Author's response to reviews

Title: The ongoing impacts of hepatitis C infection: a systematic narrative review of the literature

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Author's response to reviews: see over
2 August 2012

The Editors
BMC Public Health
BioMed Central
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Dear Editors

Thank you for allowing me to respond to the Reviewers’ comments. I have addressed each point in order below and have described all the resultant changes to the manuscript under each point.

Regards

Dr Emma Miller

Reviewer 1
Title: The ongoing impacts of hepatitis C infection: a systematic review of the literature
Version: 3 Date: 19 July 2012
Reviewer: Michael Wilson

The authors should be congratulated on a fine manuscript that is a comprehensive review of the topic. They have successfully addressed all major and compulsory critiques.

As an additional minor discretionary revision, I would urge the authors to expand their discussion. They note in the first sentence that "...we reviewed the biomedical and social literature on the ongoing clinical and psychosocial impacts of diagnoses with hepatitis C infection. The published literature provides useful information on selected aspects of living with hepatitis C."

This is of course true, but as a busy healthcare professional, I found myself wishing for a "recap" or bulleted summary of their most important conclusions. I should emphasize that this critique in no way detracts from the quality of the manuscript. If the authors choose not to address this point, the manuscript stands well on its own and certainly merits publication.

Level of interest: An article of outstanding merit and interest in its field

We thank the reviewer for his comments. In regards to expanding the discussion, we trust that our specific responses to Reviewer 2 (described below) are satisfactory.

We appreciate the Reviewers comment in regard to a ‘recap’ of the findings but we are concerned about the overall length of the article. Nonetheless, we have developed a Box of bullet points (Box 3) which could be inserted on page 18, between the ‘Discussion’ and ‘Conclusion’. We request advice from the Editors about whether this will unduly increase the length of the article. If nothing else, we hope that the
Reviewer might obtain some benefit from this information even if it isn’t ultimately published.

**Box 3: Bullet list of findings from the biomedical and social literature on the ongoing clinical and psychosocial impacts of diagnoses with hepatitis C infection**

<table>
<thead>
<tr>
<th>Transmission</th>
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<tbody>
<tr>
<td>• Strongly associated with injection drug use – likely to occur early in injecting career.</td>
</tr>
<tr>
<td>• Maternal transmission associated with hepatitis C viraemia – more frequent in maternal HIV co-infection.</td>
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<tr>
<td>• Prisoner populations at enhanced risk for infection.</td>
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<tr>
<th>Natural history</th>
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<tbody>
<tr>
<td>• Chronic infection can progress to fibrotic changes and development of liver cirrhosis, development of hepatocellular carcinoma (HCC) and increased liver-specific mortality</td>
</tr>
<tr>
<td>o Complications of chronic infection predicted by persistent viraemia, moderate to high alcohol consumption and increasing age.</td>
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<tr>
<td>o Liver cirrhosis and HCC occur in persistently low serum alanine amino transaminase (ALT), but frequency and rate of disease progression low relative to consistently high serum ALT.</td>
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<tr>
<td>• Hepatitis B co-infection associated with greater incidence of HCC and lower survival than mono-infection with either virus.</td>
</tr>
<tr>
<td>• HIV-HCV co-infection found to accelerate progression to AIDS, end stage liver disease and liver-related death (mostly due to HCC).</td>
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<thead>
<tr>
<th>Health related quality of life (QoL)</th>
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<tbody>
<tr>
<td>• Relatively consistent evidence of reduced QoL in untreated hepatitis C in most populations.</td>
</tr>
<tr>
<td>• Variation among studies about the relative impact of a range of co-factors on QoL, although disease activity found to be independent of QoL.</td>
</tr>
<tr>
<td>• Interferon-based treatments associated with further reductions in health related QoL, with depression playing a significant role.</td>
</tr>
<tr>
<td>o QoL improves post treatment – particularly if sustained viral responses achieved.</td>
</tr>
<tr>
<td>o QoL benefits of successful treatment can be sustained over time (possibly the deleterious effects).</td>
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<table>
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<tr>
<th>Health outcomes after antiviral treatment or liver transplant</th>
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</thead>
<tbody>
<tr>
<td>• In most populations, including IDUs, sustained viral responses attained from 20% to 80% depending on viral genotype (types other than 1 and 4 considered the most favourable).</td>
</tr>
<tr>
<td>• Sustained viral response associated with lower incidence of complications (e.g. HCC and death).</td>
</tr>
<tr>
<td>• Hepatitis C associated with lower survival and reduced overall health and function in organ transplant patients.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Psychosocial experience of living with hepatitis C infection</th>
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<tbody>
<tr>
<td>• Diagnosis with hepatitis C reported to have profound impacts on social function.</td>
</tr>
<tr>
<td>• Perceived stigma led to high levels of anxiety and over-inflated assessments of transmission risks.</td>
</tr>
<tr>
<td>• Fatigue the most common symptom reported, followed by depression and other mental health issues, myalgia.</td>
</tr>
<tr>
<td>• Symptoms independent of disease activity or disease severity, but reported to be associated with depression, anxiety and other psychosocial factors but some biological mechanisms proposed.</td>
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<table>
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<tr>
<th>Responses to diagnosis and management of hepatitis C</th>
</tr>
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<tbody>
<tr>
<td>• Diagnosis with hepatitis C often reported to be a stressful event, potentially mediated by personal and social context.</td>
</tr>
<tr>
<td>• Perceived discrimination reported in multiple settings, including in interactions with health care services.</td>
</tr>
<tr>
<td>o Potentially a barrier to health service access and treatment</td>
</tr>
<tr>
<td>• Fear of side effects reported as a major influence on treatment decisions.</td>
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</table>
Reviewer 2

title: The ongoing impacts of hepatitis C infection: a systematic review of the literature

version: 3 date: 20 july 2012

reviewer: magdalena harris

reviewer's report:

this article has benefited from revision and i would like to thank the authors for their comprehensive response letter. i feel however, that further revision would result in a stronger article.

minor essential revisions

1. the rationale and objectives of the article now sit better with its format. one reason for this is the clarification regarding 'psychosocial' instead of social – the latter speaking to a broader remit which is not covered here. i would recommend changing 'social' to 'psychosocial' in the methods section of the abstract for congruence and clarity. also in the heading on page 11.

we have made both of these amendments as suggested by the reviewer.

2. i am still unsure regarding the sensitivity of the search strategy. i know this sounds overly pedantic, but i quickly identified a number of articles not included in your additional file that are within your timeframe and appear to come within your remit. these are included below for your interest only. so – my suggestion here is at least to think about revisiting your use of the word 'sensitive' in regard to the search strategy – i.e on page 4 and page 17 (at least revisit 'highly sensitive')

thank you for providing the list of references, two of which were already included in the review (golden et al 2006, and sutton and treloar 2007). several of the other listed studies were identified with our search terms but were excluded for various reasons including that they were review papers rather than primary studies, or were focused on non-exclusively hepatitis issues or behaviours (e.g. injecting behaviour, drug use or treatment, or violence) rather than hep c infection impacts (i.e. no hcv specific outcome data were retrievable). there were, however, a number of potentially eligible articles that were not captured by our search terms and were therefore not reviewed by the team at the time. i thank the reviewer for her observation and we have amended our description as suggested.

1st sentence ‘methods’ page 4:

‘to ensure that all relevant papers were reviewed, our search strategy was designed to be as sensitive as possible.”

changed to:

‘we developed an inclusive search strategy aimed at including studies using both qualitative and quantitative approaches.”

last sentence “discussion” page 17:

‘...we searched three major data bases using a highly sensitive search strategy...”

changed to:

‘...we searched three major data bases using an inclusive search strategy...”
3. Page 14: this sentence ‘feelings of hopelessness ... relative to HIV infection’ requires revision. As it stands it is unclear and I am not sure what you are trying to say.

The Grassi et al study compared the experiences of people with HIV and hepatitis C, we have clarified this statement as follows:

2nd sentence, last paragraph, page 14:

“Feelings of hopelessness in conjunction with uncertainty were heightened in hepatitis C relative to HIV infection.”

Changed to:

“One study found that feelings of hopelessness in conjunction with uncertainty were experienced by people with either hepatitis C or HIV, but tended to be heightened in hepatitis C.”

4. The ‘psychosocial experiences’ section (p 13 – 15) has been improved with referencing, but would be further improved with the removal of definitive statements (as they preclude any acknowledgement of variance). For example, the statement ‘diagnosis with HCV appeared to have profound impacts on social functioning’ – this is reported for the majority of cases but as you acknowledge on the following page is not the case for all. Again, in relation to the statement ‘infection with HCV had substantial impacts of health and well being ...’ this is also not the case for all. There is a need to moderate/contextualise these definitive statements – for example by adding in ‘a number of studies have found’... ‘many research participants report ...’ etc.

2nd sentence, paragraph 1, page 14:

“Diagnosis with hepatitis C was reported to have profound impacts on social functioning.”

Changed to:

“In a majority of studies, diagnosis with hepatitis C was reported to have profound impacts on social functioning”

1st sentence, paragraph 3, page 14:

“Infection with hepatitis C had substantial impacts on health and well-being...”

Changed to:

“Infection with hepatitis C has been found by a number of studies to have substantial impacts on health and well-being...”

5. As in the point above, the following sentence (‘perceived stigma and discrimination impeded adaptation to HCV diagnosis’) implies this is the case for ALL people with HCV whereas research has found that for some a diagnosis is not experienced as disruptive. These statements, including those
in the following sentences, are reported as definitive whereas the findings are from discrete research studies – and a wide variance reported in people’s reactions and experiences of diagnosis and living with HCV. I encourage a more nuanced reading for this section.

3rd sentence, paragraph 3, page 1:

“Perceived stigma and discrimination impeded adaptation to the hepatitis diagnosis and was a common source of anxiety in people with chronic hepatitis C. [55, 56] The psychosocial stress associated with hepatitis C was found to be less in those with a history of IDU, which may arise from greater resilience in coping with hepatitis C stemming from experiences of marginalisation for people who inject drugs. [57]”

Changed to:

“Perceived stigma and discrimination has been noted to be an impediment to adaptation to the hepatitis diagnosis and a common source of anxiety in people with chronic hepatitis C. [56, 57] Hopwood and Treloar [58] found that the psychosocial stress associated with hepatitis C was less in those with a history of IDU, which may arise from greater resilience in coping with hepatitis C stemming from experiences of marginalisation for people who inject drugs.”

6. I realise that you wish to limit your reference list, but providing more references to back up statements in the psycho-social section would strengthen your article. It still feels under referenced, for example references for the de-prioritisation of HCV by PWID (middle para, pg14), after ‘several authors’ (last para pg 14) and at the next sentence after ‘factors’.

Last sentence, paragraph 2, page 14:

“In the context of competing priorities including housing, employment and legal implications of injecting, hepatitis C was viewed to be of less consequence by people who inject drugs, but some modification of risk behaviour (such as cleaning of syringes and spoons, and less sharing of injecting paraphernalia) was reported. [53]”

Changed to:

“In the context of competing priorities including housing, employment and legal implications of injecting, hepatitis C was viewed to be of less consequence by some study participants who injected drugs, but modification of risk behaviours (such as cleaning of syringes and spoons, and less sharing of injecting paraphernalia) was reported. [53, 54]”

7. I would encourage revising the sentence ‘the perception of stigma is generally an internalised phenomenon’ – if you are referring to both felt and experienced stigma here, surely perceptions of stigma can arise from tangible experiences of discrimination?

1st sentence, third paragraph, page 15:

“The perception of stigma is generally an internalised phenomenon resulting from individually held understandings and interpretations.”
“The perception of stigma is generally an internalised phenomenon resulting from individually held understandings and interpretations, or arising in response to actual or perceived discrimination.”

8. There is no ‘et al’, for the Harris reference (page 15)
Corrected as suggested (end 1st paragraph page 16).

9. The discussion feels a bit thin – it would be helpful here to refer back to the National Strategies addressed in the introduction – how might these findings help inform the strategies.

Added to the beginning of the 2nd paragraph, ‘Discussion’, page 16:

“The findings summarised here contribute to the knowledge base and could inform the continuing development, and revision, of national strategies aimed at reducing the harms associated with hepatitis C around the world. That the findings are synthesised from a wide range of methodological and discipline related perspectives could potentially enhance their relevance to strategy development and health service planning into the future. Yet the picture still remains fragmented and incomplete.”

10. The article (ie page 5) and authors’ letter refer to the narrative synthesis of their material. The final line of the conclusion refers to ‘this narrative review’. In this light, it would be appropriate to refer to the review in the title as a narrative review or to omit the word systematic.

Title changed from:

‘The ongoing impacts of hepatitis C infection: a systematic review of the literature’

Changed to:

‘The ongoing impacts of hepatitis C infection: a systematic narrative review of the literature’