

To the Editor  
World Journal Gastroenterology

ESPS Manuscript No 14399 - Revised by Adinolfi LE et al.

Dear Editor

Enclosed please find the revised manuscript entitled: "Chronic HCV infection and neurological and psychiatric disorders: an overview".

We want to thank the reviewers for their favorable comments and suggestions. Below you can find a point-by-point replay to the reviewer's comments.

The English is of grade A/B as also evaluated by a native English person (University teacher).

Point-by-point replay to referee comments:

Referee 1.

Comment 1. The authors should add the occurrence of lichen planus as extrahepatic manifestations in introduction. (Please refer to manuscript "Nagao Y, Sata M. Hepatitis C virus and Lichen planus. Journal of Gastroenterology and Hepatology 2004 Oct; 19(10): 1101-1113")

Replay1: The reference has been added as ref. 10.

Comment 2. The authors should describe the general view of comparison between HBV and HCV regarding neurological and psychiatric disorders, although they cited two papers (reference number 111,112). In other words, is there much difference between HBV and HCV concerning neurological and psychiatric disorders?

Replay 2. The review is focused on HCV infection. The two papers (ref. 111 and 112) that have compared psychiatric disorders in HCV and HBV have been cited and discussed. These papers showed significant difference between the two infections that are underlined in the paper.

Comment 3. In clinical settings, what do the authors emphasize the clinical manifestations in chronic HCV infected patients? In other words, what kind of symptoms should the clinician be most careful for in clinical setting?

Replay 3. Due to the difficult to report all symptoms of the different neuropsychiatric disorders, in the last line of conclusions we summarized: “in the diagnostic work-up of a patient with the above reported neuropsychiatric disorders, clinicians should also consider to screen for HCV infection.”

Comment 4. The authors should describe or speculate the relationship between Alzheimer's disease and HCV infection, although they described the relationship between cognitive impairment and HCV in Conclusions and critical considerations.

Replay 4. There are no studies that have investigated the relationship between Alzheimer's disease and HCV. A study on the relation between dementia and HCV has just published and it has been discussed (page 10, lines 11-17) and added as references 68.

Referee 2.

The manuscript by Adinolfi et al, well reviewed the current knowledge on neurological and psychiatric conditions associated with chronic HCV infection and for this reason the manuscript is interesting to read and can be of a great interest for the WJG readership. The english language evaluation is very good. Although the manuscript can be published in this form, I would suggest few minor revisions in order to improve the manuscript:

Suggestion 1. At the end of the paragraph “HCV infection and psychiatric disorders” page 12 or in the “conclusion” section is better to add few sentences and references dealing with the importance to take into account antidepressant medications with a possible implication in HCV replication.

Answer 1. Treatment of depression in HCV is complex and should require a large chapter that is out of the aim of this review. However, we underline two important aspects: 1) that anti-serotonergic drug could be an effective treatment (page 17); and 2) that HCV clearance might improve both neurological and psychiatric disorders (page 19).

Suggestion 2. The impact of HCV genetic differences on pathobiology of disease well reviewed in Ripoli M, Pazienza V. Expert Rev Anti Infect Ther. 2011 Sep;9(9):747-59. In this manuscript only at page 12 is reported that HCV genotype 3 infected patients might be at increased risk of depression. What about the other extrahepatic events manifestation? Is there any genotype association reported?

Answer 3. The impact of HCV genotypes on hepatic and extrahepatic manifestations is different, e.g. genotype 1 is associated with IR and type 2 diabetes. However, there is only one study that evaluated the association between HCV genotype and depression and it has been discussed (ref.111). To discuss the role of HCV genotype in the other extrahepatic manifestations is out of aim of this review.

References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Best regards

Professor Luigi E. Adinolfi, M.D.