

Peer Review File

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Reviewer A

Tetali and Suresh compiled treatment approaches for irritable bowel syndrome in a review. Included treatment approaches were pharmacological therapies, dietary management, probiotics, fecal microbiota transplant, behavioral therapies and complementary and alternative medicine.

IBS is a complex condition which needs integrated care. The review covers the area well but there are some issues which need to be addressed before it can be considered for publication.

INTRODUCTION

Comment 1: The text gives me the impression that IBS is a complex condition but today there are effective treatments for IBS and that there are individualized approaches to treatments. However, the pathophysiology of IBS is not well understood. There are no objective markers that can be used for IBS diagnosis and there are no accepted objective markers for response to any treatment in IBS. Even if there are many treatment options for IBS patients it is often difficult to find effective treatment strategies. The complexity of IBS treatment outcome should be highlighted.

Reply 1: We have revised the text to emphasize the unclear pathophysiology of IBS, the lack of standardized objective markers for response to treatment, and the possibility that it may still be difficult to find effective treatment strategies despite current options.

Changes in the text: In the introduction, we have added “The pathophysiology of IBS remains unclear with present theories encompassing a range of factors including irregularities in motility, visceral sensation, gut-brain interaction, gut dysbiosis, and psychosocial distress (4,5)” Later in the introduction, we added “Despite the numerous therapeutic options for IBS patients, it may still be difficult to find effective treatment strategies since there is still much to learn about this condition and objective markers for assessing treatment response are not yet standardized.” See page 3.

Comment 2: IBS has an important psychological factor. Theories of the etiology of IBS could briefly be presented.

Reply 2: Theories on the etiology of IBS are complex and cannot be discussed thoroughly in this paper without detracting from the main focus which is IBS management strategies. We briefly added broad categories of theories as noted in the response to comment 1 above and opted to forgo further detailed discussion.

Changes in the text: In the introduction, we have added “The pathophysiology of IBS remains unclear with present theories encompassing a range of factors including irregularities in motility, visceral sensation, gut-brain interaction, gut dysbiosis, and psychosocial distress (4,5)”. See page 3.

THERAPEUTICS AND MODALITIES

Comment 3: Page 4, line 87-91: Fiber is a treatment option in IBS-C. However, the description of fibers could be clarified. In addition of oatbran, barley and beans, the typical type of fibers could also be presented.

Betaglucan is associated with oat and barley and GOS is associated with beans. These and psyllium are presented to have laxative effects. But these fibers have different functions. Psyllium: viscous and not fermentable, betaglucan viscous and fermentable, GOS not viscous and does not have a water holding capacity but is highly fermentable. It is an important distinction since eg. psyllium is considered as a treatment in IBS and GOS is reduced in the low FODMAP diet. Similarly, type of insoluble fibers should briefly be described. Similarly, at line 91-95, specify type of fiber.

Reply 3: We have added all the above details.

Changes in the text: We have added, “Types of soluble fiber include psyllium, betaglucan and galacto-oligosaccharides (GOS) (10). Psyllium is often used for treatment in IBS since it is viscous and not fermentable. Betaglucan, found in oat bran and barley, is viscous and fermentable, and may lead to gas and flatus (10). Galacto-oligosaccharides (GOS), found in beans, is not viscous and does not have water holding capacity but is fermentable, and may also lead to gas and flatus (10). Common sources of insoluble fibers include wheat bran, cellulose found in whole grains and nuts, and lignin found in flax and rye (10). See page 5.

Page 11: ‘Dietary modifications.’

Comment 4: How were the selected diets chosen? The section lacks inclusion of common dietary strategies as a gluten free diet, traditional dietary advice in IBS and NICE guidelines. Also, it includes un-common treatment strategies, the text about kiwifruit consumption should be removed. If highlighting just one food many studies of different foods should be included.

Reply 4: Diets were chosen based on the search methodology and recommendations by the AGA and/or ACG. We did not initially discuss a gluten free diet based on the 2022 AGA Clinical Practice Update advising that although observational studies found that most patients with IBS improve with a gluten-free diet, randomized controlled trials have yielded mixed results. We will add this guidance to the manuscript. Additionally, we will remove the text regarding kiwifruit.

Changes in the text: We have added “Another common dietary approach for IBS treatment is a gluten free diet. While this approach has shown symptom improvement in observational studies, there have been mixed results in randomized controlled trials (23).” We have deleted the text about kiwifruit. See page 12.

Comment 5: Indeed, the low FODMAP is a common treatment strategy in IBS. It should be strengthened by more references. However, there are also major methodological challenges when evaluating the low FODMAP diet since studies mainly have been small and single blinded, therefore the quality of the evidence is low <https://pubmed.ncbi.nlm.nih.gov/30046155/>. Further major challenges with the evidence of FODMAPs in IBS are discussed in this text: <https://www.frontiersin.org/articles/10.3389/fmed.2023.1123576/full>. Lack of robust evidence should be highlighted in the text.

Reply 5: We have moved the references (6,19-22) to the correct location in the text. We have also highlighted the lack of robust evidence in the text.

Changes in the text: We have added “Notably, there have been significant methodological challenges in evaluating the low FODMAPs diet since most studies have been small and single-blinded, therefore yielding low quality of evidence.” See page 12.

Comment 6: Line 234. Refer to reference 14-17. All these do not indicate that individuals with more severe symptoms may experience more favorable outcomes by a low FODMAP diet. Please, specify the references more accurately.

Reply 6: We have edited the text to accurately refer to references 19 and 21. The references are numbered differently from before due to other additions to the paper.

Changes in the text: As above. See page 12.

Comment 7: Line 239-240. This sentence comes suddenly. If mentioning adherence to the low FODMAP diet there should be some introduction to that before this sentence.

Reply 7: We have removed this text since we do not discuss adherence to the low FODMAPs diet in detail in this manuscript.

Changes in the text: We have deleted “There is also data suggesting that the use of artificial intelligence dietary mobile apps can enhance adherence to the low FODMAPs diet (21).”

Page 12 (section Probiotics)

Comment 8: Line 255. It is stated ‘Pre-and probiotics’, but the section only covers probiotics. I suggest to remove ‘prebiotics’.

Reply 8: We have removed “prebiotics” from the text.

Changes in text: We have deleted “prebiotics”.

Comment 9: Yes, it is unclear what effect probiotics have on IBS. However, several systematic review and meta-analyses have concluded that multistrain probiotics have some effect, but there is a general lack of knowledge of which strain, or combinations, are most promising. Now the section ends by highlighting specific strains, which I suggest should be changed/include to highlight findings of multistrain probiotics.

Reply 9: We have added text and references as requested about the efficacy of multi-strain probiotics at the beginning of this section. We did not highlight specific multi-strain combinations since the studies identified selected different combinations.

Changes in the text: We have added “Multiple studies have concluded that multi-strain probiotics have some effect on IBS symptoms, but there is a general lack of knowledge of which strain, or combinations, are most promising (26,27).” See page 12.

Comment 10: Page 13 (‘Behavioral therapies’) line 283: should include several references

Reply 10: We have added references 41 and 42 which are a review paper and a systematic review and meta-analysis respectively. The meta-analysis refers to at least 20 published RCTs on CBT for IBS treatment.

Changes in the text: We have added references 41 and 42. See page 14.

Page 15 (‘Integrated care’).

Comment 11: Line 321: should include several references, it is a strong statement.

Reply 11: We have added references 54 and 55 which discusses how the combination of behavioral interventions, dietary modification, and medications for IBS treatment leads to better clinical outcomes and reduced cost per cure compared with traditional care.

Changes in the text: We have added references 54 and 55 to this statement. See page 15.

Comment 12: Line 324: Requires a reference

Reply 12: We have added reference 56 to this line. This study was previously referenced in the following sentence in the manuscript. It now appears in both places.

Changes in the text: We have added reference 56 to this line. See page 15.

Comment 13: It has been suggested that it is not possible to evaluate dietary interventions in IBS without considering mental disorders (<https://pubmed.ncbi.nlm.nih.gov/33587890/>), highlighting the complexity of IBS. Could be added to this section.

Reply 13: We have added the suggested text and reference to this section.

Changes in the text: We have added “In fact, it has been suggested that it is not possible to evaluate pharmaceutical or dietary interventions in IBS without considering mental disorders since any improvement in GI symptoms may influence mood (57).” See page 16.

Comment 14: Page 15 (‘Conclusion’): I suggest to add a sentence about the complexity of IBS and even if there are many treatment options, there is a great need of further research for a greater understanding of its pathophysiology to gain effective treatment options and personalized care.

Reply 14: We have modified the paragraph to highlight the complexity of IBS and the need for further research to better understand the disease.

Changes in the text: We have modified the first two sentences of the Conclusion to indicate IBS is a complex condition and this review focuses on current therapeutic options only. We have also added “Despite the many treatment options that are available, there is a great need for further research to gain a better understanding of the pathophysiology of IBS.” See page 16.

Comment 15: In general, the review limits their searches to year 2020-2022, but several of the included trials are from before 2020, as reference 42 and 45.

Reply 15: We reviewed references of identified studies to further identify relevant studies. We have clarified this in the methodology.

Changes in the text: We have added “The references of identified studies were examined to further identify relevant studies” to the Methods section. See page 4.

Reviewer B

In their narrative review, the authors provide a well-researched overview of currently available treatment options for IBS. They used the ACG guidelines from 2020, the AGA guidelines from 2022 and their own research in PubMed/Medline when inserting the keyword "irritable bowel syndrome".

The topic is currently very important, as an increasing proportion of the population suffers from this disease, at least temporarily. The pathophysiology is explained multifactorial, the treatment options are individually different and still limited. It is therefore important for healthcare professionals to have access to evidence-based reviews on the topic.

I highly appreciate the work the authors put into their research and wording.

The article is clearly structured and described, and most necessary studies have been cited.

But still, I have a few points I would like to add:

Comment 16: Introduction: Although the review is primarily concerned with treatment options, I would ask the authors to provide an overview of IBS, including information on its definition, diagnostic criteria and prevalence.

Reply 16: We have added text about definition/diagnostic criteria of IBS, prevalence, and healthcare costs. Changes in the text: See page 3. We have added "According to a 2020 nationwide cross-sectional study, the prevalence of IBS is estimated to be 6.1% in the United States, surpassing previous estimates (1). Beyond significantly impacting the quality of life for affected individuals, IBS imposes a substantial healthcare burden, with patients incurring an estimated annual direct cost ranging from \$742 to \$7547 (2). The diagnosis of irritable bowel syndrome (IBS) relies on the Rome criteria, which have undergone periodic updates, with the latest version being Rome IV. IBS is diagnosed when an individual consistently experiences abdominal pain, averaging at least one day per week over the past three months (3). This pain should be linked to two or more of the following factors: 1) related to defecation, 2) associated with a change in the frequency of stool, and 3) associated with a change in the form (appearance) of stool (3). These criteria must be met for the preceding three months, and the onset of symptoms should be at least six months before the diagnosis (3).

Comment 17: Methods: I would add the number of articles that were listed according to the search strategy used and information about how many articles were included.

Reply 17: We have added this information to Table 1: The search strategy summary.

Changes in the text: We have added "141 studies were listed according to the search strategy. 43 studies were included after review." See Table 1.

Comment 18: Please include a table summarizing all used studies, their sample size and the effect of the treatment.

Reply 18: While this is generally found in a systematic review, we believe this is not within the scope of a Narrative Review. As noted in the Author Instructions, "Through a narrative review, readers could gain more comprehensive and enlightening knowledge on a particular field. A narrative review is less methodologically demanding than a systematic review, as it does not require a search of all literature in a field, nor does it necessarily require a rigorous appraisal of the included literature." We have provided the search strategy summary as recommended.

Changes in the text: N/A

Comment 19: Summary: Please provide information about possible study limitations.

Reply 19: We have added a Limitations section at the end of the manuscript.

Changes in the text: We have added “While this review provides a comprehensive overview of therapeutic modalities for managing irritable bowel syndrome (IBS), there are several limitations that should be considered. The review mentions the difficulty in finding effective treatment strategies for IBS due to the lack of standardized objective markers for assessing treatment response. This limitation highlights a broader challenge in the field of IBS and emphasizes the need for more robust outcome measures in clinical trials. Additionally, the search strategy is based on a single key term ("irritable bowel syndrome") and the guidelines from two gastroenterological societies. This approach may result in the omission of studies that use different terminology or focus on IBS from diverse perspectives. Finally, the review excluded non-clinical studies, proof-of-concept articles with no patient enrollment, and studies on interventions that do not have prior data/validation. While this criterion aims to ensure high-quality evidence, it may lead to the exclusion of valuable information, especially in areas with limited research.” See page 16-17.

Comment 20: Some recent studies including studies of population-based cohorts studying IBS on a population level are missing.

Reply 20: We have added data from the most recent population level study performed in the United States in the Introduction. This study focuses on the prevalence and burden of illness of IBS in the United States in 2020.

Changes in the text: In the introduction, we added “According to a 2020 nationwide cross-sectional study, the prevalence of IBS is estimated to be 6.1% in the United States, surpassing previous estimates (1).” See page 3.

Comment 21: Please include a figure underlining the pathways where the different treatment options are targeting IBS.

Reply 21: We have added Figure 1 which outlines the evidence-based treatment options discussed in the paper.

Changes in the text: We have added Figure 1 in the Integrated Care section. See Figure 1.