Phosphodiesterase-5 inhibitors for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a systematic review and meta-analysis

Liu L, Zheng S, Han P, Wei Q

CRD summary
This review concluded that phosphodiesterase-5 inhibitors were safe and effective for lower urinary tract symptoms secondary to benign prostatic hyperplasia. These conclusions were supported by the data, but should be interpreted with some caution given the possibility of missed studies and the limitations of the included trials (small number, small size and unclear methodological quality).

Authors' objectives
To evaluate the efficacy and safety of phosphodiesterase-5 inhibitors for treating lower urinary tract symptoms secondary to benign prostatic hyperplasia.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to April 2010. Search terms were reported. Reference lists of identified studies and other relevant reviews and publications were screened. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that compared the efficacy and safety of phosphodiesterase-5 inhibitors in patients with benign prostatic hyperplasia were eligible for inclusion.

The primary outcomes were the change in the International Prostate Symptom Score (IPSS) and maximal urinary flow rate. Secondary outcomes were changes in the IPSS irritative and obstructive subscores, IPSS quality of life index, erectile function domain score of the International Index of Erectile Function (IIEF-EF), post-void residual urine volume, and adverse events.

Included trials assessed the phosphodiesterase-5 inhibitors sildenafil (50 to 100mg), tadalafil (2.5 to 20mg) and vardenafil (10mg twice daily) versus placebo control. All trials were multi-centre with the number of participating centres ranging from 16 to 92. Most trials were conducted in one or two countries (USA, Canada and Germany); one trial was conducted in 10 countries (details not reported). Most trials included men aged 45 years or older with benign prostatic hyperplasia of six months duration or more.

Two reviewers independently assessed studies for inclusion, with discrepancies referred to a third reviewer.

Assessment of study quality
Trials were assessed for methodological quality using the Jadad scale which assigned trials a score of out 5 points based on randomisation, blinding and withdrawals.

Two reviewers independently performed the quality assessment.

Data extraction
Two reviewers independently extracted data to calculate mean differences (MDs) with 95% confidence intervals (CIs) between treatment and control groups for changes from baseline to endpoint. Where changes from baseline were not reported, endpoint data were extracted. For dichotomous data, data were extracted to calculated relative risks (RRs) with 95% confidence intervals. For trials that evaluated more than two interventions, data were extracted separately for each intervention compared to control. Authors were contacted for additional data where necessary. If further information could not be obtained, missing data were imputed.
Methods of synthesis
Summary relative risks and weighted mean differences (WMD) with 95% confidence intervals were estimated. In the absence of heterogeneity, a fixed-effect model was used; otherwise a random-effects model was used. Heterogeneity was assessed using $X^2$ and $I^2$.

Heterogeneity was investigated using subgroup analyses based on the specific phosphodiesterase-5 inhibitor assessed and by restricting the analysis to patients with comorbid benign prostatic hyperplasia and erectile dysfunction.

Publication bias was assessed using a funnel plot.

Results of the review
Five RCTs reported in 11 publications were included in the review ($n=2119$ patients in table, 2054 patients in figure). All trials were double blinded. The proportion of withdrawals ranged from 3 to 16%. Four trials scored 3 on the Jadad scale and one scored 4. Duration of follow-up ranged from eight to 12 weeks.

Compared with placebo, phosphodiesterase-5 inhibitors were associated with a significant reduction in the overall International Prostate Symptom Score (IPSS) (WMD -2.6%, 95% CI -3.12 to -2.07; five RCTs), IPSS irritative subscore (WMD -0.96%, 95% CI -1.22 to -0.71; four RCTs), IPSS obstructive subscore (WMD -1.57%, 95% CI -1.92 to -1.21; four RCTs), the IPSS quality of life subscore (WMD -0.39%, 95% CI -0.52 to -0.27; three RCTs) and the IIEF-EF (WMD 5.74%, 95% CI 4.78 to 6.70; four RCTs). There was no significant difference between phosphodiesterase-5 inhibitors and placebo for post-void residual urine volume or maximal urinary flow rate. There was no evidence of heterogeneity for any of these analyses. Subgroup analyses showed similar results.

Phosphodiesterase-5 inhibitors were associated with significantly more adverse events than placebo (RR 1.87, 95% CI 1.31 to 2.68; five RCTs). There was substantial heterogeneity for this outcome ($I^2=80\%$). The most commonly reported adverse events were headache, flushing, dyspepsia, and back pain. There was no significant difference between interventions for serious adverse events.

Authors' conclusions
Phosphodiesterase-5 inhibitors were safe and effective for lower urinary tract symptoms secondary to benign prostatic hyperplasia.

CRD commentary
The review assessed a focused question. Inclusion criteria were clearly defined for population, intervention and study design. It was unclear whether the review was restricted to studies that included a placebo control group, although all included studies did. The literature search was adequate for published studies but specific attempts were not made to locate unpublished data, so there was a possibility of publication bias. The authors did state that this would be assessed in the review, but the results of the publication bias assessment were not reported. Appropriate steps were taken to minimise bias and errors at all stages of the review process.

Trial quality was assessed using some relevant criteria, but the results of the assessment were only presented as summary quality scores with no details on the individual items fulfilled. Appropriate methods were used to pool data. The results were clearly presented, with the aid of forest plots.

The authors’ conclusions were supported by the data but should be interpreted with some caution due to the possibility of missed studies and the small number of included trials (which were small in size with short duration of follow-up) of unclear methodological quality.

Implications of the review for practice and research
Practice: The authors stated that phosphodiesterase-5 inhibitors are effective and safe for lower urinary tract symptoms secondary to benign prostatic hyperplasia and can be considered as the first-line treatment of patients with comorbid benign prostatic hyperplasia and erectile dysfunction.
Research: The authors stated that larger-scale well-designed clinical trials are needed to ascertain the safety, efficacy, and cost-effectiveness of phosphodiesterase-5 inhibitors in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Basic scientific studies are needed to elicit the exact mechanisms involved in lower urinary tract symptoms.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.