

Format for ANSWERING REVIEWERS

June 09, 2013

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: Review PDE.doc).

Title: Phosphodiesterase inhibitors for treatment of voiding dysfunction: an overview of experimental and clinical evidence.

Author: Ricardo Reges, Rommel Prata Regadas, João Batista Gadelha Cerqueira, Lúcio Flávio Gonzaga-Silva

Name of Journal: World Journal of Clinical Urology

ESPS Manuscript NO: 10982

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

Reviewer 1 –

Title: Ok. Perhaps add "...voiding dysfunction in men: an overview of experimental and clinical evidence". **corrected**

Abstract: It doesn't reflect the content of the article and looks more like an introduction. I recommend to change it. **Abstract was completely reformulated.**

Text: Well developed; only small suggestions:

- a) Initial evidence: Please check the number of patients of the study cited in Reference 8, and the % of patients with LUTS + ED and those with LUTS without ED. **It was checked the % of patient with LUTS and DE according with severity and it was all set. It was also include the number of patients (1.274). See highlighted text in pp 3.**
- b) Begin of clinical use of phosphodiesterase...: Last 2 cited studies don't have reference. **corrected. see references 17 and 18**
- c) Experimental studies: From the 4 principal hypotheses proposed, the calcium-independent Rho-kinase activation pathway theory is not explained. **The followed paragraph was added in pp 9 section 4: "Rho-kinase/RhoA activation has been shown to mediate detumescence and maintain flaccidity. Rho kinase inhibits the regulatory subunit of myosin phosphatase within smooth muscle cells and maintains contractile tone under low-cytosolic calcium concentration. Upregulated Rho-Kinase activity has been reported in ED, as consequence inhibitors of Rho-Kinase have been search to treat ED." reference 34**

- d) Combination of phosphodiesterase inhibitors with alpha-blockers: 4th paragraph: Description of Reference 40: Correct: tadalafil 20 mg + tamsulosin 0,4 mg versus tadalafil 0,4 mg. **corrected**
- e) Check the use of abbreviations: use well established abbreviations; don't repeat description of them; if you have used "lower urinary tract symptoms" (LUTS) it doesn't mean that you don't have to describe LUT (lower urinary tract); cGKI not described. **revised**

Reference: Please follow the "instruction to authors" about abbreviation of the names of the journals (References 2, 3, 11, 13, 23, 24) and of initials of names of authors going after the family name., and: **corrected**

- a) References missing: see Text b).
- b) Incomplete citation: Reference 39. **corrected**
- c) References not directly related to the text: 1, 2, 20. **removed**

Tables: Few suggestions:

- a) Table 1: See Text a).
- b) Table 1 and 2. Summarize the text of "Major conclusions". **corrected**
- c) Table 2: 4th column: Participant (with capital letter). "Participants/Inclusion criteria": Put first the characteristics of the patients (age, symptoms, tests) and then the number of patients in each study arm. **corrected**

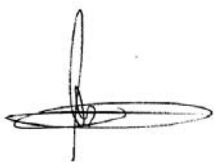
Reviewer 2

- English language to be reviewed. **Revised**
- Section N°3: Clinical randomized trials are not completely reported (a table would be of value here) and some references are missing throughout the text. Most important metanalises should be also mentioned. **The references 1-3 were include in manuscript, see pp 6 paragraphs 3,4, and 5; pp 7.**
- It would be of interest to note that the improvement in LUTS/BPH seems to be independent of ED alterations [4,5]. **It was mentioned in section 3 pp 7 the references 4,5 as recommended.**
- Evidence on the localization of PDE5 in the prostate and on the role of NO/cGMP signaling pathway should be reported [4,6,7]. **As recommended it was include the following sentence in pp 10, citing the references: The cornerstone of process seems to be cycle nucleotide monophosphates cycle adenosine monophosphate (cAMP) and cycle guanosine monophosphate (cGMP). Cycle nucleotides are synthesized from the corresponding nucleoside triphosphates by the activity of adenylyl and guanilyl cyclases. The soluble guanylyl cyclase (sGC) is a widely distributed signal transduction enzyme that, under activation by NO, converts GTP into the second messenger cGMP, which exerts its effect by activating cycle guanilyl kinase I (cGKI) and cycle guanilyl kinase II (cGKII), cGMP-gated ion**

channels, and/or cGMP-regulated phosphodiesterases (PDE). The accumulation of intracellular cGMP triggers a cascade, leading to decreased intracellular calcium level and subsequent relaxation of SMC.

1. The Efficacy of PDE5 Inhibitors Alone or in Combination with Alpha-Blockers for the Treatment of Erectile Dysfunction and Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia: A Systematic Review and Meta-Analysis. Yan H, Zong H, Cui Y, Li N, Zhang Y. J Sex Med. 2014 Mar 13.
2. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with α -blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Gacci M, Corona G, Salvi M, Vignozzi L, McVary KT, Kaplan SA, Roehrborn CG, Serni S, Mirone V, Carini M, Maggi M. Eur Urol. 2012 May;61(5):994-1003
3. Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia and on erectile dysfunction in sexually active men with both conditions: analyses of pooled data from four randomized, placebo-controlled tadalafil clinical studies. Porst H, Roehrborn CG, Seccombe RJ, Esler A, Viktrup L. J Sex Med. 2013 Aug;10(8):2044-52
4. Broderick GA, Brock GB, Roehrborn CG, Watts SD, Elion-Mboussa A, Viktrup L. Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia in men with or without erectile dysfunction. Urology 2010, 75: 1452-1457
5. Porst H, Kim ED, Casabé AR, Mirone V, Seccombe RJ, Xu L, Sundin DP, Viktrup L, LVHJ study team. Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial. Eur Urol 2011, 60: 1105-1113
6. Hedlund P. Nitric oxide/cGMP-mediated effects in the outflow region of the lower urinary tract—is there a basis for pharmacological targeting of cGMP? World J Urol 2005, 23: 362-367
7. Kedia GT, Ückert S, Jonas U, Kuczyk MA, Burchardt M. The nitric oxide pathway in the human prostate: clinical implications in men with lower urinary tract symptoms. World J Urol 2008, 26: 603-609

Thank you again for publishing our manuscript in the World Journal of Clinical Urology.



Dr. Ricardo Reges, M.D. Ph.D

Universidade Federal do Ceara
Division of Urology
[5753, Santos Dumont av.](#)
[Room 1204](#)
Fortaleza, Ceara [60175-047](#)
BRAZIL

Ph: [55-85-32623730](#)
Fax: [55-85-32623730](#)
Email: consultoriodeurologia@gmail.com; ricardoreges@me.com