Peer Review File

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Review Comments A

Comment 1:

It is not clear how many sexually active patients were there in the selected studies and if there was sufficient power to assess differences in the sexual function domain?

Reply 1:

We agree with the reviewer and thank the reviewer for this great point. We apologize to you for the unclear statement. Since there is only one RCT [1] we included that explains the number of sexually active patients. So we did not discuss the sexual activity of patients we included, which may cause a bias in the evaluation of differences in the sexual function domain. As your suggestion, we have described the section of the number of sexually active patients. We will continue to pay attention to this issue in future research. We thank the reviewer again for this suggestion to make our study more logical. The manuscript was corrected as follows: (Please see Page 15, Line 325-330)

1. Bhattar R, Tomar V, Yadav SS et al. Comparison of safety and efficacy of silodosin,

solifenacin, tadalafil and their combinations in the treatment of double-J stent- related lower urinary system symptoms: A prospective randomized trial. Turkish journal of urology 2018;44:228-38. doi: 10.5152/tud.2018.50328.

Changes in the text:

"Some limitations of this study should be noted. Firstly, Bhattar R et al. took sexual activity as the inclusion index of patients who participated in their study, with 352 patients being included [25]. However, other RCTs included in our meta-analysis did not specify the sexual activity of the included patients, and therefore, limitations may exist in our conclusions regarding the improvement in sexual function with PDE5 inhibitor therapy.**"**

Comment 2:

There is no single score for the additional health domain. How was the analyses performed? Were there any particular questions in this domain that showed significant differences?

Reply 2:

We thank the reviewer for this suggestion. We apologize to you for the unclear statement again. As your suggestion, we have carefully reviewed the included RCTs again, focusing on the single score for the additional health domain. The 4 RCTs did not show the single score of the additional health domain but the additional health was

generally analyzed as an indicator. So in our meta-analysis, we did not analyze the differences in the additional health domain. We will continue to focus the latest RCTs to resolve this question. We thank the reviewers again for this valuable suggestion. (Please see Page 15-16, Line 330-333)

Changes in the text:

"Also, while additional health was chosen as an indicator for assessing stent-related symptoms in our study, none of the included RCTs reported the single score for the additional health domain. To address this, we will continue to focus on future research on the most recent RCTs.**"**

Comment 3:

More interpretative details need to be provided in the results section describing differences for each domain.

Reply 3:

We agree with the reviewer and thank the reviewer for this great point and suggestion. Based on your suggestion, we have added the corresponding content in the results section to describing differences for each domain. We thank the reviewers again for this suggestion to make this paper a better one according to reviewer's suggestion. The manuscript was corrected as follows: (Please see Page 8-12, Line 155-244)

Changes in the text:

"Urinary symptoms score

Two of the four RCTs included in our meta-analysis reported changes in urinary symptoms scores from 186 patients (94 treated with PDE5 inhibitors and 92 given a placebo) (Figure 2A). The MD was used to compare effect measures between the PDE5 inhibitors groups and the placebo groups. Since P>0.05, a fixed-effects model was used to analyze the results of these two RCTs and revealed that MD was -2.81, 95CI% was -3.72 to -1.90, I^2 was 13%, and Chi-square (Chi^2) was 1.15 (P<0.00001). Based on these results, we concluded that PDE5 inhibitors improved urinary symptoms scores at the 1-week treatment stage.

Body pain score

Two RCTs reported body pain scores of 186 patients after 1 week of ureteral stenting (Figure 2B). Since P>0.05, we used a fixed-effects model and concluded that PDE5 inhibitors produce little relief in body pain at 1-week (MD= 0.43, 95%CI: -0.40 to 1.26, I^2 =70%, Chi^2=1.15, P=0.31).

Sexual health score

Two RCTs reported changes in sexual health scores from 186 patients (Figure 2C). Since P>0.05, a fixed-effects model was used to evaluate the results, which showed that MD was -0.57, 95%CI was -1.13 to -0.01, I^2 was 54%, and Chi^2 was 2.17 (P=0.04). Thus, patients experienced improved sexual health following treatment with PDE5 inhibitors for 1 week.

General health score

Since P<0.05, a random-effects model was used to analyze the general health scores for two RCTs. Results showed a MD of -0.82 (95%CI: -4.35 to 2.71, I^2 =91%, Chi^2=10.58, P=0.65) (Figure 2D). We suggest that the effect of PDE5 inhibitors on general health was similar to that of placebo after 1 week of treatment.

Work performance score

Since P<0.05, we utilized a random-effects model to study the effect of PDE5 inhibitors on work performance from two RCTs (Figure 2E). The pooled estimate of MD was −0.16, 95 %CI was −1.75 to 1.42, I^2 was 76%, and Chi^2 was 4.18 (P=0.84). The results revealed that therapy with PDE5 inhibitors exhibited similar effects on work performance as a placebo after 1 week of treatment.

Additional health score

Two RCTs involving 186 patients reported the efficacy indices of PDE5 inhibitors on the additional health score (Figure 2F). Since P<0.05, we utilized a random-effects model to analyze the data. We did not find any statistically significant relationship between the two groups on additional health after 1 week of treatment with PDE5 inhibitors (MD= -2.25, 95%CI: -4.91 to 0.42, I^2 =94%, Chi^2=18.06, P=0.10).

Results after 3 weeks of treatment with PDE5 inhibitors

Urinary symptoms score

Four RCTs involving 352 patients (179 treated with PDE5 inhibitors and 173 given a placebo) recorded the changes in urinary symptoms scores after 3 weeks of treatment (Figure 3A). Since P<0.05, we employed a random-effects model, which reflected a

MD of -11.94 (95CI%: -22.58 to -1.3, I^2 =99%, Chi^2=466.83, P= 0.03). The results suggest that PDE5 inhibitors showed a greater reduction in the urinary symptoms scores compared with a placebo.

Body pain score

Four RCTs involving 352 patients reported changes in body pain scores (Figure 3B). Since P<0.05, a random-effects model was used. Results showed a reduction in body pain in the PDE5 inhibitors group compared to the placebo group after 3 weeks of treatment. (MD= -5.38, 95%CI= -9.35 to -1.41, I^2 =95%, Chi^2=65.81, P=0.008).

Sexual health score

Four RCTs involving 352 patients reported the differences in sexual health scores (Figure 3C). Heterogeneity was found in the trials (P=0.004, I^2=78%), and since P<0.05, we used a random-effects model to analyze the data. Based on the results, therapy with PDE5 inhibitors was shown to improve the sexual health of patients with ureteral stents. The results of integrative data analysis indicated that MD was -4.13, 95%CI was -5.07 to -3.19, and Chi^2 was 13.35 (P<0.00001).

General health score

Four RCTs involving 352 patients were used to analyze general health scores (Figure 3D). Since P<0.05, a random-effects model was employed, and showed a MD of -3.92 (95%CI: -5.76 to -2.08, I^2 =88%, Chi^2=24.61, P<0.0001). From these results, we concluded that PDE5 inhibitors had a significant benefit on general health scores after 3 weeks of treatment.

Work performance score

Four RCTs analyzed the changes in work performance scores of 352 patients (Figure 3E). Since P<0.05, we performed a random-effects model analysis that showed MD was -2.25, 95%CI was -5.13 to 0.62, I^2 was 95%, and Chi^2 was 57.80 (P=0.12). These results reflect no significant effect on work performance after 3 weeks of therapy with PDE5 inhibitors.

Additional health score

Three RCTs reported the additional health score data of 258 patients (Figure 3F). Since P<0.05, the RCTs were assessed using a random-effects model. The MD was -2.21, 95%CI was -4.03 to -0.40, I^2 was 89%, and Chi^2 was 18.54 (P=0.02), indicating a significantly greater reduction in the additional health scores after 3 weeks of treatment with PDE5 inhibitors.

Safety

Gastrointestinal complications

Two RCTs, including 166 patients (85 treated with PDE5 inhibitors and 81 given a placebo), documented the risk of gastrointestinal complications (Figure 4A). Since P>0.05, we utilized a fixed-effects model. The OR was 1.25, 95%CI was 0.51 to 3.04, I^2 was 0%, and Chi^2 was 0.30 (P=0.63), indicating no significant differences in the incidence of gastrointestinal complications between the two groups after 3 weeks.

Respiratory complications

Two RCTs analyzed the incidence of respiratory complications of 166 patients after 3 weeks of treatment with PDE5 inhibitors (Figure 4B). Since P>0.05, we used a

fixed-effects model. The OR was 1.48, 95%CI was 0.50 to 4.44, I^2 was 0%, and Chi^2 was 0.20 (P=0.48), indicating that there was no significant difference in the incidence of respiratory complications between the PDE5 inhibitors group and the placebo group after 3 weeks.”

Comment 4:

All the references need to be revised to include author names (not just initials).

Reply 4:

We are sorry for our nonstandard references styles. We have corrected carefully all references styles according to reviewer’s suggestion. Thank you for your insightful advice again. (Please see Page 18-23, Line 378-503)

Comment 5:

Need grammatical corrections.

Reply 5:

We are sorry for our poor expression in English, and we have tried our best to revise the manuscript by AME Editing Service, and we hope it will meet the criteria to publish.

Review Comments B

Comment 1:

The authors present a necessary meta analysis on the effect of PDE 5 inhibitors on stent related symptoms.

Reply 1:

Thank you for spending time in reviewing our manuscript. Your comments will help us to make our analysis more logical. We have tried best to revise the manuscript, and we hope it will meet the criteria to publish.

Comment 2:

The paper reveals important facts on an interesting topic and is well written, nevertheless the grammar needs a closer look and small modifications, that can easily be done.

Reply 2:

We are sorry for our poor expression in English, and we have tried our best to revise the manuscript by AME Editing Service, and we hope it will meet the criteria to publish.

EDITORIAL CERTIFICATE

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the manuscript listed below was edited for proper English language, grammar,
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Comment 3:

But there are some small things, that need to be mentioned. First of all, in the studies included in this meta analysis Tadalafil and placebo and sildenafil and placebo are compared, respectively. In the forrest plots, Sildenafil seems to show better results than Tadalafil, maybe this could be commented in the discussion.

Reply 3:

We agree with the reviewer and thank the reviewer for this great point. We apologize to you for the unclear statement. According to your suggestion, we carefully reviewed the RCTs we included. Regrettably, we did not find that Sildenafil show better results than Tadalafil. There is no significant difference between Sildenafil and Tadalafil in terms of urinary symptoms scores, body pain scores, and general health scores. Because of the limited number of RCTs met our inclusion criteria, our meta-analysis have therefore combined the Sildenafil and Tadalafil into one group and did not analyze the difference between Sildenafil and Tadalafil on relieving stent related symptoms. We have added the corresponding content in the discussion section. In the following work, we will continue to focus this issue in future research. Thank you for your insightful suggestion again. (Please see Page 16, Line 343-346)

Changes in the text:

"Furthermore, due to the limitations of the included RCTs, different PDE5 inhibitors (Tadalafil and Sildenafil) could not be grouped in our study, which may also lead to a bias in the results. In the future, we will continue to focus on high-quality related

studies (especially RCTs), which will allow for more robust conclusions to be drawn."

Comment 4:

Also, different sizes of stents were used (4.8 up to 8.5F). In 2019, Nestler et al showed significant differences in stent related symptoms according to the diameter. This should be mentioned in the discussion as well as potential bias.

Reply 4:

We agree with the reviewer and thank the reviewer for this great point. We apologize to you for our ambiguous describing again. As your suggestions, we have carefully reviewed the included RCTs again. Besides, we studied Nestler et al's article[1] regarding the effect of size of stents on stent related symptoms. Now, we have emphasized the influence of size of ureteral stents on stent-related symptoms. Accordingly, we added the following sentences to the discussion to explain this limitation. We will continue to pay attention to the latest RCTs and further analyze the differences. We appreciate the reviewer's positive comments again. The manuscript was corrected as follows: (Please see Page 16, Line 334-340)

1. Nestler S, Witte B, Schilchegger L, et al. Size does matter: ureteral stents with a smaller diameter show advantages regarding urinary symptoms, pain levels and general health. World journal of urology. 2020;38(4):1059-63.doi:10.1007/s00345-019-02829-0

Changes in the text:

“Moreover, potential limitations may exist due to the multiple causes of stent-related urinary symptoms. Nestler et al. showed that stents with larger diameters exacerbated related symptoms [39]. Three of the four RCTs included in our meta-analysis reported that patients involved in their studies had a 6 French (F) polyurethane double pigtail stent [25-27], while the remaining RCT described that patients included in their study used 4.8 F double-J ureteral stents [28]. This discrepancy may lead to a potential bias in the results.”

Comment 5:

And last, we knopw there is a difference, whether the stones are in the distal or the proximal ureter since distal ureter stones cause LUTS and therefore alter the stent related symptoms. This should be analysed if possible in the original studies and mentioned as well in results and discussion.

Reply 5:

Thank you for these important suggestions. We apologize for our negligence of analyzing the factors affecting stent related symptoms. As to your suggestion, we have carefully reviewed the included RCTs again, focusing on whether the stones are in the distal or the proximal ureter. Unfortunately, at present, all RCTs we included did not showed that the effect of stone location on stent related symptoms. Hence, there is some missing data with this domain in our study. We added the following

sentences to the discussion to explain this limitation. To compensate for that, we will continue our follow-up to confirm our conclusion. Thank you for this suggestion to improve the readability of our manuscript again. (Please see Page 16, Line 340-342)

Changes in the text:

“Also, the stone level may cause urinary symptoms; the RCTs included in our meta-analysis do not mention differences in urinary symptoms caused by stone location. We will pay particular attention to this in future research.”