

RESPONSE TO THE ISSUES RAISED BY THE REVIEWERS

April 10, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (Pharmacological Treatment of Obesity - review.doc).

Title: Anti-obesity drugs currently used and new compounds in clinical development

Author: Armindo Martins, Sandra Morgado, Manuel Morgado

Name of Journal: *World Journal of Meta-Analysis*

ESPS Manuscript NO: 9651

The authors would like to thank all the comments of the reviewers. All of them were considered valuable and have been incorporated into the revised version, which improved the quality of the manuscript. We hope that it is now accepted for publication.

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer 00506113

- (1) **Introduction should be shortened. I believe that the references about drugs that have been withdrawn from the market should be incorporated in a separate chapter.**

The authors consider that this is a pertinent recommendation and reorganized the manuscript, creating a separate chapter (Section 4) which incorporates the withdrawn drugs (*i.e.*, sibutramine and rimonabant). The authors also revised the Introduction, removing the references about the mentioned drugs.

- (2) **The chapters for sibutramine and CB1 antagonists should be removed since these drugs have been withdrawn. Few information about their action, reverse events and cause of withdrawal could be included in the aforementioned separate chapter.**

As mentioned above, the authors decided to include sibutramine and rimonabant in a separate chapter. With respect to the other CB1 antagonists (*i.e.*, taranabant and CP-945,398), the authors decided to remove the respective chapters, as their clinical trials were discontinued.

- (3) **Chapter 3.7 (Anorexigenic Gut Hormones) has also to be omitted since it confers information only about the physiologic action of the hormones.**

The authors agree with this recommendation and have removed this chapter. However, it was decided to maintain the first two paragraphs of the mentioned chapter, as they help to understand the section concerning the Glucagon-like Peptide-1 Receptor Agonists.

- (4) **"However, Contrave®, liraglutide and tesofensine have shown cardiovascular side effects in clinical trials, which led FDA not to approve them yet." Please provide a reference that liraglutide is not approved due to cardiovascular side effects. According to my knowledge**

GLP-1 antagonism has probably favourable actions to heart and vasculature.

This is a very pertinent comment. In fact, it was a mistake of ours to state that liraglutide has shown cardiovascular side effects. The authors would like to apologize for this fact and have corrected this sentence as it follows "However, Contrave® and tesofensine have shown cardiovascular side effects in clinical trials, which led FDA not to approve them yet". Liraglutide is currently approved by FDA to the T2DM treatment, not as an anti-obesity agent. However, it shows weight loss properties, also reducing lipid levels and cardiovascular risk biomarkers.

(5) Figure 3 Proportion of participants who lost at least 5%, 10% and 15% of baseline weight at week 56." (which study ?)

The study is indicated in reference 24, that is: Greenway, F. L., Fujioka, K., Plodkowski, R. A., Mudaliar, S., Guttadauria, M., Erickson, J., Kim, D. D. & Dunayevich, E. (2010). Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*, 376(9741), 595-605.

(6) Figures 4 and 5 are better to be omitted (for reasons I explained before).

In response to this recommendation, the authors have omitted Figure 4. However, the authors decided to maintain Figure 5 (now Figure 4), since they consider it important for a better understanding of the sections 3.5 and 3.6.

(7) Tables 1 and 2 could be merged (Drug/Placebo subtracted mean weight loss/ Mechanism of action/Other positive Effects/Adverse effects). Information about status can be added to Figure 6, since it has already some data about this.

Indeed, this is a very pertinent suggestion. The authors followed your recommendation and have merged Tables 1 and 2 into one only (Table 1). Furthermore, the authors have added information about status to previous Figure 6 (now Figure 5), considering this recommendation of great value.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Meta-Analysis*.

Sincerely yours,

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