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Management of Chronic Prostatitis/ Chronic Pelvic Pain Syndrome: A Systematic Review and Network Meta-analysis FREE

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ABSTRACT

Context Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is common, but trial evidence is conflicting and therapeutic options are controversial.

Objective To conduct a systematic review and network meta-analysis comparing mean symptom scores and treatment response among α-blockers, antibiotics, anti-inflammatory drugs, other active drugs (phytotherapy, glycosaminoglycans, finasteride, and neuromodulators), and placebo.

Data Sources We searched MEDLINE from 1949 and EMBASE from 1974 to November 16, 2010, using the PubMed and Ovid search engines.

Study Selection Randomized controlled trials comparing drug treatments in CP/CPPS patients.

Data Extraction Two reviewers independently extracted mean symptom scores, quality-of-life measures, and response to treatment between treatment groups. Standardized mean difference and random-effects methods were applied for pooling continuous and dichotomous outcomes, respectively. A longitudinal mixed regression model was used for network meta-analysis to indirectly compare treatment effects.

Data Synthesis Twenty-three of 262 studies identified were eligible. Compared with placebo, α-blockers were associated with significant improvement in symptoms with standardized mean differences in total symptom, pain, voiding, and quality-of-life scores of −1.7 (95% confidence interval [CI], −2.8 to −0.6), −1.1 (95% CI, −1.8 to −0.3), −1.4 (95% CI, −2.3 to −0.5), and −1.0 (95% CI, −1.8 to −0.2), respectively. Patients receiving α-blockers or anti-inflammatory medications had a higher chance of favorable response compared with placebo, with pooled RRs of 1.6 (95% CI, 1.1-2.3) and 1.8 (95% CI, 1.2-2.6), respectively. Contour-enhanced funnel plots suggested the presence of publication bias for smaller studies of α-blocker therapies. The network meta-analysis suggested benefits of antibiotics in decreasing total symptom scores (−9.8; 95% CI, −15.1 to −4.6), pain scores (−4.4; 95% CI, −7.0 to −1.9), voiding scores (−2.8; 95% CI, −4.1 to −1.6), and quality-of-life scores (−1.9; 95% CI, −3.6 to −0.2) compared with placebo. Combining α-blockers and antibiotics yielded the greatest benefits compared with placebo, with corresponding decreases of −13.8 (95% CI, −17.5 to −10.2) for total symptom scores, −5.7 (95% CI, −7.8 to −3.6) for pain scores, −3.7 (95% CI, −5.2 to −2.1) for voiding, and −2.8 (95% CI, −4.7 to −0.9) for quality-of-life scores.

Conclusions α-Blockers, antibiotics, and combinations of these therapies appear to achieve the greatest improvement in clinical symptom scores compared with placebo. Anti-inflammatory therapies have a lesser but measurable benefit on selected outcomes. However, beneficial effects of α-blockers may be overestimated because of publication bias.

Prostatitis is a common condition, with an estimated prevalence in the community of about 9%,[1] and accounts for nearly 2 million ambulatory care encounters annually in the United States.[2] However, prostatitis represents a heterogeneous mix of conditions, including acute prostatitis, chronic bacterial prostatitis, and asymptomatic inflammatory prostatitis. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), which accounts for 90% to 95% of cases,[3,4] is a clinical entity defined as urologic pain or discomfort in the pelvic region,

associated with urinary symptoms and/or sexual dysfunction, lasting for at least 3 of the previous 6 months. Chronic prostatitis/chronic pelvic pain syndrome is a diagnosis of exclusion that can be made after ruling out active urethritis, urogenital cancer, urinary tract disease, urethral stricture, or neurological disease affecting the bladder. Symptoms of CP/CPPS can diminish quality of life and impair physical and psychological function.[5]

The etiology of CP/CPPS is uncertain but may include inflammatory or noninflammatory etiologies.[6-8] An inciting agent may cause inflammation or neurological damage in or around the prostate and lead to pelvic floor neuromuscular and/or neuropathic pain. Predisposing factors for CP/CPPS may include heredity, infection, voiding abnormalities, hormone imbalance, intraprostatic reflux, immunological or allergic triggers, or psychological traits. A wide variety of therapies including α-blockers, antibiotics, anti-inflammatory medications, and other agents (eg, finasteride, phytotherapy, and gabapentinoids) are routinely used. However, the efficacy of these treatments is controversial,[9-15] partly because many clinical trials testing these therapies have been small, with little statistical power to detect treatment effects.

To date, only 1 systematic review[6] and 1 meta-analysis[16] of α-blockers vs placebo of which we are aware have been performed for treatment of CP/CPPS. We therefore performed a systematic review and network meta-analysis mapping all treatment regimens, with 2 aims. First, we compared total symptom, pain, voiding, and quality-of-life scores at the end of therapy with α-blockers (the most commonly evaluated therapy for CP/CPPS), other active drugs, or placebo. Second, we compared rates of responses to therapies available for treating CP/CPPS.

METHODS

We searched the MEDLINE and EMBASE databases for relevant studies published in English from 1949 (for MEDLINE) or 1974 (for EMBASE) through November 16, 2010. Search terms and strategies for each database are described in the eAppendix. Reference lists of included trials and the previous systematic reviews[6,16] were explored.

Identified studies were selected based on title and abstract by 2 independent authors (T.A. and S.T.). Full articles were retrieved if a decision could not be made based on the abstracts. Agreement between the 2 reviewers was measured using the κ statistic. Disagreement was resolved by consensus and by discussion with a third party (J.C.N. or A.T.).

Randomized controlled trials that were published in English were selected if they met the following criteria: (1) Participants met criteria for CP/CPPS categories IIIA or IIIB according to the National Institutes of Health classification.[4] (2) The study compared any pair of the following interventions: α-blockers, antibiotics, steroidal and nonsteroidal anti-inflammatory drugs, finasteride, glycosminoglycans, phytotherapy, gabapentinoids, and placebo. (3) The study measured any of the following outcomes: pain scores, voiding scores, quality-of-life scores, and total symptom scores. The total symptom score is a summation of pain, voiding, and quality-of-life scores. (4) The full article could be retrieved and had sufficient data for extraction, including number of patients, means and standard deviations of continuous outcomes in each group, and/or numbers of patients per group for dichotomous outcomes.

Two authors (T.A. and S.T.) independently extracted data using a standardized extraction form. Disagreement was resolved by discussion or consensus with a third party (A.T.). Missing information was sought by contacting the corresponding authors of the studies.

Two authors (T.A and P.N.) independently assessed risk of bias of each study using an established tool.[17] Six domains were assessed: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Disagreement between 2 authors was resolved by consensus and discussion. Levels of agreement for each domain and the overall domains were assessed using the κ statistic.

The outcomes of interests were total symptom, pain, voiding, and quality-of-life scores and response rates as defined in the original articles. The following tools were used in these assessments: (1) The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) consists of 3 domains (ie, pain, voiding, and quality of life). The total scores range from 0 to 43.[18] (2) The International Prostate Symptom Score (IPSS) questionnaire[19] consists of 3 domains (ie, pain, voiding, and quality of life), with combined scores ranging from 0 to 51. (3) The Prostatitis Symptom Score Index (PSSI) measures only pain scores, with a total score of

0 to 12. (4) Other pain and voiding questionnaires[20] consist of 7 and 5 items, respectively, with each item graded as 0 to 3.

For each measurement, scores closer to 0 reflect more favorable status. The minimal clinical significant difference for all these scales is 3 to 6 points.[21-24] For response to treatment, various definitions were used in the original studies; eg, 25%, 33%, or 50% decreases in the NIH-CPSI or 4 (clinically perceptible improvement) to 6 (clinically significant improvement) unit score decreases in the NIH-CPSI from baseline.

For the direct meta-analysis, mean differences of continuous outcomes (ie, total symptom, pain, voiding, and quality-of-life scores) between treatment groups were estimated for each study and were pooled using a standardized mean difference (SMD) if the scales used for outcome measures differed. Otherwise, an unstandardized mean difference (USMD) was applied. Heterogeneity of the mean difference was assessed using Q and I^2 statistics. If heterogeneity was present or the degree of heterogeneity (I^2) was greater than 25%, the SMD was estimated using a random-effects model. Otherwise, a fixed-effects model was applied.

Relative risks (RRs) of response to treatment were estimated for each study. If there was evidence of heterogeneity, a random-effects model was used for pooling. Otherwise, the inverse-variance method was used. The source of heterogeneity was explored by fitting covariables (ie, mean age, duration of treatment, and baseline total symptom scores) one by one in the meta-regression. Publication bias was assessed using contour-enhanced funnel plots and the Egger test.[25,26]

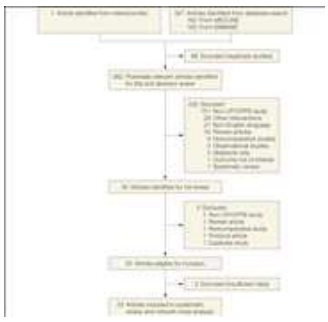
For indirect comparisons, network meta-analyses were applied to assess treatment effects for all possible treatment groups if summary data were available.[27-29] Linear regression models weighted by inverse variance were applied to assess treatment effects for continuous outcomes. Effects of study were included as covariates in the model. For response to treatment, summary data were expanded to individual patient-level data using the "expand" command in Stata. Treatment groups were considered in a mixed-effect hierarchical model with a log-link function using the "xtpoisson" command.[27] Pooled RRs and 95% confidence intervals (CIs) were estimated by exponential coefficients of treatments. All analyses were performed using Stata software, version 11.0.[30] Two-sided $P < .05$ was considered statistically significant except for the heterogeneity test, in which a 1-sided $P < .10$ was used.

RESULTS

Among 262 identified studies, 25 studies were eligible for inclusion (Figure). Two studies[31,32] had insufficient data (ie, did not report means and standard deviations). For these studies, one corresponding author[31] was contacted for additional information but did not respond, while the author of the other study[32] could not be contacted. This left 23 studies[9-15,21,22,24,33-45] with sufficient data for extraction. Agreement on study selection between the 2 reviewers was high at 98% ($\kappa = 0.91$; $P < .001$). Disagreements were present for 5 studies (selected by one reviewer but not the other) and included 2 duplicate reports, 1 non–randomized controlled trial, 1 protocol report, and 1 study with mixed CP/CPPS and bacterial prostatitis patients.

Figure. Study Selection

CP/CPPS indicates chronic prostatitis/chronic pelvic pain syndrome.



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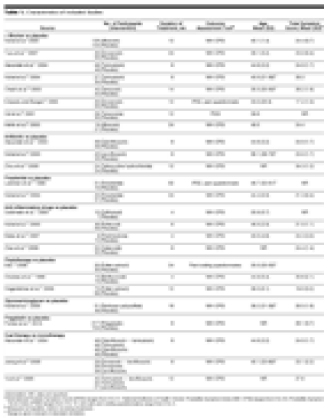
Twenty studies[9-15,22,24,33-35,37-41,43-45] compared outcomes between 1 active treatment and placebo (Table 1). These treatments were α-blockers in 7 studies,[9,10,24,33-35,38] antibiotics in 2 studies,[39,44] finasteride in 2 studies,[37,40] anti-inflammatory drugs in 4 studies,[11,12,22,43] phytotherapy in 3 studies,[13-15] glycosaminoglycan in 1 study,[41] and pregabalin in 1 study.[45] Three studies[21,36,42] had more than 2 treatment groups as follows: α-blockers plus antibiotics, α-blockers alone, and antibiotics alone in 2 studies[36,42]; and α-blockers plus antibiotics, α-blockers alone, antibiotics alone, and placebo in 1 study.[21] Treatment duration ranged from 4 to 52 weeks. Most studies used NIH-CPSI scores for measurement of outcomes. Mean age of participants ranged from 29.1 to 56.1 years.

Table 1. Characteristics of Included Studies



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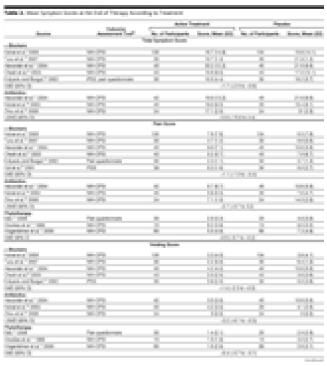
eTable 1 reports the quality assessments of included studies. The agreement between 2 reviewers for each bias assessment domain ranged from 56% to 100% and the overall agreement was 91%. The highest quality was in the domain of selective outcome reports (95.7% low-risk) followed by blinding (87.4%). The lowest quality was in allocation concealment (adequate in 21.7%).

Pooled Mean Scores. Eight studies compared mean scores between α-blockers and placebo. Among them, 4 studies[10,33-35] reported mean scores at follow-up, while the remainder[9,21,24,38] reported change in mean score. Among the latter, 2 studies[9,21] reported information that allowed data simulation and pooling.[9,10,21,33,34]

Three studies[21,39,44] compared antibiotics with placebo and 3 studies[13-15] compared phytotherapy with placebo.

Total Symptom Scores. Five studies[9,10,21,33,34] (n = 568) comparing α-blockers and placebo were pooled (Table 2). Total symptom scores were assessed at the end of treatment, which ranged from 6 to 24 weeks. Mean differences and 95% CIs are shown in eFigure 1A. The total symptom score SMD in the α-blocker group vs the placebo group was −1.7 (95% CIs, −2.8 to −0.6), with high heterogeneity (I^2 = 96.4%). This is equivalent to −5.5 (95% CI, −10.0 to −0.9) units on the NIH-CPSI or IPSS scales. Meta-regression did not identify the source of heterogeneity. Sensitivity analysis was performed by pooling the 4 studies[9,21,33,34] with adequate sequence generation of randomization. In this analysis, the treatment effect was still significant, with a USMD of −4.0 (95% CI, −6.4 to −1.6). The Egger test indicated the presence of publication bias (coefficient = −9.3; SE, 2.5; P = .03) (eFigure 2A). Adjusting for publication bias using regression-based analysis resulted in no evidence of treatment benefit (coefficient = 0.47; P = .39).

Table 2. Mean Symptom Scores at the End of Therapy According to Treatment



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Three studies[21,39,44] (n = 215) were pooled to compare antibiotics with placebo (Table 2). The USMD was −5.8 (95% CI, −15.9 to 4.4). That is, the mean total symptom score in the antibiotic group was 5.8 units lower on the NIH-CPSI scale than in the placebo group, but this did not reach statistical significance ($P = .26$).

Pain Scores. Six studies[9,10,21,33-35] (n = 637) compared mean pain scores between α-blockers and placebo (Table 2 and eFigure 1B). The SMD in the random-effects model was −1.1 (95% CI, −1.8 to −0.3). Patients receiving α-blockers had a 1.1-unit (equivalent to 2.2 points for the NIH-CPSI or 1.9 points for the PSSI/pain questionnaire) significantly lower pain score than patients who received placebo, but this was highly heterogeneous across studies ($I^2 = 94\%$). The source of this heterogeneity was not apparent. A sensitivity analysis limited to the 4 studies[9,21,33,34] with adequate sequence generation yielded an SMD of −0.3 (95% CI, −0.5 to −0.1). The Egger test suggested publication bias due to small-study effect (coefficient = −8.9; $P = .02$) (eFigure 2B). Adjusting for this bias removed the beneficial effect of α-blockers (coefficient = 1.2; 95% CI, −0.1 to 2.4; $P = .06$).

Three studies[21,39,44] with a total of 215 patients compared mean pain scores between antibiotics and placebo. The USMD was −2.7 (95% CI, −8.7 to 3.2); ie, the mean pain score in the antibiotic group was 2.7 NIH-CPSI units lower than in the placebo group, a difference that was not statistically significant (Table 2). There was no evidence of publication bias (coefficient = −9.3; SE, 4.2; $P = .27$).

Three studies[13-15] comparing phytotherapy and placebo were pooled (n = 222). The SMD was −0.5 (95% CI, −0.7 to −0.2); ie, patients receiving phytotherapy had a 0.5-unit significantly lower pain score than patients receiving placebo (Table 2). There was no evidence of publication bias (coefficient = −2.0; $P = .08$).

Voiding Scores. Five studies[9,10,21,33,34] compared α-blockers and placebo for the outcome of voiding scores (n = 568). In the random-effects model, the SMD was −1.4 (95% CI, −2.3 to −0.5). That is, the mean voiding scores were 1.4 units significantly lower in the α-blocker groups than in the placebo groups (Table 2 and eFigure 1C). This difference translates into 3.1 units on the NIH-CPSI and IPSS scales. In sensitivity analyses limited to the 4 studies[9,21,33,34] with adequate randomization, the SMD was −0.7 (95% CI, −1.2 to −0.2). The Egger test suggested publication bias due to small-study effects (coefficient = −9.5; $P = .02$). The contour-enhanced funnel plot indicated asymmetry (eFigure 2C), and adjusting for this bias removed any favorable treatment effect (coefficient = 1.1; 95% CI, −0.4 to 2.6; $P = .10$).

Three studies[21,39,44] comparing antibiotics and placebo (n = 215) had a pooled SMD of −3.2 (95% CI, −6.1 to −0.3) (Table 2). Three studies comparing phytotherapy with placebo (n = 223)[13-15] had an SMD of −0.4 (95% CI, −0.7 to −0.1) (Table 2).

Quality-of-Life Scores. Five studies compared quality-of-life scores between α-blocker and placebo groups (n = 568).[9,10,21,33,34] The SMD was −1.0 (95% CI, −1.8 to −0.2) (or approximately 1.4 units on the NIH-CPSI and IPSS scales) lower in the α-blocker group than in the placebo group. However, results were heterogeneous (eFigure 1D). The contour-enhanced funnel plot suggested publication bias from 2 small studies[10,34] that had strong treatment effects (eFigure 2D); adjusting for this bias removed the significant benefit of α-blockers (coefficient = 1.2; 95% CI, −0.6 to 2.9; $P = .13$).

Three studies[21,39,44] (n = 215) compared quality of life between antibiotics and placebo. The estimated USMD was −1.5 (95% CI, −3.6 to 0.6) NIH-CPSI units lower in antibiotics groups than placebo groups, but this

difference was not statistically significant (Table 2). The Egger test did not suggest publication bias (coefficient = −13.2; SE, 2.7; P = .13).

Pooled Response Rate. Nine studies[9,10,12,21,22,24,33,38,43] included a dichotomized treatment response as the outcome of interest. Of these, 6 studies[9,10,21,24,33,38] compared α-blockers with placebo and 3 studies[12,22,43] compared anti-inflammatory drugs with placebo. Among 6 studies (n = 602) comparing α-blockers with placebo, various criteria were used for assessing treatment responses (Table 3). The pooled RR was 1.6 (95% CI, 1.1-2.3); ie, patients receiving α-blockers were 60% more likely to have a response than patients receiving placebo (eFigure 3A). However, there was moderately high heterogeneity. Meta-regression evaluating duration of treatment reduced the I^2 from 64.2% to 12.8%, indicating that treatment duration may explain the heterogeneity (eFigure 3A). Duration of treatment was 6 to 12 weeks in 3 studies[9,21,24] and 14 to 24 weeks in the other 3 studies.[10,33,38] Pooled RRs within these subgroups were homogeneous (eFigure 3A) at1.0 (95% CI, 0.8-1.3) for 6 to 12 weeks' duration and 2.0 (95% CI, 1.4-3.0) for 14 to 24 weeks' duration, respectively.

Table 3. Treatment Response Rates for α-Blockers and Anti-inflammatory Drugs

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The contour-enhanced funnel plot suggested asymmetry, especially within the 3 studies in which treatment duration ranged from 14 to 24 weeks (eFigure 3B). Metatrim indicated that 3 studies with negative effects of α-blockers were missing. Adding these studies into pooling yielded no benefit from α-blockers, with a pooled RR of 1.1 (95% CI, 0.8-1.7).

Three studies[12,22,43] were pooled to compare anti-inflammatory therapies with placebo (n = 190). The types of anti-inflammatory drugs were cyclooxygenase 2 inhibitors in 2 studies[12,43] and a corticosteroid in 1 study.[22] The pooled RR was 1.8 (95% CI, 1.2-2.6), with mild heterogeneity (I^2 = 24.4%). These results indicate that patients receiving anti-inflammatory drugs were 80% more likely to have a favorable response than patients receiving placebo (Table 3). The Egger test did not suggest publication bias (coefficient = −0.36; P = .90).

Total Symptom Scores. Data from 13 studies (n = 1541)[9,10,14,15,21,33,39-45] using the NIH-CPSI were included in network meta-analyses for the outcome of total symptom score (eTable 2). Treatment comparisons are described in eTable 3 and eFigure 4. Mean total scores at follow-up were, for α-blockers, −11.0 (95% CI, −13.9 to −8.1), for antibiotics, −9.8 (95% CI, −15.1 to −4.6), for α-blockers plus antibiotics, −13.8 (95% CI, −17.5 to −10.2), and for finasteride, −4.6 (95% CI, −8.7 to −0.5) units significantly lower than placebo groups. In this instance, α-blockers plus antibiotics were better than any other therapy and were significantly better than α-blockers alone (−2.9; 95% CI, −5.2 to −0.5).

Pain Scores. The network meta-analysis was performed with 14 studies[9-11,13-15,21,33,39,41-45] that used similar NIH-CPSI scores (eTable 2). α-Blockers, antibiotics, α-blockers plus antibiotics, and anti-inflammatory drugs were associated with significantly better pain scores at follow-up than placebo, with pain scores of −4.1 (95% CI, −5.9 to −2.3), −4.4 (95% CI, −7.0 to −1.9), −5.7 (95% CI, −7.8 to −3.6), and −3.0 (95% CI, −5.7 to −0.4), respectively (eTable 3 and eFigure 5). Again, the most favorable therapy was α-blockers plus antibiotics (eFigure 5).

Voiding Scores. Thirteen studies[9,10,13-15,21,33,39,41-45] (n = 631) were included in the voiding analysis (eTable 2 and eFigure 6). Mean voiding scores at follow-up for α-blockers, antibiotics, and α-blockers plus antibiotics were −3.4 (95% CI, −4.8 to −2.1), −2.8 (95% CI, −4.1 to −1.6), and −3.7 (95% CI, −5.2 to −2.1) units significantly lower than for placebo (eTable 3). Again, the best treatment in the network comparisons was α-blockers plus antibiotics.

Quality-of-Life Scores. Twelve studies (n = 1477)[9,10,14,15,21,33,39,41-45] were included in the quality-of-life analysis (eTable 2). Associations of α-blockers, antibiotics, and α-blockers plus antibiotics (−1.9; 95% CI, −3.6 to −0.2) were significantly better than placebo (eTable 3 and eFigure 7). α-Blockers plus antibiotics was the best treatment in the network comparisons, with a decrease of −2.8 (95% CI, −4.7 to −0.9) units in the quality-of-life score.

Response Rate. Fourteen studies[9,10,12,15,21,22,24,33,36,38-40,43,45] (n = 1561) reported favorable response to treatment (eFigure 8 and eTable 4). The RR of treatment response was highest with anti-inflammatory drugs (RR, 1.8; 95% CI, 1.3-2.6), followed by phytotherapy (RR, 1.6; 95% CI, 1.1-2.4) and α-blockers (RR, 1.3; 95% CI, 1.0-1.6) compared with placebo (eTable 5). Anti-inflammatory therapies were the best treatment in the network comparisons.

COMMENT

We performed a systematic review and meta-analysis of outpatient treatments for CP/CPPS. We studied relevant clinical outcomes, including total clinical symptom, voiding, pain, and quality-of-life scores, as well as treatment response rates. α-Blockers, antibiotics, and a combination of the 2 appear to improve all clinical symptom scores compared with placebo, while anti-inflammatory drugs, finasteride, and phytotherapies have a lesser but measureable effect on select variables (ie, pain, voiding symptoms, and treatment response rate, respectively). However, the treatment effects of α-blockers are distorted by publication bias/small-study effects, and adjusting for this removes any treatment benefit.

Given the large number of treatment options, meta-analyses of direct comparisons are limited by the small number of studies that evaluated a particular pair of treatments. Network meta-analysis circumvents this problem by creating indirect comparisons and allowing data synthesis that can help identify the most effective therapy. In this case, α-blockers plus antibiotics was consistently the best therapy when the outcome was symptom scores. Anti-inflammatory drugs were the best therapy when treatment response was the outcome; although steroids and nonsteroidal anti-inflammatory drugs were pooled together because of the small number of studies, the heterogeneity was low, indicating that their effects may be similar.

Treatment benefits (whether we measured effect on symptom scores or responder rates) were modest for some therapies and nonexistent for others. This probably reflects the heterogeneous nature of patients presenting with CP/CPPS. Patients with CP/CPPS represent a group of divergent clinical phenotypes based on the various etiologies and pathogenic pathways that underlie this enigmatic condition.[46] As a result of difficulties in diagnoses, some patients (in clinical trials and practice) likely receive inappropriate therapies. It makes clinical sense that patients with predominant voiding dysfunction may respond best to α-blockers, those with a history of urinary tract infection may respond best to antibiotics, and those with pain/inflammation may respond best to anti-inflammatory drugs and/or gabapentinoids. However, further study is needed to determine whether patient characteristics determine the most effective therapy for CP/CPPS.

Because the diagnosis of CP/CPPS requires exclusion of infection, the reason for the benefit associated with antibiotics is not immediately clear. This observed effect may be due to the eradication or suppression of uncultured or unrecognized uropathogens that may be measurable with polymerase chain reaction.[47-49] In addition, it is important to point out that quinolones have anti-inflammatory[50,51] and analgesic properties.[52]

While the results of our analyses demonstrate that α-blockers, antibiotics, and anti-inflammatory medications are beneficial for CP/CPPS, we recognize that the total sample sizes are relatively small and that the effect sizes are modest and often below the minimal clinically significant difference. Furthermore, even these estimates may be overinflated given the evidence for publication bias. Our results suggest that future research should focus on using these treatments rationally, perhaps using individualized patient therapy or multiple therapies directed toward the specific clinical phenotype of each unique patient.[53] This concept is presently being evaluated.[49]The decision to use these therapies also needs to take account of the adverse event profile: α-blockers can cause postural hypotension, edema, and drowsiness; quinolones can cause dizziness, headaches, and gastrointestinal upset; and nonsteroidal anti-inflammatory drugs can cause gastritis, renal impairment, and edema. The risk-benefit ratio remains to be determined.

Our study has several strengths. The review methods were systematic and exhaustive. Contour-enhanced funnel plots helped to identify possible publication bias due to small-study effects, which tend to lead to higher treatment effects than large studies.[25,26] We mapped all possible treatment comparisons (9 treatments with 36 possible pairwise comparisons) using a network meta-analysis.[27-29] An advantage of network meta-analysis is the ability to “borrow” information on the treatment groups from other studies, thereby increasing the total sample sizes. For example, direct comparisons in a previous meta-analysis[16] included 466, 236, and 123 patients in pooling for total symptom, pain, and voiding scores, respectively, comparing α-blockers vs placebo. In the current analysis, the corresponding numbers of patients were 1549, 1556, and 1546. We applied a mixed

model, which is thought to be the most appropriate method for network meta-analysis.[27,54] Although our pooled estimates were quite heterogeneous, the mixed model with random intercept takes into account variations at the study level.

These methods have limitations, however. Although all studies were randomized controlled trials, most studies were unclear in randomization sequence generations and, hence, selection bias or confounding might be present. Pooled results were often heterogeneous and the source of this difference was not apparent.

CONCLUSION

Our review suggests that α-blockers, antibiotics, or combinations of both are most appropriate for therapy of CP/CPPS, particularly for patients with voiding symptoms. However, the magnitude of apparent benefit with α-blockers may be distorted by publication bias. Anti-inflammatory medications remain an option for patients presenting with pain. While finasteride and phytotherapy may provide benefit to some patients, these therapies require more evaluation, perhaps in selected subgroups of CP/CPPS patients.

ARTICLE INFORMATION

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Author Contributions: Dr Thakkinstian had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Anothaisintawee, Attia, Nickel, McEvoy, Thakkinstian.

Drafting of the manuscript: Anothaisintawee, Thakkinstian.

Critical revision of the manuscript for important intellectual content: Attia, Nickel, Thammakraisorn, Numthavaj, McEvoy, Thakkinstian.

Statistical analysis: Anothaisintawee, Thakkinstian.

Administrative, technical, or material support: Thammakraisorn, Numthavaj, Thakkinstian.

Study supervision: Attia, Nickel, Thakkinstian.

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