Author's response to reviews

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

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Version: 3 Date: 21 December 2008

Author's response to reviews: see over
December 21, 2008

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's report

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

Version: 2 Date: 26 August 2008
Reviewer: Jari Haukka

Reviewer's report:

This interesting report based on large amount of data. I have following comments

Major Compulsory Revisions
1. In abstract it is stated “Prescription dispensing events were drawn from a national claims database including over 80 managed-care plans.” Probably this means USA national database.

Suggested change was made to text.
2. It is said that “...study was a retrospective claims analysis of data obtained from the PharMetrics, Inc. data warehouse on October 6, 2005.”. How did authors get access to this database? Who gave permission? Is this database open to all research workers? Do people in different health care programs give their permission to use their data in research? I think some more details how data was gathered is needed. What kind of selection there is in this kind of database compared to whole population of USA.

As suggested, additional detail was added to the text. Pharmetrics is commercially available and strictly adheres to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). The data contains data from a specific slice of the whole population of the USA, those covered by managed care. We have given as much demographic detail as available to allow readers to compare to other slices of the population or the population as a whole.

3. Page 8. results from logistic regression are presented. Did authors test any interactions? In this first study on this topic, only main effects were tested. The complexity of the analysis and volume of results already pose challenges to clear presentation. The authors would prefer not to delve into further complexities at this point. Please consider also our response to point 4. It is the authors’ position that the most meaningful presentation includes all variables in the model at the same time with the variables being the same for the different treatments. This approach becomes prohibitive were interactions to be included as well.

4. Figure 1. text should be clarified. Explanation for “AXT” and “LAS” in figure. We all variables presented in figure same time in model. It would be informative to have similar figure but with univariate results (probably these figure could presented side by side).

As requested, we have added additional explanation of the abbreviations to assist the readers. All variables were included in the model at the same time. The authors feel this is the most meaningful approach in that the entire collection of factors, both significant and non-significant, give perspective on the relative magnitude of effects and the power of the study to detect effects.

Minor Essential Revisions
1. Table 1. could contain producer name for each drug (because Eli Lilly is funding this study).

Unfortunately, this is not feasible in this study. The drug classes represented in the study represent a huge and diverse collection including in some cases generic formulations. The number of individual NDC codes represented is in the tens of thousands.

2. Table 2. too many decimals, %-sign not needed after each number, should be put in header. It is a bit confusing that some categories add to 100% (age) and others do not (e.g. prior claim diag.)

Prior claim diagnoses are binary outcomes: the beneficiary either did or did not have a prior claim. We did not list the complementary “did not” value to conserve space. In the case of gender, we did include both categories so as not to suggest any gender bias in the presentation.
3. Table 3. Caption is not clear “Percent of Non-First Months of Treatment in which Multiple ADHD Medications were Prescribed”, but in foot note months are referred. The caption and footnote should be rewritten, because table in this form is difficult to interpret.
Caption and footnote were rewritten.

4. In “LIMITATIONS” section it is stated “Second, the provider type “psychiatrist” is imputed within the PharMetrics database and may include some psychologists and social workers billing for services typical of psychiatrists.” Where do this refer? Probably something is missing from “METHODS” section? Are psychologists and social workers entitled to prescribe drugs in all part of USA?

Sorry for the confusion. It is not the prescription that we are referring to. As explained in the Methods section, the factor examined was whether or not the enrollee had a “claims history of prior psychiatric visits”, that is, we are looking at claims for service as the factor. The attribution that the services were rendered by a psychiatrist is somewhat imprecise in the database and that is what is noted in the limitations. We added an additional sentence to help alleviate any confusion readers may have when they encounter this in the Limitations section.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I have served as consultant to Janssen-Cilag.

Reviewer's report
Title: A retrospective claims analysis of combination therapy in the treatment of adult attention-deficit/hyperactivity disorder (ADHD)
Version: 2 Date: 4 September 2008
Reviewer: Michael C. Monuteaux
Reviewer's report:
Re: A retrospective claims analysis of combination therapy in the treatment of adult attention-deficit/hyperactivity disorder (ADHD)
This was in insurance claims study that examined patterns of pharmacotherapy for ADHD among adults. The authors found that long-acting stimulants (LAS) and atomoxetine (ATX) were the least likely medications to be used in combination with other drugs. Also, several factors were identified that predicted combination therapy within persons taking LAS and ATX. The strengths of this study include the use of a large, national database with information about specific prescription uses. However, several concerns were also noted, as follows:
Major Compulsory Revisions
1. The most important issue with this study is that the findings do not seem to represent a contribution to the scientific literature. The authors need to develop and present a compelling argument for why this information is important to the field and how it advances the state of knowledge about adult ADHD.
Relatively little is known regarding treatment patterns used in this patient population. This first study of its type attempts to inform readers particularly from a payer or benefit management perspective exactly what therapies are being used in the care of these patients. It
has important public health implications both from a budgetary perspective and the perspective of documenting standards of care.

2. According to information on page 6, among all the patients with at least one claim for ADHD, only 3.7% were treated during the study period. So, 96% of patients diagnosed with ADHD by a health care professional are not given any pharmacotherapy? This does not seem plausible. Can the authors clarify? 
   The 3.7% refers to a collection of requirements for entry into the dataset and not only to simple criterion of receiving treatment at some time in their claims history. Patients were required also to have 6 months of continuous enrollment prior to the study period over which time baseline characteristics were determined. The patients also were required to have 12 months of continuous enrollment during the study period during which use of combinations of ADHD medications was assessed. This collection of requirements yields the seemingly small value of 3.7% of all patients who ever had a claim for an ADHD drug.

3. The authors should discuss the rationale for restricting the testing of predictors for combination therapy to only LAS and ATX. Why are the predictors for combination therapy for SAS, for example, not of interest?  
   We have added a clarifying sentence to the last paragraph of the introduction.

4. Since it cannot be determined from these data why each medication was prescribed, it would seem a more prudent approach to only consider medications in the various analyses looking at combination treatment that are primarily prescribed for ADHD. For example, given the high rates of comorbid disorders in this sample, it is not surprising that bupropion was given to patients on an ADHD drug. Also, it is not surprising to see that comorbid depression predicted combination treatment in both models, since one of the drugs that could designate an observation as “combination treatment” was a depression drug.  
   Yes, the authors very much appreciate the comments of the reviewer. We had considered restricting the drug classes but in the end felt that readers would more likely fault us for not including these other treatments as they are commonly used in this disease population. We did, however, restrict the models to only LAS and ATX in part to avoid such confounding.

5. On page 12 (and elsewhere), the authors state that LAS and ATX are least likely to be associated with combination therapy. While this is true, the rates of monotherapy for LAS and ATX, 21% and 19.7%, are very close to that of SAS, 23.1%. Why designate only LAS and ATX as those least likely to be associated with combination therapy? Was this cut-off made a priori? What was the rationale for this decision?  
   The statement is meant only to be descriptive of the values reported and reflect the focus on comparing these two classes of longer-acting therapies.

Minor Essential Revisions
1. The figure is difficult to interpret. Can the authors present two figures, one for each model?  
   The authors feel like the combined figure allows the reader to more easily compare the characteristics of the models between the therapies.
Level of interest: An article of limited interest
Quality of written English: Acceptable
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