Implications of Removing Rosiglitazone's Black Box Warning and Restricted Access Program on the Uptake of Thiazolidinediones and Dipeptidyl Peptidase-4 Inhibitors Among Patients with Type 2 Diabetes

Ryan P. Hickson, PharmD, MPH; Ashley L. Cole, PhD, MPH; and Stacie B. Dusetzina, PhD

ABSTRACT

BACKGROUND: Medications are increasingly being approved with limited, short-term evidence regarding safety. Regulatory safety concerns may emerge for these drugs but later may be reversed if additional evidence suggests no warning is indicated.

OBJECTIVE: To describe trends over time in the initiation of rosiglitazone and pioglitazone—both in the thiazolidinedione (TZD) class—and medications from the dipeptidyl peptidase-4 (DPP-4) inhibitor class before and after the FDA removed a black box warning and restricted access program for rosiglitazone regarding an increased risk of myocardial infarction.

METHODS: This retrospective study evaluated initiation of TZDs and DPP-4 inhibitors using 2001–2015 administrative claims data from a U.S. commercially insured population. Patients were aged 18–64 years and were new users of either a TZD or DPP-4 inhibitor. Among all patients who were new users of either a TZD or a DPP-4 inhibitor during each quarter-year (Q), the percentage of patients who initiated rosiglitazone, pioglitazone, and DPP-4 inhibitors were calculated.

RESULTS: There were 630,977 patients eligible for the study. During 2007, rosiglitazone initiators decreased from 39.1% to 8.0% in 2007 Q4 when the black box warning was implemented. During 2010, rosiglitazone initiators decreased from 7.6% to 1.0%, as safety evidence accumulated and the restricted access program requirement was announced. Rosiglitazone initiation remained below 1.0%, even after regulatory restrictions were removed in November 2013. Pioglitazone initiation decreased from 46.4% in 2010 Q1 to 14.8% in 2011 Q4 and remained relatively constant between 14.5% and 17.8% after regulatory restrictions for rosiglitazone were removed. After DPP-4 inhibitors first became available in 2006 Q3, initiation of this medication class increased rapidly, stayed relatively constant between 42.8% and 45.5% in 2009, and then quickly rose and remained above 80% from 2012 through 2015.

CONCLUSIONS: This case study provides some evidence that adding and later reversing drug safety warnings—particularly those with restricted access requirements—may affect the uptake of the targeted product into the population when multiple clinically relevant treatment alternatives are available (such as type 2 diabetes). Once a treatment falls out of favor, removal of safety warnings and/or restricted access programs may not lead to increased use.

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What is already known about this subject

- In November 2007, a black box warning was mandated for rosiglitazone regarding an increased risk of ischemic cardiovascular events, and in November 2011, a restricted access program was implemented for rosiglitazone.
- The drug-specific warning for rosiglitazone has been associated with significant decreases in its use.
- In November 2013, the FDA reversed these regulatory decisions, removing this black box warning and restricted access program for rosiglitazone.

What this study adds

- This study evaluated U.S. medication utilization trends before, during, and after this safety warning was in place for rosiglitazone.
- After the restricted access program was announced, rosiglitazone initiation dipped below 1% and never rose above this threshold, even after the safety decisions were reversed.
- According to study findings, once a treatment falls out of favor with patients, prescribers, and payers, reversing safety decisions may not change utilization patterns.

Rosiglitazone, a thiazolidinedione (TZD) used to treat type 2 diabetes (T2DM), has experienced a complex regulatory life cycle. In November 2007, the U.S. Food and Drug Administration (FDA) mandated that products containing rosiglitazone include a black box warning regarding increased ischemic cardiovascular risk.^{1–4} In September 2010, the FDA announced that after evaluating additional evidence,^{5,6} only patients who were already successfully treated with rosiglitazone or not adequately controlled on other medications could receive it.⁷ In November 2011—as part of an FDA Risk Evaluation and Mitigation Strategy (REMS) program—patients could only receive rosiglitazone through specialty mail-order pharmacies.⁷ Previous research has shown that the implementation of these warnings resulted in reduced use of rosiglitazone.⁸

However, in November 2013, the FDA's decision to require a black box warning and a restricted access program was reversed after new evidence suggested that there was no increased risk of

myocardial infarction (MI) for patients receiving rosiglitazone compared with metformin or a sulfonylurea.⁹⁻¹¹ The FDA has relaxed labeling requirements or eliminated REMS programs in some instances,¹²⁻¹⁴ but rosiglitazone is one of the only prescription drugs on the market to have a black box warning added and subsequently removed.^{1,15,16} Therefore, rosiglitazone is a useful case study for understanding the potential effect of safety warning reversals on medication use.

Although the black box warning mentioned here specifically targeted rosiglitazone, drug-specific warnings may negatively affect the use of other medications within the same therapeutic class (e.g., pioglitazone).⁸ Previous research has shown that the use of therapeutic alternatives for rosiglitazone—within class and out of class—increased following the black box warning.¹⁷⁻¹⁹ However, it is unknown how the use of these therapeutic alternatives was affected once the rosiglitazone black box warning was reversed. In addition, in August 2007, a black box warning for heart failure was required for all TZDs.²⁰ Because use may shift away from drug classes with safety warnings toward a therapeutically similar class, we evaluated changes in the use of TZDs and dipeptidyl peptidase-4 (DPP-4) inhibitors, a clinically relevant therapeutic alternative to TZDs; both of these medication classes are typically second- or third-line T2DM therapies, are similarly efficacious, and are taken orally.²¹⁻²⁴ Initiation of metformin and sulfonylureas was not evaluated because they are typically first- or second-line therapies and were included in generic drug discount programs.²⁵⁻²⁷

To evaluate changes in the initiation of T2DM medications after removal of the rosiglitazone black box warning and restricted access program, the objectives of this study were (a) to describe trends over time in the initiation of rosiglitazone compared with pioglitazone, and (b) to describe trends over time in the initiation of the TZD class compared with the DPP-4 inhibitor class.

Methods

Data Source

Data from the MarketScan Commercial Claims and Encounters database were used. This database includes medical (inpatient and outpatient) and prescription drug claims for over 20 million patients annually (employees and their dependents aged <65 years) from approximately 100 payers across the United States.^{28,29} This study received an institutional review board waiver from the University of North Carolina at Chapel Hill.

Study Population

Eligible patients met the following criteria: (a) ≥ 1 outpatient pharmacy claim for a TZD or DPP-4 inhibitor between January 1, 2001, and September 30, 2015 (index claim); (b) ≥ 12 months of continuous enrollment before the index claim; (c) no claims for either TZDs or DPP-4 inhibitors during the 12 months before the index claim (i.e., new users); and (d) aged 18-64 years. If patients had multiple index dates, only the first date was included.

Claims for TZDs and DPP-4 inhibitors were selected using National Drug Code (NDC) numbers, which were identified from the RED BOOK database (Truven Health Analytics, an IBM Company). TZDs included rosiglitazone, pioglitazone, and troglitazone. Besides rosiglitazone, pioglitazone was the only other TZD available on the market during the study (troglitazone was used only to exclude prevalent TZD users in 2001, since it was removed from the U.S. market in 2000).³⁰ DPP-4 inhibitors included sitagliptin, saxagliptin, linagliptin, and alogliptin. Patients with index claims for TZDs and DPP-4 inhibitors on the same date or who filled a fixed-combination TZD/DPP-4 inhibitor (pioglitazone/alogliptin) were excluded (<1% of population). Patients with index claims for other fixed-dose combinations (e.g., pioglitazone/glimepiride) were included if one of the active ingredients was a TZD or DPP-4 inhibitor.

Analyses

The primary endpoint was the share of prescription fills for rosiglitazone compared with pioglitazone among all new users of TZDs and DPP-4 inhibitors. This was calculated as the percentage of all relevant patients whose index fill was for rosiglitazone versus pioglitazone, during each quarter-year (Q) of the study period (2001 Q1 through 2015 Q3). The secondary endpoint was the share of fills for TZDs compared with DPP-4 inhibitors, by quarter-year. The denominator for each quarter-year in the study period was the total number of new users of either a TZD or a DPP-4 inhibitor. From 2001 Q1 to 2006 Q3, the denominator consisted of only new users of TZDs: the percentage of rosiglitazone and pioglitazone initiators summed to 100%. In 2006 Q4, when the first DPP-4 inhibitor (sitagliptin) became available on the U.S. market, the denominator was all patients who initiated rosiglitazone, pioglitazone, or a DPP-4 inhibitor (i.e., the percentage of rosiglitazone, pioglitazone, and DPP-4 inhibitor new users summed to 100%). These estimates were overlaid on a timeline of major safety and market events that occurred for all drugs of interest.^{3-7,9,10,20,31-40} All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Among 1,698,574 patients who filled a TZD or DPP-4 inhibitor prescription between 2001 Q1 and 2015 Q3, 630,977 were identified as eligible new users. Before DPP-4 inhibitors were available on the market (2001 Q1 to 2006 Q3), 184,028 new users of TZDs were identified: 92,065 new users of rosiglitazone, 91,915 new users of pioglitazone, and 48 patients who started rosiglitazone and pioglitazone on the same day. After DPP-4 inhibitors entered the market (2006 Q4 to 2015 Q3), there were 165,980 new users of TZDs (29,219 initiated rosiglitazone, 136,738 initiated pioglitazone, and 23 initiated both) and 280,969 new users of DPP-4 inhibitors. The 71 patients who filled rosiglitazone and pioglitazone on the index date were excluded from the rosiglitazone versus pioglitazone analysis.

Implications of Removing Rosiglitazone's Black Box Warning and Restricted Access Program on the Uptake of Thiazolidinediones and Dipeptidyl Peptidase-4 Inhibitors Among Patients with Type 2 Diabetes

FIGURE 1 Percentage of Patients Initiating Rosiglitazone and Pioglitazone Before, During, and After a Safety Warning Was in Place for Rosiglitazone Regarding an Increased Risk of Myocardial Infarction, 2001 Q1 to 2015 Q3

- Rosiglitazone with 95% CI
- Pioglitazone with 95% CI
- * Studies showing increased risk of MI with rosiglitazone
- ε Study showing no risk of MI with rosiglitazone
- α, β, γ, δ Studies showing increased risk of HF associated with pioglitazone, rosiglitazone, all TZDs, and DPP-4 inhibitors, respectively
- λ Study showing increased risk of bladder cancer associated with pioglitazone

Notes: Percentage of new users for rosiglitazone, pioglitazone, and DPP-4 inhibitors sum to 100% for each quarter-year.

Detailed description of chronological events:

2005 Q4: α Study showed association with pioglitazone and HF.³⁷

2006 Q4: In October, FDA approved sitagliptin, the first DPP-4 inhibitor.

2007 Q2: β Study showed association between rosiglitazone and HF.³⁶ *Meta-analysis showed association between rosiglitazone and MI.³

2007 Q3: FDA implemented HF black box warning for TZD class.^{20,36-38} γ Meta-analysis showed association between TZD class and HF.³⁹

2007 Q4: In November, FDA implemented MI black box warning for rosiglitazone.^{3,4}

2009 Q3: FDA approved saxagliptin.

2010 Q3: *New study⁵ and updated meta-analysis⁶ showed association between rosiglitazone and MI. In September, FDA announced that access to rosiglitazone would be restricted to T2DM patients who cannot control their blood sugar after other medications.^{3,5-7}

2011 Q1: λ Study showed association between long-term pioglitazone use and bladder cancer.⁴⁰

2011 Q2: FDA approved linagliptin. FDA required warning for potential risk of bladder cancer with pioglitazone.³⁵

2011 Q4: In November, FDA implemented REMS that restricted access to rosiglitazone through specialty mail-order pharmacies.⁷

2012 Q3: FDA approved generic pioglitazone.

2013 Q1: FDA approved alogliptin.

2013 Q2: *FDA-mandated study to reevaluate rosiglitazone trial data showed no increased risk of MI associated with rosiglitazone compared with metformin and sulfonylureas.¹⁰

2013 Q4: δ Study showed association between saxagliptin and HF.³³ In November, FDA removed requirement for rosiglitazone black box warning for MI and eliminated restricted access program.^{9,10}

2014 Q1: FDA announced that it will further evaluate association between saxagliptin and HF.^{31,33}

2015 Q2: ε Study showed association between alogliptin and HF.³⁴

CI = confidence interval; Cx = cancer; DPP-4 = dipeptidyl peptidase-4; FDA = U.S. Food and Drug Administration; HF = heart failure; MI = myocardial infarction; Q = quarter; REMS = Risk Evaluation and Mitigation Strategy; T2DM = type 2 diabetes; TZD = thiazolidinedione; Y = year.

Implications of Removing Rosiglitazone's Black Box Warning and Restricted Access Program on the Uptake of Thiazolidinediones and Dipeptidyl Peptidase-4 Inhibitors Among Patients with Type 2 Diabetes

FIGURE 2 Percentage of Patients Initiating TZDs and DPP-4 Inhibitors Before, During, and After a Safety Warning Was in Place for Rosiglitazone Regarding an Increased Risk of Myocardial Infarction, 2006 Q4 to 2015 Q3

Notes: Percentage of new users for rosiglitazone, pioglitazone, and DPP-4 inhibitors sum to 100% for each quarter-year. For a detailed description of chronological events, see notes under Figure 1.

CI = confidence interval; Cx = cancer; DPP-4 = dipeptidyl peptidase-4; FDA = U.S. Food and Drug Administration; HF = heart failure; MI = myocardial infarction; Q = quarter; TZD = thiazolidinedione; Y = year.

Rosiglitazone Versus Pioglitazone

From 2001 Q1 through 2006 Q3, before DPP-4 inhibitors came on the market, rosiglitazone's share of fills fluctuated between 35.8% (95% confidence interval [CI] = 34.9-36.6) and 59.2% (95% CI = 58.3-60.2); this pattern was cyclical and complementary to pioglitazone's share of fills (Figure 1). Between 2006 Q3 and 2007 Q3, sitagliptin entered the market, all TZDs added a heart failure black box warning,²⁰ and a meta-analysis associating rosiglitazone with MIs was published.³ During this time period, the share of fills for rosiglitazone decreased from 42.6% (95% CI = 41.7-43.5) to 8.6% (95% CI = 8.1-9.2), and pioglitazone decreased from 57.4% (95% CI = 56.5-58.3) to 47.0% (95% CI = 46.0-47.9). Following this, utilization remained relatively constant through 2010 Q1.

After the rosiglitazone restricted access program was announced in September 2010 (Q3), rosiglitazone's share of fills dropped below 1.0% and never rose above this threshold, even after removal of the black box warning and restricted access program in November 2013 (Q4). Pioglitazone's share decreased significantly from 41.2% (95% CI = 40.3-42.2) to 14.8% (95% CI = 14.2-15.4) after the rosiglitazone restricted access program was announced, but new evidence also became available that pioglitazone use may increase the risk of bladder cancer.^{40,41} After generic pioglitazone market entry and rosiglitazone's regulatory action reversals, pioglitazone's use remained relatively constant.

TZDs Versus DPP-4 Inhibitors

The share of fills for patients initiating DPP-4 inhibitors increased rapidly after 2006 Q3, when sitagliptin was approved (Figure 2). From 2007 Q4 through 2010 Q1—when the rosiglitazone black box warning was in place—the share for DPP-4 inhibitors stayed relatively constant between 42.8% (95% CI=41.9-43.6) and 47.8% (95% CI=46.9-48.8). After the rosiglitazone restricted access program was announced in 2010 Q3, DPP-4 inhibitors' share of fills sharply rose to 88.2% (95% CI=87.6-88.7) by 2012 Q2, while TZDs' share of fills sharply declined to 11.8% (95% CI=11.3-12.4). Given that rosiglitazone's share of fills was less than 1% from 2010 Q4 onwards, the shares for all TZDs after this point (shown in Figure 2) were nearly identical to those for pioglitazone (shown in Figure 1). The share of fills for DPP-4 inhibitors and TZDs remained relatively constant after this point.

Discussion

Our results aligned with previous findings that rosiglitazone use decreased significantly after the MI black box warning was imposed in 2007.^{8,17-19,42,43} We also found that rosiglitazone's share of prescription fills among all new users of TZDs and DPP-4 inhibitors was negligible at the introduction of the restricted access program (November 2011) and did not increase after this program and the black box warning were removed in November 2013. In addition, there was no increase in pioglitazone uptake after the rosiglitazone MI black box warning was removed. While previous research has shown that drug-specific warnings may be associated with decreased use of other medications within the same therapeutic class,⁸ our findings suggest—in this specific scenario that included removal of a black box warning and ending a restricted access program—that the reversal of these rosiglitazone safety decisions did not lead to increased uptake of either TZD.

There are several potential reasons that rosiglitazone use did not increase following these regulatory action reversals. The initial decrease in rosiglitazone use was highly elastic in relation to news coverage concerning the warning.^{42,44} However, many patients and providers may have been unaware of the warning reversals due to a lack of marketing and media coverage (109 articles from 2013-2015; Lexis Nexis Academic search) relative to coverage when the safety concerns emerged (769 articles from 2007-2009 and 644 articles from 2010-2012; Lexis Nexis Academic search). To further complicate the scenario, while some online drug information sources have removed the MI black box warning for rosiglitazone,^{45,46} other resources still list it,⁴⁷ adding confusion for patients and providers. Because rosiglitazone was nearing the end of patent life at the time the warning was reversed, it may also have reduced company motivation to disseminate updated drug safety information. Also, DPP-4 inhibitor manufacturers may have increased marketing activities as their products entered the market.

Furthermore, providers and patients may elect not to initiate a drug that has been previously subjected to a restricted access program due to safety concerns, since there are several acceptable therapeutic alternatives. Previous research has shown that the availability of therapeutic alternatives is a major factor influencing responsiveness to drug safety warnings and may also explain the lack of responsiveness to a warning's reversal in this setting.⁸ Additional reasons include risk aversion by patients and providers because of uncertainty regarding safety evidence for rosiglitazone and that payers may continue to restrict access to rosiglitazone from formularies due to concerns about MIs or a belief that other T2DM products have better risk-benefit profiles.¹⁸ Finally, while Teva Pharmaceuticals USA received FDA approval to market a generic version of rosiglitazone in 2013,⁴⁸ to our knowledge it has never been available in the United States.⁴⁵⁻⁴⁷

For better or worse, rosiglitazone's share of the T2DM market was decimated: a fact that could not be changed by these FDA reversals. While the elimination of rosiglitazone from the market was unlikely to directly affect T2DM patients clinically, since so many therapeutic alternatives were available, the effect of these decisions may not have been completely benign. By 2015, significantly more patients were initiating DPP-4 inhibitors compared with pioglitazone, even though they had similar efficacy, and some DPP-4 inhibitors may come with an increased risk of heart failure similar to TZDs. While concerns about heart failure (all TZDs) and bladder cancer (pioglitazone) may have decreased pioglitazone use,^{20,35-41} the uncertainty surrounding rosiglitazone's MI risk may have led to the unintended consequence of further channeling patients away from pioglitazone to DPP-4 inhibitors, a therapeutically alternative class to TZDs that was significantly more expensive. Beginning in 2012, a generic was available for pioglitazone, which might have improved affordability of treatments for patients compared with branded DPP-4 inhibitors—the median list price for pioglitazone in 2015 from this study's data source was \$21 (interquartile range \$10-\$64), significantly cheaper than \$338 for DPP-4 inhibitors (interquartile range \$331-\$643). It is possible that these higher prices may have translated into decreased access for patients due to cost-sharing arrangements set by their health plans. Given that the FDA is relying more on postmarket studies to understand the safety of new medications, it is important to understand how these reversals affect the populations being treated, since they are likely to become more common in the future.¹

Limitations

Our study has some limitations. First, it was not possible to disentangle trends in utilization due to changes in rosiglitazone safety warnings versus other safety and market events that occurred at the same time. Our primary goal was to describe changes in initiation of TZDs and DPP-4 inhibitors attributable

to the implementation and reversal of rosiglitazone regulatory decisions, but these events occurred at almost the same time as other warnings were announced by the FDA (e.g., safety concerns regarding heart failure for TZDs), new DPP-4 inhibitors entered the market, and generic pioglitazone entered the market (Figures 1 and 2).

Second, although our study focused on new users of TZDs and DPP-4 inhibitors, the effect of these regulatory actions on prevalent users of these medications is also important to understand. However, the decision to change a patient's medication is likely influenced by other factors, such as response to therapy, which are unavailable in claims data. This is an important area for future research.

Third, our results may not be generalizable to other populations. Future work could investigate changes in the use of other T2DM medications and/or changes observed in other populations—such as patients with other commercial plans or Medicare, Medicaid, or uninsured populations—to see if our findings hold.

Finally, we could not observe medications received outside of patients' prescription plans. Therefore, some patients included in this study may not be new users if they recently received a TZD or DPP-4 inhibitor outside of their prescription drug plan. Given that the study sample came from an employed, commercially insured population and the study medications were not included in generic drug discount programs to our knowledge, free drug samples are likely to be the most common way these medications would have been received outside of a prescription plan. Only 6% of patients with private insurance from a 2013 nationally representative population reported using sample medications, and oral medications for T2DM were not among the most commonly sampled drugs.⁴⁹ Therefore, our findings would likely only be minimally affected by this limitation.

Conclusions

To our knowledge, this is the first investigation of changes in drug use in the United States after reversal of an FDA advisory and removal of a product's black box warning. Use of rosiglitazone and pioglitazone failed to increase compared with DPP-4 inhibitors after removal of the MI black box warning and restricted access program for rosiglitazone. Since drugs are approved earlier with less safety data, reversal of warnings imposed early in a product's life cycle may become more common. The implications of these decisions—on the specific medications and others used to treat the same condition—need to be considered carefully. While findings may differ with other conditions, medications, or regulatory decisions, this case study suggests that once a treatment falls out of favor, removal of safety warnings may not lead to increased use.

Authors

RYAN P. HICKSON, PharmD, MPH, Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy, and Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina, Chapel Hill. ASHLEY L. COLE, PhD, MPH, Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy, and Cecil G. Sheps Center for Health Services Research, University of North Carolina, Chapel Hill. STACIE B. DUSETZINA, PhD, Department of Health Policy, Vanderbilt University School of Medicine, Nashville, Tennessee.

AUTHOR CORRESPONDENCE: Ryan P. Hickson, PharmD, MPH, Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy, University of North Carolina, CB# 7573, Chapel Hill, NC 27599. Tel.: 919.966.1169; E-mail: ryan.hickson@unc.edu.

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Implications of Removing Rosiglitazone's Black Box Warning and Restricted Access Program on the Uptake of Thiazolidinediones and Dipeptidyl Peptidase-4 Inhibitors Among Patients with Type 2 Diabetes

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Implications of Removing Rosiglitazone's Black Box Warning and Restricted Access Program on the Uptake of Thiazolidinediones and Dipeptidyl Peptidase-4 Inhibitors Among Patients with Type 2 Diabetes

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