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July 25, 2017

Scientific Editor:
World Journal Gastroenterology

Re: Revision Submission 34646

Dear Dr. Ze-Mao Gong:

Enclosed please find our revised review article entitled "Treatment Options for Alcoholic and Non-Alcoholic Fatty Liver Disease: A Review" **which we submit for publication in *World Journal Gastroenterology*. Please note that Sukhpreet Singh is the first author, Natalia A. Osna is the middle and Kusum K. Kharbanda is the last author of this manuscript.**

We thank the reviewers for their constructive comments and valuable suggestions. We have revised the manuscript accordingly to their suggestions and the editors' comments and requests. Our responses to the comment are below the reviewer's individual comments. The changes in the revised manuscript are highlighted in yellow.

Reviewer 1 (2017-05-29 19:08):

Comment 1: Authors should emphasize the relevance of intravenous thiamine when treating patients with withdrawal alcohol syndrome, because oral thiamine is inadequate for preventing permanent brain damage. Please see Flynn A et al, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4578911/> -

Our Response: We have added thiamine-related text and appropriate references (Page 6 of the revised manuscript).

Comment 2: Among factors potentially associated with ALD outcome, I suggest authors include HCV. Although prevalence of this infection is decreasing in the Western world (please see Novo-Veleiro et al, <https://www.ncbi.nlm.nih.gov/pubmed/26819510>), it is still a major factor contributing to alcoholic liver disease. It could be mentioned that HCV infection should be screened among patients with ALD and that treatment of this infection ameliorate liver disease among alcoholics.

Our Response: We have added HCV-related text and appropriate references (Page 8 of the revised manuscript).

Comment 3: Among drugs used to treat alcohol abuse or dependence, authors could include that drugs like disulfiram or naltrexone are best avoided in patients with liver disease, being better options acamprosate, topiramate or baclofen (the only drug specifically tested for treatment of alcohol dependence in ALD patients). Please see Vuittonet CL et al, <http://www.ajhp.org/content/71/15/1265?sso-checked=true> and Addolorato G et al, <https://academic.oup.com/alcalc/article-lookup/doi/10.1093/alcalc/agr017>.

Our Response: We have added appropriate warning for disulfiram and naltrexone use, added acamprosate, topiramate or baclofen-related text and appropriate references (Page 7-8 of the revised manuscript).

Comment 4: Among vitamins which are often found to be altered in ALD, authors should include vitamin B12.

Our Response: We have added vitamin B12-related text and appropriate references (Page 8 of the revised manuscript).

Comment 5: The role of genetic polymorphisms, mainly rs738409 within PNPLA3 gene, should be included, as risk factors for advanced liver disease in both alcoholic liver disease and non-fatty liver disease. This polymorphism may identify patients with higher risk of cirrhosis, thus promoting intensive treatment. Please see Chamorro AJ et al, <https://www.ncbi.nlm.nih.gov/pubmed/25060292> and Anstee QM et al, <https://www.ncbi.nlm.nih.gov/pubmed/26378644> -

Our Response: We have added PNPLA3-related text and appropriate references (Page 4-5 of the revised manuscript).

Comment 6: Among potential therapeutic targets of non-alcoholic fatty liver disease, authors could include p38 mitogen-activated kinases. Please see Gonzalez-Teran B et al, <https://www.ncbi.nlm.nih.gov/pubmed/26843485> -

Our Response: We have added p38 mitogen-activated kinases-related text and appropriate references (Page 25 of the revised manuscript).

Comment 7: One or two tables could be included, particularly summarizing potential therapeutic targets, to improve the readability of the manuscript

Our Response: We have added 2 tables in the revised manuscript.

Comment 8: There are some minor typos and formatting errors (e.g. missing page numbers) as well.

Our Response: We have carefully edited the revised submission for minor typos and formatting errors and have added page numbers.

Reviewer 2 (2017-06-02 14:09):

Comment 1: The review is substantial, clinically important in general, however I am still not convinced that ALD and NAFLD reviews should be published as a single review as these two topics are substantially different and the treatment modalities are also highly differing. Provided that the Editorial decision is to proceed with it in its current form (and not to split it up to two different review articles), then I have the following comments, many of them might be considered as major. for the ALD chapter

Our Response: Since we did not have the editor suggest splitting the paper in two, our revised submission still includes the review on both ALD and NAFLD.

Comment 2: Authors do not mention the drug Metadoxine in their review, despite even an RCT has been recently reported a survival benefit in patients with severe alcoholic hepatitis (in combination with steroid tx and pentoxifylline also). Although the sample size is low it may be worth to mention as it is a well-designed RCT. (Higuera-de la Tijera F, et al. World J Gastroenterol. 2015 Apr 28;21(16):4975-85. doi: 10.3748/wjg.v21.i16.4975. Metadoxine

improves the three- and six-month survival rates in patients with severe alcoholic hepatitis. Randomized controlled trial.)

Our Response: We have added Metadoxine-related text and appropriate references (Pages 7-8 of the revised manuscript).

Comment 3 On page 7 – it may be mentioned that AASLD recommends (Class I, level A) the use of a four-week course of prednisolone (40 mg/day for 28 days, typically followed by discontinuation or a 2-week taper) for patients with severe disease (MDF score of ≥ 32 , with or without hepatic encephalopathy) and lacking contraindications to steroid use should be considered. Class I, level A recommendation level might be outlined in such a review from the literature that they also referenced as ref. No. 38.

Our Response: We have modified the text as recommended (Page 10 of the revised manuscript).

Comment 3: In many studies, authors did observe an increase of sepsis in patients with ALD on the steroid arm. Sepsis should be outlined in the text, not only as a contraindication, but also as a possible side effect regarding the appropriate studies.

Our Response: We have modified the text as recommended (Page 10 of the revised manuscript).

Comment 4: Pentoxifylline is suggested as a second line treatment, especially when steroid is contraindicated – (Class I, level B) – again this statement should be outlined in the review (on page 8). for the NAFLD chapter:

Our Response: We have modified the text as recommended (Page 10 of the revised manuscript).

Comment 5: There is currently a subchapter as indicated about the “incretin based therapies” (page 22). There are a few comments to this subchapter: ☐ The whole subchapter should be in a more outlined position in the text, not at the end somewhere well after caspase inhibition or (clinically failed) drugs acting on the cannabinoid axis, etc. This suggestion for repositioning is due to that the GLP-1 agonists (liraglutide) and DPP-4 inhibitors (e.g.: sitagliptin) have demonstrated either reliable safety benefit or neutrality in RCTs conducted with a large number of patients with diabetes in contrast to for example ASK-1 inhibitors, caspase inhibitors and rimonabant. For example, rimonabant is outlined earlier in the text, despite it was withdrawn due to safety concerns (Prescrire Int. 2007 Dec;16(92):250. Rimonabant: suicide and depression. Depression and suicidal tendencies are about twice as frequent with rimonabant as with placebo. <http://www.modernmedicine.com/modern-medicine/news/clinical/clinical-pharmacology/rimonabant-trial-stopped-early-due-suicide-risk?page=full>) ASK-1 and caspase inhibitors are still more kind of experimental drugs in contrast to liraglutide or sitagliptin that are used every day with excellent, proven safety profiles. It should and may not be concluded based on animal studies that larger human trials are needed with Rimonabant due to safety concerns that would be unacceptable to conduct any such trial in humans with Rimonabant. It is also questionable why rimonabant should be mentioned at all (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000666/human_med_000623.jsp&mid=WC0b01ac058001d124, <https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-backgrounder.pdf>) ☐ ☐ It would be worth to split up this subchapter to two different subchapters (both placed in a more outlined position in the text): one for the GLP-1 agonists and one for the DPP-4 inhibitors. It is

due to that there is more convincing evidence for GLP-1 agonists to be effective for the treatment of NASH in terms of biopsy proven histological improvement (Lancet. 2016 Feb 13;387(10019):679-90. doi: 10.1016/S0140-6736(15)00803-X. Epub 2015 Nov 20. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Armstrong MJ) and metabolic improvement than for the DPP-4 inhibitors. □ As in this form the presentation is somewhat mixed in the review, i.e. still within the incretin axis subchapter authors mention animal studies earlier than for example the LEAN trial and therefore these statements should be somehow more clearly separated. I would suggest a separate table for those drugs that were already conducted in human trials for NASH, were not withdrawn from the market due to other reasons (like rimonabant) and preferably in the order of the quality of evidence supporting its use in NASH (e.g. prioritize LEAN trial, etc) and also indicating the phase of the clinical trial (e.g. phase 2 for LEAN) the sample size and methods used for assessment and the conclusion. □ When the data about DPP-4 is summarized authors state that “NAFLD patients have been found to show higher DPP-IV expression, thus an increase in hepatic steatosis” based on a single reference by Balaban et al. It should be outlined that the substantially more data support the correlation between DPP-4 and NAFLD and I would suggest to include these references also (page 22): It was reported that serum DPP-4 activity is increased in NAFLD and correlated with liver tests and HOMA-IR indicating that the excess is of hepatic origin and contributing to the speedup of metabolic deterioration. Authors concluded that the serum DPP-4 activity should be considered as a novel liver disease biomarker. (G. Firneisz, et al (2010) Serum Dipeptidyl Peptidase-4 Activity in Insulin Resistant Patients with Non-Alcoholic Fatty Liver Disease: A Novel Liver Disease Biomarker. PLoS ONE 5(8): e12226. <https://doi.org/10.1371/journal.pone.0012226>) Subsequently the Analysis of human liver biopsy specimens revealed a correlation of DPP4 expression and DNA methylation to stages of hepatosteatosis and nonalcoholic steatohepatitis – in line and explaining the prior results. Authors proposed a crucial role for the liver in participation of determining systemic DPP4 levels. (C. Baumeier et al. (2017) Hepatic DPP4 DNA Methylation Associates With Fatty Liver - Diabetes 2017 Jan; 66(1): 25-35. <https://doi.org/10.2337/db15-1716>) Authors stated correctly that sitagliptin was shown to be no more effective than placebo for improving hepatic steatosis on page 22 (ref: 173), however it should be indicated that J. Cui et al reported the increase in hyaluronic acid levels and also the increase in FIBROSpect II index on the placebo arm that was withheld on the sitagliptin arm (same study: ref 173). □ It may be added and discussed that a 6 months long trial may not necessarily be long enough to assess the improvement in liver fibrosis in NAFLD, therefore – in the view of these results (and also in the view of the study conducted by Tisha Joy et al: reporting a NS trend with decreasing gGT levels on the sitagliptin arm (62U/L mean decrease), but an increase on the placebo arm) in patients with biopsy proven NASH. I would rather suggest to phrase it as: □ Despite there is no convincing evidence for the improvement for sitagliptin in the few clinical trials conducted with small sample sizes for 6 months an existing effect still can not be ruled out (possibly on fibrosis?), however it should likely be assessed in longer clinical trials than 6 months in larger number of patients with NAFLD/NASH. Please also cite the reference for the above: TR Joy, et al. World J Gastroenterol. 2017 Jan 7; 23(1): 141–150. doi: 10.3748/wjg.v23.i1.141 □ The GR-MD-02 (Galectin 3 inhibitor) is not assessed in general for the treatment of liver fibrosis in NASH patients in a phase II study as stated on page 24, but more specifically for Liver Fibrosis and Resultant Portal Hypertension in Patients With NASH Cirrhosis <https://clinicaltrials.gov/ct2/show/NCT02462967> Therefore there might be a lot of expectations from the helapotolgical aspect, but please do indicate the aim and the title of this trial correctly and also please include the estimated study completion date and primary

completion dates. The authors must cite and analyses some studies conducted in this area Abelouhab et al , 2012 ; Toumi et al, 2014, Soufli et al, 2015, 2016.


Our Response: Thank you for the suggestions. We have modified all the text as recommended and added appropriate references (Pages 20-23, 27 of the revised manuscript).

Reviewer 3 (2017-06-05 13:53): This paper provides readers new insight and knowledge of the treatment of ALD and NAFLD. Therefore, it is recommended to be published. Overall suggestion: accept.

Our Response: We thank the reviewer for their positive comments.

Thank you for your consideration of our manuscript.

Sincerely,

A handwritten signature in blue ink that reads "Kusum K. Kharbanda". The signature is written in a cursive, flowing style.

Kusum K. Kharbanda, Ph.D.