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Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus (Review)

Vardi M, Nini A

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Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD002187.
DOI: 10.1002/14651858.CD002187.pub3.

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[Intervention Review]

Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus

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Editorial group: Cochrane Metabolic and Endocrine Disorders Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Citation: Vardi M, Nini A. Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD002187. DOI: 10.1002/14651858.CD002187.pub3.

ABSTRACT

Background

Erectile dysfunction is a common multi-factorial complication of diabetes mellitus. Numerous strategies have been tried to overcome this diabetic complication. In recent years, phosphodiesterase type 5 (PDE-5) inhibitors have been introduced in the management of erectile dysfunction.

Objectives

The objective of this review was to assess the effect of PDE-5 inhibitors on the management of erectile dysfunction in diabetic men.

Search methods

Studies were obtained from computerised searches of MEDLINE, EMBASE and *The Cochrane Library*.

Selection criteria

Randomised controlled trials, in which treatment with PDE-5 inhibitors was compared to control, in diabetic patients with erectile dysfunction.

Data collection and analysis

Two reviewers independently extracted data and assessed trial quality.

Main results

Eight randomised controlled trials were identified. A total 976 men were allocated to receive a PDE-5 inhibitor and 741 were randomised to the control groups. Overall, 80% of the participants suffered from type 2 diabetes mellitus. The weighted mean difference (WMD) for the International Index of Erectile Function (IIEF) questions 3 and 4 (frequency of penetration during and maintaining erection to completion of intercourse) was 0.9 (95% CI 0.8 to 1.1) and 1.1 (95% CI 1.0 to 1.2) at the end of the study period, in favour of the intervention group. The WMD for the IIEF erectile dysfunction domain at the end of the study period was 6.6 (95% CI 5.2 to 7.9) in favour of the PDE-5 inhibitors arm. The relative risk (RR) for answering "yes" to a global efficacy question ("did the treatment improve your erections?") was 3.8 (CI 95% 3.1 to 4.5) in the PDE-5 inhibitors compared with the control arm. The WMD between the percentage of successful attempts in the PDE-5 inhibitors and in the control arm was 26.7 (95% CI 23.1 to 30.3). Mortality was not reported in any of the included trials. Adverse cardiovascular effects were reported in one study. Headache was the most frequent adverse event reported, flushing was the second most common event, with upper respiratory tract complaints and flu like syndromes, dyspepsia, myalgia, abnormal vision and back pain also reported in a descending order of frequency. The overall risk ratio for developing any adverse reaction was 4.8 (CI 95% 3.74 to 6.16) in the PDE-5 inhibitors arm as compared to the control.

Authors' conclusions

Sufficient evidence exists that PDE-5 inhibitors form a care that improves erectile dysfunction in diabetic men.

PLAIN LANGUAGE SUMMARY

Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus

Erectile dysfunction is a common multi-factorial complication of diabetes mellitus. Newer medications, like the so-called PDE-5 inhibitors result in enhancement of penile erection. The introduction of sildenafil (Viagra), vardenafil (Levitra) and tadalafil (Cialis), have altered the management of erectile dysfunction. In this review we assessed the effect of these agents on erectile dysfunction in diabetic people. Eight studies with 976 men randomised to PDE-5 inhibitor therapy and a duration of mainly 12 weeks were evaluated. Compared to placebo treatment, these agents showed favourable effects in scores estimating sexual life, with an increased rate of adverse effects like headache and flushing after PDE-inhibitor therapy. Mortality was not reported in any of the included trials. Quality of life, with the exception of scores for sexual life, was not relevantly affected. If taken as prescribed, PDE-5 inhibitors comprise a valuable treatment option for erectile dysfunction in men with diabetes.

BACKGROUND

Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action or both. A consequence of this is chronic hyperglycaemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease is increased. For a detailed overview of diabetes mellitus, please see under 'Additional information' in the information on the Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About the Cochrane Collaboration', 'Collaborative review groups (CRGs)'). For an explanation of methodological terms, see the main Glossary in *The Cochrane Library*.

Diabetes mellitus is accompanied by a variety of other chronic complications. Erectile dysfunction, defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse (NIH Consensus 1993), is one such complication of diabetic patients. Approximately 50% of diabetic men experience erectile dysfunction at least once in the course of their disease. In the Massachusetts Male Aging Study (MMAS), a landmark community-based survey of predominantly Caucasian men aged 40 to 69 years, the age adjusted risk for developing erectile dysfunction for treated or untreated self reported diabetic patients was 1.83 and statistically significant (Johannes 2000).

Various factors are thought to contribute to the development of erectile dysfunction in diabetic men. Neuropathy, vascular disease, diabetes control, nutrition, endocrine disorders and psychogenic factors, as well as drugs used in the treatment of diabetes mellitus and its complications play a role (Vinik 1998a; Vinik 1998b).

Description of the intervention

Numerous strategies have been tried to overcome this diabetic complication. These include improving glycaemic control, a range of drugs that influence penile rigidity, the use of vacuum assisted devices to produce an erection-like state, operations to apply prostheses within the penis and psychological counselling. In recent years, three phosphodiesterase type 5 (PDE-5) inhibitors, that is sildenafil (Viagra), vardenafil (Levitra) and tadalafil (Cialis), have been introduced in the management of erectile dysfunction.

How the intervention might work

Nitric oxide is an important regulator of cavernosal smooth muscle relaxation. Nitric oxide also induces arterial dilatation. The actions of nitric oxide on the cavernosal smooth muscle and the arterial blood flow are mediated through the activation of guanyl cyclase and production of cyclic guanidine-mono-phosphate (cGMP) (Andersson 1995; Christ 1995; Lue 1988; Lue 2000; McDonald 1996; Naylor 1998; Nehra 1999; Rajfer 1992). The enzyme phosphodiesterase type 5 is a selective inactivator of cGMP in the cavernosal smooth muscle (Andersson 1995; Lue 2000; Naylor 1998). Hydrolysis of cGMP by this enzyme results in reversal of the smooth muscle relaxation and reversal of penile erection. PDE-5 inhibitors prevent breakdown of cGMP and thereby enhance penile erection (Goldstein 1998).

When sexual stimulation releases nitric oxide into the penile smooth muscle, inhibition of phosphodiesterase type 5 causes a marked elevation of cGMP concentrations in the glans penis, corpus cavernosum and corpus spongiosum, resulting in better erection. PDE-5 inhibitors have no effect on the penis in the absence of sexual stimulation, when the concentrations of nitric oxide and cGMP are low (Lue 2000).

We defined our main outcome measure as the achievement of penile rigidity satisfactory for penetration and sufficiently prolonged to enable sexual intercourse to be completed. This was assessed using the self-administered International Index of Erectile Function (IIEF), a 15-item questionnaire and validated measure of erectile function (Rosen 1997, see Appendix 2). Each question is scored using a five point ordered categorical scale, with a score of one representing the worst response (almost never/never) and a score of five representing the best response (almost always/always).

Adverse effects of the intervention

Adverse effects associated with PDE-5 inhibitors are related to their vasodilatory properties and are similar to those induced by nitrates. These include headache, lightheadedness, dizziness, flushing, distorted vision, and, in some cases, syncope. Men at highest risk for syncope are those who take other vasodilators such as nitrates. Thus, men should be cautioned against the combined use of sildenafil and a nitrate because of the risk of hypotension and syncope.

Why it is important to do this review

Since the release of sildenafil to the market in March 1998, it has become the treatment of choice for most men with erectile dysfunction. Vardenafil and tadalafil are two new PDE-5 inhibitors with reported better tissue specificity and pharmacokinetic profiles than sildenafil. Much have been reported about the clinical efficacy, side effect profile and cost effectiveness of these agents. Publications and reviews on the subject of erectile dysfunction in diabetic patients also exist. Nevertheless, to our knowledge, no formal systematic review and meta-analysis have been conducted to assess the management of diabetic men with phosphodiesterase-5 inhibitors.

OBJECTIVES

To assess the effects of phosphodiesterase type 5 inhibitors for erectile dysfunction in patients with diabetes mellitus.

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria

Trial design

Randomised controlled trials, in which treatment with phosphodiesterase-5 (PDE-5) inhibitors was compared to control, in diabetic patients with erectile dysfunction. Trials with more than two treatment groups were to be included and analysed accordingly. We also considered cross-over trial design (no wash-out period is required in this case due to the temporary nature of treatment interventions).

Trial duration

Trials with interventions and follow-up period of any duration were included.

Exclusion criteria

Controlled randomised trials in which allocation to the treatment or control group was not truly random or in which treatment allocation was not concealed, were to be excluded, in view of the fact that prior knowledge of treatment allocation may have led to biased patient allocation, treatment or reporting. It is acknowledged that useful information about this problem might be gained from non-randomised studies or other randomisation methods (for example cluster randomisation). However, for this review, such studies were not considered.

Types of participants

Inclusion criteria

Patients known to have diabetes mellitus and at the time of study known to have erectile dysfunction and treated for this disorder in a prospective trial design in which at least one treatment option included phosphodiesterase type 5 inhibitors.

Diagnostic criteria for diabetes mellitus

Ideally, the diagnostic criteria for diabetes mellitus should have been described in the trial. To be consistent with changes in classification and diagnostic criteria of the disease through the years, the diagnosis should have been established using the standard criteria valid at the time of the beginning of the trial (for example, ADA 1997; WHO 1985; WHO 1998). Changes in the diagnostic criteria may have produced significant variability on the clinical characteristics of the patients included as well as in the results obtained. These differences were considered and explored in a sensitivity analysis.

Diagnostic criteria for erectile dysfunction

Erectile dysfunction is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse (NIH Consensus 1993).

Types of interventions

Treatment for erectile dysfunction in diabetic patients with a phosphodiesterase type 5 (PDE-5) inhibitor, orally administered at any regimen, in trials of any duration.

(1) PDE-5 inhibitors:
(a) sildenafil (Viagra);
(b) vardenafil (Levitra);
(c) tadalafil (Cialis).

(2) Comparison group:
(a) no treatment;
(b) placebo;
(c) other PDE-5 inhibitors.
(d) other therapeutic options for erectile dysfunction in diabetic patients:
(d i) psychosexual counselling;
(d ii) vacuum devices for inducing erection;
(d iii) hormonal manipulations;
(d iv) intra urethral therapies - alprostadil with or without prazosin;
(d v) intra cavernosal injection of vasoactive agents - alprostadil or papaverine or phentolamine;
(d vi) penile prosthesis.

Types of outcome measures

Primary outcomes

The main outcome measure was the achievement of penile rigidity satisfactory for penetration and sufficiently prolonged to enable sexual intercourse to be completed.
This was assessed through validated questionnaires and scales for erectile function, sexual function, quality of life, and a global efficacy questions.

Secondary outcomes

- morbidity due to the interventions;
- adverse effects;
- all-cause mortality.

Covariates, effect modifiers and confounders

Covariates that were considered:

- patients' compliance;
- glycaemic control throughout the trial, ideally through measurements of glycated haemoglobin; and
- changes in concomitant medications throughout the trial.

Search methods for identification of studies

Electronic searches

We used electronic search strategies to identify relevant trials (as defined under 'type of studies'), as well as reviews and meta-analyses (for identification of additional trials). The following databases were searched:

- *The Cochrane Library* (Issue 1, 2006);
- MEDLINE (until October 2005);
- EMBASE (until October 2005).

We also searched databases for ongoing trials:

- Current Controlled Trials (http://www.controlled-trials.com);
- UK National Research Register (http://www.update-software.com/national/nrr-frame.html);
- Center Watch Clinical Trials Listing Service (http://www.CenterWatch.com/);
- National Institute of Health (http://clinicalstudies.info.nih.gov/).

The described search strategy (see for a detailed search strategy under Appendix 1) was used for MEDLINE. For use with EMBASE and *The Cochrane Library* this strategy was slightly adapted.

Search for identification of studies was not restricted by language.

Searching other resources

We tried to identify additional studies by searching the reference lists of relevant trials and reviews identified.

Manufacturers of sildenafil (Viagra), vardenafil (Levitra) and tadalafil (Cialis) (Pfizer, Bayer, Lilly, respectively) were contacted, as well as the authors of published trials.

Data collection and analysis

Selection of studies

Two reviewers (MV, AN) independently scanned the titles, abstract sections and keywords of every record retrieved. Full articles were retrieved for further assessment if the information given suggested that the study fulfilled the inclusion criteria and did not meet the exclusion criteria. If there was any doubt regarding these criteria from the information given in the title and abstract, the full article was retrieved for clarification. Interrater agreement for study selection was measured using the kappa statistic (Cohen 1960). Where differences in opinion existed, they were resolved through open discussion. The level of interrater agreement for study selection is reported.

Data extraction and management

A data extraction form was used and submitted with this protocol. The following data were extracted.

- general information: author, title, publication (type, unpublished), language of publication, year of publication, country, complete reference or source, contact details, duplicate publication, multiple publication, rural or city, single centre versus multi centre, setting, stated aim of the study, sponsor, ethic committee approval and description of conflict of interests.
- trial design: prospective study, control group, parallel study, placebo controlled, active medication controlled, cross-over study, run-in period, wash-out period (for cross-over trials), carryover effect described (for cross-over trials), period effect described, sampling method, power calculation, selection bias (randomisation, unit of randomisation and allocation concealment adequacy), performance bias (blinding of patients and caregivers, method of blinding, check of blinding, check of blinding method), attrition bias (intention-to-treat analysis, withdrawals description, drop-outs description, losses to follow-up description, change of groups (cross-overs), number of drop-out and withdrawals and losses to follow-up, reasons for drop-outs or withdrawals or losses to follow-up description), detection bias (blinding of outcome assessors), overall quality assessment, definition of inclusion criteria, definition of exclusion criteria, specification of exclusion criteria, predefined subgroups, posthoc defined subgroups and specification of subgroups.
- participants: diabetes mellitus diagnostic criteria description, diabetes mellitus diagnostic criteria validity, erectile dysfunction diagnostic criteria description, erectile dysfunction diagnostic criteria validity, exclusion criteria definition, baseline characteristics that is age, gender, race, body mass index, glycated haemoglobin, fasting plasma glucose, duration of diabetes mellitus, type of diabetes mellitus, diabetes mellitus related complications, diabetes mellitus related treatment, co morbidities, other medications, identical treatment of groups (apart from intervention), prior treatment for erectile dysfunction and baseline erectile dysfunction status.
- intervention: nature of therapy, regimen (dose, schedule and units), duration of therapy, length of follow-up, compliance.
- outcomes: total deaths, adverse events, efficacy as measured with regards to erectile dysfunction status.
- covariates: glycated haemoglobin, fasting plasma glucose, compliance, change of concomitant medication.

Authors of studies were contacted concerning missing information in their trials.

Assessment of risk of bias in included studies

The quality of reporting each trial was assessed based largely on the quality criteria specified by Schulz and by Jadad (Jadad 1996; Schulz 1995). In particular, the following factors were studied:
(1) minimisation of selection bias - was the randomisation procedure adequate? Was the allocation concealment adequate?
(2) minimisation of performance bias - were the patients and people administering the treatment blind to the intervention?
(3) minimisation of attrition bias - were withdrawals and dropouts completely described? Was analysis by intention-to-treat?
(4) minimisation of detection bias - were outcome assessors blind to the intervention?

Based on these criteria, studies were broadly subdivided into the following three categories:
(A) all quality criteria met: low risk of bias;
(B) one or more of the quality criteria only partly met: moderate risk of bias; and
(C) one or more criteria not met: high risk of bias.

This classification was used as the basis of a sensitivity analysis. Additionally, we explored the influence of individual quality criteria in a sensitivity analysis.

Two reviewers (MV, AN) assessed each trial. Interrater agreement was calculated using the kappa statistic (Cohen 1960), and reported. In cases of disagreement, judgment was made based upon consensus.

Measures of treatment effect

The outcome data were generally of ordinal nature (including measurement scales), where the outcome is one of several ordered categories or generated by scoring and summing categorical responses (such as in the case of self reported quality of life assessment scale). Some data were presented as counts, for example number of satisfying penetrations per time period.
Effect measures for ordinal data was assessed as continuous data. Weighted mean difference was measured. This method was used for each of the parameters assessed, after assuring that the different scales used in the trials point towards a single direction. Whenever dichotomizing results seemed statistically feasible and clinically logical, effect measurements for dichotomous data were used, that is risk ratios and odds ratios.
Effect measures for count and rates data were assessed as continuous data given the anticipation for common event occurrence. Weighted mean difference was used to assess the difference in the mean number of events per group of patients.

Short-, intermediate- and long-term assessment of effect in the case of repeated observations per participant did not seem clinically significant in our review. Therefore, in the case of multiple observations we selected the longest follow-up for each trial and analyse results to that point. This method may induce lack of consistency across trials and give rise to heterogeneity, which was addressed in a sensitivity analysis.

Intention-to-treat analysis aims to include all participants randomised into a trial irrespective of what happened subsequently. This means that trial participants should be analysed

in the group to which they were randomised regardless of which treatment they actually received or other protocol irregularities and all participants should be included regardless of whether their outcomes were actually collected. In this review we adopted an available-case-analysis, in which only the former criterion is met, and analysis was performed for every participant for whom data were available. Thus, filling-in for missing data was not conducted. Special attention was given for three types of exclusions:
(a) participants excluded for predefined exclusion criteria using information collected before randomisation - considered as legitimate;
(b) participants excluded immediately after randomisation- considered as illegitimate;
(c) very high dropout rates or inconsistency across study groups, which may indicate low quality of trial conduction.

Assessment of heterogeneity

Heterogeneity is a term used to describe variability among trials encountered in a meta-analysis. In our review, we anticipated some clinical diversity, for example diabetes status, erectile dysfunction status or treatment, as well as methodological diversity, both giving rise to statistical heterogeneity. On the one hand, the scope of our review was relatively confined, therefore heterogeneity is not inherently large. On the other hand, disease status may be variable among participants and treatment in the study group relates to three different drugs. Methodologically there was no promise for comparable quality. In this review, it seemed appropriate to aim at broader perspective, thus, primarily evaluate the average effect of phosphodiesterase type 5 inhibitors by combining results from trials that evaluate the different drugs in this pharmacological class.
Heterogeneity was identified using the formal chi-square test, which is intended to assess whether observed differences in results are compatible with chance alone. Chi-squared test have low power when trials have small sample size or are few in number. Therefore a P value of less than 0.10 was considered statistically significant. We also tried to quantify the amount of heterogeneity by describing the percentage of the variability in effect estimates that is due to heterogeneity rather than chance (Higgins 2002; Higgins 2003).
A negative chi-square does not necessarily mean that no heterogeneity exists or should not be further explored. In this view, a subgroup analysis was performed as discussed below.

Assessment of reporting biases

Small study bias was analysed with the funnel plot method. It is, however, important to realise that publication bias is only one of a number of possible causes of funnel-plot asymmetry.

Data synthesis

Data were summarised statistically if they were available, sufficiently similar and of sufficient quality. Heterogeneity was addressed using two meta-analytical methods. Due to the limited number of studies retrieved, a fixed-effect meta-analysis was carried out, ignoring heterogeneity, thus calculating the typical group treatment effect. Fixed-effect analysis was performed using the Mantel-Haenszel methods, which have been shown to have better statistical properties when there are few events.
When addressing dichotomous data types, the effect of treatment was expressed with relative effect measures, that is risk ratio and odds ratio, which are more consistent than absolute measures. These were calculated for an event (rather then for a non-event).
When addressing continuous data type, we expressed the effect of treatment using weighted mean difference.

Subgroup analysis and investigation of heterogeneity

To further explore heterogeneity and investigate the effect modification of participants and treatment types, we performed a subgroup analysis, according to the following predefined groups.

(1) participants:
(a) gender - male versus female;
(b) diabetes status - mild to moderate versus severe (according to clinical status and treatment);
(c) erectile dysfunction status - mild to moderate versus severe (according to baseline status).

(2) intervention:
(a) phosphodiesterase type 5 inhibitors: sildenafil, vardenafil and tadalafil.

A dose-response analysis was not performed, nor any indirect comparisons between groups not directly evaluated head to head in a clinical trial.

Sensitivity analysis

We performed a sensitivity analyses in order to explore the influence of the following factors on effect size by:

- repeating the analysis excluding unpublished studies (if there were any);
- repeating the analysis taking account of study quality (low-, moderate- or high-risk of bias);
- repeating the analysis taking account of specific quality criteria (that is selection, performance, attrition and detection biases);
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results;
- repeating the analysis excluding studies using the following filters: diagnostic criteria for diabetes mellitus and erectile dysfunction, language of publication, source of funding (industry versus other), country and scales used for measuring effect (validated versus other).

The robustness of the results was also tested by repeating the analysis using different measures of effects size (risk difference, odds ratio etc.) and different statistical models (fixed and random effects models).

RESULTS

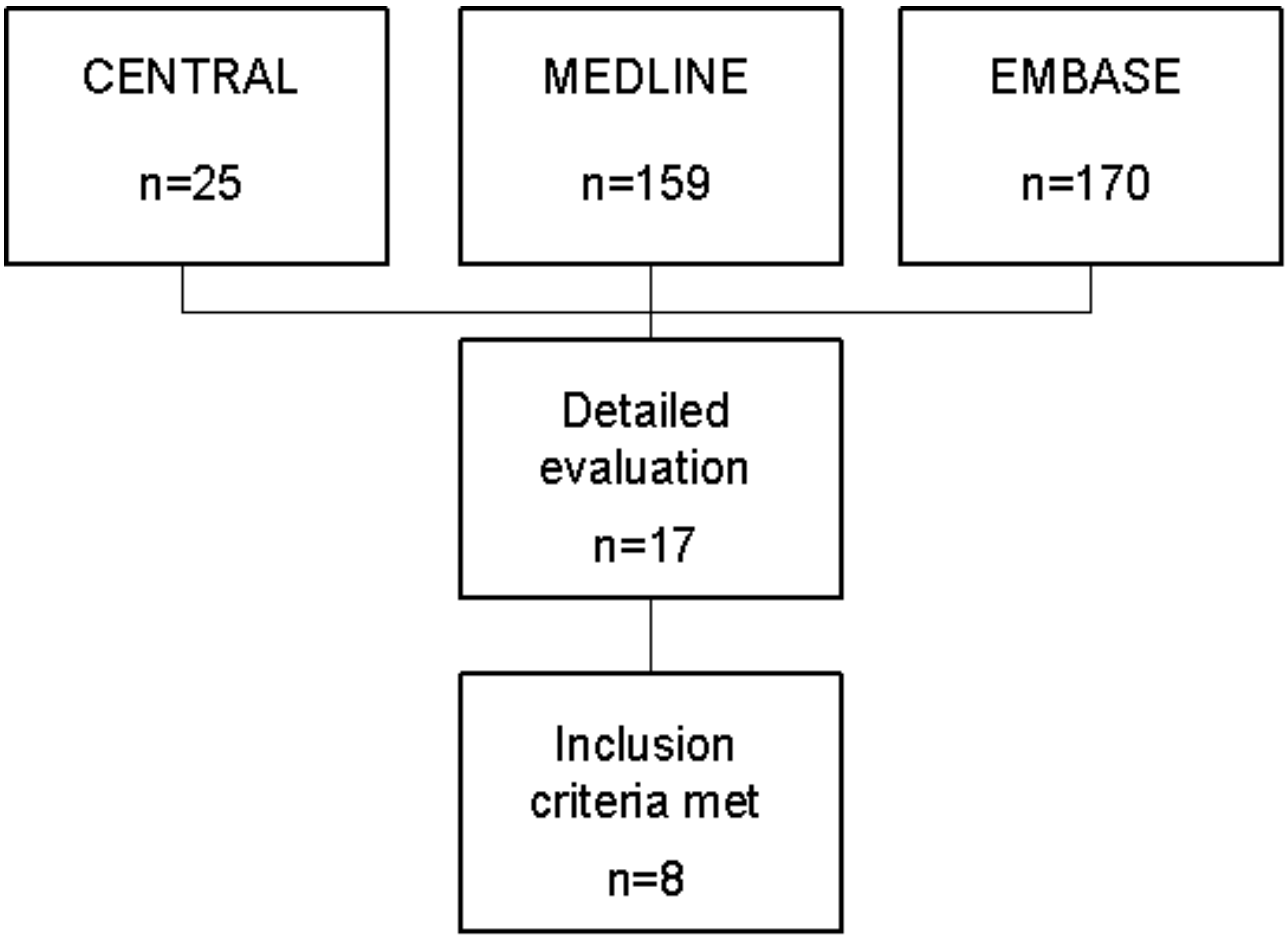
Description of studies

Results of the search

Twenty-five, 159 and 170 records were retrieved using the electronic search strategy of this review in CENTRAL, MEDLINE and EMBASE respectively ('Additional Figures' - Figure 1). Hand searching through the reference lists of relevant trials and reviews identified did not yield additional records for assessment, nor did a search of databases for ongoing trials. The manufacturers of sildenafil (Viagra), vardenafil (Levitra) and tadalafil (Cialis) (Pfizer, Bayer, Lilly, respectively) were contacted but no additional data were obtained. Seventeen records were retrieved for a more detailed evaluation. Eight studies met the inclusion criteria for this review. Of these - seven studies were of parallel group design

(Boulton 2001; Escobar-Jimenez 2002; Goldstein 2003; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003) and one of cross-over design (Price 1998).

Figure 1.



Interrater agreement

Interrater agreement for study inclusion was 0.94. Differences in opinions were resolved through open discussion.

Missing data

The authors of the included trials were contacted for methodological clarifications, individual patient data, and knowledge of other studies conducted in the field. Two authors replied, but neither additional data nor individual patient data were supplied.

Included studies

Studies

Eight truly randomised-controlled trials were identified, in which treatment of erectile dysfunction with a phosphodiesterase-5 inhibitor (PDE-5) was compared to control in diabetic patients. Trial duration was 12 weeks, excluding Safarinejad 2004 in which duration of trial was 16 weeks and Price 1998 in which the duration was 10 days for each of the treatment arms. The run-in phase for all studies was four weeks, except in Price 1998 in which the run-in period was two weeks. Due to the temporary nature of the intervention this duration was considered sufficient. Five trials were sponsored by the manufacturer of the intervention group drug (Goldstein 2003; Price 1998; Rendell 1999; Saenz de Tejada 2002; Stuckey 2003). In the remaining three trials sponsorship was not revealed (Boulton 2001; Escobar-Jimenez 2002; Safarinejad 2004). One trial was published in Spanish (Escobar-Jimenez 2002), while the other seven were published in English.

Participants

A total of 1759 participants were recruited in eight trials. 976 were randomised to receive a PDE-5 inhibitor and 741 were randomised to the control groups. Twenty-one participants in the one cross-over design study received both a PDE-5 inhibitor and placebo. All were men. Treatment groups within studies did not differ significantly with respect to age, medical history, concomitant medication, diabetes mellitus severity or duration, and erectile dysfunction severity (when described). Valid diagnostic criteria for diabetes mellitus were described in four trials (Boulton 2001; Rendell 1999; Saenz de Tejada 2002; Stuckey 2003). Valid diagnostic criteria for erectile dysfunction were described in four trials (Escobar-Jimenez 2002; Price 1998; Rendell 1999; Safarinejad 2004). One study (Stuckey 2003) assessed the efficacy of a PDE-5 inhibitor in a type 1 diabetes mellitus population, two studies (Boulton 2001; Escobar-Jimenez 2002) recruited only type 2

diabetic participants, and the remaining five studies recruited both type 1 and type 2 diabetic patients. Overall, 80% of the participants suffered from type 2 diabetes mellitus.
For details about baseline characteristics of study participants Appendix 5.

Interventions

All eight trials compared a phosphodiesterase-5 inhibitor with placebo. No head to head comparisons between the different PDE-5 inhibitors, or any comparison with other treatment modalities for erectile dysfunction were conducted. One trial compared tadalafil at a fixed dose of 10 mg and 20 mg with placebo (Saenz de Tejada 2002). Another trial compared vardenafil at a fixed dose of 10 mg and 20 mg with placebo (Goldstein 2003). The remaining six trials compared sildenafil with placebo at doses titrated between 25 mg and 100 mg. Patients were instructed to use the medication no more than once daily, within 30 minutes to one hour of sexual intercourse. Treatment duration was 10 days in one study (Price 1998), 16 weeks in one study (Safarinejad 2004) and 12 weeks in the remaining trials.

Outcome measures

The main outcome measure was defined as the achievement of penile rigidity satisfactory for penetration and sufficiently prolonged to enable sexual intercourse to be completed. This was assessed using the self-administered International Index of Erectile Function (IIEF), a 15-item questionnaire and validated measure of erectile function (Rosen 1997, see Appendix 2). Each question is scored using a five point ordered categorical scale, with a score of one representing the worst response (almost never/never) and a score of five representing the best response (almost always/always). We focused on two questions within the IIEF questionnaire which specifically address the key aspects of erectile dysfunction as defined by the National Institute of Health: IIEF question 3, which assesses the ability to achieve an erection for sexual intercourse, and IIEF question 4, which assesses the ability to maintain an erection after penetration. Additionally, we assessed the Erectile Function domain within the IIEF, which is a summation of questions 1 through 5 and question 15. Efficacy was assessed via the difference in means at the end of the study period.
A global efficacy question ("did the treatment improve your erections?") and an event log in which patients recorded the number of attempts at sexual intercourse and the number of attempts that were successful were also addressed. Quality of life was also investigated.
Additional outcome measures were predefined as all-cause mortality, morbidity and adverse effects. Issues regarding costs were not addressed.

Excluded studies

Of the studies retrieved for further evaluation in full text nine were excluded. One was a retrospective study (Fonseca 2004), two were open label (El-Sakka 2004; Perimenis 2002), three included non-diabetic patients (Carson 2005; Palumbo 2001; Salama 2004), two were not randomised trials (Behrend 2005; Kalinchenko 1999) and one was a review (Vickers 2002).

Risk of bias in included studies

Selection bias

Only three of the eight studies described their randomisation and allocation concealment methods (Rendell 1999; Safarinejad 2004; Stuckey 2003). Of these, all were adequate. Unit of randomisation was individuals for all the included studies.

Performance bias

All included studies reported the blinding of patients and caregivers, but only Stuckey 2003 reported the method of blinding. Testing of blinding was not reported by any of the authors.

Attrition bias

In all but two studies (Boulton 2001; Escobar-Jimenez 2002), withdrawals, drop-outs, losses to follow-up and their reasons were adequately described. Intention-to-treat analysis was performed by Escobar-Jimenez 2002; Goldstein 2003; Rendell 1999; Saenz de Tejada 2002 and Safarinejad 2004. Information regarding intention-to-treat analysis was missing for Boulton 2001; Price 1998 and Stuckey 2003.

Detection bias

Goldstein 2003 had included a description of the blinding of outcome assessors. All other authors did not describe this issue.

A summery of quality characteristics and the overall quality of the studies is given in Appendix 3 and Appendix 4. The overall quality was roughly assessed on a three point scale according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005). None of the included studies included a full report of all quality characteristics. Seven studies were defined as showing a moderate risk of bias and one a high risk for bias.

Effects of interventions

For details about outcome data and adverse events see Appendix 6 and Appendix 7.

Index of Erectile Function (IIEF)

Only five of eight studies included scores for IIEF question 3 and 4 (Boulton 2001; Escobar-Jimenez 2002; Rendell 1999; Safarinejad 2004; Stuckey 2003). The weighted mean difference (WMD) for IIEF question 3 and 4 was 0.9 (95% confidence interval (CI) 0.8 to 1.1) and 1.1 (95% CI 1.0 to 1.2) at the end of the study period, in favour of the intervention group. Seven studies (Boulton 2001; Escobar-Jimenez 2002; Goldstein 2003; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003) included scores for the IIEF erectile function domain. The WMD at the end of the study period was 6.6 (95% CI 5.2 to 7.9) in favour of the PDE-5 inhibitors arm.

Global efficacy question

All eight studies included the number of participants answering "yes" to the question "did the treatment improve your erections?". The relative risk (RR) for answering "yes" was 3.75 (CI 95% 3.12 to 4.51) in the PDE-5 inhibitors arm compared with the control arm. This has to be interpreted with caution due to significant heterogeneity between trials (I^2 = 77.4%).

Percentage of successful attempts

Four (Boulton 2001; Goldstein 2003; Saenz de Tejada 2002; Stuckey 2003) trials included an adequate report of the mean percentage of successful intercourse attempts per participant. The weighted mean differences between the percentage of successful attempts in the PDE-5 inhibitors arm and in the control arm was 26.7 (95% CI 23.1 to 30.3). Price 1998 reported a geometric mean number of erections per week sufficiently rigid for sexual intercourse of 0.6, 1.3 and 1.6 (placebo, sildenafil 25 mg and sildenafil 50 mg, respectively). These differences are reported to be statistically significant.

Quality of life

Quality of life was addressed by two reports (Boulton 2001; Escobar-Jimenez 2002) through the Life Satisfaction Checklist, a quality-of-life questionnaire (Fugl-Meyer questionnaire, Fugl-Meyer 1997). Sildenafil has shown to significantly improve the scores for sexual life. Differences in other domains were non significant in both studies (that is life as a whole, partnership relation, family life, contact with friends, leisure situation, vocational situation and financial situation).

Mortality, morbidity and adverse reactions

Mortality was not reported in any of the included trials. Only one study (Safarinejad 2004) reported treatment related cardiovascular morbidity in the intervention arm. The 10 events (7%) recorded were four incidents of chest pain, of which two were myocardial infarctions with a documented ST-elevation, two cases of congestive heart failure and four cases of hypertension. Headache was the most frequent adverse event reported, with a total of 141 of 1012 patients in the PDE-5 inhibitors arm as compared to 28 of 755 in the control arm, a risk ratio of 3.66 (95% CI 2.51 to 5.35). Flushing was the second most common event, with 103 reports in 970 patients in the PDE-5 inhibitors arm, a relative risk of 13.21 (95% CI 6.01 to 29.03) as compared with control. Upper respiratory tract complaints and flu like syndromes, dyspepsia, myalgia, abnormal vision and back pain were also reported in a descending order of frequency. The overall risk ratio for developing any adverse reaction was 4.8 (95% CI 3.74 to 6.16) in the PDE-5 inhibitors arm as compared to the control.

Heterogeneity and subgroup analysis

Due to the limited number of studies retrieved for this meta-analysis, a fixed effect meta-analytic model was used (Mantel-Haenszel method). The chi-squared test was performed with a P value of less than 0.10. When addressing the global efficacy question, the chi-squared test yielded a P value < 0.0001 with I^2=77.4%. Therefore, the effect of treatment for this particular question must be interpreted cautiously, as observed differences in results are probably not compatible with chance alone, and statistical heterogeneity exists. For all other effect estimates, no significant heterogeneity was found.
To further explore heterogeneity we explored treatment effect with respect to baseline diabetes status. Only three studies addressed this issue. In the study of Boulton 2001, effect of sildenafil versus placebo was significant for IIEF question 3, IIEF question 4, IIEF EF domain, percentage of successful attempts and the global efficacy question for both low and high baseline glycated haemoglobin groups (threshold was defined as 8.3%). In the study of Saenz de Tejada 2002, baseline glycated haemoglobin did influence response to tadalafil treatment, particularly in the poorly controlled diabetic patients receiving a low dose tadalafil, whereas the change in the IIEF EF-domain was similar for both placebo and tadalafil 10 mg groups (groups were stratified according to glycated haemoglobin - below 7%, 7% to 9.5% and above 9.5%). Stuckey 2003 showed the relationship between response to treatment and baseline glycated haemoglobin to be non-significant with respect to the individual success rate of erection with a duration sufficient to complete intercourse from a diary question sexual encounter profile.
Baseline erectile function status was addressed by two authors: Stuckey 2003 reported significant treatment effects for sildenafil in type 1 diabetic patients regardless of erectile dysfunction severity (defined as mild or moderate versus severe), with respect to IIEF question 3, IIEF question 4, IIEF EF domain and percent of successful intercourse; Goldstein 2003 reported a significantly higher rate of successful intercourse attempts in the severe baseline erectile dysfunction group receiving a high dose vardenafil (20 mg).

We intended to perform a subgroup analysis with respect to gender but all participants across studies were male. A subgroup analysis for the type of PDE-5 inhibitor revealed that all three types of PDE-5 inhibitors were superior to placebo in the IIEF EF domain and global efficacy question. Studies addressing IIEF questions 3 and 4 have all compared sildenafil with placebo.

Sensitivity analysis

Unpublished data

No unpublished data were available for analysis.

Study quality

The influence of quality of studies was assessed by a sensitivity analysis. All studies were classified as moderate risk for bias, but one (Boulton 2001) which was classified as high risk for bias. IIEF EF domain, questions 3 and 4, global efficacy question and the number of successful intercourse attempts remained statistically significant after removing this study.

Specific quality criteria

We repeated the analysis taking account of specific quality criteria (Appendix 4). Selection was reported appropriately by three studies (Rendell 1999; Safarinejad 2004; Stuckey 2003). Repeating the analysis after excluding the studies in which selection bias was not adequately reported did not influence the significance of the results in any of the efficacy parameters. Performance was reported adequately by one study (Stuckey 2003), in which all efficacy parameters were significant in favour of PDE-5 inhibitors. Attrition was inadequate in one study (Boulton 2001), inadequately reported by another (Stuckey 2003), and adequate in all others. Repeating the analysis taking account of attrition quality did not influence the significance of the results. Detection was reported adequately by one study (Goldstein 2003) in which all efficacy parameters were significant in favour of PDE-5 inhibitors.

Long or large trials

All studies were clinically similar in terms of duration (ranging from 17 days to 16 weeks). None of the studies was larger than all others in a manner that dominated the results.

The differences in favour of the PDE-5 inhibitors and placebo remained statistically significant after repeating the analysis in view of diabetes mellitus and erectile dysfunction diagnostic criteria and language of publication. Source of funding was not an influencing factor.

The robustness of the results was tested by repeating the analysis using different measures of effects size (risk difference, odds ratio etc.) and different statistical approaches (fixed and random effects models). The use of different measures of effect size as well as different statistical models did not influence the results.

Assessment of publication bias

Funnel plots were not drawn due to insufficient number of studies.

DISCUSSION

Diabetes mellitus is a common and debilitating disease that affects patients' quality of life, morbidity and mortality. In particular, its multifactorial effect on sexual performance is of high prevalence and impact on one's perception of well-being. Many therapeutic options have been proposed prior to the introduction of phosphodiesterase type 5 (PDE-5) inhibitors, none of which showed a definite therapeutic effect. PDE-5 inhibitors have shown to be effective in the treatment of erectile dysfunction in the general population. The goal of this review was to systematically analyse their effect in diabetic patients. The meta-analysis presented here has clearly shown that when comparing PDE-5 inhibitors as a group with placebo, their relative as well as absolute effect on sexual activity is clinically favourable, with consistent statistical significance. This is reflected in the scores of the International Index of Erectile Function, the percentages of successful attempts, and in a global efficacy question. Interestingly, quality of life questionnaires have shown improvement in scores for sexual life, but did not yield statistically significant differences in other domains, such as life as a whole, partnership relation, family life, contact with friends, leisure situation, vocational situation and financial situation. Presumably, this result is a reflection of the complexity of one's life experience.

In terms of adverse reactions, only one study reported serious cardiovascular morbidity in the intervention arm, including four events of documented myocardial infarction with ST-elevation and congestive heart failure. These events were not reported by other authors. Effects of PDE-5 inhibitors on the cardiovascular system have been studied thoroughly, specifically with sildenafil which was first developed as an anti-anginal agent. A recent review has been published on the subject (Culley 2005). In short, clinical trials not specifically designed for diabetic patients showed no statistically significant difference in myocardial infarctions or other vascular deaths between PDE-5 inhibitors users and placebo users. On the contrary, a trend of reduction in these events in the investigational arm was noted (Bischoff 2004; Cialis presc info; Kloner 2003; Levita presc info; Mittleman 2003; Zusman 1999). Specifically in men with diabetes, one study showed that placebo-treated patients had a rate of myocardial infarction of 2.1 per 100 patient-years, compared with 0.7 in patients treated with tadalafil (Kloner 2004). Thus, PDE-5 inhibitors should be considered safe for treatment of erectile dysfunction in stable coronary artery disease, and should probably be considered safe in diabetic patients as well.

In general, the prevalence of other mild adverse effects was low, and was considered by authors to be none-significant clinically. When prescribing these agents, physician and patients must be aware of their tendency to elicit headaches, flushing, upper respiratory tract complaints and flu like syndromes, dyspepsia, myalgia, abnormal vision and back pain.

One methodological drawback must be emphasized. None of the studies included in this review has shown a low risk for bias. This may reflect flaws in conduction, or merely lack of adequate reporting. Nevertheless, sensitivity analyses taking account of specific quality criteria and excluding trials with inadequate reporting did not influence the robustness of the results.

It is clear from the meta-analysis presented that PDE-5 inhibitors should be considered a primary treatment for erectile dysfunction in diabetic men. They have proved to be effective and safe. It seems that their effect may wane in low doses in patients with uncontrolled diabetes, with higher baseline glycated haemoglobin. Higher doses may be required for this particular subgroup.

Unfortunately, we found no head to head comparisons between the three available PDE-5 inhibitors, and no trials comparing them with other available therapeutic options. Another issue of interest which is yet in its infancy is the effect of PDE-5 inhibitors on female sexual dysfunction, particularly diabetic women.

AUTHORS' CONCLUSIONS

Implications for practice

Sufficient evidence exists that phosphodiesterase type 5 (PDE-5) inhibitors form a care that improves erectile dysfunction in diabetic men.

Implications for research

More research is needed in the following areas:

- assessing the effects of PDE-5 inhibitors in uncontrolled diabetic patients with erectile dysfunction;
- assessing the effects of PDE-5 inhibitors in diabetic women with sexual dysfunction;
- further assessment of the effects of PDE-5 inhibitors on the cardiovascular system in diabetic patients who are prone to coronary arterial disease, and may suffer silent ischemia;
- direct comparisons between the three different available PDE-5 inhibitors;
- direct comparisons between PDE-5 inhibitors and other therapeutic options.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Boulton 2001

Methods	DURATION OF INTERVENTION: 12 weeks. DURATION OF FOLLOW-UP: N/A RUN-IN PERIOD: 4 weeks. LANGUAGE OF PUBLICATION: English.
Participants	WHO PARTCIPATED: Type 2 diabetic male patients. INCLUSION CRITERIA: 37 years of age or older, clinical diagnosis of ED, stable relationship over six months duration with a female partner, clinical diagnosis of type 2 diabetes mellitus over 2 years duraion, at least 35 years of age at the time of diagnosis of DM, glycated haemoglobin < 11%. EXCLUSION CRITERIA: Genital anatomical deformities, major psychiatric disorders, history of alcohol or drug abuse, ED due to spinal cord injury, history of myocardial infarction, stroke, heart failure, unstable angina- in the last six months, history of hypotension, current use of nitrates. Also excluded were patients with type 1 DM, glycated haemoglobin > 11%, recurrent hypoglycaemic episodes, severe neuropathy, diabetes secondary to pancreatic damage, Cushing's syndrome, and acromegaly. DIAGNOSTIC CRITERIA: DM- National Diabetes Data Group (1979). ED- Data missing.
Interventions	NUMBER OF STUDY CENTRES: Multiple (not stated). COUNTRY/ LOCATION: Denmark, Finland, France, Germany, Sweden, UK. SETTING: Out-patient. INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Oral sildenafil 25-100mg. CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo. TREATMENT BEFORE STUDY: N/A TITRATION PERIOD: N/A

Boulton 2001 *(Continued)*

Outcomes	PRIMARY OUTCOME(S): IIEF questions 3 and 4 at week 0 and week 12. SECONDARY OUTCOMES: Event log of erectile function, global efficacy question, IIEF domain, life satisfaction check list at week 0 and 12, partner questionnaire at week 12.
Notes	STATED AIM OF STUDY: To assess the efficacy and safety of sildenafil in men with Type II diabetes and ED, with particular emphasis on glycaemic control and the presence and number of diabetic complications.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Escobar-Jimenez 2002

Methods	DURATION OF INTERVENTION: 12 weeks. DURATION OF FOLLOW-UP: N/A RUN-IN PERIOD: 4 weeks. LANGUAGE OF PUBLICATION: Spanish.
Participants	WHO PARTCIPATED: Type 2 diabetic male patients. INCLUSION CRITERIA: 40 years of age or older, clinical diagnosis of ED more than six months, clinical diagnosis of DM. EXCLUSION CRITERIA: Genital anatomical deformities, a major psychiatric disorder, history of alcohol or substance abuse, haematological, renal or liver abnormalities, spinal cord injury, type 1 DM, secondary diabetes, history of MI or stroke within 6 months, heart failure (NYHA 3-4), unstable angina, malignant hypertension, history of nitrates use, autonomic neuropathy with hypotension. DIAGNOSTIC CRITERIA: DM- Data missing. ED- NIH consensus conference (1993).
Interventions	NUMBER OF STUDY CENTRES: Multiple (16). COUNTRY/ LOCATION: Spain. SETTING: Out-patient. INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Oral sildenafil 25-100mg. CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo. TREATMENT BEFORE STUDY: N/A TITRATION PERIOD: N/A
Outcomes	PRIMARY OUTCOME(S): IIIEF questions 3 and 4 at week 0 and week 12.

Escobar-Jimenez 2002 *(Continued)*

	SECONDARY OUTCOMES: Event log of erectile function, global efficacy question, IIEF domains.
Notes	STATED AIM OF STUDY: Efficacy, safety and tolerability of sildenafil in type 2 diabetic patients with ED

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Goldstein 2003

Methods	DURATION OF INTERVENTION: 12 weeks. DURATION OF FOLLOW-UP: N/A RUN-IN PERIOD: 4 weeks. LANGUAGE OF PUBLICATION: English.
Participants	WHO PARTCIPATED: Diabetic male patients. INCLUSION CRITERIA: 18 years of age or older, clinical diagnosis of ED, stable heterosexual relationship, glycated haemoglobin < 12%. EXCLUSION CRITERIA: Prior radical prostatectomy, primary hypoactive sexual desire, spinal cord injury, history of myocardial ischemia, life-threatening arrhythmia or stroke within 6 months, uncontrolled atrial arrhythmia, unstable angina pectoris, severe chronic liver disease, clinically significant chronic haematologic disease or bleeding disorder, hypotension, uncontrolled hypertension, symptomatic postural hypotension within 6 months, retinitis pigmentosa, progressive proliferative retinopathy, autonomic neuropathy with gastroparesis, hypo-hyperthyroidism, recent severe uncontrolled migrane. DIAGNOSTIC CRITERIA: DM- Data missing. ED- Data missing.
Interventions	NUMBER OF STUDY CENTRES: Multiple (47). COUNTRY/ LOCATION: USA and Canada. SETTING: Out-patient. INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Oral vardenafil 10-20mg. CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo. TREATMENT BEFORE STUDY: N/A TITRATION PERIOD: N/A
Outcomes	PRIMARY OUTCOME(S): IIEF EF domain, two diary questions: (1) were you able to insert your penis into your partner's vagina?; and (2) did your erection last long enough for you to have a satisfactory intercourse?.

Goldstein 2003 *(Continued)*

	SECONDARY OUTCOMES: Global assessment question.
Notes	STATED AIM OF STUDY: To assess the efficacy, tolerability, and safety of vardenafil in the treatment of ED in men with diabetes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Price 1998

Methods	DURATION OF INTERVENTION: 10 days. DURATION OF FOLLOW-UP: 17 DAYS. RUN-IN PERIOD: 2 weeks. LANGUAGE OF PUBLICATION: English.
Participants	WHO PARTCIPATED: Diabetic male patients. INCLUSION CRITERIA: 18-70 years of age, history of DM over 5 years, clinical diagnosis of ED more than 6 months. EXCLUSION CRITERIA: clinical significant ischemic heart disease or pripheral vascular disease, treatment with antidepressants or tranquilizers, nitrates, salicylates or anticoagulants in the 2 weeks prior to the study, bleeding disorder, severe untreated proliferative retinopathy. DIAGNOSTIC CRITERIA: DM- Data missing. ED- Clinical, laboratory or other diagnostic precedures prior to study.
Interventions	NUMBER OF STUDY CENTRES: Multiple (2). COUNTRY/ LOCATION: UK. SETTING: Out-patient. INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Oral sildenafil 25mg and 50 mg. CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo. TREATMENT BEFORE STUDY: N/A TITRATION PERIOD: N/A
Outcomes	PRIMARY OUTCOME(S): Duration of penile regidity over 60% (with penile plethysmography during sexual stimulation), daily diary of erectile activity, global efficacy question.
Notes	STATED AIM OF STUDY: Efficacy and safety of 25 or 50 mg sildenafil taken as a single dose, followed by once daily dosing for 10 days in diabetic men with ED.

Price 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rendell 1999

Methods	DURATION OF INTERVENTION: 12 weeks. DURATION OF FOLLOW-UP: N/A RUN-IN PERIOD: 4 weeks. LANGUAGE OF PUBLICATION: English.
Participants	WHO PARTCIPATED: Diabetic male patients. INCLUSION CRITERIA: 18 years of age or older, clinical diagnosis of ED at least six months, stable relationship over six months duration with a female partner, glycated haemoglobin < 0.12 and FBS < 200mg/dl for at least three months prior to screening, normal serum testosterone and prolactin levels. EXCLUSION CRITERIA: Genital anatomical deformities, spinal cord injury, primary diagnosis of another sexual disorder, major haematological, renal or liver disease, major psychiatric disorder, history of MI or stroke within six months, active peptic ulcer disease, hypotension, uncontrolled hypertension, use of nitrates or androgens, proliferative retinopathy, severe autonomic neuropathy, history of ketoacidosis in the previous three years DIAGNOSTIC CRITERIA: DM- National Diabetes Data Group (1979). ED- NIH consensus conference (1993).
Interventions	NUMBER OF STUDY CENTRES: Multiple (19). COUNTRY/ LOCATION: USA. SETTING: Out-patient. INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Oral sildenafil 25-100mg. CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo. TREATMENT BEFORE STUDY: N/A TITRATION PERIOD: N/A
Outcomes	PRIMARY OUTCOME(S): IIEF domains, global efficacy question, event log.
Notes	STATED AIM OF STUDY: To assess the efficacy and safety of sildenafil in the treatment of ED in men with diabetes.

Risk of bias

Rendell 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Saenz de Tejada 2002

Methods	DURATION OF INTERVENTION: 12 weeks. DURATION OF FOLLOW-UP: N/A RUN-IN PERIOD: 4 weeks. LANGUAGE OF PUBLICATION: English.
Participants	WHO PARTCIPATED: Diabetic male patients. INCLUSION CRITERIA: 18 years of age or older, minimal three months history of mild-severe ED, stable heterosexual relationship EXCLUSION CRITERIA: Glycated haemoglobin > 13%, recent history of ketoacidosis (>two episodes), over three episodes of hypoglycaemia, angina during intercourse, unstable angina pectoris, recently diagnosed coronary artery disease, poorly controlled hypertension, orthostatic hypotension, congestive heart failure, arrhythmia, significant renal or hepatic insufficiency, anaemia, prostatectomy, pelvic surgery, stroke, spinal cord injury within six months, patients receiving nitrates, antiandrogens or chemotherapy. DIAGNOSTIC CRITERIA: DM- Clinical, laboratory and medication history. ED- Data missing.
Interventions	NUMBER OF STUDY CENTRES: Multiple (18). COUNTRY/ LOCATION: Spain. SETTING: Out-patient. INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Oral tadalafil 10-20mg. CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo. TREATMENT BEFORE STUDY: N/A TITRATION PERIOD: N/A
Outcomes	PRIMARY OUTCOME(S): IIEF domains, IIEF EF domain, sexual encounter profile diary question 2 and 3. SECONDARY OUTCOMES: IIEF questions 3 and 4, global assessment question.
Notes	STATED AIM OF STUDY: To assess the efficacy and safety of tadalafil in the treatment of mild-to-severe ED in men with diabetes

Risk of bias

Bias	Authors' judgement	Support for judgement

Saenz de Tejada 2002 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Safarinejad 2004

Methods	DURATION OF INTERVENTION: 16 weeks. DURATION OF FOLLOW-UP: N/A RUN-IN PERIOD: 4 weeks. LANGUAGE OF PUBLICATION: English.
Participants	WHO PARTCIPATED: Diabetic male patients. INCLUSION CRITERIA: 18 years of age or older, medically documented ED at least six months duration, stable relationship over six months duration with a female partner, clinical diagnosis of type 2 diabetes mellitus over five years duration, glycated haemoglobin < 0.12 and FBS < 300mg/dl at screening. EXCLUSION CRITERIA: Genital anatomical deformities, history of priapism, history of prostatectomy, primary diagnosis of another sexual disorder, major haematological, renal or liver disease, major psychiatric disorder, history of myocardial infarction, stroke, coronary arterial disease, peptic ulcer disease, hypotension, uncontrolled hypertension, history of alcohol or drug abuse, use of nitrates, proliferative retinopathy, poorly controlled DM, autonomic neuropathy, history of ketoacidosis in the previous two years. DIAGNOSTIC CRITERIA: DM- Data missing. ED- NIH consensus conference (1993).
Interventions	NUMBER OF STUDY CENTRES: Single. COUNTRY/ LOCATION: Iran. SETTING: Out-patient. INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Oral sildenafil 100mg. CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo. TREATMENT BEFORE STUDY: N/A TITRATION PERIOD: N/A
Outcomes	PRIMARY OUTCOME(S): IIEF questions 3 and 4 at week 0 and week 16, IIEF domains, global efficacy question, event log.
Notes	STATED AIM OF STUDY: To determine if sildenafil administered orally in single doses effectively and safely improves penile erections in diabetic men with ED.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Stuckey 2003

Methods	DURATION OF INTERVENTION: 12 weeks. DURATION OF FOLLOW-UP: N/A RUN-IN PERIOD: 4 weeks. LANGUAGE OF PUBLICATION: English.
Participants	WHO PARTCIPATED: Type 1 diabetic male patients. INCLUSION CRITERIA: 18 years of age or older, clinical diagnosis of ED more than six months, stable heterosexual relationship more than six months, clinical diagnosis of type 1 DM, had required insulin within one month of diagnosis, stable diabetes with glycated haemoglobin < 11%. EXCLUSION CRITERIA: Genital anaomical deformities, a major psychiatric disorder, history of alcohol or substance abuse, spinal cord injury, history of myocardial infarction, stroke, heart failure or unstable angina within 6 months, history of hypotension or nitrates use, glycated haemoglobin > 11%, severe autonomic neuropathy, diabetes secondary to pancreatic damage, cushing's syndrome, acromegaly. DIAGNOSTIC CRITERIA: DM- National Diabetes Data Group (1979). ED- Data missing.
Interventions	NUMBER OF STUDY CENTRES: Multiple (not stated). COUNTRY/ LOCATION: Unknown. SETTING: Out-patient. INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Oral sildenafil 25-100mg. CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo. TREATMENT BEFORE STUDY: N/A TITRATION PERIOD: N/A
Outcomes	PRIMARY OUTCOME(S): IIIEF questions 3 and 4 at week 0 and week 12. SECONDARY OUTCOMES: Event log of erectile function, global efficacy question, IIEF domains.
Notes	STATED AIM OF STUDY: To assess sildenafil efficacy exclusively in men with type 1 diabetes and ED

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Abbreviationes used:
IIEF = International Index of Erectile Function; ED = erectile dysfunction; EF = erectile function; DM = diabetes mellitus; N/A = not acknowledged

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Behrend 2005	Non RCT
Carson 2005	Included non-diabetic patients
El-Sakka 2004	Open label
Fonseca 2004	Retrospective study
Kalinchenko 1999	Non RCT
Palumbo 2001	Included non-diabetic patients
Perimenis 2002	Open label
Salama 2004	Included non-diabetic patients
Vickers 2002	Review

DATA AND ANALYSES

Comparison 1. Efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IIEF EF Domain	7	1542	Mean Difference (IV, Fixed, 95% CI)	6.56 [5.18, 7.93]
2 IIEF Q3	5	968	Mean Difference (IV, Fixed, 95% CI)	0.94 [0.81, 1.07]
3 IIEF Q4	5	904	Mean Difference (IV, Fixed, 95% CI)	1.09 [0.95, 1.23]
4 Global Efficacy Question	8	1645	Risk Ratio (M-H, Fixed, 95% CI)	3.75 [3.12, 4.51]
5 % Succesful Attempts	4	924	Mean Difference (IV, Fixed, 95% CI)	26.69 [23.11, 30.28]
6 IIEF EF Domain- Subgroups by PDE-Inhibitor Type	7	1542	Mean Difference (IV, Fixed, 95% CI)	6.56 [5.18, 7.93]
6.1 Sildenafli versus placebo	5	904	Mean Difference (IV, Fixed, 95% CI)	7.08 [5.31, 8.86]
6.2 Tadalafil versus placebo	1	216	Mean Difference (IV, Fixed, 95% CI)	6.40 [2.70, 10.10]
6.3 Vardenafil versus placebo	1	422	Mean Difference (IV, Fixed, 95% CI)	5.42 [2.72, 8.12]

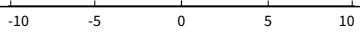
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Global Efficacy Question- Subgroup by PDE-Inhibitor Type	8	1645	Odds Ratio (M-H, Fixed, 95% CI)	7.37 [5.77, 9.43]
7.1 Sidenafil versus placebo	6	1028	Odds Ratio (M-H, Fixed, 95% CI)	7.19 [5.30, 9.76]
7.2 Tadalafil versus placebo	1	216	Odds Ratio (M-H, Fixed, 95% CI)	4.42 [2.35, 8.29]
7.3 Vardenafil versus placebo	1	401	Odds Ratio (M-H, Fixed, 95% CI)	11.46 [6.51, 20.19]
8 IIEF EF Domain- by Quality	7	1542	Mean Difference (IV, Fixed, 95% CI)	6.56 [5.18, 7.93]
8.1 Category B	6	1399	Mean Difference (IV, Fixed, 95% CI)	6.08 [4.57, 7.59]
8.2 Category C	1	143	Mean Difference (IV, Fixed, 95% CI)	8.90 [5.56, 12.24]
9 IIEF Q3- by Quality	5	968	Mean Difference (IV, Fixed, 95% CI)	0.94 [0.81, 1.07]
9.1 Category B	4	766	Mean Difference (IV, Fixed, 95% CI)	0.91 [0.78, 1.04]
9.2 Category C	1	202	Mean Difference (IV, Fixed, 95% CI)	1.56 [0.94, 2.18]
10 IIEF Q4- by Quality	5	904	Mean Difference (IV, Fixed, 95% CI)	1.09 [0.95, 1.23]
10.1 Category B	4	756	Mean Difference (IV, Fixed, 95% CI)	1.07 [0.93, 1.21]
10.2 Category C	1	148	Mean Difference (IV, Fixed, 95% CI)	1.51 [0.86, 2.16]
11 Global Efficacy Question- by Quality	8	1645	Risk Ratio (M-H, Fixed, 95% CI)	3.75 [3.12, 4.51]
11.1 Category B	7	1440	Risk Ratio (M-H, Fixed, 95% CI)	3.51 [2.88, 4.27]
11.2 Category C	1	205	Risk Ratio (M-H, Fixed, 95% CI)	6.15 [3.46, 10.94]
12 % Succesful Attempts- by Quality	4	924	Mean Difference (IV, Fixed, 95% CI)	26.69 [23.11, 30.28]
12.1 Category B	3	802	Mean Difference (IV, Fixed, 95% CI)	26.19 [22.56, 29.83]
12.2 Category C	1	122	Mean Difference (IV, Fixed, 95% CI)	44.4 [22.76, 66.04]
13 IIEF EF Domain- by Selection	7	1542	Mean Difference (IV, Fixed, 95% CI)	6.56 [5.18, 7.93]
13.1 Adequate	4	861	Mean Difference (IV, Fixed, 95% CI)	6.75 [5.15, 8.35]
13.2 Other	3	681	Mean Difference (IV, Fixed, 95% CI)	6.01 [3.30, 8.72]
14 IIEF Q3- bySelection	5	968	Mean Difference (IV, Fixed, 95% CI)	0.94 [0.81, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Adequate	2	282	Mean Difference (IV, Fixed, 95% CI)	1.43 [0.99, 1.87]
14.2 Other	3	686	Mean Difference (IV, Fixed, 95% CI)	0.89 [0.76, 1.03]
15 IIEF Q4- by Selection	5	904	Mean Difference (IV, Fixed, 95% CI)	1.09 [0.95, 1.23]
15.1 Adequate	2	228	Mean Difference (IV, Fixed, 95% CI)	1.31 [0.92, 1.69]
15.2 Other	3	676	Mean Difference (IV, Fixed, 95% CI)	1.06 [0.91, 1.21]
16 Global Efficacy Question- by Selection	8	1645	Risk Ratio (M-H, Fixed, 95% CI)	3.75 [3.12, 4.51]
16.1 Adequate	5	963	Risk Ratio (M-H, Fixed, 95% CI)	4.06 [3.15, 5.23]
16.2 Other	3	682	Risk Ratio (M-H, Fixed, 95% CI)	3.37 [2.58, 4.40]
17 % Succesful Attempts- by Selection	4	924	Mean Difference (IV, Fixed, 95% CI)	26.69 [23.11, 30.28]
17.1 Adequate	3	762	Mean Difference (IV, Fixed, 95% CI)	31.01 [21.37, 40.66]
17.2 Other	1	162	Mean Difference (IV, Fixed, 95% CI)	26.0 [22.14, 29.86]
18 IIEF EF Domain- by Attrition	7	1542	Mean Difference (IV, Fixed, 95% CI)	6.56 [5.18, 7.93]
18.1 Adequate	5	1232	Mean Difference (IV, Fixed, 95% CI)	6.10 [4.42, 7.77]
18.2 Other	2	310	Mean Difference (IV, Fixed, 95% CI)	7.52 [5.10, 9.94]
19 IIEF Q3- by Attrition	5	968	Mean Difference (IV, Fixed, 95% CI)	0.94 [0.81, 1.07]
19.1 Adequate	3	594	Mean Difference (IV, Fixed, 95% CI)	0.98 [0.63, 1.34]
19.2 Other	2	374	Mean Difference (IV, Fixed, 95% CI)	0.93 [0.79, 1.07]
20 IIEF Q4- by Attrition	5	904	Mean Difference (IV, Fixed, 95% CI)	1.09 [0.95, 1.23]
20.1 Adequate	3	594	Mean Difference (IV, Fixed, 95% CI)	1.11 [0.79, 1.44]
20.2 Other	2	310	Mean Difference (IV, Fixed, 95% CI)	1.08 [0.93, 1.24]
21 Global Efficacy Question- by Attrition	8	1645	Risk Ratio (M-H, Fixed, 95% CI)	3.75 [3.12, 4.51]
21.1 Adequate	6	1278	Risk Ratio (M-H, Fixed, 95% CI)	4.11 [3.28, 5.16]
21.2 Other	2	367	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [2.14, 4.03]
22 % Succesful Attempts- by Attrtition	4	924	Mean Difference (IV, Fixed, 95% CI)	26.69 [23.11, 30.28]
22.1 Adequate	2	640	Mean Difference (IV, Fixed, 95% CI)	27.69 [16.91, 38.47]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.2 Other	2	284	Mean Difference (IV, Fixed, 95% CI)	26.57 [22.77, 30.37]
23 IIEF EF Domain- by Sponsor	7	1542	Mean Difference (IV, Fixed, 95% CI)	6.56 [5.18, 7.93]
23.1 Pharmaceutical	3	635	Mean Difference (IV, Fixed, 95% CI)	6.29 [3.90, 8.69]
23.2 Other	4	907	Mean Difference (IV, Fixed, 95% CI)	6.69 [5.01, 8.37]
24 IIEF Q3- by Sponsor	5	968	Mean Difference (IV, Fixed, 95% CI)	0.94 [0.81, 1.07]
24.1 Pharmaceutical	2	424	Mean Difference (IV, Fixed, 95% CI)	0.91 [0.77, 1.05]
24.2 Other	3	544	Mean Difference (IV, Fixed, 95% CI)	1.11 [0.76, 1.45]
25 IIEF Q4- by Sponsor	5	904	Mean Difference (IV, Fixed, 95% CI)	1.09 [0.95, 1.23]
25.1 Pharmaceutical	2	414	Mean Difference (IV, Fixed, 95% CI)	1.07 [0.92, 1.22]
25.2 Other	3	490	Mean Difference (IV, Fixed, 95% CI)	1.18 [0.86, 1.49]
26 Global Efficacy Question- by Sponsor	8	1645	Risk Ratio (M-H, Fixed, 95% CI)	3.75 [3.12, 4.51]
26.1 Pharmaceutical	4	697	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [2.19, 3.58]
26.2 Other	4	948	Risk Ratio (M-H, Fixed, 95% CI)	4.92 [3.73, 6.50]
27 % Succesful Attempts- by Sponsor	4	924	Mean Difference (IV, Fixed, 95% CI)	26.69 [23.11, 30.28]
27.1 Pharmaceutical	2	378	Mean Difference (IV, Fixed, 95% CI)	26.05 [22.30, 29.80]
27.2 Other	2	546	Mean Difference (IV, Fixed, 95% CI)	33.49 [21.31, 45.67]

Analysis 1.1. Comparison 1 Efficacy, Outcome 1 IIEF EF Domain.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Boulton 2001	45	20.4 (8.3)	98	11.5 (11.6)		17%	8.9[5.56,12.24]
Escobar-Jimenez 2002	37	17.4 (7.5)	43	10.5 (7.5)		17.49%	6.9[3.61,10.19]
Goldstein 2003	284	18 (13.3)	138	12.6 (13.3)		25.95%	5.42[2.72,8.12]
Rendell 1999	131	17.5 (28.6)	121	10.4 (28.6)		3.81%	7.1[0.04,14.16]
Saenz de Tejada 2002	145	18.6 (13)	71	12.2 (13)		13.83%	6.4[2.7,10.1]
Safarinejad 2004	134	16.8 (22.3)	128	11.4 (22.3)		6.52%	5.4[0.01,10.79]
Stuckey 2003	86	20 (11.6)	81	14 (11.6)		15.4%	6[2.49,9.51]
Total * **	**862**		**680**			**100%**	**6.56[5.18,7.93]**
Heterogeneity: Tau^2=0; Chi^2=2.92, df=6(P=0.82); I^2=0%							
Test for overall effect: Z=9.34(P<0.0001)							



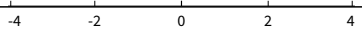
Favours Control — Favours PDE-5 Inh

Analysis 1.2. Comparison 1 Efficacy, Outcome 2 IIEF Q3.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Boulton 2001	101	3.4 (2.3)	101	1.9 (2.2)		4.29%	1.56[0.94,2.18]
Escobar-Jimenez 2002	37	3 (1.4)	43	1.7 (1.4)		4.34%	1.3[0.68,1.92]
Rendell 1999	131	3.2 (2.9)	121	2 (2.9)		3.36%	1.2[0.5,1.9]
Safarinejad 2004	134	2.8 (2.3)	128	2.2 (2.3)		5.44%	0.6[0.05,1.15]
Stuckey 2003	90	3.6 (0.5)	82	2.7 (0.5)		82.57%	0.9[0.76,1.04]
Total * **	**493**		**475**			**100%**	**0.94[0.81,1.07]**
Heterogeneity: Tau²=0; Chi²=7.37, df=4(P=0.12); I²=45.75%							
Test for overall effect: Z=14.26(P<0.0001)							

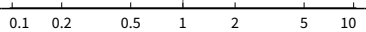
Analysis 1.3. Comparison 1 Efficacy, Outcome 3 IIEF Q4.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Boulton 2001	47	3.4 (1.6)	101	1.8 (2.3)		4.52%	1.51[0.86,2.16]
Escobar-Jimenez 2002	37	2.6 (1.1)	43	1.4 (1.1)		8.49%	1.2[0.73,1.67]
Rendell 1999	131	2.9 (3.1)	121	1.6 (3.1)		3.28%	1.3[0.54,2.06]
Safarinejad 2004	134	2.9 (2.3)	128	2 (2.3)		6.25%	0.9[0.35,1.45]
Stuckey 2003	85	3.3 (0.5)	77	2.2 (0.5)		77.46%	1.06[0.9,1.22]
Total * **	**434**		**470**			**100%**	**1.09[0.95,1.23]**
Heterogeneity: Tau²=0; Chi²=2.69, df=4(P=0.61); I²=0%							
Test for overall effect: Z=15.45(P<0.0001)							



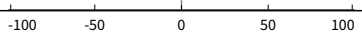
Analysis 1.4. Comparison 1 Efficacy, Outcome 4 Global Efficacy Question.

Study or subgroup	PDE-5 Inhibitors n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Boulton 2001	67/102	11/103		9.13%	6.15[3.46,10.94]
Escobar-Jimenez 2002	17/37	6/43		4.63%	3.29[1.45,7.48]
Goldstein 2003	168/268	17/133		18.96%	4.9[3.12,7.72]
Price 1998	21/41	2/20		2.24%	5.12[1.33,19.72]
Rendell 1999	74/131	13/127		11.02%	5.52[3.23,9.44]
Saenz de Tejada 2002	87/145	18/71		20.17%	2.37[1.55,3.6]
Safarinejad 2004	68/134	14/128		11.95%	4.64[2.75,7.82]
Stuckey 2003	44/85	25/77		21.89%	1.59[1.09,2.34]
Total (95% CI)	**943**	**702**		**100%**	**3.75[3.12,4.51]**
Total events: 546 (PDE-5 Inhibitors), 106 (Placebo)					
Heterogeneity: Tau²=0; Chi²=30.96, df=7(P<0.0001); I²=77.39%					
Test for overall effect: Z=14(P<0.0001)					



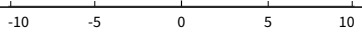
Analysis 1.5. Comparison 1 Efficacy, Outcome 5 % Succesful Attempts.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Boulton 2001	40	58.8 (57.2)	82	14.4 (57.2)		2.74%	44.4[22.76,66.04]
Goldstein 2003	287	51.4 (72.4)	137	23 (72.4)		5.91%	28.43[13.69,43.17]
Saenz de Tejada 2002	145	28.7 (55.6)	71	1.9 (55.6)		5.15%	26.84[11.04,42.64]
Stuckey 2003	85	65 (12.5)	77	39 (12.5)		86.19%	26[22.14,29.86]
Total ***	**557**		**367**			**100%**	**26.69[23.11,30.28]**
Heterogeneity: Tau²=0; Chi²=2.75, df=3(P=0.43); I²=0%							
Test for overall effect: Z=14.6(P<0.0001)							



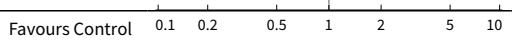
Analysis 1.6. Comparison 1 Efficacy, Outcome 6 IIEF EF Domain- Subgroups by PDE-Inhibitor Type.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.6.1 Sildenafli versus placebo							
Boulton 2001	45	20.4 (8.3)	98	11.5 (11.6)		17%	8.9[5.56,12.24]
Escobar-Jimenez 2002	37	17.4 (7.5)	43	10.5 (7.5)		17.49%	6.9[3.61,10.19]
Rendell 1999	131	17.5 (28.6)	121	10.4 (28.6)		3.81%	7.1[0.04,14.16]
Safarinejad 2004	134	16.8 (22.3)	128	11.4 (22.3)		6.52%	5.4[0.01,10.79]
Stuckey 2003	86	20 (11.6)	81	14 (11.6)		15.4%	6[2.49,9.51]
Subtotal ***	**433**		**471**			**60.22%**	**7.08[5.31,8.86]**
Heterogeneity: Tau²=0; Chi²=1.89, df=4(P=0.76); I²=0%							
Test for overall effect: Z=7.83(P<0.0001)							
1.6.2 Tadalafil versus placebo							
Saenz de Tejada 2002	145	18.6 (13)	71	12.2 (13)		13.83%	6.4[2.7,10.1]
Subtotal ***	**145**		**71**			**13.83%**	**6.4[2.7,10.1]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.39(P=0)							
1.6.3 Vardenafil versus placebo							
Goldstein 2003	284	18 (13.3)	138	12.6 (13.3)		25.95%	5.42[2.72,8.12]
Subtotal ***	**284**		**138**			**25.95%**	**5.42[2.72,8.12]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.93(P<0.0001)							
Total ***	**862**		**680**			**100%**	**6.56[5.18,7.93]**
Heterogeneity: Tau²=0; Chi²=2.92, df=6(P=0.82); I²=0%							
Test for overall effect: Z=9.34(P<0.0001)							
Test for subgroup differences: Chi²=1.03, df=1 (P=0.6), I²=0%							



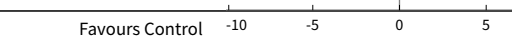
Analysis 1.7. Comparison 1 Efficacy, Outcome 7 Global Efficacy Question- Subgroup by PDE-Inhibitor Type.

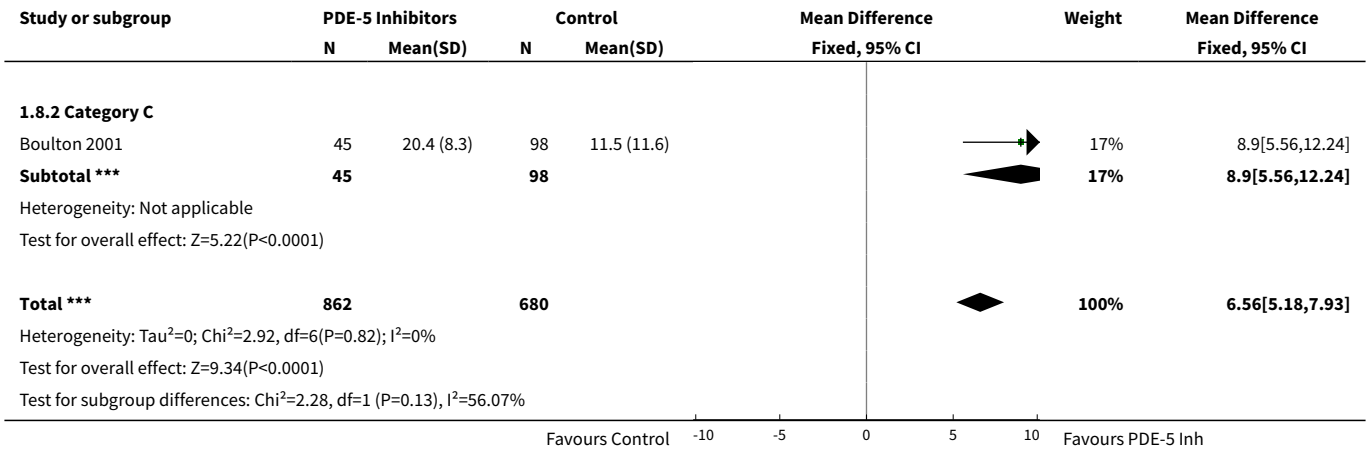
Study or subgroup	PDE-5 Inhibitors n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.7.1 Sidenafil versus placebo					
Boulton 2001	67/102	11/103		7.27%	16.01[7.59,33.79]
Escobar-Jimenez 2002	17/37	6/43		5.81%	5.24[1.78,15.4]
Price 1998	21/41	2/20		2.54%	9.45[1.94,46.06]
Rendell 1999	74/131	13/127		11.12%	11.38[5.83,22.24]
Safarinejad 2004	68/134	14/128		13.65%	8.39[4.38,16.07]
Stuckey 2003	44/85	25/77		24.49%	2.23[1.18,4.23]
Subtotal (95% CI)	**530**	**498**		**64.88%**	**7.19[5.3,9.76]**
Total events: 291 (PDE-5 Inhibitors), 71 (Control)					
Heterogeneity: Tau^2=0; Chi^2=19.75, df=5(P=0); I^2=74.68%					
Test for overall effect: Z=12.64(P<0.0001)					
1.7.2 Tadalafil versus placebo					
Saenz de Tejada 2002	87/145	18/71		18.71%	4.42[2.35,8.29]
Subtotal (95% CI)	**145**	**71**		**18.71%**	**4.42[2.35,8.29]**
Total events: 87 (PDE-5 Inhibitors), 18 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.62(P<0.0001)					
1.7.3 Vardenafil versus placebo					
Goldstein 2003	168/268	17/133		16.41%	11.46[6.51,20.19]
Subtotal (95% CI)	**268**	**133**		**16.41%**	**11.46[6.51,20.19]**
Total events: 168 (PDE-5 Inhibitors), 17 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=8.45(P<0.0001)					
Total (95% CI)	**943**	**702**		**100%**	**7.37[5.77,9.43]**
Total events: 546 (PDE-5 Inhibitors), 106 (Control)					
Heterogeneity: Tau^2=0; Chi^2=24.69, df=7(P=0); I^2=71.65%					
Test for overall effect: Z=15.91(P<0.0001)					
Test for subgroup differences: Not applicable					



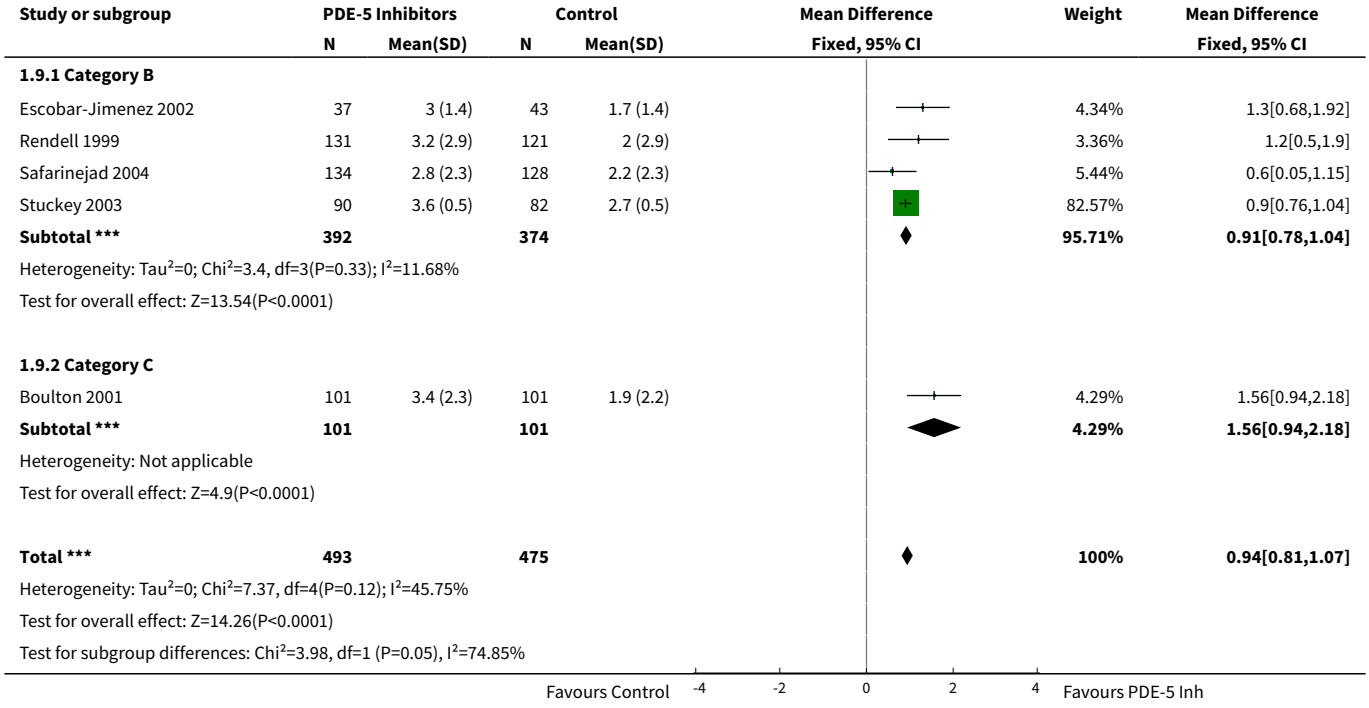
Analysis 1.8. Comparison 1 Efficacy, Outcome 8 IIEF EF Domain- by Quality.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.8.1 Category B							
Escobar-Jimenez 2002	37	17.4 (7.5)	43	10.5 (7.5)		17.49%	6.9[3.61,10.19]
Goldstein 2003	284	18 (13.3)	138	12.6 (13.3)		25.95%	5.42[2.72,8.12]
Rendell 1999	131	17.5 (28.6)	121	10.4 (28.6)		3.81%	7.1[0.04,14.16]
Saenz de Tejada 2002	145	18.6 (13)	71	12.2 (13)		13.83%	6.4[2.7,10.1]
Safarinejad 2004	134	16.8 (22.3)	128	11.4 (22.3)		6.52%	5.4[0.01,10.79]
Stuckey 2003	86	20 (11.6)	81	14 (11.6)		15.4%	6[2.49,9.51]
Subtotal ***	**817**		**582**			**83%**	**6.08[4.57,7.59]**
Heterogeneity: Tau^2=0; Chi^2=0.64, df=5(P=0.99); I^2=0%							
Test for overall effect: Z=7.88(P<0.0001)							

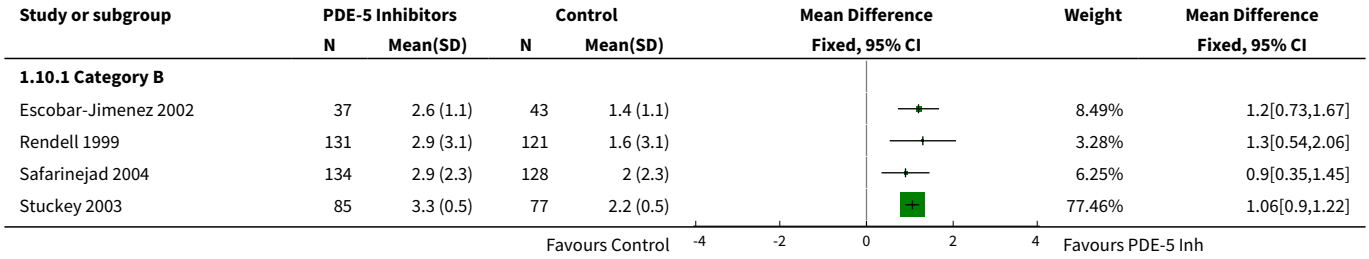




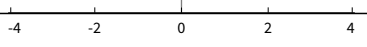
Analysis 1.9. Comparison 1 Efficacy, Outcome 9 IIEF Q3- by Quality.



Analysis 1.10. Comparison 1 Efficacy, Outcome 10 IIEF Q4- by Quality.

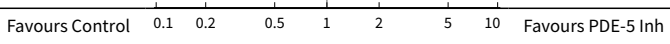


Study or subgroup	PDE-5 Inhibitors N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Subtotal ***	**387**		**369**			**95.48%**	**1.07[0.93,1.21]**
Heterogeneity: Tau²=0; Chi²=1.01, df=3(P=0.8); I²=0%							
Test for overall effect: Z=14.82(P<0.0001)							
1.10.2 Category C							
Boulton 2001	47	3.4 (1.6)	101	1.8 (2.3)		4.52%	1.51[0.86,2.16]
Subtotal ***	**47**		**101**			**4.52%**	**1.51[0.86,2.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.55(P<0.0001)							
Total ***	**434**		**470**			**100%**	**1.09[0.95,1.23]**
Heterogeneity: Tau²=0; Chi²=2.69, df=4(P=0.61); I²=0%							
Test for overall effect: Z=15.45(P<0.0001)							
Test for subgroup differences: Chi²=1.68, df=1 (P=0.2), I²=40.4%							



Analysis 1.11. Comparison 1 Efficacy, Outcome 11 Global Efficacy Question- by Quality.

Study or subgroup	PDE-5 Inhibitors n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 Category B					
Escobar-Jimenez 2002	17/37	6/43		4.63%	3.29[1.45,7.48]
Goldstein 2003	168/268	17/133		18.96%	4.9[3.12,7.72]
Price 1998	21/41	2/20		2.24%	5.12[1.33,19.72]
Rendell 1999	74/131	13/127		11.02%	5.52[3.23,9.44]
Saenz de Tejada 2002	87/145	18/71		20.17%	2.37[1.55,3.6]
Safarinejad 2004	68/134	14/128		11.95%	4.64[2.75,7.82]
Stuckey 2003	44/85	25/77		21.89%	1.59[1.09,2.34]
Subtotal (95% CI)	**841**	**599**		**90.87%**	**3.51[2.88,4.27]**
Total events: 479 (PDE-5 Inhibitors), 95 (Placebo)					
Heterogeneity: Tau²=0; Chi²=25.99, df=6(P=0); I²=76.92%					
Test for overall effect: Z=12.55(P<0.0001)					
1.11.2 Category C					
Boulton 2001	67/102	11/103		9.13%	6.15[3.46,10.94]
Subtotal (95% CI)	**102**	**103**		**9.13%**	**6.15[3.46,10.94]**
Total events: 67 (PDE-5 Inhibitors), 11 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=6.18(P<0.0001)					
Total (95% CI)	**943**	**702**		**100%**	**3.75[3.12,4.51]**
Total events: 546 (PDE-5 Inhibitors), 106 (Placebo)					
Heterogeneity: Tau²=0; Chi²=30.96, df=7(P<0.0001); I²=77.39%					
Test for overall effect: Z=14(P<0.0001)					
Test for subgroup differences: Not applicable					

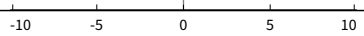


Analysis 1.12. Comparison 1 Efficacy, Outcome 12 % Succesful Attempts- by Quality.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.12.1 Category B							
Goldstein 2003	287	51.4 (72.4)	137	23 (72.4)		5.91%	28.43[13.69,43.17]
Saenz de Tejada 2002	145	28.7 (55.6)	71	1.9 (55.6)		5.15%	26.84[11.04,42.64]
Stuckey 2003	85	65 (12.5)	77	39 (12.5)		86.19%	26[22.14,29.86]
Subtotal ***	**517**		**285**			**97.26%**	**26.19[22.56,29.83]**
Heterogeneity: Tau^2=0; Chi^2=0.1, df=2(P=0.95); I^2=0%							
Test for overall effect: Z=14.12(P<0.0001)							
1.12.2 Category C							
Boulton 2001	40	58.8 (57.2)	82	14.4 (57.2)		2.74%	44.4[22.76,66.04]
Subtotal ***	**40**		**82**			**2.74%**	**44.4[22.76,66.04]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.02(P<0.0001)							
Total ***	**557**		**367**			**100%**	**26.69[23.11,30.28]**
Heterogeneity: Tau^2=0; Chi^2=2.75, df=3(P=0.43); I^2=0%							
Test for overall effect: Z=14.6(P<0.0001)							
Test for subgroup differences: Chi^2=2.65, df=1 (P=0.1), I^2=62.2%							

Analysis 1.13. Comparison 1 Efficacy, Outcome 13 IIEF EF Domain- by Selection.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.13.1 Adequate							
Boulton 2001	45	20.4 (8.3)	98	11.5 (11.6)		17%	8.9[5.56,12.24]
Escobar-Jimenez 2002	37	17.4 (7.5)	43	10.5 (7.5)		17.49%	6.9[3.61,10.19]
Goldstein 2003	284	18 (13.3)	138	12.6 (13.3)		25.95%	5.42[2.72,8.12]
Saenz de Tejada 2002	145	18.6 (13)	71	12.2 (13)		13.83%	6.4[2.7,10.1]
Subtotal ***	**511**		**350**			**74.27%**	**6.75[5.15,8.35]**
Heterogeneity: Tau^2=0; Chi^2=2.56, df=3(P=0.46); I^2=0%							
Test for overall effect: Z=8.28(P<0.0001)							
1.13.2 Other							
Rendell 1999	131	17.5 (28.6)	121	10.4 (28.6)		3.81%	7.1[0.04,14.16]
Safarinejad 2004	134	16.8 (22.3)	128	11.4 (22.3)		6.52%	5.4[0.01,10.79]
Stuckey 2003	86	20 (11.6)	81	14 (11.6)		15.4%	6[2.49,9.51]
Subtotal ***	**351**		**330**			**25.73%**	**6.01[3.3,8.72]**
Heterogeneity: Tau^2=0; Chi^2=0.14, df=2(P=0.93); I^2=0%							
Test for overall effect: Z=4.34(P<0.0001)							
Total ***	**862**		**680**			**100%**	**6.56[5.18,7.93]**
Heterogeneity: Tau^2=0; Chi^2=2.92, df=6(P=0.82); I^2=0%							
Test for overall effect: Z=9.34(P<0.0001)							
Test for subgroup differences: Chi^2=0.21, df=1 (P=0.65), I^2=0%							

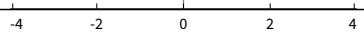


Analysis 1.14. Comparison 1 Efficacy, Outcome 14 IIEF Q3- bySelection.

Study or subgroup	PDE-5 Inhibitors N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.14.1 Adequate							
Boulton 2001	101	3.4 (2.3)	101	1.9 (2.2)		4.29%	1.56[0.94,2.18]
Escobar-Jimenez 2002	37	3 (1.4)	43	1.7 (1.4)		4.34%	1.3[0.68,1.92]
Subtotal ***	**138**		**144**			**8.63%**	**1.43[0.99,1.87]**
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%							
Test for overall effect: Z=6.37(P<0.0001)							
1.14.2 Other							
Rendell 1999	131	3.2 (2.9)	121	2 (2.9)		3.36%	1.2[0.5,1.9]
Safarinejad 2004	134	2.8 (2.3)	128	2.2 (2.3)		5.44%	0.6[0.05,1.15]
Stuckey 2003	90	3.6 (0.5)	82	2.7 (0.5)		82.57%	0.9[0.76,1.04]
Subtotal ***	**355**		**331**			**91.37%**	**0.89[0.76,1.03]**
Heterogeneity: Tau^2=0; Chi^2=1.82, df=2(P=0.4); I^2=0%							
Test for overall effect: Z=12.96(P<0.0001)							
Total ***	**493**		**475**			**100%**	**0.94[0.81,1.07]**
Heterogeneity: Tau^2=0; Chi^2=7.37, df=4(P=0.12); I^2=45.75%							
Test for overall effect: Z=14.26(P<0.0001)							
Test for subgroup differences: Chi^2=5.22, df=1 (P=0.02), I^2=80.85%							

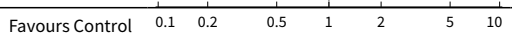
Analysis 1.15. Comparison 1 Efficacy, Outcome 15 IIEF Q4- by Selection.

Study or subgroup	PDE-5 Inhibitors N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.15.1 Adequate							
Boulton 2001	47	3.4 (1.6)	101	1.8 (2.3)		4.52%	1.51[0.86,2.16]
Escobar-Jimenez 2002	37	2.6 (1.1)	43	1.4 (1.1)		8.49%	1.2[0.73,1.67]
Subtotal ***	**84**		**144**			**13.01%**	**1.31[0.92,1.69]**
Heterogeneity: Tau^2=0; Chi^2=0.57, df=1(P=0.45); I^2=0%							
Test for overall effect: Z=6.69(P<0.0001)							
1.15.2 Other							
Rendell 1999	131	2.9 (3.1)	121	1.6 (3.1)		3.28%	1.3[0.54,2.06]
Safarinejad 2004	134	2.9 (2.3)	128	2 (2.3)		6.25%	0.9[0.35,1.45]
Stuckey 2003	85	3.3 (0.5)	77	2.2 (0.5)		77.46%	1.06[0.9,1.22]
Subtotal ***	**350**		**326**			**86.99%**	**1.06[0.91,1.21]**
Heterogeneity: Tau^2=0; Chi^2=0.7, df=2(P=0.7); I^2=0%							
Test for overall effect: Z=13.98(P<0.0001)							
Total ***	**434**		**470**			**100%**	**1.09[0.95,1.23]**
Heterogeneity: Tau^2=0; Chi^2=2.69, df=4(P=0.61); I^2=0%							
Test for overall effect: Z=15.45(P<0.0001)							
Test for subgroup differences: Chi^2=1.42, df=1 (P=0.23), I^2=29.74%							



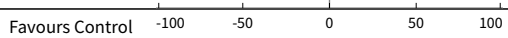
Analysis 1.16. Comparison 1 Efficacy, Outcome 16 Global Efficacy Question- by Selection.

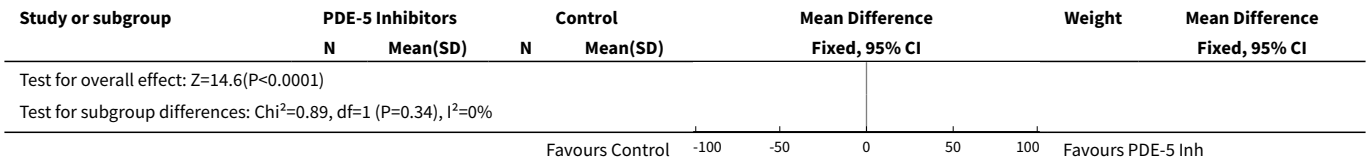
Study or subgroup	PDE-5 Inhibitors n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.16.1 Adequate					
Boulton 2001	67/102	11/103		9.13%	6.15[3.46,10.94]
Escobar-Jimenez 2002	17/37	6/43		4.63%	3.29[1.45,7.48]
Goldstein 2003	168/268	17/133		18.96%	4.9[3.12,7.72]
Price 1998	21/41	2/20		2.24%	5.12[1.33,19.72]
Saenz de Tejada 2002	87/145	18/71		20.17%	2.37[1.55,3.6]
Subtotal (95% CI)	**593**	**370**		**55.14%**	**4.06[3.15,5.23]**
Total events: 360 (PDE-5 Inhibitors), 54 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.34, df=4(P=0.05); I^2=57.2%					
Test for overall effect: Z=10.79(P<0.0001)					
1.16.2 Other					
Rendell 1999	74/131	13/127		11.02%	5.52[3.23,9.44]
Safarinejad 2004	68/134	14/128		11.95%	4.64[2.75,7.82]
Stuckey 2003	44/85	25/77		21.89%	1.59[1.09,2.34]
Subtotal (95% CI)	**350**	**332**		**44.86%**	**3.37[2.58,4.4]**
Total events: 186 (PDE-5 Inhibitors), 52 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=19.44, df=2(P<0.0001); I^2=89.71%					
Test for overall effect: Z=8.91(P<0.0001)					
Total (95% CI)	**943**	**702**		**100%**	**3.75[3.12,4.51]**
Total events: 546 (PDE-5 Inhibitors), 106 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=30.96, df=7(P<0.0001); I^2=77.39%					
Test for overall effect: Z=14(P<0.0001)					
Test for subgroup differences: Not applicable					



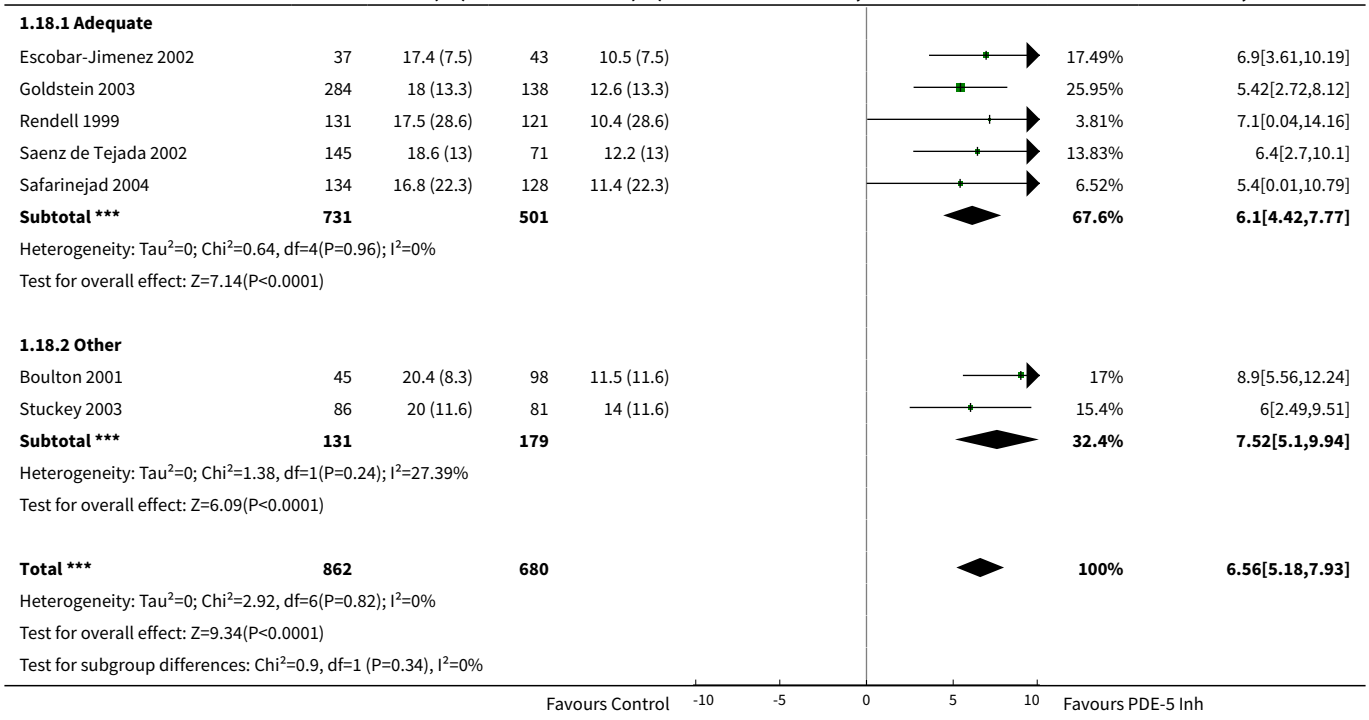
Analysis 1.17. Comparison 1 Efficacy, Outcome 17 % Succesful Attempts- by Selection.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.17.1 Adequate							
Boulton 2001	40	58.8 (57.2)	82	14.4 (57.2)		2.74%	44.4[22.76,66.04]
Goldstein 2003	287	51.4 (72.4)	137	23 (72.4)		5.91%	28.43[13.69,43.17]
Saenz de Tejada 2002	145	28.7 (55.6)	71	1.9 (55.6)		5.15%	26.84[11.04,42.64]
Subtotal ***	**472**		**290**			**13.81%**	**31.01[21.37,40.66]**
Heterogeneity: Tau^2=0; Chi^2=1.86, df=2(P=0.4); I^2=0%							
Test for overall effect: Z=6.3(P<0.0001)							
1.17.2 Other							
Stuckey 2003	85	65 (12.5)	77	39 (12.5)		86.19%	26[22.14,29.86]
Subtotal ***	**85**		**77**			**86.19%**	**26[22.14,29.86]**
Heterogeneity: Not applicable							
Test for overall effect: Z=13.2(P<0.0001)							
Total ***	**557**		**367**			**100%**	**26.69[23.11,30.28]**
Heterogeneity: Tau^2=0; Chi^2=2.75, df=3(P=0.43); I^2=0%							

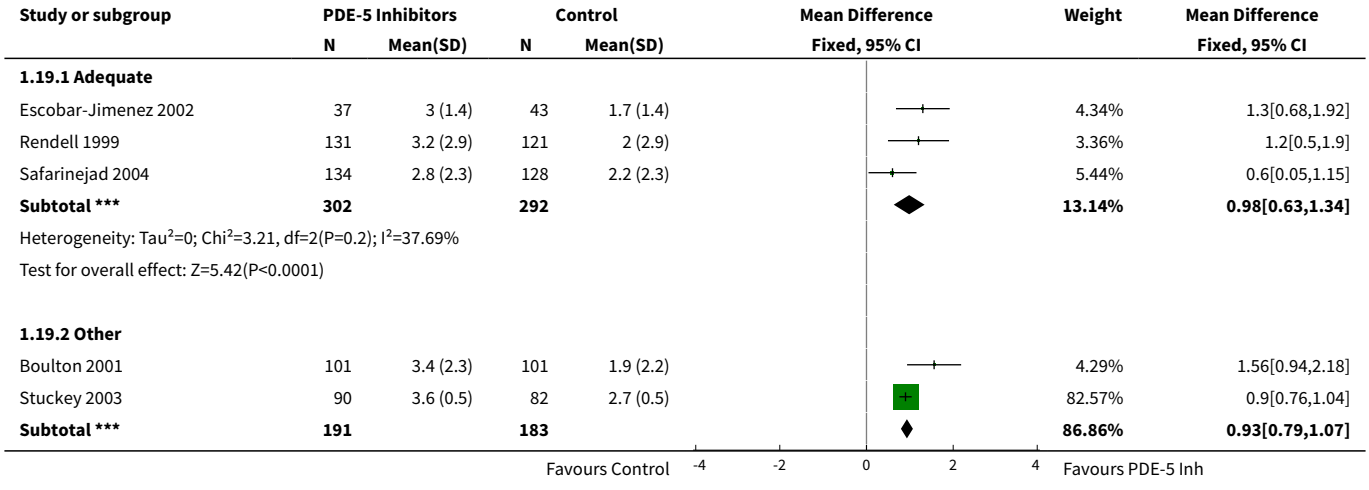




Analysis 1.18. Comparison 1 Efficacy, Outcome 18 IIEF EF Domain- by Attrition.



Analysis 1.19. Comparison 1 Efficacy, Outcome 19 IIEF Q3- by Attrition.



Study or subgroup	PDE-5 Inhibitors N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=4.09, df=1(P=0.04); I²=75.56%							
Test for overall effect: Z=13.2(P<0.0001)							
Total ***	**493**		**475**			**100%**	**0.94[0.81,1.07]**
Heterogeneity: Tau²=0; Chi²=7.37, df=4(P=0.12); I²=45.75%							
Test for overall effect: Z=14.26(P<0.0001)							
Test for subgroup differences: Chi²=0.07, df=1 (P=0.79), I²=0%							

Favours Control -4 -2 0 2 4 Favours PDE-5 Inh

Analysis 1.20. Comparison 1 Efficacy, Outcome 20 IIEF Q4- by Attrition.

Study or subgroup	PDE-5 Inhibitors N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.20.1 Adequate							
Escobar-Jimenez 2002	37	2.6 (1.1)	43	1.4 (1.1)		8.49%	1.2[0.73,1.67]
Rendell 1999	131	2.9 (3.1)	121	1.6 (3.1)		3.28%	1.3[0.54,2.06]
Safarinejad 2004	134	2.9 (2.3)	128	2 (2.3)		6.25%	0.9[0.35,1.45]
Subtotal ***	**302**		**292**			**18.02%**	**1.11[0.79,1.44]**
Heterogeneity: Tau²=0; Chi²=0.93, df=2(P=0.63); I²=0%							
Test for overall effect: Z=6.7(P<0.0001)							
1.20.2 Other							
Boulton 2001	47	3.4 (1.6)	101	1.8 (2.3)		4.52%	1.51[0.86,2.16]
Stuckey 2003	85	3.3 (0.5)	77	2.2 (0.5)		77.46%	1.06[0.9,1.22]
Subtotal ***	**132**		**178**			**81.98%**	**1.08[0.93,1.24]**
Heterogeneity: Tau²=0; Chi²=1.74, df=1(P=0.19); I²=42.48%							
Test for overall effect: Z=13.92(P<0.0001)							
Total ***	**434**		**470**			**100%**	**1.09[0.95,1.23]**
Heterogeneity: Tau²=0; Chi²=2.69, df=4(P=0.61); I²=0%							
Test for overall effect: Z=15.45(P<0.0001)							
Test for subgroup differences: Chi²=0.03, df=1 (P=0.87), I²=0%							

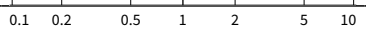
Favours Control -4 -2 0 2 4 Favours PDE-5 Inh

Analysis 1.21. Comparison 1 Efficacy, Outcome 21 Global Efficacy Question- by Attrition.

Study or subgroup	PDE-5 Inhibitors n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.21.1 Adequate					
Escobar-Jimenez 2002	17/37	6/43		4.63%	3.29[1.45,7.48]
Goldstein 2003	168/268	17/133		18.96%	4.9[3.12,7.72]
Price 1998	21/41	2/20		2.24%	5.12[1.33,19.72]
Rendell 1999	74/131	13/127		11.02%	5.52[3.23,9.44]
Saenz de Tejada 2002	87/145	18/71		20.17%	2.37[1.55,3.6]
Safarinejad 2004	68/134	14/128		11.95%	4.64[2.75,7.82]
Subtotal (95% CI)	**756**	**522**		**68.97%**	**4.11[3.28,5.16]**

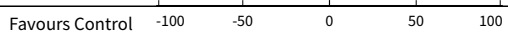
Favours Control 0.1 0.2 0.5 1 2 5 10 Favours PDE-5 Inh

Study or subgroup	PDE-5 Inhibitors n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 435 (PDE-5 Inhibitors), 70 (Placebo)					
Heterogeneity: Tau²=0; Chi²=8.95, df=5(P=0.11); I²=44.14%					
Test for overall effect: Z=12.26(P<0.0001)					
1.21.2 Other					
Boulton 2001	67/102	11/103		9.13%	6.15[3.46,10.94]
Stuckey 2003	44/85	25/77		21.89%	1.59[1.09,2.34]
Subtotal (95% CI)	**187**	**180**		**31.03%**	**2.94[2.14,4.03]**
Total events: 111 (PDE-5 Inhibitors), 36 (Placebo)					
Heterogeneity: Tau²=0; Chi²=16.15, df=1(P<0.0001); I²=93.81%					
Test for overall effect: Z=6.69(P<0.0001)					
Total (95% CI)	**943**	**702**		**100%**	**3.75[3.12,4.51]**
Total events: 546 (PDE-5 Inhibitors), 106 (Placebo)					
Heterogeneity: Tau²=0; Chi²=30.96, df=7(P<0.0001); I²=77.39%					
Test for overall effect: Z=14(P<0.0001)					
Test for subgroup differences: Not applicable					



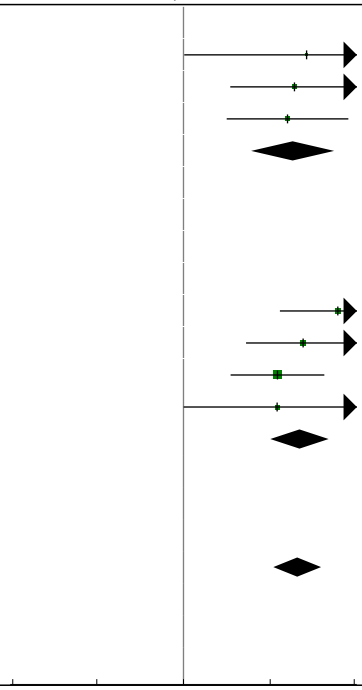
Analysis 1.22. Comparison 1 Efficacy, Outcome 22 % Succesful Attempts- by Attrtition.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.22.1 Adequate							
Goldstein 2003	287	51.4 (72.4)	137	23 (72.4)		5.91%	28.43[13.69,43.17]
Saenz de Tejada 2002	145	28.7 (55.6)	71	1.9 (55.6)		5.15%	26.84[11.04,42.64]
Subtotal ***	**432**		**208**			**11.06%**	**27.69[16.91,38.47]**
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.89); I²=0%							
Test for overall effect: Z=5.04(P<0.0001)							
1.22.2 Other							
Boulton 2001	40	58.8 (57.2)	82	14.4 (57.2)		2.74%	44.4[22.76,66.04]
Stuckey 2003	85	65 (12.5)	77	39 (12.5)		86.19%	26[22.14,29.86]
Subtotal ***	**125**		**159**			**88.94%**	**26.57[22.77,30.37]**
Heterogeneity: Tau²=0; Chi²=2.69, df=1(P=0.1); I²=62.86%							
Test for overall effect: Z=13.7(P<0.0001)							
Total ***	**557**		**367**			**100%**	**26.69[23.11,30.28]**
Heterogeneity: Tau²=0; Chi²=2.75, df=3(P=0.43); I²=0%							
Test for overall effect: Z=14.6(P<0.0001)							
Test for subgroup differences: Chi²=0.04, df=1 (P=0.85), I²=0%							



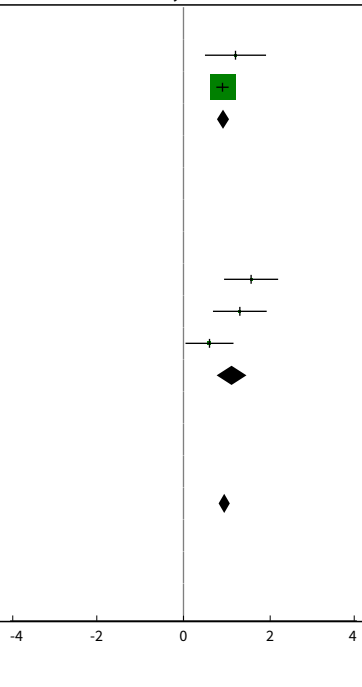
Analysis 1.23. Comparison 1 Efficacy, Outcome 23 IIEF EF Domain- by Sponsor.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.23.1 Pharmaceutical							
Rendell 1999	131	17.5 (28.6)	121	10.4 (28.6)		3.81%	7.1[0.04,14.16]
Saenz de Tejada 2002	145	18.6 (13)	71	12.2 (13)		13.83%	6.4[2.7,10.1]
Stuckey 2003	86	20 (11.6)	81	14 (11.6)		15.4%	6[2.49,9.51]
Subtotal ***	**362**		**273**			**33.04%**	**6.29[3.9,8.69]**
Heterogeneity: Tau^2=0; Chi^2=0.08, df=2(P=0.96); I^2=0%							
Test for overall effect: Z=5.15(P<0.0001)							
1.23.2 Other							
Boulton 2001	45	20.4 (8.3)	98	11.5 (11.6)		17%	8.9[5.56,12.24]
Escobar-Jimenez 2002	37	17.4 (7.5)	43	10.5 (7.5)		17.49%	6.9[3.61,10.19]
Goldstein 2003	284	18 (13.3)	138	12.6 (13.3)		25.95%	5.42[2.72,8.12]
Safarinejad 2004	134	16.8 (22.3)	128	11.4 (22.3)		6.52%	5.4[0.01,10.79]
Subtotal ***	**500**		**407**			**66.96%**	**6.69[5.01,8.37]**
Heterogeneity: Tau^2=0; Chi^2=2.77, df=3(P=0.43); I^2=0%							
Test for overall effect: Z=7.79(P<0.0001)							
Total ***	**862**		**680**			**100%**	**6.56[5.18,7.93]**
Heterogeneity: Tau^2=0; Chi^2=2.92, df=6(P=0.82); I^2=0%							
Test for overall effect: Z=9.34(P<0.0001)							
Test for subgroup differences: Chi^2=0.07, df=1 (P=0.79), I^2=0%							



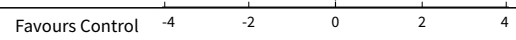
Analysis 1.24. Comparison 1 Efficacy, Outcome 24 IIEF Q3- by Sponsor.

Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.24.1 Pharmaceutical							
Rendell 1999	131	3.2 (2.9)	121	2 (2.9)		3.36%	1.2[0.5,1.9]
Stuckey 2003	90	3.6 (0.5)	82	2.7 (0.5)		82.57%	0.9[0.76,1.04]
Subtotal ***	**221**		**203**			**85.93%**	**0.91[0.77,1.05]**
Heterogeneity: Tau^2=0; Chi^2=0.67, df=1(P=0.41); I^2=0%							
Test for overall effect: Z=12.83(P<0.0001)							
1.24.2 Other							
Boulton 2001	101	3.4 (2.3)	101	1.9 (2.2)		4.29%	1.56[0.94,2.18]
Escobar-Jimenez 2002	37	3 (1.4)	43	1.7 (1.4)		4.34%	1.3[0.68,1.92]
Safarinejad 2004	134	2.8 (2.3)	128	2.2 (2.3)		5.44%	0.6[0.05,1.15]
Subtotal ***	**272**		**272**			**14.07%**	**1.11[0.76,1.45]**
Heterogeneity: Tau^2=0; Chi^2=5.62, df=2(P=0.06); I^2=64.44%							
Test for overall effect: Z=6.31(P<0.0001)							
Total ***	**493**		**475**			**100%**	**0.94[0.81,1.07]**
Heterogeneity: Tau^2=0; Chi^2=7.37, df=4(P=0.12); I^2=45.75%							
Test for overall effect: Z=14.26(P<0.0001)							
Test for subgroup differences: Chi^2=1.08, df=1 (P=0.3), I^2=7.3%							



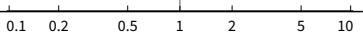
Analysis 1.25. Comparison 1 Efficacy, Outcome 25 IIEF Q4- by Sponsor.

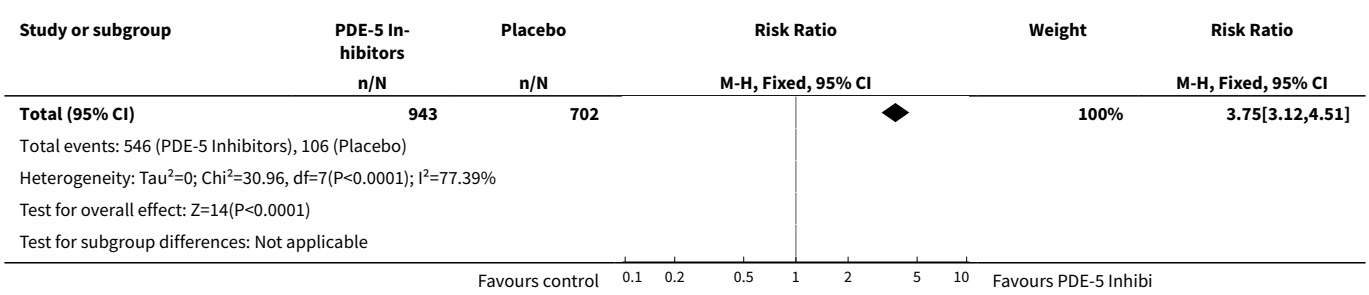
Study or subgroup	PDE-5 Inhibitors N	PDE-5 Inhibitors Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.25.1 Pharmaceutical							
Rendell 1999	131	2.9 (3.1)	121	1.6 (3.1)		3.28%	1.3[0.54,2.06]
Stuckey 2003	85	3.3 (0.5)	77	2.2 (0.5)		77.46%	1.06[0.9,1.22]
Subtotal ***	**216**		**198**			**80.74%**	**1.07[0.92,1.22]**
Heterogeneity: Tau²=0; Chi²=0.36, df=1(P=0.55); I²=0%							
Test for overall effect: Z=13.62(P<0.0001)							
1.25.2 Other							
Boulton 2001	47	3.4 (1.6)	101	1.8 (2.3)		4.52%	1.51[0.86,2.16]
Escobar-Jimenez 2002	37	2.6 (1.1)	43	1.4 (1.1)		8.49%	1.2[0.73,1.67]
Safarinejad 2004	134	2.9 (2.3)	128	2 (2.3)		6.25%	0.9[0.35,1.45]
Subtotal ***	**218**		**272**			**19.26%**	**1.18[0.86,1.49]**
Heterogeneity: Tau²=0; Chi²=1.98, df=2(P=0.37); I²=0%							
Test for overall effect: Z=7.31(P<0.0001)							
Total ***	**434**		**470**			**100%**	**1.09[0.95,1.23]**
Heterogeneity: Tau²=0; Chi²=2.69, df=4(P=0.61); I²=0%							
Test for overall effect: Z=15.45(P<0.0001)							
Test for subgroup differences: Chi²=0.35, df=1 (P=0.55), I²=0%							



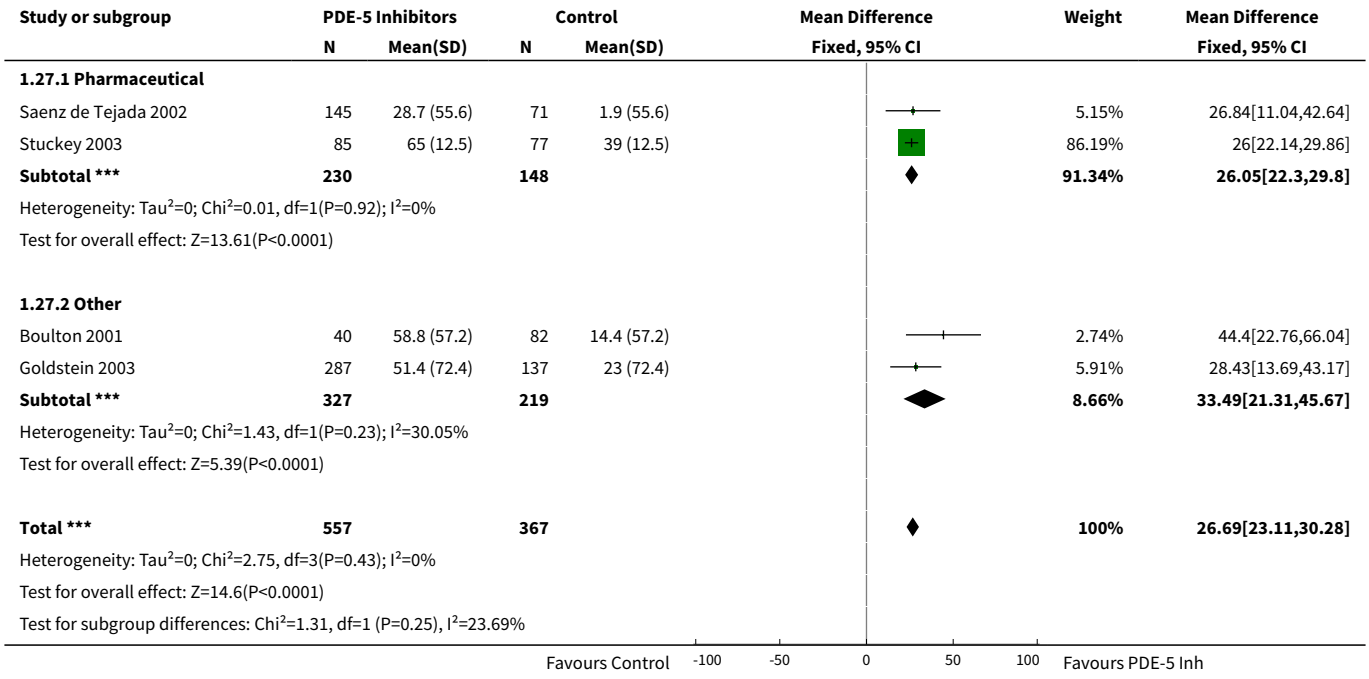
Analysis 1.26. Comparison 1 Efficacy, Outcome 26 Global Efficacy Question- by Sponsor.

Study or subgroup	PDE-5 Inhibitors n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.26.1 Pharmaceutical					
Price 1998	21/41	2/20		2.24%	5.12[1.33,19.72]
Rendell 1999	74/131	13/127		11.02%	5.52[3.23,9.44]
Saenz de Tejada 2002	87/145	18/71		20.17%	2.37[1.55,3.6]
Stuckey 2003	44/85	25/77		21.89%	1.59[1.09,2.34]
Subtotal (95% CI)	**402**	**295**		**55.32%**	**2.8[2.19,3.58]**
Total events: 226 (PDE-5 Inhibitors), 58 (Placebo)					
Heterogeneity: Tau²=0; Chi²=15.88, df=3(P=0); I²=81.11%					
Test for overall effect: Z=8.18(P<0.0001)					
1.26.2 Other					
Boulton 2001	67/102	11/103		9.13%	6.15[3.46,10.94]
Escobar-Jimenez 2002	17/37	6/43		4.63%	3.29[1.45,7.48]
Goldstein 2003	168/268	17/133		18.96%	4.9[3.12,7.72]
Safarinejad 2004	68/134	14/128		11.95%	4.64[2.75,7.82]
Subtotal (95% CI)	**541**	**407**		**44.68%**	**4.92[3.73,6.5]**
Total events: 320 (PDE-5 Inhibitors), 48 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.55, df=3(P=0.67); I²=0%					
Test for overall effect: Z=11.22(P<0.0001)					





Analysis 1.27. Comparison 1 Efficacy, Outcome 27 % Succesful Attempts- by Sponsor.



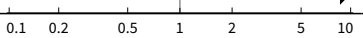
Comparison 2. Adverse Reactions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Morbidity	8	15884	Risk Ratio (M-H, Fixed, 95% CI)	4.75 [3.70, 6.09]
1.1 Cardiovascular	8	1767	Risk Ratio (M-H, Fixed, 95% CI)	20.13 [1.19, 340.27]
1.2 Flushing	8	1767	Risk Ratio (M-H, Fixed, 95% CI)	13.21 [6.01, 29.03]
1.3 Headache	8	1767	Risk Ratio (M-H, Fixed, 95% CI)	3.66 [2.51, 5.35]
1.4 Myalgia	8	1748	Risk Ratio (M-H, Fixed, 95% CI)	3.30 [1.45, 7.48]
1.5 Dyspepsia	8	1767	Risk Ratio (M-H, Fixed, 95% CI)	9.56 [3.18, 28.74]

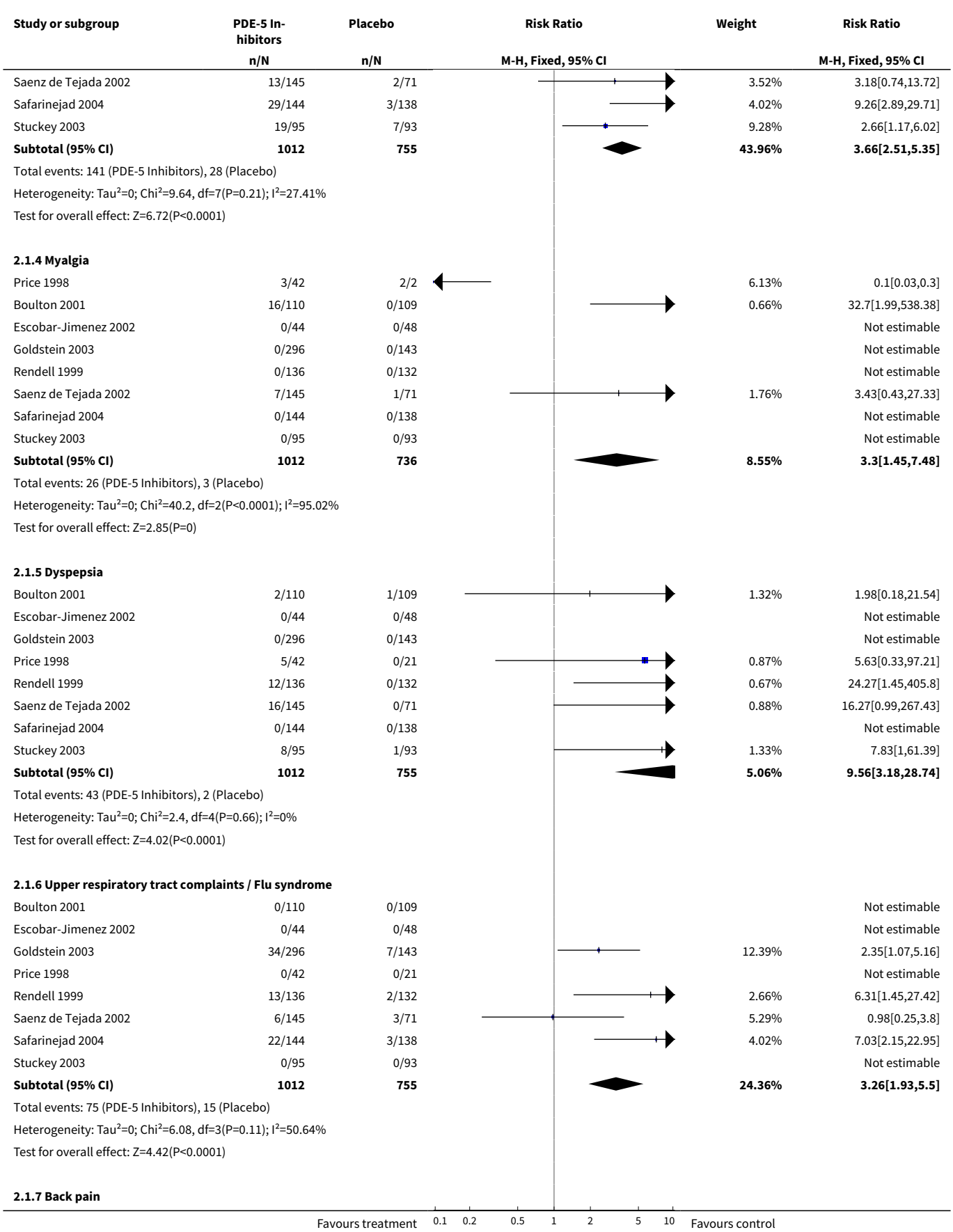
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Upper respiratory tract complaints / Flu syndrome	8	1767	Risk Ratio (M-H, Fixed, 95% CI)	3.26 [1.93, 5.50]
1.7 Back pain	8	1767	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.29, 20.56]
1.8 Nausea	8	1767	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.10, 10.41]
1.9 Abnormal vision	8	1767	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [1.08, 11.35]

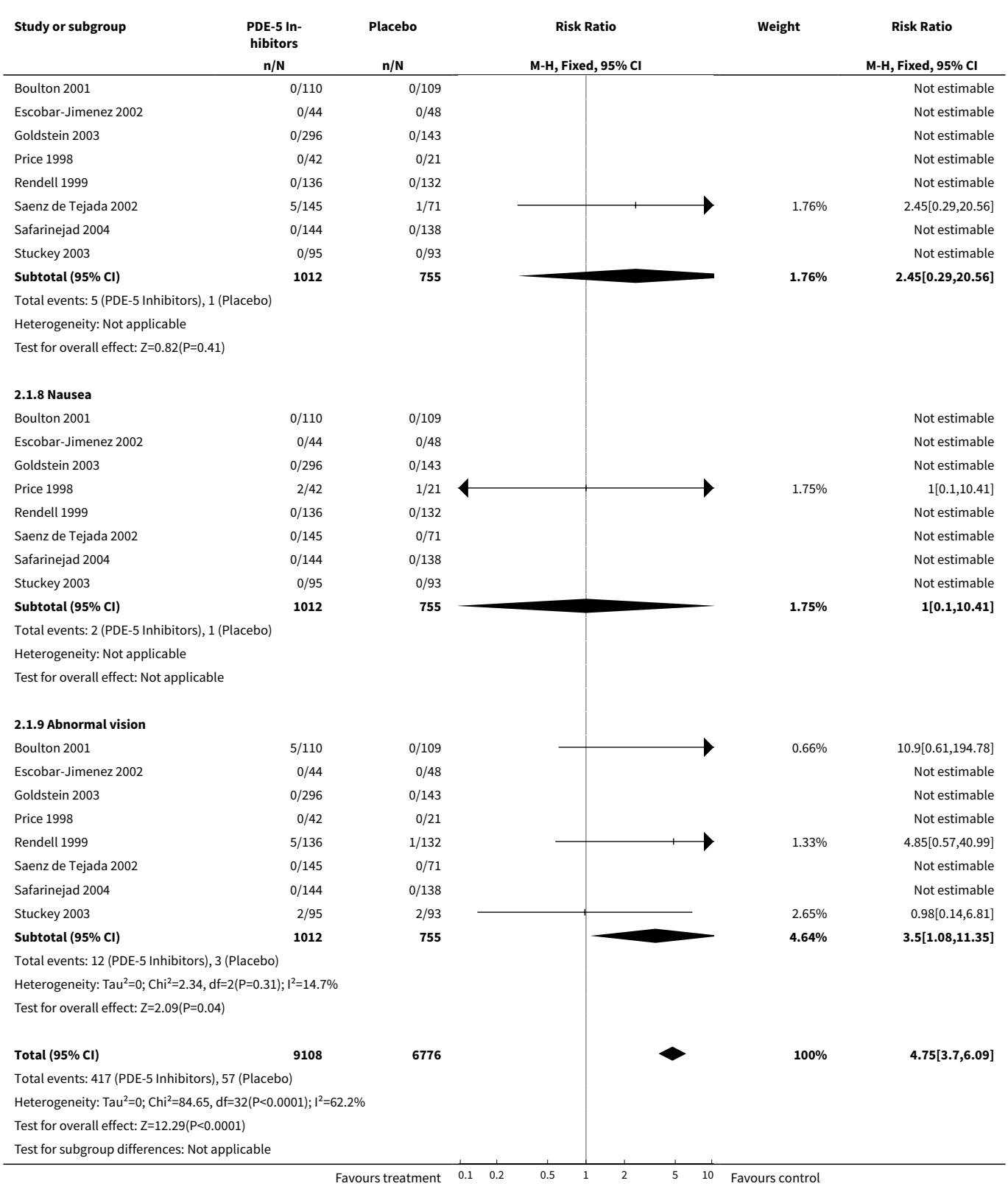
Analysis 2.1. Comparison 2 Adverse Reactions, Outcome 1 Morbidity.

Study or subgroup	PDE-5 Inhibitors n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Cardiovascular					
Boulton 2001	0/110	0/109			Not estimable
Escobar-Jimenez 2002	0/44	0/48			Not estimable
Goldstein 2003	0/296	0/143			Not estimable
Price 1998	0/42	0/21			Not estimable
Rendell 1999	0/136	0/132			Not estimable
Saenz de Tejada 2002	0/145	0/71			Not estimable
Safarinejad 2004	10/144	0/138		0.67%	20.13[1.19,340.27]
Stuckey 2003	0/95	0/93			Not estimable
Subtotal (95% CI)	**1012**	**755**		**0.67%**	**20.13[1.19,340.27]**
Total events: 10 (PDE-5 Inhibitors), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.08(P=0.04)					
2.1.2 Flushing					
Boulton 2001	16/110	0/109		0.66%	32.7[1.99,538.38]
Escobar-Jimenez 2002	4/44	0/48		0.63%	9.8[0.54,176.97]
Goldstein 2003	28/296	1/143		1.77%	13.53[1.86,98.43]
Price 1998	0/42	0/21			Not estimable
Rendell 1999	6/136	0/132		0.67%	12.62[0.72,221.82]
Saenz de Tejada 2002	5/145	0/71		0.88%	5.42[0.3,96.76]
Safarinejad 2004	27/144	0/138		0.67%	52.72[3.25,856]
Stuckey 2003	17/95	3/93		3.98%	5.55[1.68,18.3]
Subtotal (95% CI)	**1012**	**755**		**9.25%**	**13.21[6.01,29.03]**
Total events: 103 (PDE-5 Inhibitors), 4 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=3.79$, df=6(P=0.71); $I^2=0\%$					
Test for overall effect: Z=6.43(P<0.0001)					
2.1.3 Headache					
Boulton 2001	20/110	4/109		5.27%	4.95[1.75,14.02]
Escobar-Jimenez 2002	5/44	0/48		0.63%	11.98[0.68,210.54]
Goldstein 2003	36/296	10/143		17.7%	1.74[0.89,3.4]
Price 1998	4/42	0/21		0.87%	4.6[0.26,81.72]
Rendell 1999	15/136	2/132		2.66%	7.28[1.7,31.21]



Favours treatment — Favours control





Study or subgroup	PDE-5 Inhibitors n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Boulton 2001	0/110	0/109			Not estimable
Escobar-Jimenez 2002	0/44	0/48			Not estimable
Goldstein 2003	0/296	0/143			Not estimable
Price 1998	0/42	0/21			Not estimable
Rendell 1999	0/136	0/132			Not estimable
Saenz de Tejada 2002	5/145	1/71		1.76%	2.45[0.29,20.56]
Safarinejad 2004	0/144	0/138			Not estimable
Stuckey 2003	0/95	0/93			Not estimable
Subtotal (95% CI)	**1012**	**755**		**1.76%**	**2.45[0.29,20.56]**
Total events: 5 (PDE-5 Inhibitors), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					
2.1.8 Nausea					
Boulton 2001	0/110	0/109			Not estimable
Escobar-Jimenez 2002	0/44	0/48			Not estimable
Goldstein 2003	0/296	0/143			Not estimable
Price 1998	2/42	1/21		1.75%	1[0.1,10.41]
Rendell 1999	0/136	0/132			Not estimable
Saenz de Tejada 2002	0/145	0/71			Not estimable
Safarinejad 2004	0/144	0/138			Not estimable
Stuckey 2003	0/95	0/93			Not estimable
Subtotal (95% CI)	**1012**	**755**		**1.75%**	**1[0.1,10.41]**
Total events: 2 (PDE-5 Inhibitors), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.1.9 Abnormal vision					
Boulton 2001	5/110	0/109		0.66%	10.9[0.61,194.78]
Escobar-Jimenez 2002	0/44	0/48			Not estimable
Goldstein 2003	0/296	0/143			Not estimable
Price 1998	0/42	0/21			Not estimable
Rendell 1999	5/136	1/132		1.33%	4.85[0.57,40.99]
Saenz de Tejada 2002	0/145	0/71			Not estimable
Safarinejad 2004	0/144	0/138			Not estimable
Stuckey 2003	2/95	2/93		2.65%	0.98[0.14,6.81]
Subtotal (95% CI)	**1012**	**755**		**4.64%**	**3.5[1.08,11.35]**
Total events: 12 (PDE-5 Inhibitors), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.34, df=2(P=0.31); I^2=14.7%					
Test for overall effect: Z=2.09(P=0.04)					
Total (95% CI)	**9108**	**6776**		**100%**	**4.75[3.7,6.09]**
Total events: 417 (PDE-5 Inhibitors), 57 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=84.65, df=32(P<0.0001); I^2=62.2%					
Test for overall effect: Z=12.29(P<0.0001)					
Test for subgroup differences: Not applicable					

APPENDICES

Appendix 1. Search strategy

Electronic searches

Diabetes mellitus
1. exp diabetes mellitus/
2. diabet$.tw.
3. IDDM.tw.
4. NIDDM.tw.
5. MODY.tw.
6. insulin$ secret$ dysfunc$.tw.
7. impaired glucose toleran$.tw.
8. exp glucose intolerance/
9. glucose intoleran$.tw.
10. exp insulin resistance/
11. insulin$ resist$.tw.
12. (non insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).tw.
13. (insulin? depend$ or insulin?depend$).tw
14. metabolic$ syndrom$.tw.
15. (pluri metabolic$ syndrom$ or plurimetabolic$ syndrom$).tw.
16. or/1-15
17. exp diabetes insipidus/
18. diabet$ insipidus.tw.
19. 17 or 18
20. 16 not 19

Erectile dysfunction
1. exp Impotence/
2. erecti$ dysfunct$.mp.
3. sex$ dysfunct$.mp.
4. sex$ disorder$.mp.
5. exp PENILE ERECTION/
6. erect$.tw.
7. 1 or 2 or 3 or 4 or 5 or 6

Phosphodiesterase type 5 inhibiors
1. exp 3',5'-cyclic-gmp phosphodiesterase/
2. phospho?di?esterase$.mp
3. PDE?.mp
4. sildenafil$.tw
5. viagra$.tw
6. vardenafil$.tw
7. levitra$.tw
8. tadalafil$.tw
9. cialis$.tw
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

Controlled or randomised clinical trials

Phase I
1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. Randomised Controlled Trials/
4. Random Allocation/
5. Double-Blind Method/
6. Single Blind Method/
7. 1 or 2 or 3 or 4 or 5 or 6

(Continued)

8. Animal/ not Human/
9. 7 not 8

Phase II
10. clinical trial.pt.
11. exp Clinical Trials/
12. (clinic$ adj25 trial$).tw.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
14. Placebos/
15. placebo$.tw.
16. random$.tw.
17. Research Design/
18. (latin adj square).tw.
19. 10 or 13 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 19 not 8
21. 20 not 9

Phase III
22. Comparative Study/
23. exp Evaluation Studies/
24. Follow-Up Studies/
25. Prospective Studies/
26. (control$ or prospectiv$ or volunteer$).tw.
27. Cross-Over Studies/
28. 22 or 23 or 24 or 25 or 26 or 27
29. 28 not 8
30. 29 not (9 or 21)

All phases
31. 9 or 21 or 30

Meta-analysis or systematic reviews
1. exp meta-analysis/
2. exp Review Literature/
3. meta-analysis.pt.
4. review.pt.
5. 1 or 2 or 3 or 4
6. letter.pt.
7. comment.pt.
8. editorial.pt.
9. historical-article.pt.
10. 6 or 7 or 8 or 9
11. 5 not 10
12. ((systematic$ or quantitativ$ or methodologic$) adj (review$ or overview$)).tw.
13. meta?anal$.tw.
14. (integrativ$ research review$ or research integration$).tw.
15. quantitativ$ synthes$.tw.
16. (pooling$ or pooled analys$ or mantel$ haenszel$).tw.
17. (peto$ or der?simonian$ or fixed effect$ or random effect$).tw.
18. 12 or 13 or 14 or 15 or 16 or 17
19. 11 or 18
20. limit 19 to human [Limit not valid in: Pre-MEDLINE; records were retained]

Combined search:

(diabetes mellitus and erectile dysfunction and phosphodiesterase type 5 inhibiors) and (controlled/randomised clinical trials or meta-analysis/systematic reviews)

Note: (ADJn) retrieves two or more query terms within n words of each other, and in any order; a question mark (?) can be used within or at the end of a query word to substitute for one or no characters; a truncation mark ($) stands for unlimited truncation to retrieve all possible suffix variations of a root word; (exp) - all MeSH terms and a specific category will be included in the search; MeSH:

(Continued)

Medical Subject Heading; (mp) looks for exact word or phrase in the title, abstract and subject-heading fields; (tw) looks for exact word or phrase in the title and abstract.

Appendix 2. IIEF questionaire

Number	Question
1	Frequency of erections during sexual activity
2	Frequency of erections hard enough for penetration
3	Frequency of penetration during sexual intercourse
4	Frequency of maintaining erection to completion of intercourse
5	Difficulty in maintaining an erection to completion of intercourse
6	Frequency of attempts at intercourse
7	Frequency of satisfaction with intercourse
8	How enjoying is sexual intercourse?
9	Frequency of ejaculation
10	Frequency of orgasm climax
11	Frequency of sexual desire
12	Rating of sexual desire
13	Satisfaction with overall sexual life
14	Satisfaction with sexual relationship
15	Rating of confidence in achieving/maintaining erections

Appendix 3. Study overall quality- three point scale

Study	Selection bias	Performance bias	Attrition bias	Detection bias	Overall quality
Boulton 2001	?	?	N	?	C
Escobar-Jimenez 2002	?	?	Y	?	B
Goldstein 2003	?	?	Y	Y	B
Price 1998	?	?	Y	?	B

(Continued)

Rendell 1999	Y	?	Y	?	B
Saenz de Tejada 2002	?	?	Y	?	B
Safarinejad 2004	Y	?	Y	?	B
Stuckey 2003	Y	Y	?	?	B

Appendix 4. Study quality - detailed

Characteristic	Boulton 2001	Esco-bar-Jimenez 2002	Goldstein 2003	Price 1998	Rendell 1999	Saenz de Tejada 2002	Safarinejad 2004	Stuckey 2003
Intervention 1 (I1) / intervention 2 (I2) / control 1 (C1)	I1: Sildenafil 25-100mg C1: Placebo	I1: Sildenafil 25-100mg C1: Placebo	I1: Varde-nafil 10mg I2: Varde-nafil 20mg C1: Placebo	I1: Sildenafil 25mg I2: Silde-nafil 50mg C1: Placebo	I1: Sildenafil 25-100mg C1: Placebo	I1: Tadalafil 10MG I2: Tadalafil 20mg C1: Placebo	"I1: Silde-nafil 100mgC1: Placebo"	I1: Sildenafil 25-100mg C1: Placebo
Randomised controlled clinical trial (RCT)	Y	Y	Y	Y	Y	Y	Y	Y
Non-inferiority / equivalence trial	N	N	N	N	N	N	N	N
Controlled clinical trial	Y	Y	Y	Y	Y	Y	Y	Y
Design: parallel, crossover, factorial RCT	Parallel	Parallel	Parallel	Parallel	Parallel	Parallel	Parallel	Cross-over
Design: crossover study								
Design: factorial study								
Crossover study: wash-out phase								3-10 days
Crossover study: carryover effect tested								N
Crossover study: period effect tested								N
Method of randomisation	?	?	?	?	Y	?	Y	Y
Unit of randomisation (individuals, cluster - specify)	Individual	Individual	Individual	Individual	Individual	Individual	Individual	Individual
Randomisation stratified for centres	N	N	N	N	N	N	N	N
Randomisation ratio	50%-50%	47%-53%	34%-32%-32%	33%-33%-33%	57%-43%	33%-33%-33%	51%-49%	50%-50%
Concealment of allocation	?	?	Y	?	Y	Y	Y	Y
Stated blinding (open; single, double, triple blind)	Double	Double	Double	Double	Double	Double	Double	Double

(Continued)

Actual blinding: participant	Y	Y	Y	Y	Y	Y	Y	Y
Actual blinding: caregiver / treatment administrator	Y	Y	Y	Y	Y	Y	Y	Y
Actual blinding: outcome assessor	?	?	Y	?	?	?	?	?
Actual blinding: others	?	?	?	?	?	?	?	?
Blinding checked: participant	?	?	?	?	?	?	?	?
Blinding checked: caregiver / treatment administrator	?	?	?	?	?	?	?	?
Primary endpoint defined	Y	Y	Y	Y	Y	Y	Y	Y
[n] of primary endpoint(s)	2	2	3	3	3	4	5	2
[n] of secondary endpoints	5	3	1	0	0	3	0	3
Total [n] of endpoints	7	5	4	3	3	7	5	5
Prior publication of study design	N	N	N	N	N	N	N	N
Outcomes of prior / current publication identical	N	N	N	N	N	N	N	N
Power calculation	Y	?	?	?	Y	?	?	?
[n] participants per group calculated	50	?	?	?	86	?	?	?
Non-inferiority trial: interval for equivalence specified								
Intention-to-treat analysis (ITT)	?	Y	Y	Y	Y	Y	Y	N
Per-protocol-analysis								
ITT defined	?	?	Y	Y	Y	Y	N	N
Analysis stratified for centres	N	N	N	N	N	N	N	N

(Continued)

Missing data: last-observation-carried-forward (LOCF)	?	?	Y	?	?	?	?	?
Missing data: other methods	?	?	?	?	?	?	?	?
LOCF defined	?	?	Y	?	?	?	?	?
[n] of screened participants (I1/ I2 / C1 / total)	?	?	?	?	?	?	373	244
[n] of randomised participants for primary endpoint	I1: 110 C1: 119 Total: 219	I1: 44 C1: 48 Total: 92	I1: 153 I2: 149 C1: 150 Total: 452	I1: 22 I2: 22 C1: 22 Total: 22	I1: 136 C1: 132 Total: 268	I1: 73 I2: 72 C1: 71 Total: 216	I1: 144 C1: 138 Total: 282	I1: 97 C1: 94 Total: 191
[n] of participants finishing the study	202	I1: 37 C1: 43 Total: 80	I1: 152 I2: 144 C1: 143 Total: 439	I1: 21 I2: 22 C1: 22 Total: 22	I1: 131 C1: 121 Total: 252	I1: 73 I2: 72 C1: 71 Total: 216	I1: 134 C1: 128 Total: 262	I1: 85 C1: 77 Total: 162
[n] of patients analysed		I1: 44 C1: 48 Total: 92						
Description of discontinuing participants	N	N	Y	Y	Y	Y	Y	Y
Drop-outs (reasons explained)	N	N	Y	Y	Y	Y	Y	Y
Withdrawals (reasons explained)	N	N	Y	Y	Y	Y	Y	Y
Losses-to-follow-up (reasons explained)	N	N	Y	Y	Y	Y	Y	Y
[n] of participants who discontinued	17	I1: 7 C1: 5 Total: 12	I1: data missing I2: data missing C1: data missing Total: 73	I1: 1, I2: 0 C1:0 Total: 1	I1: 5 C1: 11 Total: 16	I1: data missing, I2: data missing C1: 7 Total: 25	I1: 10 C1: 10 Total: 20	I1: 10 C1: 16 Total: 26
[%] discontinuation rate	7.7	13	16.1	4.5	5.9	11.5	7	13.6
Discontinuation rate similar between groups	Y	N	Y	Y	N	Y	Y	N

(Continued)

[%] crossover between groups	0	0	0	0	0	0	0	0
Differences [n] calculated to analysed patients								
[n] of subgroups	2	0	2	0	4	3	4	3
Subgroups: pre-defined	Y	N	Y	N	Y	N	Y	Y
Subgroups: post-hoc	N	N	N	N	N	Y	N	N
Adjustment for multiple outcomes / repeated measurements	N	N	N	N	N	N	N	N
Baseline characteristics: clinically relevant differences	N	N	N	N	N	N	N	N
Treatment identical (apart from intervention)	Y	Y	Y	Y	Y	Y	Y	Y
Timing of outcomes' measurement comparable between groups	Y	Y	Y	Y	Y	Y	Y	Y
Compliance measured	Y	Y	Y	Y	Y	Y	Y	Y
Other important covariates measured (specify)	N	N	N	N	N	N	N	N
Co-morbidities measured	Y	Y	Y	Y	Y	Y	Y	Y
Co-medications measured	Y	Y	Y	Y	Y	Y	Y	Y
Specific doubts about study quality	N	N	N	N	N	N	N	N
Funding: commercial	?	?	Y	Y	Y	Y	?	Y
Funding: non-commercial	?	?	N	N	N	N	?	N
Publication status: peer review journal	Y	?	Y	Y	Y	Y	Y	Y
Publication status: journal supplement	N	N	N	N	N	N	N	N
Publication status: abstract	N	N	N	N	N	N	N	N

(Continued)

Publication status: other	N	N	N	N	N	N	N	N
Notes								
Symbols & abbreviations: Y = yes; N = no; ? = unclear I = intervention; C = control								

Appendix 5. Baseline characteristics

Characteristic	Boulton 2001	Esco-bar-Jimenez 2002	Goldstein 2003	Price 1998	Rendell 1999	Saenz de Tejada 2002	Safarinejad 2004	Stuckey 2003
Intervention 1 (I1) / intervention 2 (I2) / control 1 (C1)	I1: Sildenafil 25-100mg C1: Placebo	I1: Sildenafil 25-100mg C1: Placebo	I1: Vardenafil 10mg I2: Vardenafil 20mg C1: Placebo	I1: Sildenafil 25 mg I2: Silde-nafil 50 mg C1: Placebo	I1: Sildenafil 25-100mg C1: Placebo	I1: Tadalafil 10mg I2: Tadalafil 20mg C1: Placebo	I1: Sildenafil 100mg C1: Placebo	I1: Sildenafil 25-100mg C1: Placebo
[n] (I1/ I2 / C1 / total)	110/109/219	44/48/92	152/144/143/439	21/22/22/22	136/132/268	73/72/71/216	144/138/282	97/94/191
Sex [n,%]	All male	All male	All male	All male	All male	All male	All male	All male
Age [years] mean (SD/Range)	I1: 58.2 (38-80) C: 59.1 (45-72)	I1:57.8 (42-70) C: 56.8 (44-73)	I1: 58 I2: 56.9 C: 56.8	?	I1: 57 (33-76) C: 57 (27-79)	I1: 55.9(9.1) I2: 55.5(9) C: 55.8(9.1)	I1: 46 (37-68) C: 46 (35-68)	I1:46.8 (25-69) C: 47.8 (27-66)
Ethnic groups [%]	White 96%, black 0.9%, asian 1.8%, other 1.3%	?	Caucasian 80%, black 9%, hispanic 8%, other 3%	?	?	Caucasian 99.5%, black 0.5%	?	White 94%, black 1%, asian: 5%
Duration of disease [years] mean (SD/Range)	ED: 4.6(0.4-21)/3.7(0.7-11.1) DM: 10.1(2-34)/9.7(1-28)	?	ED: 3.4/3.3/3.7 DM: 10/10.5/12	?	ED: 5.3(0.6-22)/5.8(1-24) DM: 12.1/12.1	ED: Data missing DM: 11.9(9.4),11.2(9.5),11.9(9.6)	ED: 3.6(2.5-11)/3.9(2.5-10) DM: 9.1/11	ED: 4.5(0.5-18.7)/5.8(0.7-26.3) DM: 19.9(1.1-48.1)/20.9(2.1-46.3)
Body mass index [kg/m2] mean (SD)	?	?	30.6/30.2/31.5	?	?	?	?	?
Pharmaco-naive patients [n, %]	?	?	?	?	?	?	?	?
HbA1c [%] mean (SD)	8.3(5.1-12.1)/8.4(5.2-12.1)		Data categorised into three groups	?	?	Data categorised into three groups	8.3(5.1-12.1)/8.4(5.1-12.1)	8.5(5.1-10.9)/8.6(5.9-12.9)
Notes								

(Continued)

Symbols & abbreviations: Y = yes; N = no; ? = unclear
I = intervention; C = control

Appendix 6. Adverse events

Characteristic	Boulton 2001	Esco-bar-Jimenez 2002	Goldstein 2003	Price 1998	Rendell 1999	Saenz de Tejada 2002	Safarinejad 2004	Stuckey 2003
Intervention 1 (I1) / intervention 2 (I2) / control 1 (C1)	I1: Sildenafil 25-100mg C1: Placebo	I1: Sildenafil 25-100mg C1: Placebo	I1: Vardenafil 10mg I2: Vardenafil 20mg C1: Placebo	I1: Sildenafil 25 mg I2: Sildenafil 50 mg C1: Placebo	I1: Sildenafil 25-100mg C1: Placebo	I1: Tadalafil 10mg I2: Tadalafil 20mg C1: Placebo	I1: Sildenafil 100mg C1: Placebo	I1: Sildenafil 25-100mg C1: Placebo
[n] of participants who died	0	0	0	0	0	0	0	0
[n] adverse events (I1/ I2 / C1 / total)	65/11/76	12/3/15	56/57/23/136	8/6/3/17	51/5/56	25/27/7/59	32/2/34	67/25/92
[%] adverse events	37.3/6.4	27/6.2/14.7	36/39/16	38/28/14	38/5	34.3/37.6/9.8	22/1.4	70.5/26.8
[n] serious adverse events	0/0	0/0	0/0	0/0	0/0	0/0	4/0	5/2
[%] serious adverse events	0/0	0/0	0/0	0/0	0/0	0/0	2.75/0	5.2/2.1
[n] drop-outs due to adverse events	I1: 0/110 C1: 0/109 Total: 0/219	I1: 3/44 C1:0/48 Total: 3/102	I1: 4/152 I2 : 5/144 C1: 2/143 Total: 11/439	I1: 0/21 I2: 0/22 C1: 0/22 Total: 0/22	I1: 1/136 C1: 1/132 Total: 2/268	I1: 1/73 I2 :3/72 C1: 2/71 Total: 6/216	I1: 8/144 C1: 0/138 Total: 8/282	I1: 1/95 C1: 2/93 Total: 3/188
[%] drop-outs due to adverse events	I1: 0 C1: 0 Total: 0	I1: 6.8 C1:0 Total: 2.9	I1: 7.6 I2 : 3.4 C1: 1.3 Total: 2.5pneumococcal	I1: 0 I2:0 C1: 0 Total: 0	I1: 0.7 C1: 0.7	I1: 1.3 I2 : 4.1 C1: 2.8 Total: 2.7	I1: 5.55 C1: 0	I1: 1.2 C1: 2.1
[n] hospitalisation	0	0	0	1 (pneumococcal pneumonia)	0	0	0	0
[%] hospitalisation	0	0	0	4.5	0	0	0	0

(Continued)

[n] out-patient treatment	?	?	?	?	?	?	?	?
[%] out-patient treatment	?	?	?	?	?	?	?	?
[n] hypoglycaemic episodes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
[n] cardiovascular events	I1: 0/110 C1: 0/109	I1: 0/44 C1: 0/48	I1+2: 0/296 C1: 0/143	I1+2: 0/42 C1: 0/21	I1: 0/136 C1: 0/132	I1+2: 0/145 C1: 0/71	I1: 10/144 C1: 0/138 Total: 10/282	I1: 0/95 C1: 0/93
[n] flushing	I1: 16/110 C1: 0/109	I1: 4/44 C1: 0/48	I1+2: 28/296 C1: 1/143	I1+2: 0/42 C1: 0/21	I1: 6/136 C1: 0/132	I1+2: 5/145 C1: 0/71	I1: 27/144 C1: 0/138	I1: 17/95 C1: 3/93
[n] headache	I1: 20/110 C1: 4/109	I1: 5/44 C1: 0/48	I1+2: 36/296 C1: 10/143	I1+2: 4/42 C1: 0/21	I1: 15/136 C1: 2/132	I1+2: 13/145 C1: 2/71	I1: 29/144 C1: 3/138	I1: 19/95 C1: 7/93
[n] myalgia	I1: 16/110 C1: 0/109	I1: 0/44 C1: 0/48	I1+2: 0/296 C1: 0/143	I1+2: 3/42 C1: 2/21	I1: 0/136 C1: 0/132	I1+2: 7/145 C1: 1/71	I1: 0/144 C1: 0/138	I1: 0/95 C1: 0/93
[n] dyspepsia	I1: 2/110 C1: 1/109	I1: 0/44 C1: 0/48	I1+2: 0/296 C1: 0/143	I1+2: 5/42 C1: 0/21	I1: 12/136 C1: 0/132	I1+2: 16/145 C1: 0/71	I1: 0/144 C1: 0/138	I1: 8/95 C1: 1/93
[n] Upper respiratory tract complaints / flu syndrome	I1: 0/110 C1: 0/109	I1: 0/44 C1: 0/48	I1+2: 34/296 C1: 7/143	I1+2: 0/42 C1: 0/21	I1: 13/136 C1: 2/132	I1+2: 6/145 C1: 3/71	I1: 22/144 C1: 3/138	I1: 0/95 C1: 0/93
[n] back pain	I1: 0/110 C1: 0/109	I1: 0/44 C1: 0/48	I1+2: 0/296 C1: 0/143	I1+2: 0/42 C1: 0/21	I1: 0/136 C1: 0/132	I1+2: 5/145 C1: 1/71	I1: 0/144 C1: 0/138	I1: 0/95 C1: 0/93
[n] nausea	I1: 0/110 C1: 0/109	I1: 0/44 C1: 0/48	I1+2: 0/296 C1: 0/143	I1+2: 2/42 C1: 1/21	I1: 0/136 C1: 0/132	I1+2: 0/145 C1: 0/71	I1: 0/144 C1: 0/138	I1: 0/95 C1: 0/93
[n] abnormal vision	I1: 5/110 C1: 0/109	I1: 0/44 C1: 0/48	I1+2: 0/296 C1: 0/143	I1+2: 0/42 C1: 0/21	I1: 5/136 C1: 1/132	I1+2: 0/145 C1: 0/71	I1: 0/144 C1: 0/138	I1: 2/95 C1: 2/93
Notes		Description of adverse event lacking				Two myocardial infarctios- one in the placebo and one in tadalafil but before taking the study drug		

(Continued)

Symbols & abbreviations: Y = yes; N = no; ? = unclear
I = intervention; C = control

Appendix 7. Outcome data

Characteristic	Boulton 2001	Escobar-Jimenez 2002	Goldstein 2003	Price 1998	Rendell 1999	Saenz de Tejada 2002	Safarinejad 2004	Stuckey 2003
Intervention 1 (I1) / intervention 2 (I2) / control 1 (C1)	I1: Sildenafil 25-100mg C1: Placebo	I1: Sildenafil 25-100mg C1: Placebo	I1: Vardenafil 10mg I2: Vardenafil 20mg C1: Placebo	I1: Sildenafil 25 mg I2: Sildenafil 50 mg C1: Placebo	I1: Sildenafil 25-100mg C1: Placebo	I1: Tadalafil 10mg I2: Tadalafil 20mg C1: Placebo	I1: Sildenafil 100mg C1: Placebo	I1: Sildenafil 25-100mg C1: Placebo
All-cause mortality: [n] of participants who died	0	0	0	0	0	0	0	0
IIEF Q3 (final)	I1: 3.42 (0.23) C1: 1.86 (0.22)	I1: 3 C1: 1.7			I1: 3.2 C1: 2		I1: 2.8 C1: 2.2	I1: 3.6 C1: 2.7
IIEF Q4 (final)	I1: 3.35 (0.24) C1: 1.84 (0.23)	I1: 2.6 C1: 1.6			I1: 2.9 C1: 1.6		I1: 2.9 C1: 2	I1: 3.2 C1: 2.1
IIEF EF Domain (final)	I1: 20.4 (1.24) C1: 11.5 (1.17)	I1: 17.4 C1: 10.5	I1: 17.1 I2: 19 C1: 12.6		I1: 17.5 C1: 10.4	I1 delta: 6.4 I2 delta: 7.3 C1 delta: 0.1	I1: 16.8 C1: 11.4	I1: 20 C1: 14
IIEF Domains (final)		I1: 47.4 C1: 34.4			I1: 47.5 C1: 35.2		I1: 46.2 C1: 36.1	
GEQ (% answering yes)	I1: 65% C1: 10%	I1: 46.3% C1: 14.9%	I1: 57% I2: 72% C1: 13%		I1: 56% C1: 10%	I1: 56% I2: 64% C1: 25%	I1: 50% C1: 10%	I1: 51% C1: 32%
% successful attempts	I1: 58.8 (48-69) C1: 14.4 (8.6-23)		I1: 46% I2: 53% C1: 20%		I1: 48% C1: 12%			I1: 65% C1: 39%
SEP 2 (mean success rate [%])			I1: 61% I2: 64% C1: 36%			I1 delta: 22.2 I2 delta: 22.6 C1 delta: -4.1		
SEP 3 (mean success rate [%])			I1: 49% I2: 54% C1: 23%			I1 delta: 28.4 I2 delta: 29.1 C1 delta: 1.9		

(Continued)

Mean duration of penile base regidity > 60% [min]	I1: 5 I2: 10.1 C1: 2.8
Mean duration of penile tip regidity > 60% [min]	I1: 1.2 I2: 2.2 C1: 0.4
Adjusted geometric mean number of erection per week	I1: 1.3 I2: 1.6 C1: 0.6
Notes	
Symbols & abbreviations: Y = yes; N = no; ? = unclear I = intervention; C = control	

WHAT'S NEW

Date	Event	Description
5 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MOSHE VARDI: Protocol writing, data search and extraction, quality assessment, data analysis and review production.

ASSAF NINI: Protocol writing, data search and extraction, quality assessment and review production.

DECLARATIONS OF INTEREST

None known.

NOTES

Responsibility for this review has been taken over by Thomas Rotthoff, Germany.

INDEX TERMS

Medical Subject Headings (MeSH)

3',5'-Cyclic-GMP Phosphodiesterases [*antagonists & inhibitors]; Carbolines [adverse effects] [therapeutic use]; Cyclic Nucleotide Phosphodiesterases, Type 5; Diabetic Angiopathies [*drug therapy]; Erectile Dysfunction [*drug therapy]; Imidazoles [adverse effects] [therapeutic use]; Phosphodiesterase Inhibitors [adverse effects] [*therapeutic use]; Piperazines [adverse effects] [therapeutic use]; Purines [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Sildenafil Citrate; Sulfones [adverse effects] [therapeutic use]; Tadalafil; Triazines [adverse effects] [therapeutic use]; Vardenafil Dihydrochloride

MeSH check words

Humans; Male