Reviewer’s report

Title: Treatment Patterns and Sequences of Pharmacotherapy for Patients Diagnosed with Depression in the United States: 2014 through 2019

Version: 0 Date: 30 Oct 2019

Reviewer: David Benrimoh

Reviewers report:

Summary:

This is an interesting paper attempting to reconstruct treatment patterns for patients with MDD using national claims databases. This information would be useful for a number of reasons, from research on clinician patterns and quality of care to work aiming at better quantifying social and economic costs of care. The large sample size is a strength of the study. The reliance on claims data, however, is a weakness inherent in this kind of work given that claims do not always accurately reflect diagnostic and clinical reality. While this is counter-balanced by the fact that the data presented represent true clinical practice (and therefore also represent the real diagnostic and management inconsistencies that happen in real clinical practice), caution should be exercised on the part of the reader when assessing the paper.

Comments:

1. In the introduction (and I'm sure this was just a simple oversight), TMS was classified as an invasive treatment. This should be corrected.

2. On line 32, reference 2 refers, I believe, to a paper describing the rationale but not the actual results of STAR*D. This reference should be updated and the sentence along with it.

3. The terms "adjunctive therapy" and "adjuvant therapy" are both used. I suggest picking one and running with it for clarity's sake.

4. You explain why the end date of data collected was 1/31/2019, but it is not clear why the start dare was chosen (i.e. 1/1/2014) Is it because these databases did not exist before then? Please specify.

5. In your specification of the depression cohort, I believe the reader deserves more explanations about why you required two outpatient diagnoses, why patients already on treatment were excluded, and, most importantly, why patients needed to be consistently enrolled in the database for the time period specified. This last point is especially important, given that there may be systemic bias introduced if patients with depression, or with specific depression courses, are less likely to be enrolled in the database (which is likely to be true). These are not deal-breakers for the study, but do require full discussion in the limitations section and brief justifications in the methods section.
6. Why was a switch from one class to another and then back to another class recorded as only one switch? Clinically, it is meaningful for a patient to be on, say, sertraline, then venlafaxine, then citalopram. That sequence might be explained for example by a patient experiencing bad side effects with the first two drugs and then being switched to a third that is seen by clinicians as having fewer side effects. It might also represent loss of insurance for non-generic drugs. In sum, it might be meaningful so why ignore it? Please provide a rationale.

7. Are the databases mutually-exclusive? Is there certainty that there is no double-counting?

8. I am somewhat concerned by some of the results from table 1 and believe they should be further discussed. First, aside from anxiety disorders, dysthymia, and drug dependence, I don't see other psychiatric comorbidities one would expect (PTSD, psychotic disorders, OCD, and especially personality disorders); I also do not see a discussion of bipolar disorder anywhere, and this should be discussed especially if bipolar disorder was not ruled out. Second, the anxiety comorbidity rate is lower than I would expect, raising the very real possibility that the claims data is not complete. Third, you note an increased rate of drug dependence in Medicaid patients, but you don't offer a statistical test for this (it's likely to be significant but it would be good form to do it because I'm not sure how variable the datasets are); this same concern can be levelled at your result about suicide. These comments should be addressed in the results and discussion.

9. The high proportion of people receiving non-SSRI initial therapy is a problem for the claim that these are all really patients with depression. For example, these could be patients with psychotic disorders or bipolar disorder who happen to have experienced a depression in the period you studied; this might also explain partly why Medicaid patients received different treatment types. Also the use of non-standard treatments or combination treatments might relate to patients with a history of treatment resistant depression. These concerns betray the fundamental issue of using claims data- it is not complete and does not necessarily provide an accurate look at all patients and it may be less accurate for certain more complex patients (so the inaccuracy in itself may be biased). A full discussion of this in the limitations is warranted because without this discussion to balance your claims the reader could be misled.

10. You absolutely must further discuss the algorithm (ref 8) you used to identify depression in claims data in the methods and you should discuss it and report all of the metrics. Sure, it has a high PPV- but what is the NPV? And the PPV depends on the sample the algorithm was trained in- are you sure your sample is equivalent? I believe you need to work much harder to convince the reader of the accuracy of your depression diagnosis, because the prescribing patterns you discovered have two explanations: bad practice by clinicians (certainly possible) or bad sampling (very possible). Please expand on this in the methods and the discussion. Also, the trouble of working with claims data should also be discussed up front in the introduction.

11. In your limitations you say that you tried to limit "misclassification due to receiving therapy for reasons unrelated to depression, we required treatment to occur at the time of or following the first diagnosis of depression with no prior history of treatment"- however, this is misleading, because patients may very well have had treatment prior to the time window you are looking at, and went off
medication, then came back on when they relapsed. In addition, their "reason unrelated to depression" might very well have relapsed at the same time as the depression (for example, a schizoaffective disorder patient might relapse into a psychotic episode with depressive features, and the depression might be what is picked up by the ER doctor. As such I would recommend amending this to "…with no prior history of treatment within the time window examined." And I'd also add something about how hard it is to know for sure that the only thing being treated was a depression.

12. Table 3- how do you differentiate anxiolytics from sedatives? Benzodiazepines are both…

13. Where is the data on stimulants? These are often used as adjuncts. What about Lithium? Which is also used as an adjunct.

14. In figure 1, you discuss how you identify combinations and switches. Is this how you do it in your analysis? If so please put in methods. Also I'm not convinced by the definitions; I'm a clinician and if I forget to discontinue a drug (formally, I mean; I still tell the patient not to take it) after starting a new one because side effects were intolerable (and this happens), then if the overlap was 30 days then it's combination? Or what about cross-tapering? We often switch from one drug to another over a long time period by gradually reducing the dose of one and increasing the dose of the other; this would mean when we're actually switching, you might be calling it combination! In other words, this is a (very) rough definition of switch vs. combo and should be discussed in the results. This might explain, for example, the odd finding of switching from an SSRI to an anxiolytic- which just doesn't make sense. More likely, the patient could not tolerate the SSRI, got an anxiolytic to help with sleep, stopped the SSRI because of the side effects, but stayed on the anxiolytic because they are hard to stop. As such calling this switching without describing the (major) caveats is misleading.

Overall, this is an interesting paper with useful information, but the methods and limitations need much more beefing up and the claims made should be contextualized given these limitations.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I do not have any financial or patent-related interests directly relevant to this paper; as such the answer to 1,2,3 and 4 is no. I am currently a shareholder and director of Aifred Health, a mental health AI company seeking to improve treatment selection for depression but we do not stand to gain or lose from the publication of this paper as its content is not directly relevant to our work or related to the IP we are developing; as such the answer to 5 is no, as while I do have financial interests, they are not competing. I am however, outside of the context of this company, a collaborator on a project that is aiming at assessing clinician perspectives on claims data, with the aim of verifying our hypothesis that clinicians view claims data as incomplete and not suitable (in isolation) for research that draws strong conclusions about ground truth. This paper clearly uses claims data, and my review does raise several methodological issues with respect to the accuracy of claims data. However I believe these to be valid concerns and do not think they should prevent the publication, but rather that they should be worked
into the publication in order to provide a more balanced view of the data. As such the answer to 6 is no, qualified in the way I have done.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal