Author's response to reviews

Title: A retrospective claims analysis of combination therapy in the treatment of adult attention-deficit/hyperactivity disorder (ADHD)

Authors:

Gerhardt M Pohl (pohl_g@lilly.com)
David L Van Brunt (dvb@lilly.com)
Wenyu Ye (yewe@lilly.com)
William W Stoops (wwstoopsphd@hotmail.com)
Joseph A Johnston (johnstonja@lilly.com)

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Author's response to reviews: see over
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Melissa Norton, MD
Editor-in-Chief
BMC Health Services Research

Re: MS: 1726246094193881

Dear Dr. Norton:

We are electronically submitting our revised manuscript entitled “A retrospective claims analysis of combination therapy in the treatment of adult attention-deficit/hyperactivity disorder (ADHD)”. We have addressed our revisions below.

We would appreciate your review and consideration of our revisions and look forward to hearing from you regarding possible publication. Please address correspondence to Gerhardt Pohl, PhD, Eli Lilly and Company, Indianapolis, IN 46285; (317) 277-5113 (phone); 317-276-7100 (fax); pohl_g@lilly.com.

Sincerely,

Gerhardt M. Pohl, PhD
Eli Lilly and Company

Reviewer Comment 1: “In the Methods section, can the authors provide, out of the 2,041,434 patients with an ADHD diagnosis, what percentage had a prescription for an ADHD drug?”

Authors’ Response: We have gone back to the raw data to provide the requested information in a way that we hope will be of even more interest to the reviewer. We infer from the comment that the reviewer would like to know what proportion of adults diagnosed with ADHD actually receive a pharmaceutical treatment. We felt that just calculating the number of patients with ADHD diagnosis anywhere in their history and with a prescription during the study period might not be the best way to get to that proportion, the reason being that patients in the initial cut of 2,041,434 had widely varying amounts of enrollment. We would not be
able to ensure that the patients without ADHD prescriptions had the same opportunity to show up in the data as those with ADHD prescriptions. What we did instead was to calculate the number of patients with continuous enrollment for 18 months (from January 2003 to June 2004). From this number 435,536, there were 75,963 who received ADHD medication during the study period as we had already reported in the manuscript. This additional number has been added to the manuscript.

**Reviewer Comment 2:** “For the predictors that differed in statistical significance between LAS and ATX (e.g. having a hyperactive component to ADHD), can the authors provide a statistical test of this difference? For instance, they could test a model with monotherapy versus combination therapy as the outcome, predicted as a function of medication type (LAS versus ATX), hyperactivity status, and the medication type-by-hyperactivity status interaction. This interaction term would specifically test whether the association between hyperactivity and the odds of combination therapy differed significantly by medication type.”

**Authors’ Response:** One of the unique aspects of this manuscript is the per month analysis of usage patterns as opposed to a per-patient analysis. The per-month analysis matches well the needs of payers allowing simple, direct calculations of costs and potential budget impact. Per patient analyses can be very troublesome to interpret directly. For example, the assignment of a patient to the categories of “polypharmacy patient” or “monotherapy patient” can vary widely, yielding ambiguous and generally non-useful cost interpretations. One definition might consider a patient to be a polypharmacy patient if they had at least 1 month in which they received therapy in 2 drug classes while another might require multiple months or varying percentages of months. It is not at all clear the exact extent of overlapping therapy in such cases and the possible cost associated with the multiple drugs. A per patient analysis would lend itself well to the combined modeling suggested by the reviewer. One could then assess the statistical significance of differences in the model parameters for the 2 drug classes from the interaction terms as suggested. The combined model, unfortunately, is not applicable to the per month modeling which is the focus of the paper. To my knowledge as a practicing biostatistician, there are no methods that would adequately account for the fact the some months in model would be subject to duplicate counting in a combined model. For example, months in which a patient received both atomoxetine and a long-acting stimulant would be counted as the outcome both for months in which atomoxetine was taken in combination with another medication and for months in which long-acting stimulants were taken in combination with another medication. In such a situation, there is no way to adequately adjust the resulting p-values to accurately reflect the overlapped counting. This is also an issue in a per patient analysis; however, in that case, one might be able to arbitrarily assign membership to a group, or exclude patients in the overlapping category of the 2 drug classes. Either approach clearly distorts the picture from a utilization perspective, under-reporting the degree to which each class is used in combination with some other ADHD medication. We feel strongly that the basic structure of the analysis we have chosen is the most useful and interpretable way to handle these data. We regret that we are unable to perform a combined model as requested, but feel that the reported results represent a useful and accurate way to present data.
Reviewer Comment 3: “In the Discussion section, the authors provide useful examples of the risks associated with stimulant treatments (i.e., abuse potential, diversion). They should provide a similar statement about the risks associated with ATX treatment.”

Authors’ Response: We have added further discussion as requested.