Reviewer's report

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

Version: 1 Date: 9 March 2007

Reviewer: Michael B B Nichol

Reviewer's report:

General

----------------------------------------------------------------------------------------
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

This is an interesting manuscript detailing an innovation in conceptualizing persistence in medication taking behavior. The use of transition probabilities over time could provide new insight into long term use. The study drug, however, does not adequately show the potential value and reduces the level of interest in the article.

The problem with the use of ICS controllers is illustrated with the definition of continuous use. It is hard to argue that a prescription that is filled once a year represents ‘persistent’ use. The Markov model, and the transition states described in this article, would be considerably more interesting if the authors had used a chronic daily medication, such as those used to treat hypertension. The example of ICS means that the model must be interpreted as periodic, sometimes consistent use. The authors should point out this limitation in the discussion section.

The authors should clarify their use of specific terms in the introduction. The term “persistence” is included in the title, and in the discussion, after carefully avoiding it in the rest of the manuscript. Their definition of continuous use (at least one prescription for an ICS medication each year) doesn’t qualify under any of the definitions of persistence of which I am aware. I’m comfortable with a term like “annual periodic use” or something similar, but not adherence or persistence. What is the definition of ‘discontinuation’? Based on Figure 6 it appears that patients with long gaps in prescription filling behavior are still considered to be maintaining use.

It is also essential to provide more detail on the populations used to derive the transition probabilities. For example, a table of population characteristics is absolutely required. It would be especially helpful to contrast the baseline characteristics of the new and continuing patients.

There is also no description of eligibility. The sample was drawn from prescription records from six cities in the Netherlands, but there is no information regarding the likelihood that the patients that initiate ICS therapy continue to fill their prescriptions at pharmacies in these locations. The critical question is whether those who fail to fill their annual prescription actually have been lost to follow-up because they are no longer in that location. It would be possible to determine this by analyzing whether they’ve filled another prescription at one of the metropolitan pharmacies during the monitoring year. The authors only reference a dissertation to confirm that “more than 95% of all prescriptions” for a patient are captured in this system.

The authors appropriately highlight the fact that a two state model fails to capture the possibility of a patient restarting a medication after an extensive delay. It then appears that Figure 6 provides some evidence that patients are likely to restart ICS therapy after drug vacations. However, this figure implies that the annual gaps in therapy are nearly monotonic (about 10% per year) in samples tracked for six years or more. This seems unusual, and unfortunately there is no explanation. I would imagine that this consistent result is related to a substantial discontinuation rate. At a minimum, the sample size for each year should be noted for each year.

The second sentence in the discussion section concludes the opposite of the findings noted in the previous paragraph of the results section and Figure 6.
It’s not clear that Figure 1 is needed. This is a relatively rudimentary illustration of the Markov chain in the model that the reader will be able to understand through the other figures. I’m also not convinced that there is a need for Figure 4.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.