December 13, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6764-review.docx).

Title: Understanding irritable bowel syndrome: psychosocial perspectives (proposed new title: A cognitive behavioural approach to understanding irritable bowel syndrome)

Authors: Goran Hauser, Sanda Pletikosic, Mladenka Tkalcic

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6764

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

Reviewer 1

Major concerns:

1. a) The following paragraph was added on page 4, in order to define the aim of the review:
   "This review will address the biological and psychosocial factors which possibly contribute to the onset and perpetuation of IBS symptoms. In the first part of the review we will describe previous findings on different components of the cognitive behavioural therapy (CBT) model that are relevant for understanding IBS. In the second part of the review we will present a new model of IBS symptom perpetuation where attention to visceral sensation and different manifestations of anxiety have a central role."

   In order to clearly define the contribution of our proposed model, we added a paragraph on page 17:
   "Therefore, we propose the IBS symptom perpetuation model (Figure 2) attempting to explain the factors contributing to symptom maintenance. The novel aspect introduced by this model is the identification of key elements which drive the "vicious circle" of symptom exacerbation. These key elements (attention to visceral

sensation, trait anxiety, visceral anxiety and anxiety sensitivity) should be the target of psychosocial interventions."
We also changed the title of this section, in order to reflect its content more appropriately (From "Conclusion" to "The IBS symptom perpetuation model").

b) Considering the second reviewer proposed that we remove examples of "specific biopsychosocial models" we have accepted his/her proposal and thus we did not explain the potential shortcomings of the already existing models. We have, however, elaborated on the advantages and novel aspects of the model presented in our manuscript.

2. Statements which imply causality have been removed from the manuscript (pgs 8, 10, 12, 17). On page 7 we have removed the final sentence of the last paragraph (which contains the statement about neuroticism being undoubtedly established as a predisposing factor) because we feel this sentence does not contribute any additional information and because we would like to avoid overinterpretation of the presented data, as the reviewer suggested.

3. The abbreviations have been explained (IBD, HRQoL etc...)

Minor concerns:

1. The entire manuscript has been screened for the use of "processes" and "mechanisms". In some of the instances, when the terms were used loosely, we have replaced them with other descriptions. For example: pgs 7, 10, 12, etc…

2. The "s" was removed from the word „patients" (in the sentence „An individualised approach is necessary for each patients...") and we have elaborated on the „respective patient's status".

3. The first sentence of the introduction was reorganized in order to make it more clear (the intended meaning is: IBS is one of the most common disorders within the spectrum of FGIDs).

4. The first part of the sentence "There are a number of reasons…" on page 4, paragraph 5 has been changed in order to exclude the circular explanation "it validates the biopsychosocial approach".

5. With regard to the confusion about which model we are describing (the general CBT or our own), we have made some changes in the text. The text on page 4 refers to the general CBT model, which has been clarified in the second paragraph on page 5:

   "In Figure 1 we illustrate the core concepts of the CBT model of IBS. This model is based on the existing data on IBS patients and it incorporates various aspects of the disorder, which are already recognized as important by other researchers and presented in other articles."

   On page 17 we defined the novel aspects of our proposed model of IBS symptom perpetuation:

"Therefore, we propose the IBS symptom perpetuation model (Figure 2) attempting to explain the factors contributing to symptom maintenance. The novel aspect introduced by this model is the identification of key elements which drive the "vicious circle" of symptom exacerbation. These key elements (attention to visceral sensation, trait anxiety, visceral anxiety and anxiety sensitivity) should be the target of psychosocial interventions."

6. We added one sentence to explain the relation of gene polymorphisms to the topic discussed in this section:

   "Research has been focusing on the relations of various gene polymorphisms with IBS symptom manifestations."

7. "Conflicting data" was explained:

   on page 6: "This may be partly because of small sample sizes and ethnic heterogeneity within the cohorts studied."

   on page 13 part of the sentence ("Although the research has provided conflicting results, ") was deleted.

8. Polimorphism has been changed to polymorphism.

9. On page 7, the association was clarified: „a significant negative association"

10. The interpretations of findings for agreeableness and openness have been removed, to avoid overinterpreting the data.

11. Reference 54 is a book which contains reports from several studies regarding stressful life events in IBS patients, thus we feel it is relevant to cite it. Reference 55 is a study on a Chinese population, but we consider the findings relevant, especially because this research is recent. Cultural differences may exist, but since we are citing a finding about a reported higher number of stressful life events in the IBS population, compared to healthy people, we consider that cultural differences are not important in this context (it is not important which events are perceived as stressful, only that they are stressful).

12. Higher prevalence in comparison with the general population, it has been added to the text. (page 8)

13. We have removed the sentence which implies causality.

14. We added references regarding higher neuroticism [42-49] and lower extraversion [42,48] in IBS patients.

15. The sentence „IBS patients with comorbid psychiatric diagnoses report higher levels of anxiety, anxiety sensitivity and worry"connects the previous topics described (anxiety and depression) with the following paragraphs. We feel that this sentence adds to the fluency of that section.

16. We have added the word "brain" in the phrase "central brain control mechanism" in order to clarify this sentence. Since this refers to the biological background we think it is better not to describe it further, because that is not the primary focus of this review.

The paragraph following the one where "attention dependent alterations" are first mentioned explains this concept in detail.

17. Hypervigilance is the condition of maintaining an abnormal awareness of environmental or internal stimuli and is related to paying too much attention to disease symptoms or any sign of possible symptom generation. Hypervigilance also relates to selective attention to information that matches the patient's set of beliefs about his/her disorder. We omitted the word "hypervigilance" in the paragraph "Attention and perception" to avoid confusion with the meaning of the same concept mentioned in the paragraph Cognition.

18. We added a further explanation about the attributional styles of IBS patients: "Contrary to common opinion, they found that the normalising style was predominant among IBS patients specifically in those attending general practice compared to patients referred to hospital clinics. The latter usually have more severe symptoms and could be less likely to accept psychological or normalising explanations of their unexplained symptoms [98]."

19. We have described some of the interesting findings about the impact of IBS on cognition: "They assessed several cognitive domains including reversal learning and attentional flexibility, selective attention and response inhibition, working memory and visuospatial episodic memory. The results showed that patients with IBS exibit a deficit in visuospatial episodic memory functioning due to the negative impact of HPA axis dysregulation on hippocampal-mediated cognitive performance. The authors hypothesized that visuospatial memory impairment may be a common component of IBS."

20. The sentence "Such findings indicate microinflammation could be one of the underlying mechanisms at least in a subset of IBS patients." was deleted, as it was referring to the data presented in paragraph 1. Additional data was provided for IBS patients whose calprotectin levels correlated with HRQoL.

21. It is true that different results on HPA axis functioning in IBS are reported but we have provided a possible explanation in the third paragraph of this section:

    "However, although some studies report elevated basal plasma cortisol levels in patients with IBS compared to healthy persons[124], others show lower salivary and plasma cortisol levels[125] pointing to a decreased HPA axis reactivity[126]. A possible explanation for such contradictory results is the possibility that the type of hormonal dysregulation (reduced or elevated cortisol levels) depends on the predominant symptoms a patient is experiencing. It seems that functional pain symptoms are related to reduced cortisol secretion while depressive symptoms are related to elevated cortisol secretion[126]."

22. The findings supporting the role of female sex hormones in pain perception are more clearly related now. The text has been altered:

    "When rectal sensitivity is compared across the phases of the menstrual cycle, results indicate that women with IBS are more sensitive during menstruation, which is not the case in healthy women[131,132]. Nevertheless, upon repeated noxic stimuli (rectosygmoid distension) even healthy women show visceral sensitisation or heightened perceptual responses[124]. These findings indicate that there is a possible role of female sex hormones in increased pain perception."

23. We have explained what an integrative analysis means:

    "Because of such individual differences, related to the degree of predisposing and precipitating factors' contribution to symptom maintenance, an integrative analysis of psychological, biological and symptom measures should be performed for each patient as a part of a systematic clinical translational approach suggested by Hellhamer and Hellhamer[35]."

Reviewer 2

1. We have improved the organization of the manuscript (we added several paragraphs which contribute to the clarity and structure of the manuscript).

2. The following paragraph was added on page 4, in order to define the aim of the review:
   "This review will address the biological and psychosocial factors which possibly contribute to the onset and perpetuation of IBS symptoms. In the first part of the review we will describe previous findings on different components of the cognitive behavioural therapy (CBT) model that are relevant for understanding IBS. In the second part of the review we will present a new model of IBS symptom perpetuation where different manifestations of anxiety have a central role."

3. In accordance with the reviewer's suggestion, we propose the following title for our article:

   A cognitive behavioural approach to understanding irritable bowel syndrome

4. We searched MEDLINE, EMBASE, Science Citation Index Expanded, PsychInfo and Sciencedirect using the following keywords as a search strategy: irritable bowel syndrome (IBS), functional bowel disorder, personality in IBS patients, cognitive behavioural model of IBS, biopsychosocial model of functional bowel disorders, etc. The search was conducted until July 2013.

   We are not certain if the reviewer wanted us to add this description to the manuscript. Since this is not a meta-analysis, we are not sure where to place this text, so we kindly ask you to give us guidance.

5. We have removed the examples of specific biopsychosocial models on page 4.

Thank you for considering our manuscript for publication in your journal!

Sincerely,

Goran Hauser, Sanda Pletikosic and Mladenka Tkalcic