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29th August 2022

Re: Resubmission of manuscript NO: 78849, entitled '*Gastrointestinal and liver disease in patients with schizophrenia: a narrative review*'

Dear Editors,

Thank you for the opportunity to revise our manuscript entitled '*Gastrointestinal and liver disease in patients with schizophrenia: a narrative review*'. The reviewers' comments are very much appreciated.

There follows a copy of the revised manuscript, in addition to a point-by-point response to the reviewers' comments.

Thank you again for your consideration of this manuscript.

Yours sincerely,

Rebecca Grant
Corresponding author

REVIEWER 1:

It may be worth mentioning few sentences on the role of acetyl cysteine in paracetamol Over Dose (OD) in schizophrenia. Some evidence for N acetyl cysteine as an adjunct in schizophrenia in addition to its role in paracetamol OD and now investigated with anti-suicidal properties.

Thank you for highlighting these interesting findings. An adaptation of the text kindly suggested by Reviewer 1 has been included in the paper and has been appropriately referenced, as follows:

'Interestingly, in addition to its role in treatment of paracetamol overdose, there is ongoing research into the reduction of negative symptoms and anti-suicidal properties of N-acetyl cysteine (NAC) in the treatment of schizophrenia. Chen et al^[40] identified two placebo-controlled, double-blind, randomised clinical trials of NAC in schizophrenia and reported that NAC may be efficacious in reducing the negative and general symptoms of schizophrenia. A meta-analysis by Zheng et al^[41], which included three randomised control trials with 307 (N-acetylcysteine: 153, placebo:154) participants, showed that NAC significantly improved total symptom scores in schizophrenia. Other related systematic reviews, including a Cochrane review on antioxidant treatment for schizophrenia, have also found NAC to be a promising add-on treatment for schizophrenia^[42].'

Suggest mentioning use of anticholinergic in treating hyper salivation, which may exacerbate clozapine induced constipation. Similarly due caution may be recommended for other drugs that induces constipation, prescribed along with clozapine.

We agree that these points are important to include, they have been added to the recommendations regarding clozapine induced constipation, as detailed below:

'Caution should be exercised in the prescription of anti-cholinergics for hypersalivation (a known side effect of clozapine) due to their potential to contribute to constipation; other regular medications with constipating side effects should also be kept under close review.'

Key recommendations may be put in a box and highlighted.

The key recommendations are included in Table 1 and the structure of the table has been adjusted.

REVIEWER 2

Indeed, there is a significant burden of gastrointestinal and liver disease amongst patients with schizophrenia. The authors presented a well-structured overview, based on current understanding on this actual problem. However, I strongly recommend that the authors consider the issue of the relationship between the gut microbiome and schizophrenia. This is very important, because currently there is a real promise in the use of pre/probiotics as auxiliary treatments in schizophrenia, aimed at improving side-effects of antipsychotics and complementing their action, particularly in terms of cognitive impairments.

Thank you for this helpful suggestion. An additional section on the gut microbiome and schizophrenia has been added to the text. It considers gut dysbiosis and the use of pre and probiotics, as follows:

'GUT MICROBIOME AND SCHIZOPHRENIA

In consideration of gastrointestinal disease in schizophrenia it is important lastly to acknowledge an emerging area of active research – the gut microbiome. The gut microbiome in humans comprises a diverse population of microbes, the most numerous of which are reported to be Bacteroidetes and Firmicutes^[97]. Factors such as diet, smoking and social circumstances have been suggested to influence the composition of an individual's developing microbiome. While each microbiome is unique, when the microbial composition differs significantly from controls, it is referred to as dysbiosis. Alterations in gut microbiota have been demonstrated to be implicated in several psychiatric illnesses, including depression, addiction and eating disorders. Evidence is now emerging regarding the potential role of gut dysbiosis in the aetiology of schizophrenia and the use of pre and probiotics in treatment pathways is being explored.

In 2020 Szeligowski et al^[98] performed a narrative review of research considering the differences in microbiome between healthy controls and patients with schizophrenia; six studies were identified. The authors reported only one consistent finding between the studies – that patients with schizophrenia had significantly elevated Lactobacilli, which also correlated with symptom severity. As Lactobacilli are typically thought to be beneficial for gut health, this finding was attributed to the existence of different subtypes. The authors conclude that different exclusion criteria, stage of illness and treatments make definitive conclusions regarding the role of dysbiosis in schizophrenia challenging and further larger scale prospective studies are required.

Pre and probiotics are also being investigated for their ability to reduce the effect of antipsychotic medications on the microbiome which can lead to potentially life- threatening constipation and significant weight gain. Results of small studies which have been reported in reviews of the literature^[98–101] are encouraging, for example co-administration of prebiotics to olanzapine treated rats led to attenuation of weight gain^[102]. As with the role of dysbiosis in the aetiology of schizophrenia, more detailed studies in human subjects are of course needed but early results do suggest this may be a promising area for future treatment.'