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[Intervention Review]

Interventions for treating sexual dysfunction in patients with chronic kidney disease

Mariacristina Vecchio[1], Sankar D Navaneethan[2], David W Johnson[3], Giuseppe Lucisano[1], Giusi Graziano[1], Valeria Saglimbene[1], Marinella Ruospo[1], Marialuisa Querques[4], Emmanuele A Jannini[5], Giovanni FM Strippoli[6]

[1]Clinical Pharmacology and Epidemiology, Mario Negri Sud Consortium, Santa Maria Imbaro, Italy. [2]Department of Nephrology and Hypertension, Glickman Urological and Kidney institute, Cleveland Clinic, Cleveland, OH, USA. [3]Department of Nephrology, Princess Alexandra Hospital, Woolloongabba, Australia. [4]Department of Nephrology, University of Milan, San Raffaele, Milan, Italy. [5]School of Sexology, Department of Experimental Medicine, University of L'Aquila, L'Aquila, Italy. [6]a) Mario Negri Sud Consortium, Santa Maria Imbaro (Ch), Italy, b) Sydney School of Public Health, University of Sydney, Australia, c) Diaverum Medical-Scientific Office, Lund, Sweden

Contact address: Mariacristina Vecchio, Clinical Pharmacology and Epidemiology, Mario Negri Sud Consortium, Via Nazionale 8/A, Santa Maria Imbaro, Chieti, 66030, Italy. vecchio@negrisud.it.

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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 (Mehrsai 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-uraemic 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, α_1-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,

Johnson, and Kaplan's sexual therapies, educational intervention, systematic desensitization and sexual counselling.

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 reported 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 speciality 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 I^2 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

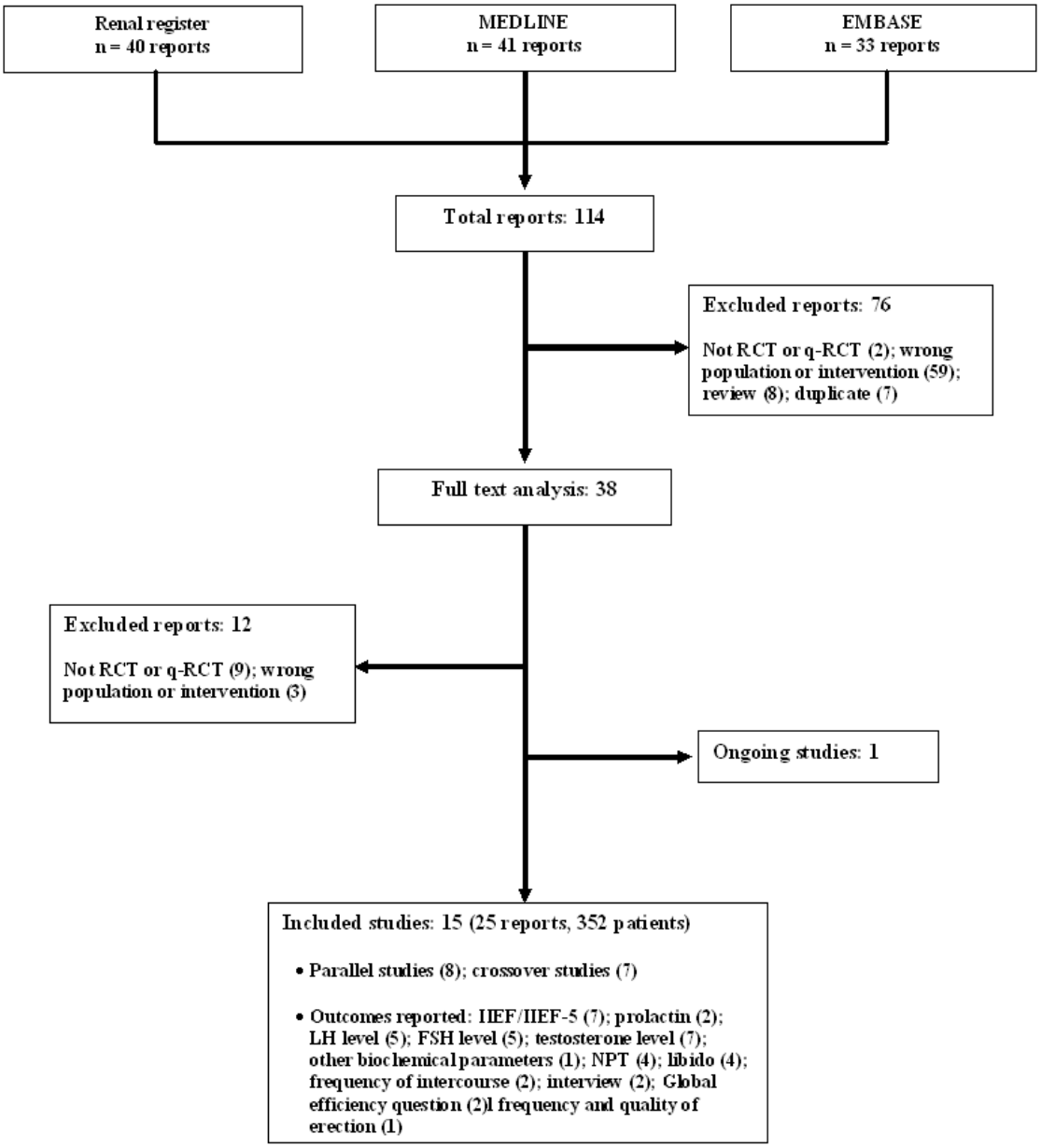
Description of studies

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



Included studies

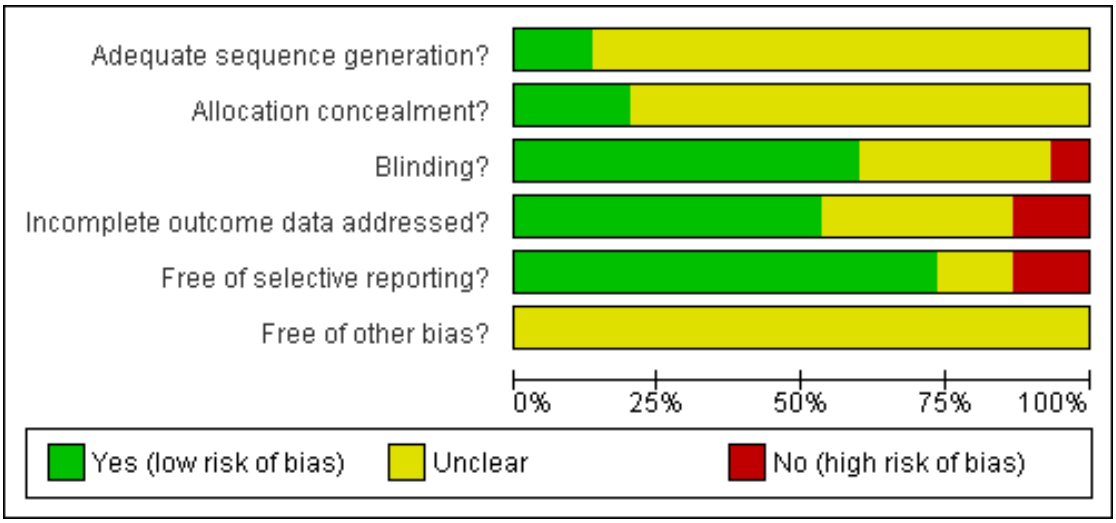
Two groups of studies were identified: eight parallel studies (Antoniou 1977; Brook 1980; Demir 2006; Mahajan 1982; Seibel 2002; Wabrek 1982; Yang 2008; Yeksan 1992) and seven crossover studies (Bellovich 2000; Blumberg 1980; Bommer 1979; Mahon 2005; Muir 1983; Sharma 2006; Turk 2010).

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 (Turk 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 -9.69 mU/mL, 95% CI -23.72 to 4.34; 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) (Wabrek 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

(MD -0.65, 95% CI -2.61 to 1.31; 1 study, 24 patients). No adverse effects were reported in this study.

Other outcomes

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

2000; Peng 2005; Peng 2007; Seidman 2006; Turk 2004), although 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.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

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

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Unclear risk	NS
Blinding? All outcomes	Unclear risk	Blinding of investigators Participants outcomes assessors and data analysis: NS
Incomplete outcome data addressed? All outcomes	High risk	Patients excluded at various stage (one patient died and three others dropped out because of intercurrent illness)

Antoniou 1977 (*Continued*)

Free of selective reporting?	Low risk	Primary outcomes for this review (plasma gonadotropins concentration) have been reported
Free of other bias?	Unclear risk	Funding source: NS

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 • Karnofsjy scale score for QoL measurement
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Unclear risk	NS
Blinding? All outcomes	Unclear risk	Data only available from conference proceedings abstract

Bellovich 2000 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear risk	Patients excluded at various stages (one transplanted, one died, seven lost to follow-up)
Free of selective reporting?	Unclear risk	Primary outcomes for this review (IIEF score) have been reported, however data only available from conference proceedings abstract
Free of other bias?	Unclear risk	Funding source: NS

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

Blumberg 1980 (*Continued*)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Unclear risk	NS
Blinding? All outcomes	Unclear risk	Blinding of participants Outcomes assessors and data analysis: NS
Incomplete outcome data addressed? All outcomes	Low risk	All patients followed up or accounted for
Free of selective reporting?	Low risk	Primary outcomes for this review (plasma gonadotropins concentration) have been reported
Free of other bias?	Unclear risk	Funding source: NS

Bommer 1979

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*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Unclear risk	NS
Blinding? All outcomes	Unclear risk	Blinding of participants Outcomes assessors and data analysis: NS
Incomplete outcome data addressed? All outcomes	Unclear risk	Patients excluded at various stage (only 7/15 patients were able to complete the study; bromocriptine caused serious hypotension in the remaining 8 men)
Free of selective reporting?	High risk	Primary outcomes for this review not reported
Free of other bias?	Unclear risk	Funding source: NS

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

Brook 1980 (*Continued*)

	• Dose, duration, frequency, administration: NS
Outcomes	• Plasma testosterone • Questionnaire about sexual dysfunction • Gonadotropin levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Unclear risk	NS
Blinding? All outcomes	Low risk	Blinding of participants and investigators Outcomes assessors and data analysis: NS
Incomplete outcome data addressed? All outcomes	Low risk	All patients followed up or accounted for
Free of selective reporting?	Low risk	Primary outcomes for this review (plasma gonadotropins concentration) have been reported
Free of other bias?	Unclear risk	Funding source: NS

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 ○ Treatment group: 48 ± 7.4 years ○ Control group: 50 ± 7.1 years • Sex: 100% male Exclusion criteria • Stroke; diabetes; myocardial infarction; coronary heart disease; overt heart failure;

Demir 2006 (*Continued*)

	significant penile anatomical abnormalities; active peptic ulcer; chronic liver disease; clinically significant hypotension; blood coagulation disorders; therapy with nitrate
Interventions	Treatment group • Vardenafil • Dose, duration, frequency, administration: 10 mg (dose could be increased to 20 mg) for 4 weeks Control group • Placebo • Dose, duration, frequency, administration: NS
Outcomes	• IIEF score • Cyclosporin concentration
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Unclear risk	NS
Blinding? All outcomes	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	All patients followed up or accounted for
Free of selective reporting?	Low risk	Primary outcomes for this review (IIEF score) have been reported
Free of other bias?	Unclear risk	Funding source: NS

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	Treatment group • Elemental zinc or zinc acetate • Dose, duration, frequency, administration: 25-50 mg Control group • Placebo (sucrose) • Dose, duration, frequency, administration: 25-50 mg
Outcomes	• Libido • Frequency of intercourse • Testosterone • LH level • FSH level • Sperm counts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Low risk	Consecutively numbered sealed envelopes
Blinding? All outcomes	Low risk	Blinding of participants and investigators Outcomes assessors and data analysis: NS
Incomplete outcome data addressed? All outcomes	Low risk	All patients followed up or accounted for
Free of selective reporting?	Low risk	Primary outcomes for this review (plasma gonadotropins concentration) have been reported
Free of other bias?	Unclear risk	Funding source: NS

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
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Unclear risk	NS
Blinding? All outcomes	Low risk	Blinding of participants and investigators Outcomes assessors and data analysis: NS
Incomplete outcome data addressed? All outcomes	High risk	Continuous results are reported as mean and no SD
Free of selective reporting?	Unclear risk	Primary outcomes for this review (IIEF score) have not been reported
Free of other bias?	Unclear risk	Funding source: NS

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	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Low risk	Tablets were dispensed in code by the hospital pharmacy
Blinding? All outcomes	Low risk	Blinding of participants and investigators Outcomes assessors and data analysis: NS

Muir 1983 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear risk	Patients excluded at various stage (two received kidney transplants and nine stopped owing to side effects)
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

Bias	**Authors' judgement**	**Support for judgement**

Seibel 2002 (*Continued*)

Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Unclear risk	"24 patients in each group received a sealed box containing the capsules"
Blinding? All outcomes	Low risk	Blinding of participants and investigators Outcomes assessors and data analysis: NS
Incomplete outcome data addressed? All outcomes	Unclear risk	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)
Free of selective reporting?	Low risk	Primary outcomes for this review (IIEF score) have been reported
Free of other bias?	Unclear risk	Funding source: NS

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

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

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

	and derivatives; uncontrolled hypertension or symptomatic hypotension; penile anatomical deformity; bleeding diathesis and peptic ulcer disease; schedule for kidney transplantation or alternate surgical procedure
Interventions	Treatment group • Sildenafil citrate • Dose, duration, frequency, administration: 50 mg, 45 min prior to sexual intercourse once per week for 4 weeks Control group • Vardenafil • Dose, duration, frequency, administration: 10 mg, 45 min prior to sexual intercourse once per week for 4 weeks
Outcomes	• IIEF-5 score • Physical component score • Mental component score
Notes	

Risk of bias

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

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

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Unclear risk	NS
Blinding? All outcomes	Low risk	Blinding of participants, investigators and outcomes assessors Data analysis: NS
Incomplete outcome data addressed? All outcomes	Unclear risk	Data only available for 7/8 patients
Free of selective reporting?	High risk	Primary outcomes for this review have not been reported
Free of other bias?	Unclear risk	Funding source: NS

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

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Unclear risk	NS
Blinding? All outcomes	Low risk	Blinding of participants and investigators Outcomes assessors and data analysis: NS

Yang 2008 (*Continued*)

Incomplete outcome data addressed? All outcomes	Low risk	All patients followed up or accounted for
Free of selective reporting?	Low risk	Primary outcomes for this review (IIEF score) have been reported
Free of other bias?	Unclear risk	Funding source: NS

Yeksan 1992

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Stated "randomised" no further information provided
Allocation concealment?	Unclear risk	NS

Yeksan 1992 (*Continued*)

Blinding? All outcomes	Low risk	Blinding of participants and investigators Outcomes assessors and data analysis: NS
Incomplete outcome data addressed? All outcomes	Low risk	All patients followed up or accounted for
Free of selective reporting?	Low risk	Primary outcomes for this review (plasma gonadotropins concentration) have been reported
Free of other bias?	Unclear risk	Funding source: NS

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 excluded studies *[ordered by study ID]*

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

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

NCT00334477

Trial name or title	Efficacy and safety of tadalafil 20 mg for the treatment of erectile dysfunction in chronic renal patients in haemodialysis

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

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

Comparison 2. Zinc versus placebo

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

Comparison 3. Vitamin E versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Prolactin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Plasma LH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Plasma FSH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Serum testosterone	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

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

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

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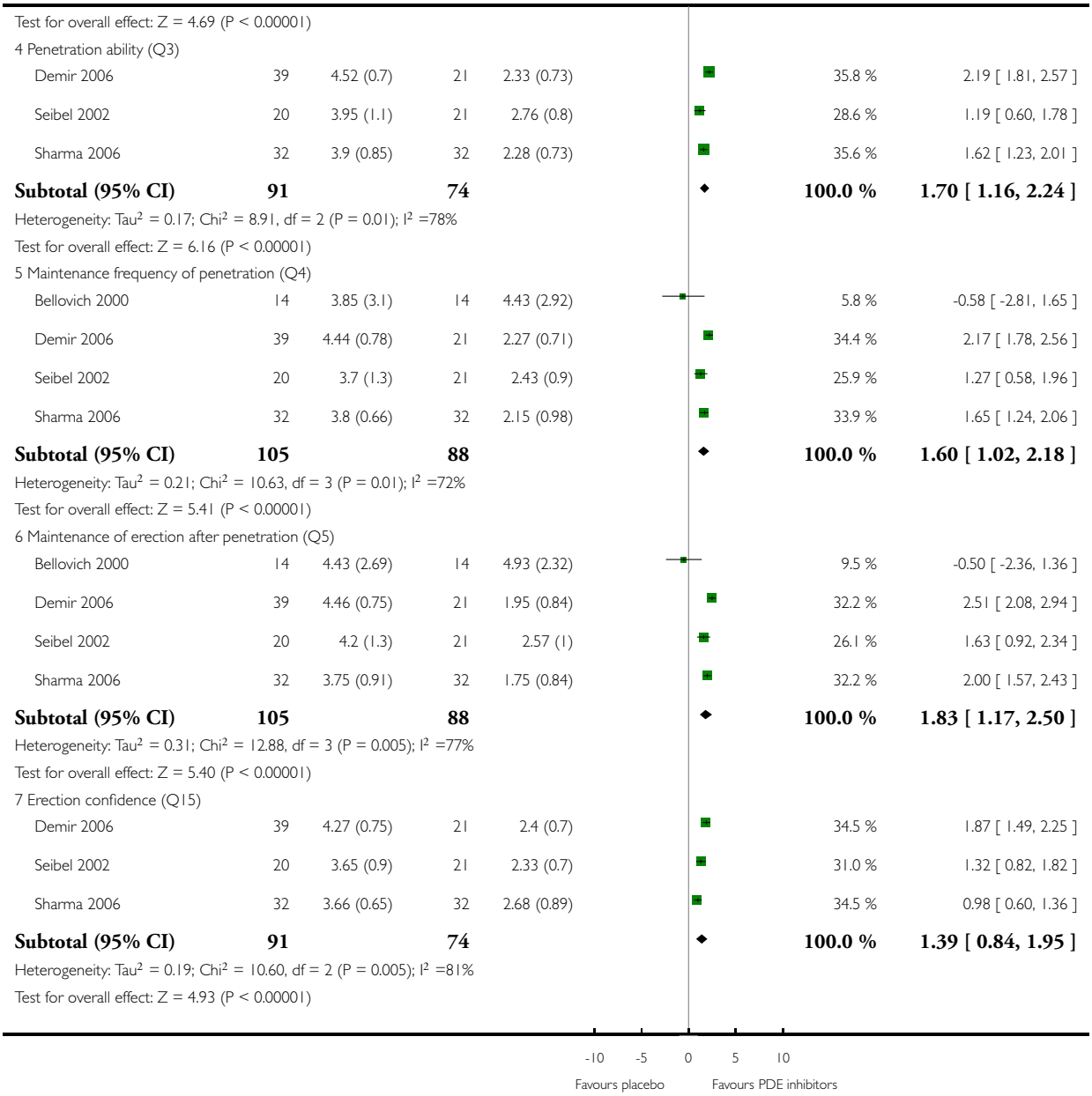
Study or subgroup	PDE inhibitors N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 4.69 (P < 0.00001)							
4 Penetration ability (Q3)							
Demir 2006	39	4.52 (0.7)	21	2.33 (0.73)		35.8 %	2.19 [1.81, 2.57]
Seibel 2002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

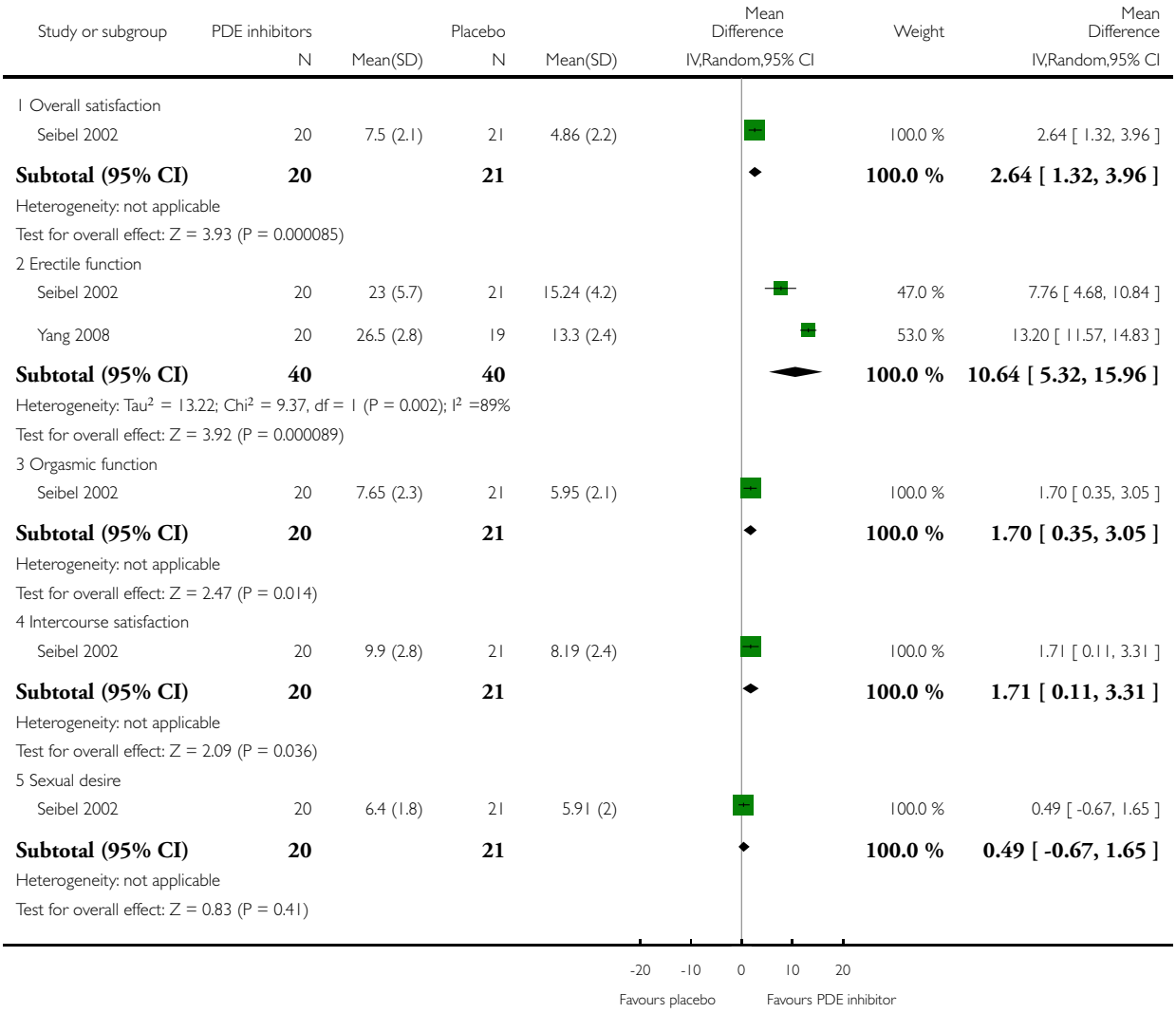


Analysis 1.2. Comparison 1 PDE inhibitors versus placebo, Outcome 2 Sexual function using IIEF-15.

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



Analysis 1.3. Comparison 1 PDE inhibitors versus placebo, Outcome 3 Headache.

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

Comparison: 1 PDE inhibitors versus placebo

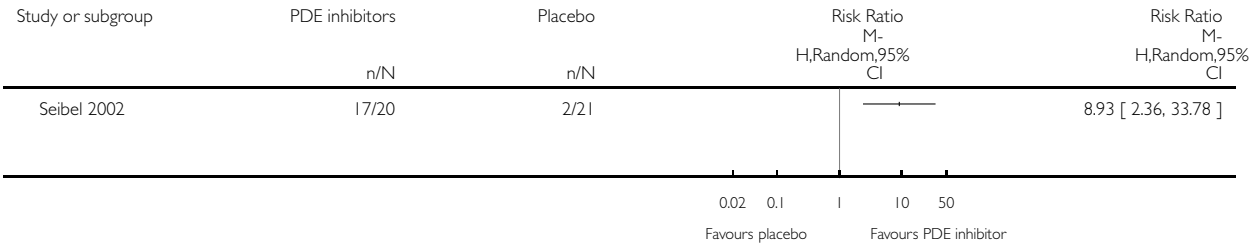
Outcome: 3 Headache

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

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

Comparison: 1 PDE inhibitors versus placebo

Outcome: 4 Improvement in erectile function

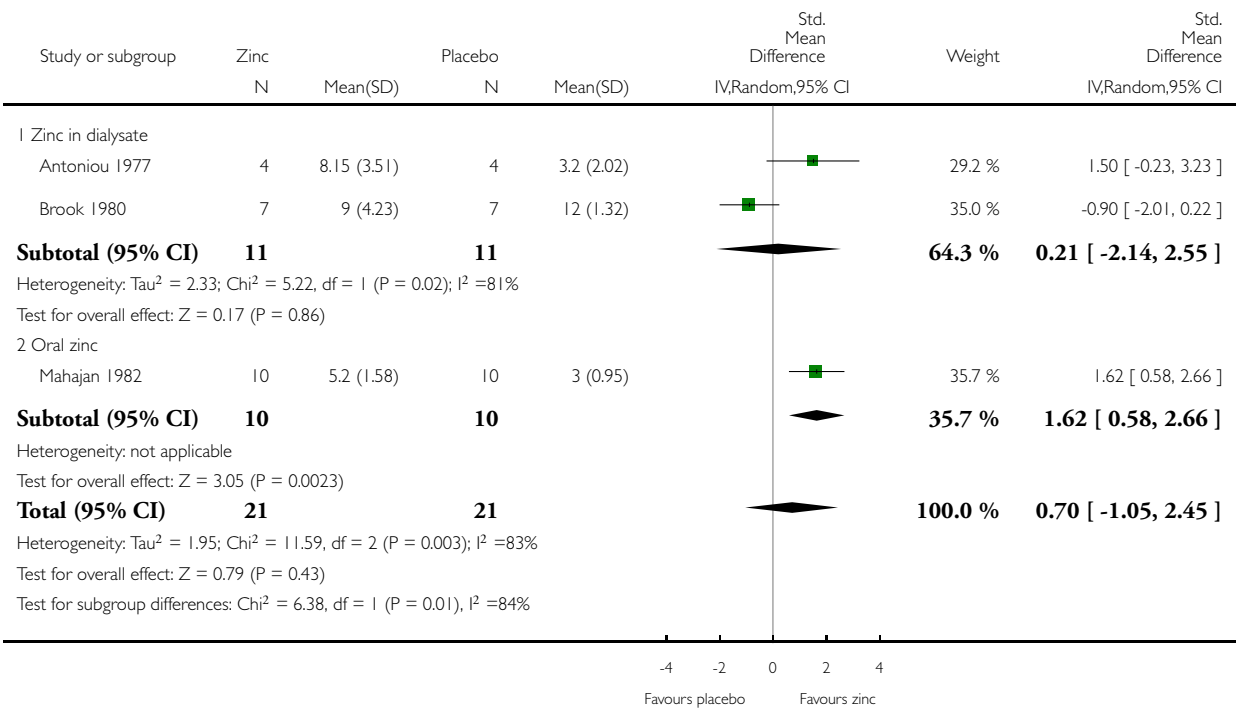


Analysis 2.1. Comparison 2 Zinc versus placebo, Outcome 1 Serum testosterone.

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

Comparison: 2 Zinc versus placebo

Outcome: 1 Serum testosterone

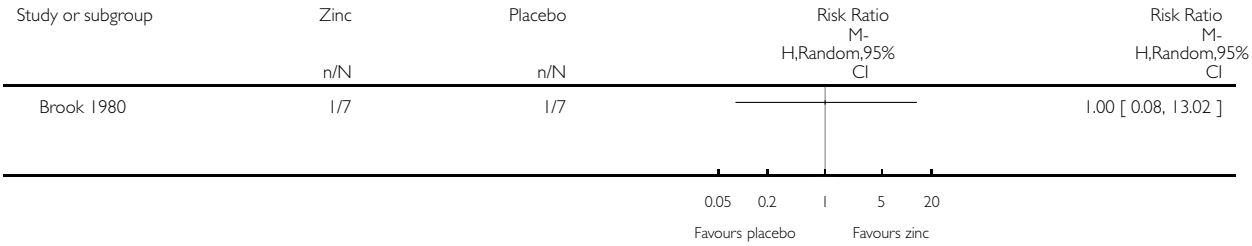


Analysis 2.2. Comparison 2 Zinc versus placebo, Outcome 2 Improvement of libido.

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

Comparison: 2 Zinc versus placebo

Outcome: 2 Improvement of libido

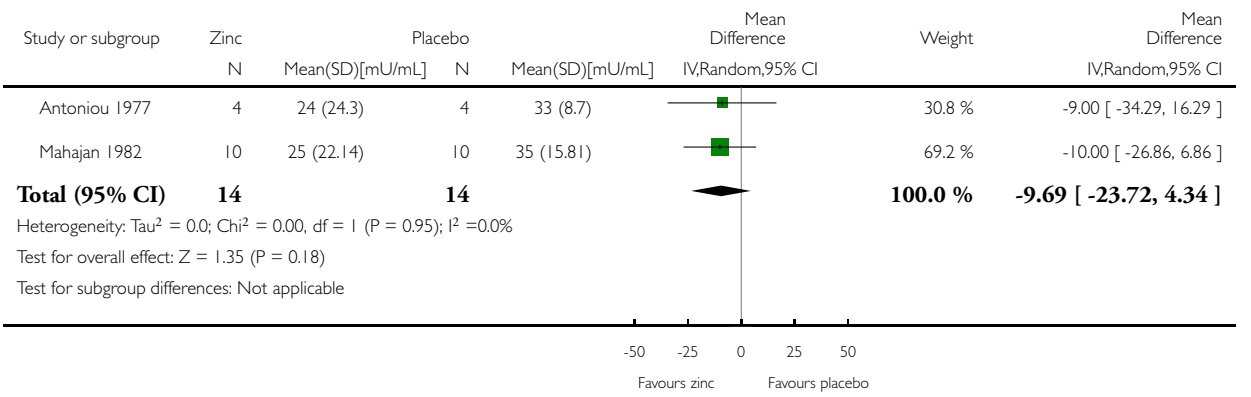


Analysis 2.3. Comparison 2 Zinc versus placebo, Outcome 3 Plasma FSH.

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

Comparison: 2 Zinc versus placebo

Outcome: 3 Plasma FSH

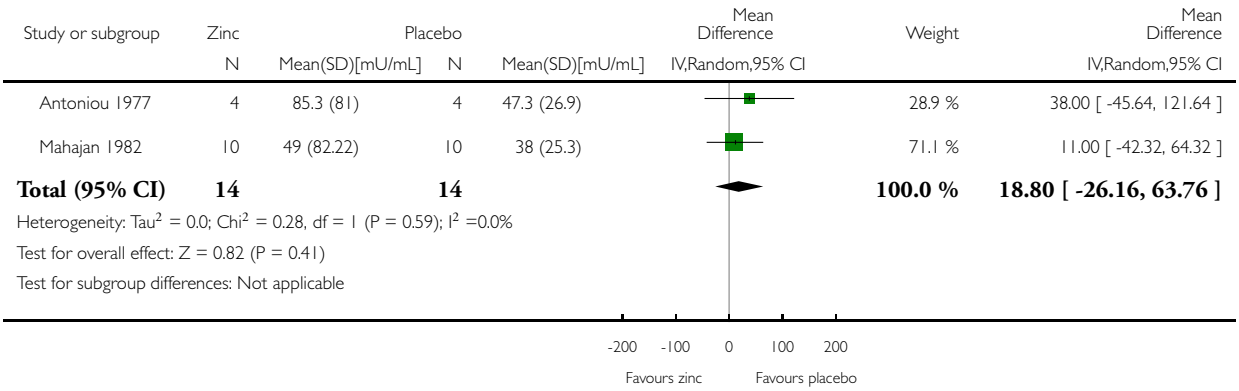


Analysis 2.4. Comparison 2 Zinc versus placebo, Outcome 4 Plasma LH.

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

Comparison: 2 Zinc versus placebo

Outcome: 4 Plasma LH

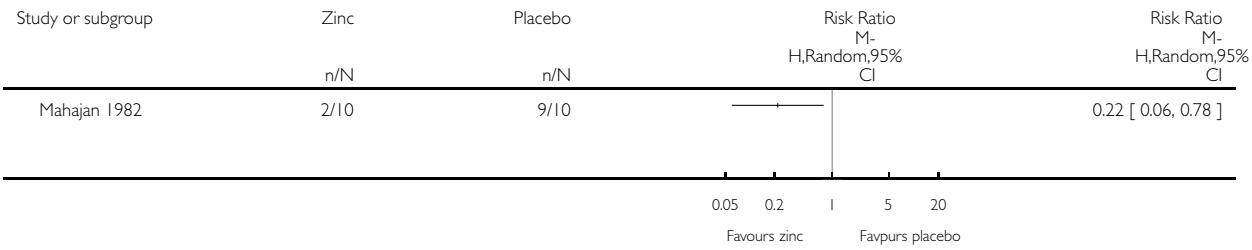


Analysis 2.5. Comparison 2 Zinc versus placebo, Outcome 5 Frequency of intercourse.

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

Comparison: 2 Zinc versus placebo

Outcome: 5 Frequency of intercourse

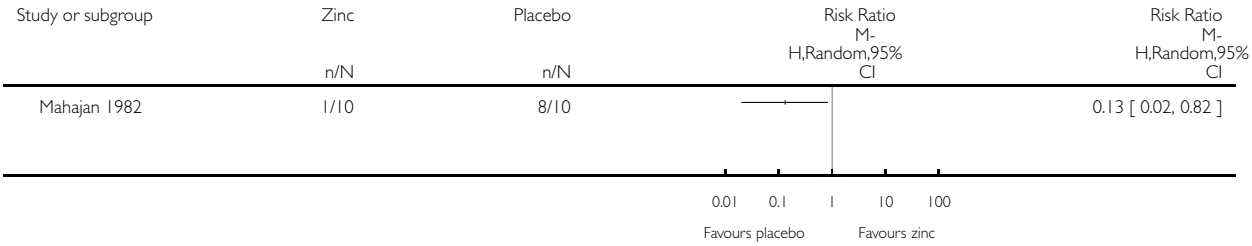


Analysis 2.6. Comparison 2 Zinc versus placebo, Outcome 6 Total/partial impotence.

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

Comparison: 2 Zinc versus placebo

Outcome: 6 Total/partial impotence

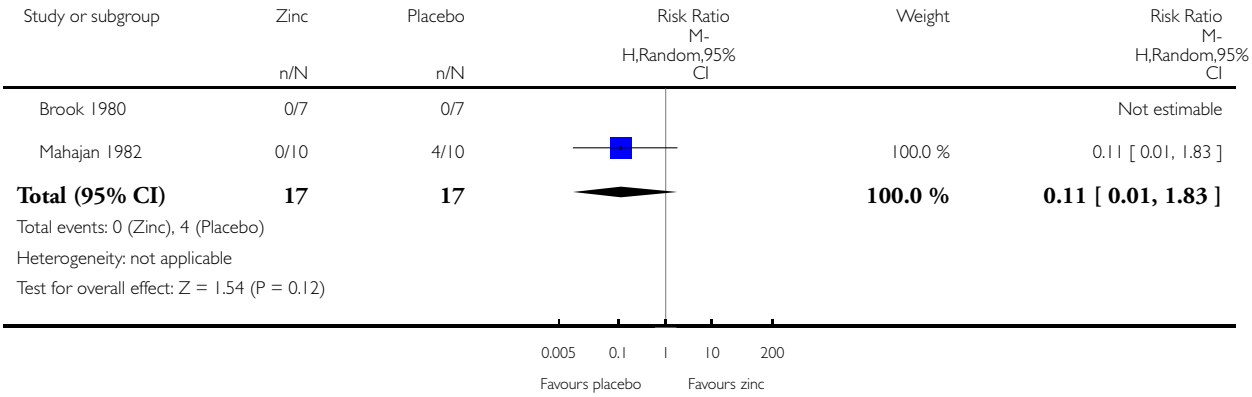


Analysis 2.7. Comparison 2 Zinc versus placebo, Outcome 7 Variations in libido.

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

Comparison: 2 Zinc versus placebo

Outcome: 7 Variations in libido

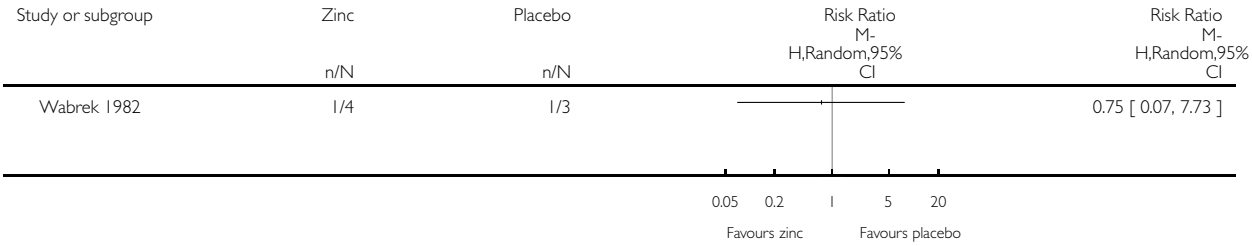


Analysis 2.8. Comparison 2 Zinc versus placebo, Outcome 8 Nocturnal penile tumescence (NPT).

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

Comparison: 2 Zinc versus placebo

Outcome: 8 Nocturnal penile tumescence (NPT)

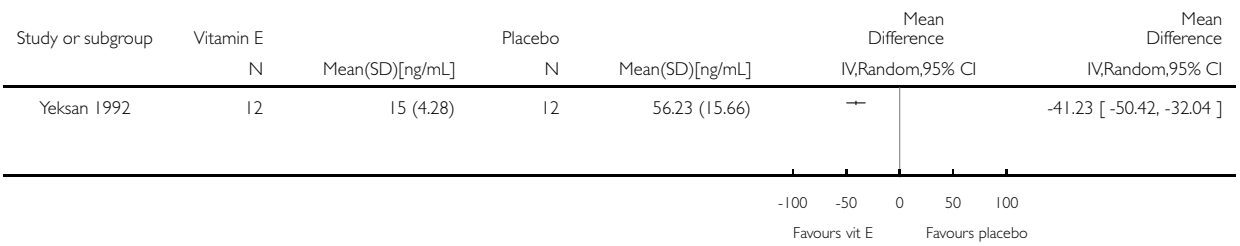


Analysis 3.1. Comparison 3 Vitamin E versus placebo, Outcome 1 Prolactin.

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

Comparison: 3 Vitamin E versus placebo

Outcome: 1 Prolactin



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

Study or subgroup	Vitamin E N	Mean(SD)[mU/mL]	Placebo N	Mean(SD)[mU/mL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Yeksan 1992	12	4.66 (1.8)	12	11.43 (5.7)		-6.77 [-10.15, -3.39]

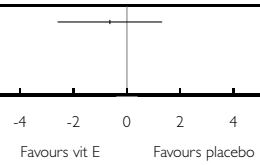
Analysis 3.3. Comparison 3 Vitamin E versus placebo, Outcome 3 Plasma FSH.

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

Comparison: 3 Vitamin E versus placebo

Outcome: 3 Plasma FSH

Study or subgroup	Vitamin E N	Mean(SD)[mU/mL]	Placebo N	Mean(SD)[mU/mL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Yeksan 1992	12	4.23 (1.83)	12	4.88 (2.94)		-0.65 [-2.61, 1.31]

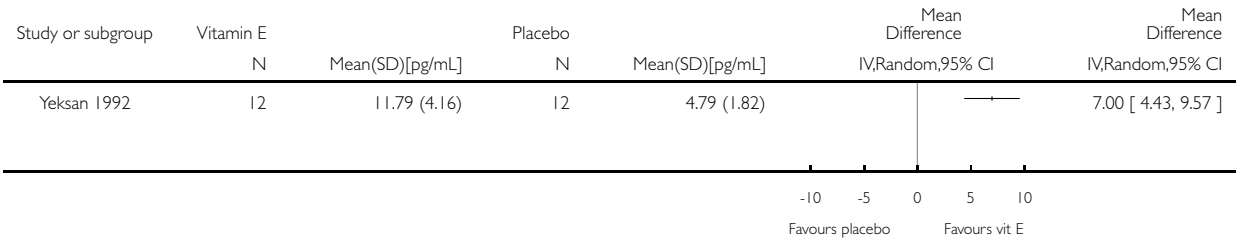


Analysis 3.4. Comparison 3 Vitamin E versus placebo, Outcome 4 Serum testosterone.

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

Comparison: 3 Vitamin E versus placebo

Outcome: 4 Serum testosterone



ADDITIONAL TABLES

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

Study ID	N	Intervention	Outcome	Mean ± SD (treatment group or baseline value) or RR (95% CI)	Mean ± SD (control group or after treatment)
Antoniou 1977	8	Oral zinc versus placebo	Testosterone concentration (ng/mL)[1]	8.00 ± 3.50	3.20 ± 2.00
			LH (mU/mL)[1]	85.30 ± 81.00	47.30 ± 26.90
			FSH (mU/mL)[1]	24.00 ± 24.30	33.00 ± 8.70
Bellovich 2000	14	Sildenafil citrate	IIEF - Frequency of penetration	3.85 ± 3.10	4.43 ± 2.92
			IIEF - Maintenance of erection penetration	4.43 ± 2.69	4.93 ± 2.32
Brook 1980	14	Zinc chloride versus placebo to dialysate	Improvement of libido	1.00 (0.08 to 13.02)	NA
			Plasma testosterone (nmol/L)[2]	9.00 ± 4.23	12.00 ± 1.32
Mahajan 1982	20	Oral zinc acetate versus placebo	Total/partial impotence	0.13 (0.02 to 0.82)	NA
			Decreased libido	0.11 (0.01 to 1.83)	NA

Table 1. Other outcomes related to sexual dysfunction as reported in the included studies *(Continued)*

			Decreased frequency of intercourse	0.22 (0.06 to 0.78)	NA
			Increased plasma testosterone[3]	5.20 ± 1.58	3.00 ± 0.95
			Decreased plasma FSH[3]	25.00 ± 22.14	35.00 ± 15.81
			Decreased plasma LH[3]	49.00 ± 82.22	38.00 ± 25.3
Mahon 2005	13	Sildenafil citrate versus placebo	Global efficacy question	2.50 (1.05 to 5.96)	NA
Muir 1983	14	Bromocriptine versus placebo	Testosterone (nmol/L)[1]	16.80 ± 4.49	17.00 ± 4.11
Sharma 2006	32	Sildenafil citrate versus placebo	Global efficacy question	4.33 (2.07 to 9.08)	
			Blood urea nitrogen (mg/dL)[2]	18.3 ± 7.6	17.9 ± 51.0
			Creatinine (mg/dL)[2]	1.48 ± 0.4	1.4 ± 0.4
			Haemoglobin (g/dL)[2]	12.3 ± 1.5	13.2 ± 1.4
Wabrek 1982	8	Oral zinc versus placebo	Tumescence episodes	0.75 (0.07 to 7.73)	NA
Yeksan 1992	24	Vitamin E versus placebo*	Prolactin (ng/mL)	15.00 ± 4.28	56.23 ± 15.66
			LH (mU/mL)	4.66 ± 1.80	11.43 ± 5.70
			FSH (mU/mL)	4.23 ± 1.83	4.88 ± 2.94
			Testosterone (pg/mL)	11.79 ± 4.16	4.79 ± 1.82

[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.

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
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.

(*Continued*)

	8. (sexual adj (arousal or aversion$)).tw. 9. fsfi.tw. 10. Female Sexual Function Index.tw. 11. International Index of Erectile Function.tw. 12. iief.tw. 13. Female Sexual Distress Score.tw. 14. FSDS.tw. 15. (impotent or impotence).tw. 16. dyspareunia.tw. 17. orgasm$.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 endstage renal or endstage 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. 9. International Index of Erectile Function.tw. 10. iief.tw. 11. Female Sexual Function Index.tw. 12. fsds.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.

(*Continued*)

	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/ 28. (chronic kidney or chronic renal).tw. 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

Potential source of bias	Assessment criteria
Was there adequate sequence generation?	*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)
	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
	Unclear: Insufficient information about the sequence generation process to permit judgement
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-

(*Continued*)

	tion; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Was knowledge of the allocated interventions adequately prevented during the study?	*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
	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
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'
Were incomplete outcome data adequately addressed?	*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
	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

(*Continued*)

	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'
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

DECLARATIONS 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