Author's response to reviews

**Title:** The changing patterns of dispensing branded and generic drugs for the treatment of gastroesophageal reflux disease between 2006 and 2011 in Japan: a retrospective cohort study

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**Author's response to reviews:** see over
Dear Editors and Reviewers,

Responses to reviewers’ comments for MS: 1776710153134212

Thank you very much for the valuable comments for our manuscript entitled “The changing patterns of dispensing branded and generic drugs for the treatment of gastroesophageal reflux disease between 2006 and 2011 in Japan: a retrospective cohort study”. We have revised the manuscript in response to the reviewers’ comments on December 30, 2014. We will send our revised manuscript and point-to-point responses.

Revisions in the text are underlined. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication.

Sincerely yours,

Koji Kawakami
Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University

Reviewer 1

1. I would expect to see more discussion on the health care market, such as health insurance, physician practice settings, of Japan in particular. What are the differences of health care delivery system in Japan, compared to systems in other countries? Does Japan have FDA to monitor the application of generic drugs? Are generic drugs bio-equivalent to brand name drugs? How long will a patent of brand name drug last in Japan?

Thank you for your suggestions. We have added a brief introduction of the Japanese healthcare system especially related to this study in the sections of Methods (Page 5, Lines 18 to 21). In addition, bioequivalence of generic drugs to the corresponding
branded drugs are reviewed by the Pharmaceuticals and Medical Devices Agency in Japan. Marketing exclusive period for new medicines is generally 8 years.

[Revised parts of the manuscript]
Page 5, Lines 18 to 21: “The Japanese healthcare system is characterized by a universal health care coverage provided by employee-based or community-based plans and free access to clinics and hospitals. The claims database for the study, which comprises data from multiple employee-based insurances, …”

2. First sentence: “Generic drugs can help reduce healthcare costs and patients’ co-payments.”. In the literature of US Pharmaceutical market, new drugs are effective in terms of improving health outcome, and probably can save cost in the long run. If authors believe generic drugs can reduce overall health care cost, please at least cite the evidence to support your statement.

Thank you for your comments. We agree with the reviewer that new drugs are generally effective in terms of improving health care outcomes. This paper is not about using old drugs instead of new ones, and it is about replacing branded drugs with generic preparations which contain the same active molecule. Generic drugs tend to be cheaper and more cost-effective than branded versions even after expiry of the patent while delivering the same drug. This has been clarified (Page 3, Lines 23 to 25).

[Revised parts of the manuscript]
Page 3, Lines 23 to 25: “Generic drugs can help reduce healthcare costs and patients’ co-payments with replacement of more expensive branded drugs including the same active molecule which have expired the patents.”

3. On page 6: authors list 7 exclusion criteria. Please justify. I am not clear about criteria 6 and 7. Also from criterion 4, it looks to me that people with different diseases might be exposed to different likelihood of receiving brand vs. generic
drugs, right?

We, including experts with affluent experience of GERD care, determined the exclusion criteria carefully to extract patients with GERD, taking into consideration how PPIs and H$_2$RAs for GERD are used in clinical practice in Japan. In addition, we investigated the reasons for the choice made both at the time of initial dispensing and switching.

Specifically, the reason for Criteria 4 (Criteria 3 in the revised manuscript) is that both PPIs and H$_2$RAs for GERD are not usually prescribed as “take when required” for the initial treatment. PPIs or H$_2$RAs are commonly prescribed for the prophylaxis of gastric ulcer induced by oral NSAIDs or corticosteroids (criterion 5 in the revised manuscript). Criteria 6 in the revised manuscript was set to determine the exact order of dispensing at the initial dispensing or switching. In addition, as described in the Introduction section with references 14 to 16, we expected that we would obtain useful findings on generic drugs use from more specific analysis such as drug class or specific disease level rather than analysis in broader therapeutic area. Exclusion criteria have also been discussed in response to Comment 5 from Reviewer 2.

[Revised parts of the manuscript]

Page 7, Lines 5 to 7: “The following exclusion criteria were set to exclude non-GERD patients and to investigate the conditions at the initial dispensing and switching of branded and generic drugs clearly: 1) patients who were…”

4. Analysis: overall, I think more rigorous analysis is required. For example, table 1 demonstrated the differences in age of populations who use brand vs. generic drugs (e.g. switch from brand to generic and vice versa: 47.3 vs. 43.9). Can the decreasing rates in brand name drugs reflect the older population, who prefer generics, over 5 years? Are the age differences or gender difference among the groups significant?
5. Authors have a rich data set. If age and gender, and chronic diseases are correlated with the likelihood of receiving brand vs. generic drugs, then multivariate regression will be more appropriate.

Response to Comment 4 and 5:
We performed multivariate logistic regression analysis to investigate factors associated with receiving generic drugs using the data on the initial dispensing. It is important to examine the factors at the initial dispensing because most of the patients did not change branded drugs to generic drugs thereafter. Covariates included sex, age, year of initial dispensing, setting of prescription and dispensing, and drug class. As a result, age and sex were not associated with receiving generic drugs. Meanwhile, other variables were significantly associated. (Revisions in the manuscript: Page 2, Lines 18 to 19; Page 3, Lines 3 to 10; Page 8, Lines 15 to 19; Page 11, Lines 11 to 20; Page 13, Lines 12 to 15; Table 2)

[Revised parts of the manuscript]
Page 2, Lines 18 to 19: “Multivariate logistic regression was applied to investigate factors associated with receiving generic drugs.”

Page 3, Lines 3 to 10: “Factors associated with receiving generic drugs included year of dispensing (adjusted OR 2.22, 95% CI 1.94 to 2.55 for 2009-11 v 2006-8), prescription and dispensing setting (OR 1.81, 95% CI 1.44 to 2.26 for prescription in hospitals and dispensing in community pharmacies; OR 2.21, 95% CI 1.80 to 2.72 for prescription in clinics and dispensing in community pharmacies; and OR 4.55, 95% CI 3.68 to 5.62 for prescription and dispensing in clinics v prescription and dispensing in hospitals) and H2RAs (OR 1.64, 95% CI 1.49 to 1.81 compared to PPIs).”

Page 8, Lines 15 to 19: “Multivariate logistic regression was performed to investigate factors associated with receiving generic drugs using data at the initial dispensing. Covariates included sex, age, year of dispensing, setting of prescription and dispensing, and drugs dispensed. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were reported as well as P values.”

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Page 11, Lines 11 to 20: “The results of multivariate logistic regression indicated that age and sex were not associated with receiving generic drugs (Table 2). Meanwhile, factors associated with receiving generic drugs included year of dispensing (adjusted OR 2.22, 95% CI 1.94 to 2.55 for 2009-11 v 2006-8), prescription and dispensing setting (OR 1.81, 95% CI 1.44 to 2.26 for prescription in hospitals and dispensing in community pharmacies; OR 2.21, 95% CI 1.80 to 2.72 for prescription in clinics and dispensing in community pharmacies; and OR 4.55, 95% CI 3.68 to 5.62 for prescription and dispensing in clinics v prescription and dispensing in hospitals) and H$_2$RAs (OR 1.64, 95% CI 1.49 to 1.81 compared to PPIs).”

Page 13, Lines 12 to 15: “Our findings on the initial dispensing of GERD treatments suggested that prescribing in hospitals, especially dispensing in in-house pharmacies adversely affected the use of generic drugs. More research is needed to identify the reasons that underlie these observations.”

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Factors associated with receiving generic drugs at initial dispensing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
<td><strong>Reference</strong></td>
</tr>
<tr>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Age: &lt;45 years old</td>
<td>≥45 years old</td>
</tr>
<tr>
<td>Dispensing: 2009–2011</td>
<td>2006–2008</td>
</tr>
<tr>
<td>Out-hospital dispensing</td>
<td>In-hospital dispensing</td>
</tr>
<tr>
<td>Out-clinic dispensing</td>
<td>In-hospital dispensing</td>
</tr>
<tr>
<td>In-clinic dispensing</td>
<td>In-hospital dispensing</td>
</tr>
<tr>
<td>H$_2$RAs</td>
<td>PPIs</td>
</tr>
</tbody>
</table>

CI: confidence interval, H$_2$RAs: histamine H$_2$-receptor antagonists, PPIs: proton pump inhibitors

6. I need to be convinced more on the drugs selected in this study. For example, lafutidine did not have generic equivalent in the market. What is the market share of lafutidine? If lafutidine as large market share, then the lack of generic of lafutidine may influence the results.
Thank you for your comments. The purpose of this study was to investigate drug utilization during 2006-2011 in the real world setting. Therefore, we included all drugs with indications for the treatment of GERD on Japanese labels regardless of availability of generic formulations, and thus lafutidine was also included. The volume share of lafutidine was approximately 5% in our data. We suppose that the impact of the introduction of generic lafutidine would be limited, taking into consideration the overall share of H2RAs has been decreasing in the treatment of GERD. (Revisions in the manuscript: Page 2, Lines 14 to 16; Page 7, Lines 17 to 18)

[Revised parts of the manuscript]
Page 2, Lines 14 to 16: “All proton pump inhibitors (PPIs) and histamine H2-receptor antagonists (H2RAs) with indications for gastroesophageal reflux disease GERD described on Japanese labels were included.”
Page 7, Lines 17 to 18: “All branded and generic drugs with indications for GERD described on Japanese labels were included in the study.”

Reviewer 2

1. The background on generics in Japan is interesting, but it would be helpful to have more of a context of the Japanese healthcare system. For example, “To date, several policies and measures…” (page 3, line 14) it would be useful to know if these are federal policies, or private insurance policies, and to know about the copayment structure in Japan.

Thank you for your suggestions. We have added the explanation of the Japanese healthcare system especially related to this study in the sections of Background and Methods (Page 3, Line 26 to Page 4, Line 4).

[Revised parts of the manuscript]
Page 3, Lines 26 to Page 4, Lines 4: “To date, several policies and measures have been… by the Ministry of Health, Labour and Welfare in Japan,… The measures
included, for example, modification of the prescription form and incentive for generic drug prescription and dispensing to medical institutions and pharmacies."

2. I’d like a better context of the data set- are the claims data for one employer, one insurance company, or...? Are these only individuals with private insurance?

Thank you for your comment. We have added information on the data source with a brief introduction of the Japanese healthcare insurance system in the sections of Methods (Page 5, Lines 18 to 21).

[Revised parts of the manuscript]
Page 5, Lines 18 to 21: “The Japanese healthcare system is characterized by a universal health care coverage provided by employee-based or community-based plans and free access to clinics and hospitals. The claims database for the study, which comprises data from multiple employee-based insurances, ...”

3. Page 4, line 6 PPI is used but hasn’t been written out- it is written out farther down on the page and should be moved up to the first use.

Thank you for pointing it out. We revised the manuscript as you indicated (Page 4, Lines 19-20; Page 5, Line 6).

[Revised parts of the manuscript]
Page 4, Lines 19-20: “… branded molecules of proton pump inhibitors (PPIs) ...”
Page 5, Line 6: “PPIs are the first-line for …”

4. Page 5, lines 15-25 The authors don’t explain why it is important to distinguish among the four dispensing patterns.

Thank you for your valuable advice. We have added the reason with a reference in the sections of Methods (Page 6, Lines 7 to 9; reference 25).
[Revised parts of the manuscript]

Page 6, Lines 7 to 9: “To date, it was shown that the share of generic drugs differed by prescription and dispensing procedure (ie, prescribing and dispensing separated or integrated) and larger hospitals used less generic drugs [25]. Therefore, we classified the prescription and dispensing process …”


5. Page 6 line 13, the exclusion criteria 2) isn’t clear- does it mean patients with any diagnosis and medication during hospitalization? Specifically a GERD diagnosis? Overall, how were the exclusion criteria determined- are the consistent with the literature?

As stated in response to reviewer 1, we, including experts with affluent experience of GERD care, determined the exclusion criteria carefully to extract patients with GERD, taking into consideration how PPIs and H₂RAs for GERD are used in clinical practice in Japan. In addition, we investigated the reasons for the choice made both at the time of initial dispensing and switching.

Patients diagnosed with GERD and receiving PPIs and/or H₂RAs at least once in outpatient were included even if patients received care in hospitalization. However, prescriptions during hospitalization were not included because we focused on drugs in the outpatient setting where most of medications for GERD are delivered. We have removed criterion 2 in the revised manuscript because we had already indicated that the focus of this study is on outpatient setting in Page 6, Line 24.

6. Page 7 the analysis section is one long paragraph that is hard to follow. Are the values plotted in figures 1, 2, and 3 adjusted at all for age, sex, etc.?

This study mainly aimed to describe the changing patterns of dispensing of branded/generic drugs using a large-scale real world data, and we did not adjust for
age and sex to draw these figures. In response to the reviewers’ comments, we performed multivariate analysis, and no associations between receiving of generic drugs and age or sex were observed. For the details on the analysis, please also see the response to Comments 4 and 5 from Reviewer 1.

7. *I am not sure I follow the interpretation of the results. Page 8 lines 14-15, what does it mean to say after switching patients were likely to receive PPIs?*

   Thank you for pointing it out. We revised the sentence more clearly (Page 9, Lines 14 to 15).

   [Revised parts of the manuscript]
   Page 9, Lines 14 to 15: “*Patients switching from generic to branded drugs were more likely to receive PPIs after the switch (patterns 6 and 8).*”

8. *Page 11, line 19 I don’t know that I would call this a longitudinal analysis. It seems you are comparing descriptive statistics for each year, and making inferences based off these changes. The data are available for regression analysis- why aren’t there regression results?*

   Thank you for your comment. We revised the sentence (Page 13, Line 4). In response to the reviewers’ comments, we added the results of multivariate analysis. For the details on the analysis, please also see the response to Comment 4 and 5 from Reviewer 1.

   [Revised parts of the manuscript]
   Page 13, Line 4: “*Changes in dispensing patterns suggested …*”