2011
Nature Reviews
Urology

Drug Therapies for CP/CPPS: help or hype

Anderson, R.U. & Nathanson, B.H., Nat.Rev.Urology 8, 236-237 (2011)
Department of Urology, Stanford University School of Medicine, CA 94305-5118,
OptiStatim LCC, P.O. Box 60844, Long Meadow, Mass 01116

In line with the recommendations of a recently published guideline,[7] the authors stated that daily SSRI treatments are the first-choice treatment for PE. This is not universally true, as some patients with PE find chronic treatment with an antidepressant excessive.[8] Furthermore, in countries where dapoxetine—a short-acting, non-antidepressant SSRI—is approved by the regulatory agencies, this drug must be considered the first choice for on-demand treatment of PE, as it is good clinical practice to use approved drugs instead of off-label treatments, such as paroxetine, unless doing so is scientifically and clinically justified.[9] At the moment, in the absence of approval from regulatory agencies to use long-acting SSRIs, and without data to support the use of alternative approaches, such as acupuncture, this is the main take-home message for the clinical urologist.

If the results of this article by Sunay *et al.*[3] are confirmed, it could open new avenues of research into the possibility that acupuncture could be a valid treatment not only for PE, but also for female sexual dysfunction with a neurogenic component, such as anorgasmia or vaginismus.

*School of Sexology, Department of Experimental Medicine, University of L'Aquila, Coppito, Building 2, Via Vetoio, 67100 L'Aquila, Italy (**E. A. Jannini**). Department of Experimental Medicine, University of Rome 'La Sapienza', Viale del Policlinico, 00161 Rome, Italy (**A. Lenzi**).*
Correspondence to: A. Lenzi
andrea.lenzi@uniroma1.it

Competing interests
E. A. Jannini declares associations with the following companies: Bayer Healthcare, Janssen, Lilly, Pfizer. A. Lenzi declares associations with the following companies: Bayer Healthcare, Lilly, Pfizer. See the article online for full details of the relationships.

1. Jannini, E. A., Simonelli, C. & Lenzi, A. Sexological approach to ejaculatory dysfunction. *Int. J. Androl.* **25**, 317–323 (2002).
2. Jannini, E. A. & Lenzi, A. Ejaculatory disorders: epidemiology and current approaches to definition, classification and subtyping. *World J. Urol.* **23**, 68–75 (2005).
3. Sunay, D. *et al.* Acupuncture versus paroxetine for the treatment of premature ejaculation: a randomized, placebo-controlled clinical trial. *Eur. Urol.* doi:10.1016/j.eururo.2011.01.019 (2011).
4. Screponi, E. *et al.* Prevalence of chronic prostatitis in men with premature ejaculation. *Urology* **58**, 198–202 (2001).
5. Fabbri, A. *et al.* Neuroendocrine control of male reproductive function. The opioid system as a model of control at multiple sites. *J. Steroid Biochem.* **32**, 145–150 (1989).
6. Abdel-Hamid, I. A., Jannini, E. A. & Andersson, K. E. Premature ejaculation: focus on therapeutic targets. *Expert Opin. Ther. Targets* **13**, 175–193 (2009).
7. Hatzimouratidis, K. *et al.* Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur. Urol.* **57**, 804–814 (2010).
8. Salonia, A. *et al.* Acceptance of and discontinuation rate from paroxetine treatment in patients with lifelong premature ejaculation. *J. Sex. Med.* **6**, 2868–2877 (2009).
9. Jannini, E. A. *et al.* Clinical challenges in the management of premature ejaculation. *European Urological Review* **5**, 48–54 (2010).

PAIN

Drug therapies for CP/CPPS: help or hype?

Rodney U. Anderson and Brian H. Nathanson

A recent network meta-analysis of α-blockers, antibiotics and other drug therapies for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) found that they provided modest-to-no benefit for this condition, confirming previous findings. However, a casual reading of the article may give a false impression of the efficacy and appropriateness of these drugs.

Anderson, R. U. & Nathanson, B. H. *Nat. Rev. Urol.* **8**, 236–237 (2011); doi:10.1038/nrurol.2011.51

The conundrum of treating CP/CPPS continues to frustrate physicians. Innumerable clinical studies have described the condition and the potential therapeutic options for its management. In an article published in the January issue of *JAMA*,[1] the authors conducted a systematic review and network meta-analysis of clinical studies of the various oral medications used for the management of CP/CPPS, and concluded that "α-blockers, antibiotics, and combinations of these therapies appear to achieve the greatest improvement in clinical symptom scores compared with placebo."

The title of the article implies a proposal from the American Medical Association for the best management of CP/CPPS. However, after adjusting for publication bias in their direct meta-analysis, there was no clinically or statistically significant treatment benefit associated with α-blockers or antibiotics in terms of reducing either total NIH Chronic Prostatitis Symptom Index (NIH-CPSI) scores or pain, voiding (urinary) and quality-of-life subscores, which should have been a main conclusion. Also, most urologists often find these treatment options to be ineffective, and, unfortunately, the article does a disservice by minimizing the factual evidence from randomized clinical trials that these universally used oral medications fail to help millions of men achieve effective symptom relief. The authors do state that "the total sample sizes [of the studies] are relatively small and 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,"[1] but these points are not adequately emphasized.

> "...the ineffectiveness of these drugs is old news to those of us who specialize in treating CP/CPPS..."

Moreover, several methodological issues in this study are worthy of comment. The outcomes of interest were the NIH-CPSI scores or related measures (such as the International Prostate Symptom Score or the Prostatitis Symptom Score Index). The authors note that a reduction of 4 points on the total NIH-CPSI score is necessary to be considered clinically perceptible, and a reduction of >6 points is considered clinically significant. A *P*-value low enough to signify statistical significance ($P < 0.05$) is misleading if the difference between groups is not clinically meaningful. To prevent this distortion, the analysis should have made the alternative hypothesis state that the significant difference was >4 (the clinically perceptible threshold) and not merely >0, and should have noted where the confidence intervals included this threshold.

The noted heterogeneity of the included studies raises serious methodological issues, particularly for the study's network (indirect) meta-analysis. A network meta-analysis is a new statistical method that is

used to compare multiple therapies when the comparisons were not performed "head to head" in a randomized trial (that is, when trials that directly compare treatment A and treatment B do not exist). The assumptions that are necessary for a valid network meta-analysis are more complex than those for a traditional meta-analysis.[2] In short, all the studies analyzed must be homogeneous enough in design, study population and placebo group, both within and among each other, to make the comparisons clinically reasonable, as the exchangeability of results across trials is even more important than in a traditional meta-analysis. We cannot tell from the manuscript whether all these assumptions have been met for each of the studies analyzed. The authors tried to analyze a dichotomous response versus non-response outcome, but the studies' thresholds were too different (for example, 'response' was defined as a 25% decrease in NIH-CPSI score in two studies, and as a 50% decrease in three studies) to make a meta-analysis appropriate.

The story of oral medications for CP/CPPS has already been told.[3] The largest NIH-sponsored randomized controlled trials do not support the use of the α-blockers alfuzosin or tamsulosin, nor the antibiotic ciprofloxacin, either alone or in combination with tamsulosin.[4,5] Randomized controlled trials are the gold standard in evidence-based medicine, and this network meta-analysis essentially confirms rather than refutes these previous findings. However, the way the authors present their conclusions, particularly in their abstract, minimizes these facts.

While the ineffectiveness of these drugs is old news to those of us who specialize in treating CP/CPPS, they are still routinely prescribed by most clinicians treating this condition—and patients continue to suffer from CP/CPPS. Underlining the failure of these conventional oral medications should have been the main conclusion of this article. The authors admit that "the reason for the benefit associated with antibiotics is not immediately clear." Other nonpharmacological therapies for CP/CPPS do exist, however, and the logical trend in the diagnostic evaluation of CP/CPPS is to utilize careful phenotyping in the initial work-up of the suffering patient. This phenotyping approach has recently been proposed and evaluated in a multimodal therapy setting, with excellent results.[6] The differences in the management strategies used depend upon recognizing the heterogeneity of the condition and the specificity of symptoms, which are characterized by the six domains of the UPOINT phenotyping system (urinary, psychosocial, organ-specific, infection, neurologic/systemic, and tenderness of skeletal muscles) that are used for focusing treatment. Each of these domains should be treated with state-of-the-art therapy, which might sometimes require more than one treatment modality. Notably, pelvic tension and muscle tenderness make up the majority of the specific symptoms and physical findings in patients with CP/CPPS.

In our personal experience of treating this condition, we have found alternatives to failed oral medications, such as multimodal physical therapy and cognitive behavioral therapy, and suggest that innovative treatment strategies be explored after patients have been carefully phenotyped and once traditional antibiotic or α-blocker therapy of CP/CPPS has been deemed inappropriate.[7]

*Department of Urology, Stanford University School of Medicine, Stanford, CA 94305-5118, USA (**R. U. Anderson**). OptiStatim LCC, P. O. Box 60844, Longmeadow, MA 01116, USA (**B. H. Nathanson**).*

Correspondence to: R. U. Anderson
rua@stanford.edu

Competing interests
The authors declare no competing interests.

1. Anothaisintawee, T. *et al.* Management of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and network meta-analysis. *JAMA* **305**, 78–86 (2011).
2. Song, F. *et al.* Methodological problems in the use of indirect comparisons for evaluations healthcare interventions: survey of published systematic reviews. *BMJ* **338**, b1147 (2009).
3. Curtis Nickel, J., Baranowski, A. P., Pontari, M., Berger, R. E. & Tripp, D. A. Management of men diagnosed with chronic prostatitis/chronic pelvic pain syndrome who have failed traditional management. *Rev. Urol.* **9**, 63–72 (2007).
4. Nickel, J. C. *et al.* Alfuzosin and symptoms of chronic prostatitis–chronic pelvic pain syndrome. *N. Engl. J. Med*. **359**, 2663–2673 (2008).
5. Alexander, R. B. *et al.* Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: a randomized, double-blind trial. *Ann. Intern. Med.* **141**, 581–589 (2004).
6. Shoskes, D. A., Nickel, J. C. & Kattan, M. W. Phenotypically directed multimodal therapy for chronic prostatitis/chronic pelvic pain syndrome: a prospective study using UPOINT. *Urology* **75**, 1249–1253 (2010).
7. Anderson, R. U., Wise, D., Sawyer, T. & Chan, C. Integration of myofascial trigger point release and paradoxical relaxation training treatment of chronic pelvic pain in men. *J. Urol.* **174**, 155–160 (2005).

INCONTINENCE

Conservative treatment of postprostatectomy incontinence

Bilal Chughtai and Jaspreet S. Sandhu

Radical prostatectomy can damage urinary function, causing incontinence. This incontinence typically resolves by the end of the first postoperative year, but it can be expedited by pelvic floor muscle exercises (PFME). A recent randomized controlled trial has demonstrated that PFME can be effective even when started years after surgery.

Chughtai, B. & Sandhu, J. S. *Nat. Rev. Urol.* **8**, 237–238 (2011); published online 5 April 2011; doi:10.1038/nrurol.2011.49

The objective of the study by Goode *et al.*[1] was to evaluate the effectiveness of behavioral therapy for reducing persistent postprostatectomy incontinence, and to determine whether biofeedback and electrical stimulation of the pelvic floor improve the results of this approach.

Although most cases of postprostatectomy incontinence resolve within the first postoperative year, the condition can be improved by the use of pelvic floor mucle exercises.[2,3] This multisite randomized controlled trial included 208 men with incontinence persisting >1 year after radical prostatectomy. The study consisted of three groups: a behavior therapy arm (treated with PFME and bladder control strategies), a behavior therapy 'plus' arm (which included biofeedback in the office and daily pelvic floor muscle stimulation [PFS] at home, in addition to behavior therapy), and a control group. The primary outcome measure was percentage reduction in mean number of incontinence episodes at 8 weeks, as documented by 7-day bladder diaries. Additional measures included multiple