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α-blockers, antibiotics and anti-inflammatories have a role in the management of chronic prostatitis/chronic pelvic pain syndrome

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Accepted for publication 9 November 2011

Study Type – Therapy (systematic review)
Level of Evidence 1a

What's known on the subject? and What does the study add?
Individual clinical trials evaluating antibiotics, anti-inflammatories and α-blockers for the treatment of chronic prostatitis/chronic pelvic pain syndrome have shown only modest or even no benefits for patients compared with placebo, yet we continue to use these agents in selected patients with some success in clinical practice.

This network meta-analysis of current evidence from all available randomized placebo-controlled trials with similar inclusion criteria and outcome measures shows that these '3-As' of chronic prostatitis/chronic pelvic pain syndrome treatment (antibiotics, anti-inflammatories and α-blockers) do offer benefits to some patients, particularly if we use them strategically in selected individuals.

OBJECTIVES

- To provide an updated network meta-analysis mapping α-blockers, antibiotics and anti-inflammatories (the 3-As) in chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).
- To use the results of this meta-analysis to comment on the role of the 3-As in clinical practice.

PATIENTS AND METHODS

- We updated a previous review including only randomized controlled studies employing the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) as one of the outcomes to compare treatment effects in CP/CPPS patients.
- A longitudinal mixed regression model (network meta-analysis) was applied to indirectly assess multiple treatment comparisons (i.e. α-blockers, antibiotics, anti-inflammatory/immune modulation therapies, α-blockers plus antibiotics, and placebo).

RESULTS

- Nineteen studies (1669 subjects) were eligible for analysis.
- α-blockers, antibiotics and anti-inflammatory/immune modulation therapies were associated with significant improvement in symptoms when compared with placebo, with mean differences of total CPSI of −10.8 (95% CI −13.2 to −8.3; $P < 0.001$), −9.7 (95% CI −14.2 to −5.3; $P < 0.001$) and −1.7 (95% CI −3.2 to −0.2; $P = 0.032$) respectively, while α-blockers plus antibiotics resulted in the greatest CPSI difference (−13.6, 95% CI −16.7 to −10.6; $P < 0.001$).
- With respect to responder analysis compared with placebo, anti-inflammatories showed the greatest response rates (risk ratio 1.7, 95% CI 1.4–2.1; $P < 0.001$) followed by α-blockers (risk ratio 1.4, 95% CI 1.1–1.8; $P = 0.013$) and antibiotics (risk ratio 1.2, 95% CI 0.7–1.9; $P = 0.527$).

CONCLUSIONS

- α-blockers, antibiotics and/or anti-inflammatory/immune modulation therapy appear to be beneficial for some patients with CP/CPPS.
- The magnitude of effect and the disconnect between mean CPSI decrease and response rates compared with placebo suggest that directed multimodal therapy, rather than mono-therapy, with these agents should be considered for optimal management of CP/CPPS.

KEYWORDS

chronic prostatitis/chronic pelvic pain syndrome, chronic prostatitis, α-blockers, antibiotics, anti-inflammatories, meta-analysis

INTRODUCTION

Prostatitis has traditionally been associated with inflammation in the prostate gland with infection and voiding disturbances being key aetiological factors [1]. Therapy was therefore directed towards infection, inflammation and voiding problems related to the prostate using a Antibiotics, Anti-inflammatories and Alpha-blockers, the so-called '3-As' of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) treatment [2]. However, our contemporary concept of CP/CPPS is that it is not necessarily prostate-centric, but rather incorporates other extra-prostatic aetio-pathogenic factors such as neurological factors, endocrine factors and muscle dysfunction [3]. A number of major clinical trials, particularly those funded by the National Institutes of Health (NIH) [4,5] failed to show any efficacy for the 3-As of CPPS therapy and physicians were either actively discouraged from prescribing them or prescribed them with the knowledge that they may be no better than placebo.

We recently performed a systematic review and network meta-analysis attempting to evaluate all available medical treatment regimens for CP/CPPS [6]. In that review, we compared total symptom, pain, voiding and quality of life scores at the end of therapy between α-blockers (the most commonly evaluated therapy for CP/CPPS) and other active drugs or placebo groups. We further compared rates of responses to other studied therapies available for treating CP/CPPS. Our conclusion was that many of these medications did have a net benefit in terms of symptom score improvement or relative risk of being a treatment responder compared with placebo; however, studies did not necessarily have similar validated outcomes, for example, the Chronic Prostatitis Symptom Index (CPSI). We now update this effort using a network meta-analysis to map treatment responses in studies that employed the CPSI for at least one of the outcome parameters between antibiotics, agents with anti-inflammatory and/or immunomodulatory activity, α-blockers, combinations of these agents, and placebo. We further include two recently reported studies comparing two doses of silodosin (α-blocker) [7] and a single dose of tanezumab (immune modulator) [8] to placebo.

MATERIALS AND METHODS

Studies were identified from the Medline and EMBASE databases up to 13 January 2011 using search strategies as detailed in a previous report [6]. In addition, two studies presented at the 2011 American Urological Association annual meeting have also been included [7,8].

Randomized controlled studies published in English were included if they met with the following criteria: (i) participants met the criteria for IIIA or IIIB CP/CPPS categories according to the NIH classification [9]; (ii) study compared any pair of the following interventions: α-blockers, antibiotics, drugs with anti-inflammatory or immune modulatory action, or placebo; (iii) at least one of the outcomes was measured by the NIH-CPSI [9] (the total symptoms score, ranged from 0 to 43, was a summation of pain, voiding and quality of life scores); and (iv) full paper or data could be retrieved and had reported number of patients, means and SD of continuous outcomes in each group; numbers available for cross-tabulation between treatment and outcome groups for dichotomous outcomes.

Data were then independently abstracted by two reviewers as described in detail in the previous report [6].

Our studied interventions were grouped into five major categories: (i) any α-blockers (terazosin, doxazosin, tamsulosin, alfuzosin, silodosin); (ii) any antibiotics (ciprofloxacin, levofloxacin, tetracyline); (iii) any medical intervention in which the mechanism of action of the drug was at least in part related to its anti-inflammatory or immune modulatory activity (steroidal and non-steroidal anti-inflammatory drugs, glycosminoglycans, phytotherapy and tanezumab); and (iv) placebo. A fifth category evaluated was the combination of antibiotics and α -blockers.

The outcomes of interests were symptom scores measured using NIH-CPSI (e.g. total symptoms, pain, voiding and quality of life scores) and response rates were as defined in the original papers (e.g. responder definition was 25%, 33% or 50% decreases in NIH-CPSI; or 4–6 (clinically perceptible to moderate improvement) unit score decreases in total NIH-CPSI from baseline).

Network meta-analyses were applied to assess treatment effects for all possible treatment arms if summary data were available [10–12]. With the five treatment groups, network meta-analysis gains over a direct meta-analysis because individual studies had different head-to-head comparisons, and there were also limitations of a small number of studies that looked at a particular comparison. The network borrows information on the treatment groups from other studies and increases the total sample sizes.

Linear regression models weighted by inverse variance were applied by including five treatment groups (i.e. α-blockers, antibiotics, anti-inflammatories, α-blockers plus antibiotics, and placebo) as the study factor and adjusting for study effects. For response to treatment, summary data were expanded to individual patient data using the 'expand' command in STATA. Treatment groups were included in a binary regression model with adjusting cluster (study) effects. The pooled risk ratios (RR) and 95% CI were estimated by exponential coefficients of treatments. All analyses were performed using STATA version 11.0 [13]. *P* values with two-sided tests <0.05 were considered statistically significant.

RESULTS

Study selection flow is described in Fig. 1. Among 19 published eligible studies based on NIH-CPSI scores, two studies were excluded because they were not compatible with the 3-A study plan (e.g. finasteride [14], pregabalin [15]). Two studies presented at the 2011 American Urological Association annual meeting have been included [7,8]. In this analysis, 13 studies had compared mean total symptom scores, 14 studies compared mean pain scores, 13 studies compared mean voiding scores, 13 studies compared quality of life scores, and 14 studies compared response to treatments. Study characteristics for clinical trials used in this analysis are given in Table 1. Mean scores at follow-up and treatment responsiveness are described in Tables 2 and 3, respectively.

Thirteen studies [4,5,7,8,16–24] with 1352 subjects were eligible for comparing mean total symptom scores. As described in Table 4 and Fig. 2, mean total scores at follow-up for all treatments were

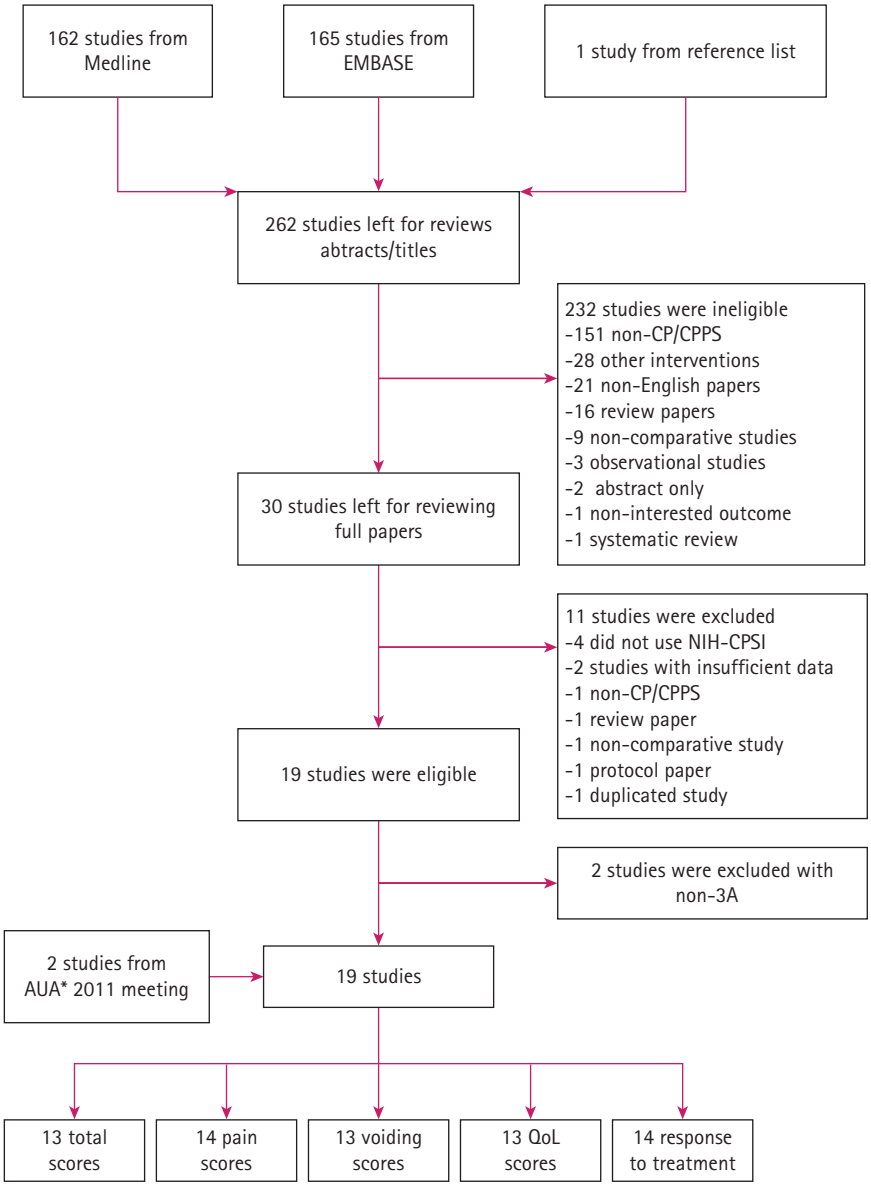
significantly lower than for placebo with the scores of −10.8 ($P < 0.001$; 95% CI −13.2 to −8.3) for α-blockers, −9.7 ($P < 0.001$; 95% CI −14.2 to −5.3) for antibiotics, −1.7 ($P = 0.032$; 95% CI −3.2 to −0.2) for anti-inflammatory drugs, and −13.6 ($P < 0.001$; 95% CI −16.7 to −10.6) for the combination of α-blockers and antibiotics. The combination of α-blockers and antibiotics was also significantly better than α-blockers alone ($P = 0.009$; −2.9, 95% CI −4.9 to −0.9) and marginally better than antibiotics alone ($P = 0.098$; −3.9, 95% CI −8.6 to 0.8). In Fig. 2, the combination of α-blockers and antibiotics is the box to which all the arrows point, indicating that this is the most effective treatment in the network of comparisons.

Fourteen studies [4,5,7,8,16–25] with 1369 subjects were included in the network meta-analysis of pain scores (Table 4). All treatments significantly improved pain scores compared with placebo with the greatest decrease registered for the combination of α-blockers plus antibiotics (−5.5, $P < 0.001$; 95% CI −7.5 to −3.6). This combination was significantly better than α-blockers alone (−1.6, $P = 0.010$; 95% CI −2.7 to −0.5) and anti-inflammatories (−4.0, $P = 0.003$; 95% CI −6.2 to −1.6) but not significantly better than antibiotics alone (−1.2, $P = 0.351$; 95% CI −3.7 to 1.4).

Thirteen studies [4,5,7,8,16–24] with 1352 subjects were included in the analysis of voiding score (Table 4). Only α-blockers, antibiotics and α-blockers plus antibiotics significantly improved voiding symptoms compared with placebo with scores of −3.2 ($P < 0.001$; 95% CI −4.3 to −2.1), −2.8 ($P < 0.001$; 95% CI −3.9 to −1.7), and −3.5 ($P < 0.001$; 95% CI −4.5 to −2.1) units, respectively.

Thirteen studies with 1352 subjects [4,5,7,8,16–24] were included in the analysis of quality of life score (Table 4). α-blockers, antibiotics, anti-inflammatories and the combination of α-blockers plus antibiotics significantly improved quality of life when compared with placebo with scores of −1.7 ($P = 0.008$; 95% CI −2.9 to −0.5) for α-blockers, −1.9 ($P = 0.008$; 95% CI −3.2 to −0.6) for antibiotics, −0.6 ($P = 0.012$; 95% CI −1.1 to −0.2) for anti-inflammatories, −2.8 ($P = 0.002$; 95% CI −4.2 to −1.3) for α-blockers plus antibiotics, respectively.

*FIG. 1. Flow of study selection. *American Urology Association.*



Fourteen studies [4,5,7,17–20,22,24,26–30] with 1349 subjects were included in the network meta-analysis of treatment responsiveness (Fig. 3, Table 5). The relative risks of treatment-response, compared with placebo, was highest for anti-inflammatories (1.7, $P < 0.001$; 95% CI 1.4–2.1) followed by α-blockers (1.4, $P = 0.013$; 95% CI 1.1–1.8,). Paradoxically, the combination of α-blockers plus antibiotics did not show any favourable response; indeed Fig. 3 shows all arrows pointing away from this option, indicating that it is the weakest therapy for this outcome.

DISCUSSION

Despite general pessimism among prostatitis researchers on the benefits of the most common traditional treatments for CP/CPPS, our updated network meta-analysis clearly indicates a treatment benefit with the 3-As of traditional therapy. α-blockers, antibiotics, anti-inflammatories/immune modulators and the combination of the α-blockers and antibiotics improved total CPSI symptom scores compared with placebo, albeit very modestly for the anti-inflammatory category. These therapies showed

TABLE 1 Characteristics of included studies

Author	Intervention	No. of subjects	Duration of treatment (weeks)	Mean age (SD)	Mean total symptom score* (SD)
Nickel [16], 2005	Pentosan polysulphate	51	16	39.2 (21–59)†	26.5 (1.6)
	Placebo	49			
Cheah [17], 2003	Terazosin	43	14	35.5 (20–50)†	26.2 (1.6)
	Placebo	43			
Nickel [18], 2003	Levofloxacin	45	6	56.1 (36–78)†	23.0 (1.7)
	Placebo	31			
Shoskes [19], 1999	Quercetin	15	4	44.9 (5.4)	20.6 (2.1)
	Placebo	13			
Tugcu [20], 2007	Doxazosin	30	24	29.1 (5.2)	23.0 (0.4)
	Placebo	30			
Ye [21], 2008	Tamsulosin + levofloxacin	42	12	–	27.6 (–)
	Tamsulosin	42			
	Levofloxacin	21			
Zhao [22], 2009	Celecoxib	32	6	-	24.4 (1.4)
	Placebo	32			
Zhou [23], 2008	Tetracycline HCl	24	12	–	34.3 (1.2)
	Placebo	24			
Alexander [4], 2004	Tamsulosin	45	6	44.6 (3.2)	24.8 (1.7)
	Ciprofloxacin	42			
	Tamsulosin + Ciprofloxacin	42			
	Placebo	45			
Nickel [5], 2008	Alfuzosin	138	12	40.1 (1.4)	24.4 (0.7)
	Placebo	134			
Wagenlehner [24], 2009	Cernilton	68	12	39.5 (8.1)	19.8 (5.2)
	Placebo	68			
Nickel [7], 2011	Silodosin	97	12	48.4(13.5)	26.9(6.1)
	Placebo	51			
Nickel [8], 2011	Tanezumab	25	6	(21–72)†	13.3 (2.0)
	Placebo	26			
Bates [26], 2007	Prednisolone	9	4	40.8 (4.6)	24.3 (3.0)
	Placebo	12			
Goldmeier [25], 2005	Zafirlukast	10	4	35.9 (5.7)	–
	Placebo	7			
Jeong [27], 2008	Doxazosin + levofloxacin	29	6	40.1 (23–60)†	23.1 (2.2)
	Doxazosin	26			
	Levofloxacin	26			
Mehik [28], 2003	Alfuzosin	17	24	49.5 (–)	24.4 (–)
	Placebo	20			
Nickel [29], 2004	Tamsulosin	27	6	40.8 (21–56)†	26.3 (–)
	Placebo	30			
Nickel [30], 2003	Rofecoxib	49	6	46.8 (2.5)	21.8 (1.1)
	Placebo	59			

**National Institutes of Health-Chronic Prostatitis Symptom Index score measured at baseline range from 0 to 43. †Range.*

improvement in all the sub-scores of the CPSI, although not all comparisons reached statistical significance (e.g. anti-inflammatory effect on voiding sub-score). On the other hand, anti-inflammatories showed a greatest responder rate compared with placebo than the other treatments.

Employing a network meta-analysis, the various treatment categories can be compared with each other with the combination of α-blockers and antibiotics showing the greatest benefit in terms of CPSI change, but paradoxically the weakest chance of being a responder.

Direct meta-analyses in CP/CPPS are limited by the large number of treatment options and small number of studies that evaluate a particular pair of treatments. The network meta-analysis circumvents this problem by borrowing common comparators to create indirect comparisons and help identify the

TABLE 2 Sample size, mean and SD between treatment groups for studies at end of each study period included in a network meta-analysis

		Total symptom scores			Pain			Voiding			Quality of life		
Author	Treatments	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Alexander [4]	α-Blockers	45	20.2	12.2	45	9.0	7.1	45	4.2	4.0	45	6.9	3.4
	Antibiotics	42	18.0	13.2	42	8.7	6.7	42	3.5	3.8	42	5.8	3.9
	α-Blockers + Antibiotics	42	21.3	11.9	42	10.2	6.9	42	3.9	3.3	42	6.9	3.3
	Placebo	45	21.6	9.8	45	10.6	5.8	45	10.6	5.8	45	7.1	3.3
Nickel [5]	α-Blockers	138	16.7	14.9	138	7.8	7.6	138	3.3	4.0	138	3.3	2.5
	Placebo	134	18.6	14.1	134	8.5	7.6	134	3.9	4.1	134	3.5	2.3
Nickel [7]	Silodosin	97	15.1	8.9	97	6.9	4.5	97	3.5	2.8	97	4.7	3.0
	Placebo	51	19.5	9.4	51	8.8	4.7	51	5.2	3.1	51	5.9	3.2
Nickel [8]	Tanezumab	25	21.0	6.8	25	10.0	3.3	25	3.9	2.5	25	7.1	3.1
	Placebo	26	22.4	7.2	26	11.3	3.6	26	3.4	3.8	26	7.7	2.8
Nickel [16]	Glycosaminoglycan	51	21.2	0.99	51	9.7	1.11	51	4.8	0.63	51	6.9	0.33
	Placebo	49	22.6	0.99	49	10.6	1.11	49	4.6	0.63	49	7.5	0.33
Cheah [17]	α-Blockers	43	10.8	9.0	43	5.2	5.7	43	2.0	2.8	43	3.6	3.4
	Placebo	43	17.0	12.1	43	7.8	6.7	43	3.6	3.6	43	5.5	3.9
Nickel [18]	Antibiotic	45	19.0	9.5	45	8.9	5.0	45	4.2	3.0	45	3.7	1.8
	Placebo	35	18.4	9.1	35	7.6	4.7	35	4.1	2.8	35	3.8	1.7
Shoskes [19]	Phytotherapy	15	13.0	6.58	15	6.2	3.87	15	1.5	1.94	15	4.9	2.67
	Placebo	13	18.8	6.85	13	9.0	3.17	13	3.0	2.7	13	6.8	2.88
Tugcu [20]	α-Blockers	30	10.7	1.3	30	4.7	1.2	30	2.2	0.8	30	3.8	1.1
	Placebo	30	21.9	1.2	30	8.6	0.8	35	4.1	2.8	30	6.9	1.1
Ye [21]	α-Blockers	42	14.32	1.19	42	6.03	0.73	42	2.05	0.66	42	6.24	0.67
	Antibiotics	21	8.05	2.16	21	8.05	2.16	21	2.76	2.05	21	7.81	2.06
	α-Blockers + Antibiotics	42	11.5	1.06	42	4.5	0.69	42	1.81	0.53	42	5.19	0.61
Zhao [22]	Anti-inflammatory	32	16.6	2.4	32	7	1.4	32	4.6	1.6	32	4.75	1.5
	Placebo	32	20.8	2.5	32	10.2	1.4	32	4.4	1.6	32	5.75	1.5
Zhou [23]	Antibiotic	24	17.1	2.8	24	7.1	1	24	5.0	0.8	24	5.5	0.6
	Placebo	24	31	2.5	24	14.5	2.0	24	8.0	0.5	24	8.5	1.0
Wagenlehner [24]	Phytotherapy	68	11.6	8.8	68	5.5	4.9	68	1.8	2.9	68	4.3	3.7
	Placebo	68	15.1	8.7	69	7.3	5.0	69	2.6	3.1	69	5.4	3.4
Goldmeir [25]	Anti-inflammatory	–	–	–	10	7.9	4.5	–	–	–	–	–	–
	Placebo	–	–	–	7	6.3	3.5	–	–	–	–	–	–

most effective therapy. Variation between studies or study effects were considered and accounted for in the regression models. In this case, α-blockers plus antibiotics were consistently the best option, followed by mono-therapy α-blockers, or antibiotics, and anti-inflammatories when the outcome was clinical symptom score. This finding is different compared with the previous pooling [6], in which anti-inflammatory effects could not be identified. This may be because combining all anti-inflammatory therapies into one group led to increased power to detect treatment effects. This pooling however does lead to increased clinical heterogeneity (e.g. pooling NSAIDS and biological immune modulators) and the treatment effect was only 1.7 units, which is probably not large enough to translate into a clinically important difference.

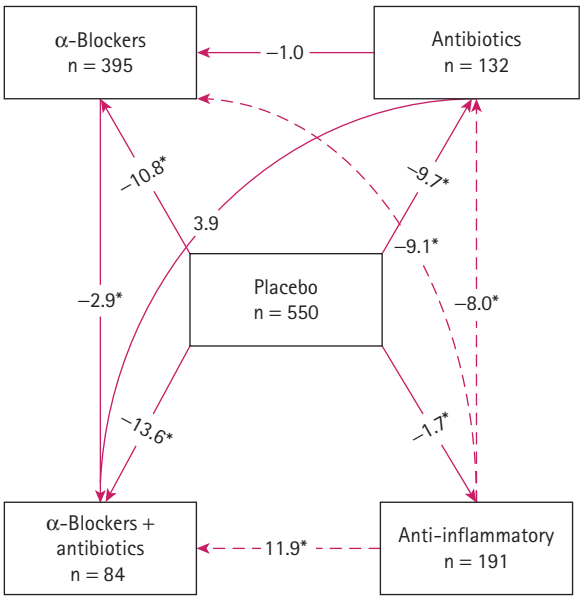


FIG. 2.
Network meta-analysis of total symptom scores. A line in the figure represents treatment comparisons with arrows and tails referring to intervention and comparators, respectively. Bold and dashed lines refer to direct and indirect comparisons, respectively. The number at the line indicates treatment difference, in which a negative figure indicates lower scores, i.e. favours intervention versus the comparator. Inteventions to which the most arrows point are therefore the strongest.

TABLE 3 Frequencies between treatments and response to treatments for studies included in a network meta-analysis

Author	Definition of response to treatments	Treatment	N	No. of responses	No. of non-responses
Alexander [4]	Score decreased 4 points from baseline	α-Blockers	45	12	33
		Antibiotics	42	11	31
		α-Blockers + Antibiotics	42	5	37
		Placebo	45	11	34
Nickel [5]	Score decreased 4 points from baseline	α-Blockers	138	68	70
		Placebo	134	66	68
Nickel [7]	Score decreased 6 points from baseline	Silodosin	87	67	20
		Placebo	61	31	30
Cheah [17]	Score decreased 4 points from baseline	α-Blockers	43	24	19
		Placebo	43	14	29
Nickel [18]	Score decreased 6 points from baseline	Antibiotics	45	20	25
		Placebo	35	13	22
Shoskes [19]	Score decreased 25% from baseline	Phytotherapy	15	10	5
		Placebo	13	3	10
Tugcu [20]	Score decreased 50% from baseline	α-Blockers	30	20	10
		Placebo	30	19	11
Zhao [22]	Score decreased 25% from baseline	Anti-inflammatory	32	25	7
		Placebo	32	10	22
Wagenlehner [24]	Score decreased 25% from baseline	Phytotherapy	68	47	21
		Placebo	69	33	36
Bates [26]	Score decreased 6 points from baseline	Anti-inflammatory	6	2	4
		Placebo	12	4	8
Jeong [27]	Score decreased 33% from baseline	α-Blockers	26	9	17
		Antibiotics	26	21	5
		α-Blockers + Antibiotics	29	21	8
Mehik [28]	Score decreased 33% from baseline	α-Blockers	17	13	4
		Placebo	29	9	20
Nickel [29]	Score decreased 50% from baseline	α-Blockers	27	9	18
		Placebo	30	5	25
Nickel [30]	Score decreased 25% from baseline	Anti-inflammatory	49	31	18
		Placebo	59	24	35

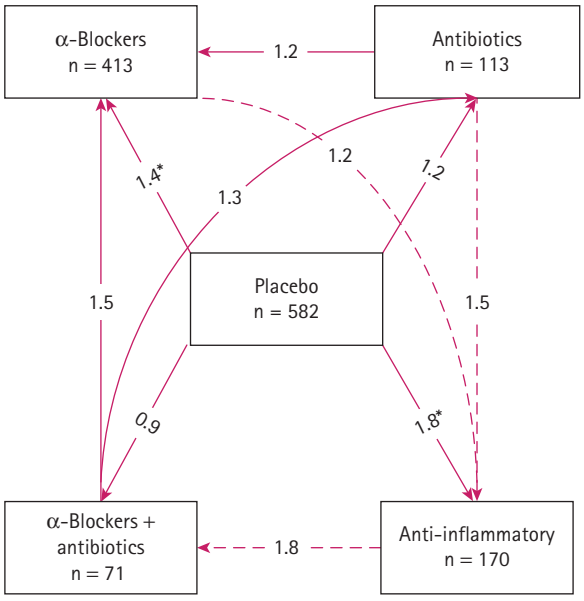


FIG. 3.
Network meta-analysis of treatment responsiveness. A line in the figure represents treatment comparisons with arrows and tails referring to intervention and comparators, respectively. Bold and dashed lines refer to direct and indirect comparisons, respectively. The number at the line indicates chance of treatment responsiveness, in which >1 indicates favours intervention versus comparator. Inteventions to which the most arrows point are therefore the strongest.

Anti-inflammatories were the best therapy followed by α-blockers when treatment response was the outcome. All anti-inflammatory drugs (i.e. NSAIDs, glycosminoglycans, phytotherapy and tanezumab) were pooled for symptom scores but only NSAIDs and phytotherapy were available to pool for response to treatments. Although the heterogeneity of anti-inflammatory effects on symptom scores was high (I^2 = 82.0%), the direction of treatment effects was similar. The heterogeneity was low (I^2 = 17.4%) for response to treatment, indicating that the effects of NSAIDs and phytotherapy may be similar.

Results are discrepant between the analyses of symptom scores and treatment responsiveness. α-blockers are better than

anti-inflammatory drugs in symptom score improvement but not for treatment responsiveness. Criteria used for classifying the treatment response were varied. Studies with α-blockers used more rigid criteria, i.e. four studies used a 4-unit change in score to define responsiveness, one study used a 6-unit score change, two studies used a 33% decrease in scores, and two studies used a 50% decrease in scores. Studies with anti-inflammatory drugs used more lenient criteria; four studies used a 25% decrease in scores, and only one study used a 6-unit decrease. Whereas each of these definitions of response have some inherent justification, the 4-unit change (clinically perceptible improvement) and 6-unit change (clinically significant improvement) have the most validity [31]. The different responder definitions in the various studies represent one of the limitations of our analysis which used summary data for symptom score and treatment responsiveness.

So how does the clinician interpret these findings, particularly the mild/modest magnitude of effect and the disconnect between CPSI decrease and response rates for the various treatments compared with placebo? It can now be unequivocally stated that the traditional 3-As of prostatitis therapy do indeed provide at least some clinical benefit for some patients. However, the benefits for symptoms are, at most, modest and, for many, probably not clinically significant. A realistic goal of clinicians and patients should not only be amelioration of symptoms but improvement in impact of the condition on their activities and quality of life. This analysis shows that a modest improvement in quality of life is possible using a 3-As medical therapy strategy. But the benefits of mono-therapy, both in this analysis and in clinical practice [32] may be deceptive, not providing as much benefit as we would like. For example, it is likely that patients who have failed previous treatment with empiric antibiotics or α-blockers will not benefit from further exposure to these medications [4]. It has been suggested that we should try and tailor the type of treatment we use to the individual patient's phenotype [32]. There are very few combination randomized controlled trials available, however, as the combination of antibiotics and α-blockers produced the greatest effect on symptoms in this analysis, it would seem that multimodal therapy may be a key to improved results. In fact,

TABLE 4 Comparison of total- and sub-NIH-CPSI scores between α-blocker, antibiotic and anti-inflammatory drugs: a network meta- analysis

	CPSI Total		CPSI Pain		CPSI Voiding		CPSI QoL/Impact	
Treatments	Mean difference (95% CI)	*P*-value	Mean difference (95% CI)	*P*-value	Mean difference (95% CI)	*P*-value	Mean difference (95% CI)	*P*-value
α-blockers versus Placebo	−10.8 (−13.2 to −8.3)	<0.001	−3.9 (−5.6 to −2.3)	<0.001	−3.2 (−4.3 to −2.1)	<0.001	−1.7 (−2.9 to −0.5)	0.008
α-blockers versus Antibiotics	−1.0 (−5.6 to 3.5)	0.630	0.4 (−2.1 to 2.9)	0.710	−0.4 (−1.9 to 1.0)	0.546	0.2 (−1.4 to 1.8)	0.827
α-blockers versus Anti-inflammatories	−9.1 (−11.9 to −6.2)	<0.001	−2.4 (−4.5 to −0.3)	0.031	−3.3 (−4.7 to −2.0)	<0.001	−1.1 (−2.4 to 0.2)	0.085
α-blockers versus α-blockers + Antibiotics	2.9 (0.9–4.9)	0.009	1.6 (0.5–2.7)	0.010	0.3 (−0.6 to 1.1)	0.514	1.0 (0.1–2.0)	0.038
Antibiotics versus Placebo	−9.7 (−14.2 to −5.3)	<0.001	−4.4 (−6.7 to −2.0)	0.001	−2.8 (−3.9 to −1.7)	<0.001	−1.9 (−3.2 to −0.6)	0.008
Antibiotics versus Anti-inflammatories	−8.0 (−12.8 to −3.3)	0.003	−2.8 (−5.4 to −0.1)	0.040	−2.9 (−4.2 to −1.5)	<0.001	−1.3 (−2.6 to 0.1)	0.068
Antibiotics versus α-blockers + Antibiotics	3.9 (−0.8 to 8.6)	0.098	1.2 (−1.4 to 3.7)	0.351	0.7 (−0.9 to 2.2)	0.365	0.9 (−0.9 to 2.6)	0.305
Anti-inflammatories versus Placebo	−1.7 (−3.2 to −0.2)	0.032	−1.6 (−2.7 to −0.5)	0.017	0.1 (−0.7 to 0.8)	0.827	−0.6 (−1.1 to 0.2)	0.012
Anti-inflammatories versus α-blockers + Antibiotics	11.9 (8.5–15.4)	<0.001	4.0 (1.6–6.2)	0.003	3.6 (2.0–5.1)	<0.001	2.1 (0.6–3.7)	0.011
α-blockers + Antibiotics vs Placebo	−13.6 (−16.7 to −10.6)	<0.001	−5.5 (−7.5 to −3.6)	<0.001	−3.5 (−4.5 to −2.1)	<0.001	−2.8 (−4.2 to −1.3)	0.002

Anti-inflammatory drugs: non-steroidal anti-inflammatories/Cox-2 inhibitor or anti-inflammatory phytotherapy or glycosaminoglycan or tanezumab.

TABLE 5 Treatment response rates for α-blockers, antibiotics, anti-inflammatories and others

Treatments	RR	*P* value	95% CI
Anti-inflammatories versus Placebo	1.7	<0.001	1.4–2.1
α-blockers versus Placebo	1.4	0.013	1.1–1.8
Antibiotics versus Placebo	1.2	0.527	0.7–1.9
α-blockers + Antibiotics versus Placebo	0.9	0.894	0.3–2.8
Anti-inflammatories versus α-blockers	1.2	0.085	0.9–1.6
Anti-inflammatories versus Antibiotics	1.5	0.122	0.9–2.4
Anti-inflammatories versus α-blockers + Antibiotics	1.8	0.296	0.6–5.8
α-blockers versus Antibiotics	1.2	0.518	0.7–1.9
α-blockers versus α-blockers + Antibiotics	1.5	0.494	0.5–4.6
Antibiotic versus α-blockers + Antibiotics	1.3	0.503	0.6–2.5

this seems to be the case in clinical practice [33] and the benefits appear to be more significant when multimodal therapy is individualized according to the patient's clinical phenotype [34]. There is no doubt that the addition of non-medical therapies including diet and behavioural modification, physiotherapy and psychotherapy must be incorporated into our therapeutic strategy.

The important question that needs to be answered, if we accept that the 3-As can provide some benefits to some patients, is how to adapt the 3-As to clinical practice? Antibiotics can be considered in patients who, despite not having a history of recurrent urinary tract infections (the definition of category II chronic bacterial prostatitis), show uropathogenic bacteria in cultures of prostate-specific specimens (e.g. expressed prostatic fluid or urine after prostate massage), in those with a previous good response to antibiotics and an argument can be made for antibiotic-naive patients. α-blockers theoretically should most benefit those with lower urinary tract symptoms (particularly voiding/obstructive), but as a mono-therapy this class will only provide modest clinical improvement for some patients. A trial of anti-inflammatories would seem to be best suited for those with pain (by definition all patients with CP/CPPS) and/or prostate inflammation (however, most physicians do not perform microscopic examination of differential urines or expressed prostatic secretions), but this present analysis shows that although there is a greater chance of being categorized as a responder with anti-inflammatories compared with placebo, the magnitude of response in the entire population of CP/CPPS men was not clinically significant. This suggests that anti-inflammatories (as well as antibiotics and α-blockers) are not effective mono-therapies, but should be used as part of a rationale multi-modal therapeutic strategy. The reader is directed to a recent review article published in *BJU International* [33] for a detailed description of this individually designed phenotype-directed treatment approach. For the reasons described above, the results from this network meta-analysis, lend further credence to this individualized therapeutic strategy.

CONFLICT OF INTEREST

J Curtis Nickel is a consultant and/or investigator for Pfizer, Watson, Farr, Triton, Cernelle.

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Abbreviations: **CP/CPPS**, chronic prostatitis/chronic pelvic pain syndrome; **NIH**, national institutes of Health; **CPSI**, Chronic Prostatitis Symptom Index.