Peer Review File

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Reviewer A: Therapy versus on-demand sildenafil for erectile dysfunction: a prospective non-randomized study. This is a prospective non-randomized study comparing LI-EWST with on-demand sildenafil on ED patients. Sadly, the manuscript cannot be accepted in its current form.

Comment 1: The authors confused IIEF-5 with IIEF - Erectile function domain
IIEF-EF has 6 questions, and is the best option for this type of study. However, the authors used IIEF-5, but called it IIEF-EF in several sentences
Reply 1: Apology for typo in some tables and charts confusing IIEF-5 and IIEF-EF. We used IIEF-5 for the study from the beginning and what we were trying to express in the text was IIEF-5, but we did write IIEF-EF in some parts (most in figure1) and we have corrected them.
Changes in the text: page7 line111, page18 line358, page19 figure1&2

Comment 2: ED is not a chronic disease
Reply 2: Actually, we used the expression of “chronic” to indicate that patients may need long-term management and erectile dysfunction is related to several chronic conditions like diabetes mellitus and cardiovascular diseases.
Changes in the text: we deleted “chronic”. (page4line 54)

Comment 3: The correct term is psychogenic ED, not psychological ED
Reply 3: Apology for misuse of term.
Changes in the text: We have corrected several parts from psychological to psychogenic. (Page6 line98, page7 line104, page12 line231, page13 line255)

Comment 4: Several issues with english grammar
Reply 4: We have edited language by AME Editing Service.
Changes in the text: Several changes have been marked in text.

Comment 5: In the Inclusion criteria: What does "Significant changes of psychological evaluation" mean
Reply 5: We included several questionnaires in evaluation phase, for example, Hamilton Depression Rating Scale (HDRS), Hospital Anxiety and Depression Scale (HAD). Besides, we referred all our patients to psychological medicine department for evaluation. Gathering all the assessment outcomes and clinical impression, we

came to the conclusion of psychological factors contributing to disease.

Comment 6: The authors should be consistent with the punctuation they used to present decimals
Reply 6: We have adjusted punctuation to be consistent, which all used dot to present decimals.

Comment 7: The phrase "Elevating erectile function" should be replaced by Improving EF
Reply 7: Apology for misuse of verbs.
Changes in the text: We have replaced elevating by improving. (page11 line209)

Comment 8: Why is the age of participants so low. The age in the shockwave groups is statically higher than the sildenafil group
Reply 8: Our patients are relatively younger than general erectile dysfunction patients because we have enrolled large proportion of honeymoon impotence patients which is also the unique ED population in our clinic. Patients affected by honeymoon impotence have more complicated pathogenesis, which includes socioeconomic, culture backgrounds. This is why our patients consist of large proportion of psychogenic ED. Because the trial is non-randomized, there may be biases due to the selection process. The reason why age is higher in shockwave group may be that older patients may have underwent longer term of medication and they are more willing to try novel treatment. We have conducted adjustment for age by GLM model to eliminate the bias.
Change in the text: We further explained the age issue in text. (page13 line254)

Comment 9: In Table 2. All parameters analyzed at the 1-month evaluation are statically different between both groups. This important fact is not discussed in the manuscript. The authors say that both groups have similar results, however this is not not true at the 1-month evaluation
Reply 9: We briefly discussed the delayed efficacy of Li-ESWT (page11line216). Thank you for reminding us this important difference between the 1-month result. So, we added some content to discuss this point.
Change in the text: We further discussed the 1-month result. (Page11 line205-207)

Reviewer B: This is a non-randomized, prospective study comparing LiESWT to on-demand sildenafil use for treatment of ED. Great study overall looking at a novel comparison, supporting the use of LiESWT in patients who are PDE5i responsive.

Comments 1: Can you discuss how patients chose their treatment plan? Do you think there is bias by patient selection, please discuss this limitation of the non-randomized study.

Reply: Thank you for mentioning this issue. Actually, this was what we concerned at the beginning of this trial. Sildenafil was used for ED patients for a long time while Li-ESWT was still novel for ED. It was not easy to conduct a randomized trial in daily clinic settings while patients might face more challenges when they randomly entered one of the treatments. So, we decided to conduct a non-randomized trial in a real-world-study way, which could help us understand the exact effect of these two therapies in real-world settings. And it turned out that patients were willing to try novel therapies and in 100 patients included, more than a half chose to enter Li-ESWT group, which made the result comparable of two groups.

ED is a disease that may accompany patient for a long time, so we do educate patient in our clinic about ED pathogenesis, treatment, prognosis and consequently build up communicable environment between physicians, patients and sometimes their partners. After entering this trial, patients were told about the mechanisms and past data supporting both treatment and were encouraged to conduct intercourse during the trial. Then they made the decision whether to enter sildenafil group or Li-ESWT group based on their own considerations which might be variable for example, some patients preferred traditional treatment due to wide usage, and some patients preferred new treatment due to novel underlying mechanisms. Doctors were not involved in this process other than educating about the basic science and clinical use behind these two therapies.

Bias may exist here due to patient selection. As we could observe, age of patients entered Li-ESWT was older, and this may be because older patients had tried other treatment like sildenafil before, so they were more willing to try new therapies. This information was also collected before treatment, which showed that among 46 patients in Li-ESWT group, 15.2% had had PDE5i pills before, while 12.5% in sildenafil group had before.

Change in the text: More discussion of this selection process and bias concern. (page13 line268)

Comments 2: Can you discuss how often patients used on-demand PDE5i during the study period?

Reply 2: Thank you so much for pointing out this problem. We did collect dosage information, but we didn't mention it in this version of manuscript because we considered that this trial was intended to assess the practical effect of on-demand

sildenafil, of which the dosage was variable among different patients. The protocol of Li-ESWT was strictly followed by patients while sildenafil dosage was self-reported. After reminded, we did notice the importance of dosage information here in this article. So, we added the information to make things clearer.
Change in the text: We added necessary data at page9 line161.

Comments 3: Could patients use on demand PDE5i while getting LiESWT treatment
Reply 3: In our trial, patients can't use on-demand PDE5i while getting Li-ESWT treatment. However, patients with ED were encouraged to undergo multi-modality treatment in our clinic if they were not in this trial setting.
Change in the text: More detail added at Page8 line163.

Comments 4: Were LiESWT patients encouraged to have intercourse as often as those in the PDE5i group?
Reply 4: Patients in both groups were encouraged to have intercourse during the trial. The intercourse frequency was not documented in Li-ESWT group while we could infer the intercourse frequency of patients in sildenafil group by their dosage frequency. So, we could not say that patients in Li-ESWT group had the same frequency of intercourse as patients in sildenafil group. However, they were both encouraged.
More detail added at Page8 line169.

Comments 5: Multiple LiESWT meta-analyses have been done and should be referenced to support the use (?intro)
Reply 5: Thank you for mention this. We added some new literatures in new version of manuscript.
Change in the text: Meta-analyses and systemic review results of both basic experiments and human trials were added in the introduction part. (see at Page4 line82 and page5 line94)

Comments 6: You report LiESWT as "long-term" benefit, but you only have 3-month follow-up data - I would not consider this long-term and should be revised.
Reply 6: Thank you for your question. 3-month could not be defined as long-term in ED treatment given that ED patients always receive treatment for a long period of time. Here, we presented this result as differentiation between Li-ESWT and sildenafil because it seemed sildenafil improved erectile condition more rapidly than Li-ESWT. On the other hand, Li-ESWT showed a latency of efficacy for ED. So, we changed this expression of long-term benefit.

Change in the text: several changes in page13 line261-274.

Comments 7: The discussion focuses on patient-reported improvement outcomes and confidence. Do you have results from your study to support that? Otherwise, please reference.
Reply 7: Thank you for pointing this out. New references have been added.
Change in the text: Page13 line278

Comments 8: Please contrast psychogenic ED to vascular/organic/mixed? Did these patients have equal outcomes?
Reply 8: we have considered to include this part of data to enrich the result. But we decided not to because the limited number of each proportion. The total number of patients underwent Li-ESWT in this trial is 46, psychogenic, organic and mixed patients accounted for 12, 17, 17 respectively, which made it hard to compare horizontally. However, we did observe parallel improvement by main parameters. Maybe in the future, we can conduct Li-ESWT trial or observance on specific ED population.

Comments 9: Can you expand on this: "Other factors such as severity and duration of ED, comorbidities, lifestyle, and relationship influenced not only the compliance but also the outcome of treatment.
Reply 9: Thank you for your suggestion. In treatment of ED patients, we realized that ED treatment was a long-term process, which needed efforts from every aspect, including physicians, patients and their partners. We tried to involve patients and their partner in the treatment process to improve the outcome. Given the fact that our patients were relatively younger than the general ED population, they were more likely to have burdensome jobs to fulfil, stay up late in the evening, heavy smoking and drinking, which might influence the erectile function and success of sexual intercourse.
Change in the text: Discuss more of this point in the text. (Page14 line304)

Comments 10:
Results:
Discussion:
Style:
- please organize your acronyms so that they appear the first time you use the word (ex: erectile dysfunction = ED, sentence 1)
Reply 10: thank you for mention this, we have corrected this.

Change in the text: multiple sites (Page4line50, page4line67)

Comments 11: Would benefit from an English langue and grammar review
Reply 11: We have edited language by AME Editing Service.
Changes in the text: Several changes have been marked in text.

Reviewer C: Authors are commended for their work in clarifying the efficacy of LIST. However, some limitation of the paper itself limit its reliability and interpretation. In particular:

Comments 1: Why patients were not randomized?
Reply 1: Thank you for mentioning this issue. Actually, this was what we concerned at the beginning of this trial. Sildenafil was used for ED patients for a long time while Li-ESWT was still novel for ED. It was not easy to conduct a randomized trial in daily clinic settings while patients might face more challenges when they randomly entered one of the treatments. So, we decided to conduct a non-randomized trial in a real-world-study way, which could help us understand the exact effect of these two therapies in real-world settings. And it turned out that patients were willing to try novel therapies and in 100 patients included, more than a half chose to enter Li-ESWT group, which made the result comparable of two groups.

Comments 2: Since randomization is lacking, baseline variables are different and this may negative impact final results.
Reply 2: Age of two groups were different, and patients in Li-ESWT were younger than patients in sildenafil group. Further analysis was all adjusted for age by GLM model to minimize the bias brought by age difference.
Change in the text: more discussion of this selection process and bias concern. (page13line268)

Comments 3: Authors should use mean change after follow-up
Reply 3: Thank you for mentioning this parameter. We did different analysis to support the similar outcomes by these parameters, including proportion of improvement, definite value before and after treatment, improvement levels. We were concerned that mean change after follow-up was redundant given all other data suggested the similar facts.

Comments 4: How treatment were allocated? based on which choice?
Reply 4: This is a great issue. ED is a disease that may accompany patient for a long

time, so we do educate patient in our clinic about ED pathogenesis, treatment, prognosis and consequently build up communicable environment between physicians, patients and sometimes their partners. After entering this trial, patients were told about the mechanisms and past data supporting both treatment and were encouraged to conduct intercourse during the trial. Then they made the decision whether to enter sildenafil group or Li-ESWT group based on their own considerations which might be variable for example, some patients preferred traditional treatment due to wide usage, and some patients preferred new treatment due to novel underlying mechanisms. Doctors were not involved in this process other than educating about the basic science and clinical use behind these two therapies.

Comments 5: Which is the sample size calculation?
Reply 5: We didn't mention sample size calculation in this version of manuscript.
Change in the text: sample size calculation was added in Materials and Methods. (Page8line199)

Comments 6: Which was the primary endpoint of the study in terms of evaluation of efficacy of treatment?
Reply 6: IIEF-5 score at third month was the primary end point of this study, with IIEF-5/EHS/SEAR score at first month, EHS/SEAR at third month, improvement proportion measured by IIEF-5/EHS/SEAR, clinical cure proportion and improvement measured by MCID criteria were secondary endpoints.

Comments 7: It would be interesting to add more information like doppler ultrasound or partner's satisfaction.
Reply 7: Thank you for your suggestion. We did value the satisfaction of partner; however, we didn't include partner's questionnaire when we conducted the trial given that not all partners have participated in this process. We are conducting another study to figure out the improvement of partners and patients by EDITS.

Reviewer D: The authors present an original work comparing the efficacy and safety of low-intensity extracoporeal shock wave therapy with on-demand sildenafil for erectile dysfunction.

Comments 1: In line 109, where it is written "Erectile hardness score", it should be "Erection hardness score".
Reply 1 & change in the text: we have corrected this typo. (page7line111)

Comments 2: In Interventions section, regarding author´s protocol, there are some methodology flaws, namely, authors state that patients were assessed at first and third month after the beginning of the treatment, so, if the Li-ESWT group were treated with 2 session/week during 3 weeks and then a 3-week interval followed by another period of 3-week treatment, the first follow-up in this group was still during treatment and not after treatment. In this setting, patients were evaluated before achieving the theoretical benefit from Li-ESWT.
Reply 2: Actually, this was one important point we considered during designing the study. At first month, patients in Li-ESWT group were undergoing the second session of treatment and this assessment was done during their therapy clinic. This could explain the significant difference between IIEF-5/EHS/SEAR at first month to some extent because patients hadn't achieved theoretical benefit from Li-ESWT.
Change in the text: Further discussed this point in discussion part. (page11line209)

Comments 3: Also, in the sildenafil group, patients should be tailored by the frequency of medication take (ex.: pills/week).
Both groups are not comparable if there is no strict protocol, namely controlling the "dosage" of each treatment.
At three months, results show a better "recovery" in patients from the Li-ESWT group, compared with the sildenafil group. Again, the dosage of sildenafil within these time frame was not controlled, namely if these patients maintained the same frequency of pills take as in the first month.
Reply 3: Thank you so much for pointing out this problem. We did collect dosage information, but we didn't mention it in this version of manuscript because we considered that this trial was intended to assess the practical effect of on-demand sildenafil, of which the dosage was variable among different patients. The protocol of Li-ESWT was strictly followed by patients while sildenafil dosage was self-reported. After reminded, we did notice the importance of dosage information here in this article. So we added the information to make things more clear.
Change in the text: Added the necessary data at page9line161.

Comments 4: In table 1, patients from the two groups are not the same, namely, in the Li-ESWT group there are more patients with moderate to severe ED and less patients with mild to moderate ED, compared to the sildenafil group, showing that these patients had worse erectile function.
To sum up, regarding author´s protocol, both groups are not comparable and no conclusion can be withdrawn.
Reply 4: Due to the small population of our samples, we have included patients of

different severity. It seems that patients of mild to moderate disease were more likely to undergo sildenafil treatment. However, when we use chi-squared tests and independent sample t tests to examine severity of parameters like EHS, we didn't observe significant difference between two group.

Change in the text: Extra examinations were added in Table 1(Page20)