The effectiveness and safety of avanafil for erectile dysfunction: a systematic review and meta-analysis


CRD summary
Avanafil was effective in doses from 50mg to 200mg and well tolerated for the treatment of erectile dysfunction. An increase in dosage was associated with a significant rise in effectiveness but not significantly more adverse events. This was a well-conducted review and the authors' call for further studies to test the effectiveness of avanafil in different ethnic groups seems appropriate.

Authors' objectives
To compare the efficacy and safety of different doses of avanafil (oral phosphodiesterase type 5 inhibitor) for the treatment of erectile dysfunction.

Searching
PubMed, The Cochrane Library, and EMBASE were searched with no language restrictions. Search terms were reported. MetaRegister and WHO International Clinical Trials Registry Platform were searched for ongoing studies. Reference lists of included studies were also searched.

Study selection
Randomised controlled trials (RCTs) that compared avanafil with placebo, or compared different dosages of avanafil in patients with erectile dysfunction were eligible for inclusion. The outcomes of interest were International Index of Erectile Function–Erectile Function domain score (IIEF-EF), Sexual Encounter Profile Question (SEP) questions 2 and 3, and adverse events.

Included trials were conducted in the USA and Korea; three doses of avanafil were used (50mg, 100mg and 200mg). Patients were primarily of Caucasian ethnicity; the mean age ranged from 54 to 59 years. Treatment duration was 12 or 52 weeks.

Two reviewers independently selected studies for inclusion; any discrepancies were resolved by discussion.

Assessment of study quality
The methodological quality and the quality of evidence were evaluated with the Cochrane risk of bias tool and the GRADE system.

Data extraction
Data were extracted to calculate mean differences and relative risks, with 95% confidence intervals, for all relevant outcomes. Trial authors were contacted for missing data.

Two reviewers independently extracted study data.

Methods of synthesis
Both pairwise meta-analysis and network meta-analysis for different dosage groups were conducted. A random-effects model was used to pool trials and calculate overall mean difference and risk ratio, with 95% confidence intervals. Heterogeneity was assessed using $\chi^2$ and $I^2$. A value of 25% or lower plus $\chi^2$ test of $p>0.1$ was considered as a low level of heterogeneity. Subgroup analysis was undertaken according to the dosage of the drug.

Bayesian network meta-analyses were conducted using a random-effects model to examine the different dosage groups. This combined the direct and indirect evidence for every pair of treatments. Placebo was used as the reference group as it was connected to every dosage group. Meta-regression analyses were performed by adding other covariate (such as trial characteristics and treatment duration) to the network meta-analysis to check the assumption of similarity.

Publication bias was examined by funnel plot and Egger's test.
Results of the review
Five RCTs were included in the review (2,225 patients). The quality of the trials was moderate; randomisation was adequate in two trials and all trials were double blinded. Loss to follow up was balanced, so the risk of bias for incomplete outcome data was low.

Effectiveness: The pairwise meta-analysis of all dosage groups suggested that avanafil was significantly more effective than placebo in improving International Index of Erectile Function–Erectile Function scores (MD 4.47, 95%CI 3.51 to 5.43), and answers to Sexual Encounter Profile question two (SEP-2, MD 17.41, 95%CI 14.03 to 20.79) and question three (SEP-3, MD 20.01, 95%CI 22.98 to 37.22). Similarly, avanafil was significantly effective compared with placebo when different dosages were used (50mg, 100mg and 200mg). There was no evidence of major heterogeneity (results not reported). Higher dosage was significantly more effective than lower dosage, except for the comparison between 100mg and 200mg. The network meta-analysis showed a similar result to pairwise meta-analysis, although some estimates from network meta-analysis failed to achieve statistical significance (results not reported). There was evidence of dose-response relationship among various dosage groups.

Safety: Avanafil was associated with significantly higher incidence of any adverse events and serious adverse events, flushing and headache (full results were reported in the paper). The risks of adverse events were similar between different dosage groups.

The meta-regression analyses did not identify any significant effect modifiers.

There was no evidence of publication bias.

Authors’ conclusions
Avanafil, from 50mg to 200mg, was effective and well tolerated for the treatment of erectile dysfunction. An increase in avanafil dosage was associated with a significant rise in effectiveness but not significantly more adverse events.

CRD commentary
The review question and inclusion criteria were clear. Efforts were made to find published and unpublished studies with no language restrictions, which reduced the potential for language and publication bias. No evidence of publication bias was found. Attempts were made to minimise reviewer errors and bias during the review process.

The quality of the included trials was assessed; this showed moderate risk of bias. Appropriate methods were used to pool data. The authors reported that the heterogeneity was low. The authors acknowledged some limitations in their review. Their recommendation for further studies to test the effectiveness of avanafil in different ethnic groups seems appropriate. Overall, this was a well-conducted review.

Implications of the review for practice and research
Practice: The authors stated that practitioners should treat erectile dysfunction patients with avanafil at a starting dose of 100mg, and then adjust the dosage on demand.

Research: The authors stated that further large studies were need to confirm the effectiveness of avanafil 50mg and also need to evaluate the effectiveness in other ethnic groups and patients with various disease severities. In addition, the safety of larger dosages (above 200mg) should also be evaluated.

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Bibliographic details

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Record Status
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.