SUPPLEMENTARY DIGITAL CONTENT

SUPPLEMENTARY DIGITAL CONTENT 1.

TABLE S1.1. FDA-Approved Prescription Medications for Overactive Bladder in Adults

Generic name	**Release mechanism**	**Formulations**	**Class**	**FDA approval**	**Earliest observed claim***
Oxybutynin	Immediate	Tablet	Antimuscarinic	1975	01/01/2000
		Syrup	Antimuscarinic	1979	01/04/2000
	Extended	Tablet	Antimuscarinic	1998	01/01/2000
		Transdermal patch†	Antimuscarinic	2003	05/01/2003
		Transdermal gel	Antimuscarinic	2009	05/12/2009
Tolterodine	Immediate	Tablet‡	Antimuscarinic	1998	01/01/2000
	Extended	Tablet	Antimuscarinic	2000	01/11/2001
Trospium	Immediate	Tablet‡	Antimuscarinic	2004	08/17/2004
	Extended	Tablet	Antimuscarinic	2007	12/31/2007
Darifenacin	Extended	Tablet	Antimuscarinic	2004	01/05/2005
Solifenacin	Extended	Tablet	Antimuscarinic	2004	01/09/2005
Fesoterodine	Extended	Tablet	Antimuscarinic	2008	03/18/2009
Mirabegron	Extended	Tablet	β_3 adrenergic agonist	2012	10/05/2012

* Date (MM/DD/YYYY) of earliest observed dispensing in this study based on available claims data from Truven Health Analytics' Medicare Supplemental databases, 2000-2015.

† An over-the-counter oxybutynin transdermal patch for women was also approved on 01/25/2013,[1] but there were no claims for this product in the available data used for this study.

‡ For this analysis, immediate-release (IR) tolterodine and IR trospium were grouped together and assessed as "other IR" medications. Prior to IR trospium market entry in August 2004, "other IR" pertains exclusively to IR tolterodine.

SUPPLEMENTARY DIGITAL CONTENT 2.

Standardized dispensing rates

To control for year-to-year variation in the geographic distribution and types of insurance plans included in Truven's Medigap data, we estimated standardized dispensing rates[2,3] for each week, which rendered time trends independent of sampling artifacts in the database. Specifically, we standardized the data nonparametrically[3] with respect to geography, insurance type, and data supplier, since dispensing rates themselves also varied by these three variables.

The geographic distribution for the standard population was derived from state-level (*i.e.*, the 52-level variable) data on Medigap enrollees in 2014.[4] Each standardized week-specific rate was a weighted average rate across states, with each state weighted to its share of the nationwide Medigap population in 2014. For example, New York accounted for 3.6% of nationwide Medigap enrollment in 2014,[4] and subsequently accounted for 3.6% of each standardized nationwide week-specific rate. Without standardizing, New York's contribution would have ranged 1.9% (in 2006) to 16.2% (in 2014), leading to spurious distortions in time trends.

In addition to geography, rates were also standardized by insurance plan type (*i.e.*, fee-for-service versus managed care), and data supplier (*i.e.*, large employer versus health plan). Truven's Medigap data were supplied exclusively by large employers until 2004; subsequently, rates during 2004-2015 were standardized by geography, insurance type, and data supplier, whereas rates during 2000-2003 could only be standardized by geography and insurance type. Weights for standardization were calculated based on the joint distribution of state, insurance type, and data supplier in 2014. Although rates varied by gender and age, the distribution of gender and age was consistent across years, and trends were proportional across gender and age groups; therefore, neither gender nor age were used in standardization.

In sensitivity analyses of the interrupted time-series data, in addition to those mentioned in the main text, rates and trends were robust to: (1) standardizing by geography using alternative state-level data from American Community Survey[5] data on Medicare enrollees age ≥65 in 2015, scaled by each state's proportion of Medicare enrollees with Medigap[6]; (2) excluding individuals insured through health maintenance organizations or point of service plans; and (3) isolating near-coincident interruptions and analyzing all interruptions separately (data not shown).

A sensitivity analysis of geography-, insurance type-, and data supplier-standardized data did not alter OAB dispensing rates by age and gender, because age and gender distributions were not different after standardizing by state, insurance plan type, or data supplier (data not shown).

Standardized payment distributions

To control for potential confounding by geography, we standardized payment distributions. Results for payments over time were susceptible to confounding by geography, given: (1) variation in dispensing rates by state, (2) year-to-year variation in each state's representation in Truven's Medigap data, and (3) potential underlying differences in payments between states. Therefore, to assess payments over time independent of geographic influences, we standardized payment data using a two-stage approach. First, we calculated the payment percentiles (5^{th}, 10^{th}, 25^{th}, median, 75^{th}, 90^{th}, 95^{th}) for each week of the study period, separately for each state. Then, weighting each state based on Medigap enrollment in 2014,[4] we computed week-specific weighted average percentiles of payments.[7]

SUPPLEMENTARY DIGITAL CONTENT 3.

TABLE S3.1. Segmented Linear Regression Model Results for Dispensing Rates (Per 1000 Person-Months) of Prescription Medications for Overactive Bladder Among Adults Age 65-104 in the United States, 2000-2015.

	All OAB medications combined		IR Oxybutynin		Other IR medications		ER Oxybutynin		ER Tolterodine		ER Darifenacin		ER Solifenacin		ER Mirabegron	
Parameter	**Est***	**(99% CI)**	**Est***	**(99% CI)**	**Est***	**(99% CI)**	**Est***	**(99% CI)**	**Est***	**(99% CI)**	**Est***	**(99% CI)**	**Est***	**(99% CI)**	**Est***	**(99% CI)**
intercept	20.7	(18.9, 22.4)	4.0	(3.5, 4.5)	12.3	(11.7, 12.8)	4.4	(3.5, 5.3)		--		--		--		--
$\text{trend}_{01Jan00\_10Jan01}$†	6.2	(3.8, 8.6)	-0.2	(-1.0, 0.5)	3.0	(2.3, 3.8)	2.8	(1.5, 4.1)		--		--		--		--
$\text{trend}_{11Jan01\_11Mar02}$†	5.7	(3.9, 7.5)	-0.4	(-1.0, 0.1)	-6.9	(-7.5, -6.4)	1.8	(0.8, 2.9)	11.8	(11.2, 12.5)		--		--		--
$\text{trend}_{12Mar02\_30Apr03}$†	-0.5	(-2.1, 1.1)	0.1	(-0.4, 0.6)	-2.7	(-3.2, -2.2)	0.8	(-0.1, 1.8)	1.2	(0.1, 2.3)		--		--		--
$\text{trend}_{01May03\_04Jan05}$†	3.1	(2.0, 4.1)	-0.3	(-0.5, 0.0)	-0.3	(-0.7, 0.0)	0.8	(0.2, 1.4)	2.7	(2.0, 3.4)		--		--		--
$\text{trend}_{05Jan05\_26Nov06}$†	-0.3	(-1.2, 0.6)	-0.2	(-0.5, 0.0)	-0.3	(-0.6, -0.1)	-2.1	(-2.7, -1.6)	-1.1	(-1.7, -0.5)	1.7	(1.4, 1.9)	1.8	(1.7, 2.0)		--
$\text{trend}_{27Nov06\_30Dec07}$†	2.0	(0.3, 3.8)	0.3	(-0.2, 0.8)	-0.2	(-0.7, 0.3)	-0.4	(-1.4, 0.6)	-0.3	(-1.4, 0.9)	1.0	(0.4, 1.6)	1.7	(1.1, 2.2)		--
$\text{trend}_{31Dec07\_17Mar09}$†	0.1	(-1.3, 1.5)	0.5	(0.1, 0.8)	-0.7	(-1.1, -0.3)	-0.7	(-1.5, 0.0)	-1.6	(-2.5, -0.7)	0.0	(-0.5, 0.6)	1.2	(0.8, 1.7)		--
$\text{trend}_{18Mar09\_04Oct12}$†	-0.9	(-1.3, -0.6)	0.4	(0.3, 0.5)	-0.1	(-0.2, 0.0)	0.3	(0.1, 0.5)	-2.1	(-2.3, -1.9)	-0.3	(-0.5, -0.1)	0.4	(0.3, 0.5)		--
$\text{trend}_{05Oct12\_31Dec15}$†	0.5	(0.0, 0.9)	0.3	(0.2, 0.4)	0.3	(0.2, 0.4)	0.4	(0.2, 0.7)	-0.8	(-1.1, -0.6)	-0.8	(-1.1, -0.6)	-0.3	(-0.4, -0.1)	1.7	(1.7, 1.7)
$\sin(2\pi i/52)$	-0.6	(-0.9, -0.3)	0.0	(-0.1, 0.1)	0.0	(-0.1, 0.1)	-0.2	(-0.3, -0.1)	-0.2	(-0.4, -0.1)	-0.1	(-0.2, 0.0)	-0.1	(-0.2, 0.0)	0.0	(-0.1, 0.0)
$\cos(2\pi i/52)$	0.1	(-0.3, 0.4)	0.0	(-0.1, 0.1)	0.0	(-0.1, 0.1)	0.0	(-0.1, 0.1)	0.0	(-0.1, 0.2)	0.0	(-0.1, 0.1)	0.0	(-0.1, 0.1)	0.0	(-0.1, 0.0)

Est = estimate; CI = confidence interval; i = week of birth during the year, i={1, 2, ..., 52}.

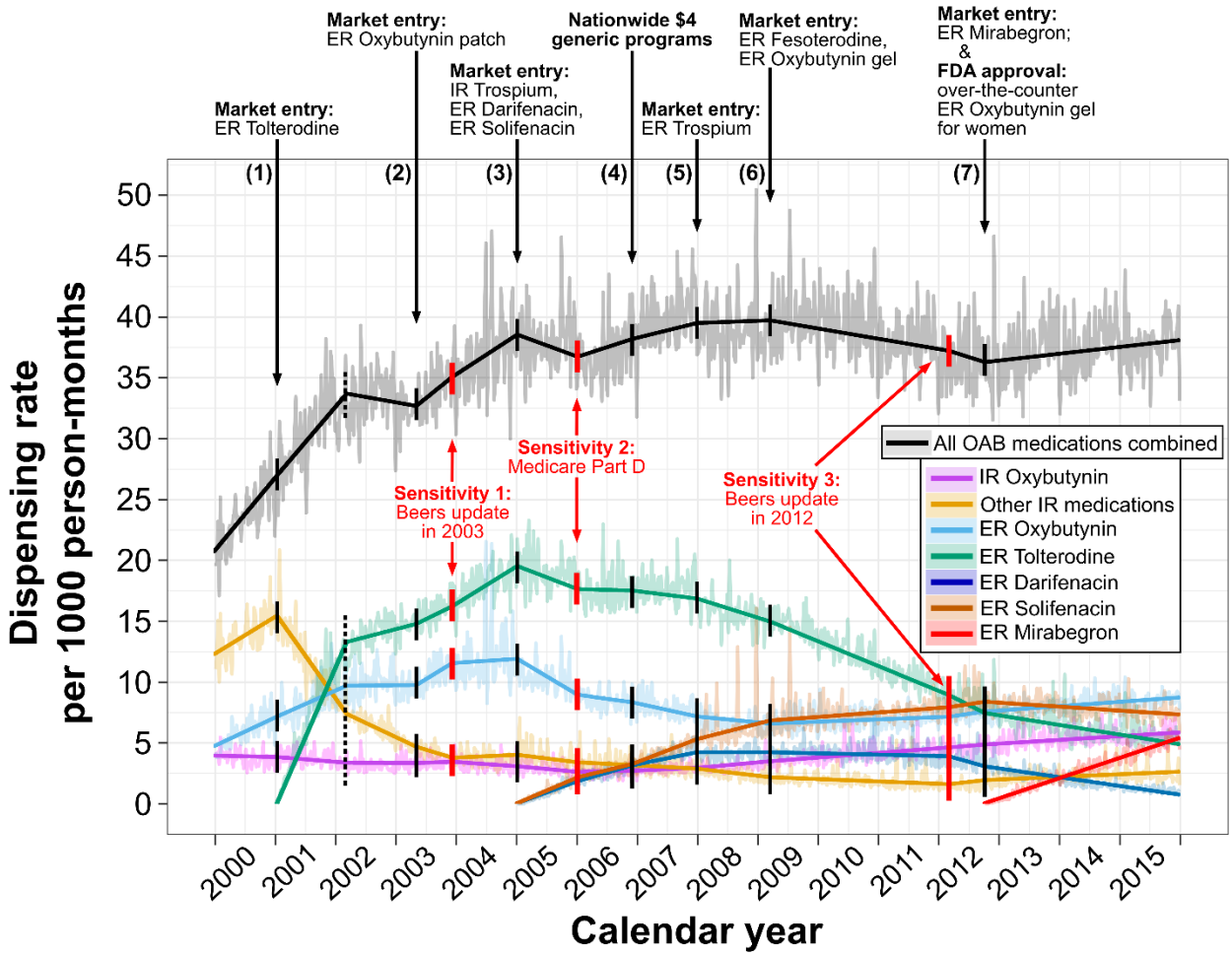
* Estimates correspond to the rate (intercept) or change in rate (other parameters) per 1000 person-months.

† Trend estimates between boundary dates (DDMMMYY) are scaled to year intervals, corresponding to change in linear rate per year of calendar time.

SUPPLEMENTARY DIGITAL CONTENT 4.

Below are the results from a sensitivity analysis that added three new interruptions to the original seven interruptions in the primary analysis. Overall, these three new interruptions had minimal impact on time trends, shown in the Figure by minimal deflections of trends at the new interruptions. Trends for IR oxybutynin and mirabegron did not change in the sensitivity analysis. Trends for other medication groups were similar, with some notable exceptions when the new interruptions added information for our regression models. The 2003 Beers criteria update was associated with an upward deflection of the trend for IR tolterodine (*i.e.*, "other IR medications" before IR trospium entry) by 1.7 more dispensed prescriptions per 1000 person-months per year (99% CI: 0.3-3.2), and a downward deflection for ER oxybutynin by 2.7 (99% CI: 0.8-4.7). The start of Medicare Part D in 2006 was associated with upward deflections for ER oxybutynin by 2.3 (99% CI: 0.8-3.8) and ER tolterodine by 1.8 (99% CI: 0.1-3.4), leading to an upward deflection for all OAB medications by 3.5 (99% CI: 0.0-6.9). The 2012 Beers criteria update was associated with a downward deflection for darifenacin by 1.3 (99% CI: 0.8-1.8).

FIGURE S4.1. Sensitivity analysis, segmented trends over calendar time for dispensing rates (per 1000 person-months) of prescription medications for overactive bladder, among adults age 65-104 in the United States, 2000-2015. The three new interruptions are indicated by red text, red arrows, and red solid vertical lines. All other figure attributes are similar to those in Figure 1.



SUPPLEMENTARY DIGITAL CONTENT 5.

Below are results on beneficiary and total payments over time by OAB medication.

Figure S5.1 pertains to immediate-release (IR) medications, as grouped in Figure 1 in the main text. It shows that there was negligible change over time in payments for IR medications.

Figure S5.2 pertains to extended-release (ER) medications, as grouped in Figure 1 in the main text. For beneficiary payments, Figure S5.2 shows stability over time for ER oxybutynin, but increases in upper-percentile payments for all other ER medications. For total payments, Figure S5.2 shows decreases for ER oxybutynin, but higher baseline costs and increasing trends over time for all other ER medications.

Figure S5.3 pertains to the three formulations of extended-release (ER) oxybutynin. It shows heterogeneity in payments over time between tablet, patch, and gel ER oxybutynin formulations.

The following general legend applies to all three figures S5.1-S5.3:
Payments per prescription over calendar time for prescription medications for overactive bladder, among adults age 65-104 in the United States, 2000-2015, adjusted for inflation to United States dollars ($) in 2015. (Left column) Beneficiary payments include deductible, coinsurance, copayment, and coordination of benefits. (Right column) Total payments include beneficiary payments and all post-discount payments by the insurer. Payment percentiles were calculated for each week of the study period, standardized by geography, and plotted using loess smoothers.

FIGURE S5.1. Immediate-release (IR) medications: oxybutynin (tablets, syrup) and other IR medications (tolterodine tablets, trospium tablets).

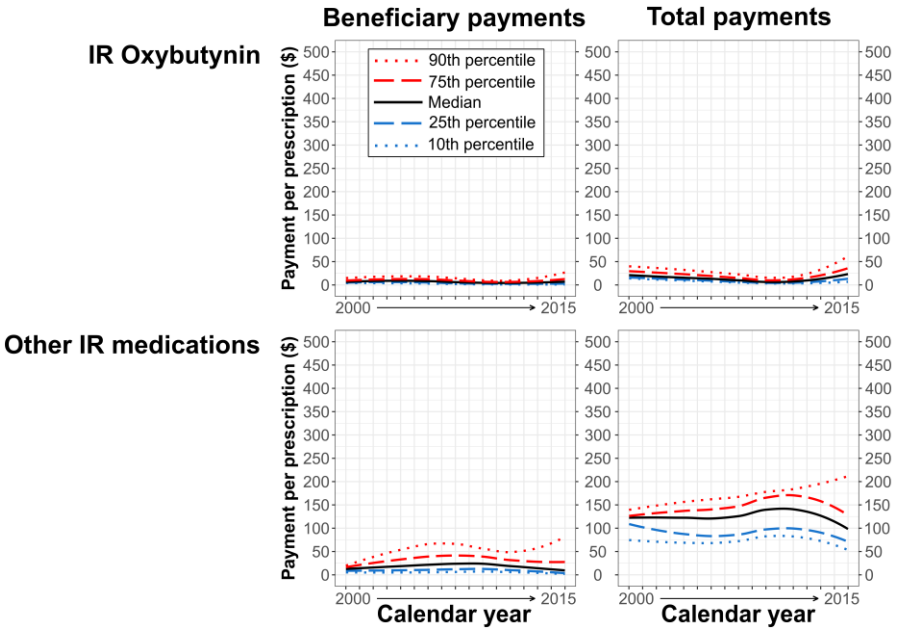


FIGURE S5.2. Extended-release (ER) medications: oxybutynin (tablets, transdermal patch, transdermal gel), tolterodine tablets, darifenacin tablets, solifenacin tablets, mirabegron tablets.

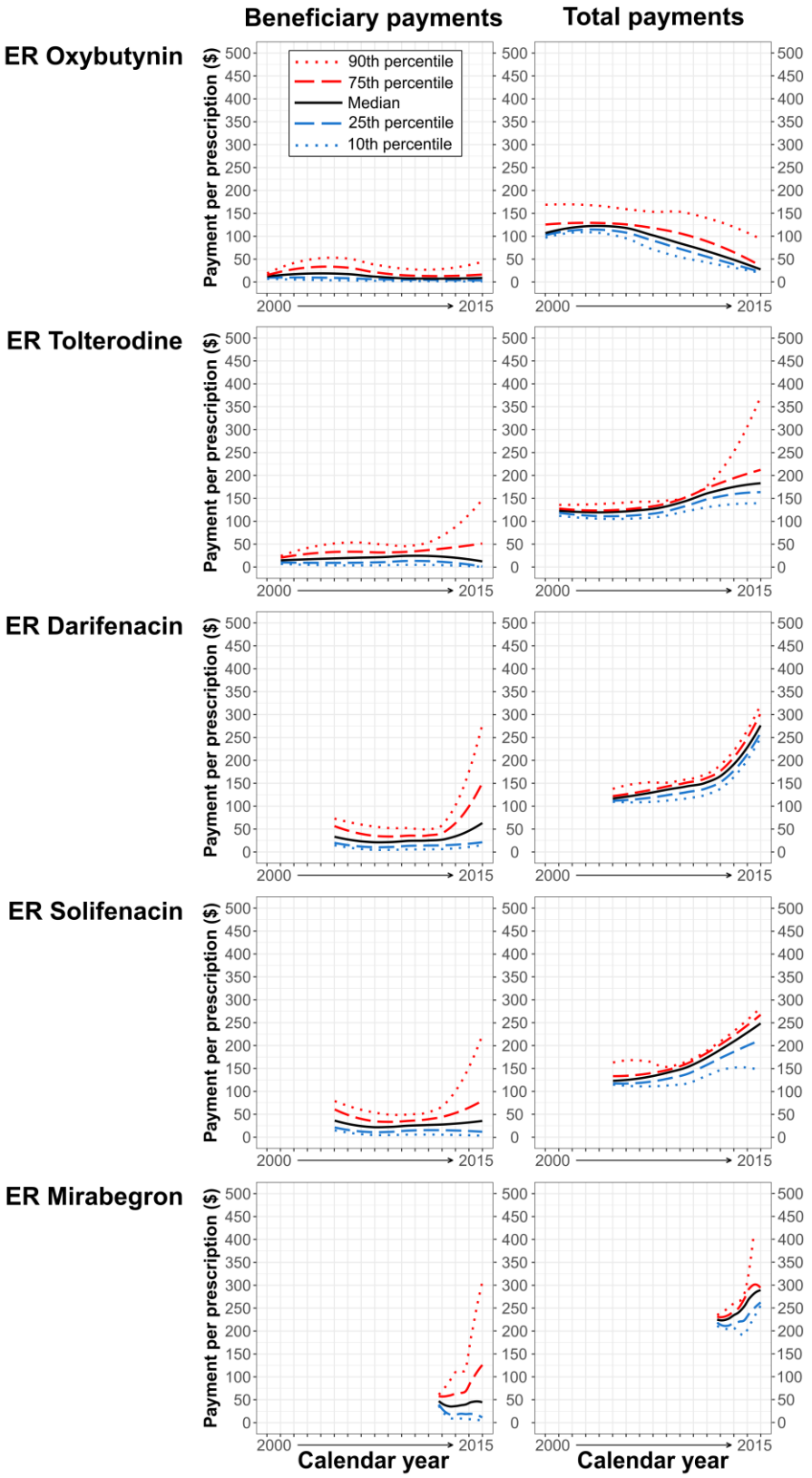
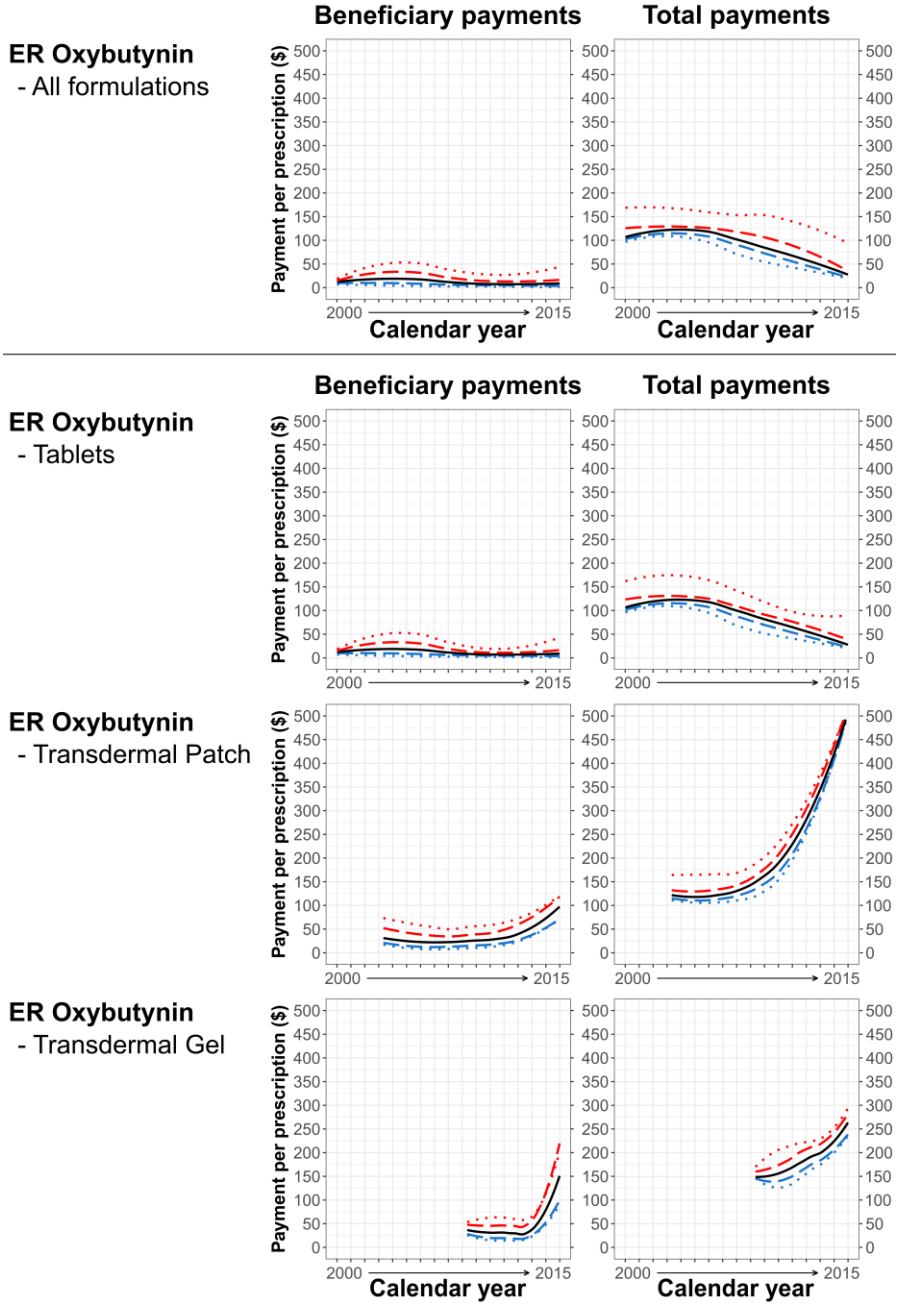


FIGURE S5.3. Extended-release (ER) oxybutynin medications. The top row shows all ER oxybutynin (tablets, patch, gel) as shown in Figure S5.2. The three rows under the solid line separate payments for ER oxybutynin tablets, transdermal patch, and transdermal gel.



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