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## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastrointestinal Pharmacology and Therapeutics

**ESPS manuscript NO:** 21596

**Title:** Electrical Stimulation Therapy of the Lower Esophageal Sphincter is Successful in Treating GERD in Proton Pump Inhibitors (PPI) Incomplete Responders

**Reviewer's code:** 00253974

**Reviewer's country:** Germany

**Science editor:** Jin-Xin Kong

**Date sent for review:** 2015-07-30 11:25

**Date reviewed:** 2015-08-20 20:13

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input checked="" type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

### COMMENTS TO AUTHORS

Regarding the thesis provided by this article we examined the recent data published in different journals, a.e. the study group published similar data in the beginning of this year. We can't determine significant new aspects or results. Furthermore, the examined group size, especially in the PPI-responding group is really low.



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Reviewer’s code: 00039422

Reviewer’s country: Italy

Science editor: Jin-Xin Kong

Date sent for review: 2015-07-30 11:25

Date reviewed: 2015-08-04 20:00

Table with 4 columns: CLASSIFICATION, LANGUAGE EVALUATION, SCIENTIFIC MISCONDUCT, CONCLUSION. It contains checkboxes for various evaluation criteria like Grade A, B, C, D, E, polishing, and search results for Google and BPG.

COMMENTS TO AUTHORS

This paper is concerning an interesting topic, i.e. alternative treatment to PPI for patients poorly responding to PPI. Obviously, as pointed by the authors, the paper has two limits: the very low number of patients in both arms (one arm include 7 patients), which strongly reduces its power, and the “open label” design. Likely more data should be elaborated in order to support the final conclusions. Generally speaking, EST cannot be considered a theoretical alternative to surgery. While surgical therapy is generally not recommended in patients who are complete non-responders to PPI therapy, as stated in the Discussion, nevertheless the barrier created by a fundoplication is valuable even for weakly acidic or non acidic reflux, hence being theoretically more effective than medical treatment. The same observations could be applied to EST, without a particular difference with traditional antireflux surgery. Accordingly, in the discussion I would not emphasize the limits of antireflux surgery in contraposition to EST: indeed, EST might be more an alternative to medical than to surgical treatment. EST was considered by the authors as an effective treatment also for non acidic reflux. Consequently, its efficacy would be much more supported by a pH Impedence test than by a

simple measurement of esophageal acid exposure. The barrier consequent to the EST would be confirmed more strongly. At least this issue should be mentioned in the Discussion. Actually, it would be of the utmost interest to evaluate the system in patients with a positive impedance for reflux and absent or weak acid reflux. A further limit of the technique is the presence of a hiatal hernia larger more than 3 cm, a finding which is not rare in patients with esophageal reflux, therefore limiting the indications of the procedure. Future studies might stimulate to consider EST also for patients with hiatal hernia, but the issue should be discussed more in detail. Esophageal acid exposure was evaluated during 24-hour pH-measurement and defined as pH < 4 for > 5% of total or > 3% of supine time. I would add De Meester score, as it was reported in the paper published by the same authors in *Surgery* in 2015 and included in the References. Although the technique has already been reported elsewhere by the authors (*Surgery* 2015; 157: 556-567), a more detailed description would be welcomed even in this paper, especially considering the presence of the related figures in the manuscript. The authors state that electrical stimulation can be optimized using the external programmer to tailor therapy to individual patients' needs. Is there any variation or any difference between the groups of responders and not responders to PPI? There has been any adjustment during time in the same patient? It would be nice to have the data of stimulation characteristics, especially in the long term follow-up. One patient quit the study for an elective Roux-en-Y gastric bypass surgery for uncontrolled Type 2 diabetes. Was the diabetes controlled when the patient was enrolled? At page 16, line 9 from below: eliminate "at" which is repeated twice. At page 17, line 4 from above: "are" is needed before the word "completely" Although 100% of responders to PPI were satisfied with their condition at one year, 30% of them are still taking PPI in spite of the EST; hence satisfaction could be consequent to medical treatment instead of EST efficacy. Moreover, the not responder group has overall better results than responder. Both issues need to be discussed. Apparently, at 24 months the outcome is less successful than at one year. Evaluation of long term results is obviously needed and this should be emphasized in the Discussion. At page 18, 2nd line from below: the first word should be "and" instead of "And". At page 20, first paragraph, the authors discuss about regurgitation, which is recognized as a true indication to antireflux surgery. However, according to the evaluation performed in the patient



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**Reviewer's code:** 00068404

**Reviewer's country:** China

**Science editor:** Jin-Xin Kong

**Date sent for review:** 2015-07-30 11:25

**Date reviewed:** 2015-08-19 22:00

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
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		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

**COMMENTS TO AUTHORS**

Thank you, I trust that you did a great job to do this clinical study. As a medical doctor, it seems we can do nothing to the refractory GERD. I think LES-EST will be another choice for us. About half a year ago, I read the paper "Long-term results of electrical stimulation of the lower esophageal sphincter for treatment of proximal GERD". I think this study was new and interesting. I still have 2 questions: 1. would you please tell us when this study started? Compared with the previous study, some patients joined both two studies? 2. I trust the stimulation parameter is important to the GI electrical stimulation, especially for the pulse width. Why do you choose the 215µsec ?