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TOPIC PAPER

Management of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): the studies, the evidence, and the impact

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Abstract
Introduction The development of an accepted clinical definition, classification system and validated outcome questionnaire for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) has led to a flurry of clinical trial activity over the last 15 years.
Methods Twenty-four of these studies enrolled a homogeneous population of CP/CPPS patients, were prospective randomized placebo or sham controlled, and employed the National Institutes of Health chronic prostatitis symptom index (CPSI) as an outcome parameter.
Results This review of the evidence and clinical impact from these studies suggests that physician's strict adherence to a rigid evidence-based approach for the treatment of a CP/CPPS patient will result in disappointed patients as well as disappointed physicians.
Conclusions There is no one particular treatment that shows significant clinical efficacy to be recommended as a mono-therapy for CP/CPPS. Therefore, the physician must adapt his knowledge and interpretation of the evidence from randomized placebo- and sham-controlled trials to determine what therapy or therapies are best indicated for each individual patient.

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Introduction

It seems almost inconceivable that only 15 years ago we would not have studies or the data to even contemplate a review article on the topic of evidence-based management of CP/CPPS. All the studies to that date in the field of prostatitis were involved in evaluating antimicrobial therapy for the small percentage of chronic prostatitis patients with a bacterial etiology characterized by recurrent urinary tract infections or uropathogenic bacteria cultured in prostate-specific specimens. For those studies, the objective outcome was eradication of the offending uropathogen in the urine or expressed prostatic secretions. Very few of these antimicrobial randomized clinical trials assessed the symptom response of patients enrolled in these specific studies. Many of us who were investigators in these studies were sometimes surprised by the lack of correlation seen in many patients between bacterial eradication and amelioration of symptoms. The National Institutes of Health/NIDDK consensus meeting in 1995 established classification of the prostatitis symptoms including definition of the often neglected enigmatic presumed prostate-related pain syndrome previously referred to as chronic non-bacterial prostatitis and/or prostatodynia. Category 3 chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) was characterized by chronic pelvic pain and possibly voiding symptoms in the absence of urinary tract infection. This definition and classification system was subsequently published in 1999 [1] and has become generally accepted worldwide in both clinical practice and research [2]. The

development [3] and subsequent validation [4] of the NIH chronic prostatitis symptom index (CPSI) provided a treatment outcome parameter that had been previously missing and thus preventing the development of properly designed randomized treatment trials in CP/CPPS. The general acceptance of the NIH definition, classification system and CPSI leads to a tsunami of clinical trials, a number of which were well-designed, randomized, placebo- or sham-controlled clinical trials evaluating both traditional and novel therapeutic avenues in this condition.

The studies

For this comprehensive review, only papers published or accepted for publication in the English peer-reviewed literature were evaluated. Papers published in non-peer-reviewed supplements were not included. Medline and Embase databases were used for identifying relevant studies published in the English literature over the last 15 years. Search terms included chronic prostatitis, chronic pelvic pain, as well as the multiple specific treatments (e.g., alpha blocker, antibiotic, anti-inflammatory, etc.). Only studies that defined a population of CP/CPPS men were of a randomized placebo- or sham-controlled design and employed the NIH–CPSI as the outcome analyses were evaluated. In all, over 250 studies were identified as potentially eligible.

The evidence

The three authors independently extracted data of the primary outcomes of interest being CPSI symptoms score and response rates (as defined in the original publications).

The impact

The studies were grouped according to the standard therapeutic domains. The interpretation of the various studies within that therapeutic domain as to its real-life impact to clinical practice was developed by discussion and consensus among the three authors.

Randomized placebo- or sham-controlled treatment trials in CP/CPPS

Among the over 250 identified studies, 24 clinical trials met the criteria and were included in this comprehensive review. These trials are described, particularly the change in CPSI scores, in the Table 1. The following sections describe these trials according to treatment category.

Antibiotics

The studies Despite the fact that antibiotics have traditionally been the most commonly prescribed therapy for chronic prostatitis syndromes, there are only three small randomized trials available in the literature [5–7], all of them quite small and apparently underpowered. A trial comparing 4 weeks of tetracycline versus placebo [5], while showing significant benefit, was judged by the authors to be of poor quality. The two 6-week randomized studies of quinolone antibiotics in CP/CPPS, a trial of levofloxacin [6] and ciprofloxacin [7], were judged to be of good quality; however, both studies were apparently underpowered to show an antibiotic effect compared to placebo.

The evidence The tetracycline study [5] suggested significant improvement of 12 weeks of tetracycline versus placebo; however, the study did suffer from some quality issues (small numbers, selected patients, and anti-nanobacterial therapy which included tetracycline). The two quinolone trials [6, 7] showed either a greater symptom score improvement or response rate; however, no statistical improvement in symptoms compared to placebo was seen in either trial.

The impact Clinical evidence does not indicate a proven efficacy of empiric antibiotics in CPPS, in the absence of positive cultures. However, antibiotics remain commonly prescribed and reports exist showing symptomatic benefit irrespective of whether patients cultured uropathogenic bacteria or not [8, 9]. Meta-analysis of antimicrobial trials [10,11], including those not using the CPSI as assessment outcomes, shows a small statistically significant overall benefit that may or may not be clinically significant for individual patients. This may be because CP/CPPS might be due in some patients to an uncultured or unculturable organism or alternatively the anti-inflammatory cytokine blocking effects of antibiotics independent of their antimicrobial properties [12, 13]. The evidence would suggest that antimicrobial therapy is not recommended as a primary therapy, particularly in patients who have previously failed treatment with antibiotics (level of evidence 1: grade of recommendations A); however, antimicrobial therapy might be contemplated for newly diagnosed, antimicrobial naive patients (level of evidence 1: grade of recommendation C-D).

Alpha blockers

The studies Eight randomized placebo-controlled trials have evaluated alpha blockers in CP/CPPS. These include studies of terazosin [14], tamsulosin [7, 15, 16], alfuzosin [17, 18], doxazosin [19], and silodosin [48].

Table 1 Summary of treatment trials that met the review criteria (see text)

Active Agent	Reference	Duration of treatment	Patients (n)		Change in NIH–CPSI		Treatment effect
			Active	Placebo	Active	Placebo	
Antibiotics							
Ciprofloxacin versus placebo	Alexander et al. [7]	6 weeks	49	49	−6.2	−3.4	2.8
Levofloxacin versus placebo	Nickel et al. [6]	6 weeks	35	45	−5.4	−2.9	2.5
Tetracycline versus placebo	Zhou et al. [5]	12 weeks	24	24	−18.5	−1.0	17.5*
Alpha blockers							
Silodosin 8 mg versus placebo	Nickel et al. [20]	12 weeks	45	54	−10.2	−8.5	1.7
Silodosin 4 mg versus placebo			52		−12.1		3.6*
Alfuzosin versus placebo	Nickel et al. [18]	12 weeks	138	134	−7.1	−6.5	0.6
Doxazosin versus placebo	Tugcu et al. [19]	24 weeks	30	30	−12.4	−1.0	11.4*
Tamsulosin versus placebo	Alexander et al. [7]	6 weeks	49	49	−4.4	−3.4	1.0
Tamsulosin versus placebo	Nickel et al. [16]	6 weeks	27	30	−9.1	−5.5	3.6*
Terazosin versus placebo	Cheah et al. [14]	14 weeks	43	43	−14.3	−10.2	4.1*
Alfuzosin versus placebo	Mehik et al. [17]	24 weeks	17	20	−9.9	−3.8	6.1*
Anti-inflammatories							
Rofecoxib 25 mg versus Placebo	Nickel et al. [22]	6 weeks	53	59	−4.9	−4.2	0.7
Rofecoxib 50 mg versus placebo			49		−6.2		2.0
Prednisolone versus placebo	Bates et al. [26]	4 weeks	6	12	n.r.	n.r.	No sig. difference
Celecoxib versus placebo	Zhao et al. [23]	6 weeks	32	32	−8.0	−4.0	4.0*
Pentosan polysulfate versus placebo	Nickel et al. [24]	16 weeks	51	49	−5.9	−3.2	2.7
Tanezumab 20 mg versus placebo	Nickel et al. [48]	Single IV dose	30	32	−4.3	−2.8	1.5
Phytotherapies							
Pollen extract (Cernilton) versus placebo	Wagenlehner et al. [28]	12 weeks	70	69	−7.5	−5.4	2.1*
Quercetin versus placebo	Shoskes et al. [27]	4 weeks	15	13	−7.9	−1.4	6.5*
Neuromodulatory Agents							
Pregabalin versus placebo	Pontari et al. [29]	6 weeks	217	104	−6.5	−4.3	2.2*
Hormonal agents							
Finasteride versus placebo	Nickel et al. [30]	24 weeks	33	31	−3.0	−0.8	2.2
Mepartricin versus placebo	de Rose et al. [31]	8 weeks	13	13	−15.0	−5.0	10.0*
Multi-modal therapies							
Alpha blocker versus Alpha blocker + anti-inflammatory + muscle relaxant versus placebo	Tugcu et al. [19]	24 weeks	30	30	−12.7	−1.0	11.7*
Tamsulosin + ciprofloxacin versus placebo	Alexander et al. [7]	6 weeks	49	49	−4.1	−3.4	0.7
Zafirlukast + doxycycline versus placebo + doxycycline	Goldmeier et al. [25]	4 weeks	10	7			No sig. difference
Physical therapies							
Directed physiotherapy versus relaxation massage	Fitzgerald et al [33]	12 weeks	10	11	−14.4	−6.8	7.6
Posterior tibial nerve stimulation versus placebo	Kabay et al. [35]	12 weeks	45	44	−13.4	−1.4	12.0*
Acupuncture versus placebo	Lee et al. [37]	10 weeks	44	45	−10	−6	4.0*
Electroacupuncture versus placebo	Lee et al. [38]	6 weeks	12	12	−9.5	−3.5	6.0*
Extracorporal shock wave therapy versus placebo	Zimmermann et al. [34]	4 weeks	30	30	−3.7	−0.1	3.6*

Treatment effect marked * indicates a significant difference in reduction in NIH–CPSI score in treatment versus placebo/sham groups

The evidence A number of studies evaluating terazosin [14], tamsulosin [15, 16], alfuzosin [17], doxazosin [19], and silodosin [48] have shown apparent benefit in CP/CPPS patients. Two large NIH-sponsored studies evaluating tamsulosin [7] and alfuzosin [18] failed to show any benefit.

Impact Many of the smaller alpha blocker studies do in fact show benefit in selected CP/CPPS patients. The two NIH-sponsored studies which failed to show benefit enrolled patients who may have failed prior alpha blocker therapy [7] were underpowered for subset analysis of tamsulosin monotherapy versus placebo [7] or the patients were not selected on the basis of voiding symptoms [7, 18]. A number of meta-analyses [10, 11, 21] examining alpha blockers clearly indicate there is likely an overall treatment effect measured by overall reduction in symptom scores; however, implications for its use in clinical practice for individual patients remain unclear. It is believed, but still unproven that patients with CP/CPPS and bothersome or measureable voiding symptoms may have the most benefit using alpha blockers as part of an overall therapeutic strategy. Therefore, we believe we can recommend alpha blocker therapy for newly diagnosed, alpha blocker naive patients who have significant voiding symptoms (level of evidence 1: grade of recommendation C). However, alpha blocker monotherapy, particularly in patients previously treated with alpha blockers, is not recommended (level of evidence 1: grade of recommendation A).

Anti-inflammatories

The studies Anti-inflammatory clinical trials are really a diverse set of therapeutic interventions. These have included studies of rofecoxib [22], celecoxib [23], pentosan polysulfate [24], zafirlukast (a leukotriene antagonist) [25], prednisone [26], and tanezumab [48].

The evidence The COX-2 inhibitor trials [22, 23] showed modest benefit [23] particularly at high dose [22]. High-dose pentosan polysulfate [24], which is a mast cell inhibitor and demonstrates other anti-inflammatory activities, showed some symptom improvement, but not really a CPSI score change significantly better than placebo. Similarly, zafirlukast [25] and corticosteroids [26] did not significantly improve symptoms. A recent well-powered study evaluating tanezumab [48], a humanized monoclonal antibody directed against nerve growth factor, was not able to show significant benefit in a generally unselected population of men with CP/CPPS.

The impact The clinical evidence strongly suggests that anti-inflammatory monotherapy is not effective. Meta-analyses [10, 11] show a possible overall small treatment effect but questionable individual clinically significant treatment response for anti-inflammatories used as a monotherapy. Therefore, anti-inflammatory monotherapy is not recommended (level of evidence 1: grade of recommendation A). It can be considered as part of a multimodal therapeutic strategy.

Phytotherapeutic agents

The studies Although there are a number of randomized trials evaluating phytochemical agents, only two met the criteria for this review. Quercetin (an antioxidant anti-inflammatory product) has been assessed in a single-center short study [27], while Cernilton (a standardized pollen extract) was assessed in a 12-week multicenter randomized placebo-controlled trial [28].

The evidence CP/CPPS patients treated with quercetin for 4 weeks showed improved symptoms, compared to placebo [27]. Pollen extract significantly improved pain and quality of life after 12 weeks of therapy, compared to placebo [28].

Impact Patients treated with phytotherapy experience very few side effects and there appears to be evidence to show efficacy for at least quercetin and Cernilton for CP/CPPS. Therefore, selected phytotherapies are recommended as a treatment modality for CP/CPPS (Cernilton level of evidence 1: grade of recommendation B and quercetin, level of evidence 2: grade of recommendation C).

Neuromodulatory therapy

The studies There is only one randomized placebo-controlled study evaluating oral neuromodulatory therapy in CP/CPPS. This was an NIH-sponsored study of pregabalin compared to placebo [29].

The evidence The pregabalin study [29] showed no statistically significant improvement in the primary outcome of a 6 point decrease in total NIH–CPSI score between treatment groups. However, there was significant improvement in total CPSI and pain scores in the treatment compared to the placebo group.

The impact There appears to be some minor benefit in some patients using oral neuromodulatory therapeutic approach in patients with CP/CPPS; however, the evidence does not support this modality of therapy as a mono-therapy (level of evidence 2: grade of recommendation B).

Hormonal agents

The studies There is only one underpowered randomized placebo-controlled trial comparing finasteride to placebo

using CPSI as an outcome parameter [30]. There is another small trial evaluating mepartricin, an agent which reduces serum estrogen levels. [31].

The evidence Finasteride showed more improvement in the treated group compared to a placebo group; however, in this underpowered study, this did not reach statistical significance [30]. In the small mepartricin trial [31], there appeared to be a statistically significant beneficial effect in total NIH–CPSI scores in men compared to placebo. The evidence suggests that hormonal therapies are likely ineffective in the majority of men with CP/CPPS. An interestingly pre-planned analysis of the impact of long-term dutasteride in patients with CP/CPPS symptoms in a prostate cancer reduction trial suggested that in an older patient population, there was clinical benefit both in clinical response and decrease in CPSI score over the long term [32]. Certainly, hormonal therapies are not recommended as empiric monotherapy in men with CP/CPPS (level of evidence 2: grade of recommendation B) but perhaps could be considered in old patients with benign prostatic hyperplasia (level of evidence 2: grade of recommendation C).

Physical therapies

The studies A multicenter randomized NIH-sponsored study compared traditional western massage with targeted myofascial release physical therapy in men and women with chronic pelvic pain [33]. Other studies examined the benefits of perineal low intensity extra corporal shock wave treatment (ESWT) versus sham [34], percutaneous tibial nerve stimulation versus sham [35], electromagnetic therapy versus sham [36], and standard acupuncture [37] or electro acupuncture [38] versus sham treatment.

The evidence The physical therapy trial [33] was not powered to detect statistically significant differences but rather was a feasibility study of carrying out a multicenter sham-controlled treatment trial. There was a clinically important CPSI difference between directed pelvic therapy and traditional western massage therapy; however, this difference in male patients in terms of improved symptoms was not statistically significant, presumably because of small numbers of men enrolled in the study. Randomized sham-controlled trials showed benefit with ESWT [34], percutaneous tibial nerve stimulation [35], electromagnetic therapy [36], acupuncture [37], and electro acupuncture [38].

The impact There are multiple non-randomized clinical intervention trials describing the benefits of physical therapy in CP/CPPS although the evidence for this is unavailable from sham-controlled trials (which can be challenging to develop and of course blind). Based on extensive clinical experience and these uncontrolled trials, it is believed that physical therapy, at least for the subgroups of patients with pelvic floor muscle spasm and pain [39], can be beneficial (level of evidence 4: grade of recommendation C). The other interventions did show benefit in small sham-controlled therapeutic trials and certainly can be considered if available but we would need more study before they can be strongly recommended as a primary intervention.

Limitations of available evidence-based clinical trials in CP/CPPS

Although the evidence from clinical trials presented in this comprehensive review employed randomization, placebo or sham control and when and if possible, blinding, the interpretation remains difficult and challenging. Many of the clinical trials are small, underpowered and did not specifically select for patients that would most likely benefit from that particular therapy. Some of the more promising therapies have not been adequately assessed and evaluated. Surgery, even for those patients with CP/CPPS and bladder outlet obstruction, has not been rigorously assessed in this type of randomized controlled clinical trial, except for one negative randomized placebo-controlled trial [40] assessing transurethral needle ablation of the prostate (TUNA). However, collective experience suggests that surgical procedures can have a role in men with symptomatic prostatic enlargement, bladder neck obstruction, urethral stricture disease, or other definitive surgical indication in addition to their CPPS, but cannot be recommended specifically for the pain of CPPS alone. Psychosocial problems are now known to be associated with the pain and poor quality of life in men with CPPS but psychosocial intervention [41] has yet to be subjected to any rigorous evaluation in this group of patients. Most of the therapies evaluated in RCTs have in fact been assessed as a mono-therapy and were used empirically in all CP/CPPS patients eligible for that clinical trial. Very few attempts were made to enroll patients with specific symptoms or mechanisms that may respond to a particular therapy. In clinical practice, mono-therapy has been shown to be reasonably ineffective [42], while pre-planned multimodal therapeutic approaches appear to result in more clinical benefit for patients [19, 25, 43]. It appears that the optimal approach would be to better phenotype patients and individualize therapy directed toward those particular patient phenotypes [44]. The evidence from clinical trials and clinical experience can be useful to detect individual therapies for specific phenotypes. This concept of phenotypic differentiation of CP/CPPS patients prior to therapy is

now being accepted as a logical therapeutic approach [45] and initial results are very encouraging [46]. The proof of the evidence of such individualized or personalized treatment strategies is, however, challenging and calls for development of new techniques in clinical trials. The UPOINT CP/CPPS phenotyping classification system and its implications for directed therapy are being addressed in another article in this World Journal of Urology section on CP/CPPS [47].

Conclusion

Although there have been great strides in developing evidence for therapy for men with CP/CPPS over the last 15 years, any physician who decides to use only an evidence-based approach treatment of a CP/CPPS patient will result in disappointed patients and disappointed physicians. There is no one particular treatment that shows significant clinical efficacy to be recommended as a mono-therapy for CP/CPPS; therefore, the physician must adapt his knowledge and interpretation of the evidence from randomized placebo- and sham-controlled trials to determine what therapy or therapies are best indicated for each individual patient. A pre-planned multi-modal therapeutic approach specifically directed to each individual patients' clinical phenotypic profile is likely the best management strategy.

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