

Peer Review File

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Comment 1: There are some inconsistencies in how the authors describe the groups. On page 6, authors describe there being 4 trials comparing acupuncture to sham acupuncture (line 20) whereas later on page 7, 5 trials are described as being included in this meta-analysis (line 3). From the provided figures, it is apparent that the Zhao 2014 study has an acupuncture / tamsulosin control arm, whereas it appears to have been included in the acupuncture vs sham-only analysis. Unless the reviewer is misunderstanding the author's intentions, this is a glaring error that must be corrected. The analyses would have to be re-run. It is possible that repeating the analyses, excluding the Zhao study from the sham-only analysis would not change the overall result, but it must be re-done to confirm this.

Reply 1:

We thank the reviewer for these important comments and questions. In our study, 10 manuscripts on RCTs for CP/CPPS were ultimately utilized for comparisons between acupuncture and sham acupuncture/standard medication as treatments for CP/CPPS. Among them, 4 trials compared acupuncture with sham acupuncture (Ref. 11, 13-15), 3 trials compared acupuncture with standard medication (Ref. 16-18), 1 trial compared acupuncture with sham acupuncture/standard medication (Ref. 19), and 2 trials compared acupuncture plus standard medication with acupuncture/standard medication alone (Ref. 20, 21). Thus, there were 5 trials being finally included in the meta-analysis between acupuncture and sham acupuncture groups (Ref. 11, 13-15, 19).

As the Zhao 2014 study (Ref. 19) had two control arms (sham acupuncture and tamsulosin 0.2mg qd), it was included in both acupuncture vs. sham acupuncture analysis (Figure 1) and acupuncture vs. medicine analysis (Figure 2) in our manuscript.

Changes in the text:

No changes was done in the revised text.

Comment 2. The authors have shown that acupuncture appears to improve the NIH-CPSI score reduction in several of their analyses, however they do not comment on the clinical significance of the findings. Is a WMD of 1.58 clinically meaningful? There is significant literature addressing the clinical value of changes in CPSI and this must be included in the discussion to put the findings of this meta-analysis into context.

Reply 2:

We thank the reviewer for this important observation. We feel sorry for mistakenly regarding SMD as WMD in the original manuscript. Thus, we reanalyzed the pool data in the revised manuscript, and the fixed WMD of NIH-CPSI score reduction was 7.28 (acupuncture vs. sham acupuncture) and 3.36 (acupuncture vs. standard medication). The pooled reduction of NIH-CPSI score in acupuncture group was 182% and 56% more than that in sham acupuncture and standard medication group, respectively. Following the comments, the latest published literatures (Ref. 27-28) addressing the clinical value of changes in CPSI are cited in the discussion section in our revised manuscript.

Changes in the text:

Since developed in 1999, NIH-CPSI has been widely used to rapidly assess the severity of CP/CPPS symptoms. This questionnaire covers the three most important symptom domains: evaluating pain, voiding and QOL, which can provide an overall and valid assessment (27). As the graded uniform outcome measure, NIH-CPSI standardizes measurement of CP/CPPS symptoms and allows more accurate comparisons between studies (28). On the contrary, the endpoint of response rate was limited because its defining standard varied among included trials. Thus, the NIH-CPSI score reduction not response rate was adopted as primary outcome in our study.

Comment 3. There is little discussion regarding the findings from the sub-group analysis of type IIIA vs IIIB - what was the authors hypothesis and intent in providing this sub-analysis? What could explain the findings of a difference between these 2

groups?

Reply 3: Thank you for the valuable suggestion. Following the comments, we explained our hypothesis and intent in providing the sub-analysis of type IIIA vs IIIB in detail in the revised manuscript. Furthermore, the discussion on the difference between these two groups was also added.

Changes in the text:

Recent evidence suggested that the category IIIA and IIIB may represent two distinct pathological conditions or, alternatively, two different stages of the same condition (30), in that patients with category IIIA showed more severe signs and symptoms (NIH-CPSI scores and Qmax) than IIIB patients. Furthermore, the improvement of symptoms after medication was significantly more pronounced in IIIA patients when compared with IIIB patients. Thus, whether the differential response to acupuncture exists between IIIA and IIIB cohorts bothers us. Our subgroup meta-analysis suggested that compared with both sham acupuncture and medication, acupuncture appeared to be more effective in patients with category IIIB than category IIIA+IIIB, in aspects of NIH-CPSI total score and pain subscale. In addition, several recent meta-analysis demonstrated that antibiotic and its combination with alpha-blocker appeared to achieve the greatest improvement in clinical symptom scores compared with placebo(31, 32). The above results supported the opinion that category IIIA was caused by the pathogens. The possible reason is that some patients with bacterial prostatitis can be misdiagnosed as nonbacterial prostatitis due to local inflammatory obstruction or difficult- to- culture pathogens in prostatic duct (16, 33). The recently discovered nanobacterial infection was implicated to be an important etiologic factor of CP/CPPS(34, 35). In their study, anti-nanobacteria therapy could significantly improve symptoms of refractory CP/CPPS compared with placebo. Many urologists still thought the optimal treatment with antibiotics should be taken after CP/CPPS subtype evaluation.

Comment 4. Acupuncture quality - the authors address the quality of studies, however there is no comment on the issue of quality of acupuncture provided. The reviewer

appreciates the details regarding acupuncture templates, however what can be done to address acupuncture quality? Does it vary significantly amongst practitioners? What sort of credentialing is required to provide this sort of therapy. Perhaps beyond the scope of this review, the authors should comment on the quality of the therapy.

Reply 4: We quite agree with the reviewer that the quality of acupuncture provided is one of the key factors affecting the treatment efficiency. Following the comments, we discuss the potential heterogeneity of practitioners and how to ensure the acupuncture quality.

Changes in the text:

Several limitations in our study that should be addressed. First, the quality assurance is very important in acupuncture clinical research or real-world practice. However, varied treatment protocols including different types and sessions of acupuncture, duration of each session, location of acupoints, and manipulation of the needle, may potentially impact clinical effects of acupuncture (45). The early work has been made to understand what aspects might constitute a quality acupuncture intervention (46-48). However, until now, no clearly reliable criteria or appraisal tools to assess the acupuncture quality has been developed (45). Second, the complexity of acupuncture also makes the differences amongst practitioners inevitable (47). Third, meta-analysis does not determine the specific patients may benefit from acupuncture due to the difficult of conducting subgroup analysis. Last, it is difficult to implement strictly double-blind trials because of the features of acupuncture.