Author's response to reviews

Title: Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings

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Author's response to reviews: see over
Dear Editor

BMC Health Service Research

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Please find enclosed a revised manuscript entitled “Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings” and the response to the reviewers.

**Reviewer: Anthony J Smith**

1. *were the TGA, EMA and FDA warnings the ONLY ones that prescribers may have received?* It seems unlikely that the companies sent warnings independently of the regulatory agencies but all sources of warnings need to be considered before attributing causality to any one(s). *Were the TGA, EMA and FDA warnings the ONLY ones that prescribers may have received?*

   Researchers are aware of other sources of information that prescribers have received such as media, medical articles, and direct letters from pharmaceutical companies. We could not find any published information such as a letter from pharmaceutical company directly to the prescriber therefore these have not been included in the model. Pharmaceutical company (GlaxoSmithKline Australia) implemented changes to the Product Information after the TGA announcement. [http://www.gsk.com.au/media-centre_detail.aspx?view=263](http://www.gsk.com.au/media-centre_detail.aspx?view=263). Currently, we are investigating how prescribers receive the drug safety information through a qualitative study. The result from this study will help us identify the sources of drug safety information among Australian prescribers.

We have included the following sentence into the methods section, paragraph 4.

   Whilst there were other plausible types of information sent to prescribers with regards to the drug safety, it is recognized that the warnings from the FDA, EMA and TGA have a large influence on drug safety communication. For example, the pharmaceutical companies marketing these medicines did not implement changes to the Product Information until after the TGA announcement.

2. **Minor revisions**

   2.1 *Background para4. Suggest last sentence to become "....the PBS restricted prescription of rosiglitazone by requiring prior telephone approval"*

   This now reads:

   On 1st July 2011, the PBS restricted prescription of rosiglitazone by requiring prior telephone approval.
2.2 Discussion para3, penultimate sentence--is there evidence to support the word "unsubstantially" as applied to Australian access to safety warnings? If not delete this word.

This now reads:

This might be associated with the way that information was delivered, since Australian warnings were delayed, less frequently communicated, and accessed compared to the FDA and European warnings[38, 53].

3. Overall - well written but at times a bit repetitive -- could be reduced in size especially the Background section.

The background section has not been changed as we feel this provides a good explanation for international readers.

4. This is the only formal assessment of changes in use of the two glitazones in Australia of which I am aware and contributes to the drug utilisation literature even though the trends identified unsurprisingly reflect those reported in Europe and the USA. The question of where Australian prescribers are getting their primary information about drug warnings warrants further work.

Thank you for recognizing the impact of this research. Currently, a qualitative study is being conducted on prescriber’s perception on drug safety warnings in Australia.

Reviewer: Atonu Rabbani

1. On page 5, authors mention that in 2008 subsidization for rosiglitazone was withdrawn and this may have an important implication for use of rosiglitazone (or not). It will be very useful if authors discuss the implications of withdrawal of subsidy on drug use in interactions with the warnings.

The following sentence has been added to the background section, paragraph 4.

Since late 2008, PBS steadily limited the subsidisation of rosiglitazone use in combination with insulin and triple oral therapy[14]. On 1st July 2011, the PBS restricted prescription of rosiglitazone by requiring prior telephone approval [15].

The following sentence has been added to the discussion section, paragraph 2.

Several restrictions in rosiglitazone subsidies from the PBS during October 2008-February 2009 were also examined; however, these impacts are not significant after adjustment for previous warnings (p=0.46).

2. On page 6, Authors may want to elaborate a little more on the datasets. Does the data set cover all Australians? Is the dataset only for the drugs subsidized by the government? How this may bias the results? A little more clarification in the data section will be really helpful for the readers who are less familiar with the
The following sentence has been added to the method section, paragraph 1.

Data on monthly dispensed medicines were obtained from the PBS database, a national administrative scheme which records drugs subsidised by the Government for Australian citizens. The PBS database captures costs and number of community pharmacy dispensing for all subsidized drug formulations [29]. Previous studies have used dispensing data from the PBS database to represent trends of drug utilisation in Australia[30, 31]. Rosiglitazone and pioglitazone are listed as subsidised drugs for all Australians therefore a complete record of dispensed medicines was obtained[3].

3. Authors discuss the time-series econometrics methods (basically ARIMA and Dickey-Fuller test) on pages 7-8. ARIMA already has an integrating factor and that may take care of the potential non-stationarity. Authors may want to include the results and discuss them later in the discussion section. Now, estimation of an ARIMA model should also include appropriate post-estimation diagnostic tests to properly locate the ARIMA parameters and model that fits the data the best. Authors should carry out the diagnostic tests and report them in the paper.

The following sentence has been added to the method section, analyses.

The auto-regressive, integrated, moving average model (ARIMA) integrates the temporal size and direction dependency (autocorrelation) inherent in time-series data to better characterize changes in data over a period of time[47]. Autocorrelation functions (ACF) and partial autocorrelation functions (PACF) was used to obtain the best fitted model for analysis as well as the Bayesian Information Criteria. The percentage change in DDD/1000pop/day was used to remove the trend component of the time series before fitting into ARIMA models. The separate and combined effects of the announcement of the EMA, FDA, and TGA warnings on trends in rosiglitazone and pioglitazone utilisation were also investigated by fitting into ARIMA models. Impacts of drug safety warnings (interventions) on the subsequent observations were then investigated using the ARIMA model as a step-function (having a permanent and immediate impact on any subsequent trends).

The following sentence has been added to the result section, paragraph 2.

There was no seasonal autocorrelation detected for both rosiglitazone and pioglitazone utilisations. Based on visual inspection of PACF and ACF plots, an ARIMA (1,0,2) model best characterised for rosiglitazone data and pioglitazone data was best characterised as an ARIMA (1,0,1).

4. The fall in Rosiglitazone use started in January, 2007. This fall precedes the first FDA warning that came out later. Was there any dissemination of information around this time that led to fall in Rosiglitazone use around this time?

The following sentence has been added to the discussion section, paragraph 1.
There are two possible explanations for the dip seen in April 2007. It might be a seasonal trend as the same fluctuation was noted in March-April 2006; however, this was not sensitive enough to be detected by the ARIMA model. Secondly, the dip is an artifact of the data, this is actually the utilisation on its way up which is demonstrated by the higher use again in May 2007.

5. Authors mention: “Australian warnings were delayed, less frequently communicated, and unsubstantially accessed compared to the FDA and European warnings” (on page 11). This is an important point. Once the adverse impact of Rosi use and associated FDA warning became public (in the US) it is very likely that Australian prescriber will internalize this information and act on it. Additional warnings may have very limited extra information content. Is there any possibility of showing some evidence on this? Any mention of FDA warning on news or some medical journal(s) would really strengthen this argument and would help to make this case. Authors should look into this.


We have included the following sentence into the methods section, paragraph 4.

In Australia, medical media picked up this side effect once it came out from the FDA as well as medical associations issued the FDA warning on their articles.

6. On Table 1 (page 18), authors should mention which ARIMA model was retained to estimate the results presented on the table.

This information has been added to table 1, please see below

<table>
<thead>
<tr>
<th>Drug authorities</th>
<th>Month-year</th>
<th>Warnings</th>
<th>Adjusted for coefficient</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rosiglitazone: ARIMA (1,0,2) model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMA1_FDA 1 May 2007</td>
<td>Ischemic heart</td>
<td>-15.04</td>
<td>[-21.86, -8.22]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>FDA2 Aug 2007</td>
<td>Label update heart related</td>
<td>-2.61</td>
<td>[-40.41, 35.20]</td>
<td>0.893</td>
<td></td>
</tr>
<tr>
<td>EMA2 Oct 2007</td>
<td>Ischemic heart</td>
<td>1.94</td>
<td>[-95.49, 99.36]</td>
<td>0.969</td>
<td></td>
</tr>
<tr>
<td>TGA1 Dec 2007</td>
<td>Ischemic heart</td>
<td>-5.25</td>
<td>[-38.01, 27.51]</td>
<td>0.837</td>
<td></td>
</tr>
</tbody>
</table>
7. Again it seems the reduction in Rosi use started to drop before FDA1 and EMI1 (as suggested by this figure). So the "right" decision to reduce use of Rosi has already started to surface. What can explain this?

There are two possible explanations for the dip seen in April 2007. It might be a seasonal trend as the same fluctuation was noted in March-April 2006; however, this was not sensitive enough to be detected by the ARIMA model. Secondly, the dip is an artifact of the data, this is actually the utilisation on its way up which is demonstrated by the higher use again in May 2007.

8. Authors do a good job in describing the background information and issues regarding the use of rosiglitazone and pioglitazone. One important thing is to keep in mind that we are using monthly data to understand the impact of warnings on drug use. Hence, it would have been very useful from the very beginning to be explicit the months when important warnings were announced.

Months of the first meta-analysis of rosiglitazone and pioglitazone study have been added to the background. To reduce repetition we have chosen not to add specific timeframe for each warning to the background section as this is explained in detail in the methods.

9. Limitations should also reflect the time-series econometrics used in the paper and the extent to which those limitations where addressed in the paper.

We have now added the following sentence to the discussion section, paragraph 4.

Since time series model prediction is based on the pattern of drug use in the past confounding influences on data may be difficult to disentangle. Although trends can be impacted by temporal changes in drug supply or the way data are recorded, we did not find those problems during study period.
10. On Figure 1 (page 19) Authors should clarify whether all the information will go into the notes for Figure 1? If not, the actual dates (up to month level) should be added to this list.

This list is intended to go into the notes for Figure 1.

![Figure 1](image)

Figure 1. Utilisation of rosiglitazone and pioglitazone by the Australian population between 2004-2012. The drop-down lines indicate months of drug safety warnings issued.

Notes:

**Rosiglitazone warnings**
- EMA1: Reminded the risk of rosiglitazone in patients with cardiac failure and other cardiac disorders including myocardial infarction.
- FDA1: Advised to evaluate the anti-diabetic treatment options other than rosiglitazone in patients who have underlying heart disease and high risk of heart attack.
- FDA2: Added warnings for heart-related risks of rosiglitazone.
- EMA2: Suggested that rosiglitazone should only be used after careful evaluation of ischemic heart disease.
- TG1: Advised that rosiglitazone should not be prescribed for patients with known ischemic heart disease or at high risk for ischemic heart disease.
- EMA3: Suggested that rosiglitazone must not be used in patients with an acute coronary disease.
- EMA4: Recommended suspension of all rosiglitazone-containing products.
- FDA3: Restricts access to rosiglitazone due to an elevated risk of cardiovascular events.
- TG3: Reinforced that rosiglitazone should not be used in patients with known ischemic heart disease.

**Pioglitazone warnings**
- FDA: Announced the warnings on a possible increased risk of bladder cancer in patients who use pioglitazone for longer than one year.
- TG1: Advised the prescribers that use of pioglitazone for more than a year may be associated with an increased risk of bladder cancer.
- EMA: Recommended new contraindications and warnings for pioglitazone to reduce small increased risk of bladder cancer.

Thank you so much for your comments.

Sincerely,

Suvimol Niyomnaitham, MD, MSCE