Author's response to reviews

Title: Characteristics of patients initiating raloxifene compared to those initiating bisphosphonates

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Author's response to reviews: see over
Response to Reviewer Comments

The authors would like to thank the reviewers for their comments and thorough review of this manuscript.

Reviewer #1:  
This is a straightforward retrospective cohort review of claims databases with predictable findings. It is well conducted with conclusions that are generally supported by the data. I question a few details that would be best to clarify:  
1. In the conclusion of the abstract and text, it is stated that patients treated with raloxifene appear to have less severe osteoporosis than those treated with bisphosphonates. While this might well be true, it is not clear to me whether most patients in either group had a densitometric or clinical diagnosis of osteoporosis. If it is not know how many patients in each group had a WHO classification of osteoporosis, osteopenia, or normal, the authors should consider rephrasing this statement.

We have changed the wording to state that raloxifene patients “appeared to be less likely to have risk factors for new osteoporotic fractures” compared to bisphosphonate patients.

2. page 5, 1st paragraph- It is stated that 6.7% of patients treated with IV bisphosphonates develop osteonecrosis, and later it is said that most cases occur in cancer patients. However, it is not made clear that IV bisphosphonates used to treat osteoporosis appear to pose no greater risk for ONJ than oral bisphosphonates for osteoporosis. It might be best to state this clearly so as not to leave the reader with the impression that IV bisphosphonates for osteoporosis are a greater risk factor for ONJ than oral.

The wording for this section has been rephrased to clearly reflect what is included in the package inserts for the oral bisphosphonate medications.

Reviewer #2:  
Authors aim to compare characteristics between patients initiating raloxifene vs. bisphosphonates for the prevention and treatment of osteoporosis. Authors raise some great discussion points, such as:
• limitation of their study in not having formulary information
• clarifying that they studied Medicare patients with employer benefits
• the fact that comparative effectiveness studies must take important differences in patient characteristics into consideration

Major compulsory revisions

To address the major compulsory revisions suggested by the reviewer we made substantial changes to our analysis and have adjusted the methods, results, discussion and conclusions to reflect the changes.
Changes to the study design and analysis will facilitate interpretation:
1. Restrict study to women. Raloxifene is approved to prevent and treat osteoporosis among postmenopausal women. Including men who essentially only contribute to bisphosphonate use can introduce bias.
   **Men have been excluded from this analysis.**

2. Restrict analyses to new users of either agent (so comparing treatment decision to start pharmacotherapy).
   **Patients with a prescription for any osteoporosis treatment during the pre-period were excluded from the study.**

3. Include only oral bisphosphonates approved for OP, i.e., exclude etidronate and daily use of 40mg alendronate and 30mg risedronate (approved for Paget’s disease of bone, not OP).
   **Patients on oral bisphosphonate medications or dosing regimens that were indicative of use for Paget’s disease have been excluded.**

4. Exclude:
   a. **Patients with Paget’s diagnosis of bone**
   b. Any prior raloxifene or any prior bisphosphonate (thus limit to new users of either agent)—as mentioned above
   **Patients with an ICD-9 code for Paget’s disease were excluded. Please see comments on #2 regarding exclusion of patients with any prior use of osteoporosis medications in the pre-period.**

5. Add multivariable logistic regression (raloxifene as the outcome) to determine independent association between each covariate and prescribing.
   **We conducted a logistic regression to simultaneously examine the factors associated with raloxifene use as opposed to a bisphosphonate. Adjusted odds ratios and 95% confidence intervals are presented in the manuscript for all model covariates.**

Minor essential revisions
1. Figures 1 and 2 and not helpful because the information is contained in the table. Suggest that authors omit these figures.
   **We have removed Figures 1 and 2.**

2. Follow current standards for reporting of observational studies (STROBE). In particular, a STROBE figure will help readers follow cohort assembly, exclusion etc.
   **We have included a table that shows the attrition of the study sample following the application of the exclusion criteria.**

3. Update literature review. *MacLean AnnInternMed 2008;148:197-213 (systematic review of OP treatment effects) + recent letters to the editor is*
particularly relevant, as is our recent study that found similar differences in background risk between raloxifene and bisphosphonates (Ann Intern Med 2008;148:637-46).

We reviewed the above mentioned articles and have referenced the Cadarette et al. article in the discussion section. After reviewing the MacLean article we chose not to include that in our discussion as it did not appear relevant to our research question.

4. Page 8, 2nd paragraph. Please clarify that you do not have prescriber ID number and thus are approximating…

To clarify this section we added an additional comment stating that “the specialty of the provider most closely associated with the index prescription was also captured using an indirect method given that provider identifiers are not available on the prescription claims.”

5. Consider adding other potential correlates of raloxifene prescribing, e.g., Mammography, stroke, DVT, diagnosis of osteoporosis

Additional covariates were included in the analysis such as mammography, DVT/PE, various GI conditions and osteoporosis diagnosis. Given the timeframe of the data (2003 – 2005) we did not include stroke as a potential correlate.

Discretionary revisions
Including an appendix with claim codes used to define background covariates may help to improve transparency of this work.

An appendix identifying the codes for diagnoses and screening tests has been included.