A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with alpha-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia


CRD summary
This review concluded that phosphodiesterase type 5 inhibitors were effective and well tolerated alone or combined with alpha-blockers in men with lower urinary tract symptoms associated with benign prostatic hyperplasia in the first 12 weeks of treatment. Long-term treatment effects remain unknown. Limitations of the evidence (including small samples) mean the reliability of the findings remains unclear.

Authors' objectives
To assess the effects of phosphodiesterase type 5 inhibitors alone or in combination with alpha 1-adrenergic blockers on lower urinary tract symptoms associated with benign prostatic hyperplasia.

Searching
MEDLINE/PubMed, EMBASE and The Cochrane Library were searched up to September 2011 without language restrictions; search terms were reported. Relevant reference lists were handsearched. Unpublished data were sought from experts in the field.

Study selection
Eligible studies were randomised controlled trials (RCTs) in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia. Trials had to compare the safety and efficacy of phosphodiesterase type 5 inhibitors alone versus placebo, or phosphodiesterase type 5 inhibitors in combination with alpha 1-adrenergic blockers versus alpha 1-blockers alone. The primary outcomes of interest were the International Prostate Symptom Score, International Index of Erectile Function and maximum flow rate ($Q_{\text{max}}$) at uroflowmetry (mL/s). Adverse events were reported.

Included trials were in men with a mean or median age between 56 and 68 years. Where reported, body mass index (BMI) ranged from 25.4 to 28.5. Baseline International Prostate Symptom Scores ranged from 15 to 19.6 (maximum score appeared to be 35 and indicated severe symptoms). Phosphodiesterase type 5 inhibitors included sildenafil (25 to 100mg), tadalafil (2.5 to 100mg), vardenafil (10mg) or UK-369003 (10 to 100mg). Patients took, four, seven or 14 pills per week. Alpha-blockers were alfuzosin or tamsulosin. Study durations lasted eight or 12 weeks.

Two reviewers independently screened studies for inclusion. Discrepancies were resolved by a third reviewer.

Assessment of study quality
The quality of RCTs was assessed according to Jadad criteria of randomisation, blinding and withdrawals/dropouts.

The authors did not state how many reviewers assessed study quality.

Data extraction
Primary outcome data were extracted to calculate mean differences between treatment and comparison groups. Numbers (%) of adverse events related to phosphodiesterase type 5 inhibitors were extracted.

Two reviewers independently extracted data. Disagreements were referred to a third reviewer.

Methods of synthesis
A random-effects model was used to calculate standardised mean differences (SMD) and 95% confidence intervals for the primary outcome. Where adverse events were reported for phosphodiesterase type 5 inhibitors versus placebo in at least two papers, event rates were extracted to calculate odds ratios and 95% confidence intervals. In studies with various dosages of treatment these were treated as separate treatment arms.
Statistical heterogeneity was assessed using the I² statistic. Meta-regression analyses were performed to assess the effects of age, BMI and baseline International Prostate Symptom Scores on the outcomes.

The Begg test was used to assess publication bias.

**Results of the review**

Twelve RCTs (3,492 patients randomised; 3,009 patients completing) were included in the review. Two trials scored 4 on the Jadad scale, nine scored 3 and one trial scored 2.

Compared to placebo, phosphodiesterase type 5 inhibitors statistically significantly improved International Prostate Symptom Scores (SMD -2.8, 95% CI -3.6 to -2.1; I²=46.4%; five RCTs) and International Index of Erectile Function scores (SMD +5.5, 95% CI +4.1 to -6.9; three RCTs) but did not statistically significantly change maximum flow rate (three RCTs).

Comparing phosphodiesterase type 5 inhibitors in combination with alpha-blockers versus alpha-blockers alone showed that combination therapy statistically significantly improved International Prostate Symptom Scores (SMD-1.8, 95% CI -3.7 to 0.0; I²=92.89%; five RCTs), although significance was borderline. Combination therapy statistically significantly improved International Erectile Function Scores (SMD +3.6, 95% CI +3.1 to +4.1; four RCTs) and maximum flow rate (SMD +1.5 mL/s, 95% CI +0.9 to +2.2; five RCTs).

Results from meta-regression analyses were reported in the review. Phosphodiesterase type 5 inhibitors statistically significantly increased risk of flushing, gastroesophageal reflux, headache and dyspepsia.

There was no evidence of major publication bias.

**Authors’ conclusions**

Phosphodiesterase type 5 inhibitors were effective and well tolerated either alone or in combination with alpha-blockers in men with lower urinary tract symptoms in association with benign prostatic hyperplasia in the first 12 weeks of treatment. Phosphodiesterase type 5 inhibitors in combination with alpha-blockers induced a small improvement in flow rate; phosphodiesterase type 5 inhibitors alone failed to show any improvement.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. The satisfactory search of the literature included a search for unpublished data. There was no evidence of major publication bias. Trial risk of bias was assessed and suggested that most trials were at moderate risk of bias; individual results were not presented. Study selection and data extraction were performed in duplicate but it was unclear whether this applied also to trial quality assessment.

The authors highlighted several limitations of the evidence including small numbers of patients, short treatment durations, differences between studies and inconsistent/unavailable reporting of safety data. Assessment of statistical heterogeneity indicated evidence of heterogeneity and appropriate statistical methods were used to account for this. It was unclear whether there may have been some double counting.

The authors’ conclusions reflect the evidence presented but the limitations highlighted by the authors suggest the reliability of the findings remains unclear. Long-term effects of treatment remain unknown.

**Implications of the review for practice and research**

**Practice:** The authors stated that younger men with lower BMI and severe urinary symptoms seem to be the best candidates for treatment with phosphodiesterase type 5 inhibitors.

**Research:** The authors stated that high quality long-term RCTs were needed to assess the safety and efficacy and overall cost-effectiveness of phosphodiesterase type 5 inhibitors.

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