

01/30/2017

Dear Editor,



Please find enclosed the edited manuscript in Word format (Manuscript NO: 31953).

**Title: Non-alcoholic fatty liver disease: an expanded review**

**Author:** Mark Benedict and Xuchen Zhang

**Name of Journal:** World Journal of Hepatology

**ESPS Manuscript NO:** 31953

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated
2. Audio core tip is added
3. Revision has been made according to the suggestions of the reviewers

**Reviewer 1:**

This is a paper on NAFLD that has been already reviewed by four reviewers. Several questions mainly on the structure and language use have been raised, with which I agree. The authors have made efforts to address these questions. However, I think that the paper is still problematic. In my opinion the main problem is that the authors have tried to encompass all the aspects of the disease ending up finally with a non-in-depth approach. Pathology section is much extended and on the other hand information on treatment is very limited. This creates a disequilibrium that may affect the interest of a common reader. In addition, differential diagnosis in my opinion is redundant as most of the diseases that are mentioned are easily differentiated (viral hepatitis, chemotherapy etc). Liver transplantation should not be included in the risk factors section.

**Answer reviewer 1:** Additional information regarding treatment was added to create a greater equilibrium. Specifically, those medications which have gained notice due to promising phase II and III clinical trial in the treatment of NAFLD have been mentioned, as well as those medications that have made their way into the most recent NAFLD treatment considerations are also included in the revised manuscript. Liver transplantation has been moved under the pathogenesis section.

**Reviewer 2:**

The paper has been reviewed critically by expert reviewers. The authors have revised the manuscript based on the reviewers' comments. In my opinion, the manuscript has potential to be valuable for this journal.

**Answer reviewer 2:** More changes have been made based on the comments from other reviewers.

**Reviewer 3:**

We read with interest the paper entitled "Non-alcoholic fatty liver disease: an expanded review" by Benedict and Zhang. The authors carried out a very exhaustive and up to date review on NAFLD addressing all the aspects of this emerging hepatologic problem. Although several reviews have been published in the last years, the present paper is well structured and references updated. The only

concern we would like to rise is the paragraph on treatment approach. It is too concise and does not provide information on new drugs for NAFLD under evaluation or recently proposed. I would like to suggest the authors to implement this issue or, otherwise, to delete the paragraph and changing the title accordingly. The language is good enough even though a style improvement would be desirable.

**Answer reviewer 3:** Treatment considerations were mentioned and bolstered in line with the most current literature as per reviewer #1 and #4's comments

**Reviewer 4:**

A large, comprehensive review, with an update of the literature. I only regrets that two issues are not adequately covered: a) genetics; b) management. As to a), at the end of the chapter on Racial and Ethnic differences – by the way, what is the difference between Racial and Ethnic? These two terms are largely interchangeable in Europe, where the term “Racial” is considered impolite – they claim that more information may be found under the “genetics” heading, but no such heading is present nor any additional information is provided. This issue is of paramount importance, and might soon dictate screening procedures according to several investigators. The manuscript does not deal with TM6SF2 and the most recent MBOAT4 polymorphisms. As to b), the manuscript does not adequately stress the recent definition of outcome targets from regulatory agencies (i.e., NASH regression without worsening of fibrosis), that might soon provide a reasonable way to compare the effects of treatment and the efficacy of new drugs. In addition, there is no warning of the difficulties in managing a reasonable screening and surveillance procedure, considering the huge number of cases at risk.

**Answer reviewer 4:** A detailed genetics section was added including Ghrelin O-acyltransferase (GOAT), a member of MBOATs family. Treatment considerations were mentioned and bolstered in line with the most current literature as per reviewer #1 and #3's comments. Heading “Racial and Ethnic Differences” was revised to just Ethnic Differences. Comments were made and a section was added detailing the current recommendations for screening/surveillance.

**Reviewer 5:**

Comments: The prevalence of NAFLD is increasing worldwide. It is helpful to the clinical practice and NAFLD related basic research by learning the latest advance in this field. This article entitled "Non-alcoholic fatty liver disease: an expanded review" by Benedict M et al. has systematically reviewed and comprehensively summarized nearly all the aspects of “NAFLD” in detail. This paper provides readers some new insight and knowledge of NAFLD. Therefore, it is recommended to be published. Overall suggestion: accepted.

**Answer reviewer 5:** More changes have been made based on the comments from other reviewers.

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

Sincerely yours,

Xuchen Zhang, MD, PhD