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Adherence and persistence of mirabegron and anticholinergic therapies in patients with overactive bladder: a real-world claims data analysis

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SUMMARY

Background: Adherence and persistence rates of anticholinergic (ACH) therapies have been well described. To date, few studies describe these metrics for mirabegron in patients with overactive bladder. **Methods:** This retrospective analysis of MarketScan® database assessed adherence and persistence of patients receiving either mirabegron or ACH. Study eligibility required an index date (first prescription filled) between July 2012 and June 2013 with 12 months of continuous enrolment preindex date and 12 months of follow-up. Adherence was defined as a proportion of days covered of ≥ 80% among patients with at least 2 fills of index medication. Persistence measures included treatment failure described as either treatment discontinuation (medication supply gap ≥ 30 days) or switching to a different medication. A medication supply gap of ≥ 45 days was used as a sensitivity analysis. **Results:** The mean age of mirabegron users (n = 4037) was 67 years and 43% were ACH naïve while the mean age of ACH users was 62 years (n = 67,943). Over the 12-month follow-up period, 44% of patients treated with mirabegron and 31% of patients treated with ACH were adherent to their indexed medications. Treatment failure was 81% for mirabegron and 88% for ACH. Most mirabegron treatment failures were because of treatment discontinuation (67%) versus switching to ACH therapy (14%). The ACH discontinuation rate was 84% and treatment switching rate was 4%. The mean (standard deviation) time to treatment failure was 143 (130) days for mirabegron and 69 (69) days for ACH. Adherence and persistence patterns were similar in the sensitivity analysis using a ≥ 45-day supply gap threshold. **Conclusions:** This real-world study demonstrated low adherence and persistence to mirabegron similar to ACH therapies.

What's known

Medication adherence and persistence to anticholinergic medications, the mainstay pharmacological treatment for patients with overactive bladder, has been previously reported. Approximately 90% of overactive bladder patients fail their first prescribed anticholinergic therapy within 2 years, leaving a substantial amount of people without symptom management. Mirabegron belongs to a different class of treatments and limited data are available on its real-world use.

What's new

This study describes the adherence, persistence and use patterns of mirabegron using a large United States claims dataset. Adherence to mirabegron (44%) and to anticholinergic agents (31%) was low in patients with overactive bladder over a 12-month period. Similarly, both agents had high treatment discontinuation rates (mirabegron 67%; anticholinergic agents 84%) and high rates of treatment failure (mirabegron 81%; anticholinergic agents 88%).

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Disclosures

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Introduction

Overactive bladder (OAB) is a clinical diagnosis defined as the presence of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of a urinary tract infection or other obvious pathology (1). The prevalence is between 12% and 17% of the general population in the United States (US), and the incidence increases with age (2). It is estimated that almost 30 million US adults over the age of 40 years have bothersome OAB symptoms (3). Furthermore, the symptoms of urgency urinary incontinence are known to be major risk factors for falls and fractures, particularly in the elderly population (4).

Traditionally, the mainstay of medical management of OAB has been anticholinergic (ACH) agents (1). Despite the development of newer preparations such as sustained release formulations and therapies utilising alternative delivery routes, adherence to and persistence with ACH medications is an ongoing challenge in clinical practice. In OAB, treatment failures can occur when patients' expectations of symptom improvement are not met or when intolerable adverse effects of therapy reduce compliance (5,6). Persistence with ACH treatment often declines markedly in the first 6 months of therapy and continues to fall during long-term, ongoing therapy (7,8). A real-world study in over 100,000 patients with OAB who received ACH therapy found that the majority were unable to meet their treatment goals over a 24-month follow-up period. 85.9% of patients discontinued and 5.8% of patients switched from their index ACH agent. Adherence, measured by a

medication possession ratio (MPR) ≥ 0.8, was 48%. The mean time to treatment failure was 159 days (8). In addition, similar reports of low patient persistence and adherence with ACH therapy in the year after treatment initiation have been published (9–12).

Mirabegron is an orally active, beta$_3$-adrenoceptor agonist approved for the treatment of OAB in July 2012 by the US Food and Drug Administration (2). There are limited published studies to date describing persistence, adherence and general usage patterns for mirabegron. Sufficient patient-use and follow-up time has now accrued since the introduction of mirabegron to allow for an evaluation of persistence and adherence using administrative claims datasets. Thus, the primary objective of this study was to evaluate adherence and persistence with mirabegron and to provide an update on adherence and persistence to ACH medications using a US, nationally representative, integrated medical and pharmacy claims dataset. A secondary objective was to assess these metrics in patients prescribed and initiating mirabegron stratified by their prior use of ACH therapies.

Methods

This was an observational real-world study with a non-interventional, retrospective cohort design. Medical, pharmacy and eligibility data from Truven MarketScan® Claims Database were used to evaluate adherence and persistence in patients with OAB to mirabegron or ACH therapies (Appendix 1).

Data source

De-identified medical and pharmacy claims analysed for the study were obtained from the Truven MarketScan® claims database. This database consists of commercial and Medicare claims for inpatient, outpatient and prescriptions for over 40 million enrolees, their spouses and dependents who are covered by employer-sponsored private health insurance. Enrollees can be followed as they move between the commercial and Medicare claims databases. The Medicare Supplemental database covers approximately 4.3 million Medicare-eligible persons with supplemental insurance plans offered by their former employer. For the purposes of this study, patients from both databases were pooled into a single population for analyses. The database study period was from July 2011 to June 2014.

Inclusion and exclusion criteria

Parallel draws were conducted to create two mutually exclusive analysis cohorts: (i) mirabegron users and (ii) ACH users. Patients were only eligible for inclusion in the ACH cohort if they did not have a claim for mirabegron during the study period.

The study sample included records with the following: first documentation of at least one pharmacy claim (the index date) for mirabegron (regardless of prior-ACH use) or ACH (for patients with no claims for mirabegron) between July 2012 and June 2013 (the enrolment period); 18 years of age or older at index; 12 months of continuous enrolment before the index date (the preindex period); and 12 months of follow-up after the index date (follow-up period). No claims for the index medication were allowed during the preindex period for either cohort.

As all of the medications evaluated were only approved for OAB and neurogenic detrusor overactivity (NDO) indications, no prior diagnosis of OAB was required. However, patients with a diagnosis of NDO during the preindex period were excluded to focus the analysis on OAB. In addition, patients were excluded if they had one or more mirabegron or ACH claims with an invalid supply value during the 12-month follow-up period. In the ACH cohort, patients were also excluded if they received any other ACH therapy in the 12-month preindex period or were initiated on treatment involving more than one ACH agent.

Outcomes and analyses

Study outcomes were evaluated over the 12 months after the index date. Outcomes of interest included treatment adherence and treatment persistence.

Treatment adherence was defined as the proportion of days covered (PDC), i.e. the number of days covered by the index therapy divided by the number of days between the index date and the end of the follow-up (365 days). A PDC of $< 80\%$ was considered non-adherent. Only patients with 2 or more prescription claims were included in the PDC analysis.

Persistence was measured by evaluating treatment failure. Treatment failure was defined as either treatment discontinuation or treatment switching. A medication supply gap of ≥ 30 days was used to define treatment discontinuation. Treatment switching included a switch to ACH therapy for patients taking mirabegron or switching between ACH agents within 30 days of the last prescription fill for patients taking an ACH agent. Within the ACH cohort, a change in dose or a change in formulation for the same agent did not qualify as a switch. A sensitivity analysis was performed by applying a medication supply gap of ≥ 45 days to test the robustness of the persistence results. Treatment re-initiation was also considered and was defined as a prescription fill of any ACH agent or mirabegron following a discontinuation period of ≥ 30 days.

Descriptive analyses were conducted on the mirabegron and ACH cohorts to characterise patients in terms of demographic and clinical characteristics. No inferential analyses were conducted to make comparisons between cohorts or subgroups. Study outcomes for the mirabegron cohort were stratified by prior-ACH use. Summary statistics of the proportion of patients who were adherent, non-adherent, persistent and non-persistent with therapy were calculated as described. Descriptive statistical analyses were performed using SAS (version 9.3; SAS Institute, Cary, NC, USA).

Results

Cohort characteristics

Records of patients with an index date for prescription fill of mirabegron (n = 24,088) or an ACH therapy (n = 374,596) during the period from July 2012 through June 2013 were collected. After applying exclusion criteria, the final patient samples of 4037 mirabegron users and 67,943 ACH users were identified for analyses (Figure 1). Patients in the mirabegron cohort had a mean age of 67 years [standard deviation (SD), 15 years], 57% were age 65 years or older and 66% were female (Table 1). The cohort of patients initiating ACH therapy had a mean age of 62 years (SD 16 years), 41% were age 65 years or older and 71% were female. Table 1 also shows the age and gender characteristics of mirabegron patients with prior exposure to ACH therapy and ACH naïve patients. Of the patients taking mirabegron, 43% (n = 1733) were naïve to ACH treatment. In the overall mirabegron patient cohort, 38% had a recorded diagnosis of OAB only, 38% had OAB with incontinence, 8% had incontinence only and 16% had neither. In the ACH cohort, 34% had OAB only, 15% had OAB with incontinence, 8% had incontinence only and 44% had neither. Also in the ACH cohort, the most commonly prescribed agent was oxybutynin and the most common formulation of oxybutynin was standard oral therapy.

Treatment failure

A high percentage of patients failed initial treatment with their index prescription. In the mirabegron cohort, 3270 subjects (81%) experienced treatment failure during the 12-month follow-up using the

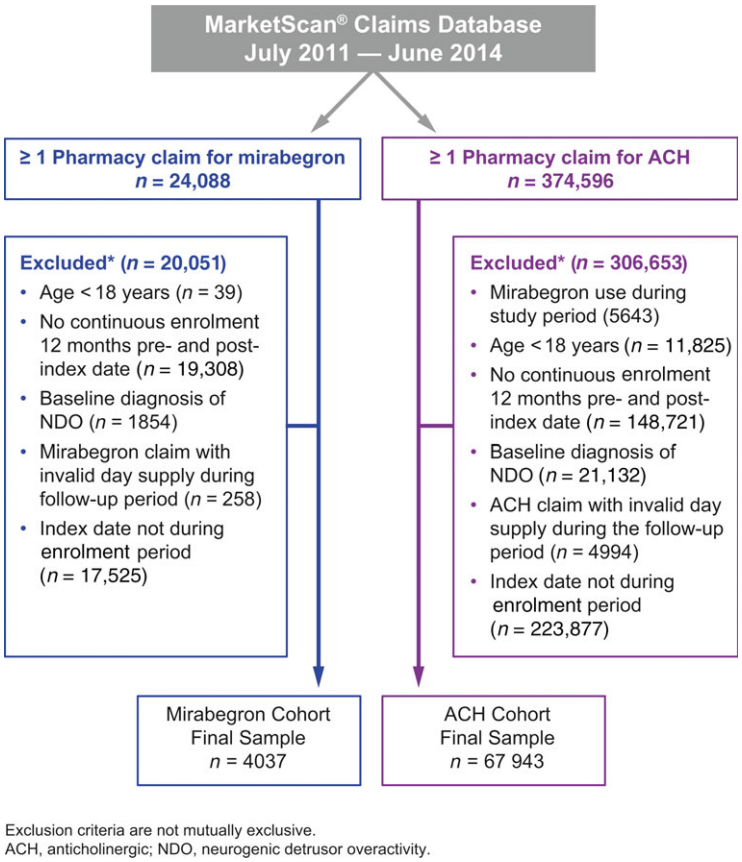

Figure 1 Patient selection using MarketScan® Claims Database from July 2011 to June 2014

Table 1 Patient demographics and clinical characteristics for the mirabegron and ACH cohort

	Overall			
	Mirabegron Cohort			ACH Cohort
		Stratification		
Parameter	Combined	Prior-ACH	ACH-naïve	Not applicable
Total, *n* (%)	4037 (100)	2304 (57)	1733 (43)	67,943 (100)
Age, years, mean (SD)	67 (15)	68 (15)	66 (15)	62 (16)
Age cohort, *n* (%)				
18–44 years	291 (7)	141 (6)	150 (9)	9607 (14)
45–64 years	1442 (36)	793 (34)	649 (37)	30,770 (45)
65+ years	2304 (57)	1370 (59)	934 (54)	27,566 (41)
Gender, *n* (%)				
Male	1355 (34)	735 (32)	620 (36)	19,870 (29)
Female	2682 (66)	1569 (68)	1113 (64)	48,073 (71)
Payer, *n* (%)				
Commercial	1742 (43)	937 (41)	805 (46)	40,243 (59)
Medicare	2295 (57)	1367 (59)	928 (54)	27,700 (41)
Type of OAB, *n* (%)				
OAB Only	1529 (38)	832 (36)	697 (40)	22,924 (34%)
OAB with incontinence	1521 (38)	970 (42)	551 (32)	10,056 (15)
Incontinence only	335 (8)	189 (8)	146 (8)	5225 (8)
No OAB	652 (16)	313 (14)	339 (20)	29,738 (44)

ACH, anticholinergic; OAB, overactive bladder; SD, standard deviation.

Table 2 Persistence of mirabegron and ACH using the 30-day threshold to define the supply gap

	Overall			
	Mirabegron Cohort			ACH Cohort
		Stratification		
Parameter	Combined	Prior-ACH	ACH-naïve	Not applicable
Total, *n* (%)	4037 (100)	2304 (57)	1733 (43)	67,943 (100)
Treatment failure, *n* (%)	3270 (81)	1846 (80)	1424 (82)	59,882 (88)
Time to treatment failure, days, mean; median (SD)	143; 90 (130)	147; 90 (132)	138; 90 (126)	68.8; 30 (69)
Treatment switch, *n* (%)	561 (14)	469 (20)	92 (5)	2730 (4)
Treatment discontinuation, *n* (%)	2709 (67)	1377 (60)	1332 (77)	57,152 (84)
Time to treatment discontinuation, days, mean; median (SD)	185; 131 (142)	209; 197.5 (144)	152; 90 (134)	68.2; 30 (67)

ACH, anticholinergic; SD, standard deviation.

30-day threshold compared with treatment failure in 59 882 ACH users (88%) (Table 2). In the mirabegron cohort, 80% of prior-ACH users and 82% of ACH-naïve users failed treatment. In the mirabegron cohort overall, the mean time to treatment failure was 143 days (median 90 days, SD 130 days). In the ACH cohort, the mean time to treatment failure was shorter than that seen for mirabegron users, at 68.8 days (median 30 days, SD 69 days). Of the 81% of mirabegron patients who experienced treatment failure, 67% ($n = 2709$) discontinued treatment at a mean of 185 days (SD 131 days) and 14% ($n = 561$) switched treatment. Of the 88% of patients who failed ACH treatment, 84% ($n = 57,152$) discontinued treatment at a mean of 68.2 days (SD 67 days) and 4% ($n = 2730$) switched treatment.

Treatment reinitiation

In the 30-day supply gap analysis of treatment patterns among all mirabegron users, 1281 (47%) of the 2709 patients who discontinued therapy later reinitiated therapy: 802 (63%) with mirabegron and 479 (37%) with another medication (Table 3). The mean time to reinitiation of the index medication for the entire mirabegron cohort was 75 days (SD 56 days). Among the 1377 mirabegron users with prior-ACH use who discontinued, 751 (55%) reinitiated therapy: 427 (57%) with mirabegron (mean time 70 days, SD 51 days) and 324 (43%) restarted with another medication. For the 1332 ACH naïve mirabegron users, 530 (40%) reinitiated therapy: 375 (71%) with mirabegron (mean time 80 days, SD 61 days) and 155 (29%) restarted with another medication. Among ACH users, 18,481 (32%) of those who discontinued therapy later reinitiated treatment with 14,399 (78%) reinitiating treatment with the index medication. The mean time to reinitiation was 95 days (SD 71 days).

Treatment adherence

Populations included in adherence analyses were those patients with at least two prescription fill claims of the index medication during the follow-up period. A total of 2877 mirabegron users (1742 prior-ACH users and 1135 ACH-naïve patients) and 35,592 ACH users were included in adherence analysis. The mean PDC over 12 months was 0.66 for the mirabegron cohort and 0.55 for the ACH cohort. Using a PDC cut-off of $\geq 80\%$, 44% of mirabegron users were adherent, whereas 31% of ACH users were adherent (Table 4). The adherence rates for mirabegron and ACH users with different types of diagnoses were similar to the adherence rate of the cohorts overall. Among mirabegron users, 48% of patients with incontinence, 44% of patients with OAB and incontinence, 44% of patients with no OAB diagnosis and 43% of patients with OAB were adherent to mirabegron therapy. Likewise, among ACH users, 34% of

Table 3 Treatment reinitiation for mirabegron and ACH using the 30-day supply gap threshold to define the supply gap

	Overall			
	Mirabegron Cohort			ACH Cohort
		Stratification		
Parameter	Combined	Prior-ACH	ACH-naïve	Not applicable
Total for re-initiation analyses, *n* (%)	2709 (100)	1377 (51)	1332 (49)	57,152 (84)
Treatment re-initiation, *n* (%)	1281 (47)	751 (55)	530 (40)	18,481 (32)
Re-initiation with index medication, *n* (%)	802 (63)	427 (57)	375 (71)	14,399 (78)
Time to treatment re-initiation, days, mean; median (SD)	75; 54 (56)	70; 52 (51)	80; 58 (61)	95; 67 (71)

ACH, anticholinergic; SD, standard deviation.

Table 4 Adherence to mirabegron and to ACH therapy in patients with at least two prescription fill claims

	Overall			
	Mirabegron Cohort			
		Stratification		ACH Cohort
Adherence	Combined	Prior-ACH	ACH-naïve	Not applicable
Total, *n* (%)	2877 (100)	1742 (61)	1135 (39)	35,592 (100)
PDC, mean (SD)	66 (30)	68 (30)	62 (31)	55 (32)
Adherent (PDC $\geq$ 80%), *n* (%)	1255 (44)	828 (48)	427 (38)	10,982 (31)
Non-adherent (PDC $<$ 80%), *n* (%)	1622 (56)	914 (52)	708 (62)	24,610 (69)

ACH, anticholinergic; PDC, proportion of days covered; SD, standard deviation.

Table 5 Persistence of mirabegron and ACH: sensitivity analysis using 45-day threshold to define supply gap

	Overall			
	Mirabegron Cohort			ACH Cohort
		Stratification		
Parameter	Combined	Prior-ACH	ACH-naïve	Not applicable
Total, *n* (%)	4037 (100	2304 (100)	1733 (100)	67,943 (100)
Treatment failure, *n* (%)	3084 (76)	1732 (75)	1352 (78)	57,859 (85)
Time to treatment failure, days, mean; median (SD)	156; 90 (136)	160; 92 (138)	151; 90 (132)	69.6; 30 (69)
Treatment switch, *n* (%)	586 (15)	488 (21)	98 (6)	2880 (4)
Treatment discontinuation, *n* (%)	2498 (62)	1244 (54)	1254 (72)	54,979 (81)
Time to treatment discontinuation, days, mean; median (SD)	199; 170 (145)	223; 262 (144)	165; 92 (138)	68.7; 30 (67)

ACH, anticholinergic; SD, standard deviation.

patients with incontinence, 29% of patients with OAB and incontinence, 31% of patients with no OAB diagnosis and 31% of patients with OAB were adherent to ACH therapy.

Sensitivity analysis

The sensitivity analysis of persistence outcomes using a 45-day threshold to define discontinuation was similar to that of the 30-day gap analysis (Table 5).

Discussion

Our study is the first since the approval of mirabegron to provide insights into how adherence and persistence of this therapy compare with adherence and persistence to ACH. This real-world observational study found low adherence (44%) and persistence (19%) to mirabegron therapy, as well as low adherence (31%) and persistence (12%) to ACH therapies, in the 12 months following treatment initiation. Treatment failure rates and times to treatment failure in patients taking mirabegron were similar regardless of prior-ACH experience.

These findings confirm and extend recent claims database evidence on ACH persistence and adherence reported by Chancellor, et al. (8) where 91.7% of patients failed treatment a mean of 159 days after initiation, with more than half permanently discontinuing therapy. In that study, which involved a 24-month follow-up period, adherence to ACH was 48% as assessed by the MPR using variable time of possession calculated based on the total number of days a medication was supplied except for the last pharmacy claim divided by the total number of days from the index fill data to the last pharmacy claim (8). In contrast, our study used PDC to define adherence over a fixed 12-month time frame and found that ACH adherence was 31%. We observed higher persistence with a 12-month follow-up (19% mirabegron; 12% ACH) compared with the 24-month follow-up period described by Chancellor, et al. (8) where approximately 8% of patients persisted with their index ACH therapy. Although a more-stringent treatment supply gap threshold of $\geq$ 30 days was used, our study observed slightly higher persistence rates for ACH, which is likely because of the shorter follow-up time. Regardless of the length of follow-up, the persistence rates in both studies are low.

There are several limitations to our study, many of which are inherent to retrospective analyses based on administrative claims data. For instance our study results show a high attrition rate as a result of requiring continuous 12-month preindex and postindex enrolment. Also, the sample population used in our study is limited to insured patients; therefore, estimates of adherence may be biased as adherence and persistence to medication are known to be associated with insurance coverage (13). Because of the limitations of the study sample population, results may only be applicable to commercial managed care and Medicare populations in the US. Inclusion criteria did not require patients to have a diagnosis of OAB as all of the medications evaluated were only indicated for OAB in adults. Although including patients without a recorded diagnosis of OAB could potentially bias the results, a subgroup analysis showed that treatment adherence rates were similar regardless of the recorded diagnosis (OAB, UI, OAB and UI, or neither) in both the mirabegron and ACH cohorts.

Study results could have been influenced by any clinical and patient demographic information that may have gone unobserved or uncollected in the database during our study's analytical period, if these demographic factors were correlated with the outcome of treatment patterns. Because of the limitations of claims data, it was not possible to ascertain whether or not patients are taking medication as prescribed; only pharmacy fill records can be verified. While the study results report persistence rates, there was no way to capture the reason for medication discontinuation (e.g. efficacy, safety, other).

Mirabegron has a different adverse event profile than ACH therapies thought to have potential for better compliance. However, the results of this study suggest that such benefits are not observed in the real-world because the difference in 12-month adherence and persistence of mirabegron, when compared with the same metrics for ACH in our study, were small (a 19% persistence rate for mirabegron versus 12% for ACH therapies). Moreover, we also observed that adherence and persistence with mirabegron were similarly low regardless of patients' prior-ACH treatment experience.

Alternative interventions for overactive bladder with greater patient acceptance, adherence and persistence would be welcome. Although more complex, onabotulinum toxin type A and neuromodulation techniques are possible treatments and will need to be directly compared with the current standard of care (14–17). Furthermore, experience with mirabegron remains limited and continued pharmacovigilance, long-term data capture and experience using this agent is required for appropriate evaluation (15).

This study provides a contemporary insight into how treatment patterns for mirabegron compare with ACH therapies in a real-world setting. Future studies are needed to identify key drivers of discontinuation, as well as to better understand the implications of non-adherence and switching in terms of symptom burden, side effect burden and economic impact. We suggest that there remains a need for earlier consideration of alternative therapies and strategies that may improve adherence and persistence to achieve optimal patient care.

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Author contributions

David Sussman and Brian Murray involved in the data interpretation, critical revision of article and approval of article. Alon Yehoshua and Jonathan Kowalski involved in the concept/design, data interpretation, critical revision of article and approval of article. Won Lee, Jonathan Kish and Sham Chaudhari contributed to the concept/design, data analysis/interpretation, critical revision of article and approval of article.

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Appendix 1: List of included OAB treatments

- Anticholinergics
  - Darifenacin
  - Fesoterodine
  - Oxybutynin (Overall)
    - Oxybutynin_Gel
    - Oxybutynin_Oral
    - Oxybutynin_Oral XL
    - Oxybutynin_TD
  - Solifenacin
  - Tolterodine (Overall)
    - Tolterodine IR
    - Tolterodine LA
  - Trospium (Overall)
    - Trospium IR
    - Trospium XR
- $Beta_3$-adrenoceptor agonist
  - Mirabegron