Author’s response to reviews

Title: Impact of a direct-to-consumer information campaign on prescription patterns for overactive bladder

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Author’s response to reviews:

Dr. Fabrizio Tediosi

BMC Health Services Research

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Dear Dr. Tediosi,

Ms. Ref. No.: BHSR-D-17-00935

Title: Impact of a direct-to-consumer information campaign on prescription patterns for overactive bladder
Please find attached a revised version of our manuscript titled “Impact of a direct-to-consumer information campaign on prescription patterns for overactive bladder” which we would like to resubmit for publication in BMC Health Services Research.

Your comments and those of the reviewers were highly insightful and enabled us to improve the quality of our manuscript significantly. In the following pages are our point-by-point responses to each of the comments of the reviewers.

Revisions in the text are tracked and highlighted in yellow. In accordance with the suggestion of Reviewers, we performed an additional interrupted time series analysis, and the results were added to the manuscript. Also, we added further explanations and relevant references, and corrected some inappropriate explanations in the text and removed some inappropriate references from the reference list. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMC Health Services Research.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Reviewer 1

#1. This manuscript assesses the impact of a direct-to-consumer campaign targeted at increasing awareness of the possibility to treat overactive bladder with medicines on medicines use in Japan. There is little evidence of unbranded advertising of prescription medicines on relevant outcomes such as health services use and costs. As such the current paper is a welcome addition to the medical literature.

Thank you.

#2. My main concern, however, is that the chosen design does not answer the research question, at least not in the most optimal way. First, the authors established a cohort of participants with an overactive bladder before start of the study. I assume that the campaign was also or even especially targeted at those who did not seek help or treatment before and may therefore not yet have a diagnosis. My impression is that the data from the Japan Medical Data Center would allow for an analysis of diagnosis for overactive bladder during the study period. In addition, it would be more interesting if the proportion of people with a new diagnosis starting treatment would be assessed than start of treatment in a small cohort with a previous diagnosis. And potentially the authors could estimate the incidence of use of medicines for overactive bladder, again over time during the study period.
Thank you. Our main outcome is to test our hypothesis that the 2011 DTCI campaign increased the prescription rate for the treatment drugs among patients with overactive bladder who had not previously used the treatment drugs, which we stated in the Background. However, we agree that seeking the impact of the DTCI campaign on new diagnosis and newly diagnosed patients treated with medication in the population level is also attractive. In our available dataset, we have 25 monthly aggregated data for the number of new diagnosis and the number of newly diagnosed patients treated with medication from the cohort of the whole JMDC during the limited period from November 2010 to November 2012 (N = 25). For these analyses, the combination of changes at November 2011 and December 2011 accounted for the effect of the DTCI-campaign.

We underwent the interrupted time series analysis (ITSA) as supplemental data analyses for the additional outcomes indicated by your comment above, following your comment #4 as well. These additional outcomes are (a) the number of new diagnosis and (b) the number of newly diagnosed patients treated with medication. We observed a statistically significant impact of the DTCI on these additional outcomes, as in the revised main text with Supplementary Figure 1 and Supplementary Table 1 as follows:

P9, 2nd paragraph, line 1: “For supplementary data analysis with a limited monthly aggregated data set extracted from the whole JMDC cohort during November 2010 to November 2012 (N = 25), we also check the changes on different but relevant outcomes (a) the number of new diagnosis and (b) the number of newly diagnosed patients treated with medication.”

The equation used for the ITSA was as follows [13,14]:

\[
\text{(Aggregated outcome)} = \beta_0 + \beta_1 \text{(time since the start of the study)} + \beta_2 \text{(post-intervention)} + \beta_3 \text{(time since the start of the study)(post-intervention)},
\]

where

1. \( \beta_0 \) is an “intercept” in a regression, representing the starting level of the outcome variable.
2. \( \beta_1 \) is a “slope” in a regression and indicates trajectory of the outcome variable prior to the introduction of the intervention. If \( \beta_1 \) is not statistically significant, the outcome level remains constant at \( \beta_0 \) prior to the intervention. In this case, \( \beta_0 \) also represents the level of the outcome variable immediately before the intervention.
3. \( \beta_2 \) represents the “one-time” change in a “regression-intercept” or the level of the outcome that occurs in the period immediately after the intervention, which is hypothesized to be caused by the intervention.
4. \( \beta_3 \) represents the “long-term” change, expressed as the “slope” difference between pre-intervention and post-intervention in a regression, which is also hypothesized to be caused by the intervention.

Time since the start of the study is a continuous variable, and post-intervention is a dummy variable (post-interrupted time point, 1; otherwise, 0).”

We have added the results of the additional outcomes as follows:

Likewise, during November 2010 to November 2012, a significant one-time increase in the regression-intercept was seen in other outcomes, i.e., the number of new diagnosis and the number of newly diagnosed patients treated with medication in the whole
JMDC cohort (Supplementary Table 1). In addition, for the number of newly diagnosed patients treated with medication, the significant inverse time trend of the slope before the DTCI campaign changed to null (Supplementary Figure 1 and Supplementary Table 1), suggesting that patients newly diagnosed with overactive bladder were consistently prescribed medication regardless of time trends only after the DTCI campaign. In the Cox model and ITSA, the release of mirabegron was not associated with the prescription rate (data not shown).”

#3. In addition, the chosen methodology could be strengthened. I had difficulties interpreting the data as currently presented. It is clear by visual inspection that something triggered an increase in use of treatment in this cohort in periods 4-6, but can this really be attributed to the campaign so many weeks earlier? In their discussion (page 11, lines 27-33) the authors suggest that this delay may be caused by the advice to start with behavioural therapy during a 3 months period. However, since all of the patients in the cohort were already diagnosed with overactive bladder, I would assume that this advice had already been given at time of (registration of) diagnosis.

Thank you for your helpful comments. We agree with you that all of the patients in the cohort may have had already the advice of behavioral therapy, and we have removed this paragraph.

By contrast, studies conducted in Japan before the DTCI campaign suggest that an average interval of clinic visits is 3 months for overactive bladder patients (ref #15,Zaitsu et al. Comparative evaluation of the safety and efficacy of long-term use of imidafenacin and solifenacin in patients with overactive bladder: A prospective, open, randomized, parallel-group trial (the LIST study). Adv Urol. 2011;2011:854697). Therefore, it would be reasonable to test a 15-week delayed time lag, using the ITSA model. We added this explanation in the method section as follows:
P8, 2nd paragraph, line 5: “We set the interrupted time point of the intervention at Period 1 in Year 1. Additionally, to assess potential time lag regarding the impact of the DTCI campaign, we performed ITSA with various interrupted time points: from Period 2 to Period 5 in Year 1 (Period 5 corresponds to a 20-week delayed time lag); because a previous study in Japan suggests that an average interval of clinic visits is three months for overactive bladder patients [15].”

#4. A better design to study the impact of an event such as a campaign during a short period of time is the interrupted time series analysis. This methodology accounts for longer term underlying trends and is able to estimate both a direct impact (level change) as well as longer term impact (slope change). I would suggest the author use this methodology for this research question.

Thank you for the constructive comments. We performed the interrupted time series analysis as we responded in comment #2.

For main outcome, using the first-prescription rate (per standardized 100,000 persons) aggregated for each period (5 weeks) (N = 30), we underwent five different ITSA models with various interrupted time points (from Period 1 to Period 5 in Year 1) due to an expected range of clinic visit interval for three months as responded your comment #3. Period 1 in Year 1 corresponds to the exact DTCI campaign period.

Based on Linden’s guidance (ref #13, 14), we ran Prais-Winsten and Cochrane-Orcutt regression. We added our methodology of the ITSA in the Method section as follows:
Additionally, to confirm the effect of DTCI campaign at the population-level, we performed interrupted time series analysis (ITSA) [13,14] with aggregated data of the first-time prescription rate per each period (5-week) per standardized 100,000 persons (N = 30). We ran user-written STATA command of “itsa” with Prais-Winsten and Cochrane-Orcutt regression [13,14].

For the main outcome, we observed an immediate one-time increase in the regression-intercept with a 15-week delayed time lag, as in the revised text with Figure 2 and Table 3 as follows:

The ITSA did not show a one-time increase in the regression-intercept during Period 1 to Period 3, as well as Period 5, in Year 1. However, as expected, the DTCI campaign significantly increased the regression-intercept at Period 4 in Year 1, which coincide with the result of our Cox model (Figure 2 and Table 3): β2 = 1128.1 (95% CI, 181.7 to 2074.4; p-value <.01). This result suggests that the DTCI campaign raised the level of prescription rate by 2.4 times (β2/β0) with a 15-week delayed time lag. This substantial one-time increase of prescription rate was followed by the decreasing time trend (long-term effect, p-value <.05).

For the additional outcomes, we responded in the comment #2.

According to our choice of the first-time prescription rate per standardized 100,000 persons for the ITSA, the description of the crude prescription rate in the result was changed from the unit per 10,000 person-days to per 100,000 person-days as follows:
P10, last paragraph, line 1: “The crude prescription rate ratios during Periods 4–6 in Year 1 compared with Period 10 in the Pre-Campaign Year were 7.13 (47.8 [per 100,000 person-days]/6.69 [per 100,000 person-days]), 13.7 (91.8/6.69), and 4.28 (28.7/6.69), respectively”

In the discussion section, we added the following explanation:

P12, 1st paragraph, line 6: “The aggregated ITSA confirmed that the DTCI-campaign was associated with the one-time increase of the level of prescription rate with the magnitude of 2.4 times that of the pre-DTCI campaign period, holding a similar time lag of 15 weeks. The post-DTCI decreasing slope (long-term effect) might be partly caused by this one-time increase in the prescription rate. Additional aggregated ITSA implied the DTCI-campaign’s impacts on other outcomes such as (a) positive immediate impact on the numbers of new diagnosis and newly diagnosed patients treated with medication, and (b) the positive long-term impact on the number of newly diagnosed patients treated with medication.”

We added the result of ITSA in the conclusion as follows:

P15, Conclusion: “The examined DTCI campaign appeared to change the pattern of prescriptions among patients with overactive bladder, increasing the prescription rate of treatment drugs for fifteen weeks and the level of prescription rate for the post-DTCI campaign period. Future studies are expected to examine whether the increased prescription rate leads to improved health outcomes.”

Minor comments:

#5. Disease awareness campaigns is an often used synonym for DTCI campaigns. I would suggest to mention this term in the introduction and add it to the selected key words.
Thank you. We added “disease awareness campaign” into the keywords.

Additionally, we modified the introduction as follows:

P3, 2nd paragraph, line 4: “In many countries including Japan, where direct brand name drug promotion has been prohibited, DTCI campaigns (also known as disease awareness campaigns) have rapidly increased.”

#6. Abstract methods: reference period is not mentioned (but see comment above on choosing different methodology)

Thank you. Along with the obtained results from ITSA, we modified the abstract as follows:

Methods: “Using Period 10 in the Pre-Campaign Year as the referent group, we applied the Cox proportional hazard model for each period. Additionally, we performed the interrupted time series analysis (ITSA) for the first-time prescription rate per 5-week period.”

Results: “The ITSA confirmed the DTCI campaign impact on the level of prescription rate (one-time increase in the regression-intercept) that increased by 1128.1 [per standardized 100,000 persons] (p<.05) during Period 4 in Year 1.”

Conclusions: “The examined DTCI campaign appeared to increase the prescription rate among patients with overactive bladder for fifteen weeks with a 15-week delay. Clinical outcomes of the patients with targeted diseases need to be monitored after DTCI campaigns by a future study.”
#7. Methods, page 7, lines 17-18: age and comorbidity were time varying variables, but only assessed at the beginning of each year. Why not per period, especially because in the results it is stated that distributions changed during the analysis period?

Thank you. Because of the limited data availability, we could only obtain this information at the beginning of each year. We clarified this as follows:

P7, 2nd paragraph, line 3: “Age and comorbidity were time-varying variables and could be assessed only at the beginning of each year due to the limited data availability.”

Additionally, we did not observe an increased prescription rate associated with covariates except age. We clarified this result in the main text as follows:

P10, 4th paragraph, line 8: “Age was associated with the increased first-time prescription; however, sex and comorbidity was not associated with the change (Table 2).”

#8. Did you observe any effect of the introduction of mirabegron in September 2011? This approximately coincides with period 8 in the pre-campaign year I suppose. The authors rightly point out in the discussion section that campaigns such as the one under study are usually accompanied by promotion targeted at health care professionals. This may also explain the large increase seen in the current study. In my view, this can be strengthened in the paper.

Thank you. The period of the introduction of mirabegron corresponds to Period 9 in Pre-campaign Year, and the HR was not elevated in our primary Cox model analysis. The ITSA did
not show a one-time increase in the starting level of prescription rate during Period 9 or a long-term change after Period 9.

We added this explanation in the result section as follows:

P11, 2nd paragraph, last part: “In the Cox model and ITSA, the release of mirabegron was not associated with the prescription rate (data not shown).”

We also added this discussion as follows:

P13, 2nd paragraph, line 1: “A potential confounder in our analysis is the synergistic effect between pharmaceutical representatives (who could appeal to physicians with the “novelty” of mirabegron in the sales promotion of their company’s drugs) and the release of mirabegron before the DTCI campaign. This synergy may have overestimated the effect of the DTCI campaign on increased prescription rates. Pharmaceutical representatives have played an important role in the increase of drug prescriptions in the US [17]. In the present study’s Cox model analysis, the HR of Period 9 in the Pre-Campaign Year, which corresponds to the release period of mirabegron, was not elevated (Table 2). Likewise, the ITSA did not show a one-time increase in the level of prescription rate or a long-term change by the release of mirabegron (data not shown).”

We added the following limitation as well:

P13, 4th paragraph, line 1: “First, the absence of the relevant dataset did not enable us to measure other factors at the individual patient level (including the launch of mirabegron and potential
pharmaceutical’s in-person marketing toward physicians) that might affect the prescription pattern.”

Again, we are grateful to you for your great inputs on the manuscript.

Reviewer: 2

#1. Introduction - this section sets the study within its context well and notes the differences between DTCA and DTCl. The research question is clear.

Thank you very much.

#2. Methods - The list of anticholinergic drugs omits fesoterodine and darifenacin - were these not available for use in Japan during the study period?

Since those drugs were not available during the study period, we clarified it by adding the following explanation:

P6, 1st paragraph, line 5: “Fesoterodine and darifenacin were not available for use in Japan during the study period.”
#3. The launch of mirabegron into Japan may well act as a confounder in this study - the launch of a new drug will serve to raise the awareness of the condition and its treatment, particularly amongst physicians.

Thank you. This point is very consistent with the critique of Reviewer 1. Our response is as follows:

The period of the introduction of mirabegron corresponds to Period 9 in Pre-campaign Year, and the HR was not elevated in our primary Cox model analysis. The ITSA did not show a one-time increase in the starting level of prescription rate during Period 9 or a long-term change after Period 9.

We added this explanation in the result section as follows:

P11, 2nd paragraph, last part: “In the Cox model and ITSA, the release of mirabegron was not associated with the prescription rate (data not shown).”

We also added this discussion as follows:

P13, 2nd paragraph, line 1: “A potential confounder in our analysis is the synergistic effect between pharmaceutical representatives (who could appeal to physicians with the “novelty" of mirabegron in the sales promotion of their company’s drugs) and the release of mirabegron before the DTCI campaign. This synergy may have overestimated the effect of the DTCI campaign on increased prescription rates. Pharmaceutical representatives have played an important role in the increase of drug prescriptions in the US [17]. In the present study’s Cox
model analysis, the HR of Period 9 in the Pre-Campaign Year, which corresponds to the release period of mirabegron, was not elevated (Table 2). Likewise, the ITSA did not show a one-time increase in the level of prescription rate or a long-term change by the release of mirabegron (data not shown).”

We added the following limitation as well:

P13, 4th paragraph, line 1: “First, the absence of the relevant dataset did not enable us to measure other factors at the individual patient level (including the launch of mirabegron and potential pharmaceutical’s in-person marketing toward physicians) that might affect the prescription pattern.”

#4. Were there any other public awareness campaigns operating over the time periods of this study, or subsequent to this campaign but still likely to influence change?

To the best of our knowledge, there were not any other public awareness campaigns for overactive bladder during the study period. We clarified the explanation as follows:

P6, Advertising Exposure section, 2nd paragraph, line 2: “To the best of our knowledge, there was no other plausible factor to affect prescription patterns (such as a guideline update or another DTICI campaign/disease awareness campaign/public awareness campaign) during the follow-up period”

#5. The results are clear and the combination of figures text and tables helps to convey the content.
Thank you very much.

#6. The confounding nature of the mirabegron launch has been noted. Was this the only activity hitch occurred over the time period of the study?

Yes. However, pharmaceutical representatives’ promotion targeting physicians may be another potential driver to increase the prescription pattern, which may be related to the launch of mirabegron and which we could not directly assess. We have stated this limitation in the response of your comment #3.

#7. Mirabegron does not have fewer adverse events than conventional drugs for overactive bladder. The registration trials show the total TEAE rate at approximately 50%, the same as antimuscarninics. Reference 15, that of Maman, (another Astellas publication) confirms that Mirabegron (unsurprisingly) has fewer anticholinergic side effects/ All others are not examined in this paper. The alternative argument for the change in prescribing was simply that mirabegron was new - and thus there is a "novelty" effect. To suggest that mirabegron is superior to antimuscarinic therapy would be misleading, unreferenced and untrue. The limitations are otherwise well considered

Thank you very much to point out the Astellas publication. We have deleted this misleading statement. Also, we modified the explanation as follows:

P13, 2nd paragraph, line 1: “A potential confounder in our analysis is the synergistic effect between pharmaceutical representatives (who could appeal to physicians with the “novelty” of mirabegron in the sales promotion of their company’s drugs) and the release of mirabegron before the DTCI campaign.”
Again, we are grateful to you for your great inputs on the manuscript.