

2016 COCHRANE REVIEW: PHARMACOLOGICAL TREATMENTS FOR BLADDER PAIN SYNDROME / INTERSTITIAL CYSTITIS

Hypothesis / aims of study

Painful bladder syndrome (PBS) is defined by the International Continence Society as “the complaint of suprapubic pain in relation to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary tract infection or other obvious pathology”. ICS reserves its diagnosis of interstitial cystitis (IC) to patients with “typical cystoscopic and histological features”. Bladder pain syndrome (BPS) is defined by the European Society for the Study of Interstitial Cystitis/Bladder Pain as “pelvic pain, pressure or discomfort perceived to be related to the bladder, lasting for at least 6 months, and accompanied by at least one other urinary symptom”. BPS is a chronic condition seen mainly in women (10:1 female to male ratio). It affects quality of life, leading to a reduction in mental and physical wellbeing.

A variety of treatment options are available and include dietary/lifestyle modifications, oral medication, intravesical instillations or injections and, in some rarer cases, surgery. Rates of treatment success are generally modest and there is little consensus as to the best form of treatment for this condition. This meta-analysis of Randomised Controlled Trials (RCTs) summarises the evidence of the effects of pharmacological treatment in the management of bladder pain syndrome.

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Study design, materials and methods

All Randomised Controlled Trials that evaluated pharmacological treatments for bladder pain syndrome, and were published or presented prior to 21st March 2016, were identified from MEDLINE, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL) and hand searching of journals and major conference proceedings. Data was extracted independently by two reviewers, a meta-analysis was performed and evidence based conclusions made.

Results

Twenty-two randomised controlled trials with 1754 participants were included. Risk of bias assessment showed that across all studies approximately 37% of all the RCTs had adequate random sequence generation, 13% had adequate allocation concealment, while 46% were adequately blinded to participants and personnel. In 13% of trials outcome assessors were adequately blinded and 40% of trials were judged as low risk for attrition bias.

When comparing pharmacological treatment versus placebo, 9 RCT's compared one single agent to placebo (including Adalimumab, Tanezumab, Sildenafil, L-Arginine, Pentosanpolysulfate sodium (PPS), calcium channel 2 ligand, Hydroxyzine, Amitriptyline, hyperbaric oxygen and mycophenolate mofetil) and 3 RCTs compared combination treatments with placebo (Hydroxyzine and PPS, Amitriptyline and educational and behavioural modification therapy (EBMT) and antibiotic combination therapy).

Subjective cure and improvement was assessed by 11 trials in this comparison. In the treatment group the range of symptom improvement was 8% to 67% with a median of 40%. Similarly, in the placebo group the range of symptom improvement was from 0% to 55 % with a median of 13%. When each of the above drugs were compared to placebo, the only significant difference in subjective cure and improvement were seen with Amitriptyline alone and in combination with EBMP (RR 15, 95% CI 2.15 to 104.75, 1 trial, 48 participants, very wide confidence intervals and RR 1.29, 95% CI 1.03 to 1.61, 1 trial, 231 participants, respectively), Sildenafil (RR 10, 95% CI 1.39 to 72.15, 1 trial, 48 participants) and antibiotic combination therapy (RR 2.11, 95% CI 1.01 to 4.42, 1 trial, 37 participants). When evaluating improvement in pain using visual analogue scale (VAS) scores 6 RCT's provided data for this outcome but only Amitriptyline showed a statistically significant difference in improving pain when compared to placebo (mean difference -2.38 95% CI -3.58 to -1.18). Mean change in O'Leary-Sant interstitial cystitis symptom index (ICSI) and interstitial cystitis problem index (ICPI) scores were reported by 5 trials, however none of these trials showed significant improvement over placebo. Significant reduction in daytime frequency was seen with Amitriptyline when compared with placebo.

For the comparison of one pharmacological treatment versus another Cyclosporin A lead to a significantly higher subjective cure and improvement rate than Pentosanpolysuphate sodium (RR 4, 95% CI 1.9 to 8.31, 1 trial, 28 patients) but with a significantly higher incidence of adverse events (RR 1.67, 95% CI 1.21 to 2.29). In the outcomes of interest for comparison of Hydroxyzine and PPS no significant differences between the groups were observed. Similarly, a combination therapy using Hydroxyzine and PPS shows no significant in outcomes measured when compared to either Hydroxyzine or PPS alone.

Interpretation of results

This comprehensive review of randomised controlled trial evidence for pharmacological treatment of BPS shows a varied number of treatments which are evaluated largely by single RCTs comprising of small sample sizes. The results for the various treatment outcomes do not meet statistical significance in the majority, and where statistical significant is achieved the confidence intervals are wide and results should be interpreted with caution.

When compared to placebo many oral treatments show no significant difference in efficacy over placebo. The evidence we have so far suggests only marginal benefits with Amitriptyline and Sildenafil over placebo.

Concluding message

This is an up-to-date review of RCT evidence for medical treatments in BPS. It illustrates the poverty of existing evidence available to inform management of this common condition. The evidence so far does not support the use of one pharmacological agent over another from the results of this review. There is a need for large clinical trials with high methodological quality reporting on patient specific outcome measures to allow us to draw more reliable conclusions to direct clinical practice.

Disclosures

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