PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk factors influencing the prescription of tiotropium Respimat® formulation: a population-based cohort study
AUTHORS	Trotta, Francesco; Da Cas, Roberto; Rajevic, Maja; Rossi, Mariangela; Traversa, Giuseppe

VERSION 1 - REVIEW

REVIEWER	Yoon K Loke Norwich Medical School University of East Anglia UK
REVIEW RETURNED	29-Sep-2014

GENERAL COMMENTS	I think the authors need to be more upfront about the limitations of the study rather than just saying "Confirming patients' diagnoses for which drugs were prescribed was outside the objectives of the study. Our intention was to verify whether relevant concomitant drug classes (e.g. beta Bblockers ..etc.) were associated with receiving Handihaler or Respimat, irrespectively of the conditions for which the concomitant drugs were prescribed. In fact, there is no a priori reason to expect that betaBblockers (to take one of the examples) were prescribed for different indications among the users of each tiotropium formulation." I suggest that this paragraph should simply state that you don't have information on the actual diagnoses for which the concomitant drugs were used, and that drug use has been interpreted as a proxy indicator for a variety of conditions (Supp file). I suggest you delete that sentence about 'no a priori reason to expect beta-blockers to be prescribed for different reasons'; you simply have no means of knowing what the beta-blockers were actually used for, so there is no point in speculating here.

REVIEWER	Antonio Clavenna IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy
REVIEW RETURNED	13-Oct-2014

GENERAL COMMENTS	I have no comments. In my opinion, the authors took into account my previous suggestions in a satisfactory manner.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author
I have a few major methodological concerns about this work.

1) The analysis relies on drug use as a proxy for comorbid conditions. There is no real measure of disease or the severity of disease. This makes things very difficult to interpret - for instance, digoxin can be used for heart failure, or as an anti-arrhythmic. It's not possible to tell in this cohort what the patients were using it for. Equally, beta-blocker use can reflect underlying ischaemic heart disease, or hypertension, or atrial fibrillation, or panic attacks.

Authors' reply:

We understand the referee's concern. However, our study was descriptive in nature and based on data coming from a regional prescription database. Confirming patients' diagnoses, with a comparison of prescription data and"…real measure of disease…" was outside the objective of the study. This is a limitation of our study that was clearly acknowledged in the discussion section. "As for other studies that used prescription databases, a limitation of our analysis is that the identification of incident users and switchers/non-switchers is based on pharmacy records. For instance, prescriptions may lead to misinterpretation if a drug is dispensed but not used as well as the use of prescriptions could be only considered a proxy of comorbidities…".

Even within this limitations, the use of drugs with non-specific indications remains of interest when the objective is to compare users of the tiotropium formulations with regard to their baseline characteristics. There is no a priori reason to expect that beta-blockers (to take one of the examples) were prescribed for different indications among users of each formulation. Moreover, with regard to changing from Handihaler to Respimat, we intended to verify whether some classes of drugs which are known for their arrhythmogenic potential (e.g. betablockers, antiarrhythmics, antiglaucoma drugs)were associated with switching, irrespective of the conditions for which they were prescribed. This information has been included in the manuscripts (see Discussion section).

2) The analysis attempts to draw associations between drug use and change from Handihaler to Respimat; however, no one actually interrogates the medical records to look for reason why the change was initiated. It may simply be that patients on >3 respiratory drugs have poor adherence, or the wrong diagnosis for their respiratory conditions, and they end up being changed because their doctors are struggling to manage the illness. Equally, use of beta-blockers may have caused worsening of airway symptoms. This is a very tangled web, and I don't feel that this type of analysis is able to shed much light on why patients are changed from Handihaler to Respimat.

Authors' reply:

Our study investigated the influence of several risk factors on the probability of receiving one of the two tiotropium formulations, and to verify the existence of the channeling bias both in incident users and in patients switching from the Handihaler to the Respimat formulation.

Our findings showed that in the incident cohort, when a physician decides for the first time which formulation (Handihaler or Respimat) needs to be prescribed, the choice does not seem influenced by the knowledge of specific risk factors related to the severity of COPD or the presence of "comorbidities". On the contrary, in patients already on treatment with tiotropium Handihaler, switching to Respimat is influenced by risk factors such as the severity (or the lack of control) of the respiratory disease itself and the presence of conditions requiring beta-blockers or antiarrhythmics.

3) There is of course the problem of multiplicity of testing, where by chance alone, some risk factor will turn out significantly different by chance alone.

Authors' reply:

We agree with the referee. This concern is present in all epidemiological studies. To overcome this potential issue, we only conducted pre-specified analyses. Moreover, our data showed consistent results in two different settings (incident users and switchers) and were also coherent with the findings of a similar study (Verhamme et al. 2013).

Reviewer: 2

Comments to the Author
This is a relevant study that evaluated the factors affecting the choice of Respimat versus Handihaler tiotropium formulation in the daily clinical practice, and it can provide useful information to identify which are the characteristics of the patients that are treated with Respimat.
The paper is well written and results are described in a clear and adequate manner.

I have a few comments.

General comments
1. It is not very clear to me how the cases and controls were matched in the "switcher analysis". Controls were defined as having "at least two prescriptions of Handihaler within 60 days one from the other in the timeframe included between the previous two months and the subsequent two months after the index date". What happened when more than one eligible controls were available?

Authors' reply:

We added, in the Methods section of the manuscript, that a random procedure was used to select a matched control among potentially eligible ones.

Moreover, it seems to me that for prevalent patients you didn't have any detail concerning the overall duration of tiotropium therapy. The length may not be the same in switcher versus non switchers, and thus this can be a factor that can not be considered in your analysis. This should be discussed, since it can not be excluded that patients more recently treated with tiotropium have a greater likelihood to receive the new formulation.

Authors' reply:

The switcher/non-switcher analysis was conducted in a cohort of prevalent users of Handihaler. and was aimed at identifying the cause of switching from Handihaler to Respimat. The duration of tiotropium use after switching was not explored because it was outside the objectives of the study.

2. I would like to suggest, if feasible, not only to consider in the analysis the presence of comorbidity (using previous drug use as a proxy), but also the number (and association) of comorbidity.

Authors' reply:

Our analyses was focussed to identify the effect of several factors on the likelihood of receiving one out of the two formulations, as well as to study the effect of single drug classes that might be associated with a worsening of COPD (e.g. betablockers), or with potential safety/efficacy issues (e.g. antiglaucoma, lipid lowering), or with a clear indication for Respimat (e.g. anti-Parkinson, antipsychotics).

Minor revisions
1. page 3, line 48 (and page 9, line 42, etc...) : "several risk factors..." In my opinion it is better to use the term "factors" with no other connotations. I mean, receiving Respimat is not necessarily a negative or harmful event
2. page 7, line 7-10: there is no a positive association between antipsychotics and Respimat prescription (95%CI 0.87-2.02).
3. page 9, line 26: please delete one "used" (not frequently used used...)
4. page 16, figure 2: 536 switchers plus 6,065 handihaler users is not equal to 6,607 (I think that the right figure is 6,601).

Authors' reply:

The manuscript has been amended according to the suggestions.