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How Did Multiple FDA Actions Affect the Utilization and Reimbursed Costs of Thiazolidinediones in US Medicaid?

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Abstract

Purpose—The US Food and Drug Administration (FDA) communicated the potential cardiovascular risk of thiazolidinediones (rosiglitazone and pioglitazone) in 2007 and required a Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone in 2010. It also communicated in 2010 the potential risk of bladder cancer with pioglitazone use. This study examined the effects of these multiple FDA actions on utilization and reimbursed costs of thiazolidinediones in state Medicaid programs.

Methods—State Drug Utilization Data from the Centers for Medicare & Medicaid Services were assessed. An interrupted time series design and segmented linear regression models were used to examine changes in market shares according to both prescription volume and reimbursed costs for rosiglitazone and pioglitazone in the Northeast and Midwest regions of the United States after multiple FDA actions.

Findings—Compared with expected rates, there were relative reductions of 65.84% (Northeast region) and 55.09% (Midwest region) in the use of rosiglitazone at 1 year after the 2007 FDA actions for thiazolidinediones and cardiac risk. At the same time, relative increases of 7.30% and 9.28% in the use of pioglitazone were observed in the Northeast and Midwest regions, respectively. Changes in both use and costs of rosiglitazone after the 2010 REMS program could not be estimated because of the already low rates (~1%) before REMS was implemented. One year after the 2010 FDA actions for pioglitazone and its possible association with bladder cancer, relative reductions in pioglitazone use of 21.41% (Northeast region) and 18.12% (Midwest region) were detected.

Implications—The Northeast and Midwest regions reported similar patterns of changes after the FDA actions. Use and costs of rosiglitazone were substantially reduced after the 2007 FDA actions for cardiovascular risk, and this drug was rarely used after the 2010 REMS program. Conversely,

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

use and costs of pioglitazone were substantially reduced after the 2010 FDA actions regarding the drug's possible risk of bladder cancer.

Keywords

FDA actions; Medicaid; thiazolidinedione; type 2 diabetes

INTRODUCTION

Thiazolidinediones, a class of antidiabetic drugs introduced in the late 1990s, have been widely used to treat patients with type 2 diabetes mellitus.^{1–3} These agents are among the medications recommended for diabetes, with the recognized clinical advantages of treating insulin resistance and achieving and sustaining glycemic control.^{4–6} Despite these benefits, contrasting but growing evidence suggests that thiazolidinediones have adverse effects on the cardiovascular system.^{7,8}

In 2007, concerns emerged regarding the potential cardiovascular risk of thiazolidinediones.⁹ Nissen and Wolski found a 43% increased risk of myocardial infarction and a nonsignificant 64% risk in cardiovascular death associated with rosiglitazone use after performing a meta-analysis of 42 randomized clinical trials.^{7,10,11} In response, the US Food and Drug Administration (FDA) issued a communication on May 21, 2007, to health care professionals that warned of the potential risk of myocardial infarction in patients taking rosiglitazone.^{12,13}

After evaluating rosiglitazone safety data from industry,¹⁴ independent researchers,⁷ and the FDA itself, as well as the results of large randomized clinical trials evaluating rosiglitazone and pioglitazone use,^{6,15} the FDA's Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee concluded on July 20, 2007, that rosiglitazone was associated with an increased risk of myocardial infarction.^{1,9} On August 14, 2007, a boxed warning was added to the prescribing information for thiazolidinediones (rosiglitazone and pioglitazone) regarding their potential to cause or exacerbate heart failure.^{16–19} However, expert consensus was that the cardiovascular risk of rosiglitazone was greater than that of pioglitazone.^{4,13}

After completion of GlaxoSmithKline's RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) randomized clinical trial,²⁰ the FDA met again in September 2010 to review emerging data, including the final results of the RECORD trial, updated meta-analyses conducted separately by the FDA and other independent researchers, and a series of observational studies comparing rosiglitazone and pioglitazone.^{11,14,21–23} The FDA then required the manufacturer to undertake a restricted access program under a Risk Evaluation and Mitigation Strategy (REMS). According to the REMS program, rosiglitazone is only recommended in patients who have no cardiovascular risk and whose diabetes is not well controlled with other antidiabetic drugs.^{24–26} The REMS has several components, including provision of complete risk information to patients (medication guide)²⁷ and to health care providers such as physicians and pharmacists (communication plan).¹⁴

Although the FDA required a boxed warning in August 2007 for pioglitazone's possible risk of heart failure, it did not issue warnings regarding myocardial ischemic risk and did not require a REMS program for pioglitazone.¹ However, results from two 3-year controlled clinical studies of pioglitazone (the PROactive [Prospective Pioglitazone Clinical Trial in Macrovascular Events] study^{15,28}) demonstrated a higher rate of bladder cancer in patients with the longest exposure to pioglitazone and those exposed to the highest cumulative dose of this drug compared with patients who had not been treated with it.²⁹ In response, the FDA issued a warning on September 17, 2010, regarding the potential increased risk of bladder cancer with pioglitazone.³⁰

These FDA actions (drug risk communication, label changes, boxed warnings, and REMS) are some of the various mechanisms by which health professionals and the public are provided with new evidence regarding a drug's safety. Other mechanisms include clinical guidelines, publication of large randomized controlled trials, and the media, which may affect patterns of prescribing and medication use.^{31–33} Several studies have examined changes in thiazolidinedione utilization after the 2007 FDA actions. Overall, these studies found substantial reductions in the use of rosiglitazone in the United States after the 2007 FDA actions while pioglitazone use was largely unchanged.^{26,34,35} Research also indicated that rosiglitazone users had a higher discontinuation rate (53.5%) compared with pioglitazone users (21.4%), and 23% of patients who discontinued rosiglitazone were switched to pioglitazone.¹³

Little is known about the effects of the REMS program for rosiglitazone and the FDA actions regarding pioglitazone and risk of bladder cancer, both of which were implemented in 2010. The goal of the present study was to address these gaps. Specifically, our aim was to evaluate the impact of multiple warnings for thiazolidinediones on their use and costs in the United States between 2005 and 2013.

MATERIALS AND METHODS

Data Source

This study used State Drug Utilization Data from the Centers for Medicare & Medicaid Services reported by states for covered outpatient drugs that are paid for by state Medicaid programs. The data elements include drug name identified by National Drug Code, product name, unit type, quarterly unit reimbursed, quarterly number of prescriptions, and quarterly total amount reimbursed for each state.

We used 2005–2013 State Drug Utilization Data for each state, and grouped all states into 4 regions (Northeast, Midwest, West, and South) based on their geographic location. Only the Northeast and Midwest regions were analyzed (Appendix) because data for several states in the West and South regions were incomplete. The oral antidiabetic drugs were identified by using American Hospital Formulary Service codes, which were classified into the following drug classes as defined by the American Society of Health-System Pharmacists: thiazolidinediones, sulfonylureas, biguanides, α -glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, and others (mitiglinide, amylinomimetics, and incretin mimetics).³⁶

Study Period and Outcome Measures

The study period included the first quarter of 2005 through the first quarter of 2013, which span the FDA actions of interest. The multiple FDA actions were considered as 3 distinct interventions: (1) the FDA's boxed warning for both rosiglitazone and pioglitazone and cardiovascular risk, released in August 2007; (2) REMS for rosiglitazone, introduced in September 2010; and (3) the FDA's safety warning about pioglitazone and bladder cancer risk, released in September 2010. The study period was divided according to the timing of the interventions and thus included 3 time segments: (1) baseline period, from the first quarter of 2005 through the second quarter of 2007 (10 quarters of observation); (2) post-2007 warning period, from the third quarter of 2007 through the second quarter of 2010 (13 quarters of observation), and (3) post-2010 warning and the REMS period, from the fourth quarter of 2010 through the first quarter of 2013 (10 quarters of observation).

The number of prescriptions and total reimbursed costs were calculated for each class of oral antidiabetic agents in the Northeast and Midwest regions, respectively. We estimated the market shares of thiazolidinediones both by prescription volumes and by reimbursed costs on a quarterly basis over the study period. Market share in use was defined as the percent share of thiazolidinediones of all prescriptions for oral antidiabetic medications. Market share in costs was defined as the percent share of thiazolidinediones of total reimbursed costs for all oral antidiabetic medications.

Statistical Analysis

An interrupted time series design, which is a strong quasi-experimental method, was used to examine the effects of the FDA actions on quarterly market shares according to use and costs of rosiglitazone and pioglitazone. This method can provide strong evidence of causal effects because it takes into consideration the question of whether an intervention causes abrupt and measurable interruptions in the pre-existing trend.^{37–39} Segmented linear regression models were used to estimate postwarning changes in both the level and trend of thiazolidinedione use and costs.^{37–41} Using baseline trends, quarterly rates were projected over time, with the assumption that the baseline trend reflected what would have happened without the FDA actions. The following linear regression model was used for 2 change points:

$$Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{intervention } 1_t + \beta_3 \times \text{time after intervention } 1_t + \beta_4 \times \text{intervention } 2_t + \beta_5 \times \text{time after intervention } 2_t + e_t$$

In our model, Y_t is the percent market share in use or in costs for thiazolidinediones in quarter t ; time is a continuous variable indicating time in quarters at time_t from the start of the study period; $\text{intervention } 1$ is an indicator for time_t occurring before or after the 2007 FDA actions ($\text{intervention } 1 = 0$ or 1); $\text{time after intervention } 1$ is a continuous variable counting the number of quarters after the 2007 FDA actions at time_t , coded 0 before the intervention; $\text{intervention } 2$ is an indicator for time_t occurring before or after the 2010 FDA actions ($\text{intervention } 2 = 0$ or 1); and $\text{time after intervention } 2$ is a continuous variable counting the number of quarters after the 2010 FDA actions at time_t , coded 0 before the

intervention. In this model, β_0 estimates the baseline level of the outcome (intercept); β_1 estimates the change in outcome that occurs with each quarter before the 2007 FDA actions (ie, the baseline trend); β_2 estimates the level change immediately after the 2007 FDA actions; β_3 estimates changes in the trend after the 2007 FDA actions; β_4 estimates the level change immediately after the 2010 FDA actions; and β_5 estimates changes in the trend after the 2010 FDA actions. The error term (ϵt) represents the random variability and autocorrelation.^{37,39} We started with the full model (including all the aforementioned terms) and excluded nonsignificant terms ($P > 0.05$) to reach the most parsimonious models.

To express results in a single metric, absolute and relative changes (with 95% CIs)^{40,41} in market shares were also calculated at 12 months after the FDA actions were issued compared with projected rates. Similar methods were used to study the effects of drug policies, including previous FDA warnings on medication use.^{38,42–46} All analyses were conducted by using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

Figure 1 and Figure 2 display the market share of thiazolidinediones by prescription volumes and by reimbursed costs, respectively, in the Northeast and Midwest regions before and after the FDA actions.

Use and Costs of Oral Antidiabetic Drugs over Time

Table I indicates the use of oral antidiabetic drugs in state Medicaid programs in the Northeast and Midwest regions over time. Use of sulfonylureas decreased during the study period. In the Northeast, sulfonylureas accounted for 35.49%, 28.84%, and 26.02% of prescriptions during the baseline, transition, and last periods, respectively; for the same periods, they accounted for 37.07%, 29.86%, and 26.45% in the Midwest. Likewise, reimbursed costs of sulfonylureas decreased. In the Northeast, sulfonylureas accounted for 17.86%, 9.66%, and 4.6% of reimbursed costs during the baseline, transition, and last periods; for the same periods, they accounted for 13.87%, 7.06%, and 5.95% in the Midwest.

Use of biguanides increased over time. In the Northeast, biguanides accounted for 35.26%, 42.52%, and 47.15% of prescriptions during the baseline, transition, and last periods, respectively, and for the same periods, they accounted for 35.27%, 47.73%, and 54.81% in the Midwest (Table I). However, market share of biguanides according to reimbursed costs declined due to their low costs compared with other medications (eg, thiazolidinediones, α -glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors). In the Northeast, biguanides accounted for 16.55%, 9.49%, and 5.64% of reimbursed costs during the baseline, transition, and last periods; for the same periods, they accounted for 11.12%, 8.84%, and 8.14% in the Midwest.

Use of dipeptidyl peptidase-4 inhibitors increased during the study period. In the Northeast, these agents accounted for 0.18%, 7.52%, and 13.93% of prescriptions during the baseline, transition, and last periods, respectively; for the same periods, they accounted for 0.08%, 3.09%, and 7.57% in the Midwest (Table I). Likewise, reimbursed costs of dipeptidyl

peptidase-4 inhibitors increased. In the Northeast, dipeptidyl peptidase-4 inhibitors accounted for 0.50%, 21.61%, and 44.93% of reimbursed costs during the baseline, transition, and last periods, and for the same periods, they accounted for 0.26%, 11.39%, and 32.45% in the Midwest.

Use of α -glucosidase inhibitors and other agents remained relatively stable during the study period.

Use and Costs of Thiazolidinediones in the Baseline Period

The average market shares by prescription volume and by reimbursed costs of thiazolidinediones were 25.05% and 58.18% in the Northeast and 24.85% and 68.86% in the Midwest, respectively. Specifically, rosiglitazone accounted for 14.06% and 12.06% of prescriptions for antidiabetic drugs in the Northeast and Midwest regions. Reimbursed costs for rosiglitazone accounted for 29.77% and 30.24% of total reimbursed costs for antidiabetic drugs in the Northeast and Midwest regions; for pioglitazone, it accounted for 11.00% and 12.79% of prescriptions for antidiabetic drugs in the Northeast and Midwest regions. Reimbursed costs for pioglitazone accounted for 28.40% and 38.62% of total reimbursed costs for antidiabetic drugs in the Northeast and Midwest regions.

Table II presents parameter estimates, SEs, and *P* values from segmented regression models predicting market share of thiazolidinediones over time.

Effects of the 2007 FDA Actions for Cardiovascular Risk on Rosiglitazone Use and Costs

At 1 year after the FDA actions, there were relative reductions of 65.84% (95% CI, -68.30 to -63.37) and 55.09% (95% CI, -57.33 to -52.85) in rosiglitazone use in the Northeast and Midwest regions, respectively, compared with expected rates (Table III).

Reimbursed costs of rosiglitazone in both the Northeast and Midwest Medicaid programs grew continuously during the baseline period but decreased rapidly after the 2007 FDA actions. One year after the FDA actions, reimbursed costs for rosiglitazone were reduced by 60.62% (95% CI, -63.17 to -58.07) and 52.09% (95% CI, -56.14 to -48.03) in the Northeast and Midwest regions, respectively.

Effects of the 2007 FDA Actions for Cardiovascular Risk on Pioglitazone Use and Costs

In the Northeast, pioglitazone use gradually increased from ~10% at the beginning of 2005 to ~12% in the third quarter of 2007, but it suddenly rose to ~14% around the time when the 2007 FDA boxed warning was issued; its use was steady after that time. Likewise, in the Midwest, there were sudden changes in pioglitazone use immediately after the FDA actions, but they subsequently declined. One year after the FDA actions, there were relative increases of 7.30% (95% CI, 3.63 to 10.96) and 9.28% (95% CI, 7.14 to 11.42) in pioglitazone use in the Northeast and Midwest regions, respectively, compared with expected rates. One year after the FDA actions, there were relative increases of 18.05% (95% CI, 9.40 to 26.71) and 27.57% (95% CI, 23.40 to 31.74) in reimbursed costs of pioglitazone in the Northeast and Midwest regions, respectively.

Effects of the 2010 Restricted Access Program by REMS on Rosiglitazone Use and Costs

Changes in market shares in both use and costs after the 2010 REMS program could not be estimated by using interrupted time series analysis and segmented regression models because of the already low rates (~1%) before REMS was implemented. Rosiglitazone use continued to be low until the end of study follow-up (<1% market share from the first quarter of 2011 to the first quarter of 2013 in both the Northeast and Midwest regions).

Effects of the 2010 Actions for Bladder Cancer Risk on Pioglitazone Use and Costs

Pioglitazone use dropped sharply after the FDA communicated the drug's possible risk of bladder cancer; there were relative reductions of 21.41% (95% CI, -23.46 to -19.36) and 18.12% (95% CI, -20.19 to -16.05) in the Northeast and Midwest regions, respectively, compared with expected rates (Table III).

Reimbursed costs of pioglitazone also fell substantially after communication of bladder cancer risk. One year after this warning was issued, reimbursed costs for pioglitazone were reduced by 23.61% (95% CI, -27.81 to -19.41) and 21.78% (95% CI, -25.67 to -17.89) in the Northeast and Midwest regions, respectively, compared with expected rates.

DISCUSSION

This interrupted time series study examined changes in use and costs of rosiglitazone and pioglitazone after multiple FDA actions, particularly the more recent 2010 REMS program for rosiglitazone and the 2010 warning for pioglitazone and bladder cancer risk. Our findings indicate that different FDA regulatory actions (boxed warnings, REMS, and public risk communications) may have differential effects on use and costs of rosiglitazone and pioglitazone in Medicaid programs in the Northeast and Midwest regions of the United States. Changes in market shares by prescription volume and by reimbursed costs were similar overall for both rosiglitazone and pioglitazone after the FDA actions in 2007 and 2010.

Previous studies found that rosiglitazone use decreased substantially after the 2007 FDA actions while pioglitazone use either remained stable³ or increased slightly.^{1,26} Our results confirm these findings. However, instead of simply comparing medication use before and after the FDA actions as in many previous studies, an advantage of our interrupted time series study is that we were able to depict the trends in use after each FDA action. Although the FDA actions in 2007 targeted both agents,¹¹ changes in the use of rosiglitazone and pioglitazone differed, possibly because the cardiovascular risk of rosiglitazone was acknowledged as being greater than that of pioglitazone.^{4,13}

Although the FDA required a REMS program instead of market withdrawal of rosiglitazone in 2010, this agent has rarely been used since the 2007 boxed warning about heart failure risk. Physicians and patients may be concerned about its cardiovascular adverse effects, and they might seek other options for diabetes treatment (eg, replacing rosiglitazone with pioglitazone or other new oral antidiabetic agents). Indeed, we observed some increases in use of dipeptidyl peptidase-4 inhibitors over the study period, suggesting substitution effects of FDA actions. In addition, the REMS program restricted access to rosiglitazone by

requiring a “medication guide” and “elements to assure safe use.” According to REMS, health care providers who prescribe rosiglitazone-containing medicines for outpatient or long-term care use are specially certified. Rosiglitazone would be dispensed only by specially certified pharmacies and only to those patients with documentation of safe-use conditions.⁴⁷ All these restricted access strategies might result in the rare use of rosiglitazone.

In contrast, the 2007 boxed warning did not reduce the use or cost of pioglitazone; in fact, its use increased slightly. Pioglitazone might have been used as a replacement for rosiglitazone, which is consistent with previous studies showing that patients switched from rosiglitazone to pioglitazone.¹³ Unlike rosiglitazone, the evidence did not suggest any associations between pioglitazone and increased risks of myocardial infarction and mortality.^{1,18,48} However, due to accumulating evidence of an increased risk of bladder cancer among patients taking high cumulative doses of pioglitazone over the long term, its use sharply decreased after the 2010 FDA warning regarding bladder cancer risk.

Importantly, declines in thiazolidinedione use after the FDA actions may have stimulated increases in use of dipeptidyl peptidase-4 inhibitors, which have no reported risks of hypoglycemia, weight gain, cardiovascular disease, or mortality.^{49–51} However, dipeptidyl peptidase-4 inhibitors are relatively more expensive than other oral antidiabetic medications. At the end of the follow-up period, dipeptidyl peptidase-4 inhibitors accounted for 13.93% of use but 44.93% of reimbursed costs in the Northeast, and in the Midwest, 7.57% of use but 32.45% of reimbursed costs. These are substantial increases from <1% of use and costs before the FDA actions. It is important to recognize that such substitution effects may have economic implications.

The present study has several limitations. First, even with our strong quasi-experimental study design, definitive conclusions cannot be provided regarding the causal relationship between FDA actions and changes in thiazolidinedione use and costs. This is because release of clinical guidelines, publications of large randomized controlled trials/meta-analyses, and the media reports that occurred around the time of the FDA actions may have contributed to the changes.^{31–33} Second, this research aimed to examine how multiple FDA actions for thiazolidinediones affected drug utilization and costs. Our analysis was based on State Drug Utilization Data, which do not contain information on patient-level use of medical procedures and hospitalizations; thus, we could not assess changes in drug switches and clinical outcomes such as glycemic control (eg, results of glycosylated hemoglobin tests for diabetes), cardiovascular events (eg, ischemic heart disease, myocardial infarction, congestive heart failure), and bladder cancer rates after the FDA actions. Third, we used data only in states from the Northeast and Midwest regions because of missing data in several states of the West and South regions; our results may therefore not be generalizable to these other regions.

Research is warranted to determine whether FDA actions affected medication adherence or real health outcomes, particularly among patients with a cardiovascular-related history and those already established on therapy with thiazolidinediones. Further research is also needed

to examine the impact of REMS programs, which are being applied to several drugs but their effects on medication access, use, and health outcomes have not been well studied.

CONCLUSIONS

The present study assessed how various FDA regulatory actions changed the utilization and costs of thiazolidinediones in the Northeast and Midwest regions of the United States. FDA actions in 2007 and in 2010 were associated with substantial reductions in use of rosiglitazone in state Medicaid programs. In contrast, although there were small changes in pioglitazone use after issuance of the 2007 FDA boxed warning, its use was substantially reduced after the 2010 communication regarding its bladder cancer risk. Further research is needed to determine how drug switches related to FDA actions affected medication adherence or real health outcomes, and the impacts of REMS programs.

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APPENDIX

The Northeast region covers 9 states: New Jersey, New York, Pennsylvania, Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont. The Midwest region covers 12 states: Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota, Illinois, Indiana, Michigan, Ohio, and Wisconsin.

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Figure 1.

Market shares of thiazolidinediones according to prescription volume in state Medicaid programs in the (A) Northeast and (B) Midwest regions after the US Food and Drug Administration's safety warnings (2005–2013). Market share in use = number of thiazolidinedione prescriptions/number of prescriptions for all oral antidiabetic drugs for each quarter (Q). REMS = Risk Evaluation and Mitigation Strategy.

Figure 2.

Market shares of thiazolidinediones according to reimbursed costs in state Medicaid programs in the (A) Northeast and (B) Midwest regions after the US Food and Drug Administration's safety warnings (2005–2013). Market share in costs = reimbursed costs of thiazolidinediones/reimbursed costs of all oral antidiabetic drugs for each quarter (Q). REMS = Risk Evaluation and Mitigation Strategy.

Table 1
Utilization and reimbursed costs of oral antidiabetic drugs in state Medicaid programs in the Northeast and Midwest regions.

Drug Class	Market Share in Use (by Prescription Volume)				Market Share in Costs (by Reimbursed Costs)			
	Baseline Period (2005Q1–2007Q2)		Transition Period (2007Q3–2010Q3)		Baseline Period (2005Q1–2007Q2)		Transition Period (2007Q3–2010Q3)	
	N	%	N	%	Cost (\$)	%	Cost (\$)	%
Northeast region								
All antidiabetic drugs	7,176,331	100.00	6,926,818	100.00	450,951,566	100.00	470,967,433	100.00
Thiazolidinediones	1,798,019	25.05	1,191,457	17.20	262,348,045	55.18	231,946,014	49.25
Rosiglitazone	1,008,734	14.06	228,672	3.30	134,257,960	29.77	37,873,792	8.04
Pioglitazone	789,285	11.00	962,785	13.90	128,090,085	28.40	194,072,222	41.21
Sulfonylureas	2,546,804	35.49	1,997,957	28.84	80,558,539	17.86	45,478,872	9.66
Biguanides	2,530,222	35.26	2,945,161	42.52	74,623,417	16.55	44,689,579	9.49
α-glucosidase inhibitors	64,539	0.90	50,713	0.73	4,501,069	1.00	4,016,109	0.85
Dipeptidyl Peptidase-4 inhibitors	13,239	0.18	521,226	7.52	2,246,515	0.5	101,770,067	21.61
Others*	223,508	3.11	220,304	3.18	26,673,980	5.92	43,066,792	9.14
Midwest region								
All Antidiabetic drugs	6,021,797	100.00	4,216,076	100.00	298,043,840	100.00	208,095,369	100.00
Thiazolidinediones	1,496,121	24.85	708,157	16.80	205,246,152	68.86	131,703,825	63.29
Rosiglitazone	726,002	12.06	159,402	3.78	90,136,632	30.24	25,922,725	12.46
Pioglitazone	770,119	12.79	548,755	13.02	115,109,520	38.62	105,781,100	50.83
Sulfonylureas	2,232,549	37.07	1,258,971	29.86	41,342,638	13.87	14,694,021	7.06
Biguanides	2,124,121	35.27	2,012,129	47.73	33,142,982	11.12	18,396,239	8.84
α-glucosidase inhibitors	33,800	0.56	17,663	0.42	2,187,101	0.73	1,268,511	0.61
Dipeptidyl Peptidase-4 inhibitors	5,050	0.08	130,215	3.09	779,279	0.26	23,691,808	11.39
Others*	130,156	2.16	88,941	2.11	15,345,688	5.15	18,340,965	8.81

Q = quarter; N = number of prescriptions.

* Mitiglinide, amylinomimetics, and incretin mimetics.

Table II

Parameter estimates, SEs, and *P* values from most parsimonious segmented regression models.

Variable	Rosiglitazone				Pioglitazone			
	Parameter Estimate	SE	t Value	P	Parameter Estimate	SE	t Value	P
Market share in use (by prescription volume)								
Northeast								
Intercept	0.1397	0.0014	100.41	<0.0001	0.1008	0.0015	69.40	<0.0001
Time	NS	NS	NS	>0.05	0.0021	0.0002	8.66	<0.0001
Intervention 1	-0.0750	0.0032	-23.14	<0.0001	0.0183	0.0018	10.30	<0.0001
Time after intervention 1	-0.0042	0.0003	-13.58	<0.0001	-0.0022	0.0003	-8.56	<0.0001
Intervention 2	NS	NS	NS	>0.05	0.0151	0.0019	8.10	<0.0001
Time after intervention 2	0.003	0.0007	4.61	<0.0001	-0.0111	0.0003	-43.30	<0.0001
Midwest								
Intercept	0.1209	0.0011	111.94	<0.0001	0.128	0.0008	154.87	<0.0001
Time	NS	NS	NS	>0.05	NS	NS	NS	>0.05
Intervention 1	-0.048	0.0024	-19.95	<0.0001	0.0202	0.0019	10.89	<0.0001
Time after intervention 1	-0.0046	0.0002	-20.10	<0.0001	-0.0021	0.0002	-11.75	<0.0001
Intervention 2	NS	NS	NS	>0.05	NS	NS	NS	>0.05
Time after intervention 2	0.0029	0.0005	6.16	<0.0001	-0.0051	0.0004	-13.88	<0.0001
Market Share in Costs (by Reimbursed Costs)								
Northeast								
Intercept	0.2995	0.003	100.31	<0.0001	0.2578	0.0074	34.87	<0.0001
Time	NS	NS	NS	>0.05	0.0055	0.001	5.62	<0.0001
Intervention 1	-0.1412	0.0072	-19.60	<0.0001	0.0605	0.0131	4.60	<0.0001
Time after intervention 1	-0.0101	0.0007	-14.58	<0.0001	NS	NS	NS	>0.05
Intervention 2	NS	NS	NS	>0.05	0.0372	0.0132	2.83	0.0086
Time after intervention 2	0.0065	0.0015	4.34	0.0002	-0.0369	0.002	-18.32	<0.0001
Midwest								
Intercept	0.2849	0.0082	34.66	<0.0001	0.3856	0.0048	79.95	<0.0001
Time	0.0042	0.0013	3.21	0.0035	NS	NS	NS	>0.05
Intervention 1	-0.1181	0.01	-11.80	<0.0001	0.0887	0.0102	8.71	<0.0001

Variable	Rosiglitazone				Pioglitazone			
	Parameter Estimate	SE	t Value	P	Parameter Estimate	SE	t Value	P
Time after intervention 1	-0.0153	0.0016	-9.59	<0.0001	0.0044	0.0011	3.89	0.0006
Intervention 2	-0.0346	0.0104	-3.34	0.0024	0.0381	0.0131	2.90	0.0072
Time after intervention 2	0.0073	0.0016	4.54	0.0001	-0.0394	0.002	-19.47	<0.0001

All terms $P < 0.05$ retained in models.

NS = nonsignificant; Intervention 1 = 2007 US Food and Drug Administration (FDA) actions regarding the potential cardiovascular risk of thiazolidinediones (rosiglitazone and pioglitazone); Intervention 2 = 2010 FDA Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone and FDA actions for pioglitazone regarding its potential risk of bladder cancer.

Estimated changes in thiazolidinedione utilization and reimbursed costs after the US Food and Drug Administration (FDA) actions in state Medicaid programs in the Northeast and Midwest regions of the United States.

Table III

Variable	<u>Impact of Cardiovascular Risk Warning for Rosiglitazone in 2007</u>		<u>Impact of REMS* Announcement for Rosiglitazone in 2010</u>	
	Absolute Change (1 year later)	Relative Change (1 year later)	Absolute Change (1 year later)	Relative Change (1 year later)
Market share in use (by prescription volume)				
Rosiglitazone				
Northeast	-9.20% (-9.65 to -8.75)	-65.84% (-68.30 to -63.37)	-	-
Midwest	-6.66% (-7.00 to -6.32)	-55.09% (-57.33 to -52.85)	-	-
Market share in costs (by reimbursed costs)				
Rosiglitazone				
Northeast	-18.15% (-19.15 to -17.16)	-60.62% (-63.17 to -58.07)	-	-
Midwest	-17.93% (-20.41 to -15.46)	-52.09% (-56.14 to -48.03)	-	-
Impact of Bladder Cancer Risk Warning for Pioglitazone in 2010				
	Absolute change (1 year later)	Relative change (1 year later)	Absolute change (1 year later)	Relative change (1 year later)
Market share in use (by prescription volume)				
Pioglitazone				
Northeast	0.95% (0.50 to 1.39)	7.30% (3.63 to 10.96)	-2.94% (-3.28 to -2.60)	-21.41% (-23.46 to -19.36)
Midwest	1.19% (0.92 to 1.45)	9.28% (7.14 to 11.42)	-2.05% (-2.33 to -1.76)	-18.12% (-20.19 to -16.05)
Market share in costs (by reimbursed costs)				
Pioglitazone				
Northeast	6.05% (3.47 to 8.63)	18.05% (9.40 to 26.71)	-11.04% (-13.42 to -8.65)	-23.61% (-27.81 to -19.41)
Midwest	10.63% (9.21 to 12.05)	27.57% (23.40 to 31.74)	-11.96% (-14.55 to -9.36)	-21.78% (-25.67 to -17.89)

* REMS = Risk Evaluation and Mitigation Strategy.

All terms with *P* value 0.05.

95% CI = estimate $\pm$ (1.96 $\times$ SE).

Absolute were estimated at 12 months after the FDA actions, compared with projected rates based on preexisting levels and trends, and relative changes