Reviewer's report

**Title:** Clinical and economic ramifications of switching antipsychotics in the treatment of schizophrenia

**Version:** 2  **Date:** 20 February 2009

**Reviewer:** Peter Weiden

**Reviewer's report:**

Clinical and economic ramifications of switching antipsychotics in schizophrenia

This is a pooled post-hoc analysis of a prospective clinical trial where patients with schizophrenia or related disorders were initially randomized to either 1) a conventional antipsychotic 2) risperidone, or 3) olanzapine. The study design required patients to remain on their initial assignment and then after 8 weeks, clinicians were allowed to change antipsychotics, with the second switch antipsychotic usually being olanzapine among patients initially assigned to either conventional antipsychotic or risperidone treatment. Overall study duration was 1 year.

**Major compulsory revisions**

The authors need to explain what this paper adds to the literature over and above the initial study paper which was published in Value in Health (Tunis, Faries, Nyhuis, et al, 2006). The initial report of this study showed that the highest switch rates were in the initial conventional antipsychotic group (53%), followed by the initial risperidone group (31.3%) and then last for the olanzapine assignment (14.4%). These are found in Figures 1 and 2 of the initial study manuscript. (Tunis, Faries, Nyhuis, et al, 2006).

In the initial report the main contrast is between the 3 medication groups as made by their initial randomization status. The current submission pools these 3 groups and now divides the entire patient group into those who switched sometime during follow-up vs. those who did not switch. While a post hoc comparison in a dichotomous outcome variable can often be very informative, in this paper it seems that many of the central findings were already reported (see below).

1. The 1st sentence of the discussion section of current manuscript states: “In this naturalistic 1-year study, switching antipsychotic medication regimens was common, occurring in nearly 1 of every 3 patients.”

The initial Value in Health paper reports the switch rates according to initial medication assignment, and the total switch rate for the entire cohort is easily calculated from the lower legend of Figure 2, which shows “% at 365 days” with 47% for remaining on the conventional, 85.6% remaining on olanzapine and 68.7% on risperidone.
2. The current manuscript states: “The new dimensions added by the present study include the findings that individuals who switched antipsychotics were significantly more likely to use a range of acute-care services, and to do so significantly earlier, compared with those remaining on their initial regimens. These disparities had economic consequences, including about a $3,000 higher annual total healthcare cost for switchers (vs continuers).”

The initial Value in Health paper reports, “Compared with patients able to remain on their initial antipsychotic regimen (n=430), those who required a switch (n=182) had treatment episodes with $3546 greater total ITT costs. (nonsignificant).”

See 1st sentence after subheader ‘Impact of Treatment Failure” (p86, column 1).

Discretionary revisions

The title states that the paper covers both clinical and economic ramifications of switching, but there is very little in the way of clinical data or information that is presented. For this paper to be clinically relevant, more specific data on the specific pre- and post-switch medication choices, dose-titration schedules, reasons for antipsychotic switching, time until treatment second episode of treatment failure (e.g. time until first hospitalization after the switch) would be very helpful. Another approach to the cost of switching would be to evaluate the initial patient cohort to ascertain the subgroup of patients who did not change medication at the time of their initial assignment, analogous to the method employed by Essock and colleagues in their secondary analysis of the CATIE Phase I data. (Essock, Covell, Davis, et al, 2006; Rosenheck, Davis, Covell, et al, 2009) The authors state that this data is missing but I suspect that more of these questions can be answered with a close look at the Case Report Form, especially the medication tracking data which presumably was carefully assessed because it is a cost variable. If this is not possible, then the authors should not state that this is a clinical paper.


**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:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I think the answer is "no" but there is another issue that may be relevant.

I had been an investigator in this study but changed institutions soon after we started the study at my site. At the time, I received grant support and speaker/consulting fees from Eli Lilly. This was over 10 years ago now, I have no current academic or financial conflict with this study and have not been a reviewer/author/etc.

I have not received any support from Lilly since 2000, but have from other companies with other antipsychotics competing with olanzapine. One might argue (from the point of the authors) that a negative review from someone who receives income from their competitors but not their own company is a COI. Good luck figuring all of this out, and let me know if you want a COI statement, etc.