The efficacy of PDE5 inhibitors alone or in combination with alpha-blockers for the treatment of erectile dysfunction and lower urinary tract symptoms due to benign prostatic hyperplasia: a systematic review and meta-analysis

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CRD summary
The combined use of PDE5 inhibitors and alpha blockers resulted in additive favourable effects in men with erectile dysfunction and lower urinary tract symptoms suggestive of benign prostatic hyperplasia compared with PDE5 inhibitor monotherapy. The quality of the included trials was unclear and several limitations of this review were highlighted by the authors that may make the authors' conclusion unreliable.

Authors' objectives
To evaluate the efficacy of phosphodiesterase type 5 (PDE5) inhibitors alone or in combination with alpha-blockers for the treatment of erectile dysfunction and lower urinary tract symptoms.

Searching
MEDLINE/PubMed, EMBASE, Cochrane CENTRAL and the Chinese Biological Medical Database were searched covering dates from 1966 to November 2013. Search terms and abbreviations were reported. Reference lists of retrieved articles were examined for further studies.

Study selection
Eligible studies were full text reports of randomised controlled trials that evaluated the efficacy of PDE5 inhibitors and alpha-blockers for the treatment of men with erectile dysfunction and lower urinary tract symptoms due to benign prostatic hyperplasia. Trials had to provide enough data for analysis, including mean values and standard deviations in relation to the International Index of Erectile Function (IIEF), International Prostate Symptom Score (IPSS) and maximum flow rate (Qmax).

The included trials were conducted in Italy, United States, Turkey, China and India. The trials compared sildenafil or tadalafil (phosphodiesterase type 5 inhibitors) combined with alfuzosin, doxazosin or tamsulosin (alpha-blockers) with sildenafil or tadalafil alone (various doses were reported in the paper). Most trials did not have a run-in period. The average age of patients ranged from 58 to 63 years.

More than one reviewer was involved in the independent selection of trials for inclusion in the review. Discrepancies were resolved by discussion.

Assessment of study quality
Trial quality was assessed using the Jadad scale, covering allocation procedures, blinding and data loss due to attrition. Studies were then classified (according to Cochrane criteria) as low risk of bias (all quality criteria were met), moderate risk of bias (one or more of the quality criteria were partially met) and high risk of bias (one or more quality criteria were not met).

It appeared that more than one reviewer carried out the quality assessment and disagreements were resolved by discussion.

Data extraction
Date were extracted to enable the calculation of mean differences (MD) and 95% confidence intervals (CI) for all outcomes.

More than one reviewer was involved in extracting the data.

Methods of synthesis
Mean differences were pooled in fixed-effect or random-effects meta-analyses. The latter was used where statistical
heterogeneity was high as measured by Cochran’s Q and $I^2$ statistics. 95% CIs were presented. A sensitivity analysis to assess the impact of low-quality trials by removing them from the meta-analysis was planned. A funnel plot was used to assess potential publication bias.

**Results of the review**

Seven trials (515 patients, range 23 to 250) were included in the review. The overall quality of trials were reported as mainly low and moderate risk of bias but this did not appear to be reflected in the detailed results. Follow-up ranged from 60 days to three months.

For the treatment of erectile dysfunction, combination treatment with PDE5 inhibitors and alpha-blockers produced statistically significant increases in the IIEF scores compared with PDE5 inhibitors alone (MD 2.25, 95% CI 0.07 to 4.43; six trials; $I^2=78\%$).

For the treatment of lower urinary tract symptoms, combination treatment with PDE5 inhibitors and alpha-blockers produced statistically significant decreases in the IPSS score (MD -4.21, 95% CI -7.09 to -1.32; five trials; $I^2=93\%$) and increases in Qmax (MD 1.43, 95% CI 0.38 to 2.47; four trials; $I^2=0\%$).

There was no evidence of publication bias.

**Authors' conclusions**

Combined use of PDE5 inhibitors and alpha blockers resulted in additive favourable effects in men with erectile dysfunction and lower urinary tract symptoms suggestive of benign prostatic hyperplasia compared with PDE5 inhibitor monotherapy.

**CRD commentary**

The review question was clear and inclusion criteria were adequately specified. Several relevant data sources were searched. It was unclear whether steps were taken to minimise language and publication biases. More than one reviewer was involved throughout the review process, helping to minimise error and bias. A suitable quality assessment tool was used but the overall scores did not reflect the individual criteria scores; therefore, the quality of included trials was unclear. Study details were presented. Suitable meta-analyses were performed. Substantial unexplained heterogeneity was found in some analyses. The authors acknowledged limitations in the evidence regarding the small number of studies and small sample sizes, dose variations and short study durations. Their recommendation for future research was justified. Given the various limitations, the authors' conclusion may be unreliable.

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

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that further high quality randomised controlled trials were needed to evaluate combination therapy for the treatment of erectile dysfunction and lower urinary tract symptoms.

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