Response to Editor and Reviewers:

Manuscript 45018: Current and future pharmacological therapies for managing cirrhosis and its complications

We greatly appreciate the Editorial team and Reviewers providing us with their carefully-considered comments on our manuscript. We were very pleased to discover that the comments were largely positive in nature. Nonetheless, we acknowledge a number of suggestive additions, which we have thoroughly contemplated and incorporated within the revised manuscript. We believe that the amendments, which we have highlighted below and in the manuscript, have helped strengthen the article.

Editor

We thank the Editor for their comments.

'Please provide point to point answer to all reviewers.'

Please find the point to point answers below.

'Please provide the postcode.'

Lines 13-16:

"Liver Unit/ Division of Integrative Systems Medicine and Digestive Disease, Department of Surgery and Cancer, Faculty of Medicine, St Mary's Hospital Campus, Imperial College London, London, W2 1NY, UK."

‘A copy of the full approved grant application form(s), consisting of the information section and body section, should be provided to the BPG in PDF format.’

A PDF file of each grant award will be uploaded to BPG.

‘Please offer the audio core tip’

The audio core tip will be uploaded to BPG.

‘Reference 69 and reference 79 are same, please delete reference 79 and rearrange the references in numeral order. Or you can use a similar reference to replace one of them.

Reference 23 and reference 133 are same, please delete reference 133 and rearrange the references in numeral order. Or you can use a similar reference to replace one of them.’

We thank the Editor for pointing out this oversight. We have deleted duplicate references.

Reviewer: 02860895

‘This is a nice review article that comprehensively covers current knowledge concerning pharmacological therapies for cirrhosis and its complications. I appreciate the authors' efforts to have written this article. I could find no major problem.’

We thank the Reviewer for their positive feedback.

'As a minor point, although anticoagulation therapies are explained in the main text, no such description is present in the abstract. I think that a concise explanation about anticoagulation should be added in the abstract because of its importance.'

We agree with the Reviewer about the importance of anticoagulation and that anticoagulative therapies should be represented within the abstract. As such, we have included the following in the abstract:

Lines 91 – 93 (abstract):

"Emerging evidence indicates that anticoagulative therapy reduces incidence and increases recanalisation rates of non-malignant portal vein thrombosis, and may impede hepatic fibrogenesis and decompensation."

Reviewer: 00071662

'I think this review is very important to aproach the treatment in these patients'

We thank the Reviewer for their positive comment.

Reviewer: 00506564

'The review is very interesting and very well written. I have to congratulate the authors on the detailed approach to this topic.'

We thank the Reviewer for their positive feedback.

'There are, however, several details that I think should be corrected before publishing: First, since the review will be published in 2019, literature review should be updated until December 2018'

We agree that it is important to ensure that the literature search is up to date. As such, we have updated the literature review until December 2018 as suggested. Thus

we have included three important recent studies within the section regarding non-selective beta-blockers:

Lines 254 – 259 (3.1.2 The 'window hypothesis'):

"A recent meta-analysis of three RCTs and 13 observational studies summarising the effect of NSBBs on mortality in cirrhotic patients with ascites found that survival was comparable between NSBB and control groups for both the overall population (HR 0.86, 95% CI 0.71 – 1.03, p=0.11) and the refractory ascites subgroup (HR 0.90, 95% CI 0.45 – 1.79, p=0.76) with significant heterogeneity between included studies[1]."

Lines 290 – 296 (3.1.3 Carvedilol)

"Zacharias *et al* recently conducted a Cochrane systematic review of 10 RCTs and 810 patients comparing the safety and efficacy of carvedilol versus traditional NSBBs in the primary and secondary prevention of variceal haemorrhage; they identified no differences in the incidence of mortality, variceal haemorrhage and serious adverse events between both groups despite greater reductions in HVPG for the carvedilol group. Due to the low quality of assessed evidence, these findings were associated with substantial uncertainty[2]."

Lines 323 – 326 (3.1.4 Haemodynamically-independent potential of beta-blockers)

"Recently, Gimenez *et al* observed that monocytes and granulocytes of cirrhotic patients on long-term NSBB therapy displayed significantly raised phagocytic capacity in the presence of bacterial DNA compared to NSBB-naïve patients[3]."

We updated the Abstract and Method section accordingly:

Line 73 (Abstract):

"PubMed/Medline/Cochrane Library were electronically searched up to December 2018 to identify studies evaluating safety, efficacy and therapeutic mechanisms of pharmacological agents in cirrhotic adults and animal models of cirrhosis."

Line 137 (Methods):

"A search of the existing literature up to December 2018 was conducted using the electronic databases PubMed, Medline and the Cochrane library, as well as relevant guidelines and reference lists."

'Second, Authors should clearly state the aims and specific objectives of the review and formulate literature search accordingly. They mention that "the present article aims to provide an overview of the complete pharmacotherapy currently available for the long-term management of cirrhotic patients as well as an insight into emerging and future directions". But they do not make a complete revision. Indeed, authors state that "Whilst previous articles have addressed individual pharmacological agents and their role in treating specific complications of cirrhosis". They are partly approaching this topic the same way, with specific subheadings for individual pharmacologic agents instead of subheadings for complications of cirrhosis. For instance, authors mention hepatorenal syndrome but they do not talk about terlipressin or octeotride. In this regard, no specific subheadings are devoted to portopulmonary hypertension, hepatopulmonary syndrome or hepatorenal syndrome (where terlipressin or octeotride may have a role). […] To sum up, authors should clearly state which drugs or which specific complications of cirrhosis they are going to review and formulate and structure this narrative review accordingly. In this present form, several important treatments are not covered and the readers may not know if they are just not covered, if they missed or if they do not have a role in the treatment of cirrhosis or its complications.'

We agree with the Reviewer that we had not stated our remit as clearly as we could have done. Our specific focus in this Review is on pharmacotherapy for cirrhotic patients that may be commenced in the outpatient/ clinic setting (as opposed to medical therapy of cirrhotic complications more typically managed as an inpatient, including acute variceal bleeding, type 1 hepatorenal syndrome, etc). To make this point clear to readers, we have made several clear references to this remit within the text, specifically:

Lines 69 – 70 (abstract):

"This article aims to provide a complete overview of pharmacotherapy options that may be commenced in the outpatient setting which are available for managing cirrhosis and its complications, together with discussion of current controversies and potential future directions."

Lines 138 – 147 (introduction):

"This development led to the UK-wide introduction of specialist cirrhosis clinics which integrate multidisciplinary services and aim to optimise supportive cirrhosis management by forestalling decompensation and facilitating recompensation. In the specialist clinic setting, one factor which has gained importance in chronic cirrhosis management is long-term, complication-guided pharmacological therapy. Whilst previous articles have addressed individual pharmacological agents and their role in treating specific complications of cirrhosis, the present article aims to provide an overview of the complete pharmacotherapy currently available for the long-term management of cirrhotic outpatients as well as an insight into emerging and future directions. "

We have considered the comment from the Reviewer about structure of the material/ text. However, we still feel it is more apropriate to maintain consideration of different drug classes in turn, rather than structure the text as consideration of various cirrhotic complications. The structure that we have used allows the reader to consider the advantages, drawbacks, uncertainties and controversies for each drug class as they are discussed, as would be the approach of a physician in a Cirrhosis Clinic considering modification of a patient's prescription. A further reason why we feel that the structure according to different drug classes rather than

complications is appropriate is that certain included medications (for example statins and proton-pump inhibitors) do not treat specific cirrhosis-related complications but are aimed at the overall holistic management of the cirrhotic outpatient.

'Neither they mention octeotride as a potential treatment for correcting serum sodium in patients with cirrhosis and hyponatremia.'

We agree that octreotide has potential for the treatment of cirrhosis-induced hyponatraemia. As such, we have included the following lines within the section regarding diuretics:

Lines 574 – 578 (3.3.1 α-1 and α-2 adrenergic agonists)

"A recent small-scale prospective observational study also suggests that oral midodrine and subcutaneous octreotide combination therapy could ameliorate cirrhosis-induced hyponatraemia (pre-treatment serum Na: 124 mmol/L vs post-treatment serum Na: 130 mmol/L, p=0.00001)[4]."

'Similarly, no specific subheading resumes the approach to hepatic encephalopathy and many treatments, such as acarbose or L-ornithine-L-aspartate are neither mentioned as new treatments nor discussed as potentially useful for hepatic encephalopathy.'

We concur that acarbose and L-ornithine-L-aspartate have important potential for the treatment of hepatic encephalopathy in an outpatient setting. We have thus included both agents in a separate paragraph within the main body of the manuscript.

Lines 512 – 539 (3.2.4 L-ornithine L-aspartate and acarbose):

3.2.4 L-ornithine L-aspartate and acarbose

As outlined, ammonia has been identified as the pivotal neurotoxin implicated in the pathogenesis of HE and its reduction is a central objective in the therapeutic approach to HE management. L-ornithine L-aspartate (LOLA) has demonstrated ammonia-lowering properties by enhancing residual hepatic urea cycle activity and skeletal muscle glutamine synthesis[79,80]. Goh *et al* performed a recent Cochrane systematic review of 36 RCTs and 2377 patients summarising the evidence of LOLA in the prevention and treatment of HE. The authors found very low quality evidence that LOLA had beneficial effects on mortality, HE and serious adverse events compared to placebo. However, these findings were not upheld when only trials with low risk of bias were considered. On subgroup analysis, there was no difference between intravenous and oral LOLA administration or between minimal and overt HE. In comparison to lactulose and rifaximin, LOLA demonstrated no effect on mortality, HE and serious adverse events. The uncertainty stemming from data quality concerns led the authors to conclude that new, high-quality RCTs are required for the definitive evaluation of evidence[79]. A randomised, placebo-controlled, quadruple blinded, phase IV trial investigating the efficacy of LOLA in treating overt HE is currently in progress and its results are awaited[81].

One randomised, double-blinded, placebo-controlled trial in 107 cirrhotic patients with HE and type 2 diabetes mellitus provided encouraging data for the safety and efficacy of acarbose in treating HE with the intervention group demonstrating lower blood ammonia levels, improved encephalopathy global score and reduced Child-Pugh score[82]. However, the generalisability of these findings is diminished by the highly selective study population of compensated Child-Pugh A cirrhotics with predominantly Grade 2 encephalopathy, as well as the scarcity of further studies investigating the efficacy of acarbose in treating HE[83]. Acarbose is not mentioned in current EASL and AASLD guidelines for HE management.

We have updated the Methods section accordingly:

Lines 154 – 155 (Methods):

“Titles and abstracts were searched for the following key terms: “Cirrhosis” AND (“beta-blockers” OR “lactulose” OR “rifaximin” OR “L-ornithine L-aspartate” OR “acarbose” OR “diuretics” OR “midodrine” OR “clonidine” OR “vaptans” OR “human serum albumin” OR “anti-coagulation” OR “caffeine” OR “faecal microbiota transplant”)”

‘It is particularly surprising that (instead of acarbose, e.g.) caffeine is mentioned and 5 references are used for illustrating this point. But caffeine is not used for treating cirrhosis or any of its complications (and maybe this article should be cited https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2783828/)’

We agree with the Reviewer that caffeine is currently not routinely used for the treatment of cirrhosis or its complications. However, we feel that its inclusion as a potential future treatment is merited given that multiple, relatively large-scale, observational studies have shown an encouraging, inverse dose-response relationship between caffeine consumption and the risk of cirrhosis, cirrhosis-related mortality and complications, as well as HCC development.

We thank the Reviewer for pointing us towards the mentioned article which we included within the section regarding caffeine:

Table 2. Summary of further pharmacological agents with potentially therapeutic effects:

“Similarly, a prospective cohort study of patients with advanced hepatitis C induced liver disease found that liver-related mortality and complication rates declined with increasing coffee consumption (12.1/100 person years for >1 cup/day; 8.2/100 for 1-3 cups/day; 6.3/100 for >3 cups/day; p-trend=0.001).[10]”

In line with the changes that we have made to address the reviewers' comments, we screened an additional 317 abstracts and included 10 additional publications. We updated the methods and reference sections, as well as Figure 1, accordingly:

Lines 161 – 163 (Methods):

"The abstracts of 2031 publications were identified and screened for studies evaluating the safety, efficacy and therapeutic mechanism of pharmacological agents in cirrhotic adults and animal models of cirrhosis. 158 publications were considered relevant to the key question and included in the present review (Figure 1)."

References:

1. **Facciorusso A**, Roy S, Livadas S, Fevrier-Paul A, Wekesa C, Kilic ID, Chaurasia AK, Sadeq M, Muscatiello N. Nonselective Beta-Blockers Do Not Affect Survival in Cirrhotic Patients with Ascites. *Dig Dis Sci* 2018; : 1-10 [PMID: 29725793 DOI: 10.1007/s10620-018-5092-6]

2. **Zacharias AP**, Jeyaraj R, Hobolth L, Bendtsen F, Gluud LL, Morgan MY. Carvedilol versus traditional, non ‐ selective beta ‐ blockers for adults with cirrhosis and gastroesophageal varices. *Cochrane Database of Systematic Reviews* 2018; [PMID: 30372514 DOI: 10.1002/14651858.CD011510.pub2]

3. **Gimenez P**, Garcia ‐ Martinez I, Francés R, Gonzalez ‐ Navajas JM, Mauri M, Alfayate R, Almenara S, Miralles C, Palazon JM, Carnicer F. Treatment with non ‐ selective beta ‐ blockers affects the systemic inflammatory response to bacterial DNA in patients with cirrhosis. *Liver International* 2018; [PMID: 29802788 PMCID: PMC6282820 DOI: 10.1111/liv.13890]

4. **Goh ET**, Stokes CS, Sidhu SS, Vilstrup H, Gluud LL, Morgan MY. L ‐ ornithine L ‐ aspartate for prevention and treatment of hepatic encephalopathy in people with

cirrhosis. *Cochrane Database of Systematic Reviews* 2018; [PMID: 29762873 DOI: 10.1002/14651858.CD012410.pub2]

5. **Bai M**, Yang Z, Qi X, Fan D, Han G. l‐ornithine‐l‐aspartate for hepatic encephalopathy in patients with cirrhosis: A meta‐analysis of randomized controlled trials. *J Gastroenterol Hepatol* 2013; **28**: 783-792 [PMID: 23425108 DOI: 10.1111/jgh.12142]

6. **Sidhu SS**. L-ornithine L-aspartate in Overt Hepatic Encephalopathy (HEAL). 2018, 08.02.2017. ISRCTN number: NCT01722578.

7. **Gentile S**, Guarino G, Romano M, Alagia IA, Fierro M, Annunziata S, Magliano PL, Gravina AG, Torella R. A randomized controlled trial of acarbose in hepatic encephalopathy. *Clinical Gastroenterology and Hepatology* 2005; **3**: 184-191 [PMID: 15704053]

8. **Mullen KD**, Howard R. Is acarbose an effective drug for treating patients with cirrhosis and hepatic encephalopathy?. *Nature Reviews Gastroenterology & Hepatology* 2005; **2**: 264 [PMID: 16265229 DOI: 10.1038/ncpgasthep0194]

9. **Patel S**, Nguyen D, Rastogi A, Nguyen M, Nguyen MK. Treatment of cirrhosis-associated Hyponatremia with Midodrine and Octreotide. *Frontiers in medicine* 2017; **4**: 17 [PMID: 28352627 DOI: 10.3389/fmed.2017.00017]

10. **Freedman ND**, Everhart JE, Lindsay KL, Ghany MG, Curto TM, Shiffman ML, Lee WM, Lok AS, Di Bisceglie AM, Bonkovsky HL. Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. *Hepatology* 2009; 50: 1360-1369 [PMID: 19676128 PMCID: PMC2783828 DOI: 10.1002/hep.23162]

Furthermore, we have formatted our manuscript according to the BPG Format for Manuscript Revision guidelines.

Line 3:

"Manuscript NO: 45018"

Lines 23 – 26:

"Author contributions: DK and RN performed the literature search and wrote the first draft of the manuscript. BHM, PM, RF and AD provided critical review of the first draft and contributed to amendment of the text. All authors contributed to and approved the final submission."

Lines 40 – 46:

Lines 100 – 101:

Lines 115 – 117:

"Kockerling D, Nathwani R, Forlano R, Manousou P, Mullish BH, Dhar A. Current and future pharmacological therapies for managing cirrhosis and its complications. *World J Gastroenterol* 2019; In press"