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Erectile dysfunction

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ABSTRACT

INTRODUCTION: Erectile dysfunction may affect 30% to 50% of men aged 40 to 70 years, with age, smoking, and obesity being the main risk factors, although 20% of cases have psychological causes. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of phosphodiesterase inhibitors in men with erectile dysfunction of any cause? What are the effects of phosphodiesterase inhibitors on erectile dysfunction in men with diabetes, with cardiovascular disease, with spinal cord injury, and with prostate cancer or undergoing prostatectomy? What are the effects of drug treatments other than phosphodiesterase inhibitors in men with erectile dysfunction of any cause? What are the effects of devices, psychological/behavioural treatments, and alternative treatments in men with erectile dysfunction of any cause? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 81 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: alprostadil (intracavernosal, intraurethral, topical), cognitive behavioural therapy, ginseng, papaverine, papaverine plus phentolamine (bimix), papaverine plus phentolamine plus alprostadil (trimix), penile prostheses, phosphodiesterase inhibitors (sildenafil, tadalafil, vardenafil), psychosexual counselling, vacuum devices, and yohimbine.

QUESTIONS

INTERVENTIONS

PHOSPHODIESTERASE INHIBITORS FOR ERECTILE DYSFUNCTION OF ANY CAUSE

Beneficial

PHOSPHODIESTERASE INHIBITORS IN MEN WITH DIABETES

Beneficial

Likely to be beneficial

PHOSPHODIESTERASE INHIBITORS IN MEN WITH CARDIOVASCULAR DISEASE

Beneficial

Unknown effectiveness

PHOSPHODIESTERASE INHIBITORS IN MEN WITH SPINAL CORD INJURY

Likely to be beneficial

Unknown effectiveness

Footnote

*Categorisation based on consensus; RCTs unlikely to be conducted.

Key points

- Erectile dysfunction may affect 30% to 50% of men aged 40 to 70 years, with age, smoking, and obesity being the main risk factors, although 20% of cases have psychological causes.
- Sildenafil improves erections and increases the likelihood of successful intercourse in men with erectile dysfunction (any cause) and in specific populations of men with erectile dysfunction and diabetes mellitus, heart disease, spinal cord injury, prostate cancer, or after radical prostatectomy.

  Tadalafil and vardenafil also improve erections in men with erectile dysfunction (any cause). They are also effective in specific populations of men with erectile dysfunction, for example in those with diabetes, or in men with prostate cancer or after radical prostatectomy; however, fewer studies were found than with sildenafil, and no high-quality evidence was found in other specific populations such as in men with cardiovascular disease.
- CAUTION: sildenafil, tadalafil, and vardenafil are contraindicated in men who are taking nitrates, as combined treatment has been associated with severe hypotension and death.
- Intracavernosal, intraurethral, and topical alprostadil improve erections compared with placebo, but can cause penile pain in up to 40% of men.

  Intracavernosal alprostadil may improve erections compared with intraurethral alprostadil and intracavernosal papaverine.

  Intracavernosal alprostadil may be as effective as sildenafil and bimix.

Adding phentolamine to intracavernosal papaverine (bimix) may increase effectiveness compared with papaverine alone, and adding alprostadil to bimix (trimix) may be more effective again. However, papaverine injections may cause altered liver function, and penile bruising and fibrosis.

- Ginseng and yohimbine may increase successful erections and intercourse compared with placebo.
- Vacuum devices may be as effective as intracavernosal papaverine, phentolamine, and alprostadil (trimix) at increasing rigidity, but less effective for orgasm, and may block ejaculation.

There is consensus that penile prostheses may be beneficial, but they can cause infections and are only used if less invasive treatments have failed.

- Psychosexual counselling and cognitive behavioural therapy may improve sexual functioning in men with psychological erectile dysfunction, but we found few good-quality studies. Several studies have demonstrated benefit of combination therapy (i.e., sex therapy and sildenafil or sex therapy and vacuum erection device) compared with monotherapy without sex therapy.

DEFINITION

Erectile dysfunction is defined as the persistent inability to obtain or maintain sufficient rigidity of the penis to allow satisfactory sexual performance. The term erectile dysfunction has largely replaced the term "impotence". For the purposes of this review we included only men with normal testosterone and gonadotrophin levels, who could gain an erection while asleep. We also included men with comorbid conditions such as cardiovascular disorders, prostate cancer, diabetes, and spinal cord injury. We excluded men with drug-induced sexual dysfunction. Because the cause of erectile dysfunction in men with cardiovascular disease is unclear (the disease or treatment drugs), we included them.

INCIDENCE/ PREVALENCE

Cross-sectional epidemiological studies from around the world [1] [2] [3] [4] reveal that 30% to 50% of men aged 40 to 70 years report some degree of erectile dysfunction. About 150 million men worldwide are unable to achieve and maintain an erection adequate for satisfactory sexual intercourse. [1] Age is the variable most strongly associated with erectile dysfunction; between the ages of 40 to 70 years, the incidence of moderate erectile dysfunction doubles from 17% to 34%, whereas that of severe erectile dysfunction triples from 5% to 15%. [4]

AETIOLOGY/ RISK FACTORS

About 80% of cases are believed to have an organic cause, the rest being psychogenic in origin. Most cases of erectile dysfunction are believed to be multifactorial and secondary to disease, stress, trauma (such as spinal cord injury, pelvic and prostate surgery), or drug adverse effects that interfere with the coordinated psychological, neurological, endocrine, vascular, and muscular factors necessary for normal erections. Risk factors include increasing age, smoking, obesity, and sedentary lifestyle. The prevalence of erectile dysfunction also increases in people with diabetes mellitus, hypertension, heart disease, anxiety, and depression. [5]

PROGNOSIS

We found no good evidence on prognosis in untreated organic erectile dysfunction.

AIMS OF INTERVENTION

To restore satisfactory erections, with minimal adverse effects of treatment.

OUTCOMES

Improvement in sexual function: self and partner reports of satisfaction and sexual function, objective tests of penile rigidity, time to take effect, duration of effect, ease of usage; **quality of life**; and **adverse effects** of treatment.

METHODS

Clinical Evidence search and appraisal August 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to August 2009, Embase 1980 to August 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 3 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We excluded studies in which <80% of participants had normal hormone levels. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to

summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 36). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of phosphodiesterase inhibitors in men with erectile dysfunction of any cause?**

OPTION **SILDENAFIL IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE**

Improvement in sexual function
Compared with placebo Sildenafil is more effective at improving erectile function, assessed by the proportion of men who reported successful intercourse and improved erections or by validated rating scales such as the International Index of Erectile Function (IIEF), in men with erectile dysfunction of any cause (high-quality evidence).

Note
Sildenafil has been associated with headache, flushing, visual disturbances, and dyspepsia. Sildenafil is contraindicated in men using oral nitrates concomitantly, in whom deaths have been reported.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Sildenafil versus placebo in men with erectile dysfunction of any cause:
We found two systematic reviews (search date 2000, 27 RCTs; [6] and search date 2004, 5 RCTs [7]). The reviews identified three RCTs in common; however, they applied different inclusion criteria (the first review included RCTs that assessed flexible or fixed-dose regimens of sildenafil, whereas the second review only included RCTs that assessed a fixed high-dose regimen of sildenafil and also reported on the outcome of International Index of Erectile Function [IIEF]), and they performed different meta-analyses, so we have included both here. We found 13 additional RCTs [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] and three subsequent RCTs. [21] [22] [23]

The first systematic review found that, compared with placebo, flexible "as needed" dosing of sildenafil significantly increased the proportion of men who experienced at least one episode of successful intercourse (14 RCTs, 2283 men with any cause of erectile dysfunction; at least 1 episode of successful intercourse in 4 weeks preceding end of treatment assessment: 83% with sildenafil *v* 45% with placebo; RR 1.8, 95% CI 1.7 to 1.9). [6] In trials that evaluated fixed doses of sildenafil (7 RCTs), efficacy in treatment responders was slightly higher on higher doses (50–100 mg) compared with doses <25 mg (successful sexual intercourse, mean percentage of attempts/person: 43% with sildenafil 25 mg *v* 17% with placebo; WMD 26, 95% CI 18 to 35; 50% with sildenafil 50 mg *v* 14% with placebo; WMD 36, 95% CI 30 to 42; 51% with sildenafil 100 mg *v* 14% with placebo; WMD 36, 95% CI 31 to 42).

The second systematic review found that fixed doses of sildenafil significantly improved erectile function, assessed using IIEF-erectile function (IIEF-EF) domain, over 4 to 12 weeks compared with placebo (3 RCTs, 998 men; IIEF-EF score [range 1–30]: WMD 9.65, 95% CI 8.50 to 10.79). [7]

The 13 additional RCTs [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] all found that sildenafil significantly improved sexual function compared with placebo.

The first subsequent RCT (209 men with erectile dysfunction, IIEF-EF score <25) found that sildenafil citrate (flexible dose 50 mg or 100 mg, as needed) significantly improved the primary outcomes of erectile function and intercourse satisfaction (assessed by change in scores in IIEF-EF domain, and IIEF-intercourse satisfaction domain) compared with placebo after 10 weeks (IIEF-EF: change in score from baseline [scale 1 to 30, higher score indicates greater improvement]: +8.0 with sildenafil *v* +2.2 with placebo; P <0.0001; IIEF-intercourse satisfaction: change in score from baseline [scale 0 to 15, higher score indicates greater improvement]: +3.4 with sildenafil *v* +1.9 with placebo; P <0.05). [21]

The second subsequent RCT (180 men with erectile dysfunction and their female partners) found that sildenafil (flexible dose 25 mg, 50 mg, and 100 mg) significantly improved erectile function and satisfaction with sexual intercourse, assessed by IIEF-EF and intercourse satisfaction domains,

after 12 weeks compared with placebo (change in IIEF-EF score from baseline [scale 1−30, higher number indicates greater improvement]: +8.9 with sildenafil *v* +3.4 with placebo; P <0.0001; change in IIEF-intercourse satisfaction score from baseline [scale 0−15, higher number indicates greater improvement]: +3.8 with sildenafil *v* +1.3 with placebo; P <0.0001). [22]

The third subsequent RCT (307 men with erectile dysfunction) found that sildenafil (flexible dose 25, 50, and 100 mg) significantly increased the proportion of successful erection responses per person (Erection Hardness Score of 3 or 4) and improved erectile function (assessed by IIEF) compared with placebo after 6 weeks (change in proportion of successful erection responses per person: 40% with sildenafil *v* 11% with placebo; P <0.0001; change in IIEF scores, all domains: P <0.0001; absolute numbers reported in RCT). [23]

Sildenafil versus tadalafil in men with erectile dysfunction of any cause:
See benefits of tadalafil in men with erectile dysfunction of any cause, p 6 .

Sildenafil versus intracavernosal alprostadil in men with erectile dysfunction of any cause:
We found one small RCT (54 men) comparing sildenafil versus intracavernosal alprostadil injections, written in Chinese. [24] It found no significant difference between sildenafil and alprostadil injections in efficacy over 4 to 9 months. However, we are awaiting full-text translation of this RCT, and will assess it for inclusion at the next update.

Harms:

Sildenafil versus placebo in men with erectile dysfunction of any cause:
The first systematic review found that in a subset of 14 flexible dose trials (3780 men), sildenafil significantly increased the risk of at least one adverse effect compared with placebo (3780 men with any cause of erectile dysfunction; AR: 48% with sildenafil *v* 36% with placebo; RR 1.4, 95% CI 1.3 to 1.6). [6] Adverse effects included headache, flushing, dyspepsia, and visual disturbance (headache: 11% with sildenafil *v* 4% with placebo; RR 2.6, 95% CI 1.8 to 3.7; flushing: 12% with sildenafil *v* 2% with placebo; RR 5.8, 95% CI 3.4 to 10; dyspepsia: 5% with sildenafil *v* 1% with placebo; RR 3.8, 95% CI 2.2 to 6.6; visual disturbance: 3.0% with sildenafil *v* 0.8% with placebo; RR 3.1, 95% CI 1.8 to 5.4). Similar proportions of those allocated to sildenafil or placebo discontinued treatment because of adverse effects (1.3% with sildenafil *v* 1.2% with placebo; RR 1.3, 95% CI 0.7 to 2.3). [6] The data from fixed-dose trials in this systematic review indicate that all these adverse effects were more frequent at higher doses of sildenafil and were mild to moderate in severity. [6]

The second systematic review did not report on adverse effects of sildenafil. [7]

One additional RCT (236 men with any cause of erectile dysfunction) found that sildenafil was associated with facial flushing (25.2%), dizziness (6.7%), headache (5.9%), and palpitations (3.4%). [8] A second RCT found that headache, flushing, dyspepsia, and abnormal perception of colour or brightness were more common with sildenafil than with placebo (headache: 20% with sildenafil *v* 6% with placebo; flushing: 15% with sildenafil *v* 1% with placebo; dyspepsia: 15% with sildenafil *v* 0% with placebo; abnormal perception of colour or brightness: 8% with sildenafil *v* 1% with placebo; significance assessment not performed for any adverse effect). [11] Three other additional RCTs reported on harms and found similar results. [13] [16] [20]

The first subsequent RCT also found that the most commonly reported adverse effects in people receiving sildenafil were flushing, headache, nasal congestion, and dizziness (flushing: 15% with sildenafil *v* 2% with placebo; headache: 14% with sildenafil *v* 6% with placebo; nasal congestion: 5% with sildenafil *v* 2% with placebo; dizziness: 3% with sildenafil *v* 0% with placebo; absolute numbers or significance assessment not reported). [21] The second and third subsequent RCTs similarly found that the most commonly reported adverse effects with sildenafil were headache, vasodilation, and rhinitis (significance assessment not reported). [22] [23]

Sildenafil versus tadalafil in men with erectile dysfunction of any cause:
See harms of tadalafil in men with erectile dysfunction of any cause, p 6 .

Sildenafil versus intracavernosal alprostadil in men with erectile dysfunction of any cause:
We found one small RCT (54 men) comparing sildenafil versus intracavernosal alprostadil injections, written in Chinese. [24] However, we are awaiting full-text translation of this RCT, and will assess it for inclusion at the next update.

Comment:

The first review commented that many of the included RCTs did not describe the procedure used to generate the randomisation sequence or conceal allocation of treatment assignment. [6] This may reflect inadequate reporting or inadequate randomisation. Trials with improper randomisation, especially those with poor concealment of allocation to treatment assignments, have been shown to overestimate treatment effects.

OPTION TADALAFIL IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function

Compared with placebo in men with erectile dysfunction of any cause Tadalafil is more effective at improving erections and successful sexual intercourse, assessed by validated rating scales such as the International Index of Erectile Function (IIEF), and response to Sexual Encounter Profile (SEP) question 2 or question 3, in men with erectile dysfunction of any cause (high-quality evidence).

Note

Tadalafil has been associated with headache, muscle pain, back ache, dyspepsia, and flushing. Tadalafil is contraindicated in people receiving nitrates concomitantly because of the risk of potentially life-threatening hypotension.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Tadalafil versus placebo in men with erectile dysfunction of any cause:

We found two systematic reviews (search date 2003, 11 RCTs, 2102 men, see comment below; [25] and search date 2004, 8 RCTs [7]). The reviews included at least two RCTs in common; however, they applied different inclusion criteria (the first review included RCTs that assessed tadalafil fixed-dose regimens of 10 mg or 20 mg [taken as needed], whereas the second review included RCTs that assessed tadalafil fixed high-dose regimens of 20 mg or 25 mg [taken as needed] and also reported on the outcome of International Index of Erectile Function [IIEF]), and they performed different meta-analyses, so we have included both here. We found one additional [26] and 8 subsequent RCTs [27] [28] [29] [30] [31] [32] [33] [34] that compared tadalafil with placebo.

The first systematic review compared tadalafil 10 mg, tadalafil 20 mg, or placebo over 12 weeks. [25] It found that tadalafil (both doses) significantly improved erectile function, assessed using IIEF-erectile function (IIEF-EF) domain compared with placebo (2036 men; mean change in IIEF-EF domain score: 6.5 with tadalafil 10 mg *v* 8.6 with tadalafil 20 mg *v* 0.9 with placebo; P <0.001 for both doses of tadalafil *v* placebo). It found that both doses of tadalafil significantly increased the proportion of sexual attempts leading to intercourse completion, as assessed by the Sexual Encounter Profile (SEP) question 3 (SEP Q3; 2055 men; mean change from baseline [range: 22–24%] for intercourse completion: 34% with tadalafil 10 mg *v* 46% with tadalafil 20 mg *v* 8% with placebo; P <0.001 for both doses *v* placebo). [25] Both doses of tadalafil also significantly improved erections compared with placebo, as assessed by the Global Assessment Questionnaire (2055 men; proportion reporting improved erections: 71% with tadalafil 10 mg *v* 84% with tadalafil 20 mg *v* 33% with placebo; P <0.001 for both doses of tadalafil *v* placebo). [25]

The second systematic review found that fixed doses of tadalafil significantly improved erectile function, assessed by IIEF-EF score, over 3 to 12 weeks compared with placebo (8 RCTs, 1587 men; IIEF-EF score [range 1–30]: WMD 8.52, 95% CI 7.61 to 9.42). [7]

The additional RCT (348 men with various causes of erectile dysfunction) compared tadalafil 20 mg with placebo taken 24 or 36 hours before sexual intercourse. [26] Tadalafil significantly increased the proportion of successful intercourse attempts compared with placebo at both 24 and 36 hours (348 men; proportion of successful intercourse attempts at 24 hours: 120/227 [53%] with tadalafil *v* 72/247 [29%] with placebo; at 36 hours: 132/223 [59%] with tadalafil *v* 60/212 [28%] with placebo; P <0.001 for both time periods *v* placebo). [26]

The first subsequent RCT (207 men with erectile dysfunction, conducted in the US and Puerto Rico) compared tadalafil 20 mg taken as needed over 12 weeks (159 men) with placebo (48 men). [27] Tadalafil significantly improved successful erection and sexual intercourse scores compared with placebo, as assessed by SEP Q2 and SEP Q3 (mean change from SEP Q2 penetration baseline score [range: 40.5–45.2%]: +31.6 with tadalafil *v* +2.3 with placebo; P <0.0001; mean change from SEP Q3 intercourse baseline score [range: 19.1–20.7%]: 43.6 with tadalafil *v* 3.5 with placebo; P <0.0001). [27]

The second subsequent RCT (342 men with erectile dysfunction and their female partners, conducted in Austria, France, Germany, Mexico, and the US) compared tadalafil 5 mg taken once daily (264 men) versus placebo (78 men) for 12 weeks. [28] It found that tadalafil significantly improved erectile function, assessed by IIEF-EF, and successful erection and sexual intercourse scores, as assessed by SEP Q2 and SEP Q3, after 12 weeks compared with placebo (change in IIEF-EF from baseline: 7.9 with tadalafil *v* 0.7 with placebo; P <0.001; SEP Q2: 28.6% with tadalafil *v* 2.7% with placebo; P <0.001; SEP Q3: 46.0% with tadalafil *v* 10.8% with placebo; P <0.001). It also found that tadalafil significantly improved sexual quality of life of men and their partners, as assessed by the Sexual Quality of Life (SQoL) domain of the Sexual Life Quality Questionnaire (SLQQ) (change in SQoL scores from baseline: men: 39.5 with tadalafil *v* 12.5 with placebo; P <0.001; female partners: 32.4 with tadalafil *v* 5.0 with placebo; P <0.001). [28]

The third subsequent RCT (121 Korean men with erectile dysfunction) compared tadalafil 20 mg taken as needed over 12 weeks (80 men) with placebo (41 men). [29] It found that tadalafil significantly improved erectile function, assessed by IIEF-EF, and successful erection and sexual intercourse scores, as assessed by SEP Q2 and SEP Q3, compared with placebo (mean change in IIEF-EF from baseline: 7.8 with tadalafil *v* 0.1 with placebo; P <0.001; mean per-person percentage change in SEP Q2 successful penetration: 17.1% with tadalafil *v* 0.5% with placebo; P <0.001; mean per-person percentage change in SEP Q3 successful intercourse: 53.6% with tadalafil *v* 10.1% with placebo; P <0.001). [29]

The fourth subsequent RCT (367 Southeast Asian men with erectile dysfunction) was a three-armed trial comparing tadalafil 20 mg versus tadalafil 10 mg versus placebo, taken as needed over 12 weeks. [30] Tadalafil significantly improved erectile function, assessed by IIEF-EF, and successful erection and sexual intercourse scores, as assessed by SEP Q2 and SEP Q3, compared with placebo (mean change in IIEF-EF from baseline: 8.1 with tadalafil 10 mg *v* 8.7 with tadalafil 20 mg *v* 2.4 with placebo; P <0.001 [either tadalafil dose *v* placebo]; mean change in SEP Q2 successful penetration: 33.5% with tadalafil 10 mg *v* 34.8% with tadalafil 20 mg *v* 7.7% with placebo; P <0.001 [either tadalafil dose *v* placebo]; mean change in SEP Q3 maintained erection: 50.0% with tadalafil 10 mg *v* 56.4% with tadalafil 20 mg *v* 18.3% with placebo; P <0.001 [either tadalafil dose *v* placebo]). [30]

The fifth subsequent RCT (343 Japanese men with erectile dysfunction) was a 4-armed trial comparing tadalafil 20 mg versus tadalafil 10 mg versus tadalafil 5 mg versus placebo, taken as needed over 12 weeks. [31] Tadalafil (at all doses) significantly improved erectile function, assessed by IIEF-EF, and successful erection and sexual intercourse scores, as assessed by SEP Q2 and SEP Q3, at 12 weeks compared with placebo (mean IIEF-EF score: 21.0 with tadalafil 5 mg *v* 23.2 with tadalafil 10 mg *v* 23.5 with tadalafil 20 mg *v* 16.0 with placebo; P <0.001 [all tadalafil doses *v* placebo]; mean per-person percentage SEP Q2 successful penetration: 71.2% with tadalafil 5 mg *v* 81.3% with tadalafil 10 mg *v* 84.1% with tadalafil 20 mg *v* 53.6% with placebo; P <0.001 [all tadalafil doses *v* placebo]; mean per-person percentage SEP Q3 maintained erection: 51.7% with tadalafil 5 mg *v* 64.6% with tadalafil 10 mg *v* 69.4% with tadalafil 20 mg *v* 27.8% with placebo; P <0.001 [all tadalafil doses *v* placebo]). [31]

The sixth subsequent RCT (132 men with erectile dysfunction, conducted in Turkey and Egypt) compared tadalafil 20 mg (101 men) versus placebo (31 men), taken as needed over 12 weeks. [32] It found that tadalafil significantly improved erectile function, assessed by IIEF-EF, and successful erection and sexual intercourse scores, as assessed by SEP Q2 and SEP Q3, at 12 weeks compared with placebo (mean change in IIEF-EF score from baseline: 9.3 with tadalafil *v* 2.3 with placebo; P <0.001; mean change in per-person percentage SEP Q2 successful penetration: +34.5% with tadalafil *v* –4.6% with placebo; P <0.001; mean change in per-person percentage SEP Q3 maintained erection: 52.2% with tadalafil *v* 16.8% with placebo; P <0.001). [32]

The seventh subsequent RCT (242 East and Southeast Asian men with erectile dysfunction) compared tadalafil 20 mg (154 men) versus placebo (83 men), taken as needed over 12 weeks. [33] It found that tadalafil significantly improved erectile function, assessed by IIEF-EF, and successful erection and sexual intercourse scores, as assessed by SEP Q2 and SEP Q3, at 12 weeks compared with placebo (mean change in IIEF-EF score from baseline: 8.5 with tadalafil *v* 2.1 with placebo; P <0.001; mean change in per-person percentage SEP Q2 successful penetration: +30.1% with tadalafil *v* –1.2% with placebo; P <0.001; mean change in per-person percentage SEP Q3 maintained erection: 46.7% with tadalafil *v* 8.9% with placebo; P <0.001). [33]

The eighth subsequent RCT (196 men with erectile dysfunction, conducted in Taiwan) was a three-armed trial comparing tadalafil 20 mg versus tadalafil 10 mg versus placebo, taken as needed over 12 weeks. [34] Tadalafil significantly improved erectile function, assessed by IIEF-EF, and successful erection and sexual intercourse scores, as assessed by SEP Q2 and SEP Q3, compared with placebo (mean change in IIEF-EF from baseline: 8.1 with tadalafil 10 mg *v* 8.0 with tadalafil 20 mg *v* 2.6 with placebo; P <0.001 [either tadalafil dose *v* placebo]; mean change in SEP Q2 successful penetration: 34.5% with tadalafil 10 mg *v* 35.3% with tadalafil 20 mg *v* 9.5% with placebo; P <0.001 [either tadalafil dose *v* placebo]; mean change in SEP Q3 maintained erection: 47.9% with tadalafil 10 mg *v* 49.7% with tadalafil 20 mg *v* 14.7% with placebo; P <0.001 [either tadalafil dose *v* placebo]). [34]

Tadalafil versus sildenafil in men with erectile dysfunction of any cause:
We found one RCT (215 men aged 18–65 years, minimum 3 months of erectile dysfunction, no previous use of tadalafil, 15.3% had received an inadequate trial of sildenafil 50 mg) that evaluated patient preference for either tadalafil or sildenafil in a double-blind crossover trial. [35] The RCT compared tadalafil 20 mg versus sildenafil 50 mg as needed for 4 weeks, and after 1 to 2 weeks of drug washout crossed them over to the alternative treatment for 4 weeks. It did not present any

data on the outcome of improvement of erectile or sexual function; however, it reported on men's preference for treatment with either drug. Of 190/215 (88%) men who expressed a preference, a significantly higher proportion preferred tadalafil (AR: 126/190 [66%] for tadalafil 20 mg *v* 64/190 [34%] for sildenafil 50 mg; P <0.001). [35]

Harms:

Tadalafil versus placebo in men with erectile dysfunction of any cause:
The integrated results of 11 RCTs suggested that a higher proportion of men treated with tadalafil experienced one or more adverse effects compared with placebo (AR: 58% with tadalafil 10 mg *v* 51% with tadalafil 20 mg *v* 39% with placebo; significance assessment not performed). [25] Although absolute numbers were few, significantly more men withdrew because of adverse effects with tadalafil than with placebo (AR: 5/321 [1.6%] with tadalafil 10 mg *v* 36/1143 [3.2%] with tadalafil 20 mg *v* 8/638 [1.3%] with placebo; P = 0.026). Adverse effects included headache, dyspepsia, back pain, nasopharyngitis, myalgia, flushing, nasal congestion, and limb pain. [25]

The second systematic review did not report on adverse effects of tadalafil. [7]

The additional and first subsequent RCTs found that more men taking tadalafil withdrew because of adverse effects compared with placebo. [26] [27] Chest pain requiring admission to hospital occurred in 2/207 (1%) men taking tadalafil 20 mg. [27] The second subsequent RCT found that the most frequently reported adverse effects with tadalafil were headache, followed by dyspepsia and nasal congestion (headache: 22/264 [8%] with tadalafil *v* 3/78 [4%] with placebo; significance assessment not performed). However, it found no significant difference in the total incidence of adverse effects between tadalafil and placebo. [28] The third subsequent RCT found no significant difference between groups in the most frequently reported adverse effects of headache, flushing, or eye pain (headache: 13/80 [16%] with tadalafil *v* 2/41 [5%] with placebo; P = 0.086). [29] The fourth subsequent RCT found that the most common adverse effects with tadalafil were headache, followed by back pain, dizziness, and dyspepsia (headache: 6/120 [5%] with tadalafil 10 mg *v* 6/125 [5%] with tadalafil 20 mg *v* 1/122 [1%] with placebo; significance assessment not reported). [30] The fifth subsequent RCT found that the most common treatment-emergent adverse effects with tadalafil were headache, followed by nasopharyngitis and flushing (headache: 5/85 [6%] with tadalafil 5 mg *v* 10/86 [12%] with tadalafil 10 mg *v* 16/86 [19%] with tadalafil 20 mg *v* 5/86 [6%] with placebo; significance assessment not reported). [31] The sixth subsequent RCT found that the most common treatment-emergent adverse effects with tadalafil were headache, followed by back pain and dyspepsia (headache: 17% with tadalafil *v* 10% with placebo; absolute results and significance assessment not reported). [32] The seventh subsequent RCT found that the most common treatment-emergent adverse effects with tadalafil were headache, followed by back pain, dizziness, dyspepsia, and myalgia; however, only headache was significantly more common with tadalafil compared with placebo (headache: 18/159 [11%] with tadalafil *v* 2/83 [2%] with placebo; P = 0.024). [33] The eighth subsequent RCT found that the most common treatment-emergent adverse effects with tadalafil were back pain, followed by dyspepsia and myalgia (back pain: 7/65 [11%] with tadalafil 10 mg *v* 5/65 [8%] with tadalafil 20 mg *v* 2/66 [3%] with placebo; significance assessment not reported). [34]

Tadalafil versus sildenafil in men with erectile dysfunction of any cause:
In the RCT, the most frequently reported adverse event was headache (24/215 [11%] with tadalafil *v* 19/215 [9%] with sildenafil; significance assessment not performed). [35] Other adverse events included dyspepsia, nasopharyngitis, flushing, myalgia, and nasal congestion. [35]

Comment:

The included trials in the first systematic review were clinically heterogeneous in aetiology of erectile dysfunction and age, and lacked homogeneous study design or outcome assessments. Statistical heterogeneity was not formally assessed. [25]

The trial comparing patient preference for tadalafil or sildenafil [35] was limited by the inclusion of people with prior experience with sildenafil.

We found no reports of visual adverse events with tadalafil.

Clinical guide:
Tadalafil provides greater flexibility in timing of sexual intercourse and requires no dietary restrictions compared with sildenafil that has a 4-hour window after dose and decreased efficacy with grapefruit juice or after a high-fat meal.

OPTION VARDENAFIL IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function
Compared with placebo in men with erectile dysfunction of any cause Vardenafil seems more effective at improving erections and successful sexual intercourse, assessed by validated rating scales such as the International Index of

Erectile Function (IIEF) and response to Sexual Encounter Profile (SEP) question 2 or question 3, in men with erectile dysfunction of any cause (moderate-quality evidence).

Note
Vardenafil has been associated with headache, flushing, and dyspepsia. Vardenafil is contraindicated in people receiving nitrates concomitantly because of the risk of potentially life-threatening hypotension.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Vardenafil versus placebo in men with erectile dysfunction of any cause:
We found two systematic reviews (search date 2002, 4 RCTs, 1448 men; [36] and search date 2004, 3 RCTs [7]). The first systematic review found two RCTs with clinical end points; however, it did not pool the data, and these two RCTs were also identified by the second systematic review and included in its meta-analysis, so we have included the results of the meta-analysis only. However, the first systematic review gave further information on adverse effects, which we have reported (see harms section). The second systematic review only included RCTs that assessed a fixed high-dose regimen of vardenafil and also reported on the outcome of International Index of Erectile Function (IIEF). We found 5 subsequent RCTs. [37] [38] [39] [40] [41]

The second systematic review found that fixed doses of vardenafil (20 mg) significantly improved erectile function, assessed by IIEF-erectile function (IIEF-EF) domain, compared with placebo, over 12 to 26 weeks (3 RCTs, 2251 men; IIEF-EF score [range 1–30]: WMD 7.50, 95% CI 6.50 to 8.50; absolute results not reported). [7]

The first subsequent RCT (323 men, mean age 54 years, 50–54% with previous sildenafil use) found that flexible doses of vardenafil significantly improved scores on the IIEF-EF compared with placebo (mean baseline IIEF-EF score 13, vardenafil 5–20 mg as desired for 8 weeks after initial 4 weeks of 10 mg; mean improvement in IIEF-EF score at 12 weeks: 3.2 with vardenafil *v* 1.9 with placebo; P <0.005). [37] Vardenafil also improved erections and successful sexual intercourse as assessed by questions 2 (Q2; penetration) and 3 (Q3; successful intercourse) of the Sexual Encounter Profile (SEP) diaries (mean per-person success with penetration at baseline: 38–39% with vardenafil *v* 44–48% with placebo; mean per-person success with successful intercourse at baseline: 14% with vardenafil *v* 18–20% with placebo; mean per-person success with penetration at week 4: 73% with vardenafil *v* 41% with placebo; week 8: 84% with vardenafil *v* 49% with placebo; week 12: 80% with vardenafil *v* 46% with placebo; P <0.001 for all comparisons with placebo; mean per-person success with intercourse at week 4: 58% with vardenafil *v* 22% with placebo; week 8: 71% with vardenafil *v* 31% with placebo; week 10: 74% with vardenafil *v* 34% with placebo; P <0.001 for all comparisons with placebo). [37]

The second subsequent RCT (395 men with erectile dysfunction and dyslipidaemia) compared on-demand, flexible-dose vardenafil 10 mg (titrated to 5 mg or 20 mg based upon efficacy and safety) versus placebo for 12 weeks. [38] It found that vardenafil significantly increased successful erections and sexual intercourse as assessed by SEP Q2 and Q3, and improved erectile function, assessed by IIEF-EF scales, after 12 weeks (SEP Q2 mean success rates: 79% with vardenafil *v* 52% with placebo; SEP Q3 mean success rates: 67% with vardenafil *v* 34% with placebo; P <0.001; IIEF-EF mean score [scale 0–30, normal EF defined as 25 or more]: 21.99 with vardenafil *v* 14.83 with placebo; P <0.001). [38]

The third subsequent RCT (crossover study, 201 men with erectile dysfunction) compared vardenafil (fixed-dose 10 mg) versus placebo. [39] The RCT consisted of two 4-week double-blind treatment periods, separated by a 1-week washout. It did not present results pre-crossover. It found that vardenafil significantly improved the primary outcome of duration of erection leading to successful intercourse, assessed by stopwatch and SEP Q3, compared with placebo after 4 weeks (159 men in analysis: mean duration of erection: 12.81 minutes with vardenafil *v* 5.45 minutes with placebo; P <0.001). It also found that vardenafil significantly improved secondary outcomes of success of insertion and maintenance of erection, assessed by SEP Q2 and Q3, improved erectile function, assessed by IIEF-EF scales, and response to Global Assessment Questionnaires after 4 weeks compared with placebo (absolute numbers reported in RCT; P <0.001). [39]

The fourth subsequent RCT (520 men with erectile dysfunction, and who responded to an initial challenge dose of vardenafil [10 mg], 509 men in intention-to-treat analysis) compared vardenafil 10 mg versus placebo for 12 weeks. [40] It found that vardenafil significantly improved reliability of penile insertion, assessed by SEP Q2, compared with placebo at the end of 12 weeks of treatment in all men regardless of comorbidity (SEP Q2 success rates: 83% with vardenafil *v* 56% with placebo; P = 0.001; absolute results not reported). It also found that vardenafil significantly improved IIEF scores (mean IIEF-EF score at 12 weeks: 23.46 with vardenafil *v* 15.81 with placebo; P <0.001). [40]

The fifth subsequent RCT (358 Asian men with erectile dysfunction) compared vardenafil 10 mg versus placebo for 12 weeks. [41] It found that vardenafil significantly improved IIEF-EF scores from baseline (mean IIEF-EF score at 12 weeks: 22.40 with vardenafil *v* 14.30 with placebo; P <0.001). It found that vardenafil significantly improved reliability of penile insertion (assessed by SEP Q2) and successful intercourse (assessed by SEP Q3) at the end of 12 weeks of treatment compared with placebo (SEP Q2 success rates: 82.2% with vardenafil *v* 43.6% with placebo; P = 0.001; SEP Q3 success rates: 66.1% with vardenafil *v* 24.0% with placebo; P = 0.001; absolute results not reported). [41]

Harms:

Vardenafil versus placebo in men with erectile dysfunction of any cause:
The first systematic review reported that adverse effects with vardenafil 5 mg to 40 mg were reported in 22% to 61% of people in 4 RCTs. In the largest RCT (762 men in safety analysis), headache was the most common reported adverse effect (10–21%) followed by rhinitis (9–17%), flushing (5–13%), and dyspepsia (1–6%). [36] The rates of adverse events with placebo were not reported in the systematic review. The review found that in one drug interaction trial in men with hypertension, the addition of vardenafil 20 mg to the vasodilator nifedipine did not result in clinically important changes in blood pressure (data not reported). [36] The same contraindications for concomitant nitrate use apply to vardenafil as with other phosphodiesterase-5 inhibitors.

The second review gave no information on adverse effects. [7]

The first subsequent RCT found that, compared with placebo, vardenafil significantly increased the proportion of men who experienced adverse effects (adverse effects reported: 14% with vardenafil 5 mg *v* 22% with vardenafil 10 mg *v* 11% with vardenafil 20 mg *v* 5% with placebo; significance assessment not performed). Overall, 45% of men with vardenafil experienced at least one treatment emergent adverse effect compared with 27% with placebo. Drug-related adverse effects reported by >2% of men included flushing, headache, rhinitis, dyspepsia, and dizziness (flushing: 18/157 [11%] with vardenafil *v* 0/164 [0%] with placebo; headache: 15/157 [10%] with vardenafil *v* 3/164 [2%] with placebo; rhinitis: 8/157 [5%] with vardenafil *v* 1/164 [1%] with placebo; dyspepsia: 4/157 [3%] with vardenafil *v* 0/164 [0%] with placebo; dizziness: 3/157 [2%] with vardenafil *v* 1/164 [1%] with placebo). [37]

The second subsequent RCT found that the two most common adverse effects with vardenafil were headache and nasal congestion (headache: 17/198 [9%] with vardenafil *v* 2/197 [1%] with placebo; nasal congestion: 9/198 [5%] with vardenafil *v* 6/197 [3%] with placebo; significance assessment not reported). [38]

The third subsequent RCT found the most common adverse effects with vardenafil treatment versus placebo were headache and flushing (headache: 5/187 [3%] with vardenafil *v* 4/184 [2%] with placebo; flushing: 10/187 [5%] with vardenafil *v* 5/184 [3%] with placebo; significance assessment not reported). [39]

The fourth subsequent RCT found that headache and flushing were the most common adverse effects reported with vardenafil. [40]

The fifth subsequent RCT found that adverse effects were reported more frequently with vardenafil compared with placebo (proportion of people with treatment-emergent adverse effects: 70/276 [25%] with vardenafil *v* 12/72 [17%] with placebo; significance assessment not reported). The most common adverse effects were headache, flushing, nasal congestion, and dizziness. [41]

Comment:

We did not find any comparisons of vardenafil with sildenafil, tadalafil, or other treatments for erectile dysfunction. We found no reports of visual adverse events with vardenafil.

We found another review (search/appraisal details not reported, 8 RCTs, 2427 men, 839 men with hypertension [42]), which identified many of the RCTs comparing flexible-dose vardenafil versus placebo in men with erectile dysfunction, included separately in this *Clinical Evidence* review; however, it pooled data on the subset of men with self-reported hypertension only from these studies. [42] It found that vardenafil significantly improved erectile function, assessed by IIEF-EF domain scores compared with placebo after 12 weeks in this subgroup. It also found that vardenafil significantly increased success rates, assessed by questions 2 and 3 on the Sexual Encounter Profile diaries, compared with placebo after 12 weeks. [42]

QUESTION **What are the effects of phosphodiesterase inhibitors on erectile dysfunction in men with diabetes?**

OPTION SILDENAFIL IN MEN WITH DIABETES

Improvement in sexual function

Compared with placebo in men with diabetes Sildenafil seems more effective at improving erections and at increasing successful intercourse, assessed by the proportion of men who experience successful intercourse and improved erections or by validated rating scales such as the International Index of Erectile Function (IIEF), in men with erectile dysfunction and diabetes (moderate-quality evidence).

Note

Sildenafil has been associated with headache, flushing, visual disturbances, and dyspepsia. Sildenafil is contraindicated in men using oral nitrates concomitantly, in whom deaths have been reported.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Sildenafil versus placebo in men with diabetes:

We found two systematic reviews (search date 2000, 2 RCTs in men with erectile dysfunction and diabetes, 14 RCTs that provided subgroup analysis in men with erectile dysfunction and diabetes; [6] and search date 2005, 6 RCTs in men with erectile dysfunction and diabetes [43]). The reviews applied different inclusion criteria, identified different studies, and presented different analyses (the first review presented a pooled analysis based on the subgroup of men with diabetes in RCTs in men with any cause of erectile dysfunction, whereas the second review only included RCTs conducted solely in men with diabetes).

The first systematic review found, based on subgroup analysis, that sildenafil significantly increased successful erections and successful intercourse compared with placebo (1019 men with diabetes; AR for erections: 63% with sildenafil *v* 19% with placebo; RR 3.0, 95% CI 2.5 to 3.7; 551 men with diabetes; AR for mean percentage of successful intercourse attempts: 44% with sildenafil *v* 16% with placebo; WMD 27, 95% CI 20 to 34). [6]

The second systematic review found that, compared with placebo, sildenafil (25–100 mg) significantly improved erectile function, assessed by the International Index of Erectile Function (IIEF), after 12 to 16 weeks (5 RCTs, 904 men; mean difference between groups in IIEF-erectile function score 7.08, 95% CI 5.31 to 8.86), and significantly increased the proportion of men with improved erections, assessed by response to a Global Efficacy Question, after 10 days to 16 weeks (6 RCTs; proportion of men with improved erections: 291/530 [55%] with sildenafil *v* 71/498 [14%] with placebo; OR 7.19, 95% CI 5.30 to 9.76). [43] However, the review found significant heterogeneity in the analysis of this outcome of global efficacy (I^2 = 75%; P = 0.001), which was not further explained.

Harms:

Sildenafil versus placebo in men with diabetes:

The first systematic review [6] did not report on adverse effects specifically in the population of people with diabetes (see harms of sildenafil in men with erectile dysfunction of any cause, p 4).

The second systematic review pooled data for the 6 RCTs comparing sildenafil versus placebo, and two RCTs comparing tadalafil or vardenafil versus placebo, and did not present separate analyses for adverse effects of sildenafil versus placebo. [43]

Comment:

The review commented that many of the included RCTs did not describe the procedure used to generate the randomisation sequence or conceal allocation of treatment assignment. [6]

OPTION TADALAFIL IN MEN WITH DIABETES

Improvement in sexual function

Compared with placebo in men with diabetes Tadalafil (taken as needed or daily) seems more effective at improving erections and sexual functioning, assessed by validated rating scales such as the International Index of Erectile Function (IIEF), and response to Sexual Encounter Profile (SEP) question 2 or question 3, in men with erectile dysfunction and diabetes (moderate-quality evidence).

Note

Tadalafil has been associated with headache, muscle pain, back ache, dyspepsia, and flushing. Tadalafil is contraindicated in people receiving nitrates because of the risk of potentially life-threatening hypotension.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Tadalafil versus placebo in men with diabetes:
We found one systematic review (search date 2005, 1 RCT [44]) [43] and one subsequent RCT [45] assessing the efficacy of tadalafil versus placebo in men with diabetes.

The RCT (216 men with type 1 or type 2 diabetes and a minimum 3-month history of erectile dysfunction), identified by the review, [43] compared tadalafil 10 mg versus 20 mg versus placebo taken up to once daily as needed without restrictions on food or alcohol intake for 12 weeks. [44] Both doses of tadalafil significantly improved erections and sexual functioning, as assessed by Index of Erectile Function (IIEF)-erectile function domain (mean change in IIEF-EF domain score: 6.4 with tadalafil 10 mg *v* 7.3 with tadalafil 20 mg *v* 0.1 with placebo; P <0.001 for both doses *v* placebo). For men taking concomitant antihypertensive medication, tadalafil 20 mg was associated with a better response than tadalafil 10 mg or placebo, assessed by IIEF-EF (mean change in IIEF-EF domain score: –1.8 with placebo *v* +3.9 with tadalafil 10 mg *v* +9.5 with tadalafil 20 mg; P value for tadalafil 10 mg *v* placebo significance assessment not performed; P <0.001 for tadalafil 20 mg *v* placebo), and Sexual Encounter Profile (SEP) question 2 (Q2; successful penetration) and question 3 (Q3; successful intercourse) (change from SEP Q2 penetration baseline score [range not reported]: +22.2% with tadalafil 10 mg *v* +30.6% with tadalafil 20 mg *v* –4.1% with placebo; P <0.001 for both doses *v* placebo; change from SEP Q3 intercourse baseline score [range not reported]: 28.4% with tadalafil 10 mg *v* 29.1% with tadalafil 20 mg *v* 1.9% with placebo; P <0.001 for both doses *v* placebo). [44]

The subsequent RCT (298 men with a minimum 3-month history of type 1 or type 2 diabetes and erectile dysfunction) compared once-daily treatment with placebo, tadalafil 2.5 mg, or tadalafil 5 mg for 12 weeks. [45] Both doses of tadalafil significantly improved IIEF-EF scores and mean success rates for vaginal penetration, completion of intercourse, and overall treatment satisfaction compared with placebo (mean changes in IIEF-EF domain scores: 4.8 with tadalafil 2.5 mg *v* 4.5 with tadalafil 5 mg *v* 1.3 with placebo; P less-than or equal to 0.005 [tadalafil at either dose *v* placebo]; mean changes in SEP Q3: 25.9% with tadalafil 2.5 mg *v* 25.0% with tadalafil 5 mg *v* 8.2% with placebo; P less-than or equal to 0.005 [tadalafil at either dose *v* placebo]; mean changes in SEP Q2: 20.5% with tadalafil 2.5 mg *v* 28.9% with tadalafil 5 mg *v* 5.3% with placebo; P less-than or equal to 0.005 [tadalafil at either dose *v* placebo]). [45]

Harms:

Tadalafil versus placebo in men with diabetes:
The RCT, identified by the review, [43] found a generally higher incidence of adverse effects with tadalafil compared with placebo, but this difference was only significant for dyspepsia (8/73 [11.0%] with tadalafil 10 mg *v* 8/72 [11.1%] with tadalafil 20 mg *v* 0/71 [0%] with placebo; P = 0.005). [44]

The subsequent RCT reported a similar incidence of adverse effects among treatment groups, with only flushing being significantly different among groups (absolute numbers and further details not reported, P = 0.018). It found that back pain was significantly greater with tadalafil 5 mg compared with tadalafil 2.5 mg (absolute numbers and further details not reported, P = 0.028). [45]

Comment:

None.

OPTION VARDENAFIL IN MEN WITH DIABETES

Improvement in sexual function
Compared with placebo in men with diabetes Vardenafil seems more effective at improving erections and sexual functioning, assessed by validated rating scales such as the Index of Erectile Function (IIEF), and response to Sexual Encounter Profile question 2 or question 3, at 12 weeks in men with erectile dysfunction and diabetes (high-quality evidence).

Note
Vardenafil has been associated with headache, flushing, and dyspepsia. Vardenafil is contraindicated in people receiving nitrates because of the risk of potentially life-threatening hypotension.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Vardenafil versus placebo in men with diabetes:
We found two systematic reviews (search dates 2002 [36] and 2005 [43]), which identified the same RCT, reported in two different publications. We found one subsequent RCT, solely in men with diabetes. [46]

The RCT identified by the reviews (452 men with type 1 or type 2 diabetes, glycosylated haemoglobin <12%, erectile dysfunction of >6 months) was a three-armed trial comparing (fixed-dose) vardenafil

10 mg or 20 mg with placebo over 12 weeks followed by an extension phase of 3 months. [36] It found that vardenafil at either dose significantly improved scores on the erectile function domain of the Index of Erectile Function (IIEF) after 12 weeks compared with placebo (mean scores for IIEF-EF at baseline 11.3; mean scores for IIEF-EF at 12 weeks: 17 with vardenafil 10 mg *v* 19 with vardenafil 20 mg *v* 13 with placebo; P <0.0001 for both comparisons *v* placebo).

The subsequent RCT (318 men with type 1 diabetes and erectile dysfunction, all phosphodiesterase-5-inhibitor naive) evaluated the safety and efficacy of flexible-dose (5–20 mg) vardenafil versus placebo. [46] It found that vardenafil significantly improved mean success rates for erection sufficient for penetration (assessed by Sexual Encounter Profile [SEP] question 2 [Q2]) and maintenance of erection sufficient for intercourse (assessed by SEP question 3 [Q3]) compared placebo at 4, 8, and 12 weeks (mean success rates for SEP Q2 at 12 weeks, 291 men in analysis: 71% with vardenafil *v* 52% with placebo; P <0.0001; mean success rates for SEP Q3 at 12 weeks, 302 men in analysis: 50% with vardenafil *v* 28% with placebo; P <0.0001; intention-to-treat [ITT] analysis). Vardenafil treatment also significantly improved the IIEF-EF scores compared with placebo (302 men in analysis; change from baseline in IIEF-EF score: 7.79 with vardenafil *v* 2.05 with placebo; P <0.0001; ITT analysis). [46]

Harms:

Vardenafil versus placebo in men with diabetes:
The first systematic review [36] did not report on adverse effects specifically in the population of men after prostatectomy (see harms of vardenafil in men with erectile dysfunction of any cause, p 8).

The subsequent RCT found that the most commonly reported treatment-emergent adverse effects with vardenafil were headache and flushing, which it described as mild to moderate and transient (headache: 5/163 [3%] with vardenafil *v* 0/155 [0%] with placebo; flushing: 4/163 [2%] with vardenafil *v* 0/155 [0%] with placebo; significance assessment not reported). [46]

Comment:

The review commented that all included RCTs excluded men who had failed to respond to previous treatment with sildenafil. [36]

QUESTION What are the effects of phosphodiesterase inhibitors on erectile dysfunction in men with cardiovascular disease?

OPTION SILDENAFIL IN MEN WITH CARDIOVASCULAR DISEASE

Improvement in sexual function
Compared with placebo in men with heart disease Sildenafil seems more effective at improving erectile function, assessed by the proportion of men who experience successful erections and intercourse and improved erections, or by validated rating scales such as the International Index of Erectile Function (IIEF), at 12 weeks in men with heart disease (moderate-quality evidence).

Note
Sildenafil is contraindicated in men using oral nitrates concomitantly, in whom deaths have been reported.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Sildenafil versus placebo in men with heart disease:
We found one systematic review (search date 2000) assessing sildenafil in men with erectile dysfunction. [6] The systematic review included a subgroup analysis of people with ischaemic heart disease. It found that sildenafil significantly improved the proportion of men with successful erections and with successful sexual intercourse compared with placebo (373 men with heart disease and erectile dysfunction; AR for successful erections: 63% with sildenafil *v* 20% with placebo; relative benefit increase 2.6, 95% CI 1.8 to 3.8; 202 men; AR for mean percentage of successful sexual intercourse attempts: 42% with sildenafil *v* 14% with placebo; WMD 23.8, 95% CI 2.1 to 45.6). [6]

We found two subsequent RCTs that compared sildenafil versus placebo in men with heart disease. [47] [48] The first subsequent RCT found that compared with placebo, flexible doses of sildenafil significantly improved mean scores for questions 3 and 4 of the International Index of Erectile Function (IIEF) after 12 weeks (224 men aged >40 years with heart disease on a variety of antihypertensive drugs [barring nitrates] and erectile dysfunction; mean question 3 score after 12 weeks: 3.7 with sildenafil *v* 2.2 with placebo; mean question 4 score after 12 weeks: 3.3 with sildenafil *v* 1.9 with placebo; P = 0.0001 for both comparisons). [47] Sildenafil significantly increased erectile function as assessed by the Global Efficacy Question compared with placebo (71% with sildenafil *v* 24% with placebo; P = 0.0001). [47] The second subsequent RCT found that flexible doses of sildenafil significantly improved scores on questions 3 and 4 of the IIEF after 12 weeks compared

with placebo (142 men aged 39–82 years with any cause of erectile dysfunction [mean duration 5 years] and stable coronary heart disease [mean duration 7 years] including 50% with previous myocardial infarctions [>8 weeks] and 50% with previous coronary angioplasties, coronary artery bypass grafting, or both; mean improvement in question 3 score after 12 weeks: 3.5 with sildenafil *v* 2.7 with placebo; mean improvement in question 4 score after 12 weeks: 3.3 with sildenafil *v* 2.3 with placebo; P <0.006 for both comparisons). [48]

Harms:

Sildenafil versus placebo in men with heart disease:
An important contraindication to prescribing sildenafil is concomitant use of oral nitrates within 24 hours, as the combination could potentially result in precipitous hypotension. [49] Two RCTs that assessed haemodynamic performance in people with heart disease on a variety of antihypertensive drugs other than nitrates found no clinically significant changes in blood pressure with sildenafil. The first RCT (224 men) evaluated the effects of sildenafil in men aged 40 years or over with cardiovascular disease on a variety of antihypertensive drugs barring nitrates. [47] Apart from flushing (17% with sildenafil *v* 2% with placebo), no other cardiovascular adverse events were reported. The second small RCT (105 men) evaluated the cardiovascular effects of sildenafil during exercise in men with coronary heart disease. [50] It found no effect on symptoms, presence, and extent of ischaemia induced by exercise.

The systematic review (27 RCTs, 4240 men on sildenafil and 2707 men on placebo) found no significant difference between sildenafil and placebo in mortality (4/4240 [0.1%] with sildenafil *v* 2/2707 [0.1%] with placebo) or serious cardiovascular morbidity (myocardial infarction: 6/4240 [0.1%] with sildenafil *v* 6/2707 [0.2%] with placebo). [6] A subgroup analysis restricted to those with ischaemic heart disease not taking nitrates found no significant difference between sildenafil and placebo in the proportion of men with angina; however, this was higher in men taking sildenafil (24 RCTs, 664 men with ischaemic heart disease not taking nitrates; AR: 2.4% with sildenafil *v* 0.4% with placebo; P = 0.06). [6] There were no deaths attributed to sildenafil treatment in the two RCTs that evaluated the cardiovascular effects of sildenafil in men with heart disease. [47] [50] One study pooled data regarding myocardial infarction and cardiovascular causes of death from >120 clinical trials (RCTs, open-label parent studies, and open-label extension studies) of sildenafil citrate conducted from 1993 to 2001. The use of sildenafil was not associated with an increase in the risk of myocardial infarction or cardiovascular causes of death (0.91/100 person-years of follow up, 95% CI 0.52 to 1.48 with sildenafil *v* 0.84/100 person-years of follow up, 95% CI 0.39 to 1.60 with placebo; RR 1.08, 95% CI 0.45 to 2.77; P = 0.88). [51]

For general information on harms in men with erectile dysfunction of any cause see harms of sildenafil in men with erectile dysfunction of any cause, p 4 .

Comment:

The review commented that many of the included RCTs did not describe the procedure used to generate the randomisation sequence or conceal allocation of treatment assignment. [6]

OPTION TADALAFIL IN MEN WITH CARDIOVASCULAR DISEASE New

We found no direct information from RCTs about tadalafil solely in men with erectile dysfunction and cardiovascular disease.

For GRADE evaluation of other interventions for erectile dysfunction, see table, p 36 .

Benefits:

We found no systematic review or RCTs assessing the efficacy of tadalafil solely in men with cardiovascular disease.

Harms:

We found no RCTs solely in men with cardiovascular disease. For general information on harms in men with erectile dysfunction of any cause see harms of tadalafil in men with erectile dysfunction of any cause, p 6 .

Comment:

None.

OPTION VARDENAFIL IN MEN WITH CARDIOVASCULAR DISEASE New

We found no direct information from RCTs about vardenafil solely in men with erectile dysfunction and cardiovascular disease.

For GRADE evaluation of other interventions for erectile dysfunction, see table, p 36 .

Benefits:

We found no systematic review or RCTs assessing the effects of vardenafil on sexual function that were conducted solely in men with cardiovascular disease.

Harms: We found one systematic review (search date 2002), which identified one crossover, single-dose study (41 men with stable angina) assessing exercise tolerance in men taking vardenafil 10 mg or placebo. Vardenafil did not reduce symptom-limited exercise time or time to awareness of angina compared with placebo (P = 0.39–0.59). Vardenafil use did increase time to ST segment depression compared with placebo (381 seconds with vardenafil *v* 334 seconds with placebo; P = 0.0004). [36] For general information on harms in men with erectile dysfunction of any cause see harms of vardenafil in men with erectile dysfunction of any cause, p 8 .

Comment: None.

QUESTION What are the effects of phosphodiesterase inhibitors on erectile dysfunction in men with spinal cord injury?

OPTION SILDENAFIL IN MEN WITH SPINAL CORD INJURY

Improvement in sexual function
Compared with placebo in men with spinal cord injury Sildenafil may be more effective at improving erections, assessed by the proportion of people reporting improved erections or preference for treatment, or by validated rating scales such as the International Index of Erectile Function (IIEF), in men with spinal cord injury (low-quality evidence).

Note
Sildenafil has been associated with dizziness and blood pressure changes in men with spinal cord injuries.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits: **Sildenafil versus placebo in men with spinal cord injury:**
We found one systematic review (search date 2003). [52] The systematic review identified two RCTs (one RCT reported in two publications) in men with spinal cord injury (SCI) assessing sildenafil versus placebo. [53] [54] [55] The review did not pool the data because of the small number of studies and diverse outcome measures, so we report separately the results of those RCTs which fulfil *Clinical Evidence* inclusion criteria. We found one subsequent crossover RCT. [56]

The first RCT (27 men with SCI [below the T5 level] and erectile dysfunction solely attributable to SCI), identified by the review, [52] compared sildenafil (50 mg, taken orally as required, approximately 1 hour before sexual activity, not more than once daily) versus placebo. [53] The RCT involved two parts: in the first part men were randomised to receive a single dose of either sildenafil or placebo, and then crossed over to receive the alternative treatment; the second part involved a parallel design, and men were randomised to receive either sildenafil or placebo for 28 days. It found that sildenafil significantly increased the proportion of people reporting improvement in erections after 28 days of treatment compared with placebo (9/12 [75%] with sildenafil *v* 1/14 [7%] with placebo; P = 0.0043). [53]

The second RCT (crossover design, 178 men, aged at least 18 years, with traumatic SCI and erectile dysfunction solely attributable to SCI), identified by the review, [52] compared sildenafil (25–100 mg orally) versus placebo, for 6 weeks each, and was reported in two publications. [54] [55] It found that sildenafil significantly increased the primary outcome of proportion of men with improved erections and a preference for that treatment, after crossover (127/168 [76%] with sildenafil *v* 7/168 [4%] with placebo; P <0.001). [54] [55] The RCT also found that sildenafil significantly improved overall satisfaction with sex life and sexual relationship with partner, assessed by International Index of Erectile Function (IIEF) questions 13 and 14 compared with placebo (percentage increase in mean score from baseline; Q13: +49% with sildenafil *v* –1% with placebo; P <0.0001; Q14: +34% with sildenafil *v* –2% with placebo; P <0.0001). [55]

The subsequent RCT (crossover design, 50 people with erectile dysfunction attributable to SCI [Sexual Health Inventory—Male score <21]) compared sildenafil (orally, 50–100 mg) versus placebo. [56] The RCT reported results before and after crossover for some outcomes; however, it reported statistical analysis after crossover only, and so the results should be interpreted with caution. It found that sildenafil significantly improved satisfaction with sex life based on IIEF Q13 and Q14 compared with placebo (increase in response score to Q13 [higher scores indicating greater satisfaction]: post-crossover: from 2.6 to 4.1 with sildenafil *v* from 2.4 to 2.4 with placebo; P <0.001; increase in response score to Q14: post-crossover: from 2.8 to 4.2 with sildenafil *v* from 2.6 to 2.5 with placebo; P = 0.002). However, it found no significant difference between groups in IIEF total score (pre-crossover: from 34.3 to 34.0 with sildenafil *v* from 30.4 to 28.9 with placebo, post-crossover: from 30.1 to 43.0 with sildenafil *v* from 30.7 to 26.9 with placebo; P = 0.63 [sildenafil *v* placebo for the pooled change from baseline]). [56]

Harms:

Sildenafil versus placebo in men with spinal cord injury:
The first RCT identified by the review reported similar rates of adverse effects between sildenafil and placebo (total adverse effects: 15 with sildenafil *v* 12 with placebo; number of men not reported; significance assessment not reported). [53]

The second RCT identified by the review found that the most frequently reported treatment-related adverse effects with sildenafil were headache, flushing, dyspepsia, and abnormal vision (usually described as a mild and transient change in colour hue) (headache: 30/178 [17%] with sildenafil *v* 8/166 [5%] with placebo; rhinitis: 3/178 [2%] with sildenafil *v* 0/178 [0%] with placebo; abnormal vision: 4/178 [2%] with sildenafil *v* 0/178 [0%] with placebo; significance assessment not reported). [54]

The subsequent RCT found no significant difference in the number of adverse effects reported between sildenafil and placebo groups (absolute numbers not reported; P = 0.19). It reported that headache and mild urinary tract infection were the most common adverse effects in both groups. [56]

We found one placebo-controlled, crossover RCT (23 men), which evaluated the cardiovascular response to sildenafil in men with complete SCI at or above the sixth thoracic level. [57] It found that sildenafil significantly decreased systolic blood pressure in men with cervical spine injury compared with placebo (12 men with cervical spine injury and erectile dysfunction; mean change in supine systolic blood pressure at 1 hour: 13.8 mmHg with sildenafil 100 mg *v* 0.4 mmHg with placebo; P <0.005). It also found that sildenafil significantly decreased diastolic blood pressure in men with cervical and thoracic spine injury (12 men with cervical spine injury and erectile dysfunction; mean change in supine diastolic blood pressure at 1 hour: 9.5 mmHg with sildenafil 50 mg *v* 1.6 mmHg with placebo; P <0.005; 11 men with thoracic spine injury and erectile dysfunction; mean change in supine diastolic blood pressure at 1 hour: 9.5 mmHg with sildenafil 100 mg *v* 0 mmHg with placebo; P <0.05). Dose-dependent dizziness was also reported in all men with spinal injury.

For general information on harms in men with erectile dysfunction of any cause see harms of sildenafil in men with erectile dysfunction of any cause, p 4 .

Comment: None.

OPTION TADALAFIL IN MEN WITH SPINAL CORD INJURY New

Improvement in sexual function
Compared with placebo in men with spinal cord injury Tadalafil seems more effective at improving sexual function, assessed by validated rating scales such as the International Index of Erectile Function (IIEF), and response to Sexual Encounter Profile (SEP) question 2 or question 3, in men with spinal cord injury (moderate-quality evidence).

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Tadalafil versus placebo in men with spinal cord injury:
We found one RCT assessing the efficacy of tadalafil versus placebo in men with spinal cord injury. [58] The RCT (186 men aged at least 18 years) compared tadalafil (10–20 mg orally on demand, maximum once per day; 142 men) or placebo (44 men) for 12 weeks. [58] It found that tadalafil significantly increased mean International Index of Erectile Function (IIEF)-erectile function domain scores after 12 weeks compared with placebo (mean change in IIEF-EF score from baseline: from 13.5 to 22.6 with tadalafil *v* from 13.0 to 13.6 with placebo; P <0.001 [difference between groups at 12 weeks]). It also found that tadalafil significantly increased successful penetration attempts assessed by Sexual Encounter Profile (SEP) question 2 and intercourse attempts assessed by SEP question 3 after 12 weeks compared with placebo (mean percentage of successful penetration attempts: 75% with tadalafil *v* 41% with placebo; P<0.001; mean percentage of successful intercourse attempts: 47.6% with tadalafil *v* 16.8% with placebo; P<0.001). [58]

Harms:

Tadalafil versus placebo in men with spinal cord injury:
The RCT found similar rates of treatment-emergent adverse effects in both groups (50/142 [35%] with tadalafil *v* 15/44 [34%] with placebo, statistical assessment not reported). The most frequently reported adverse effect in the tadalafil group was headache (12/142 [8%] people). Other adverse events reported by 2% or more of the patients in the tadalafil group were abdominal pain (2.1%), muscle spasticity (2.1%), and urinary tract infection (7.7%). There were no cases of back pain, dyspepsia, or autonomic dysreflexia. [58] For general information on harms in men with erectile dysfunction of any cause see harms of tadalafil in men with erectile dysfunction of any cause, p 6 .

Comment: None.

OPTION VARDENAFIL IN MEN WITH SPINAL CORD INJURY New

We found no direct information from RCTs about vardenafil in men with spinal cord injury.

For GRADE evaluation of other interventions for erectile dysfunction, see table, p 36 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs. For general information on harms in men with erectile dysfunction of any cause see harms of vardenafil in men with erectile dysfunction of any cause, p 8 .

Comment: None.

QUESTION What are the effects of phosphodiesterase inhibitors on erectile dysfunction in men with prostate cancer or undergoing prostatectomy?

OPTION SILDENAFIL IN MEN WITH PROSTATE CANCER OR UNDERGOING PROSTATECTOMY

Improvement in sexual function
Compared with placebo in men after radical prostatectomy or with prostate cancer Sildenafil may be more effective at improving the proportion of men with successful erections and successful intercourse (low-quality evidence).

Note
Sildenafil has been associated with headache, flushing, visual disturbances, and dyspepsia. Sildenafil is contraindicated in men using oral nitrates concomitantly, in whom deaths have been reported.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Sildenafil versus placebo in men after radical prostatectomy or with prostate cancer:
We found two systematic reviews (search dates 2000 [6] and 2004 [59]) assessing sildenafil in men after radical prostatectomy or with prostate cancer. The reviews applied different inclusion criteria (the first review presented a pooled analysis based on the subgroup of men with a history of radical prostatectomy in RCTs in men with any cause of erectile dysfunction, whereas the second review only included RCTs conducted solely in men with radical prostatectomy as treatment for prostate cancer).

The first systematic review included a subgroup analysis of men with a history of radical prostatectomy. It found that compared with placebo, sildenafil significantly improved the proportion of men with successful erections and successful intercourse (116 men with radical prostatectomy or prostate cancer and erectile dysfunction; AR for improved erections: 48% with sildenafil *v* 10% with placebo; RR 3.8, 95% CI 1.6 to 9.5; 42 men, AR for mean percentage of successful intercourse attempts: 25% with sildenafil *v* 3% with placebo; WMD 24, 95% CI 5 to 43). [6]

The second systematic review found no RCTs comparing sildenafil versus placebo solely in men with erectile dysfunction following radical prostatectomy. [59]

We found one additional RCT, which included men with erectile dysfunction after external beam radiotherapy for prostate cancer. [60] It found that compared with placebo, sildenafil significantly improved global efficacy and the proportion of men with successful intercourse after 6 weeks of treatment (60 men with radical prostatectomy or prostate cancer and erectile dysfunction; AR for global efficacy: 45% with sildenafil *v* 8% with placebo; P <0.001; AR for successful intercourse: 55% with sildenafil *v* 18% with placebo; P <0.001).

Harms:

Sildenafil versus placebo in men after radical prostatectomy or with prostate cancer:
The systematic review found that in a subset of 14 flexible-dose trials (3780 men), sildenafil significantly increased the risk of at least one adverse effect compared with placebo (3780 men with any cause of erectile dysfunction; AR: 48% with sildenafil *v* 36% with placebo; RR 1.4, 95% CI 1.3 to 1.6). [6] Adverse effects included headache (11% with sildenafil *v* 4% with placebo; RR 2.6, 95% CI 1.8 to 3.7), flushing (12% with sildenafil *v* 2% with placebo; RR 5.8, 95% CI 3.4 to 10), dyspepsia (5% with sildenafil *v* 1% with placebo; RR 3.8, 95% CI 2.2 to 6.6), and visual disturbance (3.0% with sildenafil *v* 0.8% with placebo; RR 3.1, 95% CI 1.8 to 5.4). Similar proportions of those allocated to sildenafil or placebo discontinued treatment because of adverse effects (1.3% with sildenafil *v* 1.2% with placebo; RR 1.3, 95% CI 0.7 to 2.3). [6] The data from fixed-dose trials in this systematic review indicate that all these adverse effects were more frequent at higher doses of sildenafil and were mild to moderate in severity. [6]

The second review found no RCTs in men with erectile dysfunction following radical prostatectomy.

For general information on harms in men with erectile dysfunction of any cause see harms of sildenafil in men with erectile dysfunction of any cause, p 4 .

Comment: The first review commented that many of the included RCTs did not describe the procedure used to generate the randomisation sequence or conceal allocation of treatment assignment. [6]

OPTION TADALAFIL IN MEN WITH PROSTATE CANCER OR UNDERGOING PROSTATECTOMY

N e w

Improvement in sexual function
Compared with placebo in men after radical prostatectomy or with prostate cancer Tadalafil may be more effective at improving sexual function, assessed by the proportion of men who reported successful intercourse and improved erections or by validated rating scales such as the International Index of Erectile Function (IIEF) and response to Sexual Encounter Profile (SEP) question 2 or question 3, in men who had undergone bilateral nerve-sparing radical retropubic prostatectomy or who had 3D conformal external-beam radiotherapy for prostatic carcinoma (low-quality evidence).

Note
Tadalafil has been associated with headache, muscle pain, back ache, dyspepsia, and flushing. Tadalafil is contraindicated in people receiving nitrates concomitantly because of the risk of potentially life-threatening hypotension.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Tadalafil versus placebo in men after prostatectomy or with prostate cancer:
We found one systematic review (search date 2008, 1 RCT) assessing the efficacy of tadalafil for erectile dysfunction following treatment for prostate cancer. [61] We found one additional RCT. [62]

The RCT (303 men, mean age 60 years, with preoperative normal erectile function who had undergone bilateral nerve-sparing radical retropubic prostatectomy 12 to 48 months before the study, 201 men with partial erections postoperatively), [63] identified by the review, [61] compared tadalafil (20 mg orally, taken on demand) for 12 weeks versus placebo. The RCT randomised people in a ratio of 2:1 to tadalafil or placebo. It found that tadalafil significantly improved the mean International Index of Erectile Function (IIEF)-erectile function (IIEF-EF) domain score compared with placebo (293 men; mean improvement in score: 5.3 with tadalafil *v* 1.1 with placebo; P <0.001). It found that tadalafil increased the proportion of people reporting improved erections compared with placebo (303 men; 62% with tadalafil *v* 23% with placebo; P <0.001; absolute results not reported). It found that tadalafil significantly increased positive responses to Sexual Encounter Profile (SEP) question 2 (Q2) after treatment (21.6% with tadalafil *v* 2.5% with placebo; P = 0.001). It also found that tadalafil significantly improved response to SEP Q2 and SEP Q3 in the subgroup of men with evidence of postoperative penile tumescence (SEP Q2: 22.2% with tadalafil *v* 3.4% with placebo; P = 0.001; SEP Q3: 23.0% with tadalafil *v* 2.3% with placebo; P = 0.001). The RCT found that tadalafil significantly increased treatment satisfaction on the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) compared with placebo (267 men; mean EDITS score: 58 with tadalafil *v* 34 with placebo; P <0.001). [63]

The additional RCT (60 men with erectile dysfunction following 3D conformal external-beam radiotherapy for prostatic carcinoma) was a crossover trial comparing tadalafil 20 mg versus placebo on demand for 6 weeks each. [62] The RCT did not report results before crossover. It found that tadalafil significantly increased mean scores on all the IIEF domains (higher scores indicating better response) compared with placebo after 6 weeks' treatment (erectile function: 17.7 with tadalafil *v* 9.5 with placebo; P <0.0001; orgasmic function: 7.4 with tadalafil *v* 4.9 with placebo; P <0.0001; sexual desire: 8.7 with tadalafil *v* 7.9 with placebo; P = 0.006; intercourse satisfaction: 8.2 with tadalafil *v* 5.6 with placebo; P <0.0001; overall satisfaction: 6.5 with tadalafil *v* 4.4 with placebo; P<0.0001). It also found that tadalafil significantly increased the proportion of people reporting improvement of erectile function and successful intercourse compared with placebo (assessed by "yes" or "no" response at the end of treatment) (proportion of people reporting improvement in erectile function: 67% with tadalafil *v* 20% with placebo; absolute numbers not reported; P <0.0001; proportion of people reporting successful intercourse: 48% with tadalafil *v* 9% placebo; absolute numbers not reported; P <0.0001). [62]

Harms:

Tadalafil versus placebo in men after prostatectomy or with prostate cancer:
The RCT [63] identified by the review [61] found that tadalafil significantly increased the following adverse effects compared with placebo: headache, dyspepsia, and myalgia (headache: 42/201 [21%] with tadalafil *v* 6/102 [6%] with placebo; P <0.001; dyspepsia: 27/201 [13%] with tadalafil *v* 1/102 [1%] with placebo; P <0.001; myalgia: 13/201 [7%] with tadalafil *v* 0/102 [0%] with placebo;

P = 0.006). However, it found no significant difference between groups in back pain, nasal congestion, fatigue, or flushing. [63]

The additional RCT found that tadalafil significantly increased the following adverse effects compared with placebo: headache, flushing, dyspepsia, and myalgia (headache: 16/60 [27%] with tadalafil *v* 1/60 [2%] with placebo; P <0.0001; flushing: 10/60 [17%] with tadalafil *v* 1/60 [2%] with placebo; P = 0.012; dyspepsia: 14/60 [23%] with tadalafil *v* 1/60 [2%] with placebo; P <0.0001; myalgia: 7/60 [12%] with tadalafil *v* 2/60 [3%] with placebo; P = 0.06). However, it found no significant difference between groups in nasal congestion, back pain, or dizziness. [62]

For general information on harms in men with erectile dysfunction of any cause see harms of tadalafil in men with erectile dysfunction of any cause, p 6 .

Comment: None.

OPTION VARDENAFIL IN MEN WITH PROSTATE CANCER OR UNDERGOING PROSTATECTOMY

Improvement in sexual function
Compared with placebo in men after prostatectomy Vardenafil may be more effective at improving erections and attempts at successful intercourse, assessed by validated rating scales such as the International Index of Erectile Function (IIEF) and response to Sexual Encounter Profile (SEP) question 2 or question 3, at 6 months in men with nerve-sparing radical prostatectomy (very low-quality evidence).

Note
Vardenafil has been associated with headache, flushing, and dyspepsia. Vardenafil is contraindicated in people receiving nitrates because of the risk of potentially life-threatening hypotension.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits: **Vardenafil versus placebo in men after prostatectomy:**
We found one systematic review (search date 2002, 1 RCT, published as a conference abstract) comparing vardenafil versus placebo in men after prostatectomy. [36] It found that, compared with placebo, vardenafil 10 mg or 20 mg significantly improved erections and successful attempts at intercourse as assessed by scores on the erectile function domain of the International Index of Erectile Function, questions 2 and 3 of the Sexual Encounter Profile diaries, and the Global Efficacy Question after 12 weeks (440 men with erectile dysfunction [>67% severe] at least 6 months after nerve-sparing radical retropubic prostatectomy; P <0.0001 for all comparisons *v* placebo). [36] Erectile function improved for men on vardenafil with all levels of severity of erectile dysfunction (absolute numbers not reported).

Harms: **Vardenafil versus placebo in men after prostatectomy:**
The systematic review [36] did not report on adverse effects specifically in the population of men after prostatectomy (see harms of vardenafil in men with erectile dysfunction of any cause, p 8).

Comment: The review commented that all included RCTs excluded men who had failed to respond to previous treatment with sildenafil. [36]

QUESTION What are the effects of drug treatments other than phosphodiesterase inhibitors in men with erectile dysfunction of any cause?

OPTION ALPROSTADIL (INTRAURETHRAL) IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function
Compared with placebo in men with erectile dysfunction of any cause Intraurethral alprostadil (prostaglandin E1) may be more effective at increasing the proportion of men achieving at least one successful attempt at sexual intercourse and at improving quality-of-life scores (relationship with partner, personal wellness, and quality of erection) in men who have previously responded to alprostadil (very low-quality evidence).

Compared with placebo in men after radical prostatectomy Intraurethral alprostadil seems more effective at increasing the proportion of men reporting at least one successful attempt at sexual intercourse (moderate-quality evidence).

Compared with intracavernosal alprostadil Intraurethral alprostadil may be less effective at increasing the proportion of men who achieve an erection and successful intercourse (very low-quality evidence).

Note

Alprostadil has been associated with penile pain, urethral burning sensations, and minor urethral trauma.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Intraurethral alprostadil versus placebo in men with erectile dysfunction of any cause:
We found one systematic review (search date 2003, 3 RCTs, 1828 men, mostly organic causes of erectile dysfunction) that compared 4 doses of intraurethral alprostadil (125, 250, 500, and 1000 micrograms) versus placebo. [64] Two of the RCTs were parallel-group studies and one was a crossover design. Combining the results of the two parallel-group trials, the systematic review found that, compared with placebo, intraurethral alprostadil significantly increased the proportion of men achieving at least one successful attempt at sexual intercourse over a 3-month home self-administration period (2 RCTs, 1101 men; AR for at least 1 successful attempt at intercourse: 345/528 [65%] with intraurethral alprostadil *v* 101/573 [18%] with placebo; OR 7.22, 95% CI 5.68 to 9.18). One of the parallel-group RCTs identified by the systematic review found that, compared with placebo, alprostadil-treated men reported an improvement in all three domains of an 8-item quality-of-life questionnaire (change in relationship with partner: +34% with alprostadil *v* –11% with placebo; change in personal wellness score: +5% with alprostadil *v* –8% with placebo; change in quality of erection: +71% with alprostadil *v* –1% with placebo; P <0.005 for each comparison). The partners of 35% of the men treated with alprostadil reported an improvement in their relationship compared with 12% of those treated with placebo (significance assessment not performed). The crossover RCT identified by the systematic review found that 64% of all men had "at least one successful intercourse" with at least one dose of intraurethral alprostadil (AR: 39% with alprostadil 125 micrograms *v* 33% with alprostadil 250 micrograms *v* 40% with alprostadil 500 micrograms *v* 50% with 1000 micrograms alprostadil *v* 12% with placebo; P <0.01 for each active dose compared with placebo). Alprostadil also increased the proportion of men with erections sufficient for intercourse compared with placebo (AR: 20% with alprostadil 125 micrograms *v* 30% with alprostadil 250 micrograms *v* 27% with alprostadil 500 micrograms *v* 32% with alprostadil 1000 micrograms *v* 5% with placebo; P <0.001 for all comparisons *v* placebo). [64]

Intraurethral alprostadil versus placebo in men after radical prostatectomy:
We found one RCT (270 men) that treated men with individually titrated doses of intraurethral alprostadil (125–1000 micrograms) or placebo at home for 3 months. [65] It found that intraurethral alprostadil increased the proportion of men reporting at least one successful intercourse compared with placebo (AR: 72/126 [57%] with alprostadil *v* 9/137 [7%] with placebo; P <0.001).

Intraurethral alprostadil versus intracavernosal alprostadil in men with erectile dysfunction of any cause:
We found three RCTs that compared intraurethral versus intracavernosal routes of administering alprostadil. [66] [67] [68]

The first RCT (111 men) compared home treatment with intracavernosal alprostadil (<40 micrograms) versus intraurethral alprostadil (<1000 micrograms) plus optional ACTIS (a penile constriction ring) for 4 weeks after an in-clinic dose titration period of 1 to 14 days. [66] It found that intracavernosal alprostadil increased the proportion of men achieving at least one erection sufficient for intercourse compared with intraurethral alprostadil (crossover open-label design, mean age 59.2 years with any cause of erectile dysfunction, mean duration of 4.5 years; AR: 42/68 [62%] with intraurethral alprostadil *v* 63/68 [93%] with intracavernosal alprostadil; P <0.0001). It also found that intracavernosal alprostadil increased mean scores on questions 3 and 4 of the International Index of Erectile Function (IIEF) compared with intraurethral treatment (mean score on IIEF [range 0–5]: question 3: 1.7 at baseline and 3.0 at week 4 with intraurethral alprostadil *v* 1.7 at baseline and 4.4 at week 4 with intracavernosal alprostadil; question 4: 1.3 at baseline and 2.8 at week 4 with intraurethral alprostadil *v* 1.3 at baseline and 4.2 at week 4 with intracavernosal alprostadil; P <0.0001 for both comparisons). Fewer men and their partners expressed a preference for intraurethral alprostadil compared with intracavernosal alprostadil (AR for preference of mode of delivery of alprostadil: men; 16% with intraurethral alprostadil *v* 69% with intracavernosal alprostadil; partners: 10% with intraurethral alprostadil *v* 63% intracavernosal alprostadil; significance assessment not performed). [66]

The second RCT (60 men, organic causes of erectile dysfunction) compared intracavernosal alprostadil 20 micrograms with intraurethral alprostadil 1 mg. [67] It found that intracavernosal alprostadil significantly increased the proportion of men who reported erections sufficient for sexual intercourse and more than one successful intercourse compared with intraurethral alprostadil (AR for successful erections: 60% with intraurethral alprostadil *v* 90% with intracavernosal alprostadil; AR for successful intercourse: 53% with intraurethral alprostadil *v* 87% with intracavernosal alprostadil; P <0.05 for both comparisons). [67]

The third RCT (103 men, mean age 51.7 years) compared intraurethral alprostadil (<1000 micrograms) with intracavernosal alprostadil (<20 micrograms). [68] Intracavernosal alprostadil increased rates of successful erections compared with intraurethral alprostadil (AR: 43% with intraurethral alprostadil *v* 70% with intracavernosal alprostadil; significance assessment not performed).

Harms:

Intraurethral alprostadil versus placebo in men with erectile dysfunction of any cause:
The systematic review found that, compared with placebo, intraurethral alprostadil increased penile pain compared with placebo (2 RCTs, 1056 men; AR: 170/567 [30%] with alprostadil *v* 18/589 [3%] with placebo; OR 7.39, 95% CI 5.40 to 10.12). [64] The systematic review found that intraurethral alprostadil also increased the frequency of reports of minor urethral trauma compared with placebo (AR: 26/567 [5%] with alprostadil *v* 6/589 [1%] with placebo; OR 3.79, 95% CI 1.88 to 7.65). No significant difference in rates of urinary tract infection was reported in the systematic review (AR: 0.17% with alprostadil *v* 0.51% with placebo; OR 0.39, 95% CI 0.05 to 2.78). Priapism was reported by one person on intraurethral alprostadil (AR: 1/567 [0.2%] with alprostadil *v* 0/589 [0%] with placebo; OR 7.12, 95% CI 0.14 to 359.12). Dizziness was significantly more common with intraurethral alprostadil compared with placebo (AR: 11/567 [1.9%] with alprostadil *v* 1/589 [0.2%] with placebo; OR 5.57, 95% CI 1.79 to 17.37). [64]

Intraurethral alprostadil versus placebo in men after radical prostatectomy:
One RCT also reported that men on intraurethral alprostadil reported penile pain significantly more frequently than those on placebo (AR: 39% with alprostadil *v* 2% with placebo; P <0.001) as well as urethral burning (AR: 18% with alprostadil *v* 4% with placebo; P <0.001). [65]

Intraurethral alprostadil versus intracavernosal alprostadil in men with erectile dysfunction of any cause:
The first RCT, comparing intracavernosal alprostadil versus intraurethral alprostadil, found that penile pain was the most common adverse effect for both interventions (AR: 34% with intracavernosal alprostadil *v* 25% with intraurethral alprostadil). [66] Local bleeding was reported in both intervention arms (AR: 1.5% with intracavernosal alprostadil *v* 2.9 with intraurethral alprostadil; significance assessment not performed). In the second RCT, penile pain was significantly more common with intracavernosal alprostadil (AR: 7% with intraurethral alprostadil *v* 47% with intracavernosal alprostadil; P <0.05). [67] However, the reverse was true in the third RCT (AR for penile pain/urethral burning: 31% with intraurethral alprostadil *v* 11% with intracavernosal alprostadil; significance assessment not performed). Temporary urethral bleeding was observed in 5/103 (5%) men after intraurethral alprostadil. Brief periods of dizziness (7%) and syncope (1 man) were also observed after intraurethral alprostadil, although this was not seen with the intracavernosal route of administration. [68] We found no reports of penile fibrosis or other serious adverse events.

Comment:

None of the RCTs described the randomisation or allocation concealment procedures. All the RCTs in the systematic review and two of the subsequent RCTs pre-selected men who had a good response to alprostadil before randomisation. [64] [67] [68] This would tend to increase the size of the effect compared with placebo, and affect the external validity of the results and consequently their generalisation to clinical practice.

OPTION ALPROSTADIL (TOPICAL) IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function
Compared with placebo Alprostadil (prostaglandin E1) gel applied to the tip of the penis seems more effective at improving erections and successful intercourse in men with various causes of erectile dysfunction (moderate-quality evidence).

Note
Topical alprostadil has been associated with penile pain and erythema.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Topical alprostadil versus placebo in men with erectile dysfunction of any cause:
We found no systematic review. We found two small RCTs [69] [70] and one pooled analysis of two RCTs [71] that compared alprostadil gel or cream applied topically to the tip of the penis versus placebo.

The first small RCT (42 men with various causes of erectile dysfunction) found that alprostadil cream significantly improved successful erections and sexual intercourse as assessed by questions 3 and 4 of the International Index of Erectile Function (IIEF) compared with placebo (improvement in IIEF question 3 erection score from baseline [range: 1.67–2.05]: 10.19 with alprostadil *v* 1.4 with placebo; P <0.01; improvement in IIEF question 4 successful intercourse score from baseline [range: 1.29–1.65]: 1.45 with alprostadil *v* 0.14 with placebo; P <0.01). [69] Alprostadil cream also

improved erections as assessed by the Global Assessment Questionnaire compared with placebo (42 men; 73.7% with alprostadil cream *v* 19.0% with placebo; P <0.01) and increased the proportion of successful attempts at sexual intercourse (42 men; 68.4% with alprostadil cream *v* 19.1% with placebo; P <0.01; absolute numbers not reported). [69]

The second small RCT (60 men with moderate to severe erectile dysfunction) compared alprostadil 1% in a gel formulation with SEPA 5% (soft enhancer of percutaneous absorption) versus placebo gel. It found that alprostadil gel significantly increased the proportion of men with erections judged sufficient for vaginal penetration (patient assessment of rigidity of at least 3 on a scale of 1–5, or an angle of at least 70° from vertical axis measured by physician) compared with placebo (12/31 [39%] with alprostadil *v* 2/29 [7%] with placebo; P = 0.005). [70]

The pooled analysis of two RCTs (1732 men with an erectile dysfunction score of 25 or more on the IIEF-erectile function domain [IIEF-EF]) compared topical alprostadil cream (100, 200, or 300 micrograms) versus placebo for 12 weeks. [71] It found that alprostadil cream significantly improved erectile function (assessed by IIEF-EF) compared with placebo at 12 weeks (mean changes in IIEF-EF domain scores from baseline: +1.6 with alprostadil 100 micrograms *v* +2.5 with alprostadil 200 micrograms *v* +2.4 with alprostadil 300 micrograms *v* –0.7 with placebo; P less-than or equal to 0.001 [each dose *v* placebo]). It found that a higher proportion of men reported improved erections with alprostadil cream versus placebo over 12 weeks (proportion of men reporting improved erections: 40% with alprostadil 100 micrograms *v* 47% with alprostadil 200 micrograms *v* 52% with alprostadil 300 micrograms *v* 20% with placebo). Sexual Encounter Profile (SEP) question 2 and 3 scores improved significantly in treatment groups compared with placebo (P <0.001). [71]

Harms:

Topical alprostadil versus placebo in men with erectile dysfunction of any cause:
The first RCT reported a higher proportion of men experiencing adverse events with alprostadil cream compared with placebo (30% with alprostadil cream *v* 4.8% with placebo; P <0.01). Common adverse events included mild pain of the penis and urethra. [69] In the second RCT, significantly more men had erythema with alprostadil than with placebo (absolute numbers not reported; P <0.001). Other adverse effects included conjunctivitis (2/31 [6%]) and hypotension (1/31 [3%]). [70] A further RCT of two phase II trials (303 men with moderate to severe erectile dysfunction aged 21–70 years, 90% with erectile dysfunction >1 year) compared topical alprostadil cream 0.05 mg, 0.1 mg, 0.2 mg, and 0.3 mg versus placebo. [72] It found a higher incidence of adverse events in men using alprostadil cream compared with placebo (AR for 1 or fewer adverse events: 135/230 [59%] with alprostadil cream *v* 25/75 [33%] with placebo; significance assessment not performed). Although >97% of adverse events were described as mild and lasting 60 minutes or less, more men on alprostadil withdrew from therapy because of adverse events compared with placebo (AR: 37/230 [16%] with alprostadil cream *v* 0/75 [0%] with placebo; significance assessment not performed). Events resulting in withdrawal suggested a dose relation and included urogenital pain (22/230 [10%] with alprostadil cream *v* 0/75 [0%] with placebo; significance assessment not performed), and hypotension (13/230 [6%] with alprostadil cream *v* 0/75 [0%] with placebo; significance assessment not performed). One man using alprostadil cream 200 micrograms developed a near syncopal episode lasting nearly 10 minutes. About 2% of partners reported mild, transient vaginal burning with alprostadil cream. We did not find any RCTs or observational studies of sufficient quality on penile fibrosis, prolonged erections, or other serious adverse events.

In the pooled analysis of two RCTs, the most frequently reported treatment-related adverse effects were penile burning, genital pain, and genital erythema (penile burning: 74/434 [17%] with alprostadil 100 micrograms *v* 106/430 [25%] with alprostadil 200 micrograms *v* 100/434 [23%] with alprostadil 300 micrograms *v* 26/434 [6%] with placebo; genital pain: 48/434 [11%] with alprostadil 100 micrograms *v* 67/430 [16%] with alprostadil 200 micrograms *v* 76/434 [18%] with alprostadil 300 micrograms *v* 2/434 [0.5%] with placebo; penile erythema: 33/434 [8%] with alprostadil 100 micrograms *v* 39/430 [9%] with alprostadil 200 micrograms *v* 49/434 [11%] with alprostadil 300 micrograms *v* 9/434 [2%] with placebo). Forty-six patients (3%) withdrew from the study because of treatment-related adverse effects. Most of these treatment-related adverse effects resolved within 2 hours. Partner treatment-related adverse effects were reported by 97 (6%) of the women, with the most common of these effects being vaginal burning (4%). [71]

Comment:

None of the RCTs described the methods used to generate randomisation codes and to conceal allocation to treatment arms.

OPTION ALPROSTADIL (INTRACAVERNOSAL) IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function

Compared with placebo in men erectile dysfunction of any cause Alprostadil may be more effective at increasing the proportion of clinical assessments of full rigidity and RigiScan assessment of 70% or greater rigidity for 10 minutes or longer and at increasing the number of erections judged sufficient to allow penetration (very low-quality evidence).

Compared with intraurethral alprostadil Intracavernosal alprostadil may be more effective at increasing the proportion of men who achieve an erection and successful intercourse (very low-quality evidence).

Compared with papaverine Intracavernosal alprostadil may be more effective at increasing erections (very low-quality evidence).

Compared with papaverine plus phentolamine (bimix) We don't know whether intracavernosal alprostadil is more effective at increasing the proportion of men with successful erections (very low-quality evidence).

Compared with alprostadil plus papaverine plus phentolamine (trimix) Intracavernosal alprostadil may be less effective at increasing positive erectile responses and erections in men who have previously failed to respond to bimix (very low-quality evidence).

Note
Alprostadil has been associated with penile pain over the injection site.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Intracavernosal alprostadil versus placebo in men with erectile dysfunction of any cause:
We found two RCTs that compared alprostadil injections with placebo. [73] [74] The first RCT (296 men aged 21–74 years, excluding men with penile deformities, uncontrolled diabetes or hypertension, major mental illness, infectious diseases, or a history of priapism) compared injections of 2.5 micrograms, 5 micrograms, 10 micrograms, and 20 micrograms of alprostadil with placebo. [73] None of the men responded to placebo and all doses of alprostadil increased the proportion of clinical assessment of "full rigidity" (P <0.01) and RigiScan assessment of 70% or greater rigidity for 10 minutes or longer (P <0.001). The RCT also found a higher proportion of men with a clinical response with larger doses (P less-than or equal to 0.001), suggesting a dose–response relationship. Absolute numbers were not reported and results were presented graphically. [73] The second RCT was a small crossover study (60 men, mean age 58 years, erectile dysfunction >6 months) that compared alprostadil 30 micrograms versus bimix (papaverine 30 mg plus phentolamine mesilate 0.5 mg) versus placebo (isotonic saline). [74] It found that alprostadil significantly increased the number of erections judged sufficient to allow penetration compared with placebo (successful erections: 50% with alprostadil *v* 0% with placebo; P <0.001). [74]

Intracavernosal alprostadil versus intraurethral alprostadil in men with erectile dysfunction of any cause:
See benefits of intraurethral alprostadil, p 19 .

Intracavernosal alprostadil versus papaverine in men with erectile dysfunction of any cause:
We found three crossover RCTs that compared alprostadil injections with papaverine injections. [75] [76] [77] The first crossover RCT (single blind, 205 men, mean age 57.5 years, various causes of erectile dysfunction) compared a single injection of low-dose alprostadil (5 micrograms) with papaverine (18 mg, 0.6 mL of a 30 mg/mL solution). [75] Alprostadil resulted in a significantly higher proportion of erections judged adequate for penetration 10 to 20 minutes after the injection compared with papaverine (AR for full erection: 34/129 [26%] with alprostadil 5 micrograms *v* 17/129 [13%] with papaverine; P <0.03). There was no significant difference in the percentage of successful intercourse attempts on the same day or over the next 4 weeks between alprostadil and papaverine (men attempting intercourse same day: 24/129 [19%] with alprostadil *v* 15/129 [12%] with papaverine; P = 0.077; men experiencing successful intercourse within 4 weeks: 12/129 [9%] with alprostadil *v* 6/129 [5%] with papaverine; P = 0.61). [75] The second small crossover RCT (54 men, mean age 57 years, with vascular cause of erectile dysfunction) compared intracavernosal injections of alprostadil 20 micrograms versus papaverine 60 mg. [76] Alprostadil injections resulted in partial or complete erections in more men than with papaverine (AR: 46% with alprostadil *v* 14% with papaverine; P <0.002; absolute numbers not reported). [76] The third small crossover RCT (52 men, mean age 48.6 years, duration of erectile dysfunction 0.7–6.0 years, various causes of erectile dysfunction) compared alprostadil 20 micrograms with papaverine 30 mg. [77] Alprostadil significantly increased the proportion of men with successful erections (penis erect with 90° angle to vertical body axis and duration at least 2 hours) compared with papaverine (AR: 42/52 [81%] with alprostadil *v* 33/52 [63%] with papaverine; P = 0.01). In a subgroup of 24 men with suspected vascular cause of erectile disorder, alprostadil also significantly improved successful erections compared with papaverine (AR: 16/24 [67%] with alprostadil *v* 11/24 [46%] with papaverine; P <0.04). [77]

Intracavernosal alprostadil versus papaverine plus phentolamine (bimix) in men with erectile dysfunction of any cause:
We found two crossover RCTs that compared intracavernosal alprostadil versus bimix. [74] [78] The first small crossover RCT (60 men, mean age 58 years, erectile dysfunction >6 months) compared alprostadil 30 micrograms versus bimix (papaverine 30 mg plus phentolamine mesilate 0.5 mg) versus placebo (isotonic saline). [74] It found no significant difference between alprostadil and bimix in the proportion of men with successful erections (30/60 [50%] with alprostadil *v* 34/60 [57%] with bimix; P >0.05). [74] The second crossover RCT (91 men, mean age 55 years) was a three-armed trial, comparing alprostadil (20 micrograms) versus bimix (papaverine 30 mg plus phentolamine 1 mg) versus trimix (alprostadil 10 micrograms plus papaverine 15 mg plus phentolamine 0.5 mg). [78] Penile rigidity was assessed by the same observer subjectively and objectively using callipers. The comparison between alprostadil and bimix revealed that both were equally effective in producing erections, with no significant difference in the mean total percentage of rigidity (60% with alprostadil *v* 59% with bimix; P >0.46) or the proportion of men with a positive erectile response of rigidity of 60% or greater (58/82 [71%] with alprostadil *v* 46/82 [56%] with bimix; P >0.12). [78]

Intracavernosal alprostadil versus alprostadil plus papaverine plus phentolamine (trimix) in men with erectile dysfunction of any cause:
We found two crossover RCTs that compared intracavernosal alprostadil versus trimix. [79] [78] One small crossover RCT (32 men, mean age 61.3 years, erectile dysfunction >6 months; all had failed to respond to 2 tests with papaverine plus phentolamine [bimix]) compared alprostadil 40 micrograms with trimix (1 mL solution containing alprostadil 5.8 micrograms/mL plus papaverine 17.64 mg/mL plus phentolamine 0.58 mg/mL). [79] Trimix significantly increased the proportion of men who gained an erection sufficient to allow penetration compared with alprostadil alone (AR: 7/32 [22%] with alprostadil *v* 16/32 [50%] with trimix; P <0.05). [79] The second crossover RCT (91 men, mean age 55 years) was a three-armed trial, comparing alprostadil (20 micrograms) versus bimix (papaverine 30 mg plus phentolamine 1 mg) versus trimix (papaverine 15 mg plus phentolamine 0.5 mg plus alprostadil 10 micrograms). [78] Trimix significantly increased the mean total percentage of rigidity of 60% or greater (60% with alprostadil *v* 66% with trimix; P = 0.0115) and the proportion of men with a positive erectile response of at least 60% rigidity (58/82 [71%] with alprostadil *v* 67/82 [82%] with trimix; P = 0.007) compared with alprostadil. [78]

Intracavernosal alprostadil versus sildenafil in men with erectile dysfunction of any cause:
See benefits of sildenafil, p 4 .

Harms:

Intracavernosal alprostadil versus placebo in men with erectile dysfunction of any cause:
In the first multicentre RCT, adverse effects with alprostadil included penile pain (54/237 [23%]) and priapism (5/237 [2%]). [73] A cohort of 208 men self-injecting with alprostadil followed up over 3 years reported the following adverse effects: haematomas (0.5%), priapism (1.5%), fibrosis of the corpora cavernosa (1.0%), and fibrous penile nodules (0.5%). [80]

Intracavernosal alprostadil versus intraurethral alprostadil in men with erectile dysfunction of any cause:
See harms of intraurethral alprostadil, p 19 .

Intracavernosal alprostadil versus papaverine in men with erectile dysfunction of any cause:
In the first RCT, penile pain from injection rather than needle insertion was reported with both treatments (pain on injection: 11/72 [15%] with alprostadil *v* 6/72 [8%] with papaverine; significance assessment not performed). One man (1/72) on papaverine developed priapism, which resolved spontaneously within 8 hours. [75] In the second RCT, mild pain at the injection site was reported (44% of men on papaverine *v* 45% with alprostadil; absolute numbers not reported), along with dizziness and headache in two men on papaverine and one man on alprostadil. [76] In the third RCT, 6/52 (12%) of men given alprostadil and 13/52 (25%) of men given papaverine reported transient, tolerable burning at the injection site. There were no reports of priapism, even among 8 men taking alprostadil who had previously developed priapism with papaverine. [77]

Intracavernosal alprostadil versus papaverine plus phentolamine (bimix) in men with erectile dysfunction of any cause:
The first RCT found that penile pain was more frequent with alprostadil compared with bimix (21/60 [35%] with alprostadil *v* 9/60 [15%] with bimix; P <0.05). [74] The second RCT did not report on adverse effects. [78]

Intracavernosal alprostadil versus alprostadil plus papaverine plus phentolamine (trimix) in men with erectile dysfunction of any cause:
The first RCT found that penile pain was more frequent with alprostadil compared with trimix (13/32 [41%] with alprostadil *v* 4/32 [13%] with trimix; P <0.05). [79] We found no long-term data on adverse effects. The second RCT did not report on adverse effects. [78]

Comment: None of the RCTs described the randomisation or allocation concealment procedures.

OPTION PAPAVERINE IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function
Compared with papaverine plus phentolamine (bimix) Papaverine may be less effective at increasing the proportion of men achieving full erections 20 minutes after injection and at increasing the proportion of men achieving successful intercourse on the day of the injection (low-quality evidence).

Compared with intracavernosal alprostadil Papaverine may be less effective at increasing erections (very low-quality evidence).

Note
Papaverine has been associated with transient burning pain, bruising, prolonged erections, fibrosis of the corpora cavernosa, and fibrous penile nodules. We found no direct information from RCTs about whether papaverine is better than no active treatment.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Papaverine versus placebo in men with erectile dysfunction of any cause:
We found no systematic review or RCTs.

Papaverine versus papaverine plus phentolamine (bimix) in men with erectile dysfunction of any cause:
We found no systematic review. We found one crossover RCT (40 men, any cause of erectile dysfunction for >1 year aged 40–75 years) that compared intracavernosal papaverine 40 mg versus papaverine 20 mg plus phentolamine 0.5 mg diluted with normal saline to 5 mL (bimix). [81] It found that bimix significantly increased the proportion of men with full erections compared with papaverine alone, as assessed by observers blinded to treatment allocation 20 minutes after injection (AR: 11/40 [28%] with papaverine *v* 19/40 [48%] with bimix; P <0.05). Bimix also significantly increased the proportion of men achieving successful intercourse on the day of the injection compared with papaverine alone (AR: 5/40 [13%] with papaverine *v* 15/40 [38%] with bimix; P <0.05). [81]

Papaverine versus intracavernosal alprostadil in men with erectile dysfunction of any cause:
See benefits of alprostadil (intracavernosal), p 22 .

Papaverine versus papaverine plus phentolamine plus alprostadil (trimix) in men with erectile dysfunction of any cause:
We found no RCTs.

Harms:

Papaverine versus placebo in men with erectile dysfunction of any cause:
We found no RCTs. For further information from observational studies see comment.

Papaverine versus papaverine plus phentolamine (bimix) in men with erectile dysfunction of any cause:
The RCT found that 11/40 (28%) men receiving papaverine and 7/40 (18%) men receiving bimix experienced burning pain in the shaft of the penis 30 seconds after the injection, which subsided within 2 minutes after injection (significance assessments not performed). Prolonged erection occurred in 1/40 (3%) of men receiving bimix. [81]

Papaverine versus intracavernosal alprostadil in men with erectile dysfunction of any cause:
See harms of alprostadil (intracavernosal), p 22 .

Papaverine versus papaverine plus phentolamine plus alprostadil (trimix) in men with erectile dysfunction of any cause:
See harms of papaverine plus phentolamine plus alprostadil (trimix), p 27 .

Comment: We found one crossover unblinded RCT (50 men) assessing single-dose injection of papaverine versus oral sildenafil for evaluation of erectile dysfunction in men. [82] It found no significant difference between papaverine and sildenafil in terms of penile length and circumference following genital

self-stimulation. The aim of this RCT was evaluation of erectile dysfunction in the clinician office, and so its results do not necessarily reflect the treatment setting.

Adverse effects:
In a cohort of 226 men self-injecting with papaverine and followed up for 2 years, 8% developed haematomas, 10% developed priapism, 12% developed fibrosis of the corpora cavernosa, and 9% developed fibrous penile nodules (significance assessments not performed). [80]

OPTION PAPAVERINE PLUS PHENTOLAMINE (BIMIX) IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function
Compared with placebo Intracavernosal papaverine injections plus phentolamine (bimix) may be more effective at increasing the proportion of men with erections sufficient for intercourse (very low-quality evidence).

Compared with papaverine Papaverine plus phentolamine (bimix) may be more effective at increasing the proportion of men achieving full erections 20 minutes after injection and at increasing the proportion of men achieving successful intercourse on the day of the injection (low-quality evidence).

Compared with intracavernosal alprostadil We don't know whether papaverine plus phentolamine (bimix) is more effective at increasing the proportion of men with successful erections (very low-quality evidence).

Note
Papaverine plus phentolamine (bimix) has been associated with transient pain and bruises at injection site, painless fibrous penile nodules, mild to moderate alteration in liver function, prolonged erections, and fibrosis of the corpora cavernosa. We found no clinically important results from RCTs about papaverine plus phentolamine (bimix) compared with other treatments in men with erectile dysfunction.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Papaverine plus phentolamine (bimix) versus placebo in men with erectile dysfunction of any cause:
We found no systematic review. We found one small crossover RCT (30 men, mean age 60.9 years, mean duration of erectile dysfunction 4.8 years, erectile dysfunction resulting from various causes) that compared intracavernosal injections of a combination of papaverine 30 mg plus phentolamine 1 mg (bimix) versus normal saline injections. [83] It found that papaverine 30 mg plus phentolamine 1 mg increased the proportion of men with erections satisfactory for intercourse compared with normal saline (AR: 83% with bimix *v* 0% with normal saline; significance not reported).

Papaverine plus phentolamine (bimix) versus papaverine in men with erectile dysfunction of any cause:
See benefits of papaverine, p 25 .

Papaverine plus phentolamine (bimix) versus intracavernosal alprostadil in men with erectile dysfunction of any cause:
See benefits of alprostadil (intracavernosal), p 22 .

Papaverine plus phentolamine (bimix) versus other treatments in men with erectile dysfunction of any cause:
We found no RCTs.

Harms:

For further information on harms from observational studies, see comment.

Papaverine plus phentolamine (bimix) versus placebo in men with erectile dysfunction of any cause:
One man in the RCT developed a prolonged erection that resolved spontaneously after 26 hours with no subsequent abnormality. [83] Most men (number not reported) experienced various degrees of ecchymosis at the injection site and some reported mild pain.

Papaverine plus phentolamine (bimix) versus papaverine in men with erectile dysfunction of any cause:
See harms of papaverine, p 25 .

Papaverine plus phentolamine (bimix) versus intracavernosal alprostadil in men with erectile dysfunction of any cause:
See harms of alprostadil (intracavernosal), p 22 .

Papaverine plus phentolamine (bimix) versus other treatments in men with erectile dysfunction of any cause:
We found no RCTs.

Comment: A prospective cohort study (111 men) found painless fibrous nodules in 57% of men self-injecting bimix over 12 months (results presented graphically; P = 0.005). [84] It also found that higher frequencies of injection significantly increased the proportion of men who developed nodules compared with a lower frequency (nodules present in men with a mean of 51.3 injections *v* no nodules present in men with a mean of 20 injections; significance assessment not performed). Priapism did not occur during home treatment but was seen in 2/329 (0.6%) of physician-administered injections. Fifty men had at least one liver function test after the start of bimix injections; 20/50 [40%] of those 50 men had at least one abnormality in liver function, mostly involving mild to moderate elevation in alkaline phosphatase and lactic dehydrogenase (significance assessment not performed). A retrospective cohort study (224 men) found that 5% developed haematomas, 7% developed priapism, 9% developed fibrosis of the corpora cavernosa, and 8% developed fibrous plaques after self-injecting with bimix over 2 years. [85]

OPTION PAPAVERINE PLUS PHENTOLAMINE PLUS ALPROSTADIL (TRIMIX) IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function
Compared with intracavernosal alprostadil A mixture of papaverine, phentolamine, and alprostadil (trimix) may be more effective at increasing positive erectile responses and erections in men who have previously failed to respond to bimix (very low-quality evidence).

Compared with vacuum devices We don't know whether intracavernosal injection of papaverine, phentolamine, and alprostadil (trimix) is more effective at achieving an erection but it may be more effective at increasing overall satisfaction scores and the ability to achieve an orgasm (very low-quality evidence).

Note
We found no direct information from RCTs about whether papaverine plus phentolamine plus alprostadil (trimix) is better than no active treatment.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Papaverine plus phentolamine plus alprostadil (trimix) versus placebo in men with erectile dysfunction of any cause:
We found no systematic review or RCTs.

Papaverine plus phentolamine plus alprostadil (trimix) versus intracavernosal alprostadil in men with erectile dysfunction of any cause:
See benefits of alprostadil (intracavernosal), p 22 .

Papaverine plus phentolamine plus alprostadil (trimix) versus papaverine in men with erectile dysfunction of any cause:
We found no systematic review or RCTs.

Papaverine plus phentolamine plus alprostadil (trimix) versus vacuum devices in men with erectile dysfunction of any cause:
We found no systematic review. We found one small crossover RCT (50 men with erectile dysfunction, 44 of whom completed the study, mean age 62.3 years, erectile dysfunction >6 months) compared intracavernosal self-injection of papaverine plus phentolamine plus alprostadil (trimix) versus external vacuum devices over 18 to 24 months. [86] The RCT reported results after crossover only. It found no significant difference in ability to achieve an erection suitable for intercourse between groups (mean self-rated erectile quality on a scale of 1–10: 5.1 with trimix *v* 4.3 with vacuum device; reported as not significant). However, it found that trimix significantly improved the ability to attain orgasm compared with vacuum device (mean self-rated penile sensation on a scale of 1–10: 5.2 with trimix *v* 4.5 with vacuum device; P <0.05). It also found that trimix significantly improved overall satisfaction scores for men and their partners compared with vacuum device (men's mean overall satisfaction on a scale of 0–10: 6.5 with trimix *v* 5.4 with vacuum device; P <0.05; partners' mean overall satisfaction on a scale of 0–10]: 6.5 with trimix *v* 5.1 with vacuum device; P <0.05). [86]

Harms:

Papaverine plus phentolamine plus alprostadil (trimix) versus placebo in men with erectile dysfunction of any cause:
We found no RCTs.

Papaverine plus phentolamine plus alprostadil (trimix) versus intracavernosal alprostadil in men with erectile dysfunction of any cause:
See harms of alprostadil (intracavernosal), p 22 .

Papaverine plus phentolamine plus alprostadil (trimix) versus vacuum devices in men with erectile dysfunction of any cause:
The RCT found no significant difference in the frequency of adverse events between vacuum devices and trimix. [86] The RCT found that vacuum devices increased bruising compared with intracavernosal trimix; however, this difference did not reach significance (7/44 [16%] with vacuum device *v* 4/44 [9%] with intracavernosal trimix; reported as not significant; P value not reported). [86]

Comment:

Papaverine plus phentolamine plus alprostadil (trimix) versus vacuum devices in men with erectile dysfunction of any cause:
The RCT used outcome assessments that were not validated. [86] In the RCT, 80% of the 44 couples who completed the study were still using one or the other treatment after 18 to 24 months. [86]

QUESTION What are the effects of devices in men with erectile dysfunction of any cause?

OPTION PENILE PROSTHESES IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

We found no direct information from RCTs about penile prostheses in men with erectile dysfunction. There is consensus that penile prostheses are likely to be beneficial. Mechanical failure and infections are the most serious complications of penile prosthesis implantation. Use of penile prostheses is usually considered only after less invasive treatments have failed.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits: We found no systematic review or RCTs. For ethical reasons, RCTs of penile implants versus non-operative treatments for erectile dysfunction are unlikely to be carried out. Anecdotal evidence suggests that patient satisfaction may be high, but we found no studies of adequate quality to assess this. However, there is consensus belief that penile prostheses are likely to be beneficial.

Harms: We found no RCTs. For further information on harms from observational studies, see comment.

Comment: We found one prospective cohort study (331 men with erectile dysfunction implanted with different types of penile prosthesis) with 10-year follow-up. [87] Adverse effects of surgery included postoperative wound infection (19/331 [6%]), most of which involved abscesses requiring surgery for prosthesis removal. Additional complications included pain lasting >1 week (20/331 [6%]), local swelling lasting >1 month (18/331 [5%]), temporary haematoma of the penis and scrotum (16/331 [5%]), appearance of deformity requiring revision (9/331 [3%]), and inconvenience in daily life requiring removal of prosthesis (3/331 [1%]). Mechanical failure of the prosthesis was another complication of implantation (22/331 [7%]). [87]

Clinical guide:
Use of penile prostheses is usually considered only after less invasive treatments have failed.

OPTION VACUUM DEVICES IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function
Compared with papaverine, phentolamine, and alprostadil (trimix) We don't know how vacuum devices and intracavernosal injections of papaverine, phentolamine, and alprostadil (trimix) compare at achieving an erection, but intracavernosal injection of trimix may be more effective at increasing overall satisfaction scores and the ability to achieve an orgasm (very low-quality evidence).

Note
Vacuum devices have been associated with haematoma and blocked ejaculations. We found no direct information from RCTs about whether vacuum devices are better than no active treatment.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Vacuum devices versus placebo in men with erectile dysfunction of any cause:
We found no systematic review or RCTs.

Vacuum devices versus papaverine, phentolamine, and alprostadil (trimix) in men with erectile dysfunction of any cause:
See benefits of papaverine, phentolamine, and alprostadil (trimix), p 27 .

Harms:

Vacuum devices versus placebo in men with erectile dysfunction of any cause:
We found no RCTs.

Vacuum devices versus papaverine, phentolamine, and alprostadil (trimix) in men with erectile dysfunction of any cause:
See harms of papaverine, phentolamine, and alprostadil (trimix), p 27 .

Comment:

Vacuum devices have been associated with haematoma and blocked ejaculations.

Vacuum devices versus vacuum devices plus psychosexual therapy:
We found one RCT (45 couples) that compared a combination of a vacuum device plus psychosexual therapy versus psychosexual therapy alone. We will address this intervention in full in future updates of this review. [88]

QUESTION What are the effects of psychological/behavioural treatments in men with erectile dysfunction of any cause?

OPTION PSYCHOSEXUAL COUNSELLING IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function
Compared with waiting list control Psychosexual counselling may be more effective at improving sexual function in men with psychological erectile dysfunction (very low-quality evidence).

Compared with interpersonal therapy We don't know whether psychosexual counselling is more effective at improving sexual functioning or sexual satisfaction at 15 weeks in men with psychological erectile dysfunction. Interpersonal therapy aimed at improving social skills may be more effective than psychosexual counselling at increasing the proportion of men who no longer have erectile dysfunction at 6 to 12 months and when combined with psychosexual counselling may be more effective than either treatment alone (very low-quality evidence).

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

We found one systematic review (search date 2007, 9 RCTs and 2 quasi-randomised RCTs, 398 men) assessing psychological interventions for the treatment of erectile dysfunction, compared with oral drugs, local injection, vacuum devices, or other psychological intervention. [89] We found one additional RCT. [90]

Psychosexual counselling versus a waiting list control in men with erectile dysfunction of any cause:
The review found that group therapy significantly reduced the proportion of men with "persistence of erectile dysfunction" compared with waiting list control after treatment (5 RCTs, 80 men; 19/55 [35%] with group therapy *v* 40/45 [89%] with waiting list control/no treatment; RR 0.40, 95% CI 0.17 to 0.98; NNT 1.61, 95% CI 0.97 to 4.76). [89] It also found that group therapy significantly reduced the proportion of men with "persistence of erectile dysfunction" compared with waiting list control at 6 months' follow-up (2 RCTs, 37 men; 8/22 [36%] with group therapy *v* 15/15 [100%] with waiting list control/no treatment; RR 0.43, 95% CI 0.26 to 0.72; NNT 1.58, 95% CI 1.17 to 2.43). All the RCTs were small, and one was described as "quasi-randomised". [89]

The additional RCT (69 single men, excluded those with an organic basis for erectile dysfunction) compared 4 interventions: standard psychosexual counselling versus interpersonal difficulties oriented therapy (individually tailored social skills training) versus a combination of psychosexual counselling and interpersonal difficulties oriented training versus a 15-week waiting list control group. [90] At the end of the 15-week treatment period, the combined scores for all forms of psychological treatments improved sexual activities (P <0.03) and sexual satisfaction (P <0.004) compared with scores of the men in the waiting list control group, who had not made clinically meaningful gains as assessed by the 258-item Derogatis Sexual Functioning Inventory.

Psychosexual counselling versus interpersonal therapy in men with erectile dysfunction of any cause:
The additional RCT described above found no significant difference between psychosexual counselling alone, interpersonal therapy alone, or combination therapy in sexual functioning or sexual satisfaction at the end of 15 weeks of treatment. [90] However, over the 6- and 12-month follow-up, the proportion of men who no longer had erectile dysfunction was significantly greater for those treated with interpersonal therapy than those treated with psychosexual counselling (AR for men not meeting DSM III criteria for erectile dysfunction at 1 year: 78% with interpersonal therapy *v* 40% with psychosexual counselling; P <0.02). Combination treatment also increased the proportion of men who no longer had erectile dysfunction at 6-month and 1-year follow-up compared with either

interpersonal therapy or psychosexual counselling alone (P <0.03 for combination treatment *v* interpersonal therapy alone post treatment and *v* psychosexual therapy alone at 6 months and 1 year; results presented graphically).

Psychosexual counselling versus sildenafil citrate in men with erectile dysfunction of any cause:
The review [89] identified one small RCT comparing group therapy versus sildenafil citrate; however, this RCT did not meet *Clinical Evidence* inclusion criteria (see comment).

Harms: The review gave no information on adverse effects. [89]

Comment:

Psychosexual counselling versus sildenafil citrate in men with erectile dysfunction of any cause:
The small three-armed RCT (30 men with psychogenic erectile dysfunction) identified by the review compared group psychotherapy (weekly sessions of time-limited theme-based group psychotherapy) plus sildenafil citrate (50 mg orally on demand) versus sildenafil citrate alone versus group psychotherapy alone, for 6 months. [91] This RCT did not meet *Clinical Evidence* inclusion criteria because of poor follow-up. However, because of paucity of data on this comparison, we have included a comment on this study. It found that psychotherapy alone significantly improved erectile function, assessed by change in International Index of Erectile Function (IIEF)-erectile function domain scores from baseline, at the end of treatment, and 3 months after treatment ended compared with sildenafil alone.

Sex therapy versus intracavernosal alprostadil injection in men with erectile dysfunction of any cause:
The review [89] identified one RCT comparing standard sex therapy for 12 weeks versus self-injection therapy using low-dose alprostadil prostaglandin E1 (2.5–5.0 micrograms). This RCT (50 men with psychogenic erectile dysfunction) did not meet *Clinical Evidence* inclusion criteria because of low follow-up; however, we have included a comment here because of paucity of data on this comparison. It found no significant difference between groups in the proportion of people who were able to obtain an unassisted erection, or in the proportion of people satisfied with treatment or in Sexual Life Quality Questionnaire scores at the end of treatment. [92]

Psychosexual counselling plus sildenafil versus sildenafil citrate in men with erectile dysfunction of any cause:
The review also identified two small RCTs comparing combined group therapy plus sildenafil citrate versus sildenafil citrate alone in men with psychogenic erectile dysfunction, and pooled these data. We will assess this comparison in full in future updates of this *Clinical Evidence* review. It found that psychotherapy plus sildenafil significantly decreased the proportion of men with "persistence of erectile dysfunction" compared with sildenafil alone after treatment. [89]

Papaverine plus phentolamine plus counselling versus papaverine plus phentolamine alone in men with erectile dysfunction of any cause:
The review identified one quasi-randomised RCT comparing papaverine plus phentolamine (intracavernosal injection) plus counselling versus papaverine plus phentolamine alone. We will assess this comparison in full in future updates of this *Clinical Evidence* review. It found no significant difference between groups in "persistence of erectile dysfunction". [89]

OPTION COGNITIVE BEHAVIOURAL THERAPY IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

We found no direct information from RCTs about cognitive behavioural therapy in men with erectile dysfunction. Anecdotal evidence suggests that this may be an effective treatment.

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment:

Clinical guide:
Cognitive behavioural therapy involves attempts to elicit and modify maladaptive thoughts and to address relationship issues, in addition to behavioural exercises (as in standard sex therapy). Modern sex therapy incorporates some aspects of cognitive behavioural therapy and conversely, cognitive behavioural therapy includes many elements of sex therapy. Anecdotal evidence suggests that it may be an effective treatment but we found no studies of adequate quality to assess this.

QUESTION What are the effects of alternative treatments in men with erectile dysfunction of any cause?

OPTION GINSENG IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function
Compared with placebo Red ginseng seems more effective at improving erectile function rates in men with erectile dysfunction (moderate-quality evidence).

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Ginseng versus placebo in men with erectile dysfunction of any cause:
We found one systematic review (search date 2008, 7 RCTs, 363 men) assessing red ginseng for the treatment of erectile dysfunction. [93] The review found that ginseng significantly improved erectile function rates compared with placebo over 4 to 12 weeks (6 RCTs, 349 men; proportion of men with successful improvement in sexual function: 108/185 [58%] with ginseng *v* 33/164 [20%] with placebo; RR 2.40, 95% CI of 1.65 to 3.51; P <0.00001). The review found that most of the RCTs had small sample sizes and variable methodological quality.

We found one subsequent RCT (69 men with mild to moderate erectile dysfunction), which also assessed efficacy and safety of red ginseng extract powder versus placebo. [94] However, this RCT was written in Korean. We are awaiting full-text translation of this RCT, and will assess it for inclusion at the next update.

Harms:

Ginseng versus placebo in men with erectile dysfunction of any cause:
The review found that adverse effects of red ginseng were reported in 5 RCTs, and included headache or insomnia (6 cases), gastric upset (4 cases), and constipation (2 cases) with ginseng; and gastric upset (3 cases) with placebo (no significance assessment reported). [93]

Comment:

Clinical guide:
Ginseng is a traditional Asian remedy with rare adverse effects in the recommended dose of 0.5–2.0 g daily.

OPTION YOHIMBINE IN MEN WITH ERECTILE DYSFUNCTION OF ANY CAUSE

Improvement in sexual function
Compared with placebo Yohimbine may be more effective at improving self-reported sexual function and penile rigidity at 2 to 10 weeks (very low-quality evidence).

For GRADE evaluation of interventions for erectile dysfunction, see table, p 36 .

Benefits:

Yohimbine versus placebo in men with erectile dysfunction of any cause:
We found one systematic review (search date 1997, 7 RCTs [including 5 crossover trials], 419 men with various causes of erectile dysfunction) [95] and one subsequent RCT [96] comparing yohimbine versus placebo.

The review conducted a meta-analysis, and found that yohimbine significantly improved erectile response (measurement varied between studies and included objective and subjective assessments of penile rigidity and sexual function) compared with placebo (erectile response: 34–73% with yohimbine *v* 9–45% with placebo; OR 3.85, 95% CI 2.22 to 6.67; absolute numbers not reported). [95]

The subsequent RCT, a small crossover study (29 men, mixed types of erectile dysfunction, mean age 51 years) compared yohimbine 36 mg daily with placebo over two 25-day treatment periods with a 14-day washout period in between. It found no significant difference in positive clinical responses between yohimbine and placebo (positive clinical response: 12/27 [44%] with yohimbine *v* 13/27 [48%] with placebo; reported as not significant). [96]

Harms:

Yohimbine versus placebo in men with erectile dysfunction of any cause:
The review reported that adverse effects were generally minor and reversible, and included agitation, anxiety, headache, mild increase in blood pressure, increased urinary output, and gastrointestinal upset. Yohimbine was associated with a higher proportion of adverse events compared with placebo (10–30% with yohimbine *v* 5–16% with placebo; significance assessment not performed). [95] Two men withdrew from the subsequent crossover RCT because of a hypertensive crisis in one and severe palpitations in the other. [96]

Comment: None of the RCTs in the systematic review [95] nor the subsequent RCT [96] described the method of randomisation. The trials included in the systematic review were clinically heterogeneous in aetiology of erectile dysfunction and age, and lacked homogeneous study designs (combined partial crossover and parallel RCTs) or homogeneous outcome assessments. The forest plot of the meta-analysis did not indicate heterogeneity, but statistical heterogeneity was not assessed. [95]

GLOSSARY

Priapism Prolonged, and often painful, erections of the penis in the absence of sexual desire that can last for several hours to days. Prompt treatment to relieve the erection and prevent scarring is recommended if the erection does not subside in 4 hours.

Ecchymosis Skin discoloration caused by the escape of blood into the tissues from ruptured blood vessels.

Global Assessment Questionnaire A self-administered questionnaire that allows men to rate improvement in erectile function.

Global Efficacy Question Asks, "Did the treatment you have been taking over the past 4 weeks improve your erections?" This question is answered with a "yes" or "no". In some trials, responses are scored on a 7-point scale ranging from "no improvement" to "intense improvement".

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

International Index of Erectile Function (IIEF) intercourse satisfaction domain The IIEF is a brief 15-item, self-administered questionnaire developed to assess the effects of treatments for men with erectile dysfunction. Each question is answered on a 5- or 6-point Likert-type scale (scores of 0–5 or 1–5). The intercourse satisfaction domain score is calculated by summing the scores for questions 6, 7, and 8, for a total possible score of 0–15, with higher scores indicating less dysfunction.

International Index of Erectile Function (IIEF) overall satisfaction The IIEF is a brief 15-item, self-administered questionnaire developed to assess the effects of treatments for men with erectile dysfunction. Each question is answered on a 5- or 6-point Likert-type scale (scores of 0–5 or 1–5). The overall satisfaction domain score is calculated by summing the scores for questions 13 and 14, for a total possible score of 2–10, with higher scores indicating less dysfunction.

International Index of Erectile Function (IIEF) questions 3 and 4 The IIEF is a brief 15-item, self-administered questionnaire developed to assess the effects of treatments for men with erectile dysfunction. Questions 3 and 4 ask, "over the past 4 weeks, when you have attempted sexual intercourse, how often were you able to penetrate (enter) your partner?", and "Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you have penetrated (entered) your partner?" Each question is answered on a 6-point scale of 0–5.

International Index of Erectile Function (IIEF-EF) erectile function domain The IIEF is a brief 15-item, self-administered questionnaire developed to assess the effects of treatments for men with erectile dysfunction. Each question is answered on a 5- or 6-point Likert-type scale (scores of 0–5 or 1–5). The erectile function domain score is calculated by summing the scores for questions 1, 2, 3, 4, 5, and 15, for a total possible score of 1–30, with lower scores indicating worse dysfunction.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Sexual Encounter Profile (SEP) questions 2 and 3 This is a diary maintained by men after each sexual attempt consisting of a series of yes/no questions regarding specific aspects of each encounter. Question 2 asks, "Were you able to insert your penis into your partner's vagina?" and question 3 asks, "Did your erection last long enough for you to complete intercourse with ejaculation?"

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Tadalafil in men with cardiovascular disease New option added. Categorised as Unknown effectiveness, as we found no RCT evidence to assess the effects of this intervention.

Vardenafil in men with cardiovascular disease New option added. Categorised as Unknown effectiveness, as we found no RCT evidence to assess the effects of this intervention.

Tadalafil in men with spinal cord injury New option added. [58] Categorised as Likely to be beneficial.

Vardenafil in men with spinal cord injury New option added. Categorised as Unknown effectiveness, as we found no RCT evidence to assess the effects of this intervention

Tadalafil in men with prostate cancer or undergoing prostatectomy New option added. [61] [62] [63] Categorised as Likely to be beneficial.

Alprostadil (topical) in men with erectile dysfunction of any cause New evidence added. [71] Categorisation unchanged (Trade-off between benefits and harms).

Ginseng in men with erectile dysfunction of any cause New evidence added. [93] Categorisation unchanged (Likely to be beneficial).

Psychosexual counselling in men with erectile dysfunction of any cause New evidence added. [89] Categorisation unchanged (Likely to be beneficial).

Sildenafil in men with diabetes New evidence added. [43] Categorisation unchanged (Beneficial).

Sildenafil in men with erectile dysfunction of any cause New evidence added. [7] [21] [22] [23] Categorisation unchanged (Beneficial).

Sildenafil in men with prostate cancer or undergoing prostatectomy New evidence added. [59] Categorisation unchanged (Likely to be beneficial).

Sildenafil in men with spinal cord injury New evidence added. [52] [53] [54] [55] [56] Categorisation unchanged (Likely to be beneficial).

Tadalafil in men with diabetes New evidence added. [43] [45] Categorisation unchanged (Likely to be beneficial).

Tadalafil in men with erectile dysfunction of any cause New evidence added. [7] [28] [29] [30] [31] [32] [33] [34] Categorisation unchanged (Beneficial).

Vardenafil in men with diabetes New evidence added. [43] [46] Categorisation unchanged (Likely to be beneficial).

Vardenafil in men with erectile dysfunction of any cause New evidence added. [7] [38] [39] [40] [41] Categorisation unchanged (Beneficial).

Alprostadil (intracavernosal) in men with erectile dysfunction of any cause No new evidence added. Existing evidence re-evaluated and categorisation changed from Beneficial to Trade-off between benefits and harms, because of the association with penile pain.

Alprostadil (intraurethral) in men with erectile dysfunction of any cause No new evidence added. Existing evidence re-evaluated and categorisation changed from Beneficial to Trade-off between benefits and harms, because of the association with penile pain.

Vacuum devices in men with erectile dysfunction of any cause No new evidence added. Existing evidence re-evaluated and one RCT previously reported was excluded as it did not meet inclusion criteria. Categorisation changed from Likely to be beneficial to Unknown effectiveness, because evidence is insufficient to judge the effects of this intervention.

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Disclaimer

TABLE **GRADE evaluation of interventions for erectile dysfunction**

Important outcomes	Improvement in sexual function, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of phosphodiesterase inhibitors in men with erectile dysfunction of any cause?									
30 (more than 2979 men) [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23]	Improvement in sexual function	Sildenafil *v* placebo in men with erectile dysfunction of any cause	4	0	0	0	0	High	
At least 20 (at least 4146) [25] [7] [26] [27] [28] [29] [30] [31] [32] [33] [34]	Improvement in sexual function	Tadalafil *v* placebo in men with erectile dysfunction of any cause	4	0	0	0	0	High	
8 (3995) [7] [37] [38] [39] [40] [41]	Improvement in sexual function	Vardenafil *v* placebo in men with erectile dysfunction of any cause	4	−1	0	0	0	Moderate	Quality point deducted for methodological weaknesses in some RCTs (including results post crossover)
What are the effects of phosphodiesterase inhibitors on erectile dysfunction in men with diabetes?									
20 (1923) [6] [43]	Improvement in sexual function	Sildenafil *v* placebo in men with diabetes	4	−1	0	0	0	Moderate	Quality point deducted for subgroup analysis
2 (514) [44] [45]	Improvement in sexual function	Tadalafil *v* placebo in men with diabetes	4	0	0	−1	0	Moderate	Directness point deducted for differences in regimens between studies
2 (770) [36] [46]	Improvement in sexual function	Vardenafil *v* placebo in men with diabetes	4	0	0	0	0	High	
What are the effects of phosphodiesterase inhibitors on erectile dysfunction in men with cardiovascular disease?									
More than 2 RCTs (739) [6] [47] [48]	Improvement in sexual function	Sildenafil *v* placebo in men with heart disease	4	−1	0	0	0	Moderate	Quality point deducted for subgroup analysis
What are the effects of phosphodiesterase inhibitors on erectile dysfunction in men with spinal cord injury?									
3 (245) [53] [54] [55] [56]	Improvement in sexual function	Sildenafil *v* placebo in men with spinal cord injury	4	−2	0	0	0	Low	Quality points deducted for results post crossover and composite outcome in largest RCT
1 (186) [58]	Improvement in sexual function	Tadalafil *v* placebo in men with spinal cord injury	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of phosphodiesterase inhibitors on erectile dysfunction in men with prostate cancer or undergoing prostatectomy?									
2 (176) [6] [60]	Improvement in sexual function	Sildenafil *v* placebo in men after radical prostatectomy or prostate cancer	4	−2	0	0	0	Low	Quality points deducted for sparse data and for subgroup analysis
2 (363) [61] [62] [63]	Improvement in sexual function	Tadalafil *v* placebo in men after radical prostatectomy or prostate cancer	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting in 1 RCT and for results post crossover in the other RCT

Important outcomes	Improvement in sexual function, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (440) [36]	Improvement in sexual function	Vardenafil *v* placebo in men after prostatectomy	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and inclusion of unpublished study. Directness point deducted for inclusion of previous responders to treatment
What are the effects of drug treatments other than phosphodiesterase inhibitors in men with erectile dysfunction of any cause?									
3 (1828) [64]	Improvement in sexual function	Intraurethral alprostadil *v* placebo in men with erectile dysfunction of any cause	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and methodological weaknesses (uncertainty about randomisation and whether allocation concealment was performed). Directness point deducted for pre-selecting treatment responders affecting generalisability to clinical practice
1 (270) [65]	Improvement in sexual function	Intraurethral alprostadil *v* placebo in men after radical prostatectomy	4	−1	0	0	0	Moderate	Quality point deducted for uncertainty about randomisation and whether allocation concealment was performed
3 (274) [66] [67] [68]	Improvement in sexual function	Intraurethral alprostadil *v* intracavernosal alprostadil in men with erectile dysfunction of any cause	4	−2	0	−2	0	Very low	Quality points deducted for methodological weaknesses (lack of blinding and uncertainty about randomisation and whether allocation concealment was performed). Directness points deducted for pre-selecting treatment responders affecting generalisability to clinical practice, and inclusion of additional treatment in 1 RCT
4 (1834) [69] [70] [71]	Improvement in sexual function	Topical alprostadil *v* placebo in men with erectile dysfunction of any cause	4	−1	0	0	0	Moderate	Quality points deducted for not reporting methods of randomisation/allocation concealment
1 (40) [81]	Improvement in sexual function	Papaverine *v* papaverine plus phentolamine (bimix) in men with erectile dysfunction of any cause	4	−2	0	0	0	Low	Quality points deducted for sparse data and results post crossover
1 (30) [83]	Improvement in sexual function	Papaverine plus phentolamine (bimix) *v* placebo in men with erectile dysfunction of any cause	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting. Directness point deducted for no direct statistical comparison between groups
2 (356) [73] [74]	Improvement in sexual function	Intracavernosal alprostadil *v* placebo in men with erectile dysfunction of any cause	4	−3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, and for methodological weaknesses (randomisation/allocation concealment, subjective assessment of outcome, and unblinded assessment of outcome)
3 (235) [75] [76] [77]	Improvement in sexual function	Intracavernosal alprostadil *v* papaverine in men with erectile dysfunction of any cause	4	−3	0	0	0	Very low	Quality points deducted for incomplete reporting and methodological weaknesses (uncertainty about methods of randomisation and allocation concealment, subjective assessment of outcome, and results post crossover)

Important outcomes	Improvement in sexual function, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (142) [74] [78]	Improvement in sexual function	Intracavernosal alprostadil *v* papaverine plus phentolamine (bimix) in men with erectile dysfunction of any cause	4	−3	0	0	0	Very low	Quality points deducted for sparse data, and for methodological weaknesses (uncertainty about methods of randomisation and allocation concealment, subjective assessment of outcome, and results post crossover)
2 (114) [78] [79]	Improvement in sexual function	Intracavernosal alprostadil *v* alprostadil plus papaverine plus phentolamine (trimix) in men with erectile dysfunction of any cause	4	−3	0	0	0	Very low	Quality points deducted for sparse data, and for methodological weaknesses (uncertainty about methods of randomisation and allocation concealment, subjective assessment of outcome, and results post crossover
1 (44) [86]	Improvement in sexual function	Intracavernosal papaverine, phentolamine, and alprostadil (trimix) *v* vacuum devices in men with erectile dysfunction of any cause	4	−3	0	−1	0	Very low	Quality points deducted for sparse data, and for methodological weaknesses (uncertainty about methods of randomisation and allocation concealment, results post crossover). Directness point deducted for not using validated outcome assessments
What are the effects of psychological/behavioural treatments in men with erectile dysfunction of any cause?									
At least 6 (at least 159) [89] [90]	Improvement in sexual function	Psychosexual counselling *v* waiting list control in men with erectile dysfunction of any cause	4	−3	0	−1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and for methodological weaknesses (quasi-randomisation of 1 RCT included in analysis). Directness point deducted for restricted population in 1 RCT (men with psychogenic erectile dysfunction only)
1 (69) [90]	Improvement in sexual function	Psychosexual counselling *v* interpersonal therapy in men with erectile dysfunction of any cause	4	−3	0	−1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and for methodological weaknesses (uncertainty about methods of randomisation and allocation concealment). Directness point deducted for restricted population in 1 RCT (men with psychogenic erectile dysfunction only)
What are the effects of alternative treatments in men with erectile dysfunction of any cause?									
6 (349) [93]	Improvement in sexual function	Ginseng *v* placebo in men with erectile dysfunction of any cause	4	−1	0	0	0	Moderate	Quality point deducted for methodological weaknesses in included RCTs
8 (448) [95] [96]	Improvement in sexual function	Yohimbine *v* placebo in men with erectile dysfunction of any cause	4	−3	0	0	0	Very low	Quality points deducted for incomplete reporting and for methodological weaknesses (uncertainty about method of randomisation, lack of homogeneity in study design and outcome assessments, and results post crossover)

Type of evidence: 4 = RCT; 2 = Observational.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.