THE RISE AND FALL OF THE THIAZOLIDINEDIONES: IMPACT OF CLINICAL EVIDENCE PUBLICATION AND FORMULARY CHANGE ON THE PRESCRIPTION INCIDENCE OF THIAZOLIDINEDIONES

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ABSTRACT

Background
Numerous factors affect drug utilization including clinical trials, promotional activity, drug safety signals and funding practices. We sought to investigate the impact of cardiovascular safety concerns and public drug formulary restrictions on the use of the thiazolidinediones (TZDs): rosiglitazone and pioglitazone.

Methods
We conducted a population-based cross-sectional time series analysis among more than 1.6 million older residents of Ontario, Canada using administrative healthcare claims databases from January 2000 to September 2010 to examine the impact of two events on the rate of initiation of TZDs among those aged 66 years and older: 1) the publication of a prominent meta-analysis suggesting safety concerns for rosiglitazone, and 2) the introduction of prescribing restrictions for TZDs on the public formulary.

Results
Incident rosiglitazone prescribing decreased significantly from 5.32 to 0.44 prescriptions per 1,000 patients in the quarter following the publication of a meta-analysis, suggesting safety concerns for rosiglitazone (p<0.01). Similarly, incident pioglitazone prescribing continued to decline from 1.89 just prior to the publication of the meta-analysis to 0.53 prescriptions per 1,000 patients just prior to the policy implementation (p<0.01). Following the implementation of formulary restrictions for TZDs in Q2 of 2009, the rate of incident prescriptions for rosiglitazone fell further, from 0.20 prescriptions per 1,000 patients in the preceding quarter to 0.03 prescriptions per 1,000 patients in the subsequent quarter (Q3 of 2009; p<0.01). The rate of prescriptions dispensed for pioglitazone also decreased from 0.53 in Q1 of 2009 to 0.11 prescriptions per 1,000 patients in Q3 of 2009 (p <0.01).

Conclusion
Both the publication of clinical evidence and drug policy changes can significantly influence the utilization of the TZDs.

Key Words: Diabetes, drug utilization, drug policy, pharmacoepidemiology

Drug prescribing is driven by a number of factors including clinical research supporting their efficacy and safety, cost, drug policy, and marketing.¹⁻³ Fueled by clinical trials demonstrating significant reductions in hemoglobin A1c (HbA1c)⁴,⁵, thiazolidinedione drugs became popular for the treatment of type 2 diabetes. Subsequently, safety concerns⁶ led to significant policy changes related to their use in some jurisdictions.⁷ In a meta-analysis, Nissen and
Wolski\textsuperscript{8} suggested an increased risk of myocardial infarction with rosiglitazone relative to placebo. This led to warnings and eventually restrictions on the use of rosiglitazone in the United States by the Food and Drug Administration.\textsuperscript{9} Further, the European Medicines Agency has suspended use of this TZD in the European Union.\textsuperscript{10} Conversely, pioglitazone is currently still available for the management of diabetes for the general public in both the US and the EU, although some payers limit reimbursement of these drugs on public formularies.\textsuperscript{11} In Ontario, Canada, both rosiglitazone and pioglitazone were removed as unrestricted drug benefits on the public drug formulary in June 2009, and are currently only reimbursed on an ‘as requested’ basis among a select group of patients at low risk of adverse events.\textsuperscript{12} While several studies have examined the impact of the safety warnings on the use of TZDs\textsuperscript{13-19}, none have examined the impact of both warnings and formulary changes on utilization.

The objective of this study was to determine the impact of safety signals and public drug formulary listing changes arising from academic publications on the incidence of thiazolidinedione treatment in Ontario, Canada.

**DESIGN and METHODS**

We conducted a population-based cross-sectional time series analysis using administrative healthcare databases covering more than 1.6 million adults aged 66 and older in Ontario, Canada. This population has universal access to hospital care, physicians’ services, and prescription drugs on the public drug formulary. We divided the study period into quarterly intervals from January 1, 2000 to September 30, 2010. All TZD prescriptions dispensed over this period were identified using the Ontario Drug Benefit (ODB) database, which is an anonymized database containing all prescriptions dispensed to ODB eligible residents of Ontario in the community and long-term care settings and has an overall error rate of <1\textpercent.\textsuperscript{20} Pioglitazone and rosiglitazone were approved for unrestricted use in October 2006 and January 2007, respectively, on the Ontario public formulary. Within each quarter, we identified new prescriptions for rosiglitazone and pioglitazone, defined as the first prescription for the drug over the study period, with no prescription in the 365 days prior. For each quarter we determined the incident prescribing rate by dividing the number of individuals newly dispensed either TZD (rosiglitazone or pioglitazone) by the total number of individuals alive and aged 66 or older at the beginning of the interval, using population census estimates.\textsuperscript{21} Linear interpolation was used to generate quarterly denominators using annual population estimates.

We sought to determine the impact of two subsequent events on incident TZD use: 1) the publication of the Nissen study (June 14, 2007)\textsuperscript{8}, and 2) the restriction of TZDs to the OPDP’s exceptional access program (June 1, 2009).\textsuperscript{9} We applied interventional autoregressive integrated moving average (ARIMA) models to assess the impact of the above interventions on incident TZD utilization using SAS 9.2 (SAS, Cary, NC).\textsuperscript{22} This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

**RESULTS**

**Safety Warnings Published**

Incident rosiglitazone prescriptions decreased significantly from 5.32 prescriptions per 1,000 patients to 0.44 prescriptions per 1,000 patients in the quarter following publication (p<0.01). Similarly, pioglitazone initiation continued to decline from 1.89 just prior to the publication of the Nissen study to 0.53 prescriptions per 1,000 patients just prior to the policy implementation (p<0.01).

**Formulary Restrictions**

As expected, incident pioglitazone and rosiglitazone prescriptions decreased substantially following the change in funding status of pioglitazone and rosiglitazone on the public formulary in the second quarter of 2009. Incident prescriptions of pioglitazone decreased nearly five-fold from 0.53 in the first quarter of 2009 to 0.11 prescriptions per 1,000 in the third quarter of 2009 just following its removal (p <0.01). The rate of incident prescriptions for rosiglitazone...
decreased nearly 10-fold from 0.20 in the first quarter of 2009 to 0.03 prescriptions per 1,000 patients in the third quarter of 2009 just after its removal (p<0.01).

CONCLUSION

The incident use of the TZDs was significantly influenced by drug policy decisions as well as published evidence regarding their safety. These findings are consistent with those observed in previous studies studying the effects of formulary changes as well as studies examining the effect of clinical evidence – particularly safety evidence – on drug utilization. The impact of the Nissen study on pioglitazone initiation is unclear. Reliable statistical models could not be developed given the close temporal relationship with respect to rosiglitazone approval and publication of the Nissen study. However, while the introduction of rosiglitazone impacted use of pioglitazone, the initiation of therapy with pioglitazone continued to decline significantly following publication of the Nissen study which focused exclusively on rosiglitazone. This may suggest a cautionary mindset of physicians by negatively grouping a class of drugs rather than treating two drugs differently in light of adverse effects shown by only one of those drugs.

Our study also suggests that the impact of high profile clinical evidence highlighting safety concerns may have significant effects on utilization independent of drug reimbursement decisions. This may indicate the vigilance of physicians regarding a relatively novel diabetes medication and any new data on its safety.

Several study limitations warrant discussion. This study was limited to elderly patients and publicly reimbursed prescriptions only. As a result, the generalizability of our findings to a younger population is unknown. A series of events that occurred in 2007, such as FDA safety alerts and black box warnings, as well as the introduction of novel diabetes therapies, may have had a cumulative influence on the decline of both TZDs. The influence of these events on our findings is uncertain. Lastly, the generic formulation of pioglitazone was available in Canada in November 2008, possibly contributing to a decline in pioglitazone use, since promotional efforts for branded products typically decline following generic drug availability. The impact of generic pioglitazone on our findings is unknown.

The findings of this study highlight the possible influences of clinical evidence and drug policy on the initiation of TZD therapy. Once drugs are approved for reimbursement, the clinical community may be particularly sensitive to safety concerns, especially when alternative therapies are available.
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Conflicts of Interest
Over the past 3 years MMM has served on advisory boards for Hoffmann-La Roche, GlaxoSmithKlein, Pfizer, Novartis, Lilly, Astra Zeneca, BoehringerIngelheim, and Novo-Nordisk.

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