# Format for ANSWERING REVIEWERS

May 27, 2015

Dear Editor,

The authors wish to thank the reviewers for their suggestions.
Please find enclosed a point by point response to the reviewers (see below) as well as the revised manuscript in Word format (file name: 17359-review.doc).

**Title: The brain-gut-microbiota axis in Parkinson's disease**

**Authors**: Agata Mulak, Bruno Bonaz

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 17359

The manuscript has been amended according to the suggestions of the reviewers.

**First Reviewer** (3290373)
Comments to the Authors: "This is a very well written review in a new field of Knowledge. I have few points to address. 1) A couple of paragraphs about the possibilities fecal microbiota transplantation may enrich the discussion; 2) There is no doubt that brain-gut-microbiota axis interaction has an important role in the genesis of the disease, but it may be clear in the article and conclusion, that we do not exactly know what is the best probiotic or prebiotic, the better diet, or how to choose the appropriate donor for a microbiota transplantation."

Answer**:** Ad. 1) A new therapeutic approach based on the manipulation of the gut microbiota with probiotics, prebiotics, or even fecal microbiota transplantation is mentioned in the text on page 17. Only scarce reports on fecal microbiota transplantation in Parkinson's disease (PD) are available and have been cited [114]. However, there are not enough data to confirm the usefulness of fecal microbiota transplantation in PD at the present time.
Ad. 2) The additional sentence concerning a new therapeutic approach in PD based on the modification of the gut microbiota with probiotics, prebiotics, or even fecal microbiota transplantation was added to the conclusions.

**Second Reviewer** (3317125)
Comments to the Authors: "This is an interesting topic and gives a novel view for the pathogenesis of PD, but I have several points to refer: 1. In Page 3, the author state "the dysregulation may also significantly contribute to the pathogenesis of PD itself, supporting the hypothesis that the pathological process is spread from the gut to the brain [1]". Indeed, the reference did not mention the brain pathological lesion may origin from gut, the author may check it carefully. 2. To my knowledge, symptoms of lower GI tract were accompanied more frequently with PD, but it is said most enteric neurons were distributed in upper GI tract, how to explain this phenomenon? 3. As microbiota is associated with the pathogenesis of PD, advances of probiotics, prebiotics and fecal microbiota transplantation applied to PD therapy may be described in detail."

Answer**:** Ad. 1) The cited references have been modified. Ad. 2) The influence of the vagus nerve is most prominent in the upper GI tract (as mentioned on page 4) while the lower GI tract (left colon and rectum) is controlled by the pelvic nerves, however, the enteric nervous system (consisting of efferent neurons, afferent neurons, interneurons, and enteric glial cells) is distributed through the entire GI tract including the small intestine and large bowel. On the other hand, although in fact constipation is the most prominent GI dysfunction of PD, oro-pharyngeal dysfunction have been described with videofluoroscopy in more than 85% of PD cases (as mentioned on page 7).
Ad. 3) The role of the gut microbiota in the pathogenesis of PD has started to be recognized only recently. So far there are no solid data according to the evidence-based medicine to support potential therapeutic application of probiotics, prebiotics and fecal microbiota transplantation in PD. Some preliminary reports on favorable outcome of fecal microbiota transplantation in PD have been cited [114] on page 17. Hopefully, thanks to the dynamic progress in the field it would be an interesting subject of a review in the coming years.

Additionally, minor language polishing has been done.

Thank you again for the invitation to contribute to the *World Journal of Gastroenterology*.

Sincerely yours,

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