Reviewer's report

Title: Factors influencing adherence in Hepatitis-C infected patients: a systematic review

Version: 3
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Reviewer: Etienne Audureau

Reviewer's report:

This is a systematic review dealing with the factors associated with adherence to treatments of HCV, with a specific focus on ribavirin. The topic is interesting and the paper has its strengths, including a detailed search strategy and discussion of the flaws identified in current literature. However, the article also suffers from important weaknesses, including an overall unclear presentation of the results with important details lacking that could in some cases lead to misleading interpretation.

Overall, it is currently very difficult for the reader to have a clear picture of the findings and to understand what are the reasonable implications of the study.

- Major Compulsory Revisions
  1. Abstract:
     - Methods: please specify the period covered for publication extraction from Medline/Embase.
     - Results: While keeping the abstract concise, I think it is possible to expand and detail more the results section to add some numbers (e.g. n/N % of studies reporting a given risk factor for non adherence).

  2. Background:

     - Overall, the background section is very short and could be deepened so that the authors make a stronger case of why it is important to conduct the study and to restrict the study to ribavirin, including e.g. general aspects regarding available treatments against HCV, detailed results regarding the specific impact on efficacy of low adherence instead of the rather vague terms “important” or “crucial”, detailed examples for the systematic reviews about adherence conducted in other indications.

  3. Methods:

     - Overall, the search strategy is well detailed, as well as the description of the outcomes considered, the efforts made to contact authors if needed, the blinding (independent assessment) between raters and the methods to manage disagreements.
- As recommended in MOOSE guidelines, please also specify in the methods section who were the two reviewers and their qualifications

- The rationale for excluding surveys dealing with “intentional” non-adherence factors is unclear to me. How many studies were excluded using this criterion?

- The authors calculated p-value / Effect sizes when possible. Beyond the ‘double data entry’ method used to enter data, what were the statistical tests performed?

- The authors qualitatively assessed heterogeneity between studies. Yet, the rationale for not combining studies could be more detailed, because one might argue that common underlying mechanisms could be found between factors and adherence across settings and populations.

4. Results

- The assessment of the quality of the studies included should be more detailed within the text. In particular, the issue of confounding: when rated “minus”, does it mean that the studies did not use any form of statistical adjustment or that the confounders entered in multivariate analysis were inappropriate / insufficient?

- Plus, the question of the representativeness is not simple: the authors chose very wide inclusion criteria for their review (“patients with HCV”), and it is currently not clear for the reader whether a lack of representativeness of a study as stated in Table 1 refers to a bad selection process of the study (quality criterion), or to a low representativeness of the sample when compared to the “general population of patients with HCV” (e.g. Sylvestre et al surveyed heroin users and are rated “-“, what is the meaning of this rate ?)

- Table 2 lacks important aspects beyond the inclusion criteria, including the setting (health centers, community, penitentiary facility, etc.), study design (cohort study, case-control, randomized trial, etc.), duration of follow-up. For instance, Rodis et al 2010 is stated “NR” regarding the inclusion criteria, but consideration of the abstract on Pubmed gives useful information for the reader relating to setting (“interdisciplinary HCV education and monitoring service”)

- Table 3 is not self-explanatory (the title is too vague and the meaning of the OR is not obvious without digging into the methods section)

- Table 3 is cumbersome and hard to follow, because the reader has to constantly ‘navigate’ across studies to compare ORs factor by factor. In this regard, graphs might be helpful to display the relationships found for some important selected factors

- The authors describe results and directions, even though most results are not statistically significant, using terms like “strong tendency” which is too vague a term. More importantly, they do not provide to the reader a clear sense of the hierarchy or relative importance of studies, with no account for the setting or sample size; e.g. for psychiatric disorders, apparently only one study found a “significant” effect (presumably Wagner et al N=72), but “all studies that analyzed this factor showed this effect direction”. This statement is misleading, because it
includes Lo Re et al (N>5000 ) that found a not significant OR of 0.99.

5. Discussion

- Most of the discussion is dedicated to detailing and explaining the limits of the interpretation due to the high level of heterogeneity and consequently the low comparability between studies. These aspects are indeed interesting and crucial to document in a systematic review.

- However, the potential factors of risk which have been identified should be more thoroughly discussed (possible underlying mechanisms? Common or different patterns from other indications / diseases?) to provide some insights into the clinical implications of the results, beyond the limits relating to comparability.

- Relatedly, the authors conclude that patients with those factors should be closely monitored, but it seems insufficiently justified.

- Minor Essential Revisions

  None

- Discretionary Revisions

  - Figure (flow chart): the direction of the arrow for “excluded after abstract screening” should be inverted
  - Please specify briefly what “WHO mortality stratum A” countries are, because it is possibly not straightforward to all readers, (e.g. maybe add a short sentence referring to “very low child mortality and low adult mortality”, i.e. western countries)
  - Strictly speaking, the statement in methods section “no limit on the language” is incorrect, because the authors searched for English and German studies.
  - Grille NICE for prognosis : please specify Yes/No/unclear in the appendix for the NICE grid
  - Please check references (e.g. p5 Marcellin et al: name mispelled and wrong number)

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests