Author’s response to reviews

Title: Use of antidepressants and benzodiazepine-related hypnotics before and after initiation of TNF-α inhibitors or non-biological systemic treatment in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis

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Author’s response to reviews:

Dear Dr. Studenic, dear co-editors,

On behalf of all the authors I thank you for your continued interest in this manuscript, and the editors and reviewers for their thorough review and suggestions which have certainly improved the quality of the manuscript. We have addressed all of the reviewers’ comments below. Our revisions, which are visible as changes in the re-submitted manuscript, address each issue raised by the reviewers. Thank you for considering our revised manuscript for publication in your journal.

Do not hesitate to contact me at the e-mail address below if you have any questions.

Sincerely,

Philip Brenner

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Technical Comments:

Editor Comments:
There is quiet some interest in the topic of your study, also seen by the reviewers, but still controversially evaluated.
Both reviewers have outlined valid points that need to be addressed if you would like to submit a revision of your manuscript.
I would advise you, to address every point made by the reviewers and comment argument on it and also include changes in a tracked version of a revision of the manuscript.
Reviewer reports:
Diederik de Cock (Reviewer 1): Dear authors,

I have to congratulate you with this very nice paper about the use of antidepressants in patients with arthritis. In general, I think this is a good valid study with a strong methodology, but not really exciting results. I agree with the authors that a decrease in antidepressants can be expected in patients starting anti rheumatic treatment, for multiple reasons as they have implied themselves. Herein lies the biggest issue of the study. The data can only indicate a trend, not an underlying causal pathway as clinical and comorbidity data is unavailable.

ANSWER:
We agree with the reviewer. We appreciate that it is only possible to present associations (albeit of varying strengths) in observational studies, and not proofs of causal pathways.

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I have also small comments:
-medication use seems to be tailored to RA. It would be great to have in the additional table per disease an overview of medication use (which TNFi and csDMARD). This would help profiling the patients we are seeing here.

ANSWER:
This is indeed true. Two more supplemental tables (1b and 1c) have been created, presenting which substances are started at the index-date.

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- Could there be overlap of a patient first taking csDMARD and then TNFi? Normally patients first start csDMARDs and then TNFi’s. Another study could look at the effect of failing csDMARD therapy and the use of antidepressants. Perhaps rates go up, which could support the theory that the use of antidepressant (and thus potentially depression, anxiety etc) is correlated with clinical disease activity.

ANSWER:
Patients treated with csDMARD who switch to TNFi are censored in the follow-up of csDMARD, so no overlap in follow-up time is at hand.
A separate study of patients failing treatment with csDMARDs and comparing them with those who respond would indeed be feasible; thank you for the suggestion.

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- Is there info on disease duration? It would have been great to find support for a psychosocial window of opportunity where a speedy response also has a bigger effect on antidepressant use.
Disease duration is indeed an important factor. We have now, in supplemental table 1, added the mean and median of disease duration by treatment category and indication. The estimation of disease duration is however not an ideal one: it has been calculated as the time between first occurrence of the diagnosis in the patient register, and the first start of treatment. We acknowledge that this is generally an underestimation of true disease duration, but it nevertheless give an illustrative idea of the treatment cohorts.

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- There is a high use of antidepressant in general, both in controls and reuma population. I would have expected however the use of medication in the PSA higher (doubled or even trippled to controls and other diseases). This was not the case. Would this be because of the background high use or another reason? Perhaps merits a little point of attention in discussion.

ANSWER:

Thank you for this interesting point, We do not know what rates of use of anti-depressants would have been expected in the PSA-population, nor have hypothesized that it should have been considerably larger in them. However, we note (Supplemental table 1) that the rate difference in use between diseased and controls is largest in the TNF-population treated for PSA.

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- For the figures, when i first looked at them, i was seeing a decrease in use of antidepressant by the way the y-axis was ordered. It is perhaps just my mind, but i would reverse the order of time on the y-axis.

ANSWER:

Thank you for the suggestion. We have altered the direction, and also added arrows that indicate the temporal direction.

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Good luck!

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Katie Druce (Reviewer 2): General comments:

1. By the end of the introduction I am not sure that I understand why you think that changes in the use of antidepressants and benzodiazepine related hypnotics would be important? I also am not clear why you have selected these drugs as you do not mention them until the aims… are these just the most commonly used ones?

I don't really understand what this manuscript has added to our knowledge as, in my opinion there is just so much missing information.
ANSWER:

Thank you for this comment – it certainly inspired our rewriting this paper in order to make its purpose clear. The Introduction section has now been thoroughly reworked. The drugs selected are the most common ones for treating depression and anxiety (SSRIs) and sleeping problems (benzodiazepine related hypnotics). We hope that this will provide a satisfying background for our aim of performing the study and also for its interpretation.

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Specific comments:

Abstract:

2. Page 2 line 8 - I think the word "qualified" should be changed to "eligible". At this point I'm also wondering about the sentence in general, what is the evidence that mental health is worse among those eligible for TNFi? (You may cover this more in the intro).

ANSWER:

Thank you for this suggestion. In order to keep the abstract simple yet informative, we have now changed the 1st sentence to: “Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are autoimmune disorders associated with an increased risk for depression, anxiety and sleeping problems.”

3. Page 2 line 18 - The "National Patient Register" needs a location - I assume it is from Sweden, as all the co-authors are, but you need to be more clear.

ANSWER:

Thank you for pointing this out. This sentence has now been changed to: “Patients and dispensed drugs were identified in nationwide Swedish healthcare registers.”

4. Page 2 line 34-35 - inconsistent use of "-" and "to" in brackets.

ANSWER:

Thank you – it is now changed to “to”.

5. Page 2 line 45-49 - I don't think this conclusion is very meaningful or impactful.

ANSWER:

The conclusion, in accordance with suggestions from other reviewers, has now been changed to: Decreased rates of dispensed psychotropic drugs after the time of anti-TNF and NBS treatment initiation were seen among patients with autoimmune disorders but not population controls. This may correspond to treatment effects of anti-TNF and NBS also on psychiatric symptoms among these patients.
Introduction:

6. Page 3 line 10: Are the "10%-23%" data in brackets confidence intervals? Please make it clear what they are. In addition, if they are CIs, is this really higher that the ">20%" in anti-TNF eligible patients? Why be so vague about the prevalence in this population if they are of importance?

ANSWER:

This section has now been rephrased as and the second statement has been changed a more specific reference:
“RA patients have an estimated point prevalence of depression of 16.8% (95%CI 10–23%), which is significantly higher than in the general population (4, 7). Among patients starting biologic therapy with tumor necrosis factor-α inhibitors (anti-TNF) the proportion with comorbid depression is 19% (8).”

7. Page 3 line 14: again here (and throughout) please change "qualified" to "eligible".

ANSWER:

This has now been changed throughout the manuscript.

8. Page 3 line 18 to 19: the use of "both" in "increased both work disability (12) and mortality (13)" is a bit clunky and not really needed.

ANSWER:

Thank you - the word “both” has now been omitted.

9. Page 3 line 23-26: could you please separate out the references for RA and AS risk and the link between PsA QoL and anxiety. These are two different points so the original sources may be of interest to different people.

ANSWER:

Thank you for this suggestion – the references have now been separated.

10. Page 3 line 25-29: I am not sure what the relevance of the sleeping problems is, given that this appears to be about mental health complaints? If sleep problems are relevant please make more mention of this.

ANSWER:

Thank you for highlighting this important need for clarification. Sleeping problems are in diagnostic manuals classified as a mental health complaint and therefore grouped together with anxiety and
depression in this study. The impact of sleeping problems for these patients have now been emphasized in this paragraph (page 3, 1st paragraph, last sentence):
“Sleeping problems are common and among the factors which have the greatest impact of the quality of life among patients with RA (16) and PsA (17), and the risk is elevated among patients with AS as well (14).”

And, a paragraph regarding treatment with benzodiazepine related hypnotics have now added to page 4, 3rd paragraph, last sentence:
“The most commonly prescribed drug class for sleeping problems are benzodiazepine related hypnotics (BRH, zolpidem or zopiclone, also known as “z-drugs”), although they are recommended only for short-term use due to potential for dose escalation, abuse and dependence (36, 37).

11. Page 3 line 37-48: I am confused by these points. First you appear to say that cytokine promoting treatments are associated with increased depression. But then you refer to something being "even more promising", and appears that you are taking about the impact of interventions. These two points are not the same, so the results cannot be "even more promising".

ANSWER:
Thank you for noticing this proof-reading error on our part – it is due to two sentences somehow having been displaced during editing. This paragraph now reads:
“Conversely, several anti-inflammatory drugs with different mechanisms of action have been studied as treatments in major depression. A review published in 2014 suggested that non-steroidal anti-inflammatory drugs (NSAIDs) is more effective than placebo in treating depression (24). A recently published meta-analysis of 16 studies on anti-cytokine treatment showed a pooled effect estimate from randomized controlled trials of 0.40 for anti-cytokine treatment vs placebo (32).”

12. Page 3 line 53-61: I am not sure you discuss this enough. Are these increased rates during the course of biological therapy treatment, or prior to commencing it? Does this support your evidence that anti-TNFi would be useful or not?

ANSWER:
Thank you for suggesting this. This paragraph has been expanded substantially (page 4, 2nd paragraph):
“It is, however, unclear whether anti-TNF are more effective against psychiatric symptoms than other therapies among patients with autoimmune disease. Rates of anxiety, depression and suicidal ideation in one cross-sectional study were higher among RA patients with anti-TNF compared to other treatments, which the authors suggested would be due to these patients having a higher burden of disease rather than anti-TNF being less effective against psychiatric symptoms (27). Although there is lack of longitudinal studies on patients with RA, PsA or AS, a recent longitudinal study on patients with skin psoriasis – another immune-mediated condition – showed that patients with anti-TNF had a lower incidence of depressive symptoms than those receiving other therapies, although they had a higher disease burden (28).”

Methods:
13. Page 5 line 45: why were data only used until December 2013? The dates mentioned here are from approximately 6 years ago, which feels like a lot of data to not include.

ANSWER:

Our dataset only contains data up until 2013, which unfortunately made it impossible to include later years.

14. Page 6 line 15: the use of "and/or" suggests you could have multiple diagnoses. If this is correct how did this impact on the analysis?

ANSWER:

“And/or” refers to the that these drugs may be licensed for use in several diseases, which is also why we could study them as a joint exposure in the three patients groups with RA, PsA and AS. There is, to answer the question, a theoretical possibility for patients in this study to have multiple diagnoses. As the analyses and case-control sets were separate, this should not impact the analysis.

In the TNF-treated population (N=6,256), 21 (0.3%) had a diagnosis of both RA and AS; and 25 (0.4%) both RA and PSA.
In the NBS-population (N=13,241), the following combinations of indications were observed: RA, PSA, AS: 2 (0.002%); RA, PSA: 210 (1.6%); RA, AS: 111 (0.8%); PSA, AS: 8 (0.1%)

However, in the actual analyses, any patient could only be part of one indication category. The small proportions with more than one indication cannot have a substantial effect on the results, especially since the patterns of use over time are similar in the three treatment categories.

15. Page 6 line 15-24: what if people weren't on mono-therapy, how do they get included? You later mention (Page 6 line 52) that inclusion of NBD to TNFi regimen is not a reason to censor, but it is not clear if it is a reason for initial exclusion. Would inclusion of NBD not likely effect subsequent treatment choices?

ANSWER:

Patients are included and categorized in treatment groups according to their first prescribed and dispensed drug. It does not occur in this population that an NBS-regimen is started on the same date as a TNF-drug.

16. Page 7 line 21-23: This sentence is not very clear. Please revise.

ANSWER:

Thank you for pointing this out. The sentence has now been revised as:“The nominator was the number of individuals who had filled at least one prescription during the period. Any individual could fill prescriptions during more than period and therefore be counted in the nominator in several periods.”
17. Page 7 line 38-45: I am not sure you need to re-iterate the intervals. I think it is sufficient to say this only once.

ANSWER:

Thank you for this suggestion – now omitted.

18. Page 7 line 53-55: I am not sure what this sentence is here for - it feels more like a justification for the study?

ANSWER:

This sentence was intended to rationalize the study design rather than the study, but may be superfluous. Now omitted.

19. Page 8 line 5-10: Would this not make them existing participants, not controls?

ANSWER:

That is exactly the case. In order to avoid bias, the controls for every case were selected among the entire population base who at the matching time-point = the index date were eligible for control selection. A control who is censored from follow-up due to a diagnosis of RA, AS or PsA will also later appear as a case if they fulfil the criteria for case selection during the specified years. For an extended discussion on the method of incidence density sampling and the advantages in avoiding selection bias, please see e.g. Rothman KJ, “Modern epidemiology”.

20. Page 9 line 2-19: why are there no actual values of data included here? It is not sufficient to just say things are "higher" or people are "younger". Same applies in lines 21-29.

ANSWER:

Thank you for pointing this out – data values have been inserted and the whole section simplified.

21. Page 9 line 42-44: I'm not sure what "however with statistically significant PRR only for the 6 to 12 months period in the NBS-population." Given the way it is written it is not clear what the comparison was.

ANSWER:

The sentence has now been changed to:
“CIs for all time periods were, however, overlapping with those of the index period, except for the CI of the NBS group, period +6-12 months.”
22. Page 9 line 46: This is the first use of "ADs"

ANSWER:

Thank you – corrected.

23. Page 9 line 48-50: The sentence "even if the smooth increase is interrupted during the actual reference period in NBS controls." Does not read well. It does not sound very factual and is a bit "flowery".

ANSWER:

This has now been changed to:
“…however with an interruption during the actual reference period in NBS controls.”

24. Page 9 lines 31-60: Why are no actual values reported to emphasise (for example) the start and end of the trend?

ANSWER:

To do this would certainly be an option, however, we feel that it is not only the first and last estimates that are of interest, but the pattern, the entire trend over time. Ideally, all point estimates should be stated, but that would make the text very unpleasant to read. Better then, we feel, to look at the graphs and the supplemental tables with both proportions and actual counts. Of course, if the editor would feel different we would be happy to comply.

Discussion:
25. Page 11 line 51-55: Can you provide refs for this?

ANSWER:

Now provided.

26. Page 12 line 5-9: statistically significant between the treatment groups, or the time-points? As mentioned above it is not always clear what your comparison is.

ANSWER:

Thank you for emphasizing this point – the sentence has now been clarified as:
“…although differences in drug rates between the index period and the subsequent time periods were not always statistically significant.”

27. Page 12 lines 46-50: Can you provide refs for this? This feels crucial to the premise of this paper.
ANSWER:
Reference is now provided.

28. Page 12 lines 56-60: Can you provide refs for this?
ANSWER:
Reference is now provided.

29. Page 13 line 24: Is this really a crossover-study? You aren't predicting anything but are looking at prevalence rates? I am not convinced this is an appropriate description.
ANSWER:
Here, we are confident that the study design is indeed a crossover study, and are not certain in what way predictions are a part of a cohort cross-over design in an observational setting. In the paper “Should we use a case-crossover design” by Maclure and Mittleman (Annu Rev Public Health 21: 193-221) the concept of cross-over is described, and the cohort-crossover is commented (p 206) for further clarification.

30. Page 13 line 27-31: I really don't understand what you mean by this sentence.
ANSWER:
Thank you for pointing this out; the sentence has been omitted, and the section now reads:

“There are also limitations that need to be addressed. First, this crossover study used self-matching, i.e. comparison within each case, which eliminates confounding by stable and slow-varying characteristics, including unmeasured confounding. However, confounding by characteristics that change over time, such as comorbidity or use of other drugs, is still possible.”

31. Page 13 line 50-62: I am unclear what this paper has added to our knowledge, given this quite fundamental limitation.
ANSWER:
The objective of this study was to investigate rates of psychotropic drugs before and after treatment initiation of anti-TNF or NBS. The limitations listed in this section here do not concern the main study objective, they rather emphasize its hypothesis-generating nature as an observational register study. Our belief is that this study adds to the knowledge of the field by providing a rationale for further exploration of the association between treatment of these conditions and the subsequent lessened need for psychotropic drugs.
Conclusions:
32. Page 14 like 2-10: I think this conclusion is not at all supported by the data provided. You have no idea whether there was a decrease in depression, anxiety and sleeping problems. As you do not show information about this there is no reason to investigate mechanisms underlying it. I also think this does not support the final conclusion about treatment priorities.
ALSO, why sleeping problems is here when it is not a focus of the paper is confusing.

ANSWER:

Thank you for this most valid point. The conclusion has now been rephrased as:
“Patients with inflammatory disorders had decreasing prescription rates of antidepressants and benzodiazepine-related hypnotics after initiation of anti-TNF- or NBS treatment. Mechanisms underlying this association should be further investigated.”