Interventions for treating sexual dysfunction in patients with chronic kidney disease (Review)

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Interventions for treating sexual dysfunction in patients with chronic kidney disease

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ABSTRACT

Background
Sexual dysfunction is very common in patients with chronic kidney disease (CKD), but it is still significantly understudied. Treatment options exist but concerns have been raised relating to their efficacy and safety in CKD.

Objectives
We assessed the benefits and harms of existing interventions for treatment of sexual dysfunction in patients with CKD.

Search methods
In October 2010 we searched the Cochrane Renal Group’s specialised register, CENTRAL (The Cochrane Library, issue 10), MEDLINE (from 1966) and EMBASE (from 1980).

Selection criteria
Randomised controlled trials (RCTs) and quasi-RCTs of any pharmacological and non-pharmacological interventions used to treat sexual dysfunction in male and female CKD patients (predialysis, dialysis and kidney transplant) were included.

Data collection and analysis
Two authors independently selected eligible studies, extracted data and assessed study quality. Disagreements were resolved in consultation with an arbitrator. Treatment effects were summarised as risk ratios (RR), mean differences (MD) or standardised mean difference (SMD) with 95% confidence intervals (CI) using a random-effects model.
Main results

Fifteen studies (8 parallel, 7 crossover; 352 patients) were included. Only one study enrolled women. Studies evaluated the effects of phosphodiesterase-5 inhibitors (PDE5i), zinc, vitamin E, vitamin D or bromocriptine compared to placebo. PDE5i significantly increased the overall International Index of Erectile Function-5 (IIEF-5) score (2 studies, 101 patients, MD 10.65, 95% CI 5.34 to 15.96), all its individual domains and the complete 15-item IIEF tool (1 study, 41 patients, MD 2.64, 95% CI 1.32 to 3.96). End of treatment testosterone levels were not significantly increased by addition of zinc to dialysate (2 studies, 22 patients, MD 0.21 ng/mL, 95% CI -2.14 to 2.55) but oral zinc improved end of treatment testosterone levels (1 study, 20 patients, SMD 1.62, 95% CI 0.58 to 2.66). There was no difference in plasma luteinizing and follicle-stimulating hormone levels at the end of the study period with zinc therapy. Only sparse data were available for vitamin E, bromocriptine and dihydroxycholecalciferol in CKD patients and there were no studies of intracavernous injections, transurethral injections, mechanical devices or psychosexual therapies in people with CKD.

Authors’ conclusions

PDE5i and zinc are promising interventions for treating sexual dysfunction in men with CKD. Evidence supporting their routine use in CKD patients is limited. There is an unmet need for studying interventions for both male and female sexual dysfunction in CKD, considering the significant disease burden.

Plain Language Summary

Interventions for treating sexual dysfunction in men and women with chronic kidney disease

Sexual dysfunction is very common in patients with chronic kidney disease (CKD). Men with CKD frequently suffer from reduced libido, erectile dysfunction and difficulty reaching orgasm. Approximately 50% to 80% of men with CKD have erectile dysfunction and the prevalence has been found to increase with age. For women with CKD, 55% report difficulty with sexual arousal. Dysmenorrhoea, delayed sexual development, impaired vaginal lubrication, dyspareunia and difficulties in reaching orgasm are also frequently observed. Therapies that have been used to treat sexual dysfunction include phosphodiesterase-5 inhibitors (PDE5i), intracavernous injections, intraurethral suppositories, hormonal therapy, mechanical devices and psychotherapy. Although many clinical studies and reviews have explored the role of these interventions for sexual dysfunction in patients without CKD, the effectiveness and safety of these interventions in patients with CKD have not yet been studied thoroughly. The aim of this review was to assess the benefits and harms of existing interventions for treating sexual dysfunction in patients with CKD.

We identified 15 studies enrolling 352 patients with only one study enrolling both men and women. Studies evaluated the effects of phosphodiesterase-5 inhibitors (PDE5i), zinc, vitamin E, vitamin D or bromocriptine compared to placebo. In two studies (101 patients) PDE5i significantly increased the individual domains and the overall International Index of Erectile Function-5 (IIEF-5) score and the complete 15-item IIEF tool (1 study, 41 patients). End of treatment testosterone levels were not significantly increased by addition of zinc to dialysate (2 studies, 22 patients) but oral zinc improved end of treatment testosterone levels (1 study, 20 patients). There was no difference in plasma luteinizing and follicle-stimulating hormone levels at the end of the study period with zinc therapy. Little data were available for vitamin E, bromocriptine and dihydroxycholecalciferol in CKD patients and there were no studies of intracavernous injections, transurethral injections, mechanical devices or behavioural therapy in people with CKD.

PDE5i and zinc are promising interventions for treating sexual dysfunction in men with CKD however evidence supporting their routine use in CKD patients is limited. There is an unmet need for studying interventions for both male and female sexual dysfunction in CKD, considering the significant disease burden.

Background

Sexual dysfunction is a set of disorders characterised by physical and psychological changes that result in the inability to perform satisfactory sexual activities. The condition has been found to be significantly more common in both men and women with chronic kidney disease (CKD) than in the general population (Laumann 1999). Men with CKD frequently suffer from reduced libido, erec-
tile dysfunction (ED) and difficulty reaching orgasm (Finkelstein 2007). Approximately 50% of male predialysis CKD patients and 80% of male dialysis patients have ED (Anantharaman 2007; Procci 1981; Rosas 2001; Sharma 2006). Moreover, the prevalence of ED in male dialysis patients has been found to increase with age (63% of men aged < 50 years versus 90% of men aged ≥ 50 years) (Rosas 2001). Similar results have been reported in women with CKD, with 55% of female dialysis patients reporting difficulty with sexual arousal (Finkelstein 2007). Dysmenorrhoea, delayed sexual development, impaired vaginal lubrication, dyspareunia and difficulties in reaching orgasm are also frequently observed (Bellinghieri 2008; Peng 2005).

Multiple factors contribute to the frequent occurrence of sexual dysfunction in CKD patients, including hormonal disturbances (such as hyperprolactinaemia, hypogonadism in males and changes in hypothalamic-pituitary function in females) (Palmer 1999), anaemia (Lawrence 1997), CKD mineral and bone disorders (Anantharaman 2007), psychosocial factors (such as depression, anxiety, poor self-esteem, social withdrawal, marital discord, body image issues, fear of disability and death, loss of employment and financial difficulties) (Finkelstein 2007; Kimmel 1996; Kutner 2004), autonomic neuropathy (Campese 1990), medications (including antihypertensives, antidepressants and histamine receptor blockers) (Finkelstein 2007), and comorbid illness (such as diabetes mellitus, cardiovascular disease and malnutrition) (Finkelstein 2007; Naya 2002). Sexual dysfunction is inversely associated with glomerular filtration rate (Bellinghieri 2008) and is improved following kidney transplantation (Al Khallaf 2009; Mehrsai 2006), suggesting that CKD per se may contribute to sexual dysfunction in these patients (Mehsai 2006).

Studies have also identified significant associations between sexual dysfunction in CKD patients and depression (Peng 2005; Seidman 2006), impaired quality of life (Peng 2005; Seidman 2006; Turk 2004) and adverse cardiovascular outcomes (Goldstein 2000). Effective treatment of sexual dysfunction in CKD patients may, therefore, potentially lead to improvements in these patient-level outcomes, although a causal link has not been definitively established (Turk 2004).

Therapies that have been used to treat sexual dysfunction include phosphodiesterase-5 inhibitors (PDE5i), intracavernosal injections, intraurethral suppositories, hormonal therapy, mechanical devices and psychotherapy. Although many clinical studies and reviews have explored the role of these interventions for sexual dysfunction in non-uraeemic patients (Esposito 2004; Linet 1996; Melnik 2008; Padma-Nathan 2003), the effectiveness and safety of these interventions in patients with CKD have not yet been studied thoroughly.

**OBJECTIVES**

We aimed to evaluate the benefits and harms associated with various interventions for sexual dysfunction in patients with CKD.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All randomised controlled trials (RCTs) and quasi-RCTs of any treatment (hormone therapy, PDE5i, intracavernous injections, intraurethral pellets, mechanical devices and behavioural therapy) for sexual dysfunction in male and female patients with CKD were included. Studies were considered without language restrictions.

**Types of participants**

**Inclusion criteria**

Patients aged > 18 years and with any stage of CKD, including patients who were not receiving renal replacement therapy (RRT) (predialysis) and those with end-stage kidney disease (ESKD) who were receiving haemodialysis or peritoneal dialysis or who had a functioning kidney transplant, were considered for inclusion.

**Exclusion criteria**

Studies that enrolled patients without CKD were excluded.

**Types of interventions**

All studies of pharmacological and non-pharmacological interventions for treating sexual dysfunction in patients with CKD were considered for inclusion.

**Interventions related to the treatment of male sexual dysfunction**

We explored pharmacological and non-pharmacological interventions. Pharmacological agents included hormonal therapy (oral, injected or topical (transdermal) testosterone) and drugs both oral (including PDE5is sildenafil, tadalafil, vardenafil and mirodenafil) or topical (intracavernous injections of alprostadil, α1-antagonist, intraurethral alprostadil, prazosin or their combinations). Non-pharmacological strategies included mechanical devices (vacuum constriction device (VCD) for inducing erection, penile prosthesis) and psycho-educational interventions such as rational emotive therapy (RET), sex group therapy (GT), modified Masters,
Interventions related to the treatment of female sexual dysfunction

We explored pharmacological agents including hormonal therapy (oral or topical (transdermal) oestrogens, testosterone, progesterone or tibolone) and drugs (oral PDE5i). Non-pharmacological strategies included mechanical interventions (oestrogen or non-hormonal lubricating vaginal creams and clitoral therapy device), psycho-educational interventions such as RET, sex GT, modified Masters and Johnson Kaplan’s sexual therapy, educational intervention, systematic desensitization and sexual counselling.

Types of outcome measures

We planned to obtain the following outcome measures as reported in the included studies.

Male sexual dysfunction outcomes

- Changes in mean score on any standard validated sexual function scale: the various scales that were considered for inclusion included the 15-item International Index of Erectile Function (IIEF), 5-item International Index of Erectile Function (IIEF-5), Physic Component Score (PCS), Mental Component Score (MCS)
- Achievement of prolonged penile rigidity satisfactory to enable complete sexual intercourse (measurement of genital blood flow and nocturnal penile tumescence (NPT))
- Number of successful sexual intercourse attempts and number of participants who showed improved sexual function as measured by a patient log and reported by study authors
- Hormone levels as measured by trialists (including testosterone or other hormone levels)
- Major and minor adverse effects of interventions (coronary ischaemia, headache, flushing for PDE5i and priapism for intracavernous injections)
- Treatment compliance as defined by study authors
- Number of participants who dropped out

Female sexual dysfunction outcomes

- Changes in score on any standard validated sexual function scale (Female Sexual Function Index (FSFI), Female Intervention Efficacy Index (FIEI) and Female Sexual Distress Scale (FSDS))
- Variation of vaginal pressure-volume, genital threshold of perception of vibration, vaginal pH, genital blood flow, prolactin and zinc concentrations (units as reported by study authors)
- Hormonal levels as measured by trialists (including luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin levels or other)
- Levels of other markers (including zinc or other as reported by study authors)
- Number of participants who showed improved sexual function (as defined by study authors)
- Adverse effects (incidence of coronary ischaemia for PDE5i, breast cancer (ductal carcinoma in situ, lobular carcinoma in situ, invasive ductal carcinoma, invasive lobular carcinoma) for oestrogen replacement therapy and headache as reported in the study
- Treatment compliance as defined by study authors
- Number of participants who dropped out

Search methods for identification of studies

We searched the Renal Group’s specialised register, CENTRAL (The Cochrane Library, issue 10), MEDLINE (from 1950) and EMBASE (from 1980) for relevant studies. Two authors independently, assessed each study. The search strategy used to obtain titles and abstracts of studies that may be relevant to the review is reported in Appendix 1.

Date of last search: 29 October 2010.

Electronic searches

1. The Cochrane Renal Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library) contain the handsearched results of conference proceedings from general and specialty meetings. This is an ongoing activity across The Cochrane Collaboration and is both retrospective and prospective (Master List 2010). Therefore we did not specifically search conference proceedings. Please refer to The Cochrane Renal Group’s Module in The Cochrane Library for the most up-to-date list of conference proceedings (Renal Group 2010).
2. MEDLINE (1966 to most recent) using the optimally sensitive strategy developed for The Cochrane Collaboration for the identification of RCTs (Lefebvre 2008) with a search strategy developed with input from the Cochrane Renal Group’s Trial Search Co-ordinator.
3. EMBASE (1980 to most recent) using a search strategy adapted from that developed for The Cochrane Collaboration for the identification of RCTs (Lefebvre 2008) with the search strategy developed with input from the Cochrane Renal Group’s Trial Search Co-ordinator.

Searching other resources

1. Reference lists of nephrology textbooks, review articles and relevant studies.
2. Letters seeking information about unpublished or incomplete studies were sent to investigators known to be involved in previous studies.
Data collection and analysis

Selection of studies
The titles and abstracts were screened independently by the same two review authors who discarded studies that were not applicable, however studies and reviews that might include relevant data or information on studies were initially retained. The review authors independently assessed retrieved abstracts and the full text of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management
Data extraction was carried out independently by the same review authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of a study existed, only the paper with the most complete data was included. Further information required from the original author was requested by written correspondence and any relevant information obtained was included in the review. Disagreements were resolved in consultation with a third author.

Assessment of risk of bias in included studies
The following items were assessed using the risk of bias assessment tool (Higgins 2008) (see Appendix 2).
- Was there adequate sequence generation?
- Was allocation adequately concealed?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Were reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a risk of bias?

The quality of included studies was assessed independently by two authors using a checklist that included allocation concealment; blinding of participants, investigators, outcome assessors and data analyst; use of intention-to-treat analysis; and completeness of follow-up. Any discrepancy was resolved by discussion with a third author.

Measures of treatment effect
For dichotomous outcomes (adverse effects of coronary ischaemia due to PDE5i, priapism or penile pain due to intraurethral injections, vaginal itching due to vaginal cream, study withdrawal rate due to any adverse effect) results were expressed as relative risk (RR) with 95% confidence interval (CI). Data were pooled using the random-effects model but the fixed-effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers. Where continuous scales of measurement were used to assess the effects of treatment (15-IIEF score, 5-IIEF score; FSFI score; FIEI score; vaginal pH; genital blood flow; variations of vaginal pressure-volume; genital threshold of perception of vibration; measurement of testosterone, LH, FSH, prolactin and zinc concentration) the mean difference (MD) was used, or the standardised mean difference (SMD) if different measurement scale units were used.

Dealing with missing data
We contacted authors for any missing data.

Assessment of heterogeneity
Heterogeneity was analysed using the Chi² test on N-1 degrees of freedom (Cochran Q), with an alpha of 0.05 used for statistical significance; and the I² statistic (Higgins 2002).

Data synthesis
Data were pooled using the random-effects model but the fixed-effect model was also analysed to ensure robustness of the model chosen and test for susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity
Heterogeneity among participants could be related to age, presence or absence of co-morbidities such as anaemia in CKD, diabetes, endocrine disorders, cardiovascular disease and altered mineral metabolism. Heterogeneity in treatments could be related to dose, duration and type of therapy and mode of administration. Subgroup analyses were also planned by stage of CKD (predialysis, haemodialysis, peritoneal and transplant patients) but were not conducted due to the lack of data.

Results of the search
We identified 114 articles. Seventy-six studies were excluded at abstract stage as they did not meet our inclusion criteria. Of the remaining 38 citations (full text analysis), nine studies (12 reports) were excluded as they assessed populations or outcomes that were not relevant to this review. Finally 15 studies reported in 25 publications and enrolling a total of 352 patients were included in
the review (Figure 1) (Antoniou 1977; Bellovich 2000; Blumberg 1980; Bommer 1979; Brook 1980; Demir 2006; Mahajan 1982; Mahon 2005; Muir 1983; Seibel 2002; Sharma 2006; Turk 2010; Wabrek 1982; Yang 2008; Yeksan 1992).

Figure 1. Flow chart showing the number of citations retrieved by individual searches and number of studies included

- Renal register
  - n = 40 reports

- MEDLINE
  - n = 41 reports

- EMBASE
  - n = 33 reports

Total reports: 114

Excluded reports: 76
- Not RCT or q-RCT (2), wrong population or intervention (59), review (8), duplicate (7)

Full text analysis: 38

Excluded reports: 12
- Not RCT or q-RCT (9), wrong population or intervention (3)

Ongoing studies: 1

Included studies: 15 (25 reports, 352 patients)
- Parallel studies (8); crossover studies (7)
- Outcomes reported: IIEF/IIEF-5 (7); prolactin (2); LH level (5); FSH level (5); testosterone level (7); other biochemical parameters (1); NPT (4); libido (4); frequency of intercourse (2); interview (2); Global efficiency question (2); frequency and quality of erection (1)
Included studies

Two groups of studies were identified: eight parallel studies (Antoniou 1977; Brook 1980; Demir 2006; Mahajan 1982; Seibel 2002; Wabrek 1982; Yang 2008; Yeksan 1992) and seven crossover studies (Bellovich 2000; Blumberg 1980; Bommer 1979; Mahon 2005; Muir 1983; Sharma 2006; Turk 2010).

Of the eight parallel studies, four (50 patients) compared elementary zinc or zinc chloride to placebo (Antoniou 1977; Brook 1980; Mahajan 1982; Wabrek 1982). In three of these studies zinc chloride was added to the dialysis bath (Antoniou 1977; Brook 1980; Wabrek 1982), in one study elementary zinc was administered orally (Mahajan 1982). Two studies (99 patients) compared vardenafil to placebo (Demir 2006; Yang 2008) while one study (41 patients) compared sildenafil citrate to placebo (Seibel 2002). One study (24 patients) compared vitamin E to placebo (Yeksan 1992). Of the remaining seven crossover studies, three studies (62 patients) compared sildenafil citrate to placebo (Bellovich 2000; Mahon 2005; Sharma 2006). One study compared sildenafil citrate to vardenafil (Turk 2010). Two studies (29 patients) compared bromocriptine to placebo (Bommer 1979; Muir 1983) and one study (15 patients) compared 1,25 dihydroxycholecalciferol (1,25(OH)2D3) to placebo (Blumberg 1980).

Five studies included diabetic patients. Of these, one enrolled patients with diabetic kidney disease. Twelve studies included patients on haemodialysis, one included patients on peritoneal dialysis and the remaining two studies included kidney transplant recipients.

Only one study enrolled both men and women (Blumberg 1980). Other characteristics of the included studies are detailed in Characteristics of included studies.

Risk of bias in included studies

Study quality and potential for bias was variable (Figure 2).

Figure 2. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.

Allocation

Allocation concealment was adequate in only 3/15 (20%) studies (Mahajan 1982; Muir 1983; Turk 2010) and unclear in 12/15 (80%) studies (Antoniou 1977; Bellovich 2000; Blumberg 1980; Bommer 1979; Brook 1980; Demir 2006; Mahon 2005; Seibel 2002; Sharma 2006; Wabrek 1982; Yang 2008; Yeksan 1992).

Blinding

Participants were blinded in 2/15 (13%) studies (Blumberg 1980; Bommer 1979), investigators were blinded in 1/15 (7%) studies (Antoniou 1977), both participants and investigators were blinded in 9/15 (60%) studies (Brook 1980; Mahajan 1982; Mahon 2005; Muir 1983; Seibel 2002; Sharma 2006; Wabrek 1982; Yang 2008; Yeksan 1992) and outcome assessors were blinded in 1/15 studies (Wabrek 1982). Three studies (20%) did not blind all the different groups (Bellovich 2000; Demir 2006; Turk 2010).
**Incomplete outcome data**
The number of patients lost to follow-up ranged from 0% to 36%.

**Other potential sources of bias**
One of the 15 studies (7%) was analysed on an intention-to-treat basis (Türk 2010).

**Effects of interventions**

**Phosphodiesterase-5 inhibitors (PDE5i) versus placebo**
There was a consistent improvement in the overall score of the IIEF-5 with PDE5i compared to placebo (Analysis 1.1.1: MD 10.65, 95% CI 5.34 to 15.96; 2 studies, 101 patients) (Demir 2006; Seibel 2002) and also a consistent increase of the score of all individual IIEF-5 tool domains.

- Erection frequency (Analysis 1.1.2: MD 1.54, 95% CI 1.14 to 1.93; 3 studies, 149 patients) (Demir 2006; Seibel 2002; Sharma 2006),
- Erection quality (Analysis 1.1.3: MD 1.78, 95% CI 1.04 to 2.53; 3 studies, 165 patients) (Demir 2006; Seibel 2002; Sharma 2006),
- Penetration ability (Analysis 1.1.4: MD 1.70, 95% CI 1.16 to 2.24; 3 studies, 165 patients) (Demir 2006; Seibel 2002; Sharma 2006),
- Maintenance frequency of penetration (Analysis 1.1.5: MD 1.60, 95% CI 1.02 to 2.18; 4 studies, 193 patients) (Bellovich 2000; Demir 2006; Seibel 2002; Sharma 2006),
- Maintenance of erection after penetration (Analysis 1.1.6: MD 1.83, 95% CI 1.17 to 2.50; 4 studies, 193 patients) (Bellovich 2000; Demir 2006; Seibel 2002; Sharma 2006), and
- Erection confidence (Analysis 1.1.7: MD 1.39, 95% CI 0.84 to 1.95; 3 studies, 165 patients) (Demir 2006; Seibel 2002; Sharma 2006).

There was significant heterogeneity in these analyses. When two crossover studies were excluded from the analysis no significant changes were shown and the resulting effect remained the same for each domain of the overall IIEF-5 score.

We found a significant increase in the overall score of the IIEF-15 sexual assessment tool with sildenafil compared to placebo (Analysis 1.2.1: MD 2.64, 95% CI 1.32 to 3.96; 1 study, 41 patients) (Seibel 2002), and a consistent improvement in erectile function (Analysis 1.2.2: MD 10.64 95% CI 5.32 to 15.96; 2 studies, 80 patients) (Seibel 2002; Yang 2008), orgasmic function (Analysis 1.2.3: MD 1.70, 95% CI 0.35 to 3.05; 1 study, 41 patients) (Seibel 2002) and intercourse satisfaction (Analysis 1.2.4: MD 1.71, 95% CI 0.11 to 3.31; 1 study, 41 patients) (Seibel 2002), but no change in sexual desire (Analysis 1.2.5: MD 0.49, 95% CI -0.67 to 1.65; 1 study, 41 patients) (Seibel 2002).

There was a significant improvement in erectile function with sildenafil compared to placebo (Analysis 1.4: RR 8.93, 95% CI 2.36 to 33.78; 1 study, 41 patients) (Seibel 2002).

**Adverse effects**
There was no significant increase in the risk of headache when PDE5i was compared to placebo (Analysis 1.3: RR 1.05, 95% CI 0.16 to 6.76; 1 study, 41 patients) (Seibel 2002). Included studies did not report incidence of coronary ischaemia for PDE5i, priapism for intracavernous injections or breast cancer for oestrogen replacement therapy.

**Zinc versus placebo**

**Gonadotropins**
There was no consistent increase in end-of-treatment plasma testosterone concentration with the addition of zinc to the dialysate (Analysis 2.1.1: SMD 0.21, 95% CI -2.14 to 2.55; 2 studies, 22 patients) (Antoniou 1977; Brook 1980) while oral zinc significantly improved end-of-treatment plasma testosterone levels (Analysis 2.1.2: SMD 1.62, 95% CI 0.58 to 2.66; 1 study, 20 patients) (Mahajan 1982). There was no significant reduction in the end-of-treatment plasma FSH concentration (Analysis 2.3: MD -0.69 mU/mL, 95% CI -2.72 to 1.34; 2 studies, 28 patients) (Antoniou 1977; Mahajan 1982) and plasma LH level (Analysis 2.4: MD 18.80 mU/mL, 95% CI -26.16 to 63.76; 2 studies, 20 patients) (Antoniou 1977; Mahajan 1982) with zinc compared to placebo.

**Sexual function**
One study showed significant decreases in the frequencies of intercourse (Analysis 2.5: RR 0.22, 95% CI 0.06 to 0.78; 1 study, 20 patients) and total or partial impotence (Analysis 2.6: RR 0.13, 95% CI 0.02 to 0.82; 1 study, 20 patients) with zinc compared to placebo (Mahajan 1982). There was no consistent variation in libido using zinc compared to placebo (Analysis 2.7: RR 0.11, 95% CI 0.01 to 1.83; 2 studies, 34 patients) (Brook 1980; Mahajan 1982) nor a significant increase in episodes of NPT (Analysis 2.8: RR 0.75, 95% CI 0.07 to 7.73; 1 study, 7 patients) (Wåbrek 1982).

**Vitamin E versus placebo**
Yeksan 1992 showed a consistent decrease in end-of-treatment prolactin (MD -41.23, 95% CI -50.42 to -32.04; 1 study, 24 patients), LH (MD -6.77, 95% CI -10.15 to -3.39; 1 study, 24 patients) and testosterone levels (MD 7.00, 95% CI 4.43 to 9.57; 1 study, 24 patients) after administration of vitamin E compared to placebo, but no statistically significant decrease in FSH levels.
In a recent systematic review of 130 mostly short-term (<12 weeks) studies of treatments for ED in men, 2003, 2004, 2008, 2009, other outcomes reported in the included studies are summarised in Table 1.

**DISCUSSION**

**Summary of main results**

Our systematic review demonstrated that in small clinical studies, PDE5i improved various aspects of erectile function in CKD patients. No data about the safety of these agents have been reported in these studies. Oral zinc supplementation resulted in a significant increase in the potency and frequency of intercourse along with an increase in testosterone concentration. However, administration of zinc in the dialysate did not improve sexual functioning, testosterone or the other biochemical parameters of gonadal failure. Only sparse data were available for vitamin E, bromocriptine and dihydroxycholecalciferol in CKD patients and no studies were available of intracavernous injections, transurethral injections, mechanical devices or behavioural therapy in CKD. The safety and efficacy of interventions for sexual dysfunction in women with CKD were poorly studied.

**Agreements and disagreements with other studies or reviews**

PDE5i have been extensively studied in the general population and have been generally shown to improve erectile response and to be well tolerated in men with mild to severe ED due to varying aetiologies (Aranda 2004; Carson 2004; Hellstrom 2002; Keating 2003; Markou 2004; Miles 2007; Porst 2001; Tsertsvadze 2009; Vardi 2008). In a recent systematic review of 130 mostly short-term (<12 weeks) studies of treatments for ED in men, Tsertsvadze 2009 reported that PDE5i was significantly more effective than placebo in improving sexual intercourse success (69% versus 35%) and resulted in a higher proportion of men with improved erections (range 67% to 89% versus 27% to 35%), both in mixed study populations and in study populations of men with specific comorbid conditions such as diabetes mellitus, stable cardiovascular disease, hypertension, depression, multiple sclerosis, rectal excision for bowel cancer and radical prostatectomy for prostate cancer. The magnitude of improvement in erectile function was comparable between sildenafil, vardenafil and tadalafil. Balanced against these benefits, PDE5i were associated with an increased risk of any adverse event (RR 1.72, 95% CI 1.53 to 1.93), the most common of which were headache, flushing, dyspepsia, myalgia and back pain. Although the reporting of all serious adverse or cardiovascular adverse events was both inconsistent and incomplete, the overall rate of serious adverse events in men randomly assigned to PDE5i was <2% and comparable to those assigned to placebo. There was insufficient evidence to determine whether treatment with PDE5i increased the risks of serious cardiovascular events or non-arteritic anterior ischaemic optic neuropathy. Based on these findings, the American College of Physicians issued clinical practice guidelines strongly recommending PDE5i for men who seek treatment for ED and who do not have contraindications to PDE5i use (Qaseem 2009).

In keeping with the findings of Tsertsvadze 2009 in non-CKD populations, we found that administration of PDE5i to men with CKD caused clinically meaningful and statistically significant improvements in general sexual satisfaction and ED. However, in spite of the high rate of sexual dysfunction in CKD patients and concerns about the safety of pharmacologic treatments in the setting of renal impairment, we found only six small clinical studies (including comparative and crossover studies) that assessed PDE5i in CKD. The longest study duration was eight months. Comparison of the efficacy of different PDE5i was not possible as only limited data were available for sildenafil and vardenafil and no data were available for tadalafil or mirodenafil. Unfortunately, there was also a complete lack of safety data for PDE5i in CKD patients, a population which is at high risk of silent cardiovascular disease. Similar to the general population, our review did not identify any clinical study analysing the safety and efficacy of PDE5i in female CKD patients, despite the ubiquitous occurrence of sexual dysfunction in this group. Biological plausibility exists to support the use of PDE5i in female patients with sexual dysfunction (D’Amati 2002), but both efficacy and safety are unclear and there is no consensus on the best treatment options for sexual dysfunction in female patients (Brown 2009). Further studies are warranted in this important clinical area.

Our review found some earlier studies supporting the use of oral zinc therapy in patients with CKD to improve sexual dysfunction. These were short-term investigations that assessed the impact of zinc on surrogate end-points, such as gonadal hormone levels. With the declining use of zinc in clinical practice, further studies were not conducted. Most studies enrolled dialysis patients and we did not identify studies enrolling predialysis patients. As the prevalence of sexual dysfunction remains high in predialysis CKD patients, whilst the prevalence of cardiovascular disease is lower than in dialysis patients, this group may represent an opportunity to safely conduct clinical studies assessing the safety and efficacy of PDE5i.

Our systematic review also identified important opportunities for examining the impact of treatments for sexual dysfunction on patient-level outcomes, such as quality of life and cardiovascular events. Previous studies have observed strong associations between ED, depression and adverse cardiovascular outcomes (Goldstein 2002; Porst 2001; Qaseem 2009).
al-though a causal link has not been definitively established (Turk 2004). Of the studies included in our meta-analysis, none considered these patient-level outcome parameters.

Strengths and weaknesses
Our review had a number of strengths and weaknesses. The strengths included systematic searches of medical databases, data extraction, analysis and study quality assessment by two independent review authors. The key findings were limited by the lack of long-term studies analysing interventions targeting ED or sexual dysfunction in CKD patients. The included studies had relatively small sample sizes and were powered to observe differences in surrogate end-points rather than patient-focused outcomes. Seven studies had a crossover design and most did not adequately report study methods to determine study quality. Significant heterogeneity was observed for many outcomes. Publication bias might exist however, given the lack of adequate numbers of studies, formal tests could not be conducted. In the general population, a higher PDE5i dose provides a better response but whether such effects existed in CKD was unclear. In short, these issues highlight the fact that treatment of sexual dysfunction in CKD has received inadequate attention by researchers to date.

Authors’ Conclusions

Implications for practice
Modest evidence exists for the efficacy of PDE5i in CKD patients. The safety profile of these agents has not been extensively analysed in patients with CKD. Clinicians may use PDE5i in CKD patients who do not have any contraindications to PDE5i use. Oral zinc seems to increase testosterone levels and improve sexual dysfunction, but this evidence needs to be confirmed in larger studies in the future.

Implications for research
Given the high prevalence of sexual dysfunction in patients with CKD and the lack of clinical studies, further and larger studies exploring various treatment options in both male and female CKD patients are needed. These studies should focus on both biochemical and patient-centred end-points along with establishing their safety profile in both dialysis and predialysis patients. Comparative studies of the efficacy and safety of different PDE5i in CKD patients are also warranted.

Acknowledgements

We would like to thank,

- The referees for their comments and editorial advice during the preparation of this review.

References

References to studies included in this review

Antoniou 1977 [published data only]


Bellovich 2000 [published data only]

Blumberg 1980 [published data only]


Bommer 1979 [published data only]


Brook 1980 [published data only]

Demir 2006 [published data only]
Interventions for treating sexual dysfunction in patients with chronic kidney disease (Review)

Mahajan 1982 [published data only]


Mahon 2005 [published data only]


Muir 1983 [published data only]

Seibel 2002 [published data only]

Sharma 2006 [published data only]


Turk 2010 [published data only]

Wabrek 1982 [published data only]

Yang 2008 [published data only]

Yeksan 1992 [published data only]

References to studies excluded from this review

Campieri 1979 [published data only]


Grossman 2004 [published data only]

Groover-Paez 2007 [published data only]

Mahajan 1982a [published data only]
Rodger 1989 (published data only)


Schaefer 1989 (published data only)

Sprenger 1984 (published data only)

Tas 2006 (published data only)


Zetin 1980 (published data only)

References to ongoing studies

NCT00334477 (published data only)

Additional references

Al Khalaf 2009

Anantharaman 2007

Aranda 2004

Bellinghieri 2008

Brown 2009

Campese 1990

Carson 2004

D’Amati 2002

Esposito 2004

Finkelstein 2007

Goldstein 2000

Hellstrom 2002

Higgins 2002

Higgins 2008
Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.0 [updated
Keating 2003

Kimmel 1996

Kutner 2004

Laumann 1999

Lawrence 1997

Lefebvre 2008

Linet 1996

Markou 2004

Master List 2010

Mehrsai 2006

Melnik 2008

Miles 2007

Naya 2002

Padma-Nathan 2003

Palmer 1999

Peng 2005

Peng 2007

Pfost 2001

Procci 1981

Qaseem 2009

Renal Group 2010

Rosas 2001

Seidman 2006

Tsertsvadze 2009

Turk 2004

Vardi 2008

References to other published versions of this review

Veccio 2009

Veccio 2010

* Indicates the major publication for the study
Characteristics of included studies

Antoniou 1977

Methods
- Study design: Placebo controlled RCT
- Study duration: 3-4 months
- Follow-up: 4 months
- Lost to follow-up: 0

Participants
- Inclusion criteria
  - Country: USA
  - Setting: Hospital
  - Male patients undergoing maintenance HD
  - Number (treatment/control): 4/4
  - Age (treatment/control): 49/48 years
  - Sex: 100% male
- Exclusion criteria: NS

Interventions
- Treatment group
  - Zinc chloride
  - Dose, duration, frequency, administration: 400 µg/L for 3 to 4 months
- Control group
  - Placebo
  - Dose, duration, frequency, administration: NS

Outcomes
- Plasma testosterone concentration
- FSH level
- LH level

Notes

Risk of bias

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<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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### Antoniou 1977 (Continued)

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<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
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### Bellovich 2000

#### Methods
- Study design: Crossover RCT
- Study duration: 3 months
- Follow-up: 3 months
- Lost to follow-up: 9

#### Participants
- **Inclusion criteria**
  - Country: USA
  - Setting: NS
  - Male, HD patients, > 18 years and with ED
  - Number: 14
  - Age: 52.4 years
  - Sex: 100% male
- **Exclusion criteria**
  - Patients in therapy with nitrate

#### Interventions
- **Treatment group**
  - Sildenafil citrate
  - Dose, duration, frequency, administration: 25 or 50 mg for 1 month followed by crossover
- **Control group**
  - Placebo
  - Dose, duration, frequency, administration: NS

#### Outcomes
- Questions 3 and 4 of IIEF questionnaire
- Karnofsky scale score for QoL measurement

#### Notes

### Risk of bias

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**Bellovich 2000 (Continued)**

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</table>

**Blumberg 1980**

**Methods**

- Study design: Single-blind, placebo-controlled crossover RCT
- Study duration: 4 months
- Follow-up: from 2 to 4 months
- Lost to follow-up: 0

**Participants**

Inclusion criteria
- Country: Switzerland
- Setting: NS
- Patients on maintenance HD
- Number: 15
- Age: NS
- Sex (M/F): 5/10

Exclusion criteria
- External organ deficiency or other illness associated with increased catabolism

**Interventions**

- Treatment group
  - 1.25(OH)2D3
  - Dose, duration, frequency, administration: starting dose of 0.25-0.5 µg/d increased up to 0.5-1.5 µg/d until definite rise in serum calcium concentration occurred for 2/4 months
- Control group
  - Placebo
  - Dose, duration, frequency, administration: NS

**Outcomes**

- Endocrine parameters level assessment
  - Testosterone
  - LH
  - FSH
- Psychiatric interview protocol

**Notes**

**Risk of bias**
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**Blumberg 1980** (Continued)

### Methods
- Study design: Single-blind, placebo controlled, crossover RCT
- Study duration: 16 weeks
- Follow-up: 8 weeks
- Lost to follow-up: 0

### Participants
- **Inclusion criteria**
  - Country: Switzerland
  - Setting: NS
  - Home dialysis patients (on dialysis for more than 24 months), male, married, younger than 50, older than 18 years
    - Number: 15
    - Age: 28-50 years
    - Sex: 100% male
  - Exclusion criteria: NS

### Interventions
- **Treatment group**
  - Bromocriptine
  - Dose, duration, frequency, administration: 2.5 mg twice a day for 8 weeks
- **Control group**
  - Placebo
  - Dose, duration, frequency, administration: NS

### Outcomes
- Frequency of intercourse
- Tumescence
- Libido
- Prolactin concentration
### Bommer 1979

(Continued)

<table>
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### Brook 1980

#### Methods

- Study design: Double-blind, placebo-controlled RCT
- Study duration: 6 weeks
- Follow-up: 6 weeks
- Lost to follow-up: 0

#### Participants

Inclusion criteria:
- Country: UK
- Setting: Infirmary
- Male, HD patients
- Number (treatment/control): 7/7
- Mean age ± SD
  - Treatment group: 37.6 ± 2.2 years
  - Control group: 37.6 ± 2.2 years
- Sex: 100% male

Exclusion criteria: NS

#### Interventions

- Treatment group
  - Zinc
  - Dose, duration, frequency, administration: to attain a final concentration of 400 µg/L for 6 weeks
- Control group
  - Placebo
• Dose, duration, frequency, administration: NS

Outcomes
• Plasma testosterone
• Questionnaire about sexual dysfunction
• Gonadotropin levels

Notes

Risk of bias

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Demir 2006

Methods
• Study design: Prospective RCT
• Study duration: 4 weeks
• Follow-up: 4 months
• Lost to follow-up: NS

Participants
Inclusion criteria
• Country: USA
• Setting: University medical faculty
• Male patients with stable relationship with a partner; single kidney graft with the external iliac arteries used for the vascular anastomosis
• Number (treatment/control): 39/21
• Mean age ± SD
  o Treatment group: 48 ± 7.4 years
  o Control group: 50 ± 7.1 years
• Sex: 100% male
Exclusion criteria
• Stroke; diabetes; myocardial infarction; coronary heart disease; overt heart failure;
Demir 2006  (Continued)

<table>
<thead>
<tr>
<th>Significant causes for exclusion</th>
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<td>Significant penile anatomical abnormalities; active peptic ulcer; chronic liver disease; clinically significant hypotension; blood coagulation disorders; therapy with nitrate</td>
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**Interventions**

<table>
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<tbody>
<tr>
<td><strong>Vardenafil</strong></td>
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<tr>
<td><strong>Dose, duration, frequency, administration:</strong> 10 mg (dose could be increased to 20 mg) for 4 weeks</td>
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<table>
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<tr>
<th>Control group</th>
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<tr>
<td><strong>Placebo</strong></td>
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<td><strong>Dose, duration, frequency, administration:</strong> NS</td>
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</table>

**Outcomes**

|  |
|-----------------|--|
| **IIEF score** |  |
| **Cyclosporin concentration** |  |

**Notes**

**Risk of bias**

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**Mahajan 1982**

**Methods**

- Study design: Double-blind, placebo-controlled RCT
- Study duration: 6 months
- Follow-up: 6 months
- Lost to follow-up: 0

**Participants**

- Inclusion criteria
  - Country: USA
  - Setting: University medical centre
  - Male patients with ESKD, normal secondary sexual characteristics, stable relationship with a partner
Mahajan 1982  (Continued)

- Number (treatment/control): 10/10
- Mean age ± SD
  - Treatment group: 38 ± 7 years
  - Control group: 41 ± 6 years
- Sex: 100% male

Exclusion criteria
- Gynaecomastia; gastrointestinal disorders

### Interventions

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<tr>
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<tr>
<td></td>
<td>Elemental zinc or zinc acetate</td>
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### Outcomes

- Libido
- Frequency of intercourse
- Testosterone
- LH level
- FSH level
- Sperm counts

### Notes

**Risk of bias**

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### Mahon 2005

**Methods**
- Study design: Prospective, double-blind, placebo-controlled, crossover RCT
- Study duration: 11 weeks
- Follow-up: 1 months
- Lost to follow-up: 0

**Participants**

**Inclusion criteria**
- Country: UK
- Setting: NS
- Patients > 18 years
- Number: 16
- Age: 55.6 years
- Sex: 100% male

**Exclusion criteria**
- Myocardial infarction within the last 6 months; cerebrovascular event within the last 6 months; severe hepatic impairment; penile anatomic deformities; severe cardiac disease; concomitant nitrate therapy

**Interventions**

**Treatment group**
- Sildenafil citrate
- Dose, duration, frequency, administration: 50 mg (increased to 100 mg if no response after 2 weeks) for 1 month

**Control group**
- Placebo
- Dose, duration, frequency, administration: NS

**Outcomes**
- Global efficacy question

**Risk of bias**

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Muir 1983

| Methods | Study design: Double-blind, placebo-controlled, crossover RCT  
Study duration: 7 months  
Follow-up: 7 months  
Lost to follow-up: 11 |
|---|---|
| Participants | Inclusion criteria  
- Country: UK  
- Setting: NS  
- Male patients with ESKD, euthyroid and who received maintenance HD for at least 6 months, complained of impotence  
  - Number: 14  
  - Age: 44.5 years  
  - Sex: 100% male  
Exclusion criteria  
- Patients with impotence due to psychological disturbance; took some drugs known to raise serum prolactin concentration; androgen treatment; liver disease; priapism; disturbed bladder function; angina pectoris; depression; hypertension |
| Interventions | Treatment group  
- Bromocriptine  
  - Dose, duration, frequency, administration: Initial dose of one-half of one tablet was increased every fourth day by one-half tablet until one tablet (2.5 mg when bromocriptine) was taken thrice daily by 16 days. Patient then continued on the tablets for a further 3 months.  
Control group  
- Placebo  
  - Dose, duration, frequency, administration: NS |
| Outcomes | Testosterone concentration  
- Frequency of spontaneous erections  
- Frequency of all erections  
- Quality of erections  
- Libido |
| Notes | |

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Outcomes assessors and data analysis: NS |
Muir 1983  (Continued)

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<th>Patients excluded at various stage (two received kidney transplants and nine stopped owing to side effects)</th>
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Free of selective reporting?  Low risk  Primary outcomes for this review (testosterone concentration) have been reported

Free of other bias?  Unclear risk  Funding source: NS

Seibel 2002

Methods

- Study design: Double-blind, placebo-controlled RCT
- Study duration: 1 month
- Follow-up: 1 month
- Lost to follow-up: 0

Participants

Inclusion criteria

- Country: Brazil
- Setting: University teaching hospital
- Patients with chronic HD who had received treatment for at least 6 month in six dialysis units in the state of Rio Grande do Soul, male patients having a stable relationship with a female sexual partner
- Number (treatment/control): 20/21
- Mean age ± SD
  - Treatment group: 49 ± 10 years
  - Control group: 46 ± 9 years
- Sex: 100% male

Exclusion criteria

- Patients > 70 years; penile anatomic abnormalities; cirrhosis; diabetes; angina; severe anaemia; nitrate treatment; history of recent stroke or myocardial infarction; illiterate patients; patients treated for ED

Interventions

Treatment group

- Sildenafil citrate
- Dose, duration, frequency, administration: 50 mg (1 hour before each sexual intercourse) for 1 month

Control group

- Placebo
- Dose, duration, frequency, administration: NS

Outcomes

- IIEF SCORE

Notes

Risk of bias

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<th>Support for judgement</th>
</tr>
</thead>
</table>

Interventions for treating sexual dysfunction in patients with chronic kidney disease (Review)  Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Seibel 2002 (Continued)

<table>
<thead>
<tr>
<th>Adequate sequence generation?</th>
<th>Unclear risk</th>
<th>Stated “randomised” no further information provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>“24 patients in each group received a sealed box containing the capsules”</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Blinding of participants and investigators</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Outcomes assessors and data analysis: NS</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Unclear risk</td>
<td>Patients excluded at various stages (one patient asked to be excluded, two died, one withdrew the consent and three had initial IIEF scores higher than 26)</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Low risk</td>
<td>Primary outcomes for this review (IIEF score) have been reported</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Funding source: NS</td>
</tr>
</tbody>
</table>

### Sharma 2006

#### Methods
- Study design: Double-blind, placebo-controlled, crossover RCT
- Study duration: 18 weeks
- Follow-up: 8 weeks
- Lost to follow-up: NS

#### Participants
- Inclusion criteria
  - Country: India
  - Setting: University
  - Males >18 years old with kidney transplant, stable graft function in the last 6 months, medically documented ED (as defined by the NIHCP), stable relationship with a female partner in the last 6 months
  - Number: 32
  - Mean age ± SD: 40 ± 8 years
  - Sex: 100% male
- Exclusion criteria
  - Penile anatomic abnormalities; history of recent stroke or myocardial infarction; proliferative diabetic retinopathy; severe autonomic neuropathy; regular treatment with nitrates and androgens; spinal cord injury

#### Interventions
- Treatment group
  - Sildenafil citrate
  - Dose, duration, frequency, administration: 50 mg for 8 months
- Control group
  - Placebo
  - Dose, duration, frequency, administration: NS
Sharma 2006  (Continued)

Outcomes

- IIEF score
- Global efficacy question
- Cyclosporin level
- Blood urea nitrogen level
- Creatinine level
- Haemoglobin level

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Low risk</td>
<td>“randomisation table generated by the method of random permuted blocks”</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>NS</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Low risk</td>
<td>Blinding of participants and investigators</td>
</tr>
<tr>
<td>All outcomes</td>
<td>Outcomes assessors and data analysis: NS</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Low risk</td>
<td>All patients followed up or accounted for</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Low risk</td>
<td>Primary outcomes for this review (IIEF score) have been reported</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Funding source: NS</td>
</tr>
</tbody>
</table>

Turk 2010

Methods

- Study design: Open-label, prospective, crossover RCT
- Study duration: 10 weeks
- Follow-up: 10 weeks
- Lost to follow-up: NS

Participants

Inclusion criteria
- Country: Turkey
- Setting: NS
- HD patients, aged 20 to 70 years, stable heterosexual relationship for the previous 6 months, clinical diagnosis of ED for 6 months
  - Number: 32
  - Mean age ± SD: 47.2 ± 10.8 years
  - Sex: 100% male

Exclusion criteria
- Current treatment of ED regardless of drug or method; alcohol or drug abuse; inability to follow study instructions; major haematologic or hepatic abnormalities; myocardial infarction in the preceding 6 months; concomitant treatment with nitrate
Turk 2010  *(Continued)*

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Sildenafil citrate</td>
</tr>
<tr>
<td></td>
<td>- Dose, duration, frequency, administration: 50 mg, 45 min prior to sexual intercourse once per week for 4 weeks</td>
</tr>
<tr>
<td>Control group</td>
<td>- Vardenafil</td>
</tr>
<tr>
<td></td>
<td>- Dose, duration, frequency, administration: 10 mg, 45 min prior to sexual intercourse once per week for 4 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>- IIEF-5 score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Physical component score</td>
</tr>
<tr>
<td></td>
<td>- Mental component score</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th></th>
</tr>
</thead>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Low risk</td>
<td>Computer-generated randomisation sequence</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Low risk</td>
<td>Patients were randomised into either sildenafil or vardenafil groups by opening pre-numbered sealed opaque envelopes</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>High risk</td>
<td>Open-label study</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Low risk</td>
<td>All patients followed up or accounted for</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Low risk</td>
<td>Primary outcomes for this review (IIEF-5 score) have been reported</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Funding source: NS</td>
</tr>
</tbody>
</table>
Wabrek 1982

**Methods**
- Study design: Placebo-controlled RCT
- Study duration: NS
- Follow-up: NS
- Lost to follow-up: 0

**Participants**
- **Inclusion criteria**
  - Country: USA
  - Setting: Hospital’s dialysis unit
  - Male HD patients
  - Number (treatment/control): 4/4
  - Mean age ± SD
    - Treatment group: 50 ± 8 years
    - Control group: 47 ± 8 years
  - Sex: 100% male
- **Exclusion criteria:** NS

**Interventions**
- **Treatment group**
  - Zinc
  - Dose, duration, frequency, administration: solution containing 400 mg/L of zinc
- **Control group**
  - Placebo
  - Dose, duration, frequency, administration: NS

**Outcomes**
- NPT
- Penile circumference
- Increase of penile shaft

**Notes**

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Stated “randomised” no further information provided</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>NS</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Low risk</td>
<td>Blinding of participants, investigators and outcomes assessors Data analysis: NS</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Unclear risk</td>
<td>Data only available for 7/8 patients</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>High risk</td>
<td>Primary outcomes for this review have not been reported</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Funding source: NS</td>
</tr>
</tbody>
</table>
Yang 2008

Methods

- Study design: Double-blind, placebo-controlled RCT
- Study duration: 4 weeks
- Follow-up: 4 weeks
- Lost to follow-up: 0

Participants

Inclusion criteria
- Country: China
- Setting: Wuhan, China
- Kidney transplant patients with ED (average 26 months after transplant and received HD average 38 months) and serum creatinine values < 2 mg/dL, no other treatment in past 4 weeks
  - Number (treatment/control): 20/19
  - Age: NS
  - Sex: 100% male
Exclusion criteria: NS

Interventions

Treatment group
- Vardenafil
  - Dose, duration, frequency, administration: 10 mg, one hour before coitus no more than once per day
Control group
- Placebo
  - Dose, duration, frequency, administration: NS

Outcomes

- IIEF score
- Cyclosporin level
- Creatinine level
- Creatinine clearance
- Liver function
- Kidney function
- Lipid concentration
- Blood routine test
- Urine routine test
- Any other adverse events

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Stated “randomised” no further information provided</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>NS</td>
</tr>
</tbody>
</table>
| Blinding?                   | Low risk           | Blinding of participants and investigators
All outcomes                 |                    | Outcomes assessors and data analysis: NS                  |
Yang 2008  *(Continued)*

<table>
<thead>
<tr>
<th>Incomplete outcome data addressed?</th>
<th>Low risk</th>
<th>All patients followed up or accounted for</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Primary outcomes for this review (IIEF score) have been reported</td>
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<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
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</table>

Yeksan 1992

<table>
<thead>
<tr>
<th>Methods</th>
<th>Study design: Double-blind, placebo-controlled RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study duration: 8 weeks</td>
</tr>
<tr>
<td></td>
<td>Follow-up: 8 weeks</td>
</tr>
<tr>
<td></td>
<td>Lost to follow-up: 0</td>
</tr>
<tr>
<td>Participants</td>
<td>Inclusion criteria</td>
</tr>
<tr>
<td></td>
<td>Country: Turkey</td>
</tr>
<tr>
<td></td>
<td>Setting: University teaching hospital</td>
</tr>
<tr>
<td></td>
<td>HD patients on a low sodium diet containing 50 g/day protein</td>
</tr>
<tr>
<td></td>
<td>Number (treatment/control): 12/12</td>
</tr>
<tr>
<td></td>
<td>Age (treatment/control): 35/42 years</td>
</tr>
<tr>
<td></td>
<td>Sex: 100% male</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: NS</td>
</tr>
<tr>
<td>Interventions</td>
<td>Treatment group</td>
</tr>
<tr>
<td></td>
<td>Oral vitamin E</td>
</tr>
<tr>
<td></td>
<td>Dose, duration, frequency, administration: 300 mg for 8 weeks</td>
</tr>
<tr>
<td>Control group</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Dose, duration, frequency, administration: NS</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Prolactin</td>
</tr>
<tr>
<td></td>
<td>LH level</td>
</tr>
<tr>
<td></td>
<td>FSH level</td>
</tr>
<tr>
<td></td>
<td>Testosterone level</td>
</tr>
</tbody>
</table>

Notes

Risk of bias

<table>
<thead>
<tr>
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<th>Authors’ judgement</th>
<th>Support for judgement</th>
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</thead>
<tbody>
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<td>Stated “randomised” no further information provided</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>NS</td>
</tr>
</tbody>
</table>
### Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campieri 1979</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Grossman 2004</td>
<td>One off pharmacokinetic study, not an intervention for sexual dysfunction</td>
</tr>
<tr>
<td>Grover-Paez 2007</td>
<td>Wrong population</td>
</tr>
<tr>
<td>Mahajan 1982a</td>
<td>Intervention not for sexual dysfunction</td>
</tr>
<tr>
<td>Rodger 1989</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Schaefer 1989</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Sprenger 1984</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Tas 2006</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Zetin 1980</td>
<td>Not an RCT</td>
</tr>
</tbody>
</table>

1,25(OH)2D3 - 1,25 dihydroxycholecalciferol; ED - erectile dysfunction; ESKD - end-stage kidney disease; FSH - follicle-stimulating hormone; HD - haemodialysis; IIEF - International Index of Erectile Function; LH - luteinizing hormone; NS - not stated
### Characteristics of ongoing studies [ordered by study ID]

**NCT00334477**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Efficacy and safety of tadalafil 20 mg for the treatment of erectile dysfunction in chronic renal patients in haemodialysis</th>
</tr>
</thead>
</table>

#### Methods

- Study design: Double-blind, placebo-controlled parallel RCT
- Study duration: NS
- Blinding
  - Participants: yes
  - Investigators: yes
  - Outcomes assessors: NS
  - Data assessors: no
- Follow-up: NS

#### Participants

- Country: Brazil
- Setting: University teaching hospital
- Inclusion criteria: Men between 18 and 70 years old; diagnosed with ED for 6 months; Accept the protocol; Sign the informed consent; Renal chronic patients in haemodialysis
- Exclusion criteria: History of another PDE5 inhibitor use; C.C.I. grade III (NYHA)

#### Interventions

**Treatment group**
- Tadalafil
  - Dose, duration, frequency, administration: 20 mg

**Control group**
- Placebo
  - Dose, duration, frequency, administration: NS

#### Outcomes

- IIEF-5
- Adverse effect reported

#### Starting date

NS

#### Contact information

Bruno SP Carvalho: 558199757974 brunocarvalho@medscape.com

#### Notes

NS - not stated
## Data and Analyses

### Comparison 1. PDE inhibitors versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Sexual function using IIEF-5</td>
<td>4</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Total score</td>
<td>2</td>
<td>101</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>10.65 [5.34, 15.96]</td>
</tr>
<tr>
<td>1.2 Erection frequency</td>
<td>3</td>
<td>149</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.54 [1.14, 1.93]</td>
</tr>
<tr>
<td>1.3 Erection quality (Q2)</td>
<td>3</td>
<td>165</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.78 [1.04, 2.53]</td>
</tr>
<tr>
<td>1.4 Penetration ability (Q3)</td>
<td>3</td>
<td>165</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.70 [1.16, 2.24]</td>
</tr>
<tr>
<td>1.5 Maintenance frequency of penetration (Q4)</td>
<td>4</td>
<td>193</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.60 [1.02, 2.18]</td>
</tr>
<tr>
<td>1.6 Maintenance of erection after penetration (Q5)</td>
<td>4</td>
<td>193</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.83 [1.17, 2.50]</td>
</tr>
<tr>
<td>1.7 Erection confidence (Q15)</td>
<td>3</td>
<td>165</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.39 [0.84, 1.95]</td>
</tr>
<tr>
<td>2 Sexual function using IIEF-15</td>
<td>2</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 Overall satisfaction</td>
<td>1</td>
<td>41</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>2.64 [1.32, 3.96]</td>
</tr>
<tr>
<td>2.2 Erectile function</td>
<td>2</td>
<td>80</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>10.64 [5.32, 15.96]</td>
</tr>
<tr>
<td>2.3 Orgasmic function</td>
<td>1</td>
<td>41</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.70 [0.35, 3.05]</td>
</tr>
<tr>
<td>2.4 Intercourse satisfaction</td>
<td>1</td>
<td>41</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.71 [0.11, 3.31]</td>
</tr>
<tr>
<td>2.5 Sexual desire</td>
<td>1</td>
<td>41</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.49 [-0.67, 1.65]</td>
</tr>
<tr>
<td>3 Headache</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>4 Improvement in erectile function</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

### Comparison 2. Zinc versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Serum testosterone</td>
<td>3</td>
<td>42</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>0.70 [-1.05, 2.45]</td>
</tr>
<tr>
<td>1.1 Zinc in dialysate</td>
<td>2</td>
<td>22</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>0.21 [-2.14, 2.55]</td>
</tr>
<tr>
<td>1.2 Oral zinc</td>
<td>1</td>
<td>20</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>1.62 [0.58, 2.66]</td>
</tr>
<tr>
<td>2 Improvement of libido</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3 Plasma FSH</td>
<td>2</td>
<td>28</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-9.69 [-23.72, 4.34]</td>
</tr>
<tr>
<td>4 Plasma LH</td>
<td>2</td>
<td>28</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>18.80 [-26.16, 63.76]</td>
</tr>
<tr>
<td>5 Frequency of intercourse</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>6 Total/partial impotence</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>7 Variations in libido</td>
<td>2</td>
<td>34</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.11 [0.01, 1.83]</td>
</tr>
<tr>
<td>8 Nocturnal penile tumescence (NPT)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>
### Analysis 1.1. Comparison 1 PDE inhibitors versus placebo, Outcome 1 Sexual function using IIEF-5.

Review: Interventions for treating sexual dysfunction in patients with chronic kidney disease

Comparison: 1 PDE inhibitors versus placebo

Outcome: 1 Sexual function using IIEF-5

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PDE inhibitors</th>
<th>Placebo</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
<th>Weight</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Total score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demir 2006</td>
<td>39 26.46 (2.4)</td>
<td>21 13.27 (2.8)</td>
<td>53.3 % 13.19 [11.78, 14.60]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seibel 2002</td>
<td>20 23 (5.7)</td>
<td>21 15.24 (4.2)</td>
<td>46.7 % 7.76 [4.68, 10.84]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>59</strong></td>
<td><strong>42</strong></td>
<td></td>
<td></td>
<td>100.0 % 10.65 [5.34, 15.96]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 13.25; Chi² = 9.88, df = 1 (P = 0.002); I² =90%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.93 (P = 0.000084)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Erection frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demir 2006</td>
<td>39 4.4 (0.72)</td>
<td>21 2.53 (0.72)</td>
<td>39.2 % 1.87 [1.49, 2.25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seibel 2002</td>
<td>20 3.75 (1.1)</td>
<td>21 2.52 (0.9)</td>
<td>24.5 % 1.23 [0.61, 1.85]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharma 2006</td>
<td>32 3.7 (0.7)</td>
<td>16 2.32 (0.7)</td>
<td>36.3 % 1.38 [0.96, 1.80]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>91</strong></td>
<td><strong>58</strong></td>
<td></td>
<td></td>
<td>100.0 % 1.54 [1.14, 1.93]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.06; Chi² = 4.32, df = 2 (P = 0.12); I² =54%</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 7.69 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Erection quality (Q2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demir 2006</td>
<td>39 4.26 (0.58)</td>
<td>21 1.79 (0.53)</td>
<td>35.6 % 2.47 [2.18, 2.76]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seibel 2002</td>
<td>20 3.75 (1.1)</td>
<td>21 2.62 (1)</td>
<td>29.4 % 1.13 [0.49, 1.77]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharma 2006</td>
<td>32 3.53 (0.64)</td>
<td>32 1.9 (0.73)</td>
<td>35.0 % 1.63 [1.29, 1.97]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>91</strong></td>
<td><strong>74</strong></td>
<td></td>
<td></td>
<td>100.0 % 1.78 [1.04, 2.53]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.38; Chi² = 21.68, df = 2 (P = 0.00002); I² =91%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued...)

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Interventions for treating sexual dysfunction in patients with chronic kidney disease (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PDE inhibitors</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Random,95% CI</td>
<td>IV,Random,95% CI</td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z = 4.69 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Penetration ability (Q3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demir 2006</td>
<td>39 4.52 (0.7)</td>
<td>21 2.33 (0.73)</td>
<td>35.8 %</td>
<td>2.19 [ 1.81, 2.57 ]</td>
<td></td>
</tr>
<tr>
<td>Seibel 2002</td>
<td>20 3.95 (1.1)</td>
<td>21 2.76 (0.8)</td>
<td>28.6 %</td>
<td>1.19 [ 0.60, 1.78 ]</td>
<td></td>
</tr>
<tr>
<td>Sharma 2006</td>
<td>32 3.9 (0.85)</td>
<td>32 2.28 (0.73)</td>
<td>35.6 %</td>
<td>1.62 [ 1.23, 2.01 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>91</td>
<td>74</td>
<td><strong>100.0 %</strong></td>
<td><strong>1.70</strong> [ <strong>1.16, 2.24</strong> ]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.17; Chi² = 8.91, df = 2 (P = 0.01); I² =78%</td>
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<td>Test for overall effect: Z = 6.16 (P &lt; 0.00001)</td>
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</tr>
<tr>
<td>5 Maintenance frequency of penetration (Q4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bellovich 2000</td>
<td>14 3.85 (3.1)</td>
<td>14 4.43 (2.92)</td>
<td>5.8 %</td>
<td>-0.58 [ -2.81, 1.65 ]</td>
<td></td>
</tr>
<tr>
<td>Demir 2006</td>
<td>39 4.44 (0.78)</td>
<td>21 2.27 (0.71)</td>
<td>34.4 %</td>
<td>2.17 [ 1.78, 2.56 ]</td>
<td></td>
</tr>
<tr>
<td>Seibel 2002</td>
<td>20 3.7 (1.3)</td>
<td>21 2.43 (0.9)</td>
<td>25.9 %</td>
<td>1.27 [ 0.58, 1.96 ]</td>
<td></td>
</tr>
<tr>
<td>Sharma 2006</td>
<td>32 3.8 (0.66)</td>
<td>32 2.15 (0.98)</td>
<td>33.9 %</td>
<td>1.65 [ 1.24, 2.06 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>105</td>
<td>88</td>
<td><strong>100.0 %</strong></td>
<td><strong>1.60</strong> [ <strong>1.02, 2.18</strong> ]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.21; Chi² = 10.63, df = 3 (P = 0.01); I² =72%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.41 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Maintenance of erection after penetration (Q5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bellovich 2000</td>
<td>14 4.43 (2.69)</td>
<td>14 4.93 (2.32)</td>
<td>9.5 %</td>
<td>-0.50 [ -2.36, 1.36 ]</td>
<td></td>
</tr>
<tr>
<td>Demir 2006</td>
<td>39 4.46 (0.75)</td>
<td>21 1.95 (0.84)</td>
<td>32.2 %</td>
<td>2.51 [ 2.08, 2.94 ]</td>
<td></td>
</tr>
<tr>
<td>Seibel 2002</td>
<td>20 4.2 (1.3)</td>
<td>21 2.57 (1)</td>
<td>26.1 %</td>
<td>1.63 [ 0.92, 2.34 ]</td>
<td></td>
</tr>
<tr>
<td>Sharma 2006</td>
<td>32 3.75 (0.91)</td>
<td>32 1.75 (0.84)</td>
<td>32.2 %</td>
<td>2.00 [ 1.57, 2.43 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>105</td>
<td>88</td>
<td><strong>100.0 %</strong></td>
<td><strong>1.83</strong> [ <strong>1.17, 2.50</strong> ]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.31; Chi² = 12.88, df = 3 (P = 0.005); I² =77%</td>
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<td></td>
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<tr>
<td>Test for overall effect: Z = 5.40 (P &lt; 0.00001)</td>
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<td></td>
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<tr>
<td>7 Erection confidence (Q15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demir 2006</td>
<td>39 4.27 (0.75)</td>
<td>21 2.4 (0.7)</td>
<td>34.5 %</td>
<td>1.87 [ 1.49, 2.25 ]</td>
<td></td>
</tr>
<tr>
<td>Seibel 2002</td>
<td>20 3.65 (0.9)</td>
<td>21 2.33 (0.7)</td>
<td>31.0 %</td>
<td>1.32 [ 0.82, 1.82 ]</td>
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</tr>
<tr>
<td>Sharma 2006</td>
<td>32 3.66 (0.65)</td>
<td>32 2.68 (0.89)</td>
<td>34.5 %</td>
<td>0.98 [ 0.60, 1.36 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>91</td>
<td>74</td>
<td><strong>100.0 %</strong></td>
<td><strong>1.39</strong> [ <strong>0.84, 1.95</strong> ]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.19; Chi² = 10.60, df = 2 (P = 0.005); I² =81%</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 4.93 (P &lt; 0.00001)</td>
<td></td>
<td></td>
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</tbody>
</table>
### Analysis 1.2. Comparison 1 PDE inhibitors versus placebo, Outcome 2 Sexual function using IIEF-15.

**Review:** Interventions for treating sexual dysfunction in patients with chronic kidney disease

**Comparison:** 1 PDE inhibitors versus placebo

**Outcome:** 2 Sexual function using IIEF-15

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PDE inhibitors</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
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</thead>
<tbody>
<tr>
<td><strong>Overall satisfaction</strong></td>
<td></td>
<td></td>
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<tr>
<td>Seibel 2002</td>
<td>20</td>
<td>21</td>
<td>7.5 (2.1)</td>
<td>4.86 (2.2)</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>20</td>
<td>21</td>
<td></td>
<td>100.0 %</td>
<td>2.64 [1.32, 3.96]</td>
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<tr>
<td><strong>Erectile function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seibel 2002</td>
<td>20</td>
<td>21</td>
<td>23 (5.7)</td>
<td>15.24 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Yang 2008</td>
<td>20</td>
<td>19</td>
<td>26.5 (2.8)</td>
<td>13.3 (2.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>40</td>
<td>40</td>
<td></td>
<td>100.0 %</td>
<td>10.64 [5.32, 15.96]</td>
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<tr>
<td><strong>Orgasmic function</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Seibel 2002</td>
<td>20</td>
<td>21</td>
<td>7.65 (2.3)</td>
<td>5.95 (2.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>20</td>
<td>21</td>
<td></td>
<td>100.0 %</td>
<td>1.70 [0.35, 3.05]</td>
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<tr>
<td><strong>Intercourse satisfaction</strong></td>
<td></td>
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</tr>
<tr>
<td>Seibel 2002</td>
<td>20</td>
<td>21</td>
<td>9.9 (2.8)</td>
<td>8.19 (2.4)</td>
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</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>20</td>
<td>21</td>
<td></td>
<td>100.0 %</td>
<td>1.71 [0.11, 3.31]</td>
</tr>
<tr>
<td><strong>Sexual desire</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seibel 2002</td>
<td>20</td>
<td>21</td>
<td>6.4 (1.8)</td>
<td>5.91 (2)</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>20</td>
<td>21</td>
<td></td>
<td>100.0 %</td>
<td>0.49 [-0.67, 1.65]</td>
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</table>

Heterogeneity: not applicable

Test for overall effect: Z = 3.93 (P = 0.000085)

Subtotal (95% CI): 76 [54, 98] (P = 0.000009)

Test for overall effect: Z = 3.92 (P = 0.000089)

Subtotal (95% CI): 10.64 [5.32, 15.96] (P = 0.000089)

Test for overall effect: Z = 3.92 (P = 0.000089)

Subtotal (95% CI): 1.71 [0.11, 3.31] (P = 0.000089)

Test for overall effect: Z = 3.92 (P = 0.000089)

Subtotal (95% CI): 0.49 [-0.67, 1.65] (P = 0.000089)

Test for overall effect: Z = 3.92 (P = 0.000089)
Analysis 1.3. Comparison 1 PDE inhibitors versus placebo, Outcome 3 Headache.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PDE inhibitors</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seibel 2002</td>
<td>2/20</td>
<td>2/21</td>
<td>1.05 [0.16, 6.76]</td>
<td></td>
</tr>
</tbody>
</table>

Favours PDE-inhibitors | Favours placebo

Analysis 1.4. Comparison 1 PDE inhibitors versus placebo, Outcome 4 Improvement in erectile function.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PDE inhibitors</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seibel 2002</td>
<td>17/20</td>
<td>2/21</td>
<td>8.93 [2.36, 33.78]</td>
<td></td>
</tr>
</tbody>
</table>

Favours placebo | Favours PDE inhibitor
### Analysis 2.1. Comparison 2 Zinc versus placebo, Outcome 1 Serum testosterone.

**Review:** Interventions for treating sexual dysfunction in patients with chronic kidney disease

**Comparison:** 2 Zinc versus placebo

**Outcome:** 1 Serum testosterone

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV Random, 95% CI</td>
<td>IV Random, 95% CI</td>
<td></td>
</tr>
<tr>
<td>1 Zinc in dialysate</td>
<td>4 8.15 (3.51)</td>
<td>4 3.2 (2.02)</td>
<td>29.2 % 1.50 [-0.23, 3.23 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antoniou 1977</td>
<td>7 9 (4.23)</td>
<td>7 12 (1.32)</td>
<td>35.0 % -0.90 [-2.01, 0.22 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>11</strong></td>
<td><strong>11</strong></td>
<td><strong>64.3 % 0.21 [-2.14, 2.55 ]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Oral zinc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mahajan 1982</td>
<td>10 5.2 (1.58)</td>
<td>10 3 (0.95)</td>
<td>35.7 % 1.62 [0.58, 2.66 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>10</strong></td>
<td><strong>10</strong></td>
<td><strong>35.7 % 1.62 [0.58, 2.66 ]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>21</strong></td>
<td><strong>21</strong></td>
<td><strong>100.0 % 0.70 [-1.05, 2.45 ]</strong></td>
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<td></td>
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</tbody>
</table>

Heterogeneity: Tau² = 2.33; Chi² = 5.22, df = 1 (P = 0.02); I² = 81%

Test for overall effect: Z = 0.17 (P = 0.86)

Test for subgroup differences: Chi² = 6.38, df = 1 (P = 0.01), I² = 84%
**Analysis 2.2. Comparison 2 Zinc versus placebo, Outcome 2 Improvement of libido.**

Review: Interventions for treating sexual dysfunction in patients with chronic kidney disease

Comparison: Zinc versus placebo

Outcome: Improvement of libido

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
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<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
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<tr>
<td>Brook 1980</td>
<td>1/7</td>
<td>1/7</td>
<td>1.00 [0.08, 13.02]</td>
<td></td>
</tr>
</tbody>
</table>

Favours placebo  Favours zinc

---

**Analysis 2.3. Comparison 2 Zinc versus placebo, Outcome 3 Plasma FSH.**

Review: Interventions for treating sexual dysfunction in patients with chronic kidney disease

Comparison: Zinc versus placebo

Outcome: Plasma FSH

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)[mU/mL]</td>
<td>N</td>
<td>Mean(SD)[mU/mL]</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Antaniou 1977</td>
<td>4</td>
<td>24 (24.3)</td>
<td>4</td>
<td>33 (8.7)</td>
<td>30.8 %  -9.00 [-34.29, 16.29]</td>
</tr>
<tr>
<td>Mahajan 1982</td>
<td>10</td>
<td>25 (22.14)</td>
<td>10</td>
<td>35 (15.81)</td>
<td>69.2 %  -10.00 [-26.86, 6.86]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>14</td>
<td>14</td>
<td>100.0 %</td>
<td>-9.69 [-23.72, 4.34]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.0; Chi² = 0.00, df = 1 (P = 0.95); I² =0.0%

Test for overall effect: Z = 1.35 (P = 0.18)

Test for subgroup differences: Not applicable
### Analysis 2.4. Comparison 2 Zinc versus placebo, Outcome 4 Plasma LH.

Review: Interventions for treating sexual dysfunction in patients with chronic kidney disease

Comparison: Zinc versus placebo

Outcome: Plasma LH

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)[mU/mL]</td>
<td>N</td>
<td>Mean(SD)[mU/mL]</td>
<td>IV,Random,95% CI</td>
</tr>
<tr>
<td>Antoniou 1977</td>
<td>4</td>
<td>85.3 (81)</td>
<td>4</td>
<td>47.3 (26.9)</td>
<td>28.9 %</td>
</tr>
<tr>
<td>Mahajan 1982</td>
<td>10</td>
<td>49 (82.22)</td>
<td>10</td>
<td>38 (25.3)</td>
<td>71.1 %</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>14</strong></td>
<td></td>
<td><strong>14</strong></td>
<td></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.0$, $\text{Chi}^2 = 0.28$, df = 1 ($P = 0.59$); $I^2 = 0.0$

Test for overall effect: $Z = 0.82$ ($P = 0.41$)

Test for subgroup differences: Not applicable

---

### Analysis 2.5. Comparison 2 Zinc versus placebo, Outcome 5 Frequency of intercourse.

Review: Interventions for treating sexual dysfunction in patients with chronic kidney disease

Comparison: Zinc versus placebo

Outcome: Frequency of intercourse

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M- H,Random,95% CI</td>
<td>M- H,Random,95% CI</td>
</tr>
<tr>
<td>Mahajan 1982</td>
<td>2/10</td>
<td>9/10</td>
<td>0.22 ([-0.06, 0.78])</td>
<td></td>
</tr>
</tbody>
</table>

0.05 0.2 1 5 20

Favours zinc Favours placebo

---

Interventions for treating sexual dysfunction in patients with chronic kidney disease (Review)

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### Analysis 2.6. Comparison 2 Zinc versus placebo, Outcome 6 Total/partial impotence.

**Review:** Interventions for treating sexual dysfunction in patients with chronic kidney disease

**Comparison:** 2 Zinc versus placebo

**Outcome:** 6 Total/partial impotence

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>H(Random,95% CI)</td>
<td></td>
<td>H(Random,95% CI)</td>
</tr>
<tr>
<td>Mahajan 1982</td>
<td>1/10</td>
<td>8/10</td>
<td>0.13 [0.02, 0.82]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Analysis 2.7. Comparison 2 Zinc versus placebo, Outcome 7 Variations in libido.

**Review:** Interventions for treating sexual dysfunction in patients with chronic kidney disease

**Comparison:** 2 Zinc versus placebo

**Outcome:** 7 Variations in libido

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>H(Random,95% CI)</td>
<td></td>
<td>H(Random,95% CI)</td>
</tr>
<tr>
<td>Brook 1980</td>
<td>0/7</td>
<td>0/7</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mahajan 1982</td>
<td>0/10</td>
<td>4/10</td>
<td>100.0 %</td>
<td>0.11 [0.01, 1.83]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

|                | 17       | 17       | 100.0 %    | 0.11 [0.01, 1.83] |

Total events: 0 (Zinc), 4 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.54 (P = 0.12)
### Analysis 2.8. Comparison 2 Zinc versus placebo, Outcome 8 Nocturnal penile tumescence (NPT).

**Review:** Interventions for treating sexual dysfunction in patients with chronic kidney disease

**Comparison:** 2 Zinc versus placebo

**Outcome:** 8 Nocturnal penile tumescence (NPT)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Zinc</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Wabrek 1982</td>
<td>1/4</td>
<td>1/3</td>
<td>0.75 [0.07, 7.73]</td>
<td>0.25 [0.00, 11.03]</td>
</tr>
</tbody>
</table>

Favours zinc

### Analysis 3.1. Comparison 3 Vitamin E versus placebo, Outcome 1 Prolactin.

**Review:** Interventions for treating sexual dysfunction in patients with chronic kidney disease

**Comparison:** 3 Vitamin E versus placebo

**Outcome:** 1 Prolactin

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin E</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)[ng/mL]</td>
<td>N</td>
<td>Mean(SD)[ng/mL]</td>
</tr>
<tr>
<td>Yeksan 1992</td>
<td>12</td>
<td>15 (4.28)</td>
<td>12</td>
<td>56.23 (15.66)</td>
</tr>
</tbody>
</table>

Favours vit E
**Analysis 3.2. Comparison 3 Vitamin E versus placebo, Outcome 2 Plasma LH.**

Review: Interventions for treating sexual dysfunction in patients with chronic kidney disease

Comparison: 3 Vitamin E versus placebo

Outcome: 2 Plasma LH

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin E</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)[mU/mL]</td>
<td>N</td>
<td>Mean(SD)[mU/mL]</td>
</tr>
<tr>
<td>Yeksan 1992</td>
<td>12</td>
<td>4.66 (1.8)</td>
<td>12</td>
<td>11.43 (5.7)</td>
</tr>
</tbody>
</table>

-20 -10 0 10 20
Favours Vit E Favours placebo

**Analysis 3.3. Comparison 3 Vitamin E versus placebo, Outcome 3 Plasma FSH.**

Review: Interventions for treating sexual dysfunction in patients with chronic kidney disease

Comparison: 3 Vitamin E versus placebo

Outcome: 3 Plasma FSH

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin E</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)[mU/mL]</td>
<td>N</td>
<td>Mean(SD)[mU/mL]</td>
</tr>
<tr>
<td>Yeksan 1992</td>
<td>12</td>
<td>4.23 (1.83)</td>
<td>12</td>
<td>4.88 (2.94)</td>
</tr>
</tbody>
</table>

-4 -2 0 2 4
Favours vit E Favours placebo
### Analysis 3.4. Comparison 3 Vitamin E versus placebo, Outcome 4 Serum testosterone.

**Review:** Interventions for treating sexual dysfunction in patients with chronic kidney disease

**Comparison:** 3 Vitamin E versus placebo

**Outcome:** 4 Serum testosterone

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin E</th>
<th>Placebo</th>
<th>Mean Difference (IV,Random,95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeksan 1992</td>
<td>12</td>
<td>12</td>
<td>7.00 [4.43, 9.57]</td>
</tr>
</tbody>
</table>

#### ADDITIONAL TABLES

Table 1. Other outcomes related to sexual dysfunction as reported in the included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Mean ± SD (treatment group or baseline value) or RR (95% CI)</th>
<th>Mean ± SD (control group or after treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoniou 1977</td>
<td>8</td>
<td>Oral zinc versus placebo</td>
<td>Testosterone concentration (ng/mL)¹</td>
<td>8.00 ± 3.50</td>
<td>3.20 ± 2.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85.30 ± 81.00</td>
<td>47.30 ± 26.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24.00 ± 24.30</td>
<td>33.00 ± 8.70</td>
</tr>
<tr>
<td>Bellovich 2000</td>
<td>14</td>
<td>Sildenafil citrate</td>
<td>IIEF - Frequency of penetration</td>
<td>3.85 ± 3.10</td>
<td>4.43 ± 2.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IIEF - Maintenance of erection penetration</td>
<td>4.43 ± 2.69</td>
<td>4.93 ± 2.32</td>
</tr>
<tr>
<td>Brook 1980</td>
<td>14</td>
<td>Zinc chloride versus placebo to dialysate</td>
<td>Improvement of libido</td>
<td>1.00 (0.08 to 13.02)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plasma testosterone (nmol/L)²</td>
<td>9.00 ± 4.23</td>
<td>12.00 ± 1.32</td>
</tr>
<tr>
<td>Mahajan 1982</td>
<td>20</td>
<td>Oral zinc acetate versus placebo</td>
<td>Total/partial impotence</td>
<td>0.13 (0.02 to 0.82)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased libido</td>
<td>0.11 (0.01 to 1.83)</td>
<td>NA</td>
</tr>
</tbody>
</table>
Table 1. Other outcomes related to sexual dysfunction as reported in the included studies *(Continued)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Outcome Measure</th>
<th>Global efficacy question</th>
<th>Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahon 2005</td>
<td>Sildenafil citrate versus placebo</td>
<td>Decreased frequency of intercourse</td>
<td>0.22 (0.06 to 0.78)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased plasma testosterone³</td>
<td>5.20 ± 1.58</td>
<td>3.00 ± 0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased plasma FSH³</td>
<td>25.00 ± 22.14</td>
<td>35.00 ± 15.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased plasma LH³</td>
<td>49.00 ± 82.22</td>
<td>38.00 ± 25.3</td>
</tr>
<tr>
<td>Muir 1983</td>
<td>Bromocriptine versus placebo</td>
<td>Testosterone (nmol/L)¹</td>
<td>16.80 ± 4.49</td>
<td>17.00 ± 4.11</td>
</tr>
<tr>
<td>Sharma 2006</td>
<td>Sildenafil citrate versus placebo</td>
<td>Global efficacy question</td>
<td>4.33 (2.07 to 9.08)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood urea nitrogen (mg/dL)²</td>
<td>18.3 ± 7.6</td>
<td>17.9 ± 51.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine (mg/dL)²</td>
<td>1.48 ± 0.4</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haemoglobin (g/dL)²</td>
<td>12.3 ± 1.5</td>
<td>13.2 ± 1.4</td>
</tr>
<tr>
<td>Wabrek 1982</td>
<td>Oral zinc versus placebo</td>
<td>Tumescence episodes</td>
<td>0.75 (0.07 to 7.73)</td>
<td>NA</td>
</tr>
<tr>
<td>Yeksan 1992</td>
<td>Vitamin E versus placebo*</td>
<td>Prolactin (ng/mL)</td>
<td>15.00 ± 4.28</td>
<td>56.23 ± 15.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LH (mU/mL)</td>
<td>4.66 ± 1.80</td>
<td>11.43 ± 5.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FSH (mU/mL)</td>
<td>4.23 ± 1.83</td>
<td>4.88 ± 2.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Testosterone (pg/mL)</td>
<td>11.79 ± 4.16</td>
<td>4.79 ± 1.82</td>
</tr>
</tbody>
</table>

¹ significance not reported; ² P value not significant; ³ P value < 0.05; * Data pre and post vitamin E treatment only is reported; IIEF - International Index of Erectile Function; LH - luteinizing hormone; FSH - follicular stimulating hormone; SD - standard deviation; RR - relative risk; NA - not applicable or not available.
## Appendix 1. Electronic search strategies

<table>
<thead>
<tr>
<th>Database</th>
<th>Search terms</th>
</tr>
</thead>
</table>
| CENTRAL  | 1. MeSH descriptor Sexual Dysfunction, Physiological explode all trees  
2. MeSH descriptor Sexual Dysfunctions, Psychological explode all trees  
3. MeSH descriptor Orgasm, this term only  
4. sexual dysfunction*:ti,ab,kw in Clinical Trials  
5. sex* disorder*:ti,ab,kw in Clinical Trials  
6. frigid*:ti,ab,kw in Clinical Trials  
7. erectile* and (disorder* or dysfunction*):ti,ab,kw in Clinical Trials  
8. sexual and (arousal or aversion*):ti,ab,kw in Clinical Trials  
9. fsfi:ti,ab,kw in Clinical Trials  
10. Female Sexual Function Index:ti,ab,kw in Clinical Trials  
11. (International Index of Erectile Function):ti,ab,kw in Clinical Trials  
12. iief:ti,ab,kw in Clinical Trials  
13. (Female Sexual Distress Score):ti,ab,kw in Clinical Trials  
14. fsds:ti,ab,kw in Clinical Trials  
15. impotent or impotence:ti,ab,kw in Clinical Trials  
16. dyspareunia*:ti,ab,kw in Clinical Trials  
17. orgasm*:ti,ab,kw in Clinical Trials  
18. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)  
19. MeSH descriptor Renal Replacement Therapy explode all trees  
20. (hemodialysis or haemodialysis):ti,ab,kw in Clinical Trials  
21. (dialysis):ti,ab,kw in Clinical Trials  
22. (PD or CAPD or CCPD or APD):ti,ab,kw in Clinical Trials  
23. MeSH descriptor Renal Insufficiency, this term only  
24. MeSH descriptor Kidney Failure, this term only  
25. MeSH descriptor Renal Insufficiency, Chronic explode all trees  
26. MeSH descriptor Kidney Diseases, this term only  
27. MeSH descriptor Uremia, this term only  
28. "end stage renal" or "end stage kidney" or "endstage renal" or "endstage kidney":ti,ab,kw in Clinical Trials  
29. (ESRF or ESKF or ESRD or ESKD):ti,ab,kw in Clinical Trials  
30. "chronic kidney" or "chronic renal":ti,ab,kw in Clinical Trials  
31. (CKF or CKD or CRF or CRD):ti,ab,kw in Clinical Trials  
32. ur?emi*:ti,ab,kw in Clinical Trials  
33. (#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32)  
34. (#18 AND #33) |
| MEDLINE  | 1. exp Sexual Dysfunction, Physiological/  
2. exp Sexual Dysfunctions, Psychological/  
3. Orgasm/  
4. sexual dysfunction$:tw.  
5. sex$ disorder$:tw.  
6. frigid$:tw.  
7. erectile$:adj (disorder$: or dysfunction$):tw. |
8. (sexual adj (arousal or aversion$)).tw.
9. fsfi.tw.
10. Female Sexual Function Index.tw.
12. iief.tw.
13. Female Sexual Distress Score.tw.
14. FSDS.tw.
15. (impotent or impotence).tw.
16. dyspareunia.tw.
17. orgasm$.tw.
18. or/1-17
19. exp Renal Replacement Therapy/
20. (hemodialysis or haemodialysis).tw.
21. dialysis.tw.
22. (PD or CAPD or CCPD or APD).tw.
23. Renal Insufficiency/
24. Kidney Failure/
25. exp Renal Insufficiency, Chronic/
26. Kidney Diseases/
27. Uremia/
28. (end stage renal or end stage kidney or end stage renal or end stage kidney).tw.
29. (ESRF or ESKF or ESRD or ESKD).tw.
30. (chronic kidney or chronic renal).tw.
31. (CKF or CKD or CRF or CRD).tw.
32. ur?emi$.tw.
33. or/19-32
34. and/18,33

EMBASE
1. exp Sexual Dysfunction/
2. sexual dysfunction$.tw.
3. sex$ disorder$.tw.
4. frigid$.tw.
5. (erectile$ adj (disorder$ or dysfunction$)).tw.
6. (sexual adj (arousal or aversion$)).tw.
7. fsfi.tw.
8. Female Sexual Distress Score.tw.
10. iief.tw.
11. Female Sexual Function Index.tw.
12. fdds.tw.
13. (impotent or impotence).tw.
14. dyspareunia.tw.
15. orgasm$.tw.
16. or/1-15
17. exp Renal Replacement Therapy/
18. (hemodialysis or haemodialysis).tw.
19. (hemofiltration or haemofiltration).tw.
20. (hemodiafiltration or haemodiafiltration).tw.
21. dialysis.tw.
22. (PD or CAPD or CCPD or APD).tw.
23. Kidney Disease/
24. Chronic Kidney Disease/
25. Kidney Failure/
26. Chronic Kidney Failure/
27. Uremia/
29. (CKF or CKD or CRF or CRD).tw.
30. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
31. (ESRF or ESKF or ESRD or ESKD).tw.
32. ur?emi$.tw.
33. exp Kidney Transplantation/
34. or/17-33
35. and/16,34

Appendix 2. Risk of bias assessment tool

<table>
<thead>
<tr>
<th>Potential source of bias</th>
<th>Assessment criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there adequate sequence generation?</td>
<td>Yes (low risk of bias): Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)</td>
</tr>
<tr>
<td></td>
<td>No (high risk of bias): Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention</td>
</tr>
<tr>
<td></td>
<td>Unclear: Insufficient information about the sequence generation process to permit judgement</td>
</tr>
</tbody>
</table>

<p>| Was allocation adequately concealed?             | Yes (low risk of bias): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes) |
|                                                  | No (high risk of bias): Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rota- |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes (low risk of bias)</th>
<th>No (high risk of bias)</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was knowledge of the allocated interventions adequately prevented during the study?</td>
<td>No (high risk of bias): No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.</td>
<td>Yes (low risk of bias): No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.</td>
<td>Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.</td>
</tr>
<tr>
<td>Were incomplete outcome data adequately addressed?</td>
<td>No (high risk of bias): Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.</td>
<td>Yes (low risk of bias): No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.</td>
<td></td>
</tr>
</tbody>
</table>
### Are reports of the study free of suggestion of selective outcome reporting?

**Yes (low risk of bias):** The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

**No (high risk of bias):** Not all of the study’s pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

**Unclear:** Insufficient information to permit judgement of ‘Yes’ or ‘No’

### Was the study apparently free of other problems that could put it at a risk of bias?

**Yes (low risk of bias):** The study appears to be free of other sources of bias.

**No (high risk of bias):** Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

**Unclear:** Insufficient information to permit judgement of ‘Yes’ or ‘No’

### Contributions of Authors

1. Draft the protocol: MV, SDN, GFMS
2. Study selection: MV, SDN
3. Extract data from studies: MV, SDN
4. Enter data into RevMan: MV, SDN
5. Carry out the analysis: MV, SDN, GFMS
6. Interpret the analysis: MV, SDN, DWJ, GL, GG, MQ, VS, MR, EAJ, GFMS
7. Draft the final review: MV, SDN, DWJ, GL, GG, MQ, VS, MR, EAJ, GFMS
8. Disagreement resolution: GFMS
9. Update the review: MV, SDN, GFMS

DECLAREATIONS OF INTEREST

- Emmanuele A Jannini: I have been paid speaker, consultant, and grant recipient for almost all companies directly or indirectly involved in treatments of sexual dysfunction: Pfizer, Procter & Gamble, Lilly, Janssen-Cilag, Menarini, Bayer. This did not impact on my contribution to the article.
- All other authors: nothing to declare

INDEX TERMS
Medical Subject Headings (MeSH)
Bromocriptine [therapeutic use]; Chlorides [therapeutic use]; Chronic Disease; Erectile Dysfunction [drug therapy; etiology]; Kidney Diseases [*complications; therapy]; Phosphodiesterase 5 Inhibitors [therapeutic use]; Randomized Controlled Trials as Topic; Renal Dialysis; Sexual Dysfunction, Physiological [*drug therapy; etiology]; Testosterone [blood]; Vitamin D [therapeutic use]; Vitamin E [therapeutic use]; Vitamins [therapeutic use]; Zinc [therapeutic use]; Zinc Compounds [therapeutic use]

MeSH check words
Female; Humans; Male