

Dear Editor,

We would like to thank you and the reviewer for the time spent in evaluating our manuscript (Editorial) entitled: “**Adjunctive to insulin therapies in type 1 diabetes: the journey has just begun**”.

Taking into account the reviewer’s comments, we have revised the manuscript accordingly (changes made in the original text are highlighted in yellow). Please find below a rebuttal against each point raised, along with a list of submitted changes.

Thank you in advance for your time and consideration.

Sincerely yours,

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I have carefully read this new manuscript. My major questions are summarized below:
1) In the title, do the authors mean “Pharmacologic Adjunctive Therapy to Insulin ...”? Otherwise, there need to be sections added discussing weight loss & bariatric surgery and diet & activity programs.

Answer: Indeed, our manuscript focuses on pharmacologic adjunctive to insulin treatments in Type 1 Diabetes. We have revised the title of the paper, as follows: “Pharmacologic adjunctive to insulin therapies in type 1 diabetes: the journey has just begun”. Thank you for mentioning this.

2) In “Why is There a Need...”, can the authors add a description of the problems with the cost of and the availability of insulin for treatment of patients with Type 1 Diabetes?

Answer: Thank you for this comment. Indeed, insulin cost and availability may be significant barriers in treatment adherence for people with type 1 diabetes. We have added a relevant comment in the revised manuscript: “*There is data suggesting limitations in insulin availability and affordability in specific areas of the world, particularly for low-income patients^[13]. Reduction of insulin dose as a result of adjunctive therapies may prove helpful for those who consider insulin cost as a significant barrier to treatment adherence.*”. Furthermore, we have added a relevant reference (Li et al., Trop Med Int Health, 2019) in the updated reference list.

3) In “An Overview of Available Evidence”, can the authors summarize pertinent studies in a Table?

Answer: We have summarized the main advantages and pitfalls of the use of various therapeutic classes as adjunctive treatments in T1D in Table 1.

4) In “A Critical Appraisal of Relevant Studies”, can the authors summarize identified limitations in a Table?

Answer: We have summarized the main limitations of available evidence in Table 2.

5) It would be helpful if the authors had a Section more clearly labeled as “Future Clinical Research Studies”. This topic is the last sentence in the authors’ Abstract, but it is not clearly brought out in their present manuscript.

Answer: We have added in the revised manuscript a section entitled “Future Clinical Research Studies” in which we mainly focus on immunotherapy of which effectiveness and safety in T1D warrant further investigation by future research:

“Despite the initial enthusiasm for potential clinical implications of immunotherapy in T1D, research in the field has so far failed to prevent the onset or to reverse autoimmune diabetes^[35]. Stem cell therapies, immune ablation and standard immunosuppressants have been tested in several studies, nevertheless not being able to confirm the expectations derived from animal models, at least for the moment. Immune prevention strategies have tested low insulin doses and alternative administration routes (e.g. oral insulin) to prevent diabetes in individuals at high risk of T1D, still showed no remarkable benefit^[36]. Studies using non-antigen specific immunosuppressive drugs demonstrated encouraging results in prolonging remission of T1D; however, at a cost of toxicity and side effects^[37]. Leptin might prove useful in suppressing glucagon concentrations^[38], but clinical benefits of its use in T1D should be further evaluated by clinical trials. As a result, safety and efficacy of these treatments in T1D remain an area for forthcoming studies.” We have also added 4 new relevant references (35-38) in the updated reference list. Thank you for this comment.