Author’s response to reviews

Title: Racecadotril in the treatment of acute diarrhea in children: a systematic, comprehensive review and meta-analysis of randomized controlled trials

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Author’s response to reviews:

Dear Editor,

Thank you for your mail dated 7/11/2017, the reviewer comments and your editorial decision regarding our manuscript #BPED-D-17-00566. We have carefully studied those comments and reply as follows.

Reviewer 1 (Morris Gordon)

“Having already reviewed this piece for another journal, I am familiar with it. It does not appear to have changed extensively since this review I completed in February 2017. My major concern is the mismatch between the title / goal and the actual work. The paper claims to be a comprehensive systematic review of RCTs and the abstract seems to suggest that this rigour is how they explain the huge number of studies that previous high quality systematic reviews (which I have published) and the in progress Cochrane review (which I am also authoring) have not identified all these trials. This is clearly not the reality - the section on RCTs is appropriate to some degree (although I note studies where there were significant concerns previously have been
included) - this raises the question of detailed quality assessment which is not fully addressed. The main issue is the bulk of papers which are not RCTs. Instead this is a comprehensive review of all research on Racecadotril. That is fine, but not what the authors state they will do. More importantly, the methods used to quality assess, analyse and synthesise such different works are diverse and complex and I see no evidence of these. Instead, this is a narrative review and should be rewritten and refocused as that. I think the authors need to decide if this is the direction they want to go and then recruit the appropriate epidemiological support in rewriting the paper, which would then be a valuable contribution to the literature.”

Dr. Gordon is a highly respected expert in the field of acute diarrhea in children. While he has made few specific points, unfortunately his apparently most important concerns are stated in a generalizing manner only. We will first address the specific concern and then comment on the more general ones.

The reviewer is correct that an earlier version of our manuscript was submitted to another journal in the past. However, he apparently has overlooked that we have now added formal meta-analysis for the 5 most frequently reported outcomes to the manuscript. In our view, addition of formal meta-analysis does constitute an extensive change.

The main concern of Dr. Gordon is that in his opinion “the bulk of papers which are not RCTs”. In his comments on the earlier version of the manuscript submitted elsewhere, he had noted he could not “find many of them”. This is exactly a reason why we see merit in our manuscript. Most of the trials we have identified (see Figure 1 of our manuscript showing our search results according to PRISMA criteria) do not come from classic databases such as PubMed or Scopus but from Google Scholar. The vast majority of them has been published in Chinese journals, and both PubMed and Scopus are notorious for not including many of the journals published in Mandarin. Whether this is scientifically justified or a sign of cultural bias, is a more general matter to be discussed at another time. Realizing that the lion share of disease burden of acute
diarrhea in children occurs in developing countries, including China, it had been our intention to avoid cultural bias in analyzing data on racecadotril in the treatment of acute diarrhea in children. After having realized that so many studies came from China, we had enlisted a Chinese coauthor who obtained PDFs of those papers and diligently extracted them with us. Thus, as outlined in our manuscript, we consider it a major strength of our manuscript that it is the first to analyze the exist literature without language bias. We are surprised that not ignoring Chinese literature still is the exception in todays global world.

If Dr. Gordon now comments that “the bulk of papers … are not RCTs”, we assume that he meanwhile had a chance to find and read those articles that he had not been aware of when reviewing an earlier version of our manuscript in February 2017. In contrast to Dr. Gordon, we consider the papers included in our analysis to be RCTs, as this had been a specific inclusion criterion of our search. We respect that Dr. Gordon may come to a different conclusion, in which case we would like to engage in a scientific debate on the matter. However, this is only possible if we understand which specific studies included by us are not considered RCTs by Dr. Gordon, and what the specific reason is in each case. To facilitate such discussion, we had contacted him directly on 13/11/2017 and offered to share with him PDFs of studies he may not have access to. He replied to us on the same day stating that he did not wish to engage in a direct dialogue with us and suggested to do so via the editorial office. Bypassing the editorial office had never been our intention, and to this effect our mail to Dr. Gordon had a cc to the editorial office. Nonetheless, based on Dr. Gordon’s reaction, we sent a similar mail to the editorial office on the same day requesting assistance in obtaining a more specific identification of studies he considers questionable. Unfortunately, we did not have a reply until now. We wish to reiterate that we will be more than happy to engage in a scientific debate whether some of the studies included in our manuscript may not qualify as RCT, but if the reviewer fails to identify which specific studies he is thinking of and for which reason, this becomes an impossible task. Therefore, we are unable to specifically address this comment from the reviewer more scientifically.
“The paper is generally well written. It is well structured and mentions important points as per the PRISMA guidelines. In a paper with such a large amount of varied information, it is imperative that the presentation is clear and concise to allow easy comprehension. The authors have achieved this with relative ease by introducing sub sections in each topic. The material is exhaustive including more than twice the number of studies than in previous reviews with studies in different languages also being considered. The authors must be commended on their efforts to get as much information as possible from the individual authors, in case of lack of readily available data. The tables and figures are well presented and easy to understand. Overall this paper can be published once the minor comments below are addressed:”

We thank Dr. Gharial for his appreciation of our study.

“Under the methods section, page 4 line 11-13, the authors give the search string used to identify the articles included in the study. On line 18 it is further stated that articles reporting studies in adults were excluded. However no mention is made of how the articles reporting studies in children are identified (as it is noted that this was not a term included in the search string). Were the searches filtered for studies in children on the search engine? Did the authors scan the abstracts manually and decide which ones were relevant to the study? Further elaboration would be useful. Furthermore the definition of age when selecting children needs to be clearly stated (under 18 years/ under 10 years). This of course, is provided the term 'children' was neither part of the search string nor filtered from the start. This data should also be represented in figure 1.”

Thank you for addressing this point. Our formal selection criterion had been for participants under the age of 18, but it turned out that within this group only studies were found that included children of up to 10 years of age. Actually, only the comparative trial against loperamide (contra-indicated in children under the age of 2 years) had used that age range, whereas all other identified trials only included children up to 6 years. The age range of included children is documented for each study in Table 1. Our screening process of the initial hits had three stages,
first based on titles, if that was ambiguous secondarily based on abstract, and finally, if abstracts also were ambiguous based on full text. These explanations have been implemented in the revised manuscript. The sentence on exclusion of studies on adult does not relate to a search criterion but is solely intended for clarification; to avoid confusion, we have deleted this sentence (a similar sentence had also been in the Introduction).

“Page 4 line 20-21: the authors state that ‘studies comparing treatments with a combination including Racecadotril with another treatment were excluded’. Kindly clarify this as there are studies that have multiple arms, some combining Racecadotril with probiotics, that have been included.”

There were few studies in which one treatment arm was a racecadotril + X combination, whereas the other treatment arm was Y. These were excluded because they do not allow direct conclusions on the efficacy and safety of racecadotril. In contrast, studies in which one treatment arm was a racecadotril + X combination and the other treatment arm was X alone were included and are referred to as “add-on studies” in our manuscript. This clarification has been added to the revised manuscript on page #4.

“Page 4, line 23-24: the authors state that 'non-randomised studies were not systematically considered but were included in some cases when providing relevant additional information'. Kindly expound on this and state what information (apart from patient stratification) was extracted from these non-randomised studies as well as how this was used in the result analysis.”

Non-randomized studies have not been included in any of the analyses presented in tables and figures. However, we used them in the discussion of the RCT findings; an example of this is the observational study of Chacon et al. from Venezuela documenting outcomes of treatment with racecadotril in 3,873 children (p. 10, p. 14 and Table 3). The corresponding part of the manuscript has been revised (p. 4).
“Information regarding data extraction is lacking, specifically who did the data extraction in English / Chinese and how was the extracted data verified to be correct before analysis. This information is provided in brief at the end of the article in the role of the authors section, however does need to be discussed in the paper.”

There already had been some information in this regard on p. 4 when describing languages used in the various papers. We have amended this information for clarification by stating “All data extractions from the manuscripts done by one of the authors were cross-checked by members of the Dept. of Pharmacology of the Johannes Gutenberg University (Mainz, Germany) as part of medical writing support.”

“The fixed model procedure used to carry out the meta-analysis generally tends to give a more optimistic evaluation of the results. However it requires the studies included to have a close homogeneity in order to be valid. No justification is provided as to why this method of analysis was selected. Considering the studies were of different designs (double blinded and open label add on) and included racially diverse populations, was this the best analysis to use?”

Dr. Gharial raises an interesting question. The way the CMA meta-analysis software works is to initially ask whether one assumes a common among-study variance component across subgroups; the option to select the random effects model is only given if that assumption is made. We had not chosen to do so, because we felt that it was more conservative not to assume a common among-study variance. On the other hand, Dr. Gharial is certainly correct that the random effect model is more conservative. When weighing the relative benefits of either option and the problem of post-hoc changes in analysis strategy, we would rather stay with the analysis originally performed. Pilot calculations indicate to us the choice of random vs. fixed effect model does not change our conclusions, which apparently are fairly robust based on a large number of studies.
“A mention is made of the overwhelming number of studies from China over the rest of the world (44 of 58 studies). This should be further emphasized in the results once stratified (for example in the open label add on trials they make up 34 of the 41 studies)”

The inclusion of so many studies from China is a strength and a weakness of our analyses, a weakness because studies from one country dominate the overall analyses, at least for the open-label studies (only 1 of the 44 Chinese studies was blinded). We have already discussed this point in the 2nd paragraph of section 6.1. Additional wording for emphasis has been introduced at the beginning of section 4.2.

While we regret that we are unable to address the concerns of reviewer 1 more specifically for the above-mentioned reasons, we believe that we have adequately addressed all comments of reviewer 2 by additional explanations and associated modifications to the manuscript. The technical comments from the editorial office (addition of all e-mail addresses to the title page) has also been addressed. However, we did not understand the second comment from the editorial office (addition of conclusions to body) as section 7 of our manuscript does exactly that.

Kind regards, also on behalf of all coauthors,

Marion Eberlin, PhD