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Antimuscarinic use and discontinuation in an older adult population

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ABSTRACT

Introduction: Although antimuscarinics are typically the first-line pharmacological treatment option for overactive bladder, patients often discontinue therapy. The aim of this research project is to identify the rate of antimuscarinic discontinuation, switching, and continuation and differences in discontinuation among different antimuscarinics.

Methods: Using the 5% random sample of Medicare Claims Data, we identified a cohort of patients aged ≥ 66 years old who newly initiated antimuscarinics between January 1, 2007 and December 31, 2012. Treatment discontinuation was defined as no subsequent fills of the initial antimuscarinic in the days' supply plus a 30 day grace period. We ascertained percentages of patients who discontinued antimuscarinics, switched antimuscarinics, or died within 12 months of antimuscarinic initiation. Cox proportional hazards models were used to determine time to discontinuation of individual antimuscarinics relative to oxybutynin immediate-release (IR).

Results: Among the 42,886 new-users of antimuscarinics, 71.8% discontinued, 10.8% switched, and 3.2% died prior to antimuscarinic discontinuation or switching while only 14.2% continually filled an antimuscarinic for one year. In the multivariable analysis, patients who were initiated on oxybutynin extended-released (ER), tolterodine, trospium, darifenacin, solifenacin, and fesoterodine were significantly less likely to be discontinued therapy compared to oxybutynin IR ($p < 0.001$).

Conclusion: After one year of antimuscarinic initiation, only 14% of older adult patients continuously utilized their initial antimuscarinic therapy suggesting a need for clinical interventions to improve continual use of antimuscarinics.

1. Introduction

Overactive bladder (OAB) is characterized by urination with a sense of urgency, frequency of urination, and nocturia, with or without incontinence. (Gormley, Lightner, & Burgio, 2014) OAB can negatively impact a patient's quality of life including social interactions, sexual function, sleep, and mental health (Coyne, Payne, & Bhattacharyya, 2004; Hullfish et al., 2007; Liberman, Hunt, & Stewart, 2001; Melville, Delaney, Newton, & Katon, 2005; Sand, Goldberg, Dmochowski, McIlwain, & Dahl, 2006; Sexton et al., 2011; Wyman, Harkins, Choi, Taylor, & Fantl, 1987). Symptoms of OAB increase with age as approximately one-third of adults aged 65 or older expressed symptoms suggestive of OAB (Stewart, Van Rooyen, & Cundiff, 2003). Extrapolating to the U.S. population suggests that 33 million adults suffered from OAB symptoms in 2000 (Tubaro, 2004).

Antimuscarinics comprise oral and transdermal agents including oxybutynin, tolterodine, trospium, darifenacin, solifenacin, and fesoterodine. Antimuscarinics are often considered the first-line pharmacological option and are the most frequently used class of medications for OAB. (Gormley et al., 2014) Certain antimuscarinics may be preferred over beta-3 agonists and onabotulinumtoxinA primarily due to decreased costs and fewer formulary restrictions, however, the prescribing of newer antimuscarinics (e.g., darifenacin, solifenacin) may also be impacted by higher cost as these antimuscarinics are brand-name only (Gormley et al., 2014; MagellanRx Management - Genitourinary Smooth Muscle Relaxants, 2017; MagellanRx

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Management, 2018; Vouri, Schootman, Strope, Birge, & Olsen, 2018).

Many patients who initiate an antimuscarinic are unable to continue taking this medication. In previous research using administrative databases, 35%–68% of patients did not refill their initial antimuscarinic prescription, (Chancellor et al., 2013; D'Souza, Smith, Miller, Doyle, & Ariely, 2008; Mauseth, Skurtveit, & Spigset, 2013; Shaya, Blume, Gu, Zyczynski, & Jumadilova, 2005) and 52%–89% discontinued their antimuscarinic within 12 months (Chancellor et al., 2013; D'Souza et al., 2008; Mauseth et al., 2013; Shaya et al., 2005; Yu, Nichol, Yu, & Ahn, 2005; Wagg, Compion, Fahey, & Siddiqui, 2012; Gomes, Juurlink, & Mamdani, 2012; Lawrence, Guay, Benson, & Anderson, 2000). In addition 5%–20% of patients switched from their initial antimuscarinic to another antimuscarinic within 12 months (Chancellor et al., 2013; D'Souza et al., 2008; Mauseth et al., 2013; Shaya et al., 2005; Yu et al., 2005; Lawrence et al., 2000). Specific results of these prior studies are reported in Table 1.

Although many studies have explored the rate of discontinuation of antimuscarinics along with factors associated with discontinuation, (D'Souza et al., 2008; Shaya et al., 2005; Yu et al., 2005) no recent study has explored this in a contemporary population of older adults in the United States. Our study aims to identify the rate of antimuscarinic discontinuation, switching, and continuation using a Medicare Fee-for-Service population.

2. Methods and materials

2.1. Data source

We used the 5% random sample Medicare Claims Data (Chronic Condition Warehouse) linked to Part D claims in fee-for-service patients between January 1, 2007 and December 31, 2012. This study was approved by the Washington University Human Research Protection Office with a waiver of informed consent.

2.2. Study population

All patients aged 66 years or older with at least 12 months of baseline data and complete Medicare Part A (hospital), Part B (physician and outpatient facility), and Part D (prescription drug) coverage were included. Patients who were enrolled in a health maintenance organization were excluded, since claims data are incomplete in these patients.

Antimuscarinics were identified in the Part D event data for the following medications: oxybutynin, tolterodine, trospium, solifenacin, darifenacin, and fesoterodine. We specifically assessed antimuscarinics grouped as oxybutynin immediate-release (IR), oxybutynin extended-release (ER), oxybutynin transdermal patch (only available as a prescription medication during the study period) or gel, tolterodine IR or ER, trospium IR or ER, solifenacin, darifenacin, fesoterodine. Oxybutynin transdermal patch or gel, tolterodine IR or ER, and trospium IR or ER were collapsed into oxybutynin transdermal, tolterodine, and trospium, respectively, due to low counts. We did not require the diagnosis of OAB prior to the prescribing of the antimuscarinic as it would likely be undercoded, and the only indication for antimuscarinics is for OAB.

We identified patients who were new-users of an antimuscarinic agent from 1/1/2008 – 12/31/2011 (Ray, 2003). These patients had at least 12 months of antimuscarinic-free Medicare coverage, henceforth referred to as the baseline period, prior to the first antimuscarinic claim. Patients also had to have at least one medication claim other than an antimuscarinic in the baseline period to confirm use of Medicare Part D prescription drug coverage, as previous active-users for Medicare Part D may differ from non-active-users (e.g., less healthy) (Layton, Brookhart, & Jonsson Funk, 2013). The time period to identify new use of antimuscarinic agents of January 1, 2008 through December 31, 2011 was used to allow for one year of data prior to the first antimuscarinic claim and a minimum one-year follow-up. Patients who filled two or more different antimuscarinics on the date of the first antimuscarinic claim were excluded, similar to the approach of Yu and colleagues (Yu et al., 2005). Patients were not required to have a diagnosis of OAB (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 596.51; 596.59; 788.1x; 788.3x), as lower urinary tract symptoms are likely undercoded (Lin, Andersson, Lin, Kao, & Wu, 2017).

2.3. Antimuscarinic continuation

Antimuscarinic duration was defined as the continuation of the same antimuscarinic, based on subsequent fills of the initial agent. To account for possible non-adherence, a grace period, the time added to the days' supply to account for inconsistent consumption of medications (i.e., missed doses), of 30 days was used (Lawrence et al., 2000; Shaya et al., 2005; Yu et al., 2005). Hospitalization days were summed and added to the grace period of the antimuscarinic claim that occurred prior to or during the hospitalization, since during a hospitalization medications are either supplied by the hospital pharmacy or temporarily discontinued. In previous studies that assessed discontinuation of antimuscarinics, the incorporation of hospital stay(s) into the grace period was not done (Chancellor et al., 2013; D'Souza et al., 2008; Gomes et al., 2012; Lawrence et al., 2000; Mauseth et al., 2013; Shaya et al., 2005; Wagg et al., 2012; Yu et al., 2005).

2.4. Outcome of antimuscarinic discontinuation

The outcome of antimuscarinic discontinuation was defined as the last day of the earliest grace period in which no antimuscarinic claim was filled; therefore, discontinuation may have been a result of provider discontinuation or patient self-discontinuation. We also identified antimuscarinic switching, defined as the claim date of a different antimuscarinic agent within the days' supply plus grace period of the initial antimuscarinic claim. Patients who switched antimuscarinics were censored (So, Lin, & Johnston, 2014). Patients were also censored at the time of death, as identified in the Beneficiary Summary file or 12 months of continuous use from antimuscarinic initiation.

2.5. Factors potentially associated with antimuscarinic discontinuation

Factors that may confound discontinuation of antimuscarinics were explored. Significant factors associated with antimuscarinic persistence identified in previous studies included age, race, type of antimuscarinic, depression, urinary tract infection, and polypharmacy (defined previously as the use of one additional medication following antimuscarinic initiation). (D'Souza et al., 2008; Shaya et al., 2005; Yu et al., 2005) Use of one additional medication is not a traditional definition of polypharmacy; thus we did not explore polypharmacy.

Discontinuation of antimuscarinics may also have been confounded by comorbid conditions and medications; therefore, several comorbidities were examined using the Elixhauser Comorbidity algorithm, (Lin et al., 2017) modified to include medications used to treat hypertension, diabetes, and hypothyroidism. Other comorbid conditions diagnosed in older adults and comorbid conditions that may be associated with discontinuation of antimuscarinics, along with medications used to treat these conditions, including osteoporosis, Parkinson's disease, glaucoma, high cholesterol, constipation, weakness, and falls were also assessed. Potential factors associated with antimuscarinic discontinuation were collected during the baseline period (Stuart, Davidoff, & Erten, 2013).

Patient characteristics, year of the initial antimuscarinic claim, hospitalization in the previous 12 months, and clinic visits to specialist providers (e.g., geriatrician, urologist, neurologist) within 30 days before the first antimuscarinic claim were also explored as factors that may influence discontinuation of antimuscarinics. (Altman, 2004)

Table 1
Previous Studies that evaluated Initial Refill, Discontinuation, and Switching of Antimuscarinics.

Author	Database	Study Period	Baseline Characteristic Look-Back Period (months)	Study Duration (months)	Antimuscarinics Agents	Grace Period to Determine Continuation of Antimuscarinic	Age in years	Population number	Refilled Index Antimuscarinic (%)	Discontinuation (%)	Switched (%)
D'Souza et al. (2008)	Regional Managed Care	1/31/1999-12/31/2003	6	12	Oxy IR, Oxy ER, Tolt IR, Tolt ER	45 days	55.7 (mean)	1,117	55.5%	86.8%	13.3%
Mauseth et al. (2013)	Norway Prescription	1/1/2004-12/31/2010	Not used	12	Tolt, Soli, Dari, Feso	Not used	Reported in Intervals	32,178 (women only)	68.1%	51.7%	10.3%
Shaya et al. (2005)	Medicaid (Mid-Atlantic State)	1/1/2000 – 12/31/2003	6	12	Oxy IR, Oxy ER, Tolt ER	15 days	< 65	1,637	34.9%	88.4%	6.0%
Chancellor et al. (2013)	IMS Lifelink Health Plan Claims	1/2005 – 6/2010	6	24	Oxy IR, Oxy ER, Oxy TDS, Tolt IR, Tolt ER, Trosp IR, Trosp ER, Soli, Dari, Feso,	45 days	58.7 (mean)	103,250	67% (24 mo)	78.4% (12 mo) 85.9% (24 mo)	5.0% (12 mo) 5.8% (24 mo)
Yu et al. (2005)	California Medicaid (20% sample)	1/1999 – 4/20002	6	12	Oxy IR, Oxy ER, Tolt IR	30 days	63.2 (mean)	2,415	—	88.6%	19.6%
Wagg et al., 2012)	UK Prescription	1/2007 – 12/2008	6	12	Oxy IR, Oxy IR, Tolt IR, Tolt ER, Trosp, Dari, Soli, Flav, Prop	50% days' supply	Reported in Intervals	4,833	—	65.2%	—
Gomes et al. (2012)	Ontario Drug	1/1/2000 – 12/31/2007	12	12	Oxy, Tolt	50% days' supply	~77 (mean)	56,851	—	77.4%	—
Lawrence et al. (2000)	Express Scripts Prescription Claims	10/1997 – 12/1998	6	6	Oxy IR, Tolt IR	30 days	~72 (mean)	1,020	—	57.1%	16.0%

Dari = darifenacin; ER = extended-release; Feso = fesoterodine; Flav = flavoxate; IR = immediate-release; mo = month; Oxy = oxybutynin; Prop = propiverine; Soli = solifenacin; TDS = transdermal system (patch or gel); Tolt = tolterodine; UK = United Kingdom

Table 2
Percentage of New-users who Discontinued, Switched, or Died prior to Discontinuation or Switching Within One year following Antimuscarinic Initiation.

n (row%)	Discontinued Antimuscarinic n (%)	Switched Antimuscarinic n (%)	Died before Discontinued or Switched n (%)	Continued Antimuscarinic n (%)
All Antimuscarinics[a] (n = 42,886)	30,794 (71.8)	4617 (10.8)	1389 (3.2)	6086 (14.2)
Oxybutynin	6,958 (78.3)	686 (7.7)	316 (3.6)	928 (10.4)
IR (n = 8888)[b]	3606 (68.5)	550 (10.4)	183 (3.5)	923 (17.5)
ER (n = 5262)	640 (74.9)	105 (12.3)	37 (4.3)	72 (8.4)
Transdermal (n = 854)[c]				
Tolterodine (n = 14,081)	9757 (69.3)	1643 (11.7)	502 (3.6)	2179 (15.5)
Trospium (n = 1252)	907 (72.4)	160 (12.8)	25 (2.8)	160 (12.8)
Darifenacin (n = 4131)	2930 (70.9)	437 (10.6)	111 (2.7)	653 (15.8)
Solifenacin (n = 7906)	5666 (71.7)	938 (11.9)	195 (2.5)	1107 (14.0)
Fesoterodine (n = 512)	330 (64.5)	98 (19.1)	< 11	74 (14.5)

[a] All agents listed below.
[b] Oxybutynin IR tablet and Oxybutynin IR liquid.
[c] Oxybutynin patch and Oxybutynin gel.

Additionally, patients in a prescription coverage gap, also known as the 'doughnut hole,' were identified at the time of antimuscarinic initiation (Altman, 2004). A prescription coverage gap occurs when a patient reaches a spending limit on Part D prescription drugs during a calendar year. During the coverage gap patients are required to pay out-of-pocket the full costs of prescription drugs until they have reached the catastrophic phase, patients will again have complete coverage of Part D prescription drugs. (Altman, 2004) The coverage gap thus influences the affordability of medications and may result in medication discontinuation (Polinski, Kilabuk, Schneeweiss, Brennan, & Shrank, 2010; Stuart et al., 2013). A person was considered to be in the coverage gap when the benefit phase of a claim of any prescription medication plus days' supply was classified as meeting the initial coverage limit and overlapped with the initial antimuscarinic claim (Benefit Phase of Part D Event, 2018).

All ICD-9-CM diagnosis codes and names of medications used to identify factors potentially associated with antimuscarinic discontinuation are listed in Table A1 in the Appendix.

2.6. Statistical analyses

Factors potentially associated with discontinuation of antimuscarinics were compared using descriptive statistics. The number of days from antimuscarinic initiation to discontinuation and switching of antimuscarinics was calculated for antimuscarinics in aggregate and individually, using medians and interquartile ranges (IQR). Percentages of patients who discontinued antimuscarinics, switched antimuscarinics, or died within 12 months of antimuscarinic initiation were assessed; additionally, the percentages of patients who were alive and had 2 or more antimuscarinic fills within the grace period, filled for at least six months, or filled for at least 12 months were reported.

Kaplan-Meier curves and Cox proportional hazards models were used to determine time to discontinuation of individual antimuscarinics (i.e., oxybutynin ER, oxybutynin transdermal, tolterodine, trospium, darifenacin, solifenacin, fesoterodine) relative to oxybutynin IR. Potential factors associated with discontinuation with p-value < 0.1 in univariate analyses were included in the multivariable Cox models, with removal of non-significant variables by manual backward selection. Multicollinearity, defined as a variance inflation factor of > 10%, and the proportional hazards assumption, using Schoenfeld residuals, were also assessed. When the proportional hazards assumption was not met, an interaction of the variable with time was added to the model; if the was significant the new baseline risk was reported in the tables. A p-value of < 0.05 was considered significant in all analyses. All data management and statistical analyses were performed using SAS Enterprise Guide version 7.1 and SAS version 9.3 (*SAS Institute, Inc., Cary, NC*).

3. Results

Between January 1, 2007 and December 31, 2012, 42,886 antimuscarinic new-users were identified after incorporating exclusion criteria. Among the patients who were initiated on an antimuscarinic, only 39% were coded for OAB during the baseline period confirming likely undercoding of this comorbid condition.

The median age of patients was 78 years, 75% were female, and 86% were white. One-quarter of patients were seen by a urologist in the 30 days prior to antimuscarinic initiation. Table B1 in the Appendix describes the other baseline characteristics of patients who were initiated on antimuscarinics

Among the individual antimuscarinics, oxybutynin IR had the highest percentage of patients to discontinue (78.3%) and the lowest percentage of patients to switch (7.7%). In contrast fesoterodine had the lowest percentage of patients to discontinue (64.5%) and the highest percentage of patients to switch (19.1% [Table 2]).

Less than half of patients who initiated on oxybutynin IR (42.5%), oxybutynin transdermal (48.7%), or fesoterodine (47.4%) filled a second prescription within the days' supply plus grace period (Table 3). Oxybutynin IR had the lowest percentage of patients to fill continuously for 6 months (21.3%), and oxybutynin transdermal had the lowest percentage of patients to fill continuously for 12 months (9.6%). Darifenacin had the highest percentage of patients to have a second filled prescription within the days' supply plus grace period (56.6%), while oxybutynin ER had the highest percentages of patients to fill continuously for 6 months (32.5%) and 12 months (19.1%).

Unadjusted Kaplan-Meier curves show the time to discontinuation for the different antimuscarinic agents (Fig. 1). The number of days following antimuscarinic initiation in which half of patients had discontinued oxybutynin IR, oxybutynin ER, oxybutynin transdermal, tolterodine, trospium, darifenacin, solifenacin, and fesoterodine was 65, 119, 89, 117, 103, 119, 119, and 109 days, respectively. As seen in the Kaplan-Meier curve, there was a significant drop-off at day 60 following antimuscarinic initiation, in which patients were classified as having discontinued therapy. This drop-off corresponds to patients with an initial 30-day supply who did not refill the antimuscarinic within the 30-day grace period. Similar drop-offs occurred at 90 days and 120 days following antimuscarinic initiation, corresponding to a one-time fill of a 60-day and 90-day supply, respectively.

Table 4 shows the results of univariate analyses and the multivariable analysis to evaluate the association between individual antimuscarinic agents versus oxybutynin IR on discontinuation. After adjusting for confounding variables, patients who were initiated on oxybutynin ER were 30% less likely, tolterodine 27%, trospium 22%, darifenacin 29%, solifenacin 27%, and on fesoterodine were 28% less likely to discontinue therapy compared to patients initiated on oxybutynin IR. In the multivariable analysis, patients aged ≥85 years old

Table 3
Percentage of Antimuscarinic New-users with Two or more Antimuscarinic Fills, Continued Antimuscarinic Therapy for at least 6 Months, and Continued Therapy for at least 12 months.

n (row%)	Antimuscarinic Use for 2 or more fills[a] n(%)	Antimuscarinic Use for at least 6 months[b] n(%)	Antimuscarinic Use for at least 12 months[c] n(%)
All Antimuscarinics (Aggregate[d])	22,029/42,320 (52.1)	11,747/40,985 (28.7)	6,085/39,193 (15.5)
Oxybutynin	3,714/8,732	1,790/8,407	928/8,025 (11.6)
IR[e]	(42.5)	(21.3)	923/4,823 (19.1)
ER	2,825/5,187	1,637/5,030	72/754 (9.6)
Transdermal[f]	(54.5)	(32.5)	
	409/839 (48.7)	185/799 (23.2)	
Tolterodine	7,651/13,895	4,154/13,427	2179/12,791
	(55.1)	(30.9)	(17.0)
Trospium	621/1,237 (50.2)	307/1,200 (25.6)	150/1,161 (12.9)
Darifenacin	2,319/4,097	1,283/3,996	653/3,826 (17.1)
	(56.6)	(32.1)	
Solifenacin	4,249/7,825	2,252/7,631	1,106/7,331
	(54.3)	(29.5)	(15.1)
Fesoterodine	241/508 (47.4)	139/495 (28.1)	74/482 (15.4)

[a] Among patients who survived the initial days' supply plus 30 days.
[b] Among patients who survived at least 6 months.
[c] Among patients who survived at least 12 months.
[d] Aggregate is the sum and percent of the columns below.
[e] Oxybutynin IR tablet and Oxybutynin IR liquid.
[f] Oxybutynin patch and Oxybutynin gel.

were significantly less likely to discontinue antimuscarinics compared to patients aged < 75 years old. Patients with congestive heart failure, deficiency anemia, dementia / mild cognitive impairment, depression, diabetes, epilepsy, hypertension, neurological disorders, osteoporosis, paralysis, Parkinson's disease, and being in the coverage gap upon antimuscarinic initiation were also significantly less likely to discontinue. In contrast, patients who were listed as Black/ African American or Other Race compared to White, resided in other regions compared to the Midwest, initiated on antimuscarinics in 2010 and 2011 compared to 2008, and those with cancer, dry eyes, urinary retention, and visit with a urologist were significantly more likely to discontinue antimuscarinics.

4. Discussion

We found that a higher percentage of patients initiated on oxybutynin IR discontinued treatment compared to patients initiated on any of the other antimuscarinic agents. In addition, the time at which half of patients discontinued therapy was shorter in patients who were initiated on oxybutynin IR and oxybutynin transdermal, compared to the other antimuscarinics.

After controlling for factors potentially associated with discontinuation, patients who were initiated on oxybutynin ER, tolterodine, trospium, darifenacin, solifenacin, and fesoterodine were less likely to discontinue therapy compared to oxybutynin IR. There was no difference in discontinuation between oxybutynin transdermal and oxybutynin IR. Oxybutynin IR may be less well tolerated than the other antimuscarinics, especially due to the higher rates of dry mouth with this agent, which may lead to early discontinuation. (Chapple et al., 2008) This is despite the fact that oxybutynin IR is less expensive than the other antimuscarinic agents (Vouri et al., 2018).

Our results are consistent with a previous study using Medicaid data that patients listed as Black/African American or other race were more likely to discontinue antimuscarinics compared to white patients. (Yu et al., 2005) In our study, older patients were less likely to discontinue antimuscarinics, while the opposite result was found in a study by Shaya and colleagues of non-elderly Medicaid patients (Shaya et al., 2005). The use of data from a younger Medicaid population may explain the difference in our results versus those of Shaya. We also found there was no association of prior urinary tract infection with antimuscarinic discontinuation, in contrast to the finding by Yu and colleagues of increased discotninuation (Yu et al., 2005).

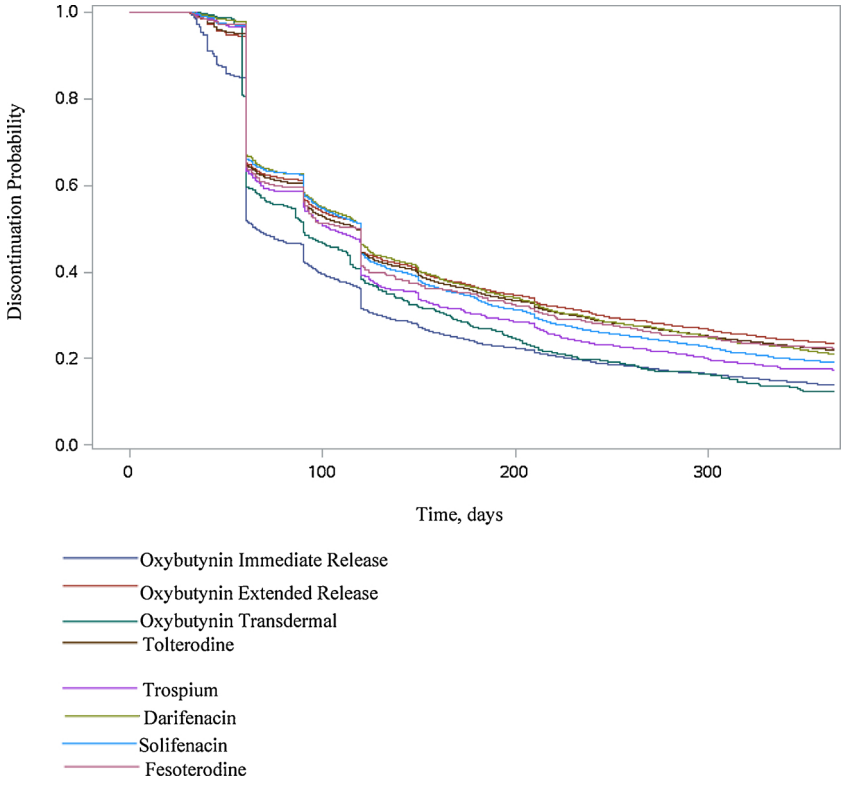

Fig. 1. Time to Discontinuation of Antimuscarinic Agents After Initiation of Therapy.

Table 4
Univariate and Multivariable Analyses Assessing Factors Associated with Discontinuation of Antimuscarinics.

	Antimuscarinic Discontinuation	
	Univariate Analysis HR (95% CI)	Multivariable Analysis[e]
Antimuscarinics		
Oxybutynin IR[a]	1.00 (reference)	1.00 (reference)
Oxybutynin ER	0.70 (0.67–0.72)	0.70 (0.67–0.72)
Oxybutynin Transdermal	0.96 (0.89–1.05)	1.00 (0.92–1.09)
Tolterodine	0.72 (0.70–0.74)	0.73 (0.71–0.75)
Trospium	0.80 (0.74–0.85)	0.78 (0.73–0.84)
Darifenacin	0.70 (0.68–0.74)	0.71 (0.68–0.74)
Solifenacin	0.74 (0.72–0.77)	0.73 (0.70–0.76)
Fesoterodine	0.72 (0.64–0.80)	0.72 (0.64–0.80)
Age (years)		
< 75	1.00 (reference)[b,c]	1.00 (reference)
75–84	0.92 (0.89–0.95)	0.99 (0.97–1.02)
≥85	0.81 (0.77–0.86)	0.94 (0.92–0.97)
Female Sex	0.84 (0.80-0.88)[b,c]	—
Race		
White	1.00 (reference)	1.00 (reference)
Black or African American	1.10 (1.05–1.14)	1.10 (1.05–1.15)
Other	1.12 (1.08–1.17)	1.11 (1.06–1.16)
Region		
Northeast	1.05 (1.01–1.08)	1.07 (1.03–1.11)
Midwest	1.00 (reference)	1.00 (reference)
South	1.09 (1.06–1.12)	1.10 (1.07–1.13)
West	1.15 (1.11–1.19)	1.11 (1.07–1.15)
Other	1.89 (1.49–2.40)	1.89 (1.49–2.41)
Year		
2008	1.00 (reference)	—
2009	1.01 (0.98–1.04)	
2010	1.03 (1.00–1.06)	
2011	1.05 (1.02–1.09)	
Median Household Income for Zip Code ($), 2011[b]		
< 40,000	1.00 (reference)	—
40,000–48,999	0.96 (0.93-0.99)	
49,000–63,999	0.99 (0.95–1.02)	
≥64,000	1.00 (0.97–1.03)	
Missing	0.97 (0.89–1.06)	
Comorbidities		
Aspiration Pneumonia	0.80 (0.71–0.91)	—
Cancer	1.24 (1.20–1.28)	1.18 (1.14–1.22)
Cardiovascular Disease	0.97 (0.94–1.01)	—
Chronic Pulmonary Disease	0.91 (0.87–0.97)[b,c]	—
Congestive Heart Failure	0.77 (0.72–0.82)[b,c]	0.88 (0.82–0.94)[b,c]
Constipation	0.92 (0.87–0.97)[b,c]	—
Deficiency Anemias	0.86 (0.81–0.90)[b,c]	0.96 (0.93–0.99)
Delirium	0.79 (0.72–0.86)	—
Dementia / Mild Cognitive	0.57 (0.54–0.61)[b,c]	0.65 (0.61–0.69)[b,c]
Impairment	0.76 (0.71–0.82)[b,c]	0.91 (0.88–0.95)
Depression	0.85 (0.81–0.89)[b,c]	0.87 (0.83–0.91)[b,c]
Diabetes Mellitus	1.06 (1.02–1.10)	1.06 (1.02–1.10)
Dry Eyes	1.01 (0.83–1.23)	—
Dry Mouth	0.97 (0.93–1.02)	—
Dysphagia	0.76 (0.70–0.83)	0.89 (0.80–0.98)
Epilepsy / Seizure	0.75 (0.66–0.86)[b,c]	—
Falls	1.01 (0.98–1.04)	—
Glaucoma	0.98 (0.96–1.00)	—
High Cholesterol	0.90 (0.86–0.94)[b,c]	—
Hypothyroidism	0.85 (0.80–0.89)[b,c]	0.93 (0.90–0.96)
Hypertension	0.97 (0.93–1.01)[b,c]	—
Malaise / Fatigue	0.74 (0.69–0.79)[b,c]	—
Memory Loss / Drug-Induced Cognitive Conditions	0.66 (0.61–0.70)[b,c]	0.94 (0.90–0.99)
Neurological Disorders	0.90 (0.86–0.94)[b,c]	—
Osteoarthritis	0.88 (0.84–0.92)[b,c]	0.92 (0.88–0.97)[b,c]
Osteoporosis	0.69 (0.60–0.79)[b,c]	0.76 (0.66–0.87)[b,c]
Paralysis	0.76 (0.70–0.83)[b,c]	0.90 (0.85–0.94)
Parkinson's Disease	0.74 (0.61–0.90)[b,c]	—
Blood Loss Anemia	0.93 (0.90–0.98)	—
Renal Failure	1.03 (0.98–1.09)	—
Rheumatoid arthritis/collagen vascular diseases	0.82 (0.75–0.89)[b,c]	—
Sleep Apnea	0.98 (0.90–1.06)	—
Syncope	1.01 (0.96–1.07)[b,c]	—
Traumatic Brain Injury	0.77 (0.70–0.86)[b,c]	—
Vertigo	0.84 (0.79–0.90)	—
Rehabilitation Services	1.00 (0.98–1.03)	—
Stroke	1.13 (1.09–1.17)	1.08 (1.04–1.12)
Urinary Tract Infection	0.77 (0.72–0.82)[b,c]	—
Urinary Retention		
Weakness		
In Coverage Gap at Time of Antimuscarinic Initiation	0.76 (0.72–0.80)[b,c]	0.87 (0.85–0.90)
Provider Types		
Neurologist / Neuropsychiatrist	0.81 (0.73–0.91)	—
Geriatrician	0.91 (0.81–1.02)	—
Urologist	1.30 (1.24–1.26)[b,d]	1.22 (1.16–1.28)[b,d]
Hospitalization in Previous 12 Months	0.92 (0.90–0.94)	—

— = Variable was not included in the multivariable analysis.
CI, confidence interval; ER = extended release; HR, Hazards ratio; IR, immediate release.
[a] Oxybutynin IR tablet and Oxybutynin IR liquid.
[b] Proportional Hazards assumption not met – variable assessed as interaction with time.
[c] Influence of variable on outcome increased over time.
[d] Influence of variable on outcome diminished over time.
[e] The p-values for the following variables were ≥ 0.1 and were not included in the multivariable analysis: cardiovascular disease, dry mouth, dysphagia, glaucoma, malaise/fatigue, blood loss anemia, rheumatoid arthritis/collagen vascular diseases, sleep apnea, vertigo, urinary tract infection, and a clinic visit to a geriatrician.

We identified several factors associated with antimuscarinic discontinuation that have not been previously described. Region of the US, diagnosis of cancer, dementia or mild cognitive impairment, diabetes mellitus, dry eyes, paralysis, urinary retention, and being seen by a urologist were all associated with discontinuation. Patients with dementia or mild cognitive impairment may have medications administered by a caregiver and thus less likely to self-discontinue. (Yap, Thirumoorthy, & Kwan, 2016) In addition, patients with dementia or mild cognitive impairment may also be less likely to discontinue therapy if they are taking an acetylcholinesterase inhibitor, which may cause worsening urinary symptoms (Gill, Mamdani, & Naglie, 2005). We also found that paralysis was associated with decreased risk of discontinuation. Paralysis is often associated with neurogenic bladder, which may a have different risk-versus-benefit ratio (Cameron, 2016). Patients with paralysis may have a lower risk of discontinuation as many of these patients require urinary catheterization, and therefore the occurrence of urinary retention associated with antimuscarinic therapy is not relevant (Cameron, 2016). Patients with baseline dry mouth or urinary retention may have been more likely to discontinue antimuscarinics because therapy may worsen these symptoms (Vouri, Kebodeaux, Stranges, & Teshome, 2017). Finally, patients who were previously seen by a urologist were more likely to discontinue antimuscarinic therapy. We hypothesize that patients who have a relationship with a urologist may have received education on potential adverse events and have follow-up after initiation, which may have result in increased detection of adverse events and thus increased likelihood to discontinue therapy (Haut & Pronovost, 2011).

More patients on non-oxybutynin IR antimuscarinics switched to a different antimuscarinic agents, compared to oxybutynin IR. We

hypothesize that increased switching with the non-oxybutynin medications may be due to higher cost of these agents and restriction by Part D plan formularies. Avoiding the use of oxybutynin IR as initial therapy may be beneficial as more patients are likely to discontinue therapy early compared to the other antimuscarinics.

This is the second largest study in the United States assessing refills, discontinuation, and switching of antimuscarinics, after that of Chancellor and colleagues, (Chancellor et al., 2013) and the largest and most current study evaluating antimuscarinics in the older adult population. In our study, 52.1% of patients obtained at least one refill within the 30-day grace period. This was similar to previous studies, in which at least one refill ranged from 34.9% to 68.1%. In contrast to our requirement for a refill within 30 days after the end of the initial prescription, Mauseth (Mauseth et al., 2013) and Chancellor (Chancellor et al., 2013) who reported refills in 68.1% and 67%, respectively, did not require the refill to be within a pre-specified period but could occur at any time within the study period. In our study, the proportion of patients who discontinued within 12 months was 71.8%; however, this proportion ranged from 64.5% to 78.3% depending on the individual agent. This was consistent with previous studies in which discontinuation within 12 months ranged from 51.7% to 88.4% (Chancellor et al., 2013; D'Souza et al., 2008; Gomes et al., 2012; Lawrence et al., 2000; Mauseth et al., 2013; Shaya et al., 2005; Wagg et al., 2012; Yu et al., 2005). Beyond study of different patient populations, different approaches may have resulted in varying assessments of discontinuation, such as the use of different grace periods (15 days (Shaya et al., 2005), 30 days (Lawrence et al., 2000; Shaya et al., 2005; Yu et al., 2005), 45 days (Chancellor et al., 2013; D'Souza et al., 2008), 150% the days' supply (Gomes et al., 2012; Wagg et al., 2012)). In the study by Mauseth the lack of a grace period resulted in the lowest percentage of patients classified as discontinuing antimuscarinic therapy within one year (51.7%) (Mauseth et al., 2013). In that study, a person who had a gap between the end of initial prescription and a subsequent fill of 6 months was classified as continuing on therapy, which likely resulted in the lower percentage of discontinuation. Overall, 10.8% of patients switched to a different antimuscarinic agent, consistent with previous studies in which switching ranged from 5.0% to 19.6%. (Chancellor et al., 2013; D'Souza et al., 2008; Mauseth et al., 2013; Shaya et al., 2005; Yu et al., 2005; Lawrence et al., 2000)

With the exception of the study by Gomes and colleagues, (Gomes et al., 2012) using the Ontario Drug Database, most studies of antimuscarinic discontinuation were not restricted to an older adult population. Similar to our approach, Gomes and colleagues assessed the differences in discontinuation rates after adjusting for other factors associated with discontinuation, but they assessed only oxybutynin and tolterodine use from 2000 to 2007 (Gomes et al., 2012).

4.1. Limitations

There are a few limitations of our study that are important to note. Although we classified discontinuation as patients who did not fill a medication within a 30-day grace period, patients may have been non-adherent to their antimuscarinic or educated to take on an 'as-needed' basis. These patients may have filled the antimuscarinic at a later time (after the end of the grace period) and did not truly discontinue therapy. Moreover, we were unable to determine if the medications were discontinued by the provider or the patient without consultation of the provider. Since we assessed a population of fee-for-service Medicare patients, these results may not be generalizable to older adults enrolled in a health maintenance organization. Although patients who had visit with a urologist were more likely to discontinue their antimuscarinic, we were unable to confirm if a specialty provider was the specific prescriber for an antimuscarinic prescription.

4.2. Strengths

There are also many strengths of this research. Along with one other study, we confirmed no other antimuscarinic claim in the 12 months prior to the initial antimuscarinic claim to better ensure a new-user design. (Gomes et al., 2012) We incorporated hospital days as part of the continuation definition which was not considered in previous studies. If time spent in the hospital was ignored, it may have led to misclassification of discontinuation. We assessed discontinuation for all available antimuscarinic agents. We excluded patients who died prior to assessing continuation so as to not penalize patients who did not fill their medication because he or she was deceased.

5. Conclusion

After one year of antimuscarinic initiation, only 14% of patients continuously utilized their initial antimuscarinic therapy. Overall in this Medicare fee-for-service population 72% of patients initiated on an antimuscarinic agent discontinued therapy, 11% switched to another antimuscarinic, and 3% died within one year. Approximately half of patients initiated on an antimuscarinic did not fill their antimuscarinic again within a 30-day period after the end of the initial prescription. Patients who were initiated on oxybutynin ER, tolterodine, trospium, darifenacin, solifenacin, or fesoterodine were less likely to discontinue therapy compared to patients initiated on oxybutynin IR, potentially due to the known higher incidence of adverse events associated with oxybutynin IR. Additional studies are needed to identify ways to improve the continued use of antimuscarinics for patients with OAB.

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Conflict of interest

The authors disclose no financial conflicts of interests.

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Appendix A

Table A1
List of ICD-9-CM Diagnosis Codes and Medications used in Analyses.

	Variables[†]	ICD-9-CM Codes	Other Codes	Medications
Demographic Information	Region		Northeast: Connecticut, Maine, Massachusetts, Rhode Island, Vermont, New Hampshire, New Jersey, New York, Pennsylvania Midwest: Indiana, Illinois, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, North Dakota, Nebraska, South Dakota South: Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia, Washington DC, Kentucky, Tennessee, Alabama, Mississippi, Arkansas, Oklahoma, Texas West: Arizona, Colorado, Montana, New Mexico, Nevada, Utah, Wyoming, Idaho, Alaska, California, Hawaii, Oregon, Washington Other: Guam, Puerto Rico, Virgin Islands	
Modified Elixhauser Comorbidity Index	Hypertension	Elixhauser Comorbidity Codes		Benazepril; Captopril; Enalapril; Fosinopril; Lisinopril; Moexipril; Perindopril; Quinapril; Ramipril; Trandolapril; Candesartan; Eprosartan; Irbesartan; Losartan; Olmesartan; Telmisartan; Valsartan; Acebutolol; Atenolol; Bisoprolol; Carvedilol; Labetalol; Metoprolol; Nadolol; Nebivolol; Penbutolol; Pindolol; Sotalol; Amlodipine; Diltiazem; Felodipine; Isradipine; Nicardipine; Nifedipine; Nisoldipine; Verapamil; Furosemide; Bumetanide; Ethacrynic Acid; Torsemide; Doxazosin; Terazosin; Prazosin; Clonidine; Guanabenz; Guanfacine; Methyldopa; Eplerenone; Spironolactone; Triamterene; Aliskiren; Chlorthalidone; Chlorothiazide; Hydrochlorothiazide; Indapamide; Metolazone; Methyclothiazide; Hydralazine; Isosorbide Dinitrate; Isosorbide Mononitrate; Minoxidil
	Diabetes mellitus	Elixhauser Comorbidity Codes		Glipizide; Glimepiride; Glyburide; Chlorpropamide; Pioglitazone; Rosiglitazone; Repaglinide; Nateglinide; Sitagliptin; Saxagliptin; Linagliptin; Alogliptin; Canagliflozin; Acarbose; Miglitol; Exenatide; Liraglutide; Pramlintide; Insulin (Aspart, Detemir, Glargine, Glulisine, Lispro, Isophane, Regular)
	Hypothyroidism	Elixhauser Comorbidity Codes		Levothyroxine; Liothyronine; Thyroid; Thyroid, Pork
Other Comorbidities	Aspiration Pneumonia	507.xx		
	Cardiovascular Disease	411.xx; 412; 413.xx; 414.2x; 414.3x; 414.4x; 414.8x; 414.9x; V45.81; V45.82[‡]		
	Constipation	564.0x		Alvimopan; Calcium Polycarbophil; Bisacodyl; Docusate; Lactulose; Linaclotide; Lubiprostone; Methylcellulose; Methylnaltrexone; Naloxegol; Polyethylene Glycol; Psyllium; Senna; Sennosides; Sorbitol; Tegaserod
	Delirium	293.0x; 293.1x; 294.9x		
	Dementia, Mild Cognitive Impairment	290.0x; 290.1x; 290.20; 290.21; 290.3x; 290.40; 290.41; 290.42; 290.43; 294.0x; 294.1x; 294.8x; 331.0x; 331.1x; 331.2x; 331.7x; 797.xx, 331.83		Donepezil; Galantamine; Rivastigmine; Memantine
	Dysphagia	280.8x; 300.11; 306.4x; 307.1x; 530.5x		
	Epilepsy / Seizure	345.0x; 345.1x; 345.2x; 345.3x; 345.4x; 345.5x; 345.6x; 345.7x; 345.8; 345.9x; 780.3x[‡]		Brivaracetam; Eslicarbazepine; Ethosuximide; Ezogabine; Felbamate; Lacosamide; Levetiracetam; Perampanel; Phenytoin; Rufinamide; Tiagabine; Vigabatrin; Zonisamide
	Falls		E-Code: E88.xx	
	Glaucoma	365.xx[‡]		Acetazolamide; Apraclonidine; Betaxolol; Bimatoprost; Brimonidine; Brinzolamide; Carbachol; Dichlorphenamide; Dorzolamide; Latanoprost;

(*continued on next page*)

Table A1 (*continued*)

	Variables[†]	ICD-9-CM Codes	Other Codes	Medications
				Levobunolol; Methazolamide; Metipranolol; Pilocarpine; Tafluprost; Timolol; Travoprost; Unoprostone
	High Cholesterol	272.0x; 272.2x; 272.4x[‡]		Atorvastatin; Fluvastatin; Lovastatin; Pitavastatin; Pravastatin; Rosuvastatin; Simvastatin; Cholestyramine; Colesevelam; Colestipol; Ezetimibe; Fenofibrate; Gemfibrozil; Niacin; Omega-3
	Malaise / Fatigue	780.7x[‡]		
	Memory Loss / Drug-Induced Cognitive Impairment	780.09; 780.93; 780.97; 292.1x; 292.81; 282.82; 292.83		
	Osteoarthritis	715.xx; 716.5x; 716.6x; 716.8x; 716.9x; 718.xx; 719.0x; 719.1x; 719.4x; 719.5x; 719.9x[‡]		
	Osteoporosis	262.2x; 275.3x; 733.0x[‡]		Alendronate; Risedronate; Ibandronate; Zoledronic Acid; Raloxifene; Denosumab; Teriparatide
	Parkinson's Disease	332.xx[‡]		Amantadine; Apomorphine; Benztropine; Bromocriptine; Carbidopa/Levodopa; Droxidopa; Entacapone; Pramipexole; Rasagiline; Ropinirole; Rotigotine; Selegiline; Tolcapone; Trihexyphenidyl
	Rehabilitation Services	V57.1; V57.21; V57.3; V57.89; V57.9		
	Skin Ulcer	707.xx		
	Sleep Apnea	327.2x[‡]		
	Stroke	430.xx–437.xx		
	Syncope	780.2x		
	Traumatic Brain Injury	850.xx–854.xx; 907.0x		
	Vertigo	386.xx; 780.4x		
	Weakness	728.2x; 728.3x; 728.87; 799.3x; V49.84		
Medications	Antipsychotic			Amisulpride; Aripiprazole; Asenapine; Chlorpromazine; Clozapine; Droperidol; Fluphenazine; Haloperidol; Iloperidone; Loxapine; Lurasidone; Olanzapine; Paliperidone; Prochlorperazine; Pimozide; Quetiapine; Risperidone; Sulpiride; Thioridazine; Thiothixene; Trifluoperazine; Ziprasidone
	Benzodiazepine			Alprazolam; Clorazepate; Chlordiazepoxide ± Amitriptyline; Clonazepam; Diazepam; Estazolam; Flurazepam; Lorazepam; Oxazepam; Midazolam; Quazepam; Temazepam; Triazolam
	Sleep Medications			Diphenhydramine; Eszopiclone; Zaleplon; Zolpidem
	Stimulant Medications			Dexmethylphenidate; Dextroamphetamine; Lisdexamfetamine; Methylphenidate
Provider Types	Geriatrics		Carrier Claims – PRVDR_SPCLTY: 38	
	Urology		Carrier Claims – PRVDR_SPCLTY: 34	
	Neurology / Neuropsychiatry		Carrier Claims – PRVDR_SPCLTY: 13, 86	

[†] Variables from Same line as Radiology Diagnostic Claim (70000–77084) and Laboratory Diagnostic Claim (88104–88399; 99000–99002) Procedure Codes were excluded.
[‡] Two or more outpatient diagnosis codes greater than 30 days apart were required.

Appendix B

Table B1
Baseline Characteristics of 42, 886 Older Adult New Users of Antimuscarinic Agents.

Baseline Characteristics	n (%)
Antimuscarinics	
Oxybutynin IR[a]	8888 (20.7)
Oxybutynin ER	5262 (12.3)
Oxybutynin Transdermal	854 (2.0)
Tolterodine	14,081 (32.8)
Trospium	1252 (2.9)
Darifenacin	4131 (9.6)
Solifenacin	7906 (18.4)
Fesoterodine	512 (1.2)
Age – median (IQR)	78 (72–84)
Age (years)	
< 75	14,674 (34.2)
75–84	17,738 (41.4)
≥85	10,474 (24.4)
Sex	
Female	32,217 (75.1)
Male	10,669 (24.9)
Race	
White	37,063 (86.4)
Black or African American	2881 (6.7)
Other	2942 (6.9)
Region	
Northeast	7314 (17.1)
Midwest	11,126 (25.9)
South	17,189 (40.1)
West	7182 (16.8)
Other	75 (0.2)
Year	
2008	12,699 (29.6)
2009	11,494 (26.8)
2010	9948 (23.2)
2011	8745 (20.4)
Median Household Income for Zip Code ($), 2011[b]	
< 40,000	11,097 (25.9)
40,000–48,999	10,246 (23.9)
49,000–63,999	10,296 (24.5)
≥64,000	10,502 (24.5)
Missing	745 (1.7)
Comorbidities	
Aspiration Pneumonia	451 (1.1)
Cancer	5037 (11.8)
Cardiovascular Disease	4576 (10.7)
Chronic Pulmonary Disease	7274 (17.0)
Congestive Heart Failure	4983 (11.6)
Constipation	7314 (17.1)
Deficiency Anemias	7996 (18.6)
Delirium	932 (2.2)
Dementia / Mild Cognitive Impairment	7774 (18.1)
Depression	4105 (9.6)
Diabetes Mellitus	11,712 (27.3)
Dry Eyes	4646 (10.8)
Dry Mouth	137 (0.3)
Dysphagia	2998 (7.0)
Epilepsy / Seizure	867 (2.0)
Falls	1142 (2.7)
Glaucoma	5389 (12.6)
High Cholesterol	27,033 (63.0)
Hypothyroidism	10,900 (25.4)
Hypertension	36,987 (86.2)
Malaise / Fatigue	13,935 (32.5)
Memory Loss / Drug-Induced Cognitive Conditions	5358 (12.5)
Neurological Disorders	5171 (12.1)
Osteoarthritis	16,030 (37.4)
Osteoporosis	16,030 (23.0)
Paralysis	1085 (2.5)
Parkinson's Disease	3055 (7.1)
Blood Loss Anemia	517 (1.2)
Renal Failure	3396 (7.9)
Rheumatoid Arthritis/Collagen Vascular Diseases	1981 (4.6)
Skin Ulcer	2.939 (6.9)

(*continued on next page*)

Table B1 (*continued*)

Baseline Characteristics	n (%)
Sleep Apnea	842 (2.0)
Syncope	3730 (8.7)
Traumatic Brain Injury	705 (1.6)
Vertigo	6994 (16.3)
Rehabilitation Services	1846 (4.3)
Stroke	1626 (3.8)
Urinary Tract Infection	16,816 (39.2)
Urinary Retention	4235 (9.9)
Weakness	4235 (9.9)
In Prescription Coverage Gap at the time of Antimuscarinic Initiation	8023 (18.7)
Provider Types	
Neurologist / Neuropsychiatrist	1,581 (3.7)
Geriatrician	456 (1.1)
Urologist	11,819 (27.6)
Hospitalization in the Previous 12 Months	14,432 (33.7)

[a] Oxybutynin IR tablet (n = 8778) and Oxybutynin IR liquid (n = 45).

[b] 2007-2011 American Community Survey 5-Year Estimates – Median Household Income in the Past 12 Months (in 2011 Inflation-Adjusted Dollars).

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