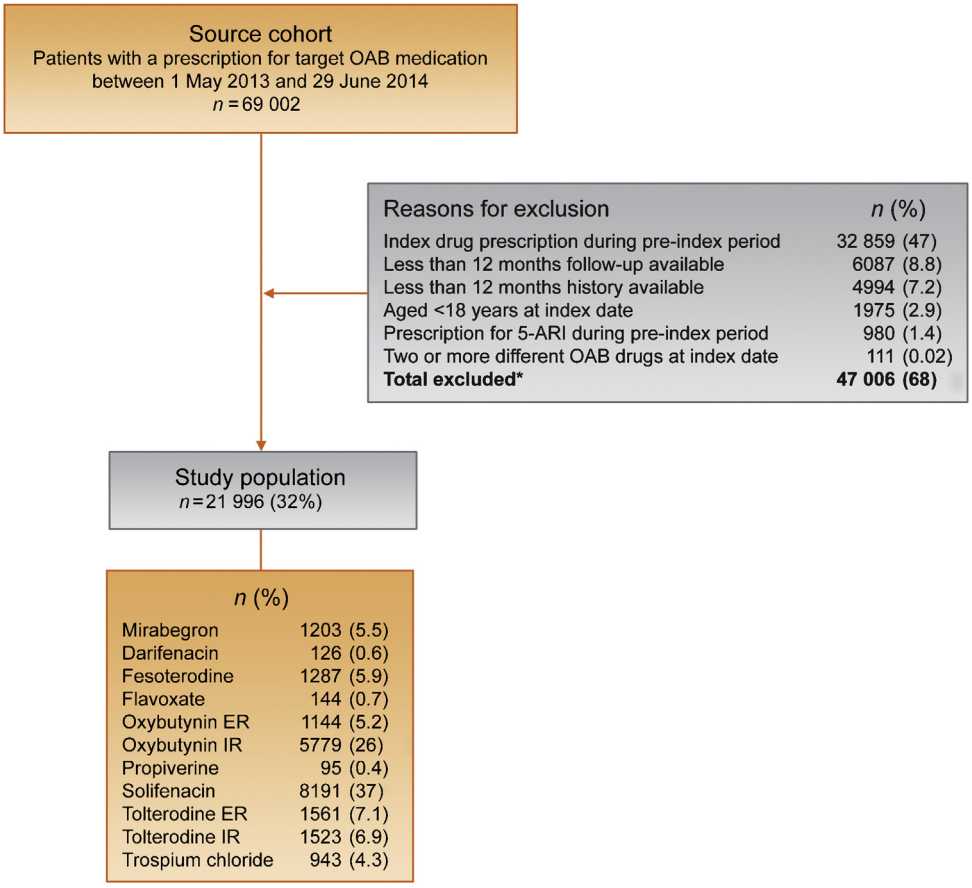

Fig. 1 – Patient selection flowchart. 5-ARI = 5α reductase inhibitor; ER = extended release; IR = immediate release; OAB = overactive bladder. *Patients may have had more than one reason for exclusion.

Table 2 – Persistence and adherence: mirabegron versus tolterodine ER (unmatched analysis)

Variable	All patients		Treatment-naïve patients		Treatment-experienced patients		Elderly patients	
	Mirabegron (*n* = 1203)	Tolterodine ER (*n* = 1561)	Mirabegron (*n* = 476)	Tolterodine ER (*n* = 1150)	Mirabegron (*n* = 411)	Tolterodine ER (*n* = 727)	Mirabegron (*n* = 661)	Tolterodine ER (*n* = 876)
Persistence								
Time to discontinuation (d)								
Median (IQR)	169 (41–NR)	56 (28–254)	132 (30–NR)	56 (28–168)	189 (56–NR)	120 (28–581)	202 (52–NR)	56 (28–264)
Hazard ratio (95% CI)[a]	1.55 (1.41–1.71)		1.66 (1.46–1.88)		1.41 (1.21–1.63)		1.70 (1.50–1.94)	
p value	<0.0001		<0.0001		<0.0001		<0.0001	
12-mo persistence, *n* (%)	454 (38)	318 (20)	164 (34)	192 (17)	290 (40)	126 (31)	274 (41)	184 (21)
Difference, % (95% CI)	17 (14–21)		18 (13–23)		9 (4–15)		20 (16–25)	
Odds ratio (95% CI)[a]	0.48 (0.40–0.58)		0.39 (0.30–0.50)		0.62 (0.48–0.81)		0.41 (0.32–0.52)	
p value	<0.0001		<0.0001		<0.0001		<0.0001	
Adherence								
Patients (*n*)	955	889	345	609	610	280	540	500
MPR								
Mean (SD)[b]	0.59 (0.33)	0.51 (0.33)	0.59 (0.33)	0.48 (0.33)	0.59 (0.34)	0.60 (0.31)	0.61 (0.33)	0.53 (0.33)
p value	<0.0001		<0.0001		0.98		<0.0001	
Adherent patients, [c] *n* (%)	410 (43)	290 (33)	150 (43)	177 (29)	260 (43)	113 (40)	252 (47)	176 (35)
Difference, % (95% CI)	10 (6–15)		14 (8–21)		2 (-5–9)		12 (5–17)	
p value	<0.0001		<0.0001		0.52		0.0002	
Median follow-up (d) [d]	525	548	500	531	546	571	515	548

CI = confidence interval; ER = extended release; IQR = interquartile range; MPR = medication possession ratio; NR = not reached; SD = standard deviation.

[a] Adjusted for gender, age group, treatment status, Charlson comorbidity index, hypertension, and polypharmacy at index date.

[b] MPRs ranged from 0 (no adherence) to 1 (perfect adherence).

[c] Patients considered to be adherent when MPR ≥ 0.8.

[d] Patients who did not discontinue treatment 12 mo after initiation.

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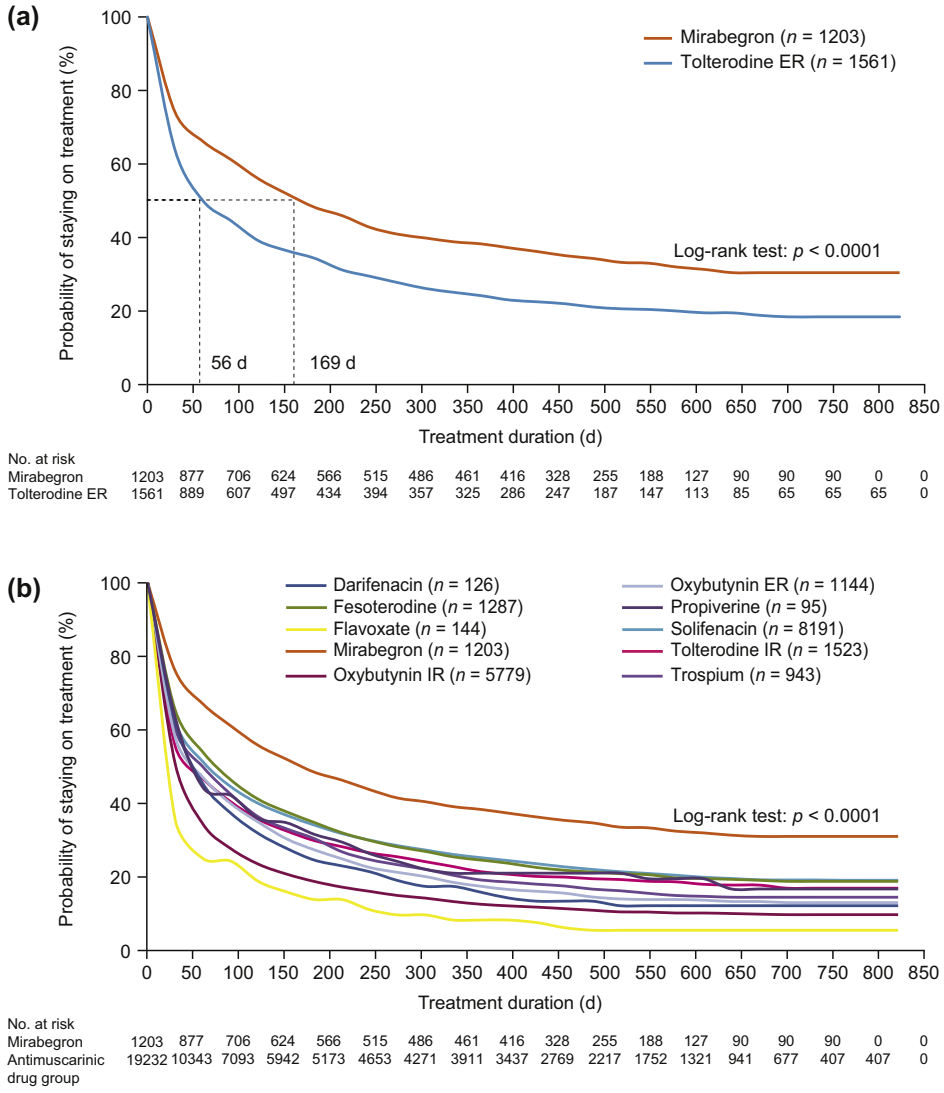

Fig. 2 – Time to discontinuation for mirabegron versus (A) tolterodine ER and (B) other antimuscarinics. ER = extended release; IR = immediate release.

persistence were statistically significantly greater with mirabegron than with tolterodine ER in all patients, as well as in all three predefined subcohorts ($p < 0.0001$ all comparisons; Supplementary Table 3). Mean MPR was significantly higher with mirabegron than with tolterodine ER in all patients (0.60 vs 0.55; $p = 0.03$), and in the treatment-naïve subcohort (0.59 vs 0.49; $p = 0.004$; Supplementary Table 3).

3.1.3. *Sensitivity analysis*

Sensitivity analyses around the MAGD yielded findings similar to the base-case analysis (Supplementary Table 4).

3.2. *Mirabegron versus other antimuscarinics*

3.2.1. *Unmatched analysis*

Persistence was statistically significantly better with mirabegron than with each of the other antimuscarinics (Table 4). The median time to discontinuation was significantly longer with mirabegron (169 d) than with other antimuscarinics (range 30–78 d), with the adjusted HR ranging from 1.24 to 2.26 ($p < 0.0001$ all comparisons; Fig. 2B). Persistence at 12 mo was also significantly greater with mirabegron (38%) than with other antimuscarinics (range 8.3–25%; $p < 0.0001$ for all agents, except $p = 0.002$ for oxybutynin IR). Mirabegron statistically significantly increased both persistence endpoints compared to each of the other antimuscarinics in all predefined subcohorts, with the exception of propiverine in treatment-experienced patients (Supplementary Tables 5–13). The mean MPR was statistically significantly greater with mirabegron (0.59) than with other antimuscarinics in all patients (range 0.41–0.53; p values 0.01 to <0.0001; Table 4) and in treatment-naïve patients (range 0.39–0.51; p values 0.02 to <0.0001; Supplementary Tables 5–13).

Treatment discontinuation was significantly more likely in women ($p = 0.0075$), in patients with more comorbidities ($p = 0.0006$), patients aged <65 yr ($p < 0.0001$), treatment-naive patients ($p < 0.0001$), and patients receiving two or more other medications (Table 3).

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Table 3 – Persistence (time to discontinuation): multivariate Cox regression model (unmatched analysis)

Covariates [a]		HR (95% CI)[b]	*p* value
Mirabegron versus tolterodine ER			
Index drug	Mirabegron (reference)	–	–
	Tolterodine ER	1.55 (1.41–1.71)	<0.0001
Gender	Male (reference)	–	–
	Female	0.96 (0.88–1.06)	0.44
Age in years	<65 yr (reference)	–	–
	≥65 yr	0.95 (0.87–1.04)	0.29
CCI score		0.95 (0.90–1.01)	0.09
Treatment status	Naïve (reference)	–	–
	Experienced	0.74 (0.68–0.82)	<0.0001
Hypertension	No (reference)	–	–
	Yes	0.90 (0.80–1.02)	0.10
Polypharmacy [a]	0 (reference)	–	–
	1	0.98 (0.89–1.08)	0.67
	2	0.78 (0.61–0.98)	0.04
	3	0.66 (0.48–0.90)	0.01
	4	0.88 (0.61–1.27)	0.49
Mirabegron versus antimuscarinics			
Index drug	Mirabegron (reference)	–	–
	Darifenacin	1.77 (1.45–2.16)	<0.0001
	Fesoterodine	1.38 (1.26–1.51)	<0.0001
	Flavoxate	2.27 (1.89–2.72)	<0.0001
	Oxybutynin ER	1.46 (1.33–1.60)	<0.0001
	Oxybutynin IR	1.90 (1.76–2.05)	<0.0001
	Propiverine	1.66 (1.31–2.10)	<0.0001
	Solifenacin	1.24 (1.15–1.34)	<0.0001
	Tolterodine IR	1.59 (1.46–1.74)	<0.0001
	Trospium chloride	1.58 (1.43–1.74)	<0.0001
Gender	Male (reference)	–	–
	Female	1.05 (0.90–1.16)	0.0075
Age	<65 years (reference)	–	–
	≥65 years	0.94 (0.86–1.09)	<0.0001
CCI score		0.97 (0.89–1.03)	0.0006
Treatment status	Naïve (reference)	–	–
	Experienced	0.69 (0.67–0.72)	<0.0001
Hypertension	No (reference)	–	–
	Yes	0.92 (0.89–0.96)	0.15
Polypharmacy [b]	0 (reference)	–	–
	1	1.03 (0.10–1.06)	0.0643
	2	0.87 (0.80–0.94)	0.0003
	3	0.81 (0.74–0.89)	<0.0001
	4	0.79 (0.69–0.89)	0.0004

CCI = Charlson comorbidity index; CI = confidence interval; ER = extended release; HR = hazard ratio; IR = immediate release.
[a] HRs compared with reference variables for each covariate; HR > 1 indicates an increased likelihood of discontinuation with the test variable versus the reference variable.
[b] Number of unique prescription drugs at the index date.

3.2.2. *Matched analysis*

Matching was successful for seven of the nine comparator antimuscarinics; propiverine and darifenacin were not considered because of small sample sizes. Persistence and adherence outcomes for the matched comparisons are presented in Supplementary Tables 6–9 and 11–13.

The median time to discontinuation (adjusted HR range 1.31–2.31; $p < 0.0001$ all comparisons) and 12-mo persistence rates (adjusted OR range 0.18–0.71; $p \leq 0.0001$ all comparisons) were statistically significantly greater with mirabegron than with other antimuscarinics in all patients. An increase in both persistence endpoints was also evident for mirabegron compared to other antimuscarinics in the three predefined patient subcohorts (*p* values 0.04 to <0.0001), except for 12-mo persistence versus solifenacin in matched analysis of treatment-experienced patients. The mean MPR was significantly greater with mirabegron than with other antimuscarinics, except for solifenacin, in all patients (*p* values 0.03 to <0.0001), and in treatment-naïve subcohorts, except for flavoxate (*p* values 0.02 to <0.0001).

4. Discussion

In this study, patients prescribed mirabegron were significantly more likely to continue treatment in the long term compared to those prescribed tolterodine ER, with 12-mo persistence rates of 38% and 20% and median times to discontinuation of 169 and 56 d, respectively. Persistence was also significantly greater with mirabegron than with each of the other comparator antimuscarinics, including the two most commonly prescribed antimuscarinic agents in this large UK population, oxybutynin IR and solifenacin.

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Table 4 – Persistence and adherence: mirabegron versus antimuscarinic agents other than tolterodine ER in all patients (unmatched analysis)

Variable	Mirabegron (*n* = 1203)	Darifenacin (*n* = 126)	Fesoterodine (*n* = 1287)	Flavoxate (*n* = 144)	Oxybutynin ER (*n* = 1144)	Oxybutynin IR (*n* = 5779)	Propiverine (*n* = 95)	Solifenacin (*n* = 8191)	Tolterodine IR (*n* = 1523)	Trospium chloride (*n* = 943)
Persistence										
Time to discontinuation (d)										
Median (IQR)	169 (41–NR)	56 (28–179)	78 (28–353)	30 (30–64)	60 (30–208)	35 (28–108)	56 (28–258)	67 (30–366)	56 (28–285)	60 (28–237)
Hazard ratio (95% CI) [a]	–	1.76 (1.44–2 .15)	1.37 (1.25–1.51)	2.26 (1.88–2.71)	1.46 (1.32–1.60)	1.90 (1.76–2.05)	1.66 (1.31–2.09)	1.24 (1.15–1.34)	1.59 (1.45–1.74)	1.57 (1.43–1.74)
p value	–	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
12-mo persistence, *n* (%)	454 (38)	20 (16)	309 (24)	12 (8.3)	197 (17)	719 (12)	20 (21)	2028 (25)	313 (21)	180 (19)
Difference, % (95% CI)	–	22 (15–29)	14 (10–17)	30 (24–35)	21 (17–24)	25 (23–28)	17 (8–25)	13 (10–16)	17 (14–21)	19 (15–22)
Odds ratio (95% CI)[a]	–	0.35 (0.21–0.57)	0.60 (0.50–0.72)	0.19 (0.10–0.34)	0.45 (0.37–0.54)	0.33 (0.28–0.38)	0.45 (0.27–0.75)	0.74 (0.65–0.85)	0.48 (0.40–0.57)	0.42 (0.34–0.51)
p value	–	<0.0001	<0.0001	<0.0001	<0.0001	0.002	<0.0001	<0.0001	<0.0001	<0.0001
Adherence										
Patients (*n*)	955	73	822	46	651	2775	55	5208	909	591
MPR										
Mean (SD)[b]	0.59 (0.33)	0.46 (0.34)	0.53 (0.33)	0.44 (0.32)	0.49 (0.32)	0.41 (0.32)	0.51 (0.32)	0.53 (0.34)	0.50 (0.34)	0.48 (0.33)
p value	–	0.002	0.001	0.004	<0.0001	<0.0001	0.07	<0.0001	<0.0001	<0.0001
Adherent patients,[c] *n* (%)	410 (43)	21 (29)	286 (35)	11 (24)	202 (31)	621 (22)	14 (25)	1846 (35)	291 (32)	169 (29)
Difference, % (95% CI)	–	14 (3–25)	8 (4–13)	19 (6–32)	12 (7–17)	21 (17–24)	18 (6–30)	8 (4–11)	11 (7–15)	14 (10–19)
p value	–	0.02	0.0005	0.01	<0.0001	<0.0001	0.01	<0.0001	<0.0001	<0.0001
Median follow-up (d) [d]	525	514	551	627	559	548	575	562	533	562

CI = confidence interval; ER = extended release; IQR = interquartile range; IR = immediate release; MPR = medication possession ratio; NR = not reached; SD = standard deviation.

[a] Adjusted for gender, age group, treatment status, Charlson comorbidity index, hypertension, and polypharmacy at the index date.

[b] MPRs ranged from 0 (no adherence) to 1 (perfect adherence).

[c] Patients considered to be adherent when MPR ≥0.8.

[d] Patients who did not discontinue treatment 12 mo after initiation.

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Improvements with mirabegron were maintained in predefined subcohorts of treatment-naïve, treatment-experienced, and older patients, as well as after matching to controls for potentially confounding differences in baseline characteristics. The findings of a sensitivity analysis that tested assumptions around the date of discontinuation were similar to those of the base-case analysis. Adherence, assessed in terms of MPR with a fixed denominator, was significantly greater with mirabegron than with all antimuscarinics in the overall study population, although these benefits appeared to be limited mainly to treatment-naïve patients in both matched and unmatched analyses. Overall, our findings suggest that persistence and adherence with mirabegron are statistically superior to those with other antimuscarinics in a large UK primary care population. The clinical significance of increased adherence has been highlighted recently in a prospective study showing that women who adhered to OAB medication had significantly greater improvements in urinary symptoms than nonadherent women did [24].

Our observations are consistent with other recent real-world studies comparing mirabegron to antimuscarinic agents under different health care systems in the US, Japan, and Canada, which reported significantly better persistence with mirabegron [15–17]. In the North American studies, both of which were based on retrospective claims data, the relative risk of discontinuation with mirabegron versus tolterodine ER was similar to the present study (HR: Canada, 1.44; USA, 1.64; UK, 1.56) [15,16]. Persistence with mirabegron versus tolterodine was also greater in treatment-naive and treatment-experienced cohorts in both studies [15,16], as in the present study. The smaller Japanese study, based on medical records, reported a significantly improved 12-mo persistence rate with mirabegron compared to tolterodine (38% vs 20%) [17], as in the present study (38% vs 20%). In addition, two noncomparative studies of persistence with mirabegron in UK populations have recently been reported [25,26], but cannot be directly compared with our study because of a shorter duration of follow-up in one study (6 mo) [25] and many patients (37%) received mirabegron in combination with antimuscarinics in the other [26].

In our study, discontinuation of antimuscarinics was less common among men than among women and generally occurred within 1–3 mo, compared to a median of 5.6 mo with mirabegron. We were unable to examine the reasons for discontinuation in our study as these data are not contained within the CPRD database. However, data from a large US survey (>5000 respondents) suggested that the most common reasons for discontinuation of antimuscarinics were treatment not working as expected, switching to a new medication, coping without medication, and side effects [27]. Other reasons described in the literature included inadequate patient counselling resulting in unrealistic patient expectations [28], cost [27,29,30], unwillingness to take long-term treatment [27], and proactive treatment holidays, all of which may have occurred in our study. It is conceivable that the initial separation of the Kaplan-Meier curves (Fig. 2) is attributable to differences between mirabegron and antimuscarinics in the occurrence of bothersome anticholinergic side effects, notably dry mouth, [9,10]. The time to onset of adverse events with antimuscarinics is approximately 1 wk [31] and fits with this early difference between groups. The gradient of the curves was generally comparable after 3 mo, suggesting that reasons for later discontinuations may have been common to both drug classes. Further efforts are needed to better understand the reasons for discontinuation of OAB medications and how to support patients so that they achieve long-term compliance.

This study has many design strengths including a large population from the CPRD database that is broadly representative of the UK general population [21] and the use of matching to control for baseline imbalances, notably the proportion of treatment-experienced patients, which was greater in the mirabegron cohort at baseline. The unmatched analysis was used as the primary analysis because, after applying the stringent inclusion/exclusion criteria, it was uncertain if there would be adequate patient numbers for matching. The main study limitations are its retrospective design and the use of prescription-event rather than patient-derived data (eg, patient diaries) to estimate outcomes. Although patients with <12-mo follow-up after treatment initiation were excluded ($n = 6078$; Fig. 1) to support the assessment of all study objectives and endpoints, these patients could have theoretically been included in the analysis of time to discontinuation. The inability to capture reasons for discontinuation of treatment, as well as any potential health benefits resulting from increased persistence in terms of symptom severity and health-related quality of life (HRQoL), were other limitations of this study. It should also be noted that there was variation in the prescribing of mirabegron relative to tolterodine ER in the early months of the study selection period (Supplementary Fig. 2), possibly because of the UK launch of mirabegron (February 2013) and the release of updated treatment guidelines to include mirabegron [32]. The relatively later availability of mirabegron and its positioning within UK guidelines [32] may also have contributed to the higher proportion of treatment-experienced patients in this group.

Analyses of health care resource use and associated costs from the present study will be reported separately. Large prospective observational studies of mirabegron are ongoing in the USA (PERSPECTIVE; https://clinicaltrials.gov/ct2/show/NCT02386072) and Europe (BELIEVE; https://clinicaltrials.gov/ct2/show/NCT02320773), which include persistence and HRQoL outcomes in a real-life setting. These studies may help to better understand the benefits of improved treatment persistence, reasons for discontinuation, and why men in our study were less likely to discontinue treatment than women.

5. Conclusions

Patients receiving mirabegron remain on treatment for significantly longer and have significantly better 12-mo persistence and adherence rates compared to tolterodine ER and other antimuscarinics commonly prescribed for OAB in

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the UK. Mirabegron provides an alternative treatment option for OAB with the potential to increase treatment persistence. This is an important consideration for clinicians when managing chronic conditions, as well as for payers when considering the economic implications of available treatments for OAB.

Author contributions: Christopher R. Chapple had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Nazir, Siddiqui, Guelfucci, Khemiri.
Analysis and interpretation of data: Chapple, Nazir, Hakimi, Fatoye, Siddiqui, Wagg, Guelfucci, Khemiri, Bowditch.
Drafting of the manuscript: Chapple, Fatoye, Siddiqui, Wagg.
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Statistical analysis: Fatoye, Guelfucci, Khemiri.
Obtaining funding: Nazir.
Administrative, technical, or material support: Nazir, Bowditch.
Supervision: Chapple, Nazir.
Other: None.

Financial disclosures: Christopher R. Chapple certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Christopher R. Chapple declares a grant from Astellas; research study fees plus nonfinancial support from Astellas and Allergan; speaker fees plus nonfinancial support from Astellas, Allergan, and Boston; and consultancy/advisory fees plus nonfinancial support from Astellas, Allergan, Medtronic, and Pfizer. Jameel Nazir, Zalmai Hakimi, Sally Bowditch, and Emad Siddiqui are employed by Astellas. Francis Fatoye declares a grant from Astellas. Florent Guelfucci and Amine Khemiri are employed by Creativ-Ceutical, which received a grant from Astellas. Adrian Wagg declares speaker, research, and consultancy fees from Astellas, Pfizer, SCA AB, and Duchesnay (Canada).

Funding/Support and role of the sponsor: The study was funded by Astellas and designed and analysed by Astellas in collaboration with the authors. Astellas had a role in the design and conduct of the study; management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript. Medical writing support, provided by Harriet Lamb and Tyrone Daniel from Bioscript Medical, was funded by Astellas Pharma Inc.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2017.01.037.

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