Author's response to reviews

Title: Distinguishing patterns in the dynamics of long-term medication use by Markov analysis: beyond persistence.

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Version: 3 Date: 13 April 2007

Author's response to reviews: see over
Dear Mrs Norton,

Thank you for reviewing our manuscript MS: 9877313331160672 entitled “Patterns of inhaled corticosteroid use in the Netherlands by Markov analysis: a ten-year follow-up study”. Your reviewers made several valuable comments, which led to a number of revisions. Please find the revised manuscript enclosed. The changes as suggested by your referees are highlighted (with Word option ‘track changes’). In this letter we provide information on how we incorporated the reviewers suggestions.

Both reviewers suggest justification of the choice of continuous use: one ICS prescription filled per year. We added results from a sensitivity analysis to demonstrate that continuous use over ten years does not differ appreciably when applying more strict definitions of at least two and at least three prescriptions filled.

Both reviewers suggest clarification on the specific terms used to describe compliance in the manuscript (adherence, persistence and discontinuation). We accordingly added clarifying passages in the introduction and methods on this subject. We would like to elaborate briefly on this issue. ICS are a type of drug that pose some methodological difficulties when analysing (non)adherence and establishing the appropriateness of medication use. Under the customary definitions, it seems hard to argue that a prescription filled once a year qualifies as persistent use as recommended by the guidelines in case of persistent asthma. However, quite a few patients suffer from seasonal complaints and consequently have annual periodic use of ICS - as reviewer 2 remarks - often based on their physicians’ advice. Markov analysis has added value compared to classic survival analysis in that it enables to describe these patterns in drug utilisation, over a prolonged period of time. Reviewer 2 rightly remarks that patients with long gaps are not regarded as discontinuing patients. They are however not considered as chronic maintaining users, but as irregular users.

Both reviewers request clarification of the definition of end of follow-up, which is of particular interest for other investigators when replicating this approach. The probabilities of continuous use, discontinuation or gap of several years were based on transition probabilities per year, which were calculated for patients that remained under observation in the PHARMO RLS during that entire year. We added a sentence in the method section on how the end of follow-up is determined in the PHARMO RLS. Patients that have migrated from pharmacy to pharmacy within the regions covered by the database remain under observation. The end of follow up is either the last prescription for any drug in the PHARMO RLS or the date of death when recorded in a hospital.

Reviewer 1 adds that we only referred to one study concerning the validity and the completeness of the PHARMO RLS. Patients in The Netherlands have always been relatively compliant in visiting one single pharmacy. A recent study from our department showed that over a period of one year only 10% of patients visit more than one pharmacy. The vast majority of patients visiting an extra pharmacy did so only incidental probably in out of opening hours. These data have been submitted for publication.

Mrs Melissa Norton MD, medical editor
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Resubmission of manuscript MS: 9877313331160672

April 13, 2007

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As requested by reviewer 2, we elaborate in more detail on the populations from which the transition probabilities were derived. Therefore we added a table of population characteristics to the manuscript (Table 2).

Reviewer 2 concludes from figure 6 that the annual gaps in therapy are nearly monotonic, but comments that this seems unusual. We can comfort reviewer 2 that these gaps are not monotonic. This can be derived from the Markov table that shows that patients that are more compliant in the previous years have a higher probability of being compliant in the next year. We have tried to clarify this more in the results and discussion. In line with the reviewer's suggestion we added the sample size for each year in figure 5.

Reviewer 2 states that the second sentence of the discussion concludes the opposite of the findings noted in the previous paragraph of the result section. We fully agree with reviewer 2. We clearly were mistaken and should have stated that that new users have a "lower" probability. We have changed this in the discussion.

We agree with Reviewer 2 that figure 1 might not be of added value and have therefore deleted this from the manuscript. Furthermore we would like to clarify that with figure 4 we intended to assist future readers in understanding the matrix of transition probabilities not only for 1993 to all other possible states (figure 3) but also for the combination of transition probabilities from several states. When the reviewer is in the opinion that this is not necessary we agree with removing figure 4.

Reviewer 1 suggests to discuss clinical implications of the findings. It is important to realise that patients might discontinue for several reasons. Patients using ICS, however most frequently do not discontinue entirely but use their medication intermittently, annually during certain periods, often based on seasonal variety of symptoms. When initiating therapy, patient and physician should therefore agree on the intended duration of use and subsequently evaluate the experience of symptoms and the use of ICS. By reviewing dispensing data pharmacists could assist physicians in monitoring adherence. Patients’ previous experiences with a specific drug treatment should be discussed as these experiences might influence future behaviour.

Yours sincerely,

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