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Mirabegron and antimuscarinic use in frail overactive bladder patients in the United States Medicare population

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Abstract

Introduction: Overactive bladder (OAB) and frailty are independently associated with patient burden. However, economic burden and treatment-taking behavior have not been well characterized among frail patients with OAB, which, given the varying safety and tolerability profiles of available treatments, is crucial.

Objectives: To assess costs, health care resource utilization, treatment-taking behavior (persistence and adherence) to OAB medication in older, frail OAB patients.

Methods: This was a retrospective cohort study using international business machines MarketScan Medicare Supplemental claims data. Eligible frail patients (per Claims-based Frailty Index score) initiating mirabegron were 1:2 propensity score matched (based on age, sex, and other characteristics) with those initiating antimuscarinics and were followed up to 1 year. All-cause, per-person, per-month costs, health care encounters, persistence (median days to discontinuation assessed using Kaplan−Meier methods) and adherence (≥80% of proportion of days covered at Day 365) were compared.

Results: From 2527 patients with incident mirabegron (21%) or antimuscarinic (79%) dispensations, 516 incident mirabegron users (median age: 82 years, 64% female) were matched to 1032 incident antimuscarinic users (median age: 81 years, 62% female). Median cost was higher in mirabegron group ($1581 vs. $1197 per month); this was primarily driven by medication cost. There was no difference in medical encounters. Adherence (39.1% vs. 33.8%) and persistence (103 vs. 90 days) were higher in mirabegron users.

Conclusions: Among frail older adults with OAB, mirabegron use was associated with higher costs and potential improvements in treatment-taking behaviors, particularly with respect to treatment adherence, versus those initiating antimuscarinics.

KEYWORDS
adherence, costs, frail, health care resource utilization, persistence

1 | INTRODUCTION

Overactive bladder (OAB) is a urologic condition characterized by urgency, with or without urge urinary incontinence, and accompanied by frequency and nocturia.[1,2] Estimates of OAB prevalence among the general US population range between 16.5% and 23.3%.[3] Research using the Timed Up and Go Test, as a parsimonious measure of frailty, has demonstrated a highly significant association between OAB and frailty, even after adjusting for age and other risk factors.[4]

Frailty is associated with older age and is a risk factor for adverse outcomes including increased health services use, institutionalization, and death.[5] Given the association between frailty and excess health care costs, the Center for Medicare and Medicaid Services applies a survey-based frailty adjustment to payments for enrollees in Program of All-Inclusive Care for the Elderly organizations.[6,7] To characterize frailty among larger populations, an index was developed and was adapted for use with administrative claims data (the claims-based frailty index [CFI]).[8] The CFI is the most widely used measure to assess frailty in administrative claims data; its use improves the prediction of adverse outcomes when added to demographics and comorbidities, and there is evidence that higher scores are associated with increased mobility impairment, falls, disability, and mortality.[8–10]

Anticholinergics are prescribed for a variety of conditions (e.g., depression, chronic obstructive pulmonary disease, Parkinson's disease, and OAB) and are associated with numerous adverse effects on physical and mental function,[11–13] particularly among older frail individuals.[14] First-line pharmacotherapy for OAB typically comprises es oral antimuscarinics, which are part of the class of anticholinergic medications indicated for and used for the treatment of OAB, and beta-3 adrenergic agonists (mirabegron and vibegron).[15,16] Recent American Urological Association Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) guidelines for OAB management state that clinicians should use caution in prescribing antimuscarinics in patients who are using other medications with anticholinergic properties, and antimuscarinics and mirabegron (the only beta-3 adrenergic agonist available at the time of guideline drafting) for frail OAB patients. These cautions are due to concerns about cumulative anticholinergic burden and that OAB medications may have a lower therapeutic index among frail individuals and a poorer safety profile.[15] However, there is an overall lack of evidence regarding symptom management among frail older adults with OAB.[17]

OAB and frailty are each associated with economic burden in the United States, although the impact of frailty on OAB-related costs has not been described. The direct costs of OAB in the United State was estimated to be $49.1 billion in 2007 (most recent data) and was projected to increase by 168% by 2020.[18] Studies have consistently demonstrated an association between frailty and increased health care costs.[19–21] In the United State, application of the CFI to Medicare claims data showed that the incremental annual costs associated with frailty were $2712, $7915, and $16 449 for prefrail, mildly frail, and moderately to severely frail patients, respectively.[22]

It is important to understand the impact of frailty on OAB-related costs, particularly among users of the most commonly prescribed OAB medications (mirabegron and antimuscarinics). Additionally, persistence and adherence among frail individuals using different OAB therapies should be evaluated to determine whether any treatment-related differences in safety or therapeutic index manifest as higher costs or poorer treatment-taking behaviors. Therefore, among a cohort of frail older adults with OAB, the objectives of this study were to compare all-cause costs and encounters and persistence and adherence between incident antimuscarinic and incident mirabegron users.

2 | MATERIALS AND METHODS

2.1 | Study design and data source

This was a retrospective cohort study using international business machines MarketScan Medicare Supplemental claims data, comprising approximately 11 million individuals covered by Medicare Supplemental plan. Elements collected include patient demographics, geographic data, inpatient and outpatient medical encounters, payment both by Medicare and commercial, and drug information.[23]

2.2 | Claims-Based assessment of frailty

Frailty was assessed using the CFI.[8] Categories of frailty derived from the calculated CFI include robust (CFI < 0.15), prefrail (0.15−0.24) mildly frail (0.25−0.34) and moderate-to-severely frail (≥0.35). Patient diagnoses used in the CFI were captured by International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes.[10,24]

2.3 | Study population

Patients were identified based on the presence of ≥1 dispensation for mirabegron (vibegron was not available

at the time of the study) or an antimuscarinic between October 1, 2016, and September 30, 2018. Patients were required to be ≥65 years of age on the date of the first observed claim for mirabegron or an antimuscarinic (i.e., the index date). Exclusion criteria were simultaneous prescriptions of both drugs at index and a record of neurogenic bladder during any point of the study. Patients were required to have ≥1 year of continuous enrollment data before index date (pre-index period) and ≥1 month of follow-up post-index. A ≤ 45-day gap in enrollment was permitted during the pre-index period.

CFI score was estimated during the pre-index period. Patients who had a CFI score of ≥0.25 were included in the study cohort.

2.4 | Study outcomes

2.4.1 | Costs and encounters

All-cause costs were calculated as the sum of all encounters and associated costs from inpatient, outpatient, emergency room, and outpatient pharmacy settings. Encounters and costs that were specific to OAB were ascertained according to the following: Medical claims with one or more ICD-9/10 codes for OAB diagnosis (regardless of whether OAB is a primary or secondary diagnosis), medical claims with one or more Current Procedural Terminology codes for onabotulinumtoxinA, sacral nerve stimulation, or percutaneous tibial nerve stimulation, and/or pharmacy claims for mirabegron or antimuscarinics.

2.4.2 | Adherence and persistence

Adherence was determined by the proportion of days covered (PDC, %), where the number of days a patient was known to have medication coverage over the period is divided by the number of days in the period. Patients were considered adherent if the PDC was ≥0.80.[25] Treatment persistence was assessed by Kaplan−Meier methods as the days to discontinuation, which was defined as (1) the absence of a prescription fill within the defined 30-day allowable gap following the end of available therapy (calculated from fill dates and days of supply) or (2) the presence of a claim for the other study treatment indicating a potential switch or add-on, whichever occurred first. Antimuscarinic drugs were treated as therapeutic equivalents; switches between antimuscarinic treatments were not considered as discontinuation events. The end of the data period and Day 365 were considered censoring events.

2.5 | Statistical analysis

2.5.1 | Propensity score (PS) matching

PS matching was used to balance the distribution of baseline characteristics that might affect the outcomes.[26] Variables included in the PS were age, sex, CFI category, Charlson Comorbidity Index (CCI) comorbidities, plan type, geographic region, pre-index health care costs, and other OAB medication class use. Nearest neighbor matching of mirabegron to antimuscarinic users was done on a 1:2 ratio, using a recommended caliper width of 0.2.[27] Incident antimuscarinic users who were within a caliper of 0.2 of the standard deviation (SD) of the logit of the PS were considered as potential matches for the incident mirabegron users. The first and second closest matches based on the smallest absolute difference in PS were selected as matched patients for the mirabegron user. If there was a tie, the match was selected randomly. Matching was conducted without replacement. Mirabegron users who were not matched to two antimuscarinic users were dropped from the matched analysis. Absolute standardized mean differences (SMD) were calculated to assess the balance between the groups before and after the matching: SMD values less than 0.1 were considered negligible.[28]

2.5.2 | Statistical comparisons

For costs and encounters, differences were estimated between matched pairs, and the medians of these differences were calculated. Distribution-free confidence limits (95% CL) for the median difference were derived using previously published methods.[29] An estimate with a CL that did not include 0 was considered statistically significant. Mean/median costs were calculated for the duration of patient follow-up and per-patient per-month (PPPM). Regarding the latter, the post-index period for each patient was partitioned into 30-day intervals, each of which was considered an analytic month. Partial months (< 30 days) were dropped from the analysis. Costs and encounters were calculated for each month for each patient. Mean and median PPPM were summarized across patients and analytic months.

Kaplan−Meier (KM) analyses were used to estimate the time to treatment discontinuation for each treatment group. The proportion of individuals still on treatment at 90, 180, and 365 days was reported with 95% confidence intervals (CIs). Mean PDC and proportion of individuals adherent to treatment were tabulated at 90, 180, and 365 days. Tests for between-group differences were conducted using the Fisher Exact test.

2.5.3 | Sensitivity analyses

Two sensitivity analyses were conducted to assess the impact of different assumptions on the study findings. First, health care costs, number of encounters and treatment adherence were calculated from index date to time of index treatment discontinuation (vs. the duration of patient follow-up). Second, the permissible gap of 30 days in the assessment of persistence was extended to 60 days.

3 | RESULTS

Among 2527 patients identified as meeting the study criteria (Table 1) before matching, 537 initiated mirabegron and 1990 initiated an antimuscarinic. Oxybutynin was the most frequently observed antimuscarinic (65.2%). The mean (SD) age was 81.3 (7.3) years for mirabegron users and 80.2 (7.96) years for antimuscarinic users; the majority of both groups were female. Groups differed somewhat in terms of geographic distribution, insurance plan type and median enrollment.

In terms of clinical characteristics, the median CFI score was similar among mirabegron and antimuscarinic users; 23.7% of antimuscarinic users had moderate/severe frailty versus 22.2% of mirabegron users. The median CCI score for both groups was 6.0. A weak positive association between CCI score and CFI score was found (Pearson correlation coefficient = 0.2), however, there was no interaction between CFI score and individual CCI conditions in the logistic regression model which used for PS match. The presence of dementia was higher among mirabegron users (44.3%) than antimuscarinic users (38.7%). 14% of mirabegron users had received an antimuscarinic in the pre-index period, while 2.6% of antimuscarinic users had received mirabegron during the pre-index period.

The median enrollment time for mirabegron users was longer than that of antimuscarinic users, as was the percentage of those who contributed a full year of follow-up (Table 1). Pre-index median health care costs were higher for mirabegron users versus antimuscarinic users (Table 1).

After PS-matching, the study sample consisted of 516 mirabegron users and 1032 antimuscarinic users. Baseline characteristics were generally well balanced (Table 1), although the SMD for age remained above 0.1 (SMD = 0.1124), as well as the SMD for previous use of an OAB medication during the pre-index period (SMD = 0.4142). Patient attrition is presented in Figure 1.

3.1 | Costs

Among matched cohorts, the largest contributor to all-cause health care costs PPPM was outpatient costs, followed by inpatient costs, and then pharmacy costs (Table 2). The mean and median total health care costs PPPM were higher among mirabegron users (mean: $6010; median: $1581) than antimuscarinic users (mean: $5515; median: $1197). The median difference in total health care costs PPPM was $308 (95% CL: $178−$470) more among mirabegron users, a difference which was statistically significant. The largest median difference was observed for pharmacy costs, which was statistically significantly higher ($218 [95% CL: $169−$263]) among mirabegron users versus antimuscarinic users. There were no differences in inpatient and outpatient costs between groups. The trends observed for OAB-related costs mirrored those for total health care costs (Table 2).

3.2 | Encounters

Regarding all-cause medical encounters, the largest median difference observed was for pharmacy claims, estimated at 0.25 more claims PPPM among mirabegron users (95% CL: 0.0−0.5; Table 2) but not statistically significant. Trends in number of OAB-related medical encounters were similar to those observed for all-cause medical encounters (Table 2). Median differences in OAB-related medical encounters PPPM were not statistically significant between groups. When health care costs and encounters were calculated from index date to time of index treatment discontinuation (instead of through end of follow-up), the observed trends were unchanged (Supporting Information: Table 1).

3.3 | Treatment persistence

The median time to treatment discontinuation (Figure 2) was nonstatistically significantly higher among mirabegron users (103 days; 95% CI: 30−360) versus antimuscarinic users (90 days; 95% CI: 30−326). A higher percentage of mirabegron users were persistent to therapy versus antimuscarinic users at all time points evaluated (90, 180, and 365 days; Table 3). Extending the allowable gap in treatment to 60 days did not change the findings (Supporting Information: Table 2).

TABLE 1 Baseline characteristics of the incident and matched-incident mirabegron and antimuscarinic groups

Category	Overall cohort			Matched cohort		
	Mirabegron users (n = 537)	Antimuscarinic users (n = 1990)	Standardized mean difference[a]	Mirabegron users (n = 516)	Antimuscarinic users (n = 1032)	Standardized mean difference[a]
Year of index date [b], n (%)						
2016	166 (30.9)	477 (24.0)	0.1561	150 (29.1)	270 (26.2)	0.0651
2017	323 (60.1)	1394 (70.1)	0.2089	319 (61.8)	661 (64.1)	0.0462
2018	48 (8.9)	119 (6.0)	0.1128	47 (9.1)	101 (9.8)	0.0232
Sex, n (%)						
Female	344 (64.1)	1372 (68.9)	0.1036	332 (64.3)	638 (61.8)	0.0522
Male	193 (35.9)	618 (31.1)		184 (35.7)	394 (38.2)	
Age at index date (years old)						
Mean (SD)	81.3 (7.26)	80.2 (7.85)	0.1453	81.3 (7.29)	80.5 (7.92)	0.1124
Median (Q1–Q3)	82.0 (76.0–87.0)	80.0 (74.0–86.0)		82.0 (76.0–87.0)	81.0 (74.0–87.0)	
Min–max	65–98	65–104		65–98	65–104	
Age category at index date, n (%)						
65[c]	4 (0.7)	10 (0.5)	0.0308	3 (0.6)	3 (0.3)	0.0441
65–69	30 (5.6)	191 (9.6)	0.1519	29 (5.6)	111 (10.8)	0.1881
70–74	75 (14.0)	362 (18.2)	0.1152	72 (14.0)	159 (15.4)	0.0411
75–79	102 (19.0)	373 (18.7)	0.0064	100 (19.4)	187 (18.1)	0.0323
80–84	141 (26.3)	442 (22.2)	0.0945	133 (25.8)	232 (22.5)	0.0771
85+	189 (35.2)	622 (31.3)	0.0837	182 (35.3)	343 (33.2)	0.0429
Region of residence at index date, n (%)						
Northeast	151 (28.1)	393 (19.7)	0.1971	150 (29.1)	298 (28.9)	0.0043
North central	118 (22.0)	836 (42.0)	0.4398	107 (20.7)	231 (22.4)	0.0401
South	228 (42.5)	633 (31.8)	0.2218	220 (42.6)	434 (42.1)	0.0118
West	40 (7.4)	125 (6.3)	0.0462	39 (7.6)	68 (6.6)	0.0378
Unknown	0 (0)	3 (0.2)	0.0550	0 (0)	1 (0.1)	0.0440

TABLE 1 (Continued)

Category	Overall cohort			Matched cohort		
	Mirabegron users (*n* = 537)	Antimuscarinic users (*n* = 1990)	Standardized mean difference[a]	Mirabegron users (*n* = 516)	Antimuscarinic users (*n* = 1032)	Standardized mean difference[a]
Claims-based frailty index during the pre-index period[d]						
Mean (SD)	0.318 (0.076)	0.319 (0.074)	0.0139	0.318 (0.075)	0.318 (0.071)	0.0092
Median (Q1–Q3)	0.289 (0.266–0.338)	0.293 (0.268–0.345)		0.289 (0.266–0.337)	0.294 (0.268–0.344)	
Min–max	0.25–0.63	0.25–0.68		0.25–0.63	0.25–0.65	
Claims-based frailty index during the pre-index period, *n* (%)						
0.25 ≤ CFI <0.35	418 (77.8)	1519 (76.3)	0.0359	404 (78.3)	796 (77.1)	0.0279
CFI > = 0.35	119 (22.2)	471 (23.7)		112 (21.7)	236 (22.9)	
Charlson comorbidity index score						
Mean (SD)	6.6 (2.98)	6.5 (2.90)	0.0359	6.6 (2.95)	6.6 (2.88)	0.0080
Median (Q1–Q3)	6.0 (4.0–9.0)	6.0 (4.0–8.0)		6.0 (4.0–9.0)	6.0 (5.0–8.0)	
Min–max	0–21	0–18		0–16	0–18	
Charlson comorbidity index, *n* (%)						
Myocardial infarction	128 (23.8)	524 (26.3)	0.0576	127 (24.6)	255 (24.7)	0.0022
Congestive Heart Failure	300 (55.9)	1138 (57.2)	0.0266	285 (55.2)	582 (56.4)	0.0234
Peripheral vascular disease	342 (63.7)	1237 (62.2)	0.0316	330 (64.0)	643 (62.3)	0.0341
Cerebrovascular disease	356 (66.3)	1256 (63.1)	0.0666	339 (65.7)	688 (66.7)	0.0205
Dementia	238 (44.3)	770 (38.7)	0.1144	227 (44.0)	410 (39.7)	0.0865
Chronic pulmonary disease	340 (63.3)	1296 (65.1)	0.0378	324 (62.8)	662 (64.1)	0.0282
Rheumatic disease	78 (14.5)	256 (12.9)	0.0483	77 (14.9)	151 (14.6)	0.0082
Peptic ulcer disease	40 (7.4)	150 (7.5)	0.0034	40 (7.8)	81 (7.8)	0.0036
Mild liver disease	71 (13.2)	272 (13.7)	0.0131	66 (12.8)	176 (17.1)	0.1199
Moderate or severe liver disease	6 (1.1)	23 (1.2)	0.0036	6 (1.2)	10 (1.0)	0.0189
Diabetes without chronic complication	78 (14.5)	323 (16.2)	0.0473	76 (14.7)	156 (15.1)	0.0109
Diabetes with chronic complication	228 (42.5)	848 (42.6)	0.0031	223 (43.2)	419 (40.6)	0.0530

(Continues)

TABLE 1 (Continued)

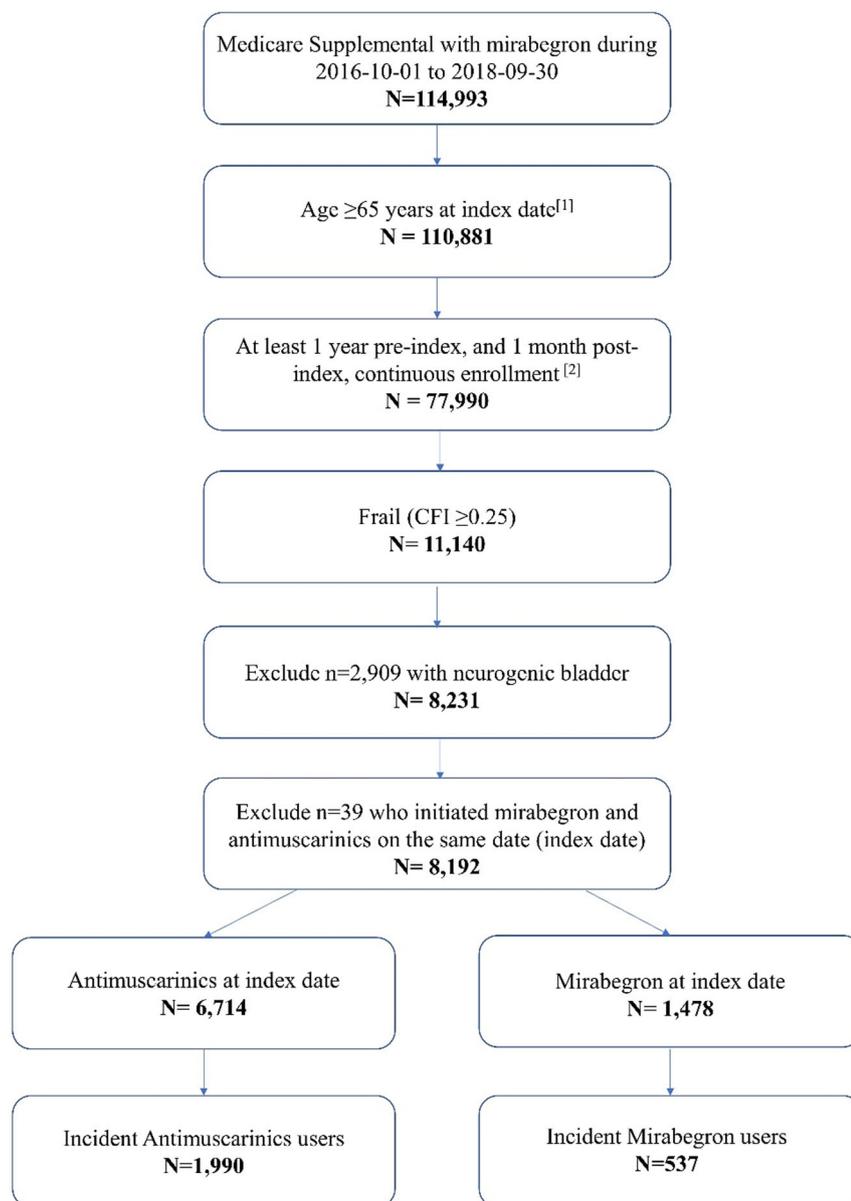|	Overall cohort			Matched cohort		
Category	Mirabegron users (n = 537)	Antimuscarinic users (n = 1990)	Standardized mean difference[a]	Mirabegron users (n = 516)	Antimuscarinic users (n = 1032)	Standardized mean difference[a]
Hemiplegia or paraplegia	61 (11.4)	260 (13.1)	0.0521	57 (11.0)	114 (11.0)	0.0000
Renal disease	254 (47.3)	934 (46.9)	0.0073	244 (47.3)	486 (47.1)	0.0039
Any malignancy[e]	128 (23.8)	417 (21.0)	0.0692	120 (23.3)	252 (24.4)	0.0273
Metastatic solid tumor	37 (6.9)	131 (6.6)	0.0123	35 (6.8)	78 (7.6)	0.0300
AIDS/HIV	2 (0.4)	1 (0.1)	0.0702	1 (0.2)	1 (0.1)	0.0254
Plan type at index date, n (%)						
Comprehensive	208 (38.7)	1180 (59.3)	0.4203	206 (39.9)	442 (42.8)	0.0590
Preferred Provider Organization	301 (56.1)	696 (35.0)	0.4331	282 (54.7)	518 (50.2)	0.0893
All other fee service plan	28 (5.2)	114 (5.7)	0.0226	28 (5.4)	72 (7.0)	0.0643
Type of antimuscarinic at index date (among antimuscarinic users),[f] n (%)						
Darifenacin	0 (0)	26 (1.3)		0 (0)	15 (1.5)	
Fesoterodine	0 (0)	25 (1.3)		0 (0)	12 (1.2)	
Oxybutynin	0 (0)	1297 (65.2)		0 (0)	677 (65.6)	
Solifenacin	0 (0)	209 (10.5)		0 (0)	135 (13.1)	
Tolterodine	0 (0)	360 (18.1)		0 (0)	162 (15.7)	
Trospium	0 (0)	75 (3.8)		0 (0)	32 (3.1)	
All-cause health care costs during pre-index period ($)						
Mean (SD)	$76 059 ($111 311)	$65 112 ($89 867)	0.1082	$76 687 ($112 355)	$80 220 ($110 839)	0.0317
Median (Q1–Q3)	$46 415 ($23 407–$92 813)	$39 025 ($20 048–$73 621)		$47 177 ($23 457–$94 247)	$45 227 ($23 004–$92 709)	
Min-max	$1021–$1 505 117	$604–$1 054 954		$1021–$1 505 117	$1235–$1 054 954	
Previous use of any OAB medication during pre-index period, n (%)						
Yes	75 (14.0)	52 (2.6)	0.4208	64 (12.4)	20 (1.9)	0.4142
Mirabegron	0 (0)	52 (2.6)		0 (0)	20 (1.9)	
Antimuscarinic	75 (14.0)	0 (0)		64 (12.4)	0 (0)	

3.4 | Treatment adherence

Treatment adherence was higher among mirabegron users compared to matched antimuscarinic users (Table 3), although mirabegron users had a longer average follow-up time. The proportion of patients adherent to treatment (i.e., proportion with PDC ≥ 0.80) was 57.8% among mirabegron users and 49.9% among antimuscarinic users at 90 days ($p < 0.01$), and 39.1% among mirabegron users and 33.8% among antimuscarinic users at 365 days ($p = 0.04$). However, no differences were noted in PDC between the matched groups across all time points considered (90, 180, and 365 days) when adherence was assessed over time on treatment (Supporting Information: Table 2).

4 | DISCUSSION

In this retrospective study, a large, US claims data set was used to assess differences in health care spending and to characterize treatment-taking behaviors among frail older patients with OAB who were newly treated with either mirabegron or antimuscarinics. To our knowledge, this is the first study to assess these outcomes among frail older adults with OAB.

New users of mirabegron had higher health care costs than new users of antimuscarinics. This difference was driven by medication costs rather than the number of claims, and no unexpected differences in terms of medical encounters were noted among frail patients taking mirabegron compared to those on antimuscarinics. The difference in pharmacy costs could indicate that those who received mirabegron had broader and more generous prescription coverage than those who received antimuscarinics. Mirabegron users were more (nonsignificantly) persistent than antimuscarinic users and had higher adherence across all time points considered. However, mirabegron users had longer follow-up times than antimuscarinic users, which allowed for more observation of medication coverage. Sensitivity analyses that considered time on treatment versus the full follow-up period were conducted to examine whether PDC was a function of longer treatment time rather than gaps in therapy. No differences in adherence were observed, which indicates that the differences observed when PDC was considered over time on treatment are likely not due to gaps in therapy. It should be noted that safety-related discontinuations could also result in decreased costs; however, reason for discontinuation were not available in the current analysis and it was not possible to determine whether they contributed to observed differences in costs.

TABLE 1 (Continued)

Category	Overall cohort			Matched cohort		
	Mirabegron users (*n* = 537)	Antimuscarinic users (*n* = 1990)	Standardized mean difference[a]	Mirabegron users (*n* = 516)	Antimuscarinic users (*n* = 1032)	Standardized mean difference[a]
Days of follow-up[g]						
Mean (SD)	285.1 (115.2)	256.3 (117.8)		290.8 (111.1)	270.3 (118.7)	
Median (Q1–Q3)	365.0 (207.0–365.0)	304.0 (145.0–365.0)		365.0 (220.5–365.0)	365.0 (152.0–365.0)	
Min–max	30–365	30–365		30–365	31–365	
12-month enrollment; n (%)	316 (59.0)	814 (41.0)		312 (60.0)	526 (51.0)	

Abbreviations: OAB, Overactive Bladder; SD, standard deviation.

[a] Absolute value of standardized mean difference is shown. A standardized mean difference < 0.1 is considered well-balanced with negligible difference between the groups.

[b] Index date was defined as the first claim date of Mirabegron or antimuscarinics during the ascertainment period (January 10, 2016–September 09, 2019).

[c] A small percentage of patients were anticipated in the 65 year old age. Age 65 is presented separately for cohort understanding. Overlap of 65 and 65–70 age groups was intentional.

[d] Pre-index period was defined as the 12-month period before index date.

[e] Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin.

[f] Sum of proportions may be greater than 100%.

[g] The period of follow-up began on the index date and ended at the end of enrollment or 1 year-post index date, whichever occurred first.

Findings from the present study regarding treatment adherence and persistence are in line with those derived from a general OAB population. In a retrospective claims analysis of OAB patients receiving either mirabegron or anticholinergic therapies (including antimuscarinics), Sussman et al. found that 44% of patients treated with mirabegron and 31% of patients treated with anticholinergics adhered to their index medication during the 12-month study period (defined as PDC ≥0.80).[25] In the present study, adherence was also higher among mirabegron users versus antimuscarinic users, although this could have been impacted by a longer persistence rate among mirabegron users. Furthermore, using a definition similar to that employed by the present study, Sussman et al. reported that 19% of mirabegron users and 12% of anticholinergic users were persistent to therapy at 12 months. The present study found higher treatment persistence among mirabegron users (25%) versus antimuscarinic users (23%) at 12 months. This suggests that relative to a general OAB population, older, frail OAB patients who receive mirabegron do not exhibit poorer treatment-taking behaviors that arise as a result of unique safety issues or decreased treatment efficacy. Overall, these findings are also consistent with observations that mirabegron is associated with better adherence and persistence than antimuscarinics, given its association with significantly fewer side effects.[30,31]

Findings from the present study suggest that compared to a general OAB population, frail OAB patients have higher health care costs. A study by Durden et al. using Truven MarketScan data reported that subsequent to PS-matching, the mean all-cause health care costs

TABLE 2 All-cause and OAB-related costs and encounters for matched cohorts

Category	Statistics	Mirabegron users (n = 516)	Antimuscarinic users (n = 1032)	Median difference (Mira-AM), (95% CL)
All-cause health care (inpatient, outpatient, and outpatient pharmacy) costs[a]				
Total health care costs	Mean (SD)	$56 590 ($89 982)	$48 084 ($88 142)	$4881 ($2560–$7267)
	Median (Q1–Q3)	$25 370 ($10 866–$67 180)	$19 651 ($6472–$50 198)	
	Min–max	$213–$1239 664	$31–$1 023 475	
Total health care costs (PPPM)	Mean (SD)	$6010 ($17 429)	$5515 ($18 015)	$308 ($178–$470)
	Median (Q1–Q3)	$1581 ($676–$3929)	$1,197 ($434–$3283)	
	Min–max	$0–$426 313	$0–$471 260	
All-cause inpatient costs				
Hospitalization costs	Mean (SD)	$20 098 ($49 234)	$17 866 ($47 660)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$17 020)	$0 ($0–$15 673)	
	Min–max	$0–$494 527	$0–$474 883	
Hospitalization costs (PPPM)	Mean (SD)	$2134 ($14 491)	$2049 ($15 037)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$422 878	$0–$468 397	
All-cause outpatient costs				
Outpatient services costs	Mean (SD)	$27 019 ($64 510)	$23 849 ($58 295)	$1046 ($228–$2100)
	Median (Q1–Q3)	$10 365 ($3482–$30 857)	$8417 ($2436–$24,283)	
	Min–max	$0–$1 180 053	$0–$896 078	
Outpatient services costs (PPPM)	Mean (SD)	$2869 ($8638)	$2735 ($8475)	$25 ($24–$68)
	Median (Q1–Q3)	$549 ($144–$1975)	$498 ($131–$1769)	
	Min–max	$0–$130 878	$0–$219 452	
Total outpatient office costs	Mean (SD)	$5293 ($10 009)	$4559 ($10254)	$324 ($125–$548)
	Median (Q1–Q3)	$2412 ($522–$6115)	$1495 ($411–$4649)	
	Min–max	$0–$147 020	$0–$199 132	
Total outpatient office costs (PPPM)	Mean (SD)	$562 ($1302)	$523 ($1538)	$11 ($0–$33)
	Median (Q1–Q3)	$181 ($0–$569)	$145 ($0–$464)	
	Min–max	$0–$27 539	$0–$38 485	
	Median (Q1–Q3)	$44 ($0–$367)	$0 ($0–$254)	
	Min–max	$0–$27 265	$0–$38 485	
All-cause outpatient pharmacy costs				
Prescription claim costs	Mean (SD)	$9473 ($13 174)	$6369 ($13021)	$2021 ($1665–$2583)
	Median (Q1–Q3)	$5974 ($2883–$11 004)	$3091 ($1089–$7220)	
	Min–max	$117–$118 706	$6–$205 579	
Prescription claim costs (PPPM)	Mean (SD)	$1006 ($1750)	$731 ($2004)	$218 ($169–$263)
	Median (Q1–Q3)	$536 ($120–$1182)	$255 ($52–$805)	
	Min–max	$0–$33 063	$0–$77 703	

(Continues)

TABLE 2 (Continued)

Category	Statistics	Mirabegron users ($n = 516$)	Antimuscarinic users ($n = 1032$)	Median difference (Mira-AM), (95% CL)
All-cause inpatient encounters				
Hospitalization encounters	N (%)	213 (41.3%)	398 (38.6%)	0 (0–0)
	Mean (SD)	0.547 (0.755)	0.525 (0.800)	
	Median (Q1–Q3)	0 (0–1)	0 (0–1)	
	Min–max	0–5	0–7	
Hospitalization encounters (PPPM)	Mean (SD)	0.058 (0.237)	0.060 (0.247)	0 (0–0)
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–2	0–3	
All-cause outpatient services				
Outpatient services encounters	N (%)	511 (99.0%)	1024 (99.2%)	4 (2–7)
	Mean (SD)	37.727 (29.137)	32.842 (28.569)	
	Median (Q1–Q3)	31.5 (16–53)	27 (12–47)	
	Min–max	0–139	0–349	
Outpatient services encounters (PPPM)	Mean (SD)	4.006 (3.810)	3.767 (3.755)	0 (0–0.5)
	Median (Q1–Q3)	3 (1–6)	3 (1–5)	
	Min–max	0–27	0–30	
Total outpatient office encounters	N (%)	492 (95.3%)	951 (92.2%)	2 (1–4)
	Mean (SD)	21.339 (21.468)	17.093 (18.482)	
	Median (Q1–Q3)	15 (5–31.5)	11 (3–24.5)	
	Min–max	0–124	0–123	
Total outpatient office encounters (PPPM)	Mean (SD)	2.266 (2.546)	1.960 (2.271)	0 (0–0)
	Median (Q1–Q3)	2 (0–3)	1 (0–3)	
	Min–max	0–18	0–23	
All-cause outpatient pharmacy				
Prescription claim encounters	N (%)	516 (100%)	1032 (100%)	5 (0–9)
	Mean (SD)	59.285 (41.798)	53.592 (44.029)	
	Median (Q1–Q3)	52 (27–80)	43 (21–72)	
	Min–max	1–246	1–297	
Prescription claim encounters (PPPM)	Mean (SD)	6.296 (4.746)	6.147 (5.181)	0.25 (0–0.5)
	Median (Q1–Q3)	5 (3–9)	5 (3–9)	
	Min–max	0–43	0–116	
OAB-related health care (inpatient, outpatient, and outpatient pharmacy) costs[a]				
Total health care costs	Mean (SD)	$2919 ($3421)	$1205 ($2988)	$1238 ($1047–$1546)
	Median (Q1–Q3)	$2147 ($825–$4199)	$335 ($103–$1138)	
	Min–max	$142–$35393	$2–$39044	
Total health care costs (PPPM)	Mean (SD)	$310 ($886)	$138 ($924)	$37 ($0–$64)
	Median (Q1–Q3)	$43 ($0–$363)	$0 ($0–$74)	
	Min–max	$0–$28 913	$0–$38 719	

TABLE 2 (Continued)

Category	Statistics	Mirabegron users (n = 516)	Antimuscarinic users (n = 1032)	Median difference (Mira-AM), (95% CL)
OAB-related inpatient costs				
Hospitalization costs	Mean (SD)	$125 ($1694)	$246 ($2469)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$28 913	$0–$38 719	
Hospitalization costs (PPPM)	Mean (SD)	$13 ($553)	$28 ($839)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$28 913	$0–$38 719	
OAB-related outpatient services costs				
Outpatient services costs	Mean (SD)	$618 ($2165)	$352 ($1241)	$0 ($0–$2)
	Median (Q1–Q3)	$109 ($0–$382)	$70 ($0–$253)	
	Min–max	$0–$32,079	$0–$17,351	
Outpatient services costs (PPPM)	Mean (SD)	$66 ($600)	$40 ($339)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$22 782	$0–$17 351	
Total outpatient office costs	Mean (SD)	$299 ($714)	$230 ($878)	$0 ($0–$0)
	Median (Q1–Q3)	$83 ($0–$284)	$0 ($0–$180)	
	Min–max	$0–$8498	$0–$15 277	
Total outpatient office costs (PPPM)	Mean (SD)	$32 ($172)	$26 ($187)	$0 ($0 - $0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$5,042	$0–$5,957	
Primary care provider outpatient office costs[b]	Mean (SD)	$60 ($210)	$58 ($211)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$2813	$0–$3625	
Primary care provider outpatient office costs (PPPM)	Mean (SD)	$6 ($52)	$7 ($60)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$1911	$0 - $3519	
Obstetrics/gynecology outpatient office costs[c]	Mean (SD)	$25 ($269)	$4 ($43)	$0 ($0 - $0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$5483	$0–$810	
Obstetrics/gynecology outpatient office costs (PPPM)	Mean (SD)	$3 ($72)	$0 ($13)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$4516	$0–$810	
Urologist outpatient office costs[d]	Mean (SD)	$188 ($604)	$141 ($816)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$143)	$0 ($0–$0)	
	Min–max	$0–$8498	$0 - $15 277	
Urologist outpatient office costs (PPPM)	Mean (SD)	$20 ($142)	$16 ($171)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$3883	$0–$5957	

(Continues)

TABLE 2 (Continued)

Category	Statistics	Mirabegron users (*n* = 516)	Antimuscarinic users (*n* = 1032)	Median difference (Mira-AM), (95% CL)
Other outpatient office costs	Mean (SD)	$26 ($128)	$27 ($214)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$1742	$0–$5638	
Other outpatient office costs (PPPM)	Mean (SD)	$3 ($29)	$3 ($45)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$0)	$0 ($0–$0)	
	Min–max	$0–$752	$0–$2581	
OAB-related outpatient pharmacy costs				
Prescription claim costs	Mean (SD)	$2176 ($1873)	$607 ($1096)	$1095 ($927–$1341)
	Median (Q1–Q3)	$1787 ($657–$3545)	$158 ($38–$599)	
	Min–max	$78–$19 159	$2–$13 150	
Prescription claim costs (PPPM)	Mean (SD)	$231 ($344)	$70 ($189)	$0 ($0–$0)
	Median (Q1–Q3)	$0 ($0–$348)	$0 ($0–$32)	
	Min–max	$0–$4044	$0–$3985	
OAB-related inpatient encounters				
Hospitalization encounters	N (%)	3 (0.6%)	15 (1.5%)	0 (0–0)
	Mean (SD)	0.006 (0.076)	0.015 (0.120)	
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–1	0–1	
Hospitalization encounters (PPPM)	Mean (SD)	0.001 (0.025)	0.002 (0.041)	0 (0–0)
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–1	0–1	
OAB-related outpatient services				
Outpatient services encounters	N (%)	319 (61.8%)	556 (53.9%)	0 (0–0)
	Mean (SD)	1.787 (2.459)	1.359 (2.273)	
	Median (Q1–Q3)	1 (0–3)	1 (0–2)	
	Min–max	0–17	0–31	
Outpatient services encounters (PPPM)	Mean (SD)	0.190 (0.515)	0.156 (0.482)	0 (0–0)
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–7	0–15	
OAB-related outpatient services				
Total outpatient office encounters	N (%)	291 (56.4%)	463 (44.9%)	0 (0–0)
	Mean (SD)	1.463 (2.140)	1.080 (2.080)	
	Median (Q1–Q3)	1 (0–2)	0 (0–1)	
	Min–max	0–17	0–31	
Total outpatient office encounters (PPPM)	Mean (SD)	0.155 (0.452)	0.124 (0.434)	0 (0–0)
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–7	0–15	

TABLE 2 (Continued)

Category	Statistics	Mirabegron users (n = 516)	Antimuscarinic users (n = 1032)	Median difference (Mira-AM), (95% CL)
Primary care provider outpatient office encounters[b]	N (%)	112 (21.7%)	253 (24.5%)	0 (0–0)
	Mean (SD)	0.395 (1.064)	0.420 (0.937)	
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–11	0–8	
Primary care provider outpatient office encounters (PPPM)	Mean (SD)	0.042 (0.243)	0.048 (0.230)	0 (0–0)
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–6	0–3	
OAB-related outpatient services				
Obstetrics/gynecology outpatient office encounters[c]	N (%)	19 (3.7%)	16 (1.6%)	0 (0–0)
	Mean (SD)	0.089 (0.665)	0.026 (0.299)	
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–11	0–8	
Obstetrics/gynecology outpatient office encounters (PPPM)	Mean (SD)	0.009 (0.131)	0.003 (0.062)	0 (0–0)
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–5	0–2	
Urologist outpatient office encounters[d]	N (%)	175 (33.9%)	195 (18.9%)	0 (0–0)
	Mean (SD)	0.808 (1.526)	0.449 (1.255)	
	Median (Q1–Q3)	0 (0–1)	0 (0–0)	
	Min–max	0–9	0–13	
Urologist outpatient office encounters (PPPM)	Mean (SD)	0.086 (0.317)	0.051 (0.251)	0 (0–0)
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–4	0–4	
OAB-related outpatient services				
Other outpatient office encounters	N (%)	49 (9.5%)	79 (7.7%)	0 (0–0)
	Mean (SD)	0.171 (0.701)	0.186 (1.272)	
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–10	0–30	
Other outpatient office encounters (PPPM)	Mean (SD)	0.018 (0.156)	0.021 (0.263)	0 (0–0)
	Median (Q1–Q3)	0 (0–0)	0 (0–0)	
	Min–max	0–4	0–15	
OAB-related outpatient pharmacy				
Prescription claim encounters	N (%)	516 (100%)	1032 (100%)	1 (0–1)
	Mean (SD)	5.355 (4.703)	4.176 (3.938)	
	Median (Q1–Q3)	4 (2–8)	3 (1–6)	
	Min–max	1–28	1–28	

(Continues)

TABLE 2 (Continued)

Category	Statistics	Mirabegron users (n = 516)	Antimuscarinic users (n = 1032)	Median difference (Mira-AM), (95% CL)
Prescription claim encounters (PPPM)	Mean (SD)	0.569 (0.709)	0.479 (0.682)	0 (0–0)
	Median (Q1–Q3)	0 (0–1)	0 (0–1)	
	Min–max	0–5	0–9	

Note: 95% CL for the median are distribution-free confidence limits of median; Median differences were derived using the CIPCTLDF option on PROC UNIVARIATE statement in SAS.

Abbreviations: CL, confidence limit; SD, standard deviation; Q1, 25th percentile; Q3, 75th percentile; min, minimum; max, maximum; PPPM, per patient per month.

[a]Total inpatient and outpatient costs include inpatient admission, outpatient service and outpatient pharmacy costs.

[b]Primary care provider includes the following physician specialties: Family Practice, Internal Medicine, MultiSpecialty Physician Group, and Medical Doctor.

[c]Obstetrics/gynecology includes the following specialties: OBGY.

[d]Urologist includes the following specialties: Urology.

Notes: 95% CI for the median are distribution-free confidence intervals for the median.

PPPM among a general population of patients with OAB were estimated at $1625 (SD: $4293; estimates in 2013 United Stated Dollars).[32] In the present study, costs were estimated to be $6010 ($17 429) in the matched mirabegron group, and $5515 ($18 015) in the matched antimuscarinic group; higher costs were driven by pharmacy costs. Both studies overlap in terms of study population; whereas the present study includes only patients from the MarketScan Medicare Supplemental database, Durden et al. includes patients from both the MarketScan commercial and Medicare Supplemental databases. Considering Medicare reimbursement rates for health care are generally lower than those seen with Commercial coverage, the magnitude of the difference between the findings observed in the present study versus those observed in Durden et al. is possibly in part attributable to differences in the study populations (general OAB vs. older frail OAB).

This study used Medicare Supplemental data, which is limited to adults who have commercial insurance. Therefore, the results of this study may limit the generalizability to that population. Other limitations include those that are inherent to administrative claims data: dispensation of medication does not indicate whether the medication was actually taken, ascertainment of conditions and treatments rely on administrative codes, which are subject to coding error, and data on subjects before enrollment is unavailable. Additionally, it is not possible to adjust for the generosity of drug benefit, as the specifics related to plan benefits are not contained in the database. Therefore, it is possible that patients who received mirabegron had a more generous drug benefit that extended to other prescription drugs.
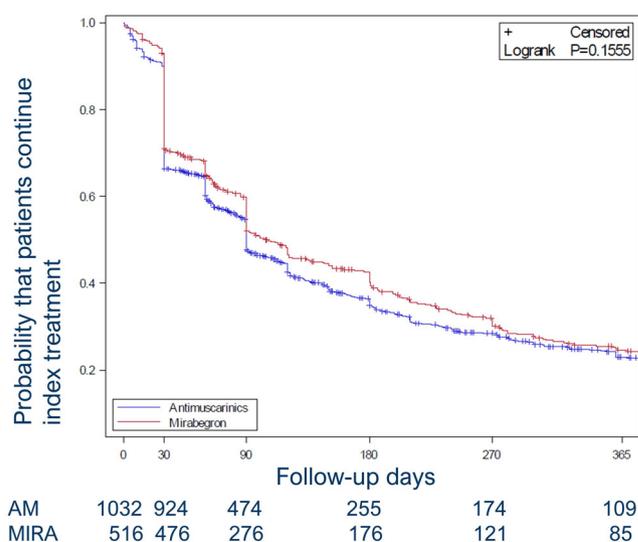

AM	1032	924	474	255	174	109
MIRA	516	476	276	176	121	85

FIGURE 2 Kaplan–Meier plots of persistence by index medication for matched cohorts (with number of patients with index medication). Abbreviations: AM, antimuscarinic; MIRA, mirabegron.

While administrative claims data provides robust information regarding health care costs, encounters, and treatment patterns, it does not fully capture OAB-related costs not covered by insurance (e.g., containment products) or clinical characteristics beyond diagnoses and treatment. In the current study, specific disease characteristics that may guide physicians to choose mirabegron over antimuscarinics cannot be ascertained. Other clinically relevant outcomes, including the specific reasons for OAB treatment discontinuation and treatment efficacy, as well as the use of non-pharmacologic OAB treatments, are also not captured in these data.

TABLE 3 Persistence and adherence (PDC) for matched cohorts

Persistence Kaplan−Meier estimates (95% CLs)	Mirabegron users (n = 516)	Antimuscarinic users (n = 1032)
90 days	52.0% (47.5−56.3)	47.7% (44.5−50.9)
180 days	40.2% (35.7−44.6)	34.8% (31.7−38.0)
365 days	24.6% (20.6−28.8)	23.0% (20.0−26.1)
Adherence (PDC)		
PDC through 90 days		
Mean (SD)	0.763 (0.279)	0.701 (0.312)
Median (Q1−Q3)	0.925 (0.515−1.000)	0.789 (0.333−1.000)
Min−max	0.022−1.000	0.011−1.000
Median difference (Mira-AM), (95%CI)	0.000 (0.000−0.000)	
PDC through 180 days		
Mean (SD)	0.664 (0.322)	0.601 (0.340)
Median (Q1−Q3)	0.753 (0.333−0.994)	0.656 (0.246−0.967)
Min−max	0.022−1.000	0.006−1.000
Median difference (Mira-AM), (95% CI)	0.011 (0.000−0.046)	
PDC through 365 days		
Mean (SD)	0.589 (0.343)	0.535 (0.355)
Median (Q1−Q3)	0.652 (0.247−0.935)	0.507 (0.173−0.921)
Min−max	0.019−1.000	0.003−1.000
Median difference (Mira-AM), (95%CI)	0.009 (0.000−0.049)	
PDC ≥ 0.80		
Through 90 days	298 (57.8%)	515 (49.9%)
Difference (95% CI)	7.85% (2.61%−13.09%)	
p Value*	0.0036	
Through 180 days	247 (47.9%)	415 (40.2%)
Difference (95% CI)	7.66% (2.41%−12.90%)	
p Value*	0.0046	
Through 365 days	202 (39.1%)	349 (33.8%)
Difference (95% CI)	5.33% (0.22%−10.43%)	
p Value*	0.0426	

Note: 95% CI for the median are distribution-free confidence intervals for the median. *p* Value was derived from Fisher's Exact Test.

Abbreviations: KM, Kaplan−Meier estimate; NE, not estimated; PDC (proportion of days covered); Q1, 25th percentile; Q3, 75th percentile; 95% CL, 95% confidence limits.

Instead, this study provides a broad overview of treatment-taking behavior and health care costs among frail, older adults with OAB.

It should be noted that we considered all antimuscarinics in one treatment category; however, there is evidence that differences exist in persistence amongst oxybutynin and the newer generation antimuscarinics (e.g., tolterodine, solifenacin).[33,34] Finally, the 1-year follow-up time does not allow for the assessment of long-term costs and outcomes, including the advancement to

more aggressive treatments, the occurrence of a prescribing cascade, and the implications of anticholinergic burden.[35,36]

5 | CONCLUSIONS

This study provides evidence regarding treatment-taking behaviors and all-cause medical costs and encounters among a population of frail older adults with OAB. There were no differences in number of encounters between treatment groups. Costs were higher among those who started mirabegron, which was driven by differences in costs specific to pharmacy claims. Incident mirabegron use was associated with potential improvements in treatment-taking behaviors, particularly with respect to treatment adherence, versus those initiating antimuscarinics.

CONFLICTS OF INTEREST
All authors all fulfill the ICMJE guidelines for authorship. D. W. and A. L. are employees of Astellas Pharma Global Development and T. K., D. N., and B. J., of Astellas Pharma US. T. M. J. received consulting fees from Astellas for the conduct of this study, as well as research support from Medtronic and Dexcom, consultation fees from Eisai, and authorship royalties from UpToDate. G. L. O. is an employee of Broadstreet HEOR which received a contract for consultant services for this study.

DATA AVAILABILITY STATEMENT
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.