Author's response to reviews

Title: Direct Acting Antivirals in Hepatitis C: A Systematic Review of Neuropsychiatric Risks and Psychiatric Drug Interactions

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Author's response to reviews: see over
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Dear BMC Gastroenterology Editorial Team,

Thank you for re-considering our manuscript entitled, “Direct Acting Antivirals in Hepatitis C: A Systematic Review of Neuropsychiatric Risks and Psychiatric Drug Interactions”. We appreciate the reviewers’ feedback and have addressed their concerns in our revised manuscript. The revisions are summarized below. We feel that the changes made and comments received have improved the manuscript further, and are grateful for the opportunity to resubmit this relevant paper to your journal.

Reviewer #1(Peter Hauser): Comments and Responses

We thank Dr. Hauser for his thoughtful comments.

Minor Essential Revisions

1. It is important to clarify that the neuropsychiatric side effects of antiviral therapy including data addition to interferon alpha is very likely an underestimate as pharma has sponsored these studies and subjects with psychiatric illness are generally excluded (even given that there is a comparison group of subjects on interferon and not receiving DAAs). Similarly the lifetime prevalence of psychiatric illness in people with HCV is very likely an underestimate as it is based on chart/clinical diagnosis and subject were not interviewed with psychiatric diagnostic instruments.

These are important points and we have inserted statements in our manuscript to highlight this underestimation of psychiatric side effects with DAAs. We thank Dr. Hauser for this helpful suggestion.

Revision: Page 6, para 2, line 4 to Page 7, para 1, line1

2. The assumption that ‘poorly controlled psychiatric illness may compromise adherence....’ is not supported in the literature and perpetuates a myth that psychiatrically ill people are not compliant with medications and therefore should
not be offered antiviral therapy. Also a large US Veteran Affairs study found no significant decrease among mild and moderate alcohol drinkers (but did in heavy drinkers) in SVR. Similarly Sylvestre found no significant decrease in SVR for intermittent IV drug users.

While we agree with Dr. Hauser’s comments that patients with psychiatric illness can have comparable HCV treatment adherence and outcomes to patients without psychiatric illness, our intention was to highlight that poorly controlled and active psychiatric illness (such as depression) could potentially have an adverse impact on DAA adherence. We propose this hypothesis based upon data from antiviral therapy adherence in HIV, which shows reduced adherence in depressed patients.

Further, we hope to advocate for HCV treatment for patients with psychiatric illness through this article. Our main point is that patients with psychiatric illness should received appropriate pharmacological and/or psychosocial interventions prior to embarking on HCV therapy to mitigate risks where possible. We have revised this section to reflect these additional comments.

Revisions: Page 4, para 2, lines 3-6
Page 15, para 1, lines 4-6

3. There are certain references that have not been included- Pariate studies- see Lancet 1999 among others, the Sylvestre study, the first prospective study of interferon induced depression by Hauser in the journal molecular psychiatry (2002), the US Veteran Affairs study that examined the effects of alcohol use on SVR in Veterans with HCV, studies of people with stable psychiatric illness who received antiviral therapy among others.

We thank Dr. Hauser for these additional resources and have included these resources in the Introduction when discussing neuropsychiatric complications of HCV therapy and in the Conclusions in our newly inserted discussion of the role of collaborative psychosocial models of HCV care.

Revisions: Page 1, para 2, line 7 (additional reference)
Page 15, para 1, lines 4-6 (additional references)

4. There is an implication that escitalopram is the antidepressant of choice for treatment of interferon-induced depression, which may be an artifact of pharma sponsored trials. Generally SSRIs as a class and one could extrapolate that most antidepressants are efficacious in treating interferon-induced depression and that selection of an antidepressant may be guided by side effects profiles and DDI with DAA.

We thank the reviewer for his comment. We agree that it is likely that all SSRIs could be considered equally efficacious. Meta-analytic studies in non-HCV populations study both tolerability and efficacy, and we did not wish to make broader conclusions in the absence of data. It is possible that in HCV-infected patients that all SSRIs are not equal, especially given their differing pharmacological profile which could impact both
tolerability and efficacy, although the latter to a lesser degree. Further, we agree that the most recent trial by Schaefer et al. was industry sponsored; however, the trial by de Knegt et al. was not industry sponsored. On page 8, we mention the consideration of drug interaction and adverse effects when selecting an antidepressant. We are hopeful that this statement addresses the reviewer’s comment.

No Revision: Please see Page 8, para 3, line 7-9

Discretionary Revisions-
1. **Consider another word for 'backbone' of HCV therapy.**

We thank the reviewer for this suggestion. We have replaced “backbone” with “the use of”.

**Revision:** Page 3, para 1, lines 6-7

2. **Expand on DDI between DAA and lamotrigine as severe rash is a side effect of DAAs and lamotrigine is associated with rash and in particular Steven's Johnson Syndrome.**

We have included this information on lamotrigine in the anticonvulsant section.

**Revision:** Page 10, para 4, line 3 to Para 11, para 1, lines 1-3

Reviewer #2 (David Back): Comments and Responses

We thank Dr. Beck for his thoughtful comments.

1. **Page 2. Line 8. pharmaceutical companies?**

We have revised the abstract read “pharmaceutical companies”.

**Revision:** Abstract – line 11

2. **Page 4 Line 13. Both agents inhibit P-gp and telaprevir may inhibit renal transporters. These statements should be referenced.**

We thank the reviewer for this comment and have inserted the appropriate references.

**Revision:** Page 4, para 3, lines 1-3

3. **Page 5. Line 4 & 6 of Methods. Some concern that the searches only went to Sept 2012. This is such a fast moving field that I would strongly urge the authors to include articles to March 2013 - else you are losing 6 months of possible important material.**
We appreciate the reviewer’s recommendations and have updated our literature review. No new abstracts or articles have been published as of March 2013.

4. Page 6 Line 14. *I would like to see some additional input here on the level of evidence and make it clear that this was only done in the context of treatment of depression.*

We have included additional information in the Methods to clearly articulate that the evidence classification only applied to antidepressants. We also have referenced the grading system used to classify each antidepressant in this sentence.

**Revision:** Page 4, lines 11-13

5. Page 7 Line 13. *Slightly confused. In Table 2 the notes state that Level 4 is anecdotal or expert opinion whereas here it implies it is literature based. Clarify.*

We appreciate the reviewer’s comment and we have clarified the term “anecdotal” evidence. This term includes case reports and case series in the referenced grading system and as a result, we have explicitly stated this definition in the Table 2 notes.

**Revision:** See Table 2 notes

6. Page 8, Line 4. *Somewhere (either here or Table 2) would like to see a comment about the Dec 11 QT warning with escitalopram and citalopram.*

We thank the reviewer for this suggestion. We have included the additional information on escitalopram and citalopram. We could not make a general statement about escitalopram given that the FDA has not issued the same warnings as citalopram in the U.S.

**Revision:** Page 7, para 3

7. Page 8 Line 8. *Sentence beginning 'Therefore, selection .....' is not clear.*

We have revised this sentence.

**Revision:** Page 8, para 3, line 7

8. Page 8 Last line. *Does not make sense. glucuronidation is conjugation!*

We thank the reviewer for identifying this error. We have revised this sentence.

**Revision:** Page 9, para 2, lines 1-2


We have replaced “suspected” with “documented”.

**Revision:**
Revision: Page 12, para 3, lines 4-5

10. Page 14. Last lines. Do the authors consider that it is realistic that future drug interaction studies will correlate changes in DAA and psychotropic drug levels with HCV treatment outcomes and relapse. Most DDI studies have PK endpoints.

We agree with the reviewer’s comments and have removed this statement from the manuscript.

Revision: Sentence removed and last paragraph page 15.

11. Table 2. Why if citalopram and escitalopram have the same metabolic pathway will citalopram levels likely increase while escitalopram have been shown to decrease with TVR?

We have revised Table 2 to reflect the reviewer’s feedback.

12. Table 2. Need some comment for nefazodone.

We have included a comment on nefazodone in Table 2.

13. Table 4. Clozapine. Is it realistic to advocate TDM?

We have modified the section on clozapine in the table and modified the recommendation to read “suggest TDM when available”. Please refer to Table 4.

14. Table 4. Paliperidone. I understood that this drug is substantially renally excreted with little evidence for CYP2D6 or CYP3A4 in vivo.

We have modified the CYP450 for paliperidone in Table 4.

We trust that the above responses have addressed the reviewers’ concerns and appreciate your re-consideration of our manuscript. We thank the reviewers for their feedback, time and assistance in enhancing our manuscript. We look forward to your response. Thank you.

Sincerely,

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University Health Network
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