

Peer Review File

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Reviewer #A:

I commend you in the objective of this paper. I would recommend that you change your approach to PTNS compared to pharmacotherapy as beta-agonists have become the mainstay of management for OAB. Rework your search to include these papers (even if prospective cohort studies) and resubmit.

Anticholinergic drugs and beta-agonists were both effective for the management of OAB. We searched again and we did not find any study comparing TNS with beta-agonists. We will perform meta-analysis comparing PTNS with beta-agonists in future studies.

Reviewer #B:

Comment 1: Micturition frequency might be the preferred term as would urinary urgency episodes and “lower discontinuation rate” and it might be useful to add “during the trials “ to this sentence for clarity. the use of english needs some revision throughout in terms of grammar and tense agreement. This would enhance the readability of the article.

Reply 1: We have modified our text as advised and we revised our English language.

Changes in the text: We have replaced micturition, urgency episodes and less discontinuation rate with micturition frequency(see Page 2, line 30), urinary urgency episodes(see Page 2, line 30) and lower discontinuation rate(see Page 2, line 39) respectively. We added “during the trials ”(see Page 2, line 40) to this sentence.

Comment 2: again the correct term should be urgency, rather than urge incontinence. The reference for the definition of OAB is missing and should probably be included references 456 are quite old there are newer references which

relate to the persistence of antimuscarinic drugs for overactive bladder

Reply 2: As “urgency” and “urge incontinence” are both the common symptoms of OAB and the definition of OAB include both “urgency” and “urge incontinence”, we did not replace urgency with urge incontinence. We added the reference for the definition of OAB and we replaced reference 456 with latest references.

Changes in the text: We added the reference for the definition of OAB(see Page 3, line 50) and we replaced reference 456 with latest references(see Page 3, line 58).

According to the latest reference, we modified the discontinuation with mean rate of 84% at 12 months (see Page 2, line 57).

Comment 3: Where the authors refer to sacral nerve stimulation, they note that this has fewer undesirable side effects but give no comparator. might I suggest that although the absolute rate of adverse events may be lower the magnitude of effect is perhaps incomparable.

Reply 3: As reviewer #B pointed out, the adverse events of TNS is incomparable with the adverse events of ACDs. In our study, we merely described the incidence adverse events of TNS and ACDs but we didn’t give statistical comparison. Besides, the incidence of discontinuation because of an AE was compared between the TNS group and ACDs group and we found that the relevant OR was 0.13 (95% CI 0.03 to 0.51, P = 0.003), indicating that TNS had significantly less discontinuation because of an AE than ACDs.

Changes in the text: We replaced “less undesirable side effects” with “less absolute side effects observed”(see Page 3, line 62-63).

Comment 4: the drugs fesoterodine, trospium and darifenacin appear to be missing from the list of anti muscarinic drugs for overactive bladder. Why were these excluded?

Reply 4: We added *the drugs fesoterodine, trospium and darifenacin* into our search strategies and we didn’t find any other studies meeting our inclusion criteria. Based on the new search strategies, we modified our PRISMA flowchart of study selection.

Changes in the text: We added *the drugs fesoterodine, trospium and darifenacin* into our search strategies (see Page 5, line 95-96). Besides, we modified the PRISMA flowchart of study selection (see Figure 1).

Comment 5: Was there a rationale for the order of sequential removal of studies in the sensitivity analysis? Otherwise, the methods and analysis plan are well described notwithstanding the need to revise the English language

Reply 5: The sensitivity analysis was performed by removal of studies in sequence and recalculate the pooled MDs of the remaining studies. We improved the English language.

Changes in the text: None.

Comment 6: I think it would be useful to include the total number of patients, the average age and the sex ratio in the overall set of trials.

Reply 6: We added the total number of patients and the average age in Table 1. The gender of all studies was female except one study.

Changes in the text: We added the total number of patients and the average age in Table 1 (see Table 1). We described the sex ratio as follows: The gender of patients was mixed in only one study, in which 96% and 92% patients were female in the TNS group and ACDs group respectively. Besides, all of the patients were female in the other studies (see Page 7, line 150-152)

Comment 7: Could we also know whether included patients had previously failed antimuscarinic therapy prior to entry into the RCTs? The treatment naive or treatment experienced patients will perhaps respond differently. Likewise, were the entry criteria for each trial comparable?

Reply 7: As you pointed out, the treatment naive patients will respond to the therapy differently compared with those treatment experienced patients. In our meta-analysis, we can't get the detailed information from the included RCTs about if patients had previously failed antimuscarinic therapy. It is a limitation of our study

and we described it in the discussion. The entry criteria for each trial was comparable on the whole but there must be some slight difference among the criteria of different RCTs.

Changes in the text: We pointed out this limitation in the discussion section as follows: Besides, the included RCTs can't provide detailed information about if patients had previously failed ACDs therapy before entry to the RCTs. Patients previously failing ACDs therapy or not may respond to the ACDs therapy differently (see Page 13, line 284-287).

Comment 8: what proportion of the included trials had a formal power calculation
With clear a priore statement about primary outcome ?

Reply 8: All of the studies had compared the outcomes of two treatment and they provided their P value. They didn't perform multivariate analysis nor calculate OR or RR. All of the studies stated their primary outcome.

Changes in the text: None.

Comment 9: Some of the language does need revision for standard expression using terms such as no statistically significant difference between the two interventions would be preferable to the variable potentially slightly biased language which is used currently

Reply 9: We modified our expression as suggested.

Changes in the text: We modified our expression as suggested (see Page 8, line 166-169, 175-176, 179).

Comment 10: Im not sure of the meaning of this sentence: "Besieds, two included RCTs have shown that the combination of TNS and ACDs had a greater effectiveness than TNS and ACDs either on symptoms [14, 18]." could the authors please clarify?

Reply 10: We intended to express that the combination of TNS and ACDs had a better effect than TNS alone or ACDs alone on improving the symptoms of OAB, and this better effect could be observed in two of our included RCTs. However, the aim of our

meta-analysis was comparing TNS with ACDs and we did not aim to compare their combination with TNS alone or ACDs alone. Thus, we removed this sentence because it is quite unrelated to our topic.

Changes in the text: We removed this sentence(see Page 10, line 217).

Comment 11: The sentence is regarding cost per QALY are fair and as the authors note limited to a single study on tolterodine. Perhaps the authors might consider revising the qualifying sentence as follows “these data refer to a single antimuscarinic and perhaps cannot be generalized to all .”

Reply 11: We revised the sentence.

Changes in the text: We revised the sentence as follows “these data refer to a single antimuscarinic drug and perhaps can’t be generalized to all .”(see Page 12, line 268-269)

Comment 12: I am not sure that the following sentence can be justified based upon the results of this study “Although our meta-analysis pointed out the superiority of TNS over ACDs” the majority of our outcome indicators showed no difference between the effect of TNS compared to antimuscarinics, a single quality of life measure and a single disease related measure showed some superiority

Reply 12: Thanks for your kind reminding. This sentence is quite unjustified and we have modified it.

Changes in the text: We modified it as following: Although our meta-analysis showed that TNS had comparable therapeutic effects on the improvement of most OAB symptoms and pointed out some superiority of TNS over ACDs on the assessment of urge incontinence and PGI-I, there were some limitations worth mention(see Page 12, line 271-273).

Comment 13: An obvious concern when next relating these results to real life clinical practice as regards to discontinuation is comparing like with like – the motivations for patients to take up the different treatment options and continue may well be different

and the time commitment likely different and thus the conclusion might be modified in the light of this.

Reply 13: We modified our conclusion as suggested.

Changes in the text: We changed the last sentence of the conclusion as following: Besides, we also found that TNS, with less discontinuation, might be more tolerable compared with ACDs. TNS may be an alternative option of ACDs for the treatment of OAB (see Page 13, line 296).

Reviewer C

Comment 1: the authors did not comment on their study about the duration of TNS treatment and if it is performed and tolerated for a longer duration than anticholinergics.

Reply 1: It is important for us to comment the duration of TNS, but all of the included RCTs did not mention the duration of TNS. We discussed this by referring to other study which found evidences that TNS had statistically significant OAB symptoms improvement in terms of frequency, urge incontinence, nocturia and voided volume from 12 weeks to 12 months.

Changes in the text: We add this sentence in the discussion section as following: all of the included studies did not assess the duration of TNS (see Page 10, line 219-220).

Comment 2: They mentioned that the discontinuation rate for antimuscarinics is high, what about TNS?

Reply 2: The discontinuation rate for antimuscarinics and TNS was 15/103 and 1/103 respectively. As shown in figure 4, the incidence of discontinuation because of an AE was compared between the TNS group and ACDs group and the relevant OR was 0.13 (95% CI 0.03 to 0.51, P = 0.003), indicating that TNS had significantly less discontinuation because of an AE than ACDs.

Changes in the text: None.

Comment 3: What are the limitations to using TNS? as a reader after reading this article, I would recommend TNS to all patients, is it practical?

Reply 2: the limitations to using TNS are as following: TNS may cost more than antimuscarinics. Besides, TNS must be conducted by specialized persons and it was a little time-wasting comparing with oral antimuscarinics.

TNS is practical for patients who are willing to accept its limitations.

Changes in the text: None.