Oral pharmacological treatments for chronic prostatitis/chronic pelvic pain syndrome: A systematic review and network meta-analysis of randomised controlled trials

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Summary

Background Pharmacological treatments for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) are empirically used. However, the quantitative comparative effectiveness and safety of multiple pharmacological treatments is lacking.

Methods PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science were searched from inception to March 22, 2022. Randomised controlled trials comparing two or more oral pharmacological treatments for patients with CP/CPPS were included. Title, abstract, and full-text screening were independently screened by four reviewers. Primary outcomes were efficacy (the National Institutes of Health Chronic Prostatitis Symptom Index [NIH—CPSI] total score, pain score, urinary score, and quality of life score [QoL]) and safety (adverse events). This study was registered with PROSPERO, CRD42020184106.

Findings 25 studies (3514 patients) assessed 26 treatments. Low to very low quality evidence indicated that doxazosin (Mean difference [MD], −11.4, 95% Credible interval [CrI], −17.5 to −5.1) and the doxazosin, ibuprofen, and thiocolchicoside combination (MD, −11.6, CrI, −18.1 to −5.3) were significantly more effective than placebo in the NIH—CPSI total score. Other NIH—CPSI relative outcomes (pain, urinary, and QoL scores) showed a similar pattern. Low and very low quality evidence suggested that combination treatment including doxazosin, ibuprofen, and thiocolchicoside (odds ratios [OR], 3.2, CrI, 0.5 to 19.3) and the tamsulosin and dapoxetine combination (OR, 6.0, CrI, 0.7 to 67.3) caused more adverse events. In half of all comparisons regarding NIH—CPSI pain scores and quality of life scores, heterogeneity was minimal or low. Heterogeneity was high in both NIH—CPSI total symptom scores (I^2 = 78.0%) and pain scores (I^2 = 87. 0%) for tamsulosin versus placebo. There was also high heterogeneity in NIH—CPSI urine scores for the combination of tamsulosin and ciprofloxacin versus tamsulosin (I^2 = 66.8%), tamsulosin and levofloxacin versus tamsulosin (I^2 = 93.3%), and tamsulosin versus placebo (I^2 = 83%).

Interpretation Pharmacological treatments have little evidence supporting efficacy in CP/CPPS. Future studies could personalise therapy for individuals according to specific symptoms and identify non-pharmacological targets for CP/CPPS.

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Research in context

Evidence before the study

We searched for articles in all languages on the oral drugs for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in men on PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials from inception to March 22, 2022 and found no study prior to this study has compared individual drugs for CP/CPPS. One systematic review and network meta-analysis (NMA) comparing among grouped drugs has been published (2011). Previous NMA concluded that α-blockers, antibiotics, and combinations of these therapies appear to achieve the greatest improvement in terms of clinical symptom scores compared to a placebo.

Added value of the study

To our knowledge, this is the first network meta-analysis on individual drugs for CP/CPPS. The certainty of evidence for NMA was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. The current study extends the findings of previous studies that synthesized individual drugs into grouped drugs. Our results showed there is little evidence supporting efficacy of individual drugs for CP/CPPS. This study offers a detailed summary of currently available evidence.

Implications of all the available evidence

CP/CPPS is a complex disease with symptoms that are difficult to both quantify and effectively treat. Current NMA results showed that most of current pharmacological management for CP/CPPS might not be more effective than placebo, especially monotherapeutic strategies for CP/CPPS may fail. We advise to carefully weigh the benefits of medications against their potential harms when multimodal approaches are used. Future studies could personalize therapy for individuals according to specific symptoms of CP/CPPS and also identify nonpharmacological treatment strategy for CP/CPPS.

Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) refers to the presence of bothersome pelvic pain symptoms, without an identifiable cause, in men.[1] It is often associated with negative cognitive, behavioural, sexual, or emotional consequences as well as with symptoms suggestive of the lower urinary tract, sexual, or bowel dysfunction. CP/CPPS affects 2–16% of adult men, thereby being one of the most common urological diseases among men.[2–5] Several therapeutic agents have been routinely used in efforts to treat this condition. The pharmacological management of CP/CPPS usually includes α-blockers, antibiotic therapy, anti-inflammatory drugs, 5-α-reductase inhibitors, and phytotherapy.[6,7] Recently, agents such as pregabalin, pentosan polysulphate, diazepam, baclofen, zafirlukast, tanezumab, and allopurinol have been tested on a small group of patients with CP/CPPS via clinical trials. Although it appears that there are many treatment options for CP/CPPS, the efficacy of these treatments remains questionable.

Some might argue the story of the use of oral medications for the treatment of CP/CPPS has already been reported.[8] The largest National Institutes of Health (NIH) sponsored randomised controlled trials did not support the use of alfuzosin or tamsulosin, which are two commonly used α-blockers in clinical practice,[9] nor the antibiotic ciprofloxacin, either alone or in combination with tamsulosin.[10] It is noteworthy that some systematic reviews have found that certain grouped drugs (e.g. all α-blockers) or the combination of grouped drugs are more efficacious than placebo or other grouped drugs.[11] Limited by the methodology of pairwise meta-analysis, the findings of previous studies were augmented by quantitative analyses only if head-to-head data were available. Network meta-analysis (NMA) is a statistical technique that allows both direct and indirect comparisons to be undertaken, even when two of the treatments have not been compared directly.[12] In 2011, Anothaisintawee and colleagues performed the first NMA for CP/CPPS, in which it was concluded that α-blockers, antibiotics, and combinations of these therapies appear to achieve the greatest improvement in terms of clinical symptom scores compared with placebo.[13,14] In this study, we performed an updated NMA to compare and rank medications regarding efficacy and safety, which have been used for the treatment of CP/CPPS.

Methods

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[15]

Ethical approval

No individual data were used in this study, there were no privacy issues to address.

Search strategy and selection criteria

We searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science databases from inception until March 22, 2022 (eTable 1 in the Supplement summarised the search strategies). The screening and selection processes were conducted independently by 4 co-authors (Z.Q., C.Z., J.G., and J.S.W. K.).

We included RCTs comparing the use of different oral drugs as a monotherapy or combined and a placebo for the treatment of CP/CPPS. Trials that enrolled participants with either a CP/CPPS diagnosis or non-bacterial chronic prostatitis according to standardised criteria were eligible. For studies using other non-standardised diagnostic criteria, we provided further details regarding the precise diagnostic approach, as reported in the studies. We included the following oral drugs: α-blockers, 5-α-reductase inhibitors, antibiotics, anti-inflammatory drugs, neuromodulators, phytotherapy, pentosan polysulfate, and combinations of oral pharmacological therapies.

Outcome definition

The primary efficacy outcome measure was the National Institutes of Health Chronic Prostatitis Symptom Index (NIH—CPSI) total score, which is a validated questionnaire and has been widely used to assess CP/CPPS symptoms. It consists of nine items divided into three discrete domains: pain (0–21 points), urinary symptoms (0–10 points), and quality of life (QoL, 0–12 points), with a total score of 0–43 points (a higher score indicates worse symptoms).[3] The three NIH—CPSI subscores (pain, urinary symptoms, and QoL) were defined as secondary outcomes. Regarding safety outcome, we defined number of adverse events for any reason.

Data extraction and quality assessment

Two co-authors (Z.Q. and J.G.) independently extracted data and evaluated studies for eligibility. Any discrepancies were resolved by consensus and arbitration by a third investigator. We assessed the methodological quality of the included studies using the version 2 Cochrane risk-of-bias tool.[16] Bias domains including bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Judging a result to be at a particular level of risk of bias for an individual domain implies that the result has an overall risk of bias at least this severe. If studies did not provide change-from-baseline data, we estimated the change value using the baseline and end-of-treatment data.[17] Whenever necessary, we approximated means and measures of dispersion from plots as previously described.[18] The full dataset included in this NMA has been submitted as an attachment in eTable 2 in the Supplement.

Certainty in evidence

The certainty of evidence for NMA was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[19] Two co-authors (Z.Q. and J.G.) with experience in using GRADE separately rated each domain for each comparison and resolved discrepancies by consensus. We rated the certainty for each comparison and efficacy and safety outcomes as high, moderate, low, or very low, on the basis of study limitations, publication bias, inconsistency, indirectness, and imprecision.

Data analysis

The outcomes were expressed as mean differences (MDs) or odds ratios (ORs) with 95% credible interval (CrIs). Heterogeneity between studies was assessed using chi-squared tests, in which the significance level was set to $P < 0.1$, as well as the I^2 statistic. We used random-effects models to conduct the meta-analysis. To determine the consistency of the NMA, we adopted the design-by-treatment interaction model with random inconsistency effects. To minimize the issues arising from the potential lack of similarity and transitivity, only oral pharmacological treatments with strict patient allocation were included. Moreover, the outcome data were transferred into change-from-baseline values to avoid significant differences at baseline. The similarity was assessed based on clinical characteristics, including sample size, age, and treatment duration.

We conducted an NMA to combine direct and indirect evidence for CP/CPPS. We used non-informative priors with vague normal (mean 0, variance 10,000) and uniform (0–1) prior distributions for parameters such as the means and standard deviations. Various levels of prior distribution were applied in the sensitivity analyses. First, 50,000 simulations were performed, and then we generated an additional 10,000 simulations with three sets of different initial values and sheared the first 20,000 simulations as the burn-in period in our model. Based on 40,000 simulations and thin = 40, the point estimate adopted the median of the posterior distribution, and the corresponding 95% CrIs used the 2.5th and 97.5th percentiles of the posterior distributions, which were interpreted similarly as conventional 95% confidence intervals.

To facilitate the interpretation of the estimated treatment effects, we calculated several metrics for each intervention. First, we calculated the effect size (MD or

OR) and its corresponding 95% CrIs. Second, we assessed whether the NIH—CPSI total score reached the minimal clinically important difference. The 6-point threshold was based on a previous epidemiological study.[20] Third, we used the surface under the cumulative ranking curve (SUCRA) to provide a summary statistic for the cumulative ranking within the Bayesian framework.[21] The SUCRA value of 1 is certain to be the best, whereas an intervention with 0 is certain to be the worst. We evaluated the global inconsistency using the "loop inconsistency" method. When the treatment effects around a loop do not conform to the consistency equations, the standard criterion states that when 95% CrIs including 0 are reported, insignificant disagreement exists. We discussed the transitivity assumption by epidemiologic judgment considering following aspects[22,23]: if studies are comparable in terms of the distribution of effect modifiers; if the direct and indirect treatment effects are in statistical agreement; and if participants included in the network could in principle be randomized to any of the treatments. To assess the consistency, a statistical evaluation was conducted. To assess the robustness of the results obtained by the primary model, we performed a sensitivity analysis, which excluded the data from the REDUCE (REduction by DUtasteride of prostate Cancer Events) study.[24] We considered that a long treatment duration and large population may cause bias in the NMA. REDUCE was a large-scale, 4-year RCT designed to determine the value of dutasteride in prostate cancer treatment compared to a placebo treatment.[25] The statistical analyses were performed using WinBUGS (version 1.4.3), Stata (version 14.0), and R (version 3.1.1) software. This study was registered with PROSPERO, CRD42020184106.

Role of the funding source

The sponsors had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript. The corresponding author (J.W.) had full access to the data used in this study and had final responsibility for the decision to submit for publication.

Results

Literature search and study selection

In total, the search yielded 4752 articles. Following abstract screening and full-text reviews, 25 randomised controlled trials involving 3514 patients with CP/CPPS were included (Figure 1).[9,24,26–48] Overall, the studies were conducted between 1999 and 2019. For the analysis, we compared 18 monotherapies, six combination therapies and placebo. Fourteen (56%) of the 25 studies compared the positive drugs with placebo treatments. Fifteen (60%) of the 25 studies were multi-center studies. The mean age of patients with CP/CPPS was 40.3 years (SD 11.4). The median treatment duration was 12 weeks (IQR 6–14). In six (24%) of the 25 studies, the participants were randomly assigned to three or more groups. In 9 (36%), 11 (44%), and 6 (24%) of 25 studies, patients were recruited from Asia, North America, and Europe, respectively, while two (8%) studies were cross-continental. Nine (36%) of the 25 studies received funding from pharmaceutical companies. The baseline characteristics and risk of bias assessment of the included studies are summarized in eTables 3 and 4 in the Supplement.

Efficacy analysis

Data on the NIH—CPSI total scores were available from 24 studies comparing 26 pharmacological or placebo treatments. Figure 2A shows the network of eligible comparisons for the NIH—CPSI total score. Only 2 treatments were significantly more effective than placebo when data were combined in the NMA: doxazosin (MD, −11.4, CrI, −17.9 to −5.1) and the doxazosin, ibuprofen, and thiocolchicoside combination (MD, −11.6, CrI, −18.1 to −5.3) (eTable 5 and 6 in the Supplement). Doxazosin yielded not only the best benefit of all monotherapies but also significant benefits compared to tamsulosin and ciprofloxacin (MD, 9.7, CrI, 1.4 to 18.0). The doxazosin, ibuprofen, and thiocolchicoside combination was shown to be the most effective combination therapy in terms of providing the best overall relief to NIH—CPSI total symptoms. Similar results were observed in the NIH—CPSI relative secondary outcomes. In terms of NIH—CPSI pain score, 19 studies comparing 23 treatment protocols or placebo treatments were included in the analysis. Figure 2B shows the network of eligible comparisons for NIH—CPSI pain scores. The NMA results showed that doxazosin (MD, −4.7, CrI, −9.1 to −0.1), the doxazosin, ibuprofen, and thiocolchicoside combination (MD, −4.8, CrI, −9.2 to −0.4), and the tamsulosin and levofloxacin combination (MD, −6.3, CrI, −10.2 to −2.4) were more effective than placebo. The analysis of the NIH—CPSI urinary and quality of life scores were based on 18 studies comparing 21 pharmacological treatments or placebo treatments. Figure 2C shows the network of eligible comparisons for both urinary and QoL scores of NIH—CPSI. The NMA results of urinary symptoms showed that doxazosin (MD, −2.8, CrI, −5.7 to −0.1), the doxazosin, ibuprofen, and thiocolchicoside combination (MD, −3.3, CrI, −6.2 to −0.4), and the tamsulosin and levofloxacin combination (MD, −4.5, CrI, −6.9 to −1.9) was more effective than the placebo treatment (eTable 5). In terms of QoL scores, the NMA results showed the similar pattern as urinary scores (eTable 5). The robustness of the results was detected by comparing the remaining treatments after the removal of the

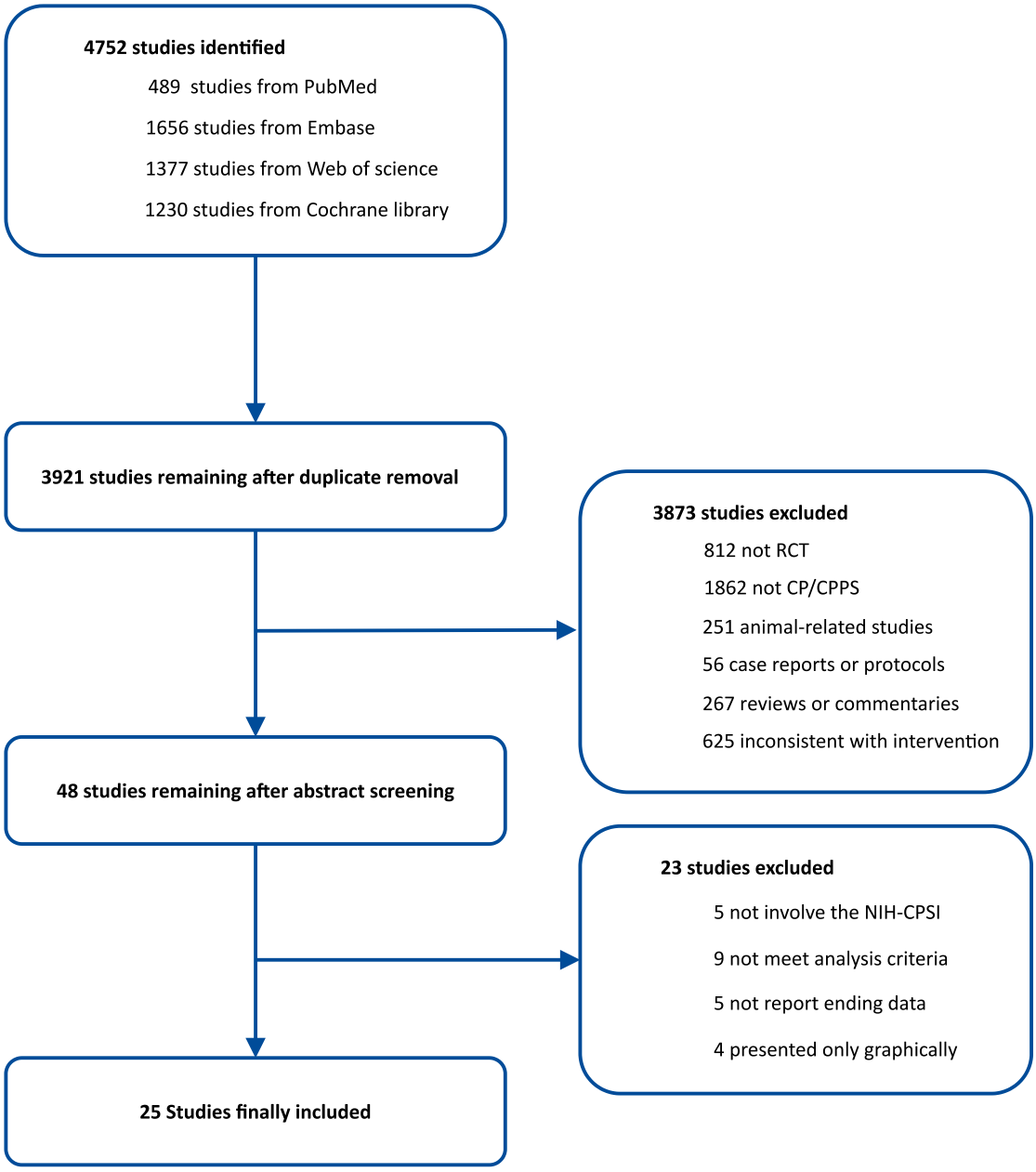

Figure 1. Study flowchart. RCT = randomized controlled trial. CP/CPPS = chronic prostatitis/chronic pelvic pain syndrome. NIH—CPSI = National Institutes of Health Chronic Prostatitis Symptom Index.

REDUCE study from the sensitivity analysis. The results did not show relevant deviations compared with the original NMA.

Safety analysis

The adverse events were generally mild to moderate. Figure 2D shows the network of eligible comparisons for adverse events. The available safety data do not allow the same extent of resolution according to different adverse events. All types of safety data, including gastrointestinal, cardiovascular, neurological, and other types of data, were summarised. Based on the effect size and ranking test, we observed fewer adverse events related to finasteride (OR, 0.6, CrI, 0.1 to 3.5) compared with placebo treatments, which had the fewest adverse events in the two compared treatments, respectively. Compared with placebo treatments, silodosin had the most adverse effects among all monotherapies (OR, 6.5, CrI, 1.1 to 63.4). Combination therapies including the doxazosin, ibuprofen, and thiocolchicoside combination (OR, 3.2, CrI, 0.5 to 19.3) and the tamsulosin and

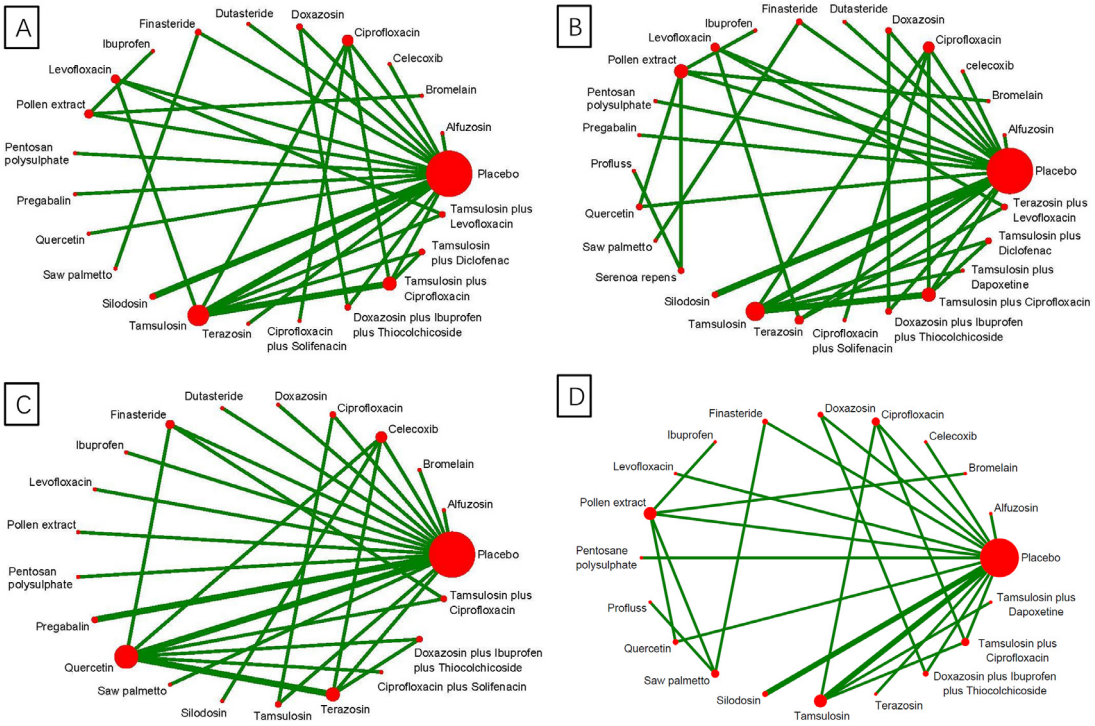

Figure 2. Network of eligible comparisons for the efficacy outcomes. Network of eligible comparisons for the NIH—CPSI total score (A), for NIH—CPSI pain score (B), for NIH—CPSI urinary and QoL scores (C), and for adverse events (D).

dapoxetine combination (OR, 6.0, CrI, 0.7 to 67.3) were associated with a higher risk of adverse events (eTable 5).

Rank probabilities

Figure 3 using a heatmap to summarize the Bayesian ranking profiles of comparable therapies for all efficacy and safety outcomes. For patients with CP/CPPS, the doxazosin, ibuprofen, and thiocolchicoside combination was most likely to be ranked first for NIH—CPSI total scores (SUCRA 94.8%). The tamsulosin and levofloxacin combination was most likely to be ranked first for NIH—CPSI pain scores (93.2%) as well as for NIH—CPSI urinary scores (95.5%). Doxazosin alone was most likely to be ranked first for NIH—CPSI quality of life scores (95.2%). Finasteride was most likely to be ranked first in terms of having the fewest adverse events (80.2%).

Heterogeneity and inconsistency assessment

The results of the heterogeneity assessment suggested minimal or low heterogeneity in half of all comparisons regarding NIH—CPSI pain scores and quality of life scores. However, moderate to high heterogeneity was detected in comparisons of tamsulosin versus placebo (I^2 = 78.0%) for NIH—CPSI total symptom scores, the tamsulosin versus placebo (I^2 = 87.0%) for NIH—CPSI pain scores, the tamsulosin and ciprofloxacin combination versus tamsulosin (I^2 = 66.8%), and the tamsulosin and levofloxacin combination versus tamsulosin (I^2 = 93.3%) for NIH—CPSI urinary scores, and tamsulosin versus placebo (I^2 = 83%). The inconsistency assessment of NMA was evaluated in each loop by contrasting direct and indirect estimates (eFigure 1A–E in Supplement). The results of the inconsistency assessment did not show significant differences in most comparisons, except for the placebo versus finasteride versus pollen extract versus saw palmetto for NIH—CPSI total scores as well as the loop of placebo versus pollen extract versus terazosin for NIH—CPSI pain, urinary, and quality of life scores. In terms of safety analysis, the results of the inconsistency assessment did not show significant differences in the comparisons performed.

Discussion

This systematic review and NMA covered a maximum amount of oral drugs for CP/CPPS. However, most of them were not beneficial compared with placebo. Doxazosin alone or doxazosin, ibuprofen, and thiocolchicoside combination showed high mean MDs compared with placebo, yet both were based on 1 study and nonsignificant given the variance within the studies. Concerning safety, the addition of other treatments, such as the doxazosin, ibuprofen, and thiocolchicoside and the

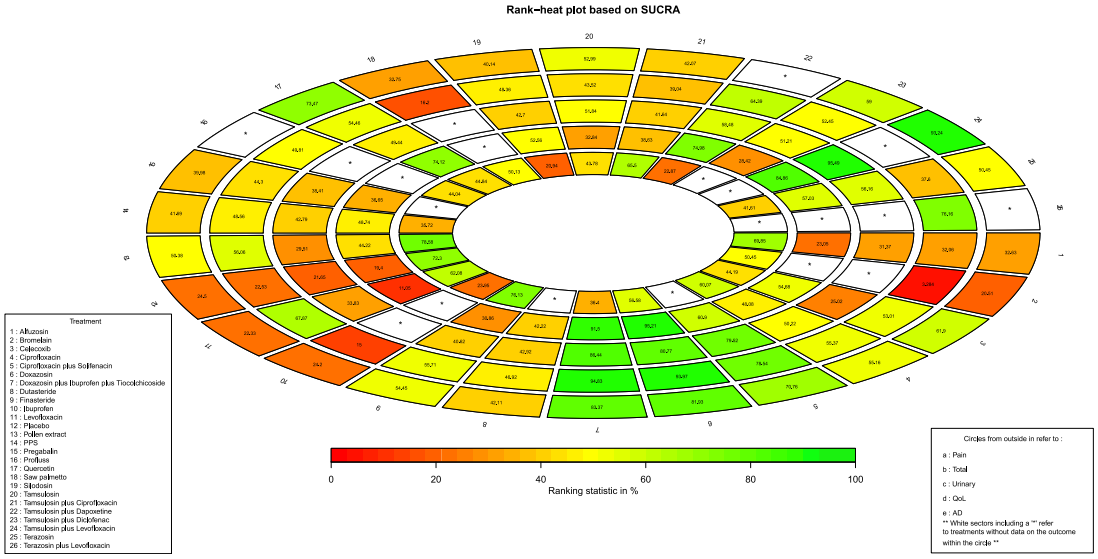

Figure 3. Bayesian ranking profiles of comparable therapies for all outcomes. QoL = Quality of life. SUCRA = surface under the cumulative ranking curve.

tamsulosin and dapoxetine combinations, to an α-blocker was associated with a higher risk of adverse events. Comparative studies have mainly investigated monotherapy using α-blockers, anti-inflammatory drugs, and antibiotics; these α-blockers have similar efficacy profiles. However, few studies compare the individual drugs in drug groups. Although results of the current NMA suggest that combination therapy may be beneficial for patients with CP/CPPS. There was no statistical difference between monotherapy and combination therapy. Taking into account the cost-effectiveness and adverse event profile, combination therapy should be individualized to the specific clinical phenotype of each CP/CPPS patient.

The first NMA for CP/CPPS concluded that α-blockers, antibiotics, and combinations of them appear to achieve the greatest improvement in NIH—CPSI total scores compared with placebo, and anti-inflammatories also have a lesser but measurable benefit on CP/CPPS clinical symptom.[14] In terms of mechanism of included pharmacological treatment, α-blockers reduce the autonomic sympathetic tone in the bladder neck and prostate, which may relieve urinary symptoms of CP/CPPS; antibiotics is empirical used although no bacterial cause can be identified among patients with CP/CPPS; anti-inflammatories could decrease inflammatory mediated pain of CP/CPPS; 5-α-reductase inhibitors reduce the production of dihydrotestosterone and prostate size, which may reduce pain and urinary symptoms; neuromodulators reduce neural sensitization and consequently relieve the neuropathic pain involving outside the prostate or pelvic area; phytomedicine may have anti-inflammatory effects, reducing pelvic pain and impaired voiding. The current study extends the findings of previous studies that synthesized individual drugs into grouped drugs.[11,13,14] Although grouped drugs such as different α-blockers have similar action mechanisms (e.g. α-blockade), they are very different in terms of α-receptor selectivity and side effects.[49–52] The clinical practice guidelines recommend some grouped drugs, such as antibiotics, α-blockers, and non-steroidal anti-inflammatory drugs, for the treatment of CP/CPPS.[53] However, clinicians require more evidence to make patient-specific choices. In this study, we included the most commonly used oral drugs in CP/CPPS. Some agents (zafirlukast, tanezumab, and allopurinol) were not included because the results of low-power placebo-controlled studies failed to show beneficial effects.[54–56] Although in previous studies researchers tried to analyze dichotomous response versus non-response outcomes, the response rate was not an outcome in our NMA because the definition of responder varied in different studies. As NMA requires more rigorous comparison than traditional meta-analysis, it is inappropriate to combine these data. A change-from-baseline instead of end-of-treatment was used in this study, which could decrease the bias caused by baseline data in different studies. The NMA results showed that the doxazosin, ibuprofen, and thiocolchicoside and the doxazosin and quercetin combinations may be beneficial in treating CP/CPPS. Direct comparisons suggested that some agents, including celecoxib, doxazosin, dutasteride, finasteride, pollen extract, pentosan polysulfate sodium, and tamsulosin have clinically relevant treatment effects on pain relief compared with placebo in patients with CP/CPPS. However, neither the monotherapies nor the combination therapies were significantly superior to placebo treatments in terms of NIH—CPSI pain scores.

This result may have been underpowered, considering the range of the 95% CrI, in detecting a clinically important benefit in favour of combination therapy. While these data are generally consistent with those of previous systematic reviews.[14,57]

During the last 5 years, ten CP/CPPS clinical trials were registered in *ClinicalTrials.gov*, among which 80% (8/10) were physical therapies (extracorporeal shock wave, acupuncture, and laser), one was a food supplement (Cinnamomum aromaticum), and only one was a pharmacological treatment (AQX-1125). These data suggest that monotherapy treatment for CP/CPPS has not provided satisfactory results for the entirety of a CP/CPPS population.

Although this NMA provided an indirect comparison that has not been undertaken previously, the findings should be interpreted taking into account certain limitations. Firstly, the results are based mostly on indirect comparisons. The number of arms in the network is higher than the number of included studies, which may cause a potentially unstable structure network. Secondly, only oral pharmacological treatments with strict patient allocation were included which may create a selection bias. Thirdly, the heterogeneity among the studies and the inconsistency of the loop may also affect the NMA results. Owing to limited data, we did not perform meta-regression to examine the impact of effect modifiers on the study effect size. Finally, the results of NMA are limited by the quality of the underlying data. Whether investigators in some trials were properly blinded was unclear, and most trials had a high risk of incomplete outcome data bias because they did not provide information about how they handled the missing data.

According to our results, pharmacological treatments have little evidence supporting efficacy for CP/CPPS. We advise to carefully weigh the benefits of medications against their potential harms. Future studies could personalize therapy for individuals according to specific symptoms of CP/CPPS and identify nonpharmacological targets for CP/CPPS.

Declaration of interests

We declare no competing interests.

Contributors

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Qin, Nickel, and Wu conceived and designed the study. All authors were responsible for acquisition, analysis, or interpretation of data. Qin, Nickel, and Wu wrote the first draft of the manuscript. Nickel and Wu supervised the study. All authors reviewed the manuscript for important intellectual content. Qin, Zhang, and Guo have verified the underlying data. All authors agreed with the results and conclusions of this article. The corresponding author (J. W.) had full access to the data used in this study and had final responsibility for the decision to submit for publication.

Data sharing

The full dataset included in this network meta-analysis has been submitted as an attachment (eTable 2) and are not subject to embargo or restrictions.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101457.

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