

FORMAT OF ANSWERING REVIEWERS



July 16, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10771-review.doc).

Title: Is phosphodiesterase type 5 inhibitors effective for the management of lower urinary symptoms suggestive benign prostatic hyperplasia?

Author: Li Tao Zhang, Jong Kwan Park

Name of Journal: *World Journal of Nephrology*

ESPS Manuscript NO: 10771

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

1 Format has been updated.

Reply: yes.

2 Revision has been made according to the suggestions of the editors and reviewers.

From the Editor:

- (1) Please clarify the “Columns” of your manuscript according to the file of “ESPS-Columns scope note”.

Reply: we are to determine the Columns as Research reports.

- (2) A short running title of less than 6 words should be provided.

Reply: We added the running title ‘PDE5-Is on LUTS/BPH’.

- (3) Please offer the postcode.

Reply: The postcode has been added into the text.

- (4) Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, detail of address (to street or avenue), city, postcode, province, country, and email.

Reply: all have been done.

- (5) An informative, structured abstracts of no less than 246 words should accompany each paper. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim in the form: “To investigate/study/...; MATERIALS AND METHODS (no less than 80 words); RESULTS (no less than 120 words): You should present P values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 vs 3.61 ± 1.67 , $P < 0.001$; CONCLUSION (no more than 26 words).

Reply: Abstracts for original contributions should be structured according to the format.

- (6) The ref 38 is repeated with 28, the ref 43 is repeated with 36, please correct it.

Reply: the repeated ref have been amended.

- (1) In page 3 (lines 15-21), the sentences of " Although the mechanisms for improvements in LUTS with PDE5-Is have yet to be fully clarified, proposed contributors include inhibition of PDE5 iso-enzymes present in the bladder, prostate, urethra, and supporting vasculature and consequent increases in intracellular nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) concentration mediated inhibition of RhoA/Rho kinase signaling pathways, relaxation of the smooth muscle cells in these structures, improved blood perfusion, and reduced afferent signaling from the urogenital tract [26, 27, 28, 29]." should be revised in a more concise statement for the readers.

Reply: We deemed that these sentence didn't present grammar errors and might the reviewer was not accustomed to the long sentence structure. Therefore, we deny the revision about this question.

- (2) The authors stated "It points that the majority of well- designed longitudinal studies emphasized causality between LUTS and ED in this review." what's the points of this sentence? Please specify the so-called "causality" between LUTS and ED.

Reply: we amended misunderstanding giving rise to this sentence to " each with a variable amount of supporting data, have been proposed to explain the relationship between LUTS and ED in this review. These consist of altered NO levels, RhoA/Rho kinase activation, and pelvic atherosclerosis."

- (3) The authors stated "An recent abstract from a larger cross-sectional and multinational assessment of LUTS and sexual function was conducted [33].", please explain why a recent "abstract"

Reply: That is because the ref 'Hartung R, Emberton M, Van Moorselaar R, Harving N, Matzkin H, Alcaraz A, Elhilali M. Sexual dysfunction in 3,230 men with luts suggestive of BPH in Europe, Russia, Middle-East, Latin America and Asia. Eur Urol Suppl 2003; 2: 27 [DOI: 10.1016/S1569-9056(03)80106-9]' did not present full text link. But some good information was provided by the abstract, we cited it in our text.

- (4) [OR, 2.0, 95% CI (1.4...., what are the "OR" and "CI"

Reply: OR = odd ratio. CI = confidence interval.

- (5) A couple of clinical studies have addressed if the improvement of BPH symptoms is linked to improved ED symptoms, please add the references to identify a couple of clinical studies.

Reply: We add ref 9 and 34 to the end of the sentence.

- (6) The authors stated "Studies involved in PED5-Is monotherapy versus alpha blocker or combination of both were excluded." please explain why the authors excluded these studies?

Reply: The disconnection between subjective and objective efficacy is still not explained coherently, like this situation, if confound factor such as combination of treatment was considered, maybe it will

be easier to perplex the readers to correctly make a sound decision. In the context of it, we currently just get the PDE5-Is included in this study.

- (7) No significant difference of Qmax were observed between two groups ($P = 0.08$), indicating that other mechanisms of pathophysiology may be involved in the etiology of LUTS/BPH (Table 2)."
this statement is not appropriate and should be revised.

Reply: we deleted the inappropriate explanation of “indicating that other mechanisms of pathophysiology may be involved in the etiology of LUTS/BPH’ and made one sound explanation.

- (1) We know that LUTS and ED are associated but please specify the "causality" between LUTS and ED.

Reply: we amended misunderstanding giving rise to this sentence to “ each with a variable amount of supporting data, have been proposed to explain the relationship between LUTS and ED in this review. These consist of altered NO levels, RhoA/Rho kinase activation, and pelvic atherosclerosis.’

- (2) Please correct "tadanafil" in tadalafil. please correct "Dmochowaki" Dmochowski

Reply: all the wrong words have been amended.

- (3) Your aim is "To review the evidence of efficacy of phosphodiesterase type 5 (PDE5) inhibitor (PDE5-I) in lower urinary tract symptoms (LUTS) suggestive benign prostate hyperplasia (LUTS/BPH)". Why did you excluded the combination therapy with alpha-blocker.

Reply: The disconnection between subjective and objective efficacy is still not explained coherently, like this situation, if confound factor such as combination of treatment was considered, maybe it will be easier to perplex the readers to correctly make a sound decision. In the context of it, we currently just get the PDE5-Is included in this study.

- (4) Why did you excluded other PDE-5Is like UK-369003 by Tamimi et al., BJU Int 2010;106:674–80?

Reply:

- (5) Different papers are present in literature about this topic and these conclusions are known since 2012 (doi: 10.1016/j.eururo.2012.02.033. Epub 2012 Feb 25. Review.). Why did you not perform a meta-analysis of the data?

Reply: we made meta-analysis and but we did consider it to be added in this paper originally.

Now, we integrated all the data and calculated with Reviwer manager 5, then we extracted the data from the graph and made a Table 3.

3 References and typesetting were corrected

Reply: yes. All the references and typesetting were corrected.0

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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