April 4, 2008

Melissa Norton, MD
Editor-in-Chief
BMC Neurology

Re: Manuscript resubmission and response to reviewers

Dear Dr. Norton:

Please accept the resubmission of the manuscript “Medication Persistence Rates and Factors Associated with Persistence in Patients Following Stroke” to BMC Neurology with the reviewer comments addressed.

Reviewer SP
1. Introduction needs to be improved.

We agree and have changed the introduction by focusing the background and rationale on the efficacy of pharmacotherapy and why adherence is important, please see paragraphs 2 and 3 under Background.

2. Methods
2.1 The source of data, study population, cohort definition, study outcome, determinants, and statistical analysis needs further explanation.

We have now provided detailed information on the data that was available from the SOS study. We have added that information not available included blood pressure measurements or lipid profile tests, health resource use, life style modifications, and reasons for changing the drug regimen (such as adverse effects). The inclusion criteria for the persistence sub-study is better defined and includes that the ischemic stroke diagnosis was made by the attending
neurologist after thorough neurological exam and CT scan to rule out hemorrhagic stroke or tumor.

The study outcome is medication persistence and has been added as a new heading. Here we have elaborated by stating that patients derive benefit if they continue taking any drug from each drug category of interest (eg. antihypertensive), so we report persistence by drug category, not individual drugs. This allows patients to switch between drugs in the same category and still be considered persistent.

For comorbidities atrial fibrillation and diabetes, we have added the method and codes used to determine whether patients had these diagnoses. The variables tested have been moved to the statistical analysis section. All variables were tested for each category (except antihyperglycemic drugs, due to low numbers in the cohort, as explained later in the text) and only those with significant univariate associations were included in the multivariate model, as explained later under Results.

2.2 Clear definition of outcome and for all variables investigated

The study outcome has been better defined in the Methods section. The variables have also been better defined under the heading “Variable Categorization” in the Methods section.

3. Sound data – the relevance of evaluating determinants of persistence, given the small numbers that were nonpersistent, wide confidence intervals

Even though our cohort had low levels of nonpersistence, nonetheless we believe important and significant results came from the multivariate analysis of the data. This research also demonstrates the fact that even though this was a large, resource intensive study where all patients with stroke were prospectively enrolled in a large tertiary care centre over two years, it is still difficult to obtain the large patient numbers needed for more precise estimates of effect.

4. Tables need to be presented more clearly

Publication guidelines limit our ability to make certain formatting changes to the Tables, but we encourage journal editorial staff to make changes with respect to font, spacing, lines and indentations in the final page proofs. To improve the tables, we have changed the heading “Stroke cohort” to “n (%)” in Table 1. As well, we have removed “OCSP” and “FSSS” for stroke subtypes and stroke severity, respectively, as these are described in the text. We have spelled out the stroke subtypes so the abbreviations no longer need to appear in a footnote. We have also changed the headings in Table 2 from “Number of users at discharge, (%)” to “Users at discharge, n (%)” for each time point. We have also added (years) to Age in Table 3. Although the reviewer did not request it, we did see some opportunities to clarify the Figure (study flowchart) and omitted the word “patients” after the first mention, and added 2 more boxes to describe the flow better between months 6 and 12.
5&6. Limitations need to be added to the discussion and explained why they do not diminish value of findings, were CAD risk factors known, could the subjects have other CVD, did the drug database include all drugs or just insured drugs, misclassification error related to drug exposure, unknown if patients took their drugs, did the patient pay some of the drug costs which may increase the likelihood of taking their medication and lowers the chance of bias.

We have now emphasized the value of our findings, in face of limitations to the research. We have mentioned that we do not know whether patients stopped taking their medications due to out of pocket drug costs. We have added some limitations about not having clinical data or information on lifestyle modifications which could lower vascular risk and remove the need for medications. Misclassification error has been added since this could have occurred and the study coordinator did her best to have the most accurate list of medications.

7. No changes required

8. Title – “prevalence” is not an appropriate term for the cohort
We agree and have changed the title to be “Medication Persistence Rates and Factors Associated with Persistence in Patients Following Stroke: A Cohort Study” and have removed references to prevalence in the text.

9. No changes required

Reviewer SS
Comment on the nature of stroke deficit in the predictor variables, it would be interesting if stroke severity and disability were subdivided and analyzed by language, motor, sensory, and coordination deficits.

Thank you for this interesting point. Unfortunately, this type of information was not available for the medication persistence sub-study. Functional disability was determined from the Oxford Handicap Scale, which ranged from 0-5, and was dichotomized for the purposes of this study into dependent (4-5) or independent (0-3).

We thank the reviewers for their useful and thoughtful comments.

Thank you for your consideration of this resubmission.

Sincerely,

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