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Penile rehabilitation for postprostatectomy erectile dysfunction (Review)

Philippou YA, Jung JH, Steggall MJ, O'Driscoll ST, Bakker CJ, Bodie JA, Dahm P

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[Intervention Review]

Penile rehabilitation for postprostatectomy erectile dysfunction

Yiannis A Philippou[1], Jae Hung Jung[2,3], Martin J Steggall[4], Stephen T O'Driscoll[5], Caitlin J Bakker[6], Joshua A Bodie[7], Philipp Dahm[7,8]

[1]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK. [2]Department of Urology, Yonsei University Wonju College of Medicine, Wonju, Korea, South. [3]Institute of Evidence Based Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea, South. [4]Faculty of Life Sciences and Education, University of South Wales, Pontypridd, UK. [5]Information Services, City University London, London, UK. [6]Health Sciences Libraries, University of Minnesota, Minneapolis, Minnesota, USA. [7]Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA. [8]Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA

Contact address: Yiannis A Philippou, Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Headington, Oxford, OX39DU, UK. yp227@doctors.org.uk.

A B S T R A C T

Background

Despite efforts to preserve the neurovascular bundles with nerve-sparing surgery, erectile dysfunction remains common following radical prostatectomy. Postoperative penile rehabilitation seeks to restore erectile function but results have been conflicting.

Objectives

To evaluate the effects of penile rehabilitation strategies in restoring erectile function following radical prostatectomy for prostate cancer.

Search methods

We performed a comprehensive search of multiple databases (CENTRAL, MEDLINE, Embase), the Cochrane Library, Web of Science, clinical trial registries (ClinicalTrials.gov, International Clinical Trials Registry Platform) and a grey literature repository (Grey Literature Report) from their inception through to 3 January 2018. We also searched the reference lists of other relevant publications and abstract proceedings. We applied no language restrictions.

Selection criteria

We included randomised or quasi-randomised trials with a parallel or cross-over design.

Data collection and analysis

We used standard Cochrane methodological procedures. Two review authors independently screened the literature, extracted data, assessed risk of bias and rated quality of evidence according to GRADE on a per-outcome basis. Primary outcomes were self-reported potency, erectile function measured by validated questionnaires (with potency defined as an International Index of Erectile Function (IIEF-EF) score of 19 or greater and or an IIEF-5 of score of 17 or greater) and serious adverse events. For all quality of life assessments on a continuous scale, higher values indicated better quality of life.

Main results

We included eight randomised controlled trials with 1699 participants across three comparisons. This abstract focuses on the primary outcomes of this review only.

Scheduled phosphodiesterase type 5 inhibitors (PDE5I) versus placebo or no treatment

Scheduled PDE5I may have little or no effect on short-term (up to 12 months) self-reported potency (risk ratio (RR) 1.13, 95% confidence interval (CI) 0.91 to 1.41; very low quality evidence), which corresponds to 47 more men with self-reported potency per 1000 (95% CI 33 fewer to 149 more) and short-term erectile function as assessed by a validated instrument (RR 1.11, 95% CI 0.80 to 1.55; very low quality evidence), which corresponds to 28 more men per 1000 (95% CI 50 fewer to 138 more), but we are very uncertain of both of these findings. Scheduled PDE5I may result in fewer serious adverse events compared to placebo (RR 0.32, 95% CI 0.11 to 0.94; low quality evidence), though this does not appear biologically plausible and may represent a chance finding. We are also very uncertain of this finding. We found no long-term (longer than 12 months) data for any of the three primary outcomes.

Scheduled PDE5I versus on-demand PDE5I

Daily PDE5I appears to result in little to no difference in both short-term and long-term (greater than 12 months) self-reported potency (short term: RR 0.97, 95% CI 0.62 to 1.53; long term: RR 1.00, 95% CI 0.60 to 1.67; both very low quality evidence); this corresponds to nine fewer men with self-reported short-term potency per 1000 (95% CI 119 fewer to 166 more) and zero fewer men with self-reported long-term potency per 1000 (95% CI 153 fewer to 257 more). We are very uncertain of these findings. Daily PDE5I appears to result in little to no difference in short-term and long-term erectile function (short term: RR 1.00, 95% CI 0.65 to 1.55; long term; RR 0.74, 95% CI 0.48 to 1.14; both very-low quality evidence), which corresponds to zero men with short-term erectile dysfunction per 1000 (95% CI 80 fewer to 125 more) and 119 fewer men with long-term erectile dysfunction per 1000 (95% CI 239 fewer to 64 more). We are very uncertain of these findings. Scheduled PDE5I may result in little or no effects on short-term adverse events (RR 0.69 95% CI 0.12 to 4.04; very low quality evidence), which corresponds to seven fewer men with short-term serious adverse events (95% CI 18 fewer to 64 more), but we are very uncertain of these findings. We found no long-term data for serious adverse events.

Scheduled PDE5I versus scheduled intraurethral prostaglandin E1

At short-term follow-up, daily PDE5I may result in little or no effect on self-reported potency (RR 1.10, 95% CI 0.79, to 1.52; very low quality evidence), which corresponds to 46 more men per 1000 (95% CI 97 fewer to 241 more). Daily PDE5I may result in a small improvement of erectile function (RR 1.64, 95% CI 0.84 to 3.20; very low quality evidence), which corresponds to 92 more men per 1000 (95% CI 23 fewer to 318 more) but we are very uncertain of both these findings. We found no long-term (longer than 12 months) data for any of the three primary outcomes.

We found no evidence for any other comparisons and were unable to perform any of the preplanned subgroup analyses based on nerve-sparing approach, age or baseline erectile function.

Authors' conclusions

Based on mostly very-low and some low-quality evidence, penile rehabilitation strategies consisting of scheduled PDE5I use following radical prostatectomy may not promote self-reported potency and erectile function any more than on demand use.

P L A I N   L A N G U A G E   S U M M A R Y

Penile rehabilitation for post prostatectomy erectile dysfunction

Review question

How well do treatments work to restore men's ability to have erections after surgery for prostate cancer?

Background

Many men have problems with erections after having their prostate removed for prostate cancer. Studies suggest that taking certain medicines or using devices to help with erection may help men's erections recover faster and better when used on a regular, scheduled basis (like daily or twice a week) rather than as needed. However, it is unclear how well these treatments actually work.

Study characteristics

We included eight randomised studies (clinical studies where people are randomly put into one of two or more treatment groups) with 1699 participants. Five trials compared the scheduled use of phosphodiesterase inhibitors (a type of medicine) to either no treatment or a placebo (a pretend drug with no effect). Two studies compared the use of phosphodiesterase inhibitors either as a daily prescription or as needed. One study compared the daily use of either a phosphodiesterase inhibitor or a medicine called prostaglandin E1 that is placed into the tip of the penis like a suppository. The main outcomes of this review that we felt were most important to men were how good they thought their erections were (self-reported potency), how good their erections were based on a specialised erection questionnaire (quality of erections) and any whether there were any major unwanted side effects.

Key results

We found that the men who used these medicines on a scheduled basis may have had similar self-reported erections and quality of erections (based on questionnaires they filled out) as men who took no medication regularly or use it as needed. They also had similar rates of serious unwanted side effects and similar rates of stopping the drug before the end of the treatment duration. However, we are very uncertain of these findings. We were unable to research whether these results would be different in different groups of men based on whether the surgeon tried to preserve the nerves that help with erections or not, based on men's age and how good their erections were beforehand because we found no studies.

Reliability of evidence

The quality of evidence was very low for most main outcomes. That means we are very uncertain of the results of this review. Further research will likely change these findings.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Scheduled PDE5I compared to on demand placebo or no treatment for post-prostatectomy erectile dysfunction (short-term)

Patient or population: post-prostatectomy erectile dysfunction (short-term)
Setting: outpatient clinic
Intervention: scheduled PDE5I
Comparison: on demand placebo or no treatment

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with on demand placebo or no treatment	Risk difference with scheduled PDE5I
Self-reported potency assessed with: Sexual Encounter Profile diary question 3 or self report follow up: range 24 weeks to 46 weeks	628 (4 RCTs)	⊕◯◯◯ VERY LOW [1][2][3]	RR 1.13 (0.91 to 1.41)	Study population	
				364 per 1,000	47 more per 1,000 (33 fewer to 149 more)
Erectile function assessed with: International Index of Erectile Function-Erectile Function domain follow up: range 24 weeks to 48 weeks	757 (5 RCTs)	⊕◯◯◯ VERY LOW [1][2][3]	RR 1.11 (0.80 to 1.55)	Study population	
				250 per 1,000	28 more per 1,000 (50 fewer to 138 more)
Serious adverse events follow up: range 24 weeks to 48 weeks	443 (3 RCTs)	⊕⊕◯◯ LOW [1][4]	RR 0.32 (0.11 to 0.94)	Study population	
				64 per 1,000	44 fewer per 1,000 (57 fewer to 4 fewer)
Sexual quality of life - not reported	-	-	-	-	-

Treatment discontinuation follow up: range 24 weeks to 48 weeks	443 (3 RCTs)	⊕◯◯◯ VERY LOW [13]	RR 0.98 (0.72 to 1.34)	Study population	
				246 per 1,000	5 fewer per 1,000 (69 fewer to 84 more)
International Index of Erectile Function assessed with: International Index of Erectile Function-Erectile Function domain Scale from: 1 (worst: severe ED) to 30 (best: no ED) follow up: mean 48 weeks	356 (2 RCTs)	⊕⊕◯◯ LOW [145]	-	The mean international Index of Erectile Function ranged from 8.8 to 12.4	MD 2.09 higher (1.85 lower to 6.03 higher)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds ratio;

__GRADE Working Group grades of evidence__
__High certainty:__ We are very confident that the true effect lies close to that of the estimate of the effect
__Moderate certainty:__ We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
__Low certainty:__ Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
__Very low certainty:__ We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level for study limitations: unclear or high risk of bias in one or more domains.
[2] Downgraded by one level for indirectness: difference in outcome measure.
[3] Downgraded by two levels for imprecision: wide confidence interval crosses assumed threshold of clinically important difference.
[4] Downgraded by one level for imprecision: confidence interval crosses assumed threshold of clinically important difference.
[5] Not downgraded for inconsistency despite substantial heterogeneity given that likely not clinically meaningful.

BACKGROUND

Prostate cancer is the most common non-skin cancer in men. In 2014 in the UK alone, there were 46,700 new cases of prostate cancer diagnosed accounting for about 13% of all new cancer diagnoses. Prostate cancer in 2016 resulted in about 11,500 deaths in the UK making it the second most common cancer related cause of death in men (Cancer Research UK). In the USA, prostate cancer accounted for 172,258 new cancer diagnoses and caused 28,343 deaths in 2014 (U.S. Cancer Statistics Working Group). For organ-confined prostate cancer (pT2), treatment options with curative intent include mainly radical prostatectomy (RP) and radiotherapy. RP can be undertaken as an open procedure typically through a retropubic approach (RRP), laparoscopic (LRP) or robotic-assisted (RARP). Radiotherapeutic options for prostate cancer include external beam radiotherapy (EBRT) typically delivered as 2 Gy fractions over seven weeks to a total of 70 Gy with or without concomitant hormone treatment. Other therapeutic options that involve radiotherapy include intensity-modulated radiotherapy and brachytherapy. Active surveillance of prostate cancer also falls into the category of treatments with curative intent. This treatment approach consists of an active decision not to treat the prostate cancer at the time of diagnosis but rather to monitor the man closely to enable the proper timing of curative treatment, taking into account the man's life expectancy. It is advocated by European Heidenreich 2014 and American Sanda 2017 urological guidelines in men with low-risk organ-confined prostate cancer.

RP has the potential to completely remove the tumour and remains a preferred and effective treatment modality utilised as a first option in approximately 33% of prostate cancer cases with organ-confined disease and in 52% of cases in men aged over 62 years of age (Lalong-Muh 2012; American Cancer Society 2014). In 2010 in the US alone, there were 11,290 prostatectomies, two-thirds of which were RARP. These figures compared to the data from 2004, when there were 6188 prostatectomies, of which only 8% were RARP, suggests that RP rates have risen exponentially since the introduction of RARP (Lowrance 2012).

The common adverse effects of RP include erectile dysfunction (ED) and urinary incontinence. Many factors influence the incidence and severity of postoperative ED, including man's age, tumour stage, preoperative potency, length of surgical intervention and experience of the surgeon (Wang 2014). Despite meticulous dissection in an attempt to preserve the neurovascular bundles with nerve-sparing surgery, ED remains common. Even with nerve-sparing surgery, there is a period of neuropraxia during which the man has no spontaneous erections. This can lead to penile hypoxia and long-lasting damage to the erectile tissue (Burnett 2005; Raina 2010). The length of time that neuropraxia and consequent ED will last is difficult to predict, with some studies suggesting many men require more than two years to recover erectile function satisfactorily (Rabbani 2010).

The introduction of the robot-assisted technology has refined nerve-sparing procedures mainly through three-dimensional magnification and movement calibration that could result in reduced postprostatectomy ED rates. One systematic review evaluated the prevalence and the potential risk factors of ED after RARP. Their findings suggested that the prevalence of ED ranged from 54% to 90% at 12 months and 63% to 94% at 24 months (Ficarra 2012). RARP had a significant advantage over RRP with an ED prevalence of 24.2% with RARP versus 47.8% with RRP at 12 months (Ficarra 2012). However, despite these technological advances, ED is still significant in this patient population. This has led to the development of penile rehabilitation programmes that aim to promote male sexual function before and after any insult to the penile erectile physiological axis. Penile rehabilitation has now become an integral part of patient management after RP and most urologists advocate that this should be commenced as soon as possible following surgery.

Description of the condition

Male sexual dysfunction related to prostate cancer treatment can be divided into three broad categories: ED and changes in penile size; ejaculatory and orgasmic dysfunction; and psychosexual impairment with changes in sexual desire, intimacy and mental health (Chung 2013). ED is defined as the inability of a man to achieve and maintain an erection of sufficient strength for satisfactory sexual activity (NIH Consensus Conference 1993). It's incidence reported in the literature after RP varies dramatically from 20% to 90% (Fowler 1993; Rabbani 2000; Stanford 2000; Kundu 2004; Rozet 2005; Penson 2008; Alemozaffar 2011). The discrepancy in the reported rates of erectile function after RP is due to many factors. These include variations in study population demographics, methods of data acquisition, variability in questionnaire use, duration of postoperative follow-up, variations in baseline erectile function status, inconsistency in defining adequate erectile function, surgical technique, and the definition of quality and consistency of erection (Mulhall 2009). ED can have a major impact on the man's self-esteem, quality of life (QoL), confidence and life satisfaction, causing depression in certain cases (Kubin 2003). Quantifying accurately the prevalence of ED after RP is of utmost importance in evaluating the burden of this treatment-related adverse effect, in order to set appropriate expectations and facilitate medical decision making. One analysis identified 24 studies that originated from major cancer centres and reported ED recovery outcomes after RP, in large participant cohorts (Mulhall 2009). In these studies, the mean overall rates of erectile function recovery were 48% (standard deviation (SD) 25%; range 12% to 96%). When nerve sparing was accounted for, as it was in 14 (58%) of the 24 articles reviewed, mean erectile function recovery rates were 50% (SD 24%) for bilateral and 34% (SD 16%) for unilateral nerve-sparing surgery.

The starting point for analysing data on penile rehabilitation is objectively defining ED and reaching a consensus as to the definition of return to potency following RARP. Unfortunately, there remains significant heterogeneity in the literature in terms of definitions of ED after RP, and a significant number of studies do not clearly state their definitions of ED or return to sexual function. Scoring systems such as Sexual Health Inventory For Men (SHIM) scores, International Index of Erectile Function (IIEF-5), sexual questionnaires, and patient and partner reporting are all prone to inaccuracies. Therefore, evaluating return of potency following RARP in the absence of a consensus definition was a challenge for this review. For the purposes of this study as outlined in more detail in the 'methodology' section, we included men with erectile function sufficient for intercourse. According to the IIEF-5 and IIEF questionnaires, we defined 'sufficient for intercourse' as men with mild (IIEF-5 greater than 17) or no (IIEF greater than 19) ED. Therefore, we defined return to sexual function as return to baseline IIEF-5/IIEF scores.

Description of the intervention

Penile rehabilitation following RP revolves around the use of medications (alone or in combination) or devices to preserve erectile tissue health and maximise erectile function recovery or both medications and devices (Mulhall 2010). The treatment options include: phosphodiesterase-5 inhibitors (PDE5I) (sildenafil citrate; tadalafil; vardenafil) scheduled or daily dosing; alprostadil preparations (prostaglandin E1, such as Viridal Duo or Caverject as injectables, or Medicated Urethral System for Erections (MUSE) as urethral pellets), and vacuum erection or vacuum constriction devices (VED/VCD) (Steggall 2011; Weyne 2015). These interventions have been used singly or in combination, either presurgery or following successful trial without catheter following surgery, and at different strengths, dosing frequencies and combinations, to attempt to identify the most suitable option to prevent or limit neuropraxia, recover erections and restore sexual activity.

How the intervention might work

The main pathophysiological mechanism which underlies the development of ED after RP is damage to the cavernosal nerves and vascular injury. Damage to these nerves occurs either due to their complete transection during non-nerve-sparing procedures or due to neuropraxia which commonly occurs during nerve-sparing RP. Neuropraxia is defined by the transient block of nerve transmission despite an anatomically intact nerve, caused in this case by direct trauma, stretching, heating due to electrocautery, ischaemia and local inflammation (Fode 2013). Vascular injury primarily involves damage to the accessory pudendal arteries. This, together with the direct effect of loss of cavernosal nerve function results in a reduction in the oxygenation of penile tissues due to structural changes in vascular smooth muscle and endothelium. This ultimately causes loss of smooth muscle due to apoptosis (Kendirci 2006), impaired veno-occlusive function, collagen accumulation and penile fibrosis (Hatzimouratidis 2009; Kacker 2013). Collectively these physiological changes result in ED and penile shortening.

Surgical intervention is known to induce hypoxia in a time-dependent manner, such that the potential for recovery of erectile function decreases with time. The goal of early intervention with penile rehabilitation strategies is to improve the oxygenation of cavernosal tissue during the period of neuropraxia, to prevent uninhibited deterioration of penile tissues and to minimise (if not abrogate) the adverse structural and physiological changes that occur in the penis following RP. Penile rehabilitation also ensures that the man is well-placed to regain presurgery erectile function and not remain dependent on erectile aids following surgery (Burnett 2013; Segal 2013). Oral PDE5I by virtue of their ease of use, are often considered as the mainstay of ED management. They are generally well-tolerated, have proved to be relatively safe and are the preferred treatment after RP in some centres. Nevertheless, there are a number of men with postsurgery ED, who do not respond to PDE5I, or who become less responsive and less satisfied as treatment progresses. In some men, PDE5I are contraindicated by virtue of the use of nitrate medication and the risk of consequent hypotension. Apart from the oral PDE5I, the other options for management of postprostatectomy ED (including MUSE and intracavernosal injections (ICIs)) are invasive, uncomfortable, unappealing and sometimes ineffective for some men. While PDE5I may be appealing as they appear 'easy' to use, there are limited data examining whether PDE5I aid penile rehabilitation in a time-dependent manner, which is critical as men often prefer to manage their incontinence before their erections, and if treatment is not introduced early, there is a risk of penile atrophy that will make the recovery of erections more problematic.

Why it is important to do this review

ED is a common adverse event of RP and it significantly affects QoL. The aforementioned new insights into the pathophysiology of post-RP ED have led to the development of a multitude of different penile rehabilitation strategies which aim to improve the oxygenation of penile tissues during the period of neuropraxia that inevitably follows RP in the hope to reduce the rate of postprostatectomy ED and restore sexual activity without the use of erectogenic aids. Several randomised controlled trials (RCTs) have been published which address the question of whether these treatment modalities (alone/in combination and at different dosages or dosing schedules) are of any benefit in reducing the incidence of ED after RP and hasten the return to unassisted sexual function. Currently there is still controversy regarding the effectiveness of rehabilitation programmes. The purpose of this review is to systematically evaluate these treatment options and combinations to

identify whether any of these can recover erections and restore sexual activity in addition to evaluating other important clinical outcomes such as adverse events, treatment acceptability by patients, treatment discontinuation rates and QoL. Our further aim is to compare, where evidence exists, different treatment modalities between them and determine which, if any, of these treatments may be most beneficial to restoring unassisted erectile function in men with postprostatectomy ED.

OBJECTIVES

To evaluate the effects of penile rehabilitation strategies in restoring erectile function following radical prostatectomy for prostate cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs with a parallel or cross-over design, and quasi-randomised controlled trials (where participants were allocated to different arms of the trial using a method of allocation that was not truly random). Due to the nature of the review question, we did not consider cluster-RCTs.

Types of participants

Men (aged 18 years or over), who received radical surgical intervention for clinically organ-confined prostate cancer (cT1 or T2, N0 and M0) irrespective of disease risk status. We also considered men with T3 disease who were treated by RP alone and received no other form of adjuvant or neoadjuvant therapy. We considered all surgical approaches of RP such as RRP, radical perineal prostatectomy, laparoscopic prostatectomy and robot-assisted laparoscopic prostatectomy, irrespective of the nerve-sparing status. We excluded men who had received RP as a salvage procedure following failed primary therapy with another treatment modality. We also excluded men who were administered androgen deprivation therapy (ADT) or salvage RT due to biochemical recurrence following RP. We only included men who had erectile function sufficient for intercourse prior to surgery, as documented by an IIEF score. We defined these men as those who had IIEF or IIEF-5 scores within the mild or no ED range (mild: IIEF 19 or greater; none: IIEF-5 17 or greater). We chose these baseline IIEF scores as they included men with mild and no erectile function which we consider as having erectile function sufficient for intercourse. Men

also needed to have a heterosexual partner and be sexually active. We focused on men in heterosexual relationships since it has been reported that anal intercourse requires 33% greater penile rigidity (Gebert 2014).

Types of interventions

To allow a fair and accurate comparison of efficacy of these agents in improving the recovery of erectile function, participants within experimental or placebo groups needed to, at the time of outcome assessment, be receiving no treatment for erectile function or be receiving the same treatment (e.g. the same type and dosage of PDE5I). We excluded any RCTs that did not provide this fair comparison. We included studies of psychological interventions only if these were offered in combination with pharmacological interventions, or were received by participants in both the intervention and control groups.

We planned to investigate the following experimental versus comparison interventions.

Experimental interventions

- PDE5I scheduled (e.g. daily or twice per week).
- Prostaglandin E1 (alprostadil) scheduled administered as ICIs.
- Prostaglandin E1 (alprostadil) scheduled administered intraurethrally (MUSE and Vitaros (alprostadil topical cream)).
- Scheduled use of VEDs or VCDs
- Scheduled use of combination treatments (e.g. PDE5I and VEDs).

Comparator interventions

- Placebo or no intervention/observation.
- On demand intervention
- Different types of active interventions listed under the experimental interventions above but administered on demand

Comparisons

Experimental intervention versus comparator intervention.

Types of outcome measures

We considered trials with a minimum follow-up of six weeks.

Primary outcomes

- Self-reported potency.
- Erectile function.
- Serious adverse events.

Secondary outcomes

- Sexual QoL.
- Treatment discontinuation.
- IIEF-5 or IIEF-EF.
- Acceptability of the intervention.

Method and timing of outcome measurement

- Self-reported potency
  ○ Number or percentage of participants achieving self-reported potency after RP defined as an erection firm enough and of sufficient duration to have sexual intercourse.
- Erectile function
  ○ Number or percentage of participants achieving potency after RP according to IIEF-EF and IIEF-5 scores (Rosen 1997). We defined achieving potency as IIEF-EF of 19 or greater (mild ED) and IIEF-5 of 17 or greater (no ED).
- Serious adverse events
  ○ Rate of participants who experienced at least one serious adverse events using an erectile aid (using the NCI Common Terminology Criteria for Adverse Events (CTCAE) reporting; grades 3 to 5) (National Cancer Institute). If the study authors of eligible studies did not use the CTCAE system, we judged the adverse events by severity using the available information described in the studies.
- Sexual QoL
  ○ Mean change assessed with validated questionnaires such as sexual domain of Expanded Prostate Cancer Index Composite (EPIC) (Wei 2000; Szymanski 2010; Chang 2011).
- Treatment discontinuation
  ○ Defined as treatment discontinuation from any cause at any time after participants were randomised to intervention/comparator groups.
- International Index of Erectile Function (IIEF) or IIEF-5
  ○ Mean change or final value, measured as EF domain of IIEF or total score of IIEF-5 questionnaire (Rosen 1997).
- Acceptability of the intervention
  ○ Evaluated by Treatment Acceptability Questionnaires (TAQ) (Hunsley 1992).

We considered clinically important difference for the review outcomes to rate quality of the evidence for imprecision in the 'Summary of findings' tables (Jaeschke 1989; Johnston 2013). There was no reported threshold in self-reported potency, erectile function, serious adverse events, treatment discontinuation, and TAQ. We considered the clinically important difference for self-reported potency, erectile function, serious adverse events, treatment discontinuation and TAQ for acceptability of the intervention as relative risk reduction of at least 25% (Guyatt 2011a). We used the minimal clinically important difference (MCID) of sexual domain of EPIC of 10 points (Skolarus 2015). We considered the MCID in the erectile function domain score of IIEF of four (Rosen 2011).

We also considered IIEF-5 of over five points as MCID (Spaliviero 2010).

We planned to assess the outcomes as short-term and long-term outcomes.

- Up to and including 12 months postintervention (short-term).
- More than 12 months postintervention (long-term).

'Summary of findings' tables

We presented 'Summary of findings' tables reporting the following outcomes listed according to priority.

- Self-reported potency.
- Erectile function.
- Serious adverse events.
- Sexual QoL.
- Treatment discontinuation.

Search methods for identification of studies

Electronic searches

We initially searched the following sources from inception of each database to 3 January 2018 (see Appendix 1).

- The Cochrane Library (via Wiley; for the search strategy)
  ○ *Cochrane Database of Systematic Reviews.*
  ○ Cochrane Central Register of Controlled Trials.
  ○ Database of Abstracts of Reviews of Effects.
  ○ Health Technology Assessment Database.
- MEDLINE (via Ovid).
- Embase (via Ovid).
- CINAHL.
- PsycINFO.

Searching other resources

- We examined the reference lists of relevant obtained articles, systematic reviews and clinical practice guidelines to check for additional related published and unpublished studies.
- We searched the Conference Proceedings Citation Index (available through the Web of Science database). Additionally, we searched specific conference proceedings for the British Association of Urological Surgeons (BAUS); European Association of Urology (EAU) and American Urological Association (AUA) (from 2008 to June 2017). We selected 2008 as a cut-off as most conference proceedings were available on international urological associations' websites from 2008 onwards.
- We searched consensus papers and proceedings from specialist meetings (e.g. Sexual Function Health Council of the American Foundation for Urologic Disease).

- We planned to contact experts in the field to enquire about any relevant clinical trials or journal articles that were not listed in other sources.
- We attempted to contact drug manufacturers, to enquire about any relevant trials or journal articles that were not listed in other sources.

Additionally, we searched the following central registers of clinical trials on 6 June 2018 to identify any unpublished, ongoing or proposed new trials:

- World Health Organization International Clinical Trials Registry (apps.who.int/trialsearch/);
- Current Controlled Trials (www.controlled-trials.com/);
- UK Clinical Research Network Portfolio Database (public.ukcrn.org.uk/search/);
- UK Clinical Trials Gateway (www.ukctg.nihr.ac.uk/default.aspx);
- ClinicalTrials.gov register (www.clinicaltrials.gov/);
- Current Controlled Trials (ISRCTN Register) (www.controlled-trials.com/mrct/);
- ClinicalStudyResults.org (www.clinicalstudyresults.org).

Data collection and analysis

Selection of studies

We used Covidence to identify and remove potential duplicate records. Two review authors (YP, MS) independently scanned the abstract, title, or both, of remaining records retrieved, to determine which records should be assessed further. Two review authors (YP, MS) investigated all potentially relevant records as full text, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification or ongoing studies, in accordance with the criteria in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We resolved any discrepancies through consensus or recourse to a third review author (PD). If resolution of a disagreement was not possible, we designated the study as 'awaiting classification' and we contacted study authors for clarification. We documented reasons for exclusion of studies that may have reasonably been expected to be included in the review in the Characteristics of excluded studies table. Studies were included regardless of whether outcomes were reported in a useable way. Any studies whereby intervention and comparator groups were not compared at time of study end-point and outcome assessment in a fair manner were excluded. For study inclusion, both intervention and comparator arms had to, at the time of outcome assessment, be receiving no intervention (i.e. no

treatment) or receiving the same intervention. If this was a PDE5I, the same dose and dosing schedule should have been used. We presented an adapted PRISMA flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

Two review authors (YP, JJH) independently extracted data using a form based on the standardised Cochrane data extraction form. We performed a pilot test run of the data abstraction form in advance to confirm its usability.

For studies that fulfilled the inclusion criteria, two review authors (YP, JJH) independently abstracted the following information, which we provided in the Characteristics of included studies table:

- study design;
- study dates (or report if these were not made available);
- participant details and baseline demographics;
- inclusion and exclusion criteria;
- number of participants by study/study arm;
- details of the intervention such as timing and dosage;
- definitions of outcomes, details of outcomes and how/when they were measured, as well as any relevant subgroups;
- study funding sources;
- declarations of interest by the investigators.

We resolved any disagreements regarding study characteristics or outcome measures by discussion, or if required, by consultation with a third review author (PD).

Assessment of risk of bias in included studies

We used the Cochrane tool for assessing risk of bias to objectively assess the included studies (Jüni 2001; Higgins 2011a). Two review authors (YP, JH) independently assessed the risk of bias of each included study. We resolved disagreements by consensus, or by consultation with a third review author (PD). We judged the risk of bias on an outcome-specific basis as 'low risk,' high risk' or 'unclear risk' for each of the following individual items:

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessors (detection bias);
- incomplete outcome reporting (attrition bias);
- selective outcome reporting;
- other biases.

We judged risk of bias domains and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We presented a 'Risk of bias' summary figure to illustrate these findings (Figure 1; Figure 2).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
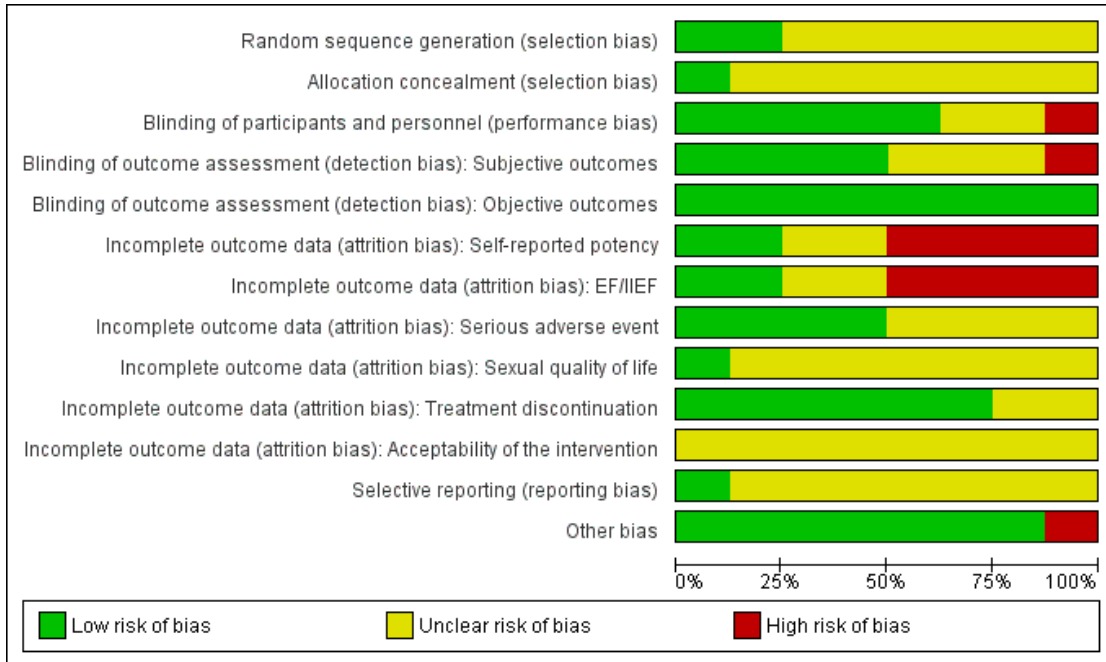
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

For selection bias (random sequence generation and allocation concealment), we evaluated risk of bias at a trial level.

For performance bias (blinding of participants and personnel), we considered all outcomes to be susceptible to performance bias and assessed this individually per outcome.

For detection bias (blinding of outcome assessment), we grouped outcomes as susceptible to detection bias (subjective) or not susceptible to detection bias (objective) outcomes.

We defined the following outcomes as subjective outcomes:

- self-reported potency;
- erectile function;
- serious adverse events;
- sexual QoL;
- IIEF;
- acceptability of the intervention.

We defined the following outcomes as objective outcomes:

- treatment discontinuation.

We initially assessed attrition bias (incomplete outcome data) on a per-outcome basis but created groups of outcomes based on similar reporting characteristics.

For reporting bias (selective reporting), we evaluated risk of bias on a trial level.

We further summarised the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome, in accordance with the approach for summary assessments of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Measures of treatment effect

We expressed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We expressed continuous data as mean differences (MDs) with 95% CIs unless different studies used different measures to assess the same outcome, in which case we used standardised mean differences (SMDs).

Unit of analysis issues

The unit of analysis was the individual participant. For cross-over trials or trials with more than two intervention groups, we planned to incorporate these study designs in meta-analyses in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Dealing with missing data

We attempted to obtain missing data from study authors and performed intention-to-treat analyses if data were available; we otherwise performed available-case analyses. We investigated attrition rates (e.g. dropouts, losses to follow-up and withdrawals), and critically appraised issues of missing data. We did not impute missing data.

Assessment of heterogeneity

We identified heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). We interpreted the I^2 statistic as follows:

- 0% to 40%: may not be important;
- 30% to 60%: may indicate moderate heterogeneity;
- 50% to 90%: may indicate substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

When we found heterogeneity, we attempted to determine possible reasons for this by examining individual study and subgroup characteristics. In the event of excessive heterogeneity unexplained by subgroup analyses, we did not report study results as the pooled effect estimate in a meta-analysis but provided a narrative description of the results of each study.

Assessment of reporting biases

If we included 10 studies or more investigating a particular outcome, we planned to use funnel plots to assess small-study effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias (Egger 1997; Sterne 2011). However, all comparisons in this review include fewer than 10 RCTs.

Data synthesis

We combined data from trials that were sufficiently similar and of sufficient quality to provide pooled effect estimates.

We summarised data using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we performed statistical analyses according to the guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). For dichotomous outcomes, we used the Mantel-Haenszel method; for continuous outcomes, we used the inverse variance method. We used Review Manager 5 to perform analyses (Review Manager 2014).

Subgroup analysis and investigation of heterogeneity

We expected the following variables to be potential sources of heterogeneity and, therefore, planned to perform the following subgroup analyses to determine potential qualitative or quantitative interactions of the following subgroups with the effect estimate.

- Nerve-sparing approach (none versus unilateral or bilateral, partial or complete nerve-sparing) since it may affect the potential for recovery.
- Age of participants (under 65 years versus 65 years or older); older men may have diminished recovery potential.
- Baseline erectile function scores (IIEF-5: 17 to 21 versus 22 to 25 or IIEF: 19 to 24 versus 25 to 30); men with diminished baseline erectile function may have diminished recovery potential.

Subgroup analyses of the nerve-sparing approach are important to determine whether differences exist in effect estimate, if any, of penile rehabilitation strategies on erectile function recovery following RP between the subgroups. Age and baseline erectile function scores are important covariates that can affect the degree of erectile function recovery offered by the penile rehabilitation strategies under investigation, and, therefore, it is important to evaluate these in separate subgroup analyses.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes.

- Restricting the analysis by taking into account risk of bias, by excluding studies at 'high risk' or 'unclear risk' of bias.
- Restricting the analysis by taking into account washout effect, by excluding studies without washout at outcome assessment.

'Summary of findings' tables

We presented the overall quality of evidence (QoE) for each outcome according to the GRADE approach, which takes into account five criteria related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and external validity (directness of results) (Guyatt 2011b). Two review authors (YP, JH) independently rated the QoE for each outcome as 'high,' 'moderate,' 'low' or 'very low;' we resolved discrepancies by consensus, or, if needed, by arbitration by a third review author (PD). We presented a summary of the evidence for the main outcomes in 'Summary of findings' tables, which provide key information about the best estimate of the magnitude of the effect, in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Schünemann 2011). This was performed in GRADEpro GDT.

R E S U L T S

Description of studies

Results of the search

We identified the 3542 records through searching electronic databases, trial registries and handsearching abstract proceedings of relevant meetings since their inception. We identified three other relevant records (Cavallini 2005; Nehra 2005; Seo 2014) by searching the reference lists of CADTH guideline (CADTH 2017). After removal of 2047 duplicates, we screened the titles and abstracts of 1498 records, and excluded 1452 records as evidently irrelevant. We screened 46 studies for full-text eligibility, and excluded 24 studies that did not meet the inclusion criteria or were not relevant to the question under trial. We included eight studies (22 records) in the review. We identified no studies as awaiting classification or part of an ongoing trial. The flow of literature through the assessment process is shown in the PRISMA flowchart (Figure 3).

Figure 3. Study flow diagram.
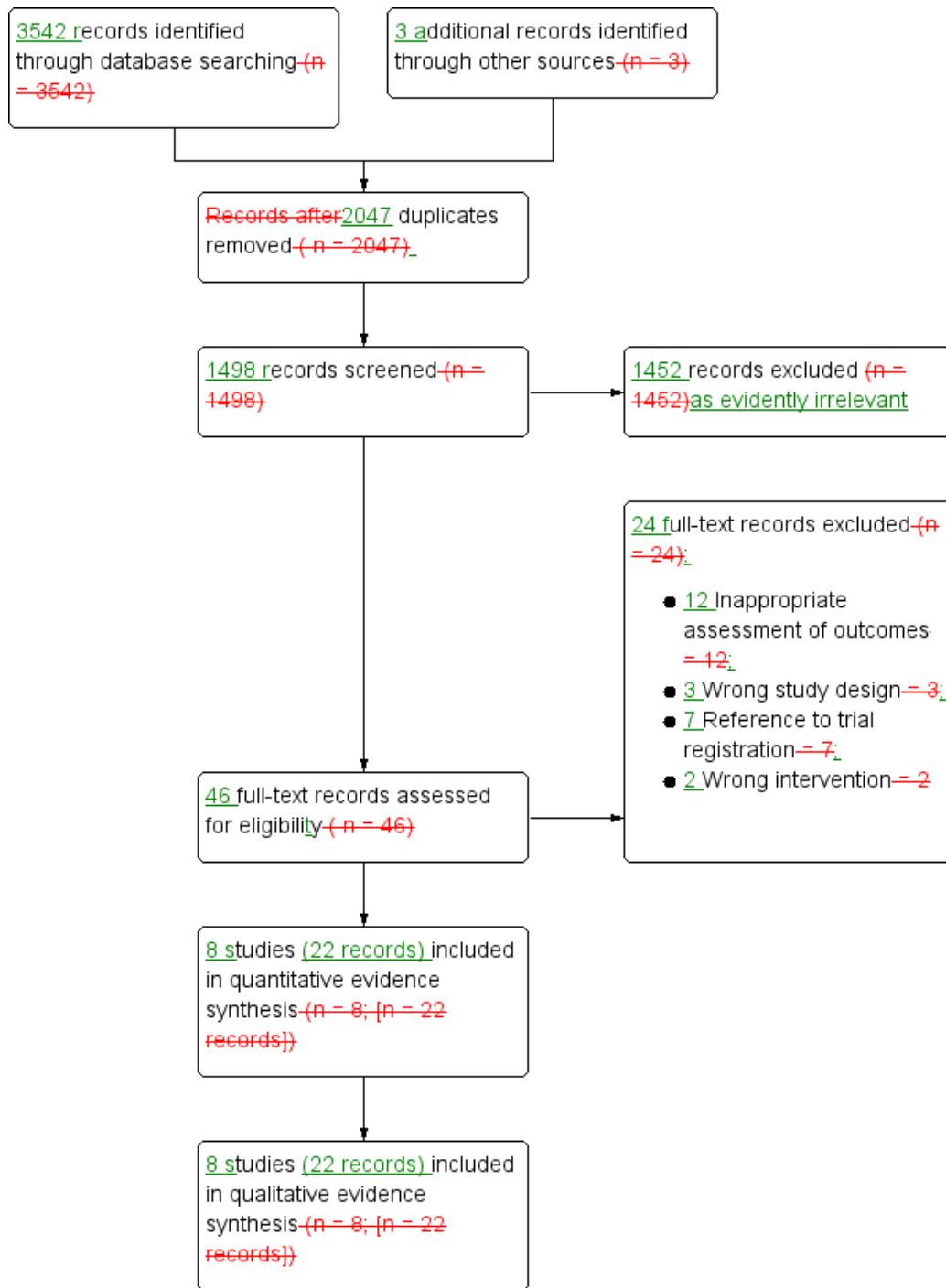
Included studies

Details of included studies are presented elsewhere (see Characteristics of included studies; Table 1; Table 2).

Source of data

We included eight published studies. All studies were identified through our electronic database search and were published in English.

Study design and settings

All included studies were parallel randomised-controlled trials. Five of seven studies were reported as "double-blinded" (Montorsi 2008; Padma-Nathan 2008; Pavlovich 2013; Montorsi 2014; Kim 2016). The participants and investigators were blinded in one study (Montorsi 2014) and participants and personnel were blinded in one study (Kim 2016). Montorsi 2008 blinded participant, personnel, and investigator. Two studies were reported to be "double-blinded" but it was not clear who was blinded (Padma-Nathan 2008; Pavlovich 2013). One study was an open label trial (McCullough 2010). The remaining trials had no information regarding blinding (Pace 2010; Aydogdu 2011). All included trials had a washout period (treatment discontinuation for all randomised participants) before the assessment of outcomes.

All studies were likely conducted in an outpatient clinic setting. Most of the included studies were performed in the US and Europe (Montorsi 2008; Padma-Nathan 2008; McCullough 2010; Pace 2010; Aydogdu 2011; Pavlovich 2013; Montorsi 2014), except one study which was performed in Asia (Kim 2016). Four trials were multicentre trials (Montorsi 2008; Padma-Nathan 2008; McCullough 2010; Montorsi 2014). The studies were performed from year 1999 to 2012.

Participants

We included 1699 randomised participants, of which 1223 participants finished the trial. The mean age was 56.7 years and mean prostate-specific antigen (PSA) was 4.98 ng/mL. Only three studies reported pathological Gleason score and tumour stage (Pace 2010; Pavlovich 2013; Kim 2016). Pathological Gleason score ranged from six to eight. Kim 2016 included one participant with T3 disease. The remaining studies included T1 and T2 disease. Bilateral nerve-sparing RP was performed in most of the included studies (Montorsi 2008; Padma-Nathan 2008; McCullough 2010; Pace 2010; Aydogdu 2011; Montorsi 2014). Kim 2016 performed bilateral nerve-sparing procedure except in one participant who underwent unilateral nerve sparing. Pavlovich 2013 used a nerve-sparing procedure but did not describe whether it was unilateral

or bilateral. RARP or LRP was performed in three of eight trials (McCullough 2010; Pavlovich 2013; Kim 2016).

Major exclusion criteria included known risk factors for ED such as diabetes mellitus and cardiovascular disease, prior treatment with experimental interventions, neoadjuvant or adjuvant treatment with other prostate cancer therapies such as radiotherapy or hormone therapy and the presence of ED at baseline. Padma-Nathan 2008 additionally described sleep disorder as an exclusion criterion. One study did not describe exclusion criteria (Aydogdu 2011).

Interventions and comparators

Sildenafil was used in all studies except three studies (vardenafil: Montorsi 2008; tadalafil: Aydogdu 2011; Montorsi 2014). Daily sildenafil was administered as an oral dose of 50 mg (McCullough 2010; Pavlovich 2013; Kim 2016) or 100 mg (Padma-Nathan 2008). One study did not specify the exact dose of sildenafil (Pace 2010; both 50 mg or 100 mg). Daily vardenafil was administrated as an oral dose of 10 mg but decreased to 5 mg, if required (Montorsi 2008). Daily tadalafil was administered as an oral dose of 5 mg (Montorsi 2014). On-demand sildenafil was also administrated as an oral dose of 50 mg (Padma-Nathan 2008; Pavlovich 2013) or 100 mg (Kim 2016). On-demand vardenafil was used as a flexible-dose (starting at 10 mg with the option to titrate to 5 mg or 20 mg) (Montorsi 2008). Tadalafil was administrated as an oral dose of 20 mg three times a week Aydogdu 2011 or on-demand (Montorsi 2014).

Daily prostaglandin E1 was administrated intraurethrally (McCullough 2010). The drug dose was titrated (125 μg followed by 250 μg) during study period.

Placebo was used as comparators in three studies (Montorsi 2008; Padma-Nathan 2008; Montorsi 2014). Two studies used 'no treatment' as a comparator (Pace 2010; Aydogdu 2011).

The duration of intervention ranged from eight weeks to 12 months. All interventions were administrated within one month after surgery in all included studies. The duration of washout ranged from four weeks to eight weeks in six of the included studies (Montorsi 2008; Padma-Nathan 2008; McCullough 2010; Pavlovich 2013; Montorsi 2014; Kim 2016). Aydogdu 2011 administrated the intervention for six months and assessed the outcomes at 12 months after surgery. One study administered the intervention for eight weeks and assessed the outcomes at 24 weeks after surgery (Pace 2010).

Comparisons

We included three comparisons in this review, which were informed by eight studies. Two studies were three-armed trials and contributed to two comparisons each.

- Five studies compared scheduled (daily or twice a week) PDE5I use to placebo or no treatment (Aydogdu 2011; Montorsi 2008; Montorsi 2014; Pace 2010; Padma-Nathan 2008).

- Four studies compared daily PDE5I to on-demand PDE5I (Montorsi 2008; Pavlovich 2013; Montorsi 2014; Kim 2016), and

- One study compared daily PDE5I to daily intraurethral prostaglandin E1 (McCullough 2010).

Tables 1 and 2 (Table 1; Table 2) provide further details about the specifics of the comparison.

Outcomes

We identified the primary outcomes in each of the included studies for all comparisons of PDE5I (i.e. versus placebo/no treatment, on-demand use and intraurethral prostaglandin E1). For self-reported potency, we used different questionnaires or definitions for outcome measurement such as Rigiscan (Kim 2016); participant-reported intercourse success rate (McCullough 2010); Sexual Encounter Profile (SEP) question (Montorsi 2008; Aydogdu 2011; Montorsi 2014); and potency rate (not defined) (Pace 2010). Return to normal erectile function was defined as IIEF-EF greater than 22 (Montorsi 2008; Pavlovich 2013; Montorsi 2014; Kim 2016); IIEF-EF greater than 26 and greater than 17 (McCullough 2010); IIEF-EF 26 or greater (Aydogdu 2011); IIEF question 3 and 4 of 8 or greater (Padma-Nathan 2008); IIEF-EF (not defined) (Pace 2010). Given that none of included studies reported serious adverse events using CTCAE, we used the available information described in the studies. No trial reported on our predefined secondary outcomes of acceptability of the intervention. Other secondary outcomes were reported in at least one of the included studies.

We used the outcomes that were assessed after washout period to make a fair comparison. For long-term follow-up, we used the sexual QoL and treatment discontinuation outcomes that were assessed after the open-label period (with all participants taking on-demand PDE5I for that time period).

Funding sources and conflicts of interest

Four studies were supported by pharmaceutical companies (Montorsi 2008; Padma-Nathan 2008; Montorsi 2014; Kim 2016), and one study explicitly reported no funding source (Pavlovich 2013). Three studies did not disclose funding sources (McCullough 2010; Pace 2010; Aydogdu 2011). Four studies reported having relationships with pharmaceutical companies (Montorsi 2008; Padma-Nathan 2008; McCullough 2010; Montorsi 2014), and three studies reported no conflicts of interests (Pace 2010; Aydogdu 2011; Pavlovich 2013). One study did not disclose whether conflicts of interest were present (Kim 2016).

Excluded studies

We assessed 46 full-text records and excluded 24 studies (see Characteristics of excluded studies table).

Studies awaiting classification

We found no studies awaiting classification.

Ongoing studies

We found no ongoing studies.

Risk of bias in included studies

See Figure 1; Figure 2.

Allocation

Random sequence generation

Two studies were at low risk of bias (Montorsi 2008; Padma-Nathan 2008). The remaining studies were at unclear risk of bias.

Allocation concealment

Only one study was at low risk of bias (Montorsi 2008), and the remaining studies were at unclear risk of bias.

Blinding

Blinding of participants and personnel

We rated five studies at low risk of bias (Montorsi 2008; Padma-Nathan 2008; Pavlovich 2013; Montorsi 2014; Kim 2016). We judged one study at high risk of bias (McCullough 2010), and the remaining studies at unclear risk of bias.

Blinding of outcome assessment

Subjective outcomes: self-reported potency, erectile function, serious adverse events, sexual quality of life, IIEF and acceptability of the intervention

We rated four studies at low risk of bias (Montorsi 2008; Padma-Nathan 2008; Pavlovich 2013; Montorsi 2014). We judged one study at high risk of bias (McCullough 2010), and the remaining studies at unclear risk of bias.

Objective outcomes: treatment discontinuation

We rated all studies at low risk of bias as objective outcomes are unlikely to be affected by lack of blinding.

Incomplete outcome data

Self-reported potency

We rated two studies at low risk of bias (Montorsi 2014; Kim 2016). We judged four studies at high risk of bias (Montorsi 2008; Padma-Nathan 2008; McCullough 2010; Pavlovich 2013), and the remaining studies at unclear risk of bias.

Erectile function/International Index of Erectile Function

We rated two studies at low risk of bias (Montorsi 2014; Kim 2016). We judged four studies at high risk of bias (Montorsi 2008; Padma-Nathan 2008; McCullough 2010; Pavlovich 2013), and the remaining studies at unclear risk of bias.

Serious adverse events

We rated four studies at low risk of bias (Montorsi 2008; Padma-Nathan 2008; Pace 2010; Pavlovich 2013), and the remaining studies at unclear risk of bias.

Sexual quality of life

We rated one study at low risk of bias (Montorsi 2014), and the remaining studies at unclear risk of bias.

Treatment discontinuation

We rated six studies at low risk of bias (Montorsi 2008; Padma-Nathan 2008; Pace 2010; Pavlovich 2013; Montorsi 2014; Kim 2016), and the two remaining studies at unclear risk of bias (Aydogdu 2011 McCullough 2010).

Acceptability of the intervention

None of the included studies reported acceptability of the intervention; therefore, we rated all studies at unclear risk of bias.

Selective reporting

We rated one study at low risk of bias (Montorsi 2008), and the remaining studies at unclear risk of bias.

Other potential sources of bias

We rated seven studies at low risk of bias (Montorsi 2008; McCullough 2010; Pace 2010; Aydogdu 2011; Pavlovich 2013; Montorsi 2014; Kim 2016). We judged one study at high risk of bias due to premature termination as a result of lack of efficacy of the intervention (Padma-Nathan 2008).

Effects of interventions

See: **Summary of findings for the main comparison** Scheduled PDE5I compared to on demand placebo or no treatment for post-prostatectomy erectile dysfunction (short-term); **Summary of findings 2** Scheduled PDE5I compared to on demand placebo or no treatment for post-prostatectomy erectile dysfunction (long-term); **Summary of findings 3** Scheduled PDE5I compared to on demand PDE5I for post-prostatectomy erectile dysfunction (short-term); **Summary of findings 4** Scheduled PDE5I compared to on demand PDE5I for post-prostatectomy erectile dysfunction (long-term); **Summary of findings 5** Scheduled PDE5I compared to scheduled intraurethral prostaglandin E1 for post-prostatectomy erectile dysfunction (short term)

1. Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment

We included five studies comparing scheduled PDE5I versus placebo or no treatment short-term (Montorsi 2008; Padma-Nathan 2008; Pace 2010; Aydogdu 2011; Montorsi 2014). We included two studies comparing daily PDE5I versus placebo long-term (Montorsi 2008; Montorsi 2014).

1.1. Self-reported potency

We included four RCTs with 628 participants in the short-term analysis (scheduled PDE5I 307, placebo or no treatment 321) (Montorsi 2008; Pace 2010; Montorsi 2014). Three studies used SEP diary question 3 (change from baseline in 'Yes' answers to questions) (Montorsi 2008; Aydogdu 2011; Montorsi 2014), and one study used self-reported potency rate that was not further defined in the methods section of the study (Pace 2010).

Scheduled PDE5I may result in little to no difference in self-reported potency (RR 1.13, 95% CI 0.91 to 1.41; I^2 = 33%; Analysis 1.1), which corresponds to 47 more men with self-reported potency per 1000 (95% CI 33 fewer to 149 more), but we are very uncertain of this finding. We rated the QoE as very low, downgrading for study limitations, indirectness and imprecision.

We found no studies that reported long-term data for self-reported potency.

1.2. Erectile function

We included five RCTs with 757 participants in the short-term analysis (scheduled PDE5I 385, placebo or no treatment 372) (Montorsi 2008; Padma-Nathan 2008; Pace 2010; Aydogdu 2011; Montorsi 2014). One study reported the proportion of participants with IIEF-EF greater than 25 (no dysfunction) (Aydogdu 2011). Two studies reported the proportion of participants with IIEF-EF greater than 21 (mild to no dysfunction) (Montorsi 2008; Montorsi 2014), and one study reported the proportion of participants who scored 8 or greater on Qquestion 3 and question 4 of the IIEF and also answered 'yes' to the question "Over the past 4 weeks, have your erections been good enough for satisfactory sexual activity?" after treatment (Padma-Nathan 2008).

Scheduled PDE5I may result in little to no difference in erectile function (RR 1.11, 95% CI 0.80 to 1.55; I^2 = 37%; Analysis 1.2), which corresponds to 28 more men per 1000 (95% CI 50 fewer to 138 more) but we are very uncertain of this finding. We rated the QoE as very low, downgrading for study limitations, indirectness and imprecision.

We found no studies that reported long-term data for erectile function.

1.3. Serious adverse events

We included three RCTs with 443 participants in the analysis (scheduled PDE5I 240, placebo or no treatment 203) (Padma-Nathan 2008; Pace 2010; Montorsi 2014).

Scheduled PDE5I may result in less serious adverse events (RR 0.32, 95% CI 0.11 to 0.94; I^2 = 0%; Analysis 1.3), which corresponds to 44 fewer men per 1000 (95% CI 57 fewer to 4 fewer), but we considered this to have low biological plausibility and to likely represent a chance finding. We rated the QoE as low, downgrading for study limitations and imprecision.

We found no studies that reported long-term data for serious adverse events.

1.4. Sexual quality of life

We found no studies that reported short-term data for sexual QoL. We included one RCT with 280 participants in the analysis (daily PDE5I 139, placebo 141) that reported long-term data (Montorsi 2014).

Scheduled PDE5I likely results in little to no difference in sexual QoL long term (MD 3.20 points, 95% CI -5.91 to 12.31; Analysis 1.6). We rated the QoE as moderate, downgrading for imprecision.

1.5. Treatment discontinuation

We included three RCTs with 443 participants in the short-term analysis (scheduled PDE5I 240, placebo or no treatment 203) (Padma-Nathan 2008; Pace 2010; Montorsi 2014).

Scheduled PDE5I appears to result in little to no difference on treatment discontinuation (RR 0.98, 95% CI 0.72 to 1.34; I^2 =

0%; Analysis 1.4),which corresponds to 5 fewer men per 1000 (95%CI 69 fewer to 84 more), but we are very uncertain of this finding. We rated the QoE as very low, downgrading for study limitations and imprecision.

We included one RCT with 420 participants in the long-term analysis (daily PDE5I 210, placebo 210) (Montorsi 2008). Scheduled PDE5I likely results in little to no difference in rates of treatment discontinuation (RR 1.12, 95% CI 0.85 to 1.48; Analysis 1.7), which corresponds to 37 more men per 1000 who discontinued treatment (95%CI 46 fewer to 149 more). We rated the QoE as moderate, downgrading for imprecision.

1.6. International Index of Erectile Function

We included two RCTs with 356 participants in the short-term analysis (scheduled PDE5I 190, placebo or no treatment 166) (Padma-Nathan 2008; Montorsi 2014). We used the change from baseline in Montorsi 2014 and final value in Padma-Nathan 2008. Scheduled PDE5I may result in little to no difference in IIEF-EF domain score (RR 2.09, 95% CI -1.85 to 6.03; I^2 = 64%; Analysis 1.5). We rated the QoE as low, downgrading for study limitations and imprecision.

We found no studies that reported long-term data for IIEF.

1.7. Acceptability of the intervention

We found no studies that reported acceptability of the intervention either short-term or long-term.

Subgroup analysis

We were unable to perform any subgroup analyses due to no relevant data in the included studies.

Sensitivity analysis

As we rated only one study at low risk of bias (Montorsi 2014), and all included studies had a washout period (Montorsi 2008; Padma-Nathan 2008; Montorsi 2014) or no treatment period (Pace 2010), we were unable to perform any meaningful sensitivity analyses.

2. Scheduled phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

We included two studies comparing daily PDE5I versus on-demand PDE5I short-term (Montorsi 2008; Montorsi 2014).

We included four studies comparing daily PDE5I versus on-demand PDE5I long-term (Montorsi 2008; Pavlovich 2013; Montorsi 2014; Kim 2016).

2.1. Self-reported potency

We included two RCTs with 532 participants in the short-term analysis (daily PDE5I 255, on-demand PDE5I 277) (Montorsi 2008; Montorsi 2014). We used the results of SEP diary question 3 to evaluate self-reported potency.

Daily PDE5I may result in little to no difference in on self-reported potency short-term (RR 0.97, 95% CI 0.62 to 1.53; I^2 = 67%; Analysis 2.1), which corresponds to nine fewer men with self-reported short-term potency per 1000 (95% CI 119 fewer to 166 more), but we were very uncertain of this finding. We rated the QoE as very low, downgrading for study limitations and imprecision.

We included one RCT with 94 participants in the long-term analysis (daily PDE5I 47, on-demand PDE5I 47) (Kim 2016). While Kim 2016 reported Rigiscan as objective assessment of erectile function; we used these data as self-reported potency.

Daily PDE5I may result in little to no difference in self-reported potency long term (RR 1.00, 95% CI 0.60 to 1.67; Analysis 2.6), which corresponds to zero fewer men with self-reported long-term potency per 1000 (95% CI 153 fewer to 257 more) but we are very uncertain of this finding. We rated the quality of evidence as very low, downgrading for study limitations and imprecision.

2.2. Erectile function

We included two RCTs with 573 participants in the short-term analysis (daily PDE5I 282, on-demand PDE5I 291) (Montorsi 2008; Montorsi 2014). All included studies reported the proportion of participants with IIEF-EF greater than 21 (mild to no dysfunction) after treatment.

Daily PDE5I may result in little to no difference in short term erectile function (RR 1.00, 95% CI 0.65 to 1.55; I^2 = 49%; Analysis 2.2), which corresponds to zero fewer men with short-term erectile dysfunction per 1000 (95% CI 79 fewer to 125 more), but we were very uncertain of this finding. We rated the QoE as very low, downgrading for study limitations and imprecision.

We included two RCTs with 168 participants in the long-term analysis (daily PDE5I 83, on-demand PDE5I 85) (Pavlovich 2013; Kim 2016). All included studies reported the proportion of participants with IIEF-EF greater than 21 (mild to no dysfunction). Daily PDE5I appears to result in little to no difference in erectile function long term (RR 0.74, 95% CI 0.48 to 1.14; I^2 = 0%; Analysis 2.7), which corresponds to 119 fewer men with long-term erectile dysfunction per 1000 (95% CI 239 fewer to 64 more), but we were very uncertain of this finding. We rated the QoE as very low, downgrading for study limitations and imprecision.

2.3. Serious adverse events

We included one RCT with 282 participants in the short-term analysis (daily PDE5I 139, on-demand PDE5I 143) (Montorsi 2014).

Daily PDE5I appeared to result in little to no difference in serious adverse events short term (RR 0.69, 95% CI 0.12 to 4.04; Analysis 2.3), which corresponds to seven fewer men with short-term serious adverse events (95% CI 18 fewer to 64 more) but we are very uncertain of this finding. We rated the QoE as very low, downgrading for study limitations and imprecision.

2.4. Sexual quality of life

We found no studies that reported short-term outcomes for sexual QoL.

We included one RCT with 281 participants in the long-term analysis (daily PDE5I 139, on-demand PDE5I 142) (Montorsi 2014).

Daily PDE5I likely results in little or no difference in sexual QoL long-term (MD 4.00 points, 95% CI -4.84 to 12.84; Analysis 2.9). We rated the QoE as moderate, downgrading for imprecision.

2.5. Treatment discontinuation

We included one RCT with 282 participants in the short-term analysis (daily PDE5I 139, on-demand PDE5I 143) (Montorsi 2014).

Daily PDE5I may result in little to no difference in treatment discontinuation short-term (RR 1.35, 95% CI 0.85 to 2.12; Analysis 2.4), which corresponds to 63 more men who discontinued treatment (95% CI 36 fewer to 203 more). We rated the QoE as low, downgrading for study limitations and imprecision.

We included three RCTs with 612 participants in the long-term analysis (daily PDE5I 307, on-demand PDE5I 305) (Pavlovich 2013; Montorsi 2014; Kim 2016).

Daily PDE5I may result in little to no difference in treatment discontinuation long-term (RR 1.09, 95% CI 0.86 to 1.38; Analysis 2.10), which corresponds to 27 more men who discontinued treatment (95% CI 41 fewer to 112 more), but we are very uncertain of this finding. We rated the QoE as very low, downgrading for study limitations, indirectness and imprecision.

2.6. International Index of Erectile Function

We included one RCT with 281 participants in the short-term analysis (daily PDE5I 139, placebo 142) (Montorsi 2014).

Daily PDE5I results in little or no difference in IIEF-EF domain score short-term (MD 0.16, 95% CI -0.15 to 0.47; Analysis 2.5). We rated the QoE as high.

We found no studies that reported long-term outcomes.

2.7. Acceptability of the intervention

We found no studies that reported short-term or long-term outcomes.

Subgroup analysis

We were unable to perform any subgroup analyses due to no relevant data in the included studies.

Sensitivity analysis

As we rated only one study at low risk of bias (Montorsi 2014), and all included studies had washout periods, we were unable to perform sensitivity analyses.

3. Daily phosphodiesterase 5 inhibitor versus daily intraurethral prostaglandin E1 (short-term)

We included one study with 156 participants (on-demand PDE5I 59, placebo 97) comparing daily PDE5I versus intraurethral prostaglandin E1 with short-term follow-up (McCullough 2010). We found no studies with long-term follow-up.

3.1. Self-reported potency

McCullough 2010 reported the proportion of participants who had successful sexual intercourse short-term.
Daily PDE5I appears to result in little to no difference in self-reported potency (RR 1.10, 95% CI 0.79, to 1.52; Analysis 3.1), which corresponds to 46 more men per 1000 (95% CI 97 fewer to 241 more) but we were very uncertain of this finding. We rated the QoE as very low, downgrading for study limitations and imprecision.

3.2. Erectile function

McCullough 2010 reported erectile function based on IIEF-EF greater than 26 (no dysfunction) and IIEF-EF greater than 17 (moderate to no dysfunction).
Daily PDE5I may result in a small improvement in erectile function (IIEF-EF greater than 26: RR 1.64, 95% CI 0.84 to 3.20; Analysis 3.2; IIEF-EF greater than 17: RR 1.20, 95% CI 0.79 to 1.81; Analysis 3.3), which corresponds to 92 more men per 1000 (95% CI 23 fewer to 318 more), but we are very uncertain of this finding. We rated the QoE as very low, downgrading for study limitations and imprecision.

3.3. Serious adverse events

We found no studies that reported serious adverse events.

3.4. Sexual quality of life

We found no studies that reported sexual QoL.

3.5. Treatment discontinuation

We found no studies that reported treatment discontinuation.

3.6. International Index of Erectile Function

We found no studies that reported IIEF.

3.7. Acceptability of the intervention

We found no studies that reported acceptability of the intervention.

Subgroup analysis

We were unable to perform any subgroup analyses due to no relevant data in the included studies.

Sensitivity analysis

We were unable to perform any subgroup analyses due to paucity of included studies.

A D D I T I O N A L   S U M M A R Y   O F   F I N D I N G S   [Explanation]

Scheduled PDE5I compared to on demand placebo or no treatment for post-prostatectomy erectile dysfunction (long-term)

Patient or population: post-prostatectomy erectile dysfunction (long-term)
Setting: outpatient clinic
Intervention: scheduled PDE5I
Comparison: on demand placebo or no treatment

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with on demand placebo or no treatment	Risk difference with scheduled PDE5I
Self-reported potency - not reported	-	-	-	-	-
Erectile function - not reported	-	-	-	-	-
Serious adverse events - not reported	-	-	-	-	-
Sexual quality of life assessed with: Expanded Prostate Cancer Index Composite (sexual domain) Scale from: 0 (worst) to 100 (best) follow up: mean 54 weeks	280 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	-	The mean quality of life was 33.4	MD 3.2 higher (5.91 lower to 12.31 higher)
Treatment discontinuation follow up: mean 54 weeks	420 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	RR 1.12 (0.85 to 1.48)	Study population	
				310 per 1,000	37 more per 1,000 (46 fewer to 149 more)

International Index of Erectile Function - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level for imprecision: confidence interval crosses assumed threshold of clinically important difference.

Scheduled PDE5I compared to on demand PDE5I for post-prostatectomy erectile dysfunction (short-term)					
Patient or population: post-prostatectomy erectile dysfunction (short-term) **Setting:** outpatient clinic **Intervention:** scheduled PDE5I **Comparison:** on demand PDE5I					
Outcomes	**№ of participants (studies)** **Follow up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects*** **(95% CI)**	
				Risk with on demand PDE5I	**Risk difference with scheduled PDE5I**
Self-reported potency assessed with: Sexual Encounter Profile diary question 3 follow up: range 42 weeks to 46 weeks	532 (2 RCTs)	⊕◯◯◯ VERY LOW [1][2][3]	RR 0.97 (0.62 to 1.53)	Study population	
				314 per 1,000	9 fewer per 1,000 (119 fewer to 166 more)
Erectile function assessed with: International Index of Erectile Function-Erectile Function domain follow up: range 42 weeks to 46 weeks	573 (2 RCTs)	⊕◯◯◯ VERY LOW [1][2][3]	RR 1.00 (0.65 to 1.55)	Study population	
				227 per 1,000	0 fewer per 1,000 (79 fewer to 125 more)
Serious adverse events follow up: mean 42 weeks	282 (1 RCT)	⊕◯◯◯ VERY LOW [1][4]	RR 0.69 (0.12 to 4.04)	Study population	
				21 per 1,000	7 fewer per 1,000 (18 fewer to 64 more)
Sexual quality of life - not reported	-	-	-	-	-

				Study population	
Treatment discontinuation follow up: mean 42 weeks	282 (1 RCT)	⊕⊕◯◯ LOW [3]	RR 1.35 (0.85 to 2.12)		
				182 per 1,000	64 more per 1,000 (27 fewer to 204 more)
International Index of Erectile Function assessed with: International Index of Erectile Function-Erectile Function domain Scale from: 1 (worst: severe ED) to 30 (best: no ED) follow up: mean 42 weeks	281 (1 RCT)	⊕⊕⊕⊕ HIGH	-	The mean international Index of Erectile Function ranged from 2.38	MD 0.16 higher (0.15 lower to 0.47 higher)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level for study limitations: unclear or high risk of bias in one or more domains.

[2] Not downgraded for inconsistency despite moderate or substantial heterogeneity given that likely not clinically meaningful.

[3] Downgraded by two levels for imprecision: wide confidence interval crosses assumed threshold of clinically important difference.

[4] Downgraded by two levels for imprecision: very rare event resulting in wide confidence interval.

Scheduled PDE5I compared to on demand PDE5I for post-prostatectomy erectile dysfunction (long-term)

Patient or population: post-prostatectomy erectile dysfunction (long-term)
Setting: outpatient clinic
Intervention: scheduled PDE5I
Comparison: on demand PDE5I

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with on demand PDE5I	**Risk difference with scheduled PDE5I**
Self-reported potency assessed with: Rigi scan follow up: mean 13 months	94 (1 RCT)	⊕○○○ VERY LOW [1][2]	RR 1.00 (0.60 to 1.67)	Study population	
				383 per 1,000	0 fewer per 1,000 (153 fewer to 257 more)
Erectile function assessed with: International Index of Erectile Function-Erectile Function domain follow up: mean 13 months	168 (2 RCTs)	⊕○○○ VERY LOW [1][2]	RR 0.74 (0.48 to 1.14)	Study population	
				459 per 1,000	119 fewer per 1,000 (239 fewer to 64 more)
Serious adverse events - not reported	-	-	-	-	-
Sexual quality of life assessed with: Expanded Prostate Cancer Index Composite (sexual domain) Scale from: 0 (worst) to 100 (best) follow up: mean 54 weeks	281 (1 RCT)	⊕⊕⊕○ MODERATE [4]	-	The mean sexual quality of life was 32.6	MD 4 higher (4.84 lower to 12.84 higher)

Treatment discontinuation follow up: range 52 weeks to 54 weeks	612 (3 RCTs)	⊕◯◯◯ VERY LOW [145]	RR 1.09 (0.86 to 1.38)	Study population	
				295 per 1,000	27 more per 1,000 (41 fewer to 112 more)
International Index of Erectile Function - not reported	-	-	-	-	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level for study limitations: unclear or high risk of bias in one or more domains.
[2] Downgraded by two levels for imprecision: wide confidence interval crosses assumed threshold of clinically important difference.
[3] Downgraded by two levels for imprecision: very rare event resulting in wide confidence interval.
[4] Downgraded by one level for imprecision: confidence interval crosses assumed threshold of clinically important difference.
[5] Downgraded by one level for indirectness: difference in intervention at the time of outcome assessment (no treatment versus on demand PDE5I).

Scheduled PDE5I compared to scheduled intraurethral prostaglandin E1 for post-prostatectomy erectile dysfunction (short term)

Patient or population: post-prostatectomy erectile dysfunction (short term)
Setting: outpatient clinic
Intervention: scheduled PDE5I
Comparison: scheduled intraurethral prostaglandin E1

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with scheduled intraurethral prostaglandin E1	Risk difference with scheduled PDE5I
Self-reported potency assessed with: Intercourse success rate follow up: mean 11 months	156 (1 RCT)	⊕◯◯◯ VERY LOW [1][2]	RR 1.10 (0.79 to 1.52)	Study population	
				464 per 1,000	46 more per 1,000 (97 fewer to 241 more)
Erectile function assessed with: International Index of Erectile Function-Erectile Function domain > 26 follow up: mean 11 months	156 (1 RCT)	⊕◯◯◯ VERY LOW [1][2]	RR 1.64 (0.84 to 3.20)	Study population	
				144 per 1,000	92 more per 1,000 (23 fewer to 318 more)
Erectile function assessed with: International Index of Erectile Function-Erectile Function domain > 17 follow up: mean 11 months	156 (1 RCT)	⊕◯◯◯ VERY LOW [1][2]	RR 1.20 (0.79 to 1.81)	Study population	
				340 per 1,000	68 more per 1,000 (71 fewer to 276 more)
Serious adverse events - not reported	-	-	-	-	-
Sexual quality of life - not reported	-	-	-	-	-

Treatment discontinuation - not reported	-	-	-	-	-
International Index of Erectile Function - not reported	-	-	-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level for study limitations: unclear or high risk of bias in almost all domains.
[2] Downgraded by two levels for imprecision: wide confidence interval crosses assumed threshold of clinically important difference.

DISCUSSION

Summary of main results

This review included eight studies with 1699 randomised participants across three comparisons. The mean participant age was 56.7 years and the preoperative PSA level was approximately 5 ng/mL.

We only included the trials with participants who received no treatment or the same treatment (e.g. the same type and dosage of PDE5I) for both intervention and control group at the time of outcome assessment to allow a fair comparison of efficacy of these agents. This is a critical methodological aspect of this review.

We found trial evidence for two comparisons that assessed scheduled medication versus placebo or no treatment or on-demand use only. Although we were very uncertain of the result due to very low QoE, neither suggested a benefit of a rehabilitation regimen that relied on scheduled medication dosage over placebo/no treatment or on-demand use only.

We found trial evidence for one comparison of different rehabilitation regimens, namely daily PDE5I versus daily intraurethral prostaglandin E1. Similarly, based on very low quality evidence, efficacy was comparable.

We found limited evidence on serious adverse events for the three available comparisons. We found no eligible trials for any other comparisons, such as those comparing scheduled intracavernosal injections versus on-demand use.

We were unable to conduct any of the preplanned subgroup analyses, namely based on nerve-sparing status, age and baseline erectile function due to lack of relevant data.

Overall completeness and applicability of evidence

Several issues impact the completeness and applicability of the summarised evidence:

Participant population

- Almost all studies were conducted in western countries. Given the increasing prevalence rate of prostate cancer in Asia further studies performed in Asian countries would be valuable in validating these findings.
- Although all studies included participants who had normal or mild erectile function at screening and developed ED as a result of prostatectomy, the definitions of baseline ED were different between studies.
- We were unable to conduct any of the preplanned subgroup analyses, namely based on nerve-sparing status, age and baseline erectile function.

Interventions and comparators

- Included studies used different PDE5I. Given that tadalafil 20 mg has a long half-life, we combined the results with scheduled tadalafil (twice a week; Aydogdu 2011) and daily dosing PDE5I. These differences in the interventions may have affected the review results.
- There were different treatment durations and follow-up periods among included studies that contributed clinical heterogeneity and may have affected the results of this review.
- There were no trials on several comparisons of interest, for example scheduled versus on-demand intracavernosal injections.

Outcomes

- Even though the primary outcome of erectile function was determined with validated questionnaires, there was clinical and/or methodological heterogeneity among studies in how they measured and reported these outcomes. Also studies used different definitions of recovery of ED for outcome measurement.
- Most included trials focused on short-term outcomes. Given the long-lasting impact of RP on ED, such short-term outcomes appear insufficient to provide assurance of long-term effectiveness.

Quality of the evidence

We downgraded the QoE to very low for nearly all primary outcomes. Issues that lowered our confidence in the estimates of the effect were study limitations, specifically selection bias (unclear allocation), performance and detection bias (lack of blinding for subjective outcomes), and other biases such as attrition bias and baseline imbalances in study characteristics.

We also downgraded for indirectness and imprecision due to differences in methods of outcome measurements (e.g. different definitions of self-reported potency and recovery of erectile function according to IIEF/IIEF-EF scores) and wide CIs.

Potential biases in the review process

Although we conducted this systematic review with a comprehensive search strategy consistent with current Cochrane standards, there was the possibility of bias.

- Despite a comprehensive search of published and unpublished studies without language restrictions, which included contacting the principal investigators of the existing studies and experts in the field, we may have missed relevant studies. This may be because they were published in non-indexed journals or were unpublished.
- Most studies were industry-sponsored and may have been particularly susceptible to publication bias. Given the paucity of

studies we encountered, statistical tests for publication bias were not meaningful.

Agreements and disagreements with other studies or reviews

Our systematic review stands out for its high methodological standards as documented by the a priori published protocol (Philippou 2016), its comprehensive search strategy with a focus on RCTs and its use of GRADE to rate the QoE on a per-outcome basis. Several systematic reviews have been published on this topic. These include Tian 2017 (eight RCTs), Qiu 2016 (14 RCTs), Cui 2016 (six RCTs), Li 2014 (seven RCTs) and Wang 2014 (eight RCTs). Universally all of these studies concluded that PDE5I were safe, well-tolerated and reported significant improvements in the IIEF-EF scores as compared with placebo or no treatment (Tian 2017: short-term: MD 2.26, 95% CI 1.45 to 3.08; P < 0.00001; long-term: MD 4.5, 95% CI 3.6 to 5.4; P < 0.00001; Qiu 2016: MD 4.89, 95% CI 4.25 to 5.53; P < 0.001; Cui 2016: MD 4.04, 95% CI 2.87 to 5.22; P < 0.00001; Li 2014: MD 4.35, 95% CI 3.42 to 5.29; P < 0.00001; Wang 2014: MD 5.63, 95% CI 4.26 to 6.99; P < 0.00001 in favour of the PDE5I arm.
Our review differed in two important ways.

- We focused on patient-important outcomes and rated the QoE using GRADE on a per-outcome basis. Therefore, this review is the first to describe the degree of certainty we can place in these results. For the most part, this confidence was very low indicating major uncertainty.

- Many existing reviews choose to include all existing trials for a given comparison irrespective of whether they provided a fair comparison when it came to outcome assessment. For example, Tian 2017 included four, Qiu 2016 included nine, Cui 2016 included two, Li 2014 included three and Wang 2014 included five such studies, which we excluded on the basis of inappropriate assessment of outcomes. This probably explained the difference in our results compared to the other systematic reviews.

Despite these results from the other reviews which concluded that PDE5I were efficacious in restoring erectile function, there appears awareness of these methodological issues mentioned above by the International Society of Sexual Medicine. In the guideline document from the Fourth International Consultation for Sexual Medicine, the authors indicated that data were conflicting as to whether penile rehabilitation with PDE5Is improved recovery of spontaneous erections (Salonia 2017). Our review underscores the concern that scheduled use of PDE5I has no advantage over on demand use, but likely increase the costs of treatment.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence summarised in this systematic review does not provide support for penile rehabilitation after radical prostatectomy (RP) as a means to restore erectile function to its unassisted pre-operative state compared to no treatment or placebo or on-demand treatment alone. However, it should be noted that the evidence provided in this review includes studies that evaluated only phosphodiesterase-5 inhibitors (PDE5I) and intraurethral prostaglandin as monotherapy from the armoury of current penile rehabilitation methods.

Implications for research

The very low quality evidence indicates major methodological limitations of this body of evidence. These relate to standard methodological issues such as allocation concealment, blinding and completeness of follow-up. In addition, there were concerns about inconsistency owing to clinical and methodological heterogeneity as well as imprecision, due to inadequately powered studies. Therefore, both for these comparisons and other rehabilitation strategies there is a need for better quality research focused on patient-important outcomes. Rather than continued use in clinical practice for which this review demonstrates no apparent benefit, the focus might be placed on patient enrolment in meaningfully designed clinical trials.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aydogdu 2011

Methods	**Study design:** parallel RCT **Setting/country:** single centre, Turkey **Dates when study was conducted:** 2006-2008
Participants	**Inclusion criteria:** aged < 65 years, preoperative full potency (IIEF-EF scores > 25 and answered SEP question 2-3 'yes'), no history of penile plaques or previous penile surgery, clinical stage T1c or lower, PSA < 10 ng/mL and biopsy Gleason score < 8 **Exclusion criteria:** NR **Total number of participants randomly assigned:** 74 **Group A** • Number of participants randomly assigned: NR • Mean age (years): 56.2 • Mean PSA (ng/mL): 6.3 • Gleason score (pathological): NA • Tumour stage (pathological): NA • IIEF-5: NR • IIEF-EF: 26.2 **Group B** • Number of participants randomly assigned: NR • Mean age (years): 58.1 • Mean PSA (ng/mL): 5.8 • Gleason score (pathological): NA • Tumour stage (pathological): NA • IIEF-5: NR • IIEF-EF: 26.5
Interventions	**Group A:** tadalafil 20 mg/day, 3 days/week **Group B:** no treatment **Surgery or cointervention:** BNSRRP **Interval between surgery and intervention:** 14-20 days **Intervention duration:** 6 months **Washout period before outcome assessment:** 5 months and 10-14 days **Total follow-up period:** 12 months
Outcomes	**Primary outcomes** • EF • Penile size How measured: IIEF-EF Questionnaire, SEP question 2 and question 3, penile length and circumference at both flaccid and at maximum erection Time points measured: baseline, 3, 6 and 12 months Time points reported: 3, 6 and 12 months **Secondary outcomes:** NR **Safety outcomes:** NR **Subgroup:** none

Aydogdu 2011 *(Continued)*

Funding sources	NR
Declarations of interest	NR
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcomes not likely affected by lack of blinding.
Incomplete outcome data (attrition bias) Self-reported potency	Unclear risk	9/74 (12.1%) randomised participants not included in analysis; group allocation unclear
Incomplete outcome data (attrition bias) EF/IIEF	Unclear risk	9/74 (12.1%) randomised participants not included in analysis; group allocation unclear
Incomplete outcome data (attrition bias) Serious adverse event	Unclear risk	No information given
Incomplete outcome data (attrition bias) Sexual quality of life	Unclear risk	No information given
Incomplete outcome data (attrition bias) Treatment discontinuation	Unclear risk	No information given
Incomplete outcome data (attrition bias) Acceptability of the intervention	Unclear risk	No information given

Selective reporting (reporting bias)	Unclear risk	Predefined outcomes well described but protocol not available
Other bias	Low risk	Not detected

Kim 2016

Methods	**Study design:** randomised, double-blind, placebo-controlled trial **Setting/country:** USA **Dates when study was conducted:** 2006-2012
Participants	**Inclusion criteria:** IIEF ≥ 21, nsRP **Exclusion criteria:** known risk factors for ED, poor surgical candidates, health conditions that are potential contraindications for PDE5I therapy, prior treatment with PDE5I, and taking potent cytochrome P450 inhibitors or alpha-adrenergic blocking agents (which could interact with sildenafil), or with known hypersensitivity to sildenafil or other ingredients of Viagra **Total number of participants randomly assigned:** 97 **Group A** • Number of participants randomly assigned: 49 • Mean age (years): 54.3 (SD 7.1) • Mean PSA (ng/mL): 5.1 (SD 2.9) • Gleason score (pathological): 3 + 3: 35 (74.5%), 3 + 4: 6 (12.8%), 4 + 3: 3 (6.4%), 4 + 4: 3 (6.4%) • Tumour stage (pathological): T1c: 34 (72.3%), T2a-T2c: 12 (25.5%), T3: 1 (2.1%) • IIEF-5: NR • Mean IIEF-EF: 28.0 (SD 4.6) **Group B** • Number of participants randomly assigned: 48 • Mean age (years): 54.3 (SD 7.1) • Mean PSA (ng/mL): 4.2 (SD 2.8) • Gleason score (pathological): 3 + 3: 39 (83.0%), 3 + 4: 5 (10.6%), 4 + 3: 0 (0.0%), 4 + 4: 3 (6.4%) • Tumour stage (pathological): T1c: 30 (63.8%), T2a-T2c: 16 (34.0%), T3: 1 (2.1%) • IIEF-5: NR • Mean IIEF-EF: 28.3 (SD 5.5)
Interventions	**Group A:** nightly PDE5I (sildenafil 50 mg) **Group B:** placebo with 6 tablets of SC (100 mg) every 30 days for on-demand use **Surgery or cointervention:** nsRP (RRP or RARP) **Interval between surgery and intervention:** 1 day **Intervention duration:** 12 months **Washout period before outcome assessment:** 1 month **Total follow-up period:** 13 months

Outcomes	**Primary outcomes** • Self-reported potency; IIEF-EF How measured: Rigiscan device; IIEF-EF Questionnaire Time points measured: 2 weeks, and then at 3, 6, 9 and 12 months Time points reported: 2 weeks, and then at 3, 6, 9 and 12 months **Secondary outcomes:** NR **Safety outcomes:** NR **Subgroup:** none
Funding sources	Pfizer Inc.
Declarations of interest	None reported
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Treatment arm was concealed from patients and clinical personnel until all interventions and assessments were complete."
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Quote: "Double-blind" Judgement: not described who was blinded.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcomes were unlikely affected by lack of blinding
Incomplete outcome data (attrition bias) Self-reported potency	Low risk	2/49 (4.0%) participants in experimental group and 1/48 (2.0%) participant in control group were not included in analysis
Incomplete outcome data (attrition bias) EF/IIEF	Low risk	2/49 (4.0%) participants in experimental group and 1/48 (2.0%) participant in control group were not included in analysis
Incomplete outcome data (attrition bias) Serious adverse event	Unclear risk	No information given

Incomplete outcome data (attrition bias) Sexual quality of life	Unclear risk	No information given
Incomplete outcome data (attrition bias) Treatment discontinuation	Low risk	All participants included in analysis
Incomplete outcome data (attrition bias) Acceptability of the intervention	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	Predefined outcomes well described but protocol not available
Other bias	Low risk	Not detected

McCullough 2010

Methods	**Study design:** parallel, open-label, randomised-controlled trial **Setting/country:** USA **Dates when study was conducted:** NR
Participants	**Inclusion criteria:** men < 70 years, sexually active in a stable relationship, with normal EF as determined by the IIEF-EF domain score (IIEF-EF score ≥ 26 was required to be eligible for study) and scheduled to undergo BNSRP **Exclusion criteria:** men with Gleason score > 7, PSA > 20 ng/mL and postoperative radiation therapy or androgen ablation **Total number of participants randomly assigned:** 212 **Group A** • Number of participants randomly assigned: 73 • Mean age (years): 55.6 (SD 5.9) • PSA: NR • Gleason score (pathological): NR • Tumour stage (pathological): NR • IIEF-5: NR • IIEF-EF: NR **Group B** • Number of participants randomly assigned: 139 • Mean age (years): 56.8 (SD 6.4) • PSA: NR • Gleason score (pathological): NR • Tumour stage (pathological): NR • IIEF-5: NR • IIEF-EF: NR
Interventions	**Group A:** nightly SC 50 mg **Group B:** intraurethral alprostadil 125 μg daily/at 2 month after surgery dose titration 250 μg **Surgery or cointervention:** BNSRP **Interval between surgery and intervention:** 1 month

	Intervention duration: 8 months **Washout period before outcome assessment:** 1 month **Total follow-up period:** 11 months
Outcomes	**Primary outcomes** • EDITS; IIEF; GAQ "Has the treatment you have been taking improved you erection?," SEP, SPL, adverse events How measured: EDITS; IIEF-EF; GAQ/SPL (SPL): measured from pubic bone to coronal sulcus with a rigid ruler, adverse events as reported in study Time points measured: EDITS: 11 months; other outcomes: 1, 9 and 11 months Time points reported: EDITS: 11 months; other outcomes: 1, 9 and 11 months **Secondary outcome:** none reported **Safety outcomes:** adverse events **How measured:** NR **Time point measured:** postoperative 1, 9 and 11 months **Time point reported:** postoperative 1, 9 and 11 months **Subgroup:** none
Funding sources	Vivus, Pfizer, Med Reviews, American Medical Systems, Auxilium, Coloplast, Cook, GlaxoSmithKline/Schering Plough, Indevus, Johnson & Johnson, Medtronic, National Institute of Health, Plethora, Sanofi-Aventis, Solvay, Theralogix, Timm Medical, Augusta Medical, Watson, Aeterna-Zentaris, Steba-Pharma, Serenity and USOHIFU
Declarations of interest	None reported
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open label study"
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "open label study"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome not likely affected by lack of blinding.

Incomplete outcome data (attrition bias) Self-reported potency	High risk	42/139 (30.2%) participants in experimental group and 14/73 (19.1%) participants in control group not included in the analysis
Incomplete outcome data (attrition bias) EF/IIEF	High risk	42/139 (30.2%) participants in experimental group and 14/73 (19.1%) participants in control group not included in the analysis
Incomplete outcome data (attrition bias) Serious adverse event	Unclear risk	No information given
Incomplete outcome data (attrition bias) Sexual quality of life	Unclear risk	No information given
Incomplete outcome data (attrition bias) Treatment discontinuation	Unclear risk	No information given
Incomplete outcome data (attrition bias) Acceptability of the intervention	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	Predefined outcomes well described but protocol not available
Other bias	Low risk	Not detected

Montorsi 2008

Methods	**Study design:** randomised, double-blind, double-dummy, multicentre, parallel group trial **Setting/country:** 87 centres across Europe, US, Canada and South Africa **Dates when study was conducted:** December 2004 to September 2007
Participants	**Inclusion criteria:** men, aged 18-64 years, in heterosexual relationship and scheduled to undergo BNSRP surgery within approximately 1 month of screening; interest in resuming sexual activity as soon as possible after surgery; normal preoperative EF (IIEF-EF domain score $\geq$ 26 at screening without use of therapy or devices for improvement of erections and no previous use of therapy or devices for ED; historical total PSA < 10 ng/mL; Gleason tumour score $\leq$ 7 on biopsy; no tumour perforation of the prostate capsule **Exclusion criteria:** men with residual prostate cancer or requirement for radiotherapy or adjuvant therapy; need for further surgery due to haemorrhage; and urethral catheter expected to be in place for $\geq$ 3 weeks due to anastomotic fistula; had contraindication of PDE5I **Total number of participants randomly assigned:** 628 **Group A** • Number of participants randomly assigned: 210

- Mean age (years): 57.4
- PSA: NR
- Gleason score (pathological): NR
- Tumour stage (pathological): NR
- IIEF-5: NR
- IIEF-EF: NR

Group B
- Number of participants randomly assigned: 208
- Mean age (years): 56.8
- PSA: NR
- Gleason score (pathological): NR
- Tumour stage (pathological): NR
- IIEF-5: NR
- IIEF-EF: NR

Group C
- Number of participants randomly assigned: 210
- Mean age (years): 57.1
- PSA: NR
- Gleason score (pathological): NR
- Tumour stage (pathological): NR
- IIEF-5: NR
- IIEF-EF: NR

Interventions	**Group A:** daily PDE5I: 10 mg nightly vardenafil (which could be decreased to 5 mg if required) plus on-demand placebo) **Group B:** on-demand PDE5i: flexible-dose (starting at 10 mg with the option to titrate to 5 mg or 20 mg), on-demand vardenafil plus nightly placebo **Group C:** nightly placebo, on-demand placebo **Surgery or cointervention:** BNSRRP **Interval between surgery and intervention:** 14 days **Intervention duration:** 9 months **Washout period before outcome assessment:** 2 months **Total follow-up period:** 13.5 months
Outcomes	**Primary outcomes** • Percentage of men with an IIEF-EF score ≥ 22 (defined as mild ED) How measured: IIEF-EF Questionnaire Time points measured: at study endpoint after the 2-month washout period Time points reported: at study endpoint after the 2-month washout period **Secondary outcomes** • Difference among treatment groups in the percentage of men with an IIEF-EF score ≥ 22 at LOCF at the end of the DBT period and at the end of the open-label period/IIEF-EF scores ≥ 17 and ≥ 26 at LOCF/SEP question 2 ("Were you able to insert your penis into your partner's vagina?") and question 3 ("Did your erections last long enough for you to have successful intercourse?") How measured: IIEF-EF Questionnaire/SEP Questionnaire Time points measured: at the end of the DBT period and at the end of the open-label period Time points reported: at the end of the DBT period and at the end of the open-label

		period **Safety outcomes** How measured: adverse events Time points measured: NR Time points reported: NR **Subgroup:** none
Funding sources		Bayer Schering Pharma AG
Declarations of interest		Professor Montorsi, Dr Brock, Dr Lee, and Professor Stief have acted as paid consultants or investigators for Bayer Schering Pharma AG
Notes		**Protocol:** NCT00492635 **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation codes were computer generated by Bayer Schering Pharma, Germany."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Triple (Participant, Care Provider, Investigator)" in the protocol
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "Triple (Participant, Care Provider, Investigator)" in the protocol
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome not likely affected by lack of blinding,
Incomplete outcome data (attrition bias) Self-reported potency	High risk	94/210 (44.7%) participants in daily vardenafil group, 73/208 (35.0%) participants in on-demand vardenafil group and 4/210 (39.5%) participants in placebo group were not included in the analysis
Incomplete outcome data (attrition bias) EF/IIEF	High risk	67/210 (31.9%) participants in daily vardenafil group, 59/208 (28.3%) participants in on-demand vardenafil group and 57/210 (27.1%) participants in placebo group were not included in the analysis

Incomplete outcome data (attrition bias) Serious adverse event	Low risk	3/210 (1.4%) participants in daily varde-nafil group, 4/208 (1.9%) participants in on-demand vardenafil group and 4/210 (1.9%) participants in placebo group were not included in the analysis
Incomplete outcome data (attrition bias) Sexual quality of life	Unclear risk	No information given
Incomplete outcome data (attrition bias) Treatment discontinuation	Low risk	All participants were included in the analysis.
Incomplete outcome data (attrition bias) Acceptability of the intervention	Unclear risk	No information given
Selective reporting (reporting bias)	Low risk	Protocol was published and prespecified study outcomes were analysed as planned
Other bias	Low risk	Not detected

Montorsi 2014

Methods	**Study design:** randomised double-blind placebo-controlled trial **Setting/country:** 50 centres from 9 European countries and Canada **Dates when study was conducted:** November 2009 to August 2011
Participants	**Inclusion criteria:** men aged < 68 years at the time of nsRP with normal preoperative EF who underwent nsRP for organ-confined, non-metastatic prostate cancer (Gleason score $\leq$ 7, PSA < 10 ng/mL). Postsurgical inclusion criteria included the development of ED, as measured by a participant-reported Residual Erection Function score of $\leq$ 3 ("penis is hard enough for penetration but not completely hard") **Exclusion criteria:** men with no history of ED, who had received previous or current treatment with tadalafil or any other PDE5I; had undergone, or planned to undergo, radiation or hormonal therapy for prostate cancer; history of prostatic surgery or prostatic physical treatments; history of diabetes mellitus; history of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption; clinically significant renal insufficiency as determined by the investigator **Total number of participants randomly assigned:** 423 **Group A** • Number of participants randomly assigned: 139 • Mean age (years): 58.6 (SD 5.07) • PSA: NA • Gleason score (pathological): NA • Tumour stage (pathological): NA • IIEF-5: • Mean IIEF-EF: 6.0 (SD 5.8) **Group B**

Montorsi 2014   *(Continued)*

	• Number of participants randomly assigned: 143 • Mean age (years): 57.5 (SD 5.91) • PSA: NA • Gleason score (pathological): NA • Tumour stage (pathological): NA • IIEF-5: NR • Mean IIEF-EF: 6.7 (SD 5.57) **Group C** • Number of participants randomly assigned: 141 • Mean age (years): 57.6 (SD 5.69) • PSA: NA • Gleason score (pathological): NA • Tumour stage (pathological): NA • IIEF-5: NR • Mean IIEF-EF: 6.5 (SD 6.08)
Interventions	**Group A:** tadalafil 5 mg once daily **Group B:** on-demand tadalafil 20 mg **Group C:** placebo **Surgery or cointervention:** bilateral nerve-sparing surgery during screening period **Interval between surgery and intervention:** NR **Intervention duration:** 9 months **Washout period before outcome assessment:** 6 weeks (washout) followed by 3 months' open label **Total follow-up period:** 13.5 months (after 3 months' open label)
Outcomes	**Primary outcomes** • Unassisted EF How measured: proportion of men achieving an IIEF-EF score $\geq$ 22 Time points measured: at end of DFW Time points reported: at end of DFW (primary outcome) **Secondary outcomes** • Montorsi 2014 publication: change from baseline in IIEF and SEP, penile length • Moncada 2015 publication: time to EF-recovery, ED severity, improvement, maintenance of treatment response How measured: Montorsi 2014: IIEF and SEP Questionnaire: measurements were taken before administration of any sedatives or anaesthetics Moncada 2015: defined as the time from baseline to reach an IIEF-EF $\geq$ 22 during DBT IIEF-EF scores were categorised into the following ED severity categories: severe (0-10), moderate (11-16), mild (17-25) and normal (26-30). ED severity was assessed at baseline, end of DBT, and end of DFW. Improvement was defined as an IIEF-EF score of $\geq$ 1 category higher than baseline (or maintaining normal EF) at the end of DBT. Maintenance of treatment response, assessed for participants who improved $\geq$ 1 category after DBT, was defined as either maintaining this improved category until the end of DFW or declining after DBT but still maintaining a higher category at the end of DFW than at baseline Time points measured: Montorsi 2014 (at 9, 10.5 and 13 months, before RP and 9 months (after DBT))/Moncada 2015 (time to event: at baseline, end of DBT and end

	of DFW; at the end of DBT; at baseline, DBT and DFW) Time points reported: Montorsi 2014 (at 9, 10.5 and 13 months, before RP and 9 months (after DBT))/Moncada 2015 (time to event: at baseline, end of DBT and end of DFW; at the end of DBT; at baseline, DBT and DFW) **Safety outcomes** How measured: adverse events Time points measured: after DBT Time points reported: after DBT **Subgroup:** none
Funding sources	Eli Lilly
Declarations of interest	I Moncada has been a consultant for, and received speaker honoraria and travel expenses from, Eli Lilly. C Henneges, C Turbi and H Buettner are employees of Eli Lilly and Company and own Eli Lilly stock. FR de Bethencourt, E Lledó-García, JI Martinez-Salamanca and J Romero-Otero have no conflicts of interest to disclose
Notes	**Protocol:** NCT01026818 **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Quote: "interactive voice response system and stratified by age group and country."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Matching placebo tablets identical to the 5-mg and 20-mg tadalafil tablets were used to ensure that the blinded regimen was identical." Judgement: "Double-blind (Participants and investigator)" in protocol and "placebo controlled" in article
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "Matching placebo tablets identical to the 5-mg and 20-mg tadalafil tablets were used to ensure that the blinded regimen was identical." Judgement: "Double-blind (Participants and investigator)" in protocol and "placebo controlled" in article
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome not likely affected by lack of blinding.

Incomplete outcome data (attrition bias) Self-reported potency	Low risk	All participants were included in the analysis except 1 participant in tadalafil on-demand group
Incomplete outcome data (attrition bias) EF/IIEF	Low risk	All participants were included in the analysis except 1 participant in tadalafil on-demand group
Incomplete outcome data (attrition bias) Serious adverse event	Unclear risk	All participants were included in the analysis.
Incomplete outcome data (attrition bias) Sexual quality of life	Low risk	All participants were included in the analysis except 1 participant in tadalafil on-demand group
Incomplete outcome data (attrition bias) Treatment discontinuation	Low risk	All participants were included in the analysis.
Incomplete outcome data (attrition bias) Acceptability of the intervention	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	While protocol was published, a few predefined outcomes in protocol were not reported in article
Other bias	Low risk	Not detected

Pace 2010

Methods	**Study design:** RCT **Setting/country:** Italy **Dates when study was conducted:** 2005-2009

Participants	**Inclusion criteria:** men with total PSA 510 ng/mL, Gleason score $\leq$ 7 on biopsy, no capsular involvement, normal preoperative EF assessed by an IIEF score $\geq$ 26, without the use of any therapy for improving erection
	Exclusion criteria: men with cardiovascular diseases and previous pharmacological treatments which did not allow the contemporary use of PDE5I
	Total number of participants randomly assigned: 40
	Group A
	  • Number of participants randomly assigned: 20
	  • Age: NR
	  • Mean PSA (ng/mL): 5.5 (range 1.2-9.9)
	  • Gleason score (pathological): 6: 18 (90.0%)/ 7: 2 (10.0%)
	  • Tumour stage (pathological): T1b and T1c: 10 (50.0%), T2a: 9 (45.0%), T2b: 1 (5.0%)
	    • IIEF-5: NR

Pace 2010 *(Continued)*

	● Mean IIEF-EF: 26.2 **Group B** ● Number of participants randomly assigned: 20 ● Age (years): NR ● PSA (ng/mL): 6 (range 1.8-8.9) ● Gleason score (pathological): 6: 18 (90.0%)/ 7: 2 (10.0%) ● Tumour stage (pathological): T1b and T1c: 9 (45.0%), T2a: 9 (45.0%), T2b: 2 (10.0%) ● IIEF-5: NR ● Mean IIEF-EF: 26.5
Interventions	**Group A:** sildenafil 50 mg or 100 mg at night **Group B:** no treatment **Surgery or cointervention:** BNSRRP **Interval between surgery and intervention:** 2 weeks **Intervention duration:** 8 weeks **Washout period before outcome assessment:** 14 weeks **Total follow-up period:** 24 weeks
Outcomes	**Primary outcomes** ● IIEF; potency rates; percentage of men who were capable of having medication-unassisted intercourse; percentage of men with normal EF domain; satisfaction rate How measured: NR (maybe IIEF-EF); NR; NR; IIEF-EF; NR Time points measured: before surgery and then at 3, 6, 12 and 24 weeks after NSRP; NR; NR; before surgery and then at 3, 6, 12 and 24 weeks after NSRP; NR Time points reported: before surgery and then at 3, 6, 12 and 24 weeks after NSRP; before and at 24 weeks; before and at 24 weeks; before and at 24 weeks; before and at 24 weeks **Secondary outcomes** ● Rates of treatment discontinuation How measured: NR Time points measured: 8 weeks Time points reported: 8 weeks **Safety outcomes** How measured: adverse events Time points measured: NR Time points reported: NR **Subgroup:** none
Funding sources	NR
Declarations of interest	NR
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome not likely affected by lack of blinding.
Incomplete outcome data (attrition bias) Self-reported potency	Unclear risk	Not available
Incomplete outcome data (attrition bias) EF/IIEF	Unclear risk	Not available
Incomplete outcome data (attrition bias) Serious adverse event	Low risk	All participants were included in the analysis.
Incomplete outcome data (attrition bias) Sexual quality of life	Unclear risk	No information given
Incomplete outcome data (attrition bias) Treatment discontinuation	Low risk	All participants were included in the analysis.
Incomplete outcome data (attrition bias) Acceptability of the intervention	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	Predefined outcomes well described but protocol was not available
Other bias	Low risk	Not detected

Padma-Nathan 2008

Methods	**Study design:** randomised, double-blind, placebo-controlled trial **Setting/country:** 16 sites in North America, France, Belgium and Australia screened participants and 11 sites in North America and France **Dates when study was conducted:** April 1999 to October 2001
Participants	**Inclusion criteria:** men aged 18-70 years; weighing 50-125 kg with normal preoperative EF (combined score of at least 8 on question 3 and question 4 of IIEF); wish to return to sexual activity after surgery and be in a stable, heterosexual relationship for the past 6 months **Exclusion criteria:** pathological stage > pT2; tumour Gleason score $\geq$ 8 on preoperative biopsy; PSA $\geq$ 20 mg/L; positive lymph nodes or required postoperative radiation or androgen ablation therapy; had a sleep disorder; were taking sedative/hypnotics as sleep aids or receiving nitrates or any treatment for ED **Total number of participants randomly assigned:** 125 **Group A** • Number of participants randomly assigned: 41 • Mean age (years): 55 (SD 6) • PSA: NR • Gleason score (pathological): NR • Tumour stage (pathological): NR • IIEF-5: NR • IIEF-EF: NR **Group B** • Number of participants randomly assigned: 40 • Mean age (years): 55 (SD 6) • PSA: NR • Gleason score (pathological): NR • Tumour stage (pathological): NR • IIEF-5: NR • IIEF-EF: NR **Group C** • Number of participants randomly assigned: 42 • Mean age (years): 57 (SD 7) • PSA: NR • Gleason score (pathological): NR • Tumour stage (pathological): NR • IIEF-5: NR • IIEF-EF: NR
Interventions	**Group A:** sildenafil 100 mg once daily night-time **Group B:** sildenafil 50 mg once daily night-time **Group C:** placebo once daily night-time **Surgery or cointervention:** BNSRRP by experienced surgeons **Interval between surgery and intervention:** 4 weeks **Intervention duration:** 36 weeks' double-blind study period **Washout period before outcome assessment:** 8 weeks **Total follow-up period:** 48 weeks

Outcomes	**Primary outcomes**
	  • Percentage of men who were responders
	How measured: stringent responder definition was established a priori as those participants who, at the end of phase 3, had a combined score of $\geq$ 8 for question 3 and question 4 of the IIEF, and also answered 'yes' to the question, "Over the past 4 weeks, have your erections been good enough for satisfactory sexual activity?"
	Time points measured: at 44 weeks of treatment (36 weeks' double blind + 8 weeks washout; 48 weeks after surgery)
	Time points reported: at 44 weeks of treatment (36 weeks' double blind + 8 weeks washout; 48 weeks after surgery)
	Secondary outcomes
	  • Changes from baseline in the 6-item Erectile Function domain of the IIEF; duration of penile tumescence and rigidity
	How measured: IIEF-EF Questionnaire; plethysmography
	Time points measured: baseline, 12, 24 and 36 weeks after treatment (double blinded; for 40 weeks after surgery), 44 weeks after treatment (additional 8 weeks' washout; 48 weeks after surgery)
	Time points reported: before and at 44 weeks of treatment (36 weeks double blinded+ 8 weeks washout; 48 weeks after surgery)
	Safety outcomes
	How measured: adverse events
	Time points measured: NR
	Time points reported: NR
	Subgroup: none

Funding sources	Pfizer Inc
Declarations of interest	R Siegel was an employee of Pfizer at the time of this research Gerald Brock: consultant, investigator for clinical research, and speakers bureau member for Pfizer Inc, Lilly-ICOS, Bayer, GSK, Johnson & Johnson, Coloplast and AMS Francois Giuliano: investigator for clinical and preclinical research, meeting lecturer and member of advisory board for Pfizer Inc, Bayer-GSK, Lilly-ICOS, Johnson & Johnson; preclinical research for Solvay Pharmaceuticals, Roche; investigator for preclinical research and meeting lecturer for Sanofi-Aventis Larry Levine: Consultant for Pfizer Inc, Lilly-ICOS, Auxillium, Johnson & Johnson; investigator for clinical research for Pfizer Inc, Bayer-GSK, Auxillium; lecturer for Pfizer Inc, Lilly-ICOS, Schering-Plough Larry Lipshultz: Consultant for Pfizer Inc, Lilly-ICOS, Auxillium, and Solvay Pharmaceuticals; investigator for clinical research for Pfizer Inc and Lilly-ICOS Andrew McCullough: Consultant for Pfizer Inc, Lilly-ICOS, Auxillium, Johnson & Johnson; investigator for clinical research for Pfizer Inc, Lilly-ICOS, Bayer-GSK, Guilford Pharmaceuticals, Ion Channel, Johnson & Johnson and Schering Plough; advisory board and lecturer for Pfizer Inc, Lilly-ICOS and Auxillium Francesco Montorsi: Consultant for American Medical System, Bayer-GSK, Johnson & Johnson, Lilly ICOS, Pfizer Inc and Takeda Harin Padma-Nathan: Consultant, received grant support (for this and other clinical trials) from, and participated in CME educational program for Pfizer Inc, Lilly-ICOS, Bayer-GSK, NexMed and Palatin Technologies

Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated randomisation was in a 1:1:1 ratio using the method of random permuted blocks and a pseudo-random number generator."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, placebo controlled"
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "Double-blind, placebo controlled"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Self-reported potency	High risk	13/41 (31.7%) participants in sildenafil 100 mg group, 17/40 (42.5%) participants in sildenafil 50 mg group and 17/42 (40.4%) participants in placebo group were not included in the analysis
Incomplete outcome data (attrition bias) EF/IIEF	High risk	13/41 (31.7%) participants in sildenafil 100 mg group, 17/40 (42.5%) participants in sildenafil 50 mg group and 17/42 (40.4%) participants in placebo group were not included in the analysis
Incomplete outcome data (attrition bias) Serious adverse event	Low risk	All participants were included in the analysis.
Incomplete outcome data (attrition bias) Sexual quality of life	Unclear risk	No information given
Incomplete outcome data (attrition bias) Treatment discontinuation	Low risk	All participants were included in the analysis.

Incomplete outcome data (attrition bias) Acceptability of the intervention	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	Predefined outcomes were well described but protocol was not available
Other bias	High risk	Premature termination due to lack of efficacy of intervention. Statistical method change during study

Pavlovich 2013

Methods	**Study design:** randomised double-blind, placebo-controlled trial **Setting/country:** single institution in USA **Dates when study was conducted:** 2006-2007
Participants	**Inclusion criteria:** men choosing to undergo nsRP who satisfied the following criteria: aged < 65 years, untreated prostate cancer < cT2b, biopsy Gleason score < 8, baseline IIEF-EF score ≥ 25/30, no PDE5I use and presence of a steady sexual partner **Exclusion criteria:** NR **Total number of participants randomly assigned:** 100 **Group A** • Number of participants randomly assigned: 50 • Mean age (years): 54.3 (range 42-63) • Mean PSA (ng/mL): 4.7 (range 0.6-14) • Gleason score (pathological): 6: 41 (82.0%); 7: 9 (18.0%) • Tumour stage (pathological): T1c: 37 (74.0%); T2a: 13 (26.0%) • IIEF-5: NR • Mean IIEF-EF: 29.4 (range 26-30) **Group B** • Number of participants randomly assigned: 50 • Mean age (years): 53.6 (range 40-64) • Mean PSA (ng/mL): 5.1 (range 0.8-9.0) • Gleason score (pathological): 6: 42 (84.0%); 7: 8 (16.0%) • Tumour stage (pathological): T1c: 40 (80.0%); T2a: 10 (20.0%) • IIEF-5: NR • Mean IIEF-EF: 29.3 (range 26-30)
Interventions	**Group A:** nightly sildenafil 50 mg with on-demand placebo **Group B:** on-demand sildenafil 50 mg (maximum 6 tablets/month) with nightly placebo **Surgery or cointervention:** nerve-sparing minimally invasive RP (either laparoscopic or RARP) **Interval between surgery and intervention:** 1 day **Intervention duration:** 1 year double-blind study period **Washout period before outcome assessment:** 4 weeks **Total follow-up period:** 13 months

Outcomes	**Primary outcomes**
	    ● EF recovery/ IIEF-EF score
	How measured: IIEF-EF Questionnaire (not defined)
	Time points measured: baseline, at 1, 3, 6, 9, 12 and 13 months
	Time points reported: baseline, at 1, 3, 6, 9, 12 and 13 months
	Secondary outcomes
	    ● EPIC Sexual Function Subscale and EPIC Sexual Bother Subscale scores, and specific items of the IIEF (2, 6 and 15, and EPIC Questionnaire (57, 59 and 63) concerning erectile confidence, quality and intercourse frequency
	How measured: EPIC Questionnaire and IIEF
	Time points measured: baseline, at 1, 3, 6, 9, 12 and 13 months
	Time points reported: baseline, at 1, 3, 6, 9, 12 and 13 months
	Safety outcomes
	How measured: adverse events
	Time points measured: NR
	Time points reported: NR
	Subgroup: none

Funding sources	None (acknowledgement: this trial was supported with an independent investigator-initiated grant from Pfizer Pharmaceuticals)
Declarations of interest	None
Notes	**Protocol: NA** **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, placebo controlled"
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "Double-blind, placebo controlled"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcomes not likely affected by lack of blinding.

Incomplete outcome data (attrition bias) Self-reported potency	High risk	Short term: 16/50 (32.0%) participants in daily group and 20/50 (40.0%) participants in on-demand group were not included in the analysis Long term: 14/50 (28.0%) participants in daily group and 12/50 (24.0%) participants in on-demand group were not included in the analysis
Incomplete outcome data (attrition bias) EF/IIEF	High risk	Short term: 16/50 (32.0%) participants in daily group and 20/50 (40.0%) participants in on-demand group were not included in the analysis Long term: 14/50 (28.0%) participants in daily group and 12/50 (24.0%) participants in on-demand group were not included in the analysis
Incomplete outcome data (attrition bias) Serious adverse event	Low risk	All participants were included in the analysis.
Incomplete outcome data (attrition bias) Sexual quality of life	Unclear risk	Quote: "None differed significantly between treatment groups" Judgement: no available data
Incomplete outcome data (attrition bias) Treatment discontinuation	Low risk	All participants were included in the analysis.
Incomplete outcome data (attrition bias) Acceptability of the intervention	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	Predefined outcomes are well described but protocol was not available
Other bias	Low risk	Not detected

BNSRP: bilateral nerve-sparing radical retropubic prostatectomy; BNSRRP: bilateral nerve-sparing radical retropubic prostatectomy; DBT: double-blind treatment; DFW: drug-free washout; ED: erectile dysfunction; EDITS: Erectile Dysfunction Inventory of Treatment Satisfaction; EF: erectile function; GAQ: Global Assessment Question; IIEF: International Index of Erectile Function; IIEF-EF: International Index of Erectile Function - Erectile Function domain; LOCF: last observation carried forward; PSA: prostate-specific antigen; NA: not applicable; NR: not reported; nsRP: nerve-sparing radical prostatectomy; PDE5I: phosphodiesterase 5 inhibitor; RARP: robot-assisted radical prostatectomy; RCT: randomised controlled trial; RP: retropubic prostatectomy; RRP: radical retropubic prostatectomy; SC: sildenafil citrate; SD: standard deviation; SEP: Sexual Encounter Profile; SPL: stretched penile length.

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

Study	Reason for exclusion
Bannowsky 2008	Inappropriate assessment of outcome (not fair comparison at the time of outcome assessment)
Bannowsky 2010	Inappropriate assessment of outcomes (not fair comparison at the time of outcome assessment)
Bannowsky 2012	Inappropriate assessment of outcomes (not fair comparison at the time of outcome assessment)
Brock 2003	Inappropriate assessment of outcome (not fair comparison at the time of outcome assessment)
Canat 2015	Inappropriate assessment of outcome (not fair comparison at the time of outcome assessment)
Cavallini 2005	Inappropriate assessment of outcome (not fair comparison at the time of outcome assessment)
Chambers 2015	Wrong intervention
Engel 2011	Inappropriate assessment of outcomes (not fair comparison at the time of outcome assessment)
Fode 2014	Wrong intervention
Kim 2017	Inappropriate assessment of outcomes (not fair comparison at the time of outcome assessment)
Kohler 2007	Inappropriate assessment of outcomes (not fair comparison at the time of outcome assessment)
Kosev 2013	Wrong study design
McCullough 2008	Inappropriate assessment of outcomes (not fair comparison at the time of outcome assessment)
Montorsi 1997	Inappropriate assessment of outcomes (not fair comparison at the time of outcome assessment)
Montorsi 2004	Inappropriate assessment of outcome (not fair comparison at the time of outcome assessment)
Mulhall 2013	Inappropriate assessment of outcomes (not fair comparison at the time of outcome assessment)
Naccarato 2016	Inappropriate assessment of outcomes (not fair comparison at the time of outcome assessment)
Nehra 2005	Inappropriate assessment of outcome (not fair comparison at the time of outcome assessment)
Raina 2007	Wrong study design
Seo 2014	Wrong study design (retrospective study)
Yassin 2010	Incorrect reference

DATA AND ANALYSES

Comparison 1.   Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Self-reported potency (short term)	4	628	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.41]
2 Erectile function (short term)	5	757	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.80, 1.55]
3 Serious adverse event (short term)	3	443	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.11, 0.94]
4 Treatment discontinuation (short term)	3	443	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.72, 1.34]
5 International Index of Erectile Function - Erectile Function domain (IIEF-EF) (short term)	2	356	Mean Difference (IV, Random, 95% CI)	2.09 [-1.85, 6.03]
6 Sexual quality of life (long term)	1	280	Mean Difference (IV, Random, 95% CI)	3.20 [-5.91, 12.31]
7 Treatment discontinuation (long term)	1	420	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.85, 1.48]

Comparison 2.   Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Self-reported potency (short term)	2	532	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.62, 1.53]
2 Erectile function (short term)	2	573	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.65, 1.55]
3 Serious adverse event (short term)	1	282	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.12, 4.04]
4 Treatment discontinuation (short term)	1	282	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.85, 2.12]
5 International Index of Erectile Function - Erectile Function domain (IIEF-EF) (short term)	1	281	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.15, 0.47]
6 Self-reported potency (long term)	1	94	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.60, 1.67]
7 Erectile function (long term)	2	168	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.48, 1.14]
8 Serious adverse event (long term)	1	100	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 71.92]
9 Sexual quality of life (long term)	1	281	Mean Difference (IV, Random, 95% CI)	4.0 [-4.84, 12.84]
10 Treatment discontinuation (long term)	3	612	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.86, 1.38]

Comparison 3.   Daily phosphodiesterase 5 inhibitor (PDE5I) versus daily intraurethral prostaglandin (IUP) E1 (short term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Self-reported potency	1	156	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.79, 1.52]
2 Erectile function (International Index of Erectile Function - Erectile Function domain (IIEF-EF) > 26)	1	156	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.84, 3.20]
3 Erectile function (IIEF-EF > 17)	1	156	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.79, 1.81]

Analysis 1.1.   Comparison 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment, Outcome 1 Self-reported potency (short term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment

Outcome: 1 Self-reported potency (short term)

Study or subgroup	Scheduled n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Aydogdu 2011	26/32	22/33		32.3 %	1.22 [0.91, 1.63]
Montorsi 2008	37/116	44/127		25.2 %	0.92 [0.64, 1.32]
Montorsi 2014	39/139	40/141		23.7 %	0.99 [0.68, 1.44]
Pace 2010	17/20	11/20		18.9 %	1.55 [1.00, 2.39]
Total (95% CI)	**307**	**321**		**100.0 %**	**1.13 [0.91, 1.41]**

Total events: 119 (Scheduled), 117 (Placebo)

Heterogeneity: Tau² = 0.02; Chi² = 4.45, df = 3 (P = 0.22); I² =33%

Test for overall effect: Z = 1.10 (P = 0.27)

Test for subgroup differences: Not applicable

```
        0.01    0.1     1      10     100
        Favours placebo    Favours scheduled
```
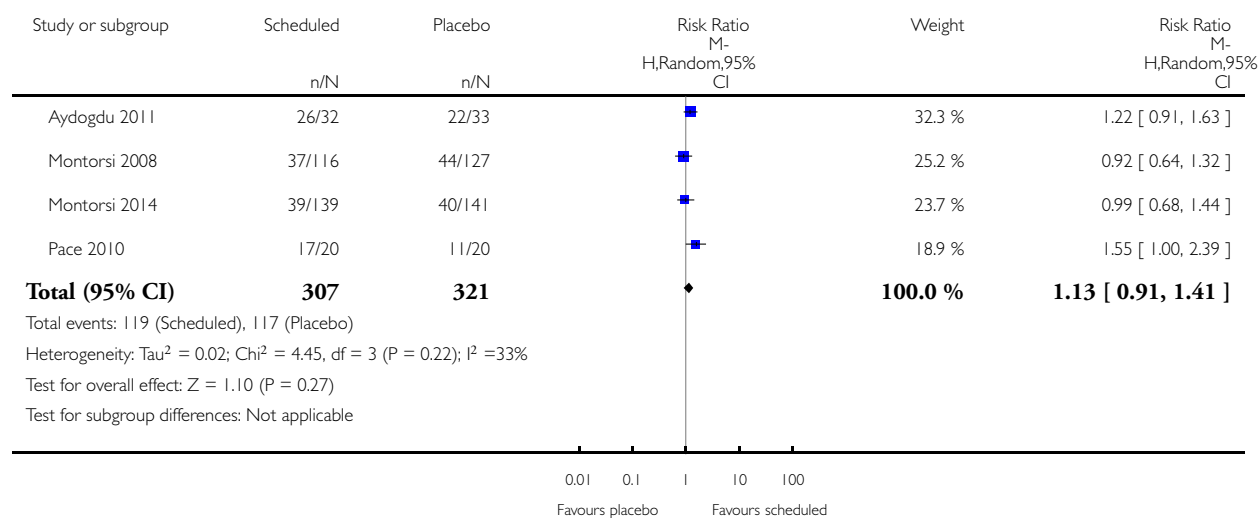
Analysis 1.2. Comparison 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment, Outcome 2 Erectile function (short term).

Study or subgroup	Scheduled	Placebo	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Aydogdu 2011	21/32	19/33		32.4 %	1.14 [0.78, 1.68]
Montorsi 2008	34/143	44/153		32.4 %	0.83 [0.56, 1.22]
Montorsi 2014	29/139	26/141		26.3 %	1.13 [0.70, 1.82]
Pace 2010	6/20	3/20		6.3 %	2.00 [0.58, 6.91]
Padma-Nathan 2008	14/51	1/25		2.6 %	6.86 [0.96, 49.29]
Total (95% CI)	**385**	**372**		**100.0 %**	**1.11 [0.80, 1.55]**

Total events: 104 (Scheduled), 93 (Placebo)

Heterogeneity: Tau² = 0.05; Chi² = 6.39, df = 4 (P = 0.17); I² =37%

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours placebo   Favours scheduled

Analysis 1.3. Comparison 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment, Outcome 3 Serious adverse event (short term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment

Outcome: 3 Serious adverse event (short term)

Study or subgroup	Scheduled n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Montorsi 2014	2/139	10/141		51.8 %	0.20 [0.05, 0.91]
Pace 2010	0/20	0/20			Not estimable
Padma-Nathan 2008	3/81	3/42		48.2 %	0.52 [0.11, 2.46]
Total (95% CI)	**240**	**203**		**100.0 %**	**0.32 [0.11, 0.94]**

Total events: 5 (Scheduled), 13 (Placebo)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.75, df = 1 (P = 0.39); I^2 =0.0%

Test for overall effect: Z = 2.07 (P = 0.038)

Test for subgroup differences: Not applicable

```
        0.01    0.1      1      10     100
        Favours scheduled    Favours placebo
```
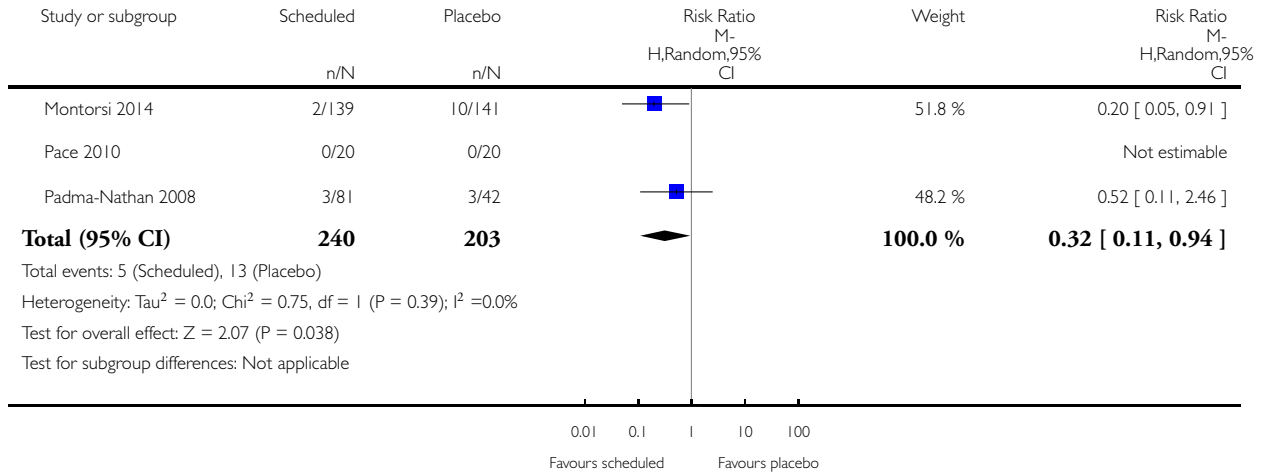
Analysis 1.4. Comparison 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment, Outcome 4 Treatment discontinuation (short term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment

Outcome: 4 Treatment discontinuation (short term)

Study or subgroup	Scheduled	Placebo	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Montorsi 2014	34/139	33/141		55.2 %	1.05 [0.69, 1.59]
Pace 2010	0/20	0/20			Not estimable
Padma-Nathan 2008	30/81	17/42		44.8 %	0.92 [0.58, 1.46]
Total (95% CI)	**240**	**203**		**100.0 %**	**0.98 [0.72, 1.34]**

Total events: 64 (Scheduled), 50 (Placebo)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.18, df = 1 (P = 0.67); I^2 =0.0%

Test for overall effect: Z = 0.10 (P = 0.92)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours scheduled   Favours placebo
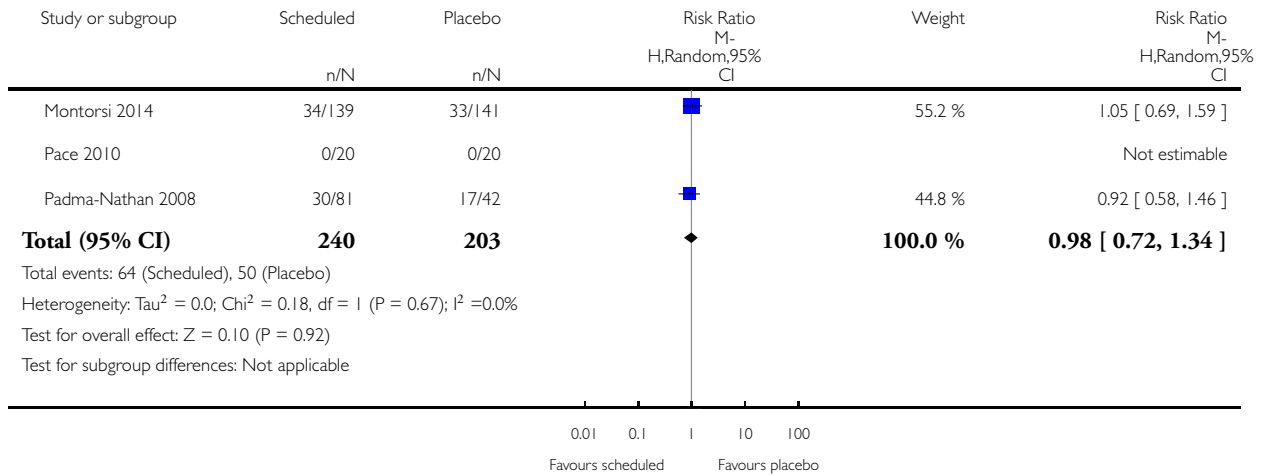
Analysis 1.5.   Comparison 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment, Outcome 5 International Index of Erectile Function - Erectile Function domain (IIEF-EF) (short term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment

Outcome: 5 International Index of Erectile Function – Erectile Function domain (IIEF-EF) (short term)

Study or subgroup	Scheduled N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Montorsi 2014	139	6.24 (12.04)	141	5.98 (12.37)		54.8 %	0.26 [-2.60, 3.12]
Padma-Nathan 2008	51	13.1 (9.4)	25	8.8 (7)		45.2 %	4.30 [0.53, 8.07]
Total (95% CI)	**190**		**166**			**100.0 %**	**2.09 [-1.85, 6.03]**

Heterogeneity: Tau² = 5.25; Chi² = 2.80, df = 1 (P = 0.09); I² =64%

Test for overall effect: Z = 1.04 (P = 0.30)

Test for subgroup differences: Not applicable

```
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        Favours placebo    Favours scheduled
```
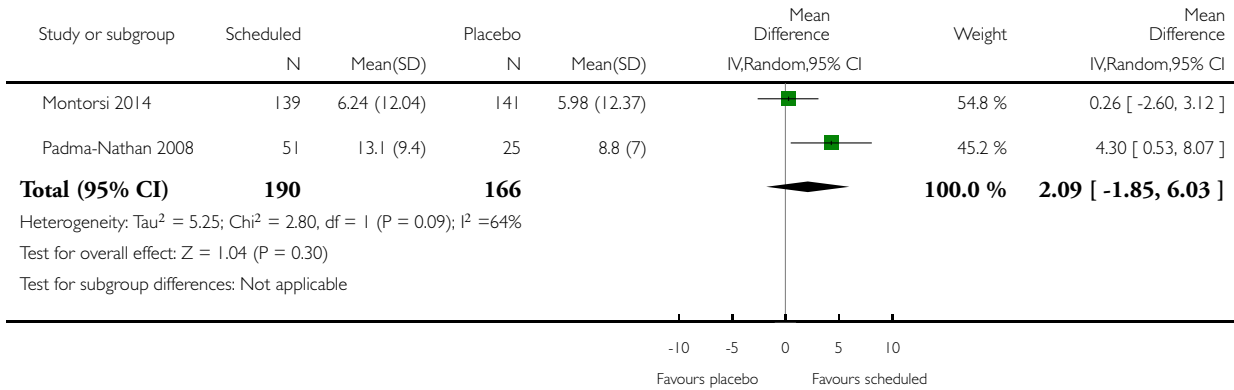
Analysis 1.6.   Comparison 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment, Outcome 6 Sexual quality of life (long term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment

Outcome: 6 Sexual quality of life (long term)

Study or subgroup	Scheduled N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Montorsi 2014	139	36.6 (39.35)	141	33.4 (38.43)		100.0 %	3.20 [-5.91, 12.31]
Total (95% CI)	**139**		**141**			**100.0 %**	**3.20 [-5.91, 12.31]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable

```
        -0.5   -0.25   0    0.25   0.5
        Favours placebo    Favours scheduled
```
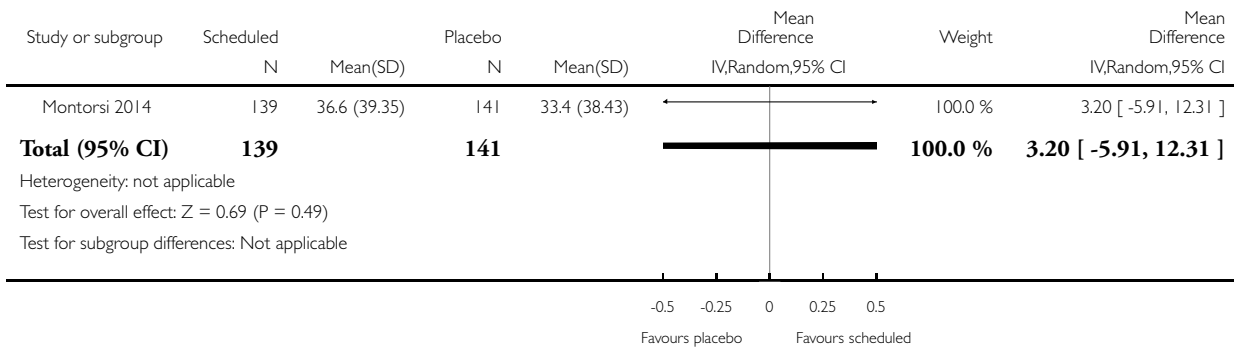
Analysis 1.7. Comparison 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment, Outcome 7 Treatment discontinuation (long term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 1 Scheduled phosphodiesterase 5 inhibitor versus placebo or no treatment

Outcome: 7 Treatment discontinuation (long term)

Study or subgroup	Scheduled n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Montorsi 2008	73/210	65/210		100.0 %	1.12 [0.85, 1.48]
Total (95% CI)	**210**	**210**		**100.0 %**	**1.12 [0.85, 1.48]**

Total events: 73 (Scheduled), 65 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
     Favours scheduled    Favours placebo
```
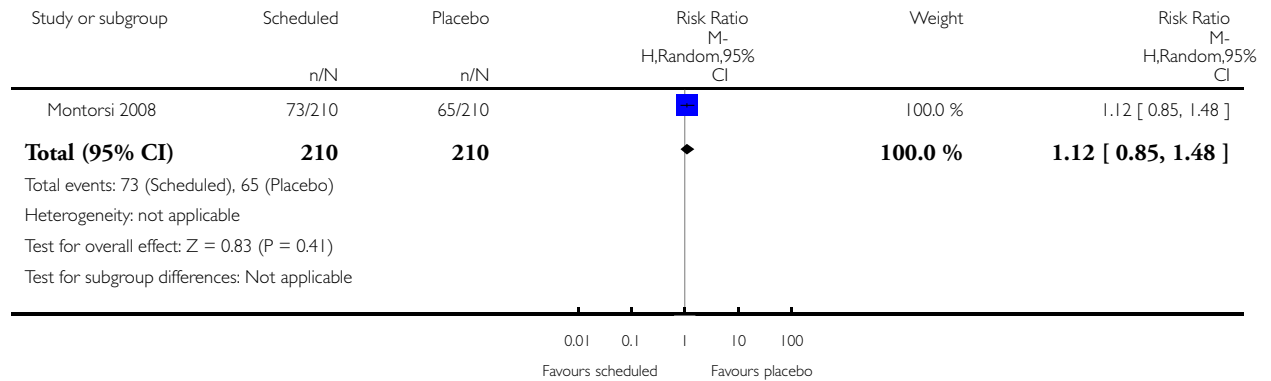
Analysis 2.1. Comparison 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor, Outcome 1 Self-reported potency (short term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

Outcome: 1 Self-reported potency (short term)

Study or subgroup	Daily n/N	On-demand n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Montorsi 2008	37/116	55/135		53.1 %	0.78 [0.56, 1.09]
Montorsi 2014	39/139	32/142		46.9 %	1.25 [0.83, 1.87]
Total (95% CI)	**255**	**277**		**100.0 %**	**0.97 [0.62, 1.53]**

Total events: 76 (Daily), 87 (On-demand)
Heterogeneity: Tau^2 = 0.07; Chi^2 = 3.01, df = 1 (P = 0.08); I^2 =67%
Test for overall effect: Z = 0.12 (P = 0.91)
Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
     Favours on-demand    Favours daily
```

Analysis 2.2.   Comparison 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor, Outcome 2 Erectile function (short term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

Outcome: 2 Erectile function (short term)

Study or subgroup	Daily n/N	On-demand n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Montorsi 2008	34/143	43/149		56.2 %	0.82 [0.56, 1.21]
Montorsi 2014	29/139	23/142		43.8 %	1.29 [0.79, 2.11]
Total (95% CI)	**282**	**291**		**100.0 %**	**1.00 [0.65, 1.55]**

Total events: 63 (Daily), 66 (On-demand)

Heterogeneity: Tau² = 0.05; Chi² = 1.95, df = 1 (P = 0.16); I² =49%

Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours on demand   Favours daily

Analysis 2.3. Comparison 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor, Outcome 3 Serious adverse event (short term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

Outcome: 3 Serious adverse event (short term)

Study or subgroup	Daily n/N	On-demand n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Montorsi 2014	2/139	3/143		100.0 %	0.69 [0.12, 4.04]
Total (95% CI)	**139**	**143**		**100.0 %**	**0.69 [0.12, 4.04]**

Total events: 2 (Daily), 3 (On-demand)

Heterogeneity: not applicable

Test for overall effect: Z = 0.42 (P = 0.68)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours daily   Favours on-demand

Analysis 2.4. Comparison 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor, Outcome 4 Treatment discontinuation (short term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

Outcome: 4 Treatment discontinuation (short term)

Study or subgroup	Daily n/N	On-demand n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Montorsi 2014	34/139	26/143		100.0 %	1.35 [0.85, 2.12]
Total (95% CI)	**139**	**143**		**100.0 %**	**1.35 [0.85, 2.12]**

Total events: 34 (Daily), 26 (On-demand)

Heterogeneity: not applicable

Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours daily   Favours on-demand

Analysis 2.5. Comparison 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor, Outcome 5 International Index of Erectile Function - Erectile Function domain (IIEF-EF) (short term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

Outcome: 5 International Index of Erectile Function – Erectile Function domain (IIEF-EF) (short term)

Study or subgroup	Daily N	Mean(SD)	On-demand N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Montorsi 2014	139	2.54 (1.37)	142	2.38 (1.26)		100.0 %	0.16 [-0.15, 0.47]
Total (95% CI)	**139**		**142**			**100.0 %**	**0.16 [-0.15, 0.47]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.02 (P = 0.31)

Test for subgroup differences: Not applicable

-100   -50   0   50   100

Favours on-demand   Favours daily

Analysis 2.6.   Comparison 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor, Outcome 6 Self-reported potency (long term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

Outcome: 6 Self-reported potency (long term)

Study or subgroup	Daily n/N	On-demand n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
Kim 2016	18/47	18/47		100.0 %	1.00 [0.60, 1.67]
Total (95% CI)	**47**	**47**		**100.0 %**	**1.00 [0.60, 1.67]**
Total events: 18 (Daily), 18 (On-demand)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					

0.01   0.1   1   10   100
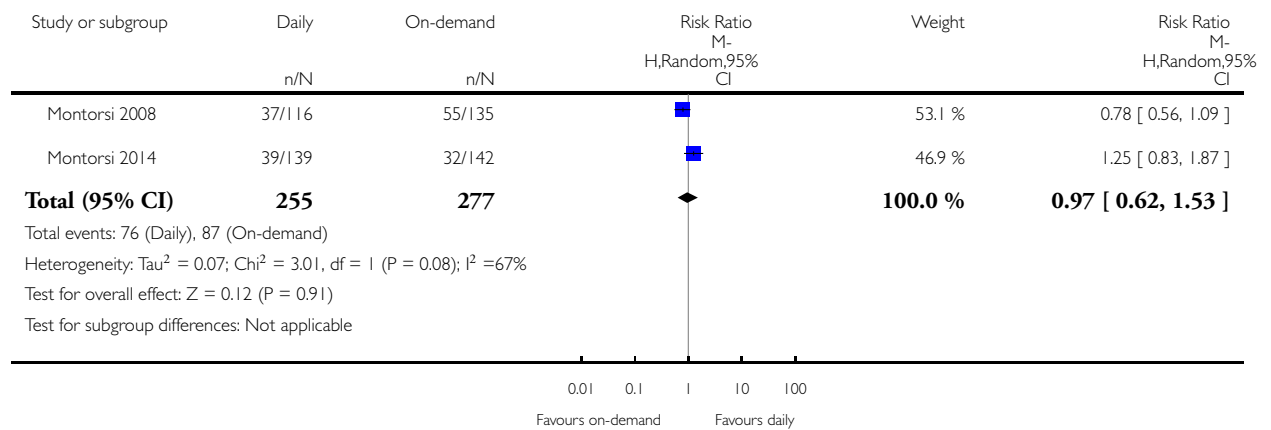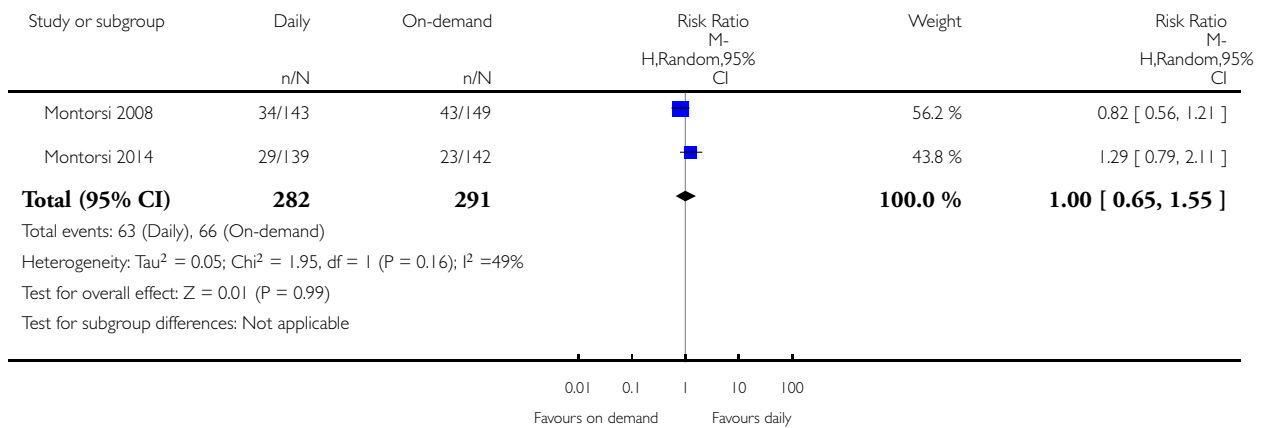
Favours on-demand   Favours daily

Analysis 2.7.   Comparison 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor, Outcome 7 Erectile function (long term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

Outcome: 7 Erectile function (long term)

Study or subgroup	Daily n/N	On-demand n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
Kim 2016	13/47	15/47		47.8 %	0.87 [0.46, 1.62]
Pavlovich 2013	11/36	18/38		52.2 %	0.65 [0.36, 1.17]
Total (95% CI)	**83**	**85**		**100.0 %**	**0.74 [0.48, 1.14]**
Total events: 24 (Daily), 33 (On-demand)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.45, df = 1 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 1.35 (P = 0.18)					
Test for subgroup differences: Not applicable					

0.01   0.1   1   10   100
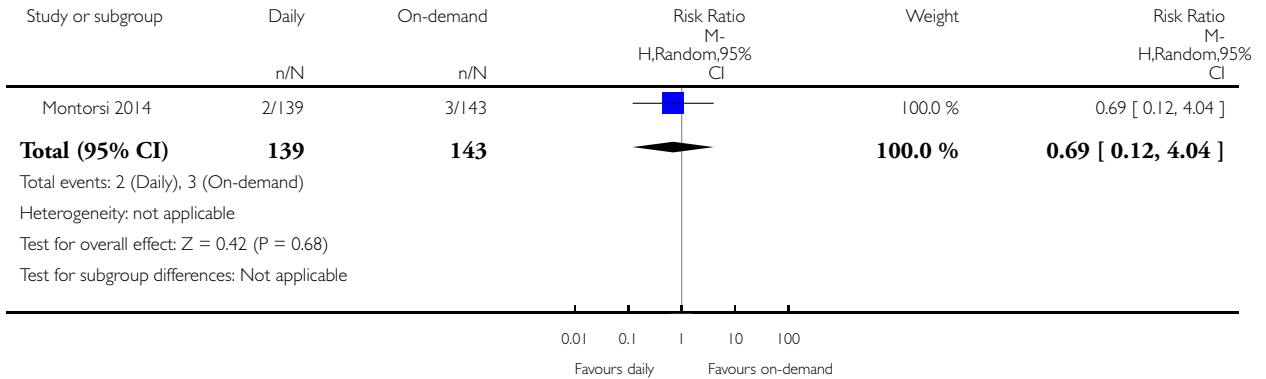
Favours on-demand   Favours daily

Analysis 2.8.   Comparison 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor, Outcome 8 Serious adverse event (long term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

Outcome: 8 Serious adverse event (long term)

Study or subgroup	Daily	On-demand	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Pavlovich 2013	1/50	0/50		100.0 %	3.00 [0.13, 71.92]
Total (95% CI)	**50**	**50**		**100.0 %**	**3.00 [0.13, 71.92]**

Total events: 1 (Daily), 0 (On-demand)

Heterogeneity: not applicable

Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Not applicable

```
        0.01    0.1     1     10    100
        Favours daily      Favours on-demand
```
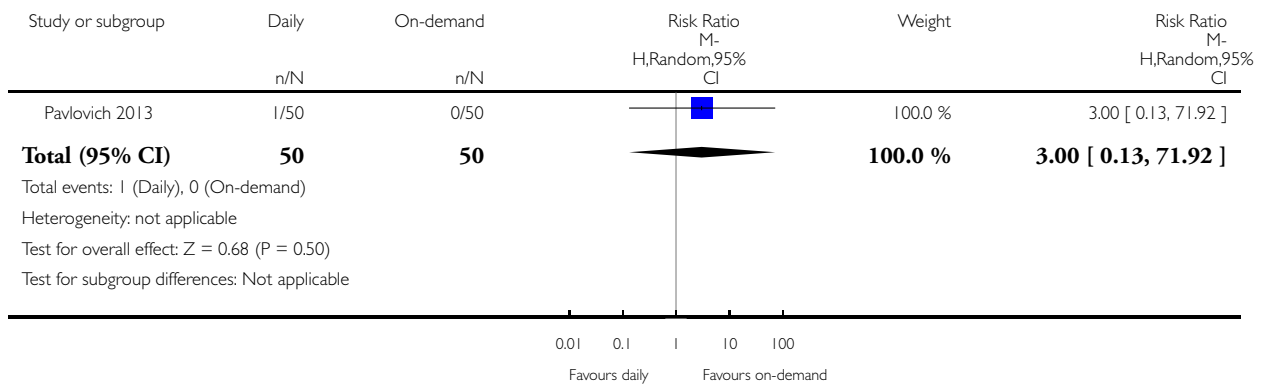
Analysis 2.9.   Comparison 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor, Outcome 9 Sexual quality of life (long term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

Outcome: 9 Sexual quality of life (long term)

Study or subgroup	Daily		On-demand		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Montorsi 2014	139	36.6 (39.35)	142	32.6 (36.16)		100.0 %	4.00 [-4.84, 12.84]
Total (95% CI)	**139**		**142**			**100.0 %**	**4.00 [-4.84, 12.84]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.89 (P = 0.38)

Test for subgroup differences: Not applicable

-100 -50 0 50 100
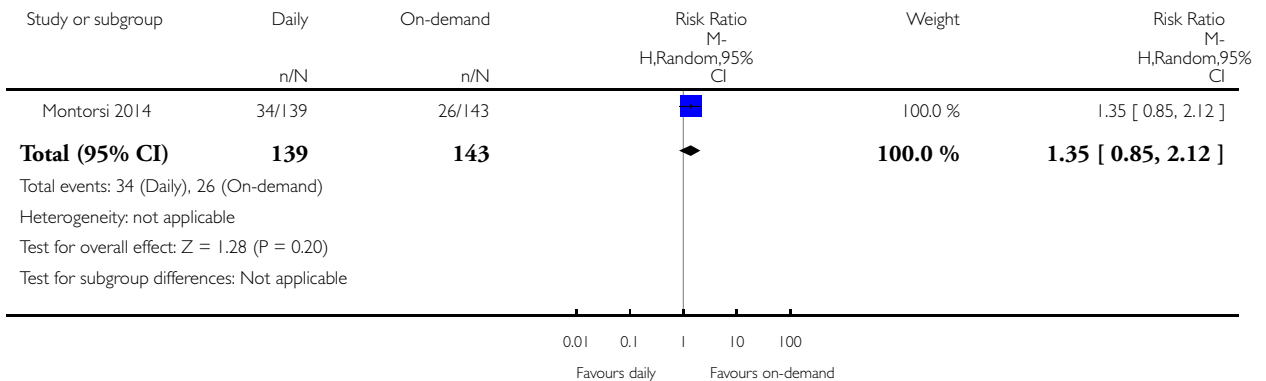
Favours on demand   Favours daily
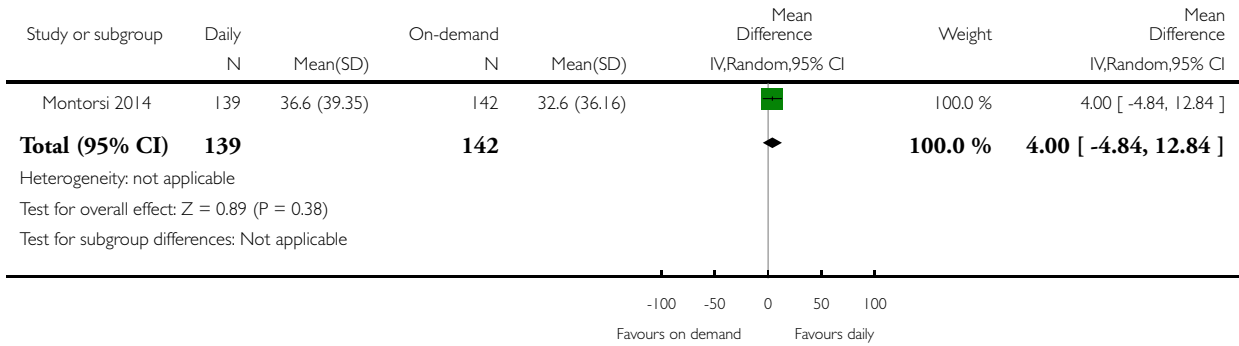
Analysis 2.10.   Comparison 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor, Outcome 10 Treatment discontinuation (long term).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 2 Daily phosphodiesterase 5 inhibitor versus on-demand phosphodiesterase 5 inhibitor

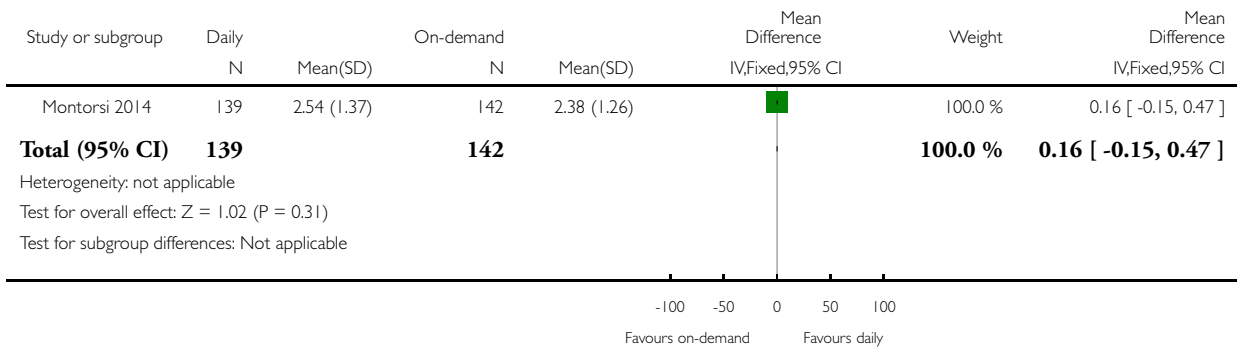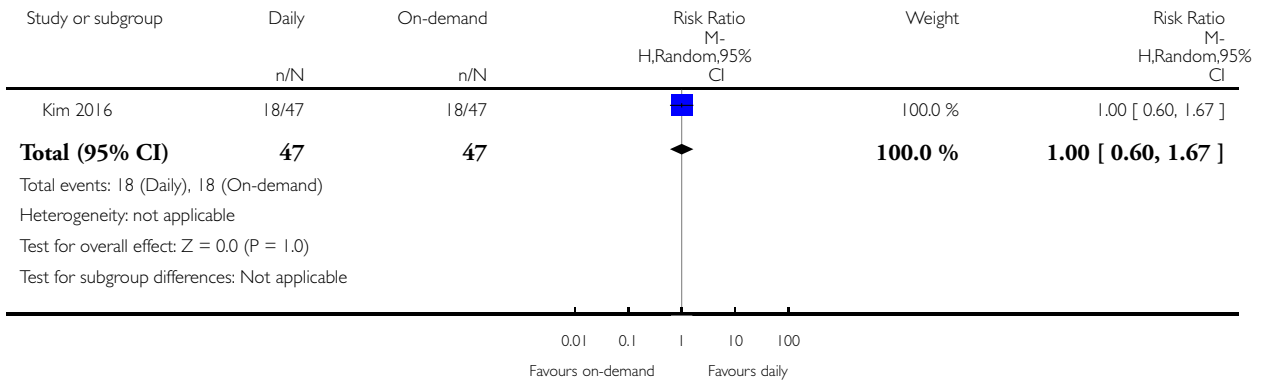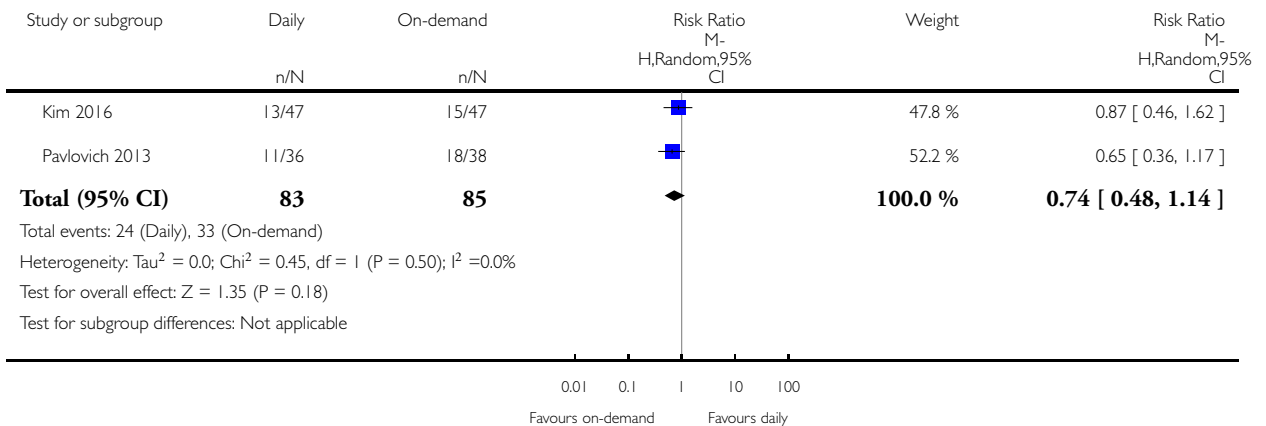Outcome: 10 Treatment discontinuation (long term)

Study or subgroup	Daily	On-demand	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Kim 2016	12/47	11/47		11.0 %	1.09 [0.54, 2.22]
Montorsi 2008	73/210	67/208		76.3 %	1.08 [0.82, 1.41]
Pavlovich 2013	14/50	12/50		12.7 %	1.17 [0.60, 2.27]
Total (95% CI)	**307**	**305**		**100.0 %**	**1.09 [0.86, 1.38]**

Total events: 99 (Daily), 90 (On-demand)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.05, df = 2 (P = 0.98); I^2 =0.0%

Test for overall effect: Z = 0.72 (P = 0.47)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours daily   Favours on-demand
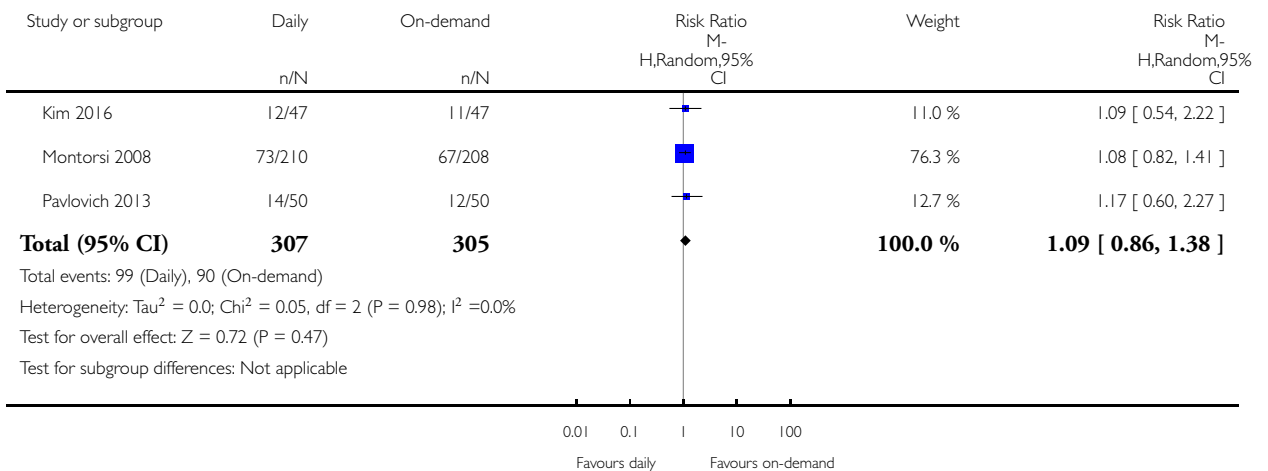
Analysis 3.1. Comparison 3 Daily phosphodiesterase 5 inhibitor (PDE5I) versus daily intraurethral prostaglandin (IUP) E1 (short term), Outcome 1 Self-reported potency.

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 3 Daily phosphodiesterase 5 inhibitor (PDE5I) versus daily intraurethral prostaglandin (IUP) E1 (short term)

Outcome: 1 Self-reported potency

Study or subgroup	PDE5I n/N	IUP n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
McCullough 2010	30/59	45/97		100.0 %	1.10 [0.79, 1.52]
Total (95% CI)	**59**	**97**		**100.0 %**	**1.10 [0.79, 1.52]**

Total events: 30 (PDE5I), 45 (IUP)

Heterogeneity: not applicable

Test for overall effect: Z = 0.55 (P = 0.59)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
      Favours daily IUP    Favours daily PDE5I
```

Analysis 3.2. Comparison 3 Daily phosphodiesterase 5 inhibitor (PDE5I) versus daily intraurethral prostaglandin (IUP) E1 (short term), Outcome 2 Erectile function (International Index of Erectile Function - Erectile Function domain (IIEF-EF) > 26).

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 3 Daily phosphodiesterase 5 inhibitor (PDE5I) versus daily intraurethral prostaglandin (IUP) E1 (short term)

Outcome: 2 Erectile function (International Index of Erectile Function – Erectile Function domain (IIEF-EF) > 26)

Study or subgroup	PDE5I n/N	IUP n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
McCullough 2010	14/59	14/97		100.0 %	1.64 [0.84, 3.20]
Total (95% CI)	**59**	**97**		**100.0 %**	**1.64 [0.84, 3.20]**
Total events: 14 (PDE5I), 14 (IUP)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.46 (P = 0.14)					
Test for subgroup differences: Not applicable					

0.01   0.1   1   10   100

Favours daily IUP   Favours daily PDE5I

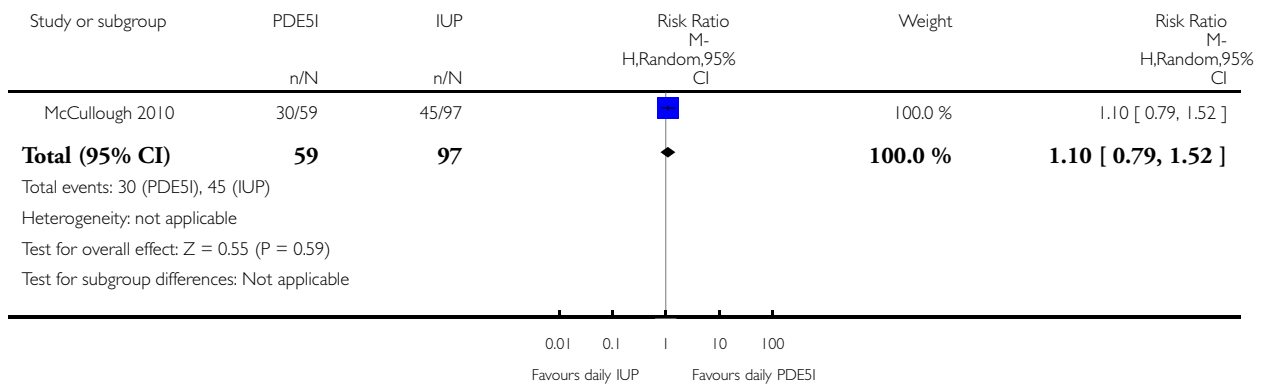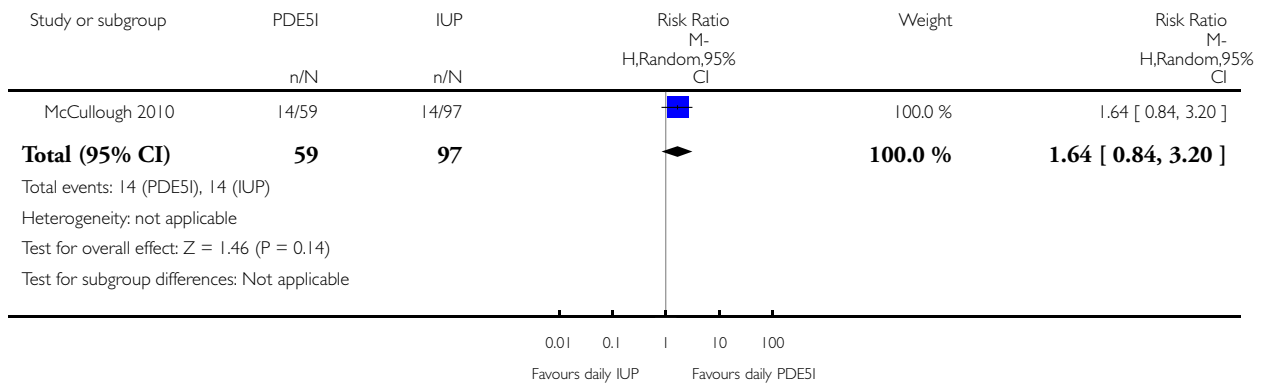**Analysis 3.3. Comparison 3 Daily phosphodiesterase 5 inhibitor (PDE5I) versus daily intraurethral prostaglandin (IUP) E1 (short term), Outcome 3 Erectile function (IIEF-EF > 17).**

Review: Penile rehabilitation for postprostatectomy erectile dysfunction

Comparison: 3 Daily phosphodiesterase 5 inhibitor (PDE5I) versus daily intraurethral prostaglandin (IUP) E1 (short term)

Outcome: 3 Erectile function (IIEF-EF > 17)

Study or subgroup	PDE5I n/N	IUP n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
McCullough 2010	24/59	33/97		100.0 %	1.20 [0.79, 1.81]
Total (95% CI)	**59**	**97**		**100.0 %**	**1.20 [0.79, 1.81]**
Total events: 24 (PDE5I), 33 (IUP)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.40)					
Test for subgroup differences: Not applicable					

0.01   0.1   1   10   100

Favours daily IUP   Favours daily PDE5I
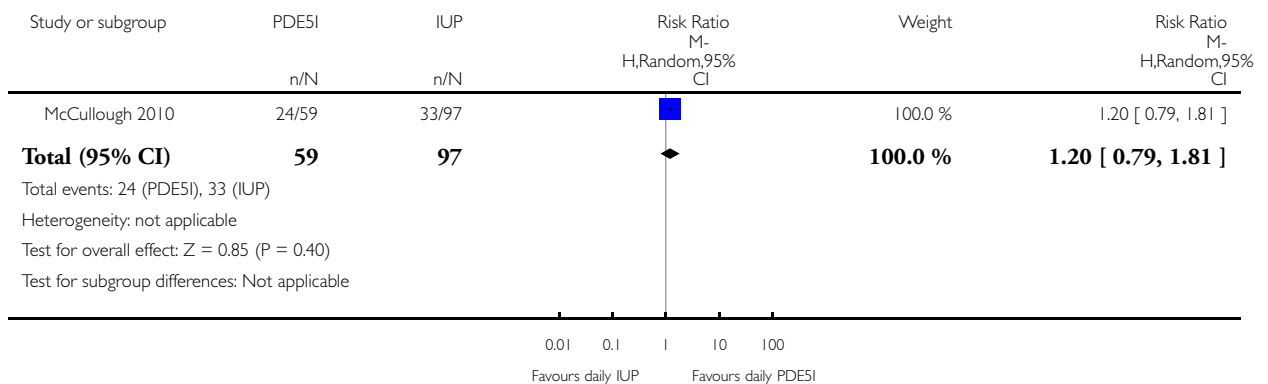
ADDITIONAL TABLES

Table 1. Baseline characteristics

Study	Trial period	Setting/ country	Description of participants	Intervention(s) and comparator(s)	Duration of intervention, washout and total follow-up[a]	Mean age (SD)	Mean PSA (SD)	Pathological Gleason score n (%)	Pathological tumour stage n (%)
Aydogdu 2011	2006-2008	Single institution/ Turkey	Men aged < 65 years, preoperative full potency (IIEF-EF scores > 25 and answered SEP questions 2-3 'yes'), no history of penile plaques or previous penile surgery, clinical stage T1c or lower, PSA < 10 ng/mL and a biopsy Gleason score < 8 No exclusion criteria reported	Tadalafil 20 mg/day, 3 days/ week	Intervention: 6 months Washout: 5 months and 10-14 days Follow-up: 12 months	56.2	6.3	NR	NR
				No treatment		58.1	5.8	NR	NR
Kim 2016	2006-2012	Single institution/USA	Men with localised prostate cancer who	Nightly sildenafil 50 mg + 6 tablets of	Intervention: 12 months Washout:	54.3 (7.1)	5.1 (2.9)	3+3: 35 (74.5) 3+4: 6 (12.	T1c: 34 (72.3) T2a-T2c:

Table 1. Baseline characteristics *(Continued)*

							8) 4+3: 3 (6. 4) 4+4: 3 (6. 4)	12 (25.5) T3:1 (2.1)
			elected to go surgical treatment. These men had nor- mal preop- erative EF, defined as Sexual Health In- dex for Men score ≥ 21 and at > 1 erectile event with tip pe- nile rigid- ity > 60% and lasting > 10 min- utes in du- ration doc- u- mented by Rigiscan Men with known risk factors for ED and men with health conditions which are potential con- traindica- tions for PDE5I therapy were excluded from study. Men taking potent cy- tochrome	sildenafil 100 mg per month for on-de- mand use	1 month Follow-up: 13 months				

Table 1. Baseline characteristics (*Continued*)

			P450 inhibitors or alpha-adrenergic blocking agents (which could interact with sildenafil), or with known hypersensitivity to sildenafil or other ingredients of Viagra were also excluded	Matched placebo + 6 tablets of sildenafil 100 mg per month for on-demand use		53.7 (7.1)	4.2 (2.8)	3+3: 39 (83.0) 3+4: 5 (10.6) 4+3: 0 (0.0) 4+4: 3 (6.4)	T1c: 30 (63.8) T2a-T2c: 16 (34.0) T3: 1 (2.1)
McCullough 2010	NA	Multicentre/USA	Men aged < 70 years, sexually active in a stable relationship, with normal EF as determined by IIEF-EF questionnaire (IIEF-EF score ≥ 26) and scheduled to undergo bilateral nsRP were included Those men with Gleason Score > 7, PSA > 20 ng/mL and post-	Nightly sildenafil 50 mg	Intervention: 9 months Washout: 1 month Follow-up: 11 months	55.6 (5.9)	NR	NR	NR

Table 1. Baseline characteristics *(Continued)*

			oper-ative RT or ADT were excluded						
				Nightly in-traurethral alprostadil		56.8 (6.4)	NR	NR	NR
Montorsi 2008	2004-2007	87 centres across Europe, the US, Canada, and South Africa	Men, aged 18-64 years, in a heterosexual relationship, and scheduled to undergo bilateral NSRP within approximately 1mo of screening; an interest in resuming sexual activity as soon as possible after surgery; normal preoperative EF (IIIEF ≥ 26 at screening without the use of therapy or devices for the improvement of erections	Nightly vardenafil 10 mg (which could be decreased to 5 mg if required) plus on-demand placebo	Intervention: 9 months Washout: 2 months Follow-up: 13.5 months	57.4	NR	NR	NR

Table 1. Baseline characteristics *(Continued)*

			and no previous use of therapy or devices for ED; historical total PSA <10 ng/ml; Gleason tumour score $\leq$ 7 on biopsy; no tumour perforation of the prostate capsule were included Men who had residual prostate cancer or requirement for RT or adjuvant therapy; need for further surgery due to haemorrhage; and urethral catheter expected to be in place for $\geq$ 3 weeks due to anastomotic fistula; had con-						

Table 1. Baseline characteristics *(Continued)*

			traindication of PDE5I were excluded							
				Flexible-dose (starting at 10 mg with the option to titrate to 5 mg or 20 mg), on-demand vardenafil plus nightly placebo		56.8		NR	NR	NR
				Nightly placebo, on-demand placebo		57.1		NR	NR	NR
Montorsi 2014	2009-2011	Multicentre/Europe & Canada	Men aged < 68 years with normal EF who underwent nsRP for organ-confined, non-metastatic prostate cancer (Gleason Score ≤ 7, PSA ≤ 10 ng/mL). Post-surgical inclusion criteria included the devel-	Tadalafil 5 mg once daily	Intervention: 9 months Washout: 6 weeks Follow-up: 13.5 months	58.6 (5.07)		NR	NR	NR

Table 1. **Baseline characteristics** *(Continued)*

			opment of ED as measured by a participant-reported Residual Erection Function Score of ≤ 3 (= "penis is hard enough for penetration but not completely hard") were included Men 1) with history of ED 2) who received prior PDE5I treatments 3) who received neoadjuvant RT or a ADT or were due to receive adjuvant RT or ADT, 4) with history of prostatic surgery or prostatic physical treatments, 5) with							

Table 1. **Baseline characteristics** *(Continued)*

			history of diabetes mellitus, 6) with history of galactose intoler- ance, lapp lactase deficiency, or glucose- galactose malab- sorption 7) who have clinically significant renal in- sufficiency were excluded						
				Tadalafil 20 mg on- demand		57.5 (5. 91)	NR	NR	NR
				Placebo		57.6 (5. 69)	NR	NR	NR
Pace 2010	2005- 2009	Single cen- tre/Italy	Men with total PSA level < 10 ng/mL, Gleason score ≤ 7 on biopsy, no capsu- lar involve- ment, a nor- mal preop- erative EF assessed by an IIEF score ≥ 26, with- out the use of any therapy for improving erection	Silde- nafil 50 mg or 100 mg at night for 8 weeks	Inter- vention: 8 weeks Washout: 14 weeks Follow-up: 24 months	NR	5.5 (range 1.2-9.9)	6: 18 (90. 0%) 7: 2 (10. 0%)	T1b and T1c: 10 (50.0%), T2a: 9 (45. 0%), T2b: 1 (5.0%)
				No treatment		NR	6 (range 1. 8-8.9)	6: 18 (90. 0%) 7: 2 (10. 0%)	T1b and T1c: 9 (45. 0%); T2a:

Table 1. Baseline characteristics   (Continued)

									0%)	9 (45.0%); T2b: 2 (10.0%)
Padma-Nathan 2008	1999-2001	16 sites in North America, France, Belgium and Australia screened participants, and 11 sites in North America and France	Men aged 18-70 years, weighing 50-125 kg who had to had normal preoperative EF (combined score ≥ 8 on questions 3 and 4 of the IIEF questionnaire) and wish to return to sexual activity after surgery and be in a stable, heterosexual relationship for the past 6 months	Sildenafil 100 mg once nightly	Intervention: 36 weeks Washout: 8 weeks Follow-up: 48 weeks	55 ± 6/	NR	NR	NR	
				Sildenafil 50 mg once nightly		55 ± 6	NR	NR	NR	
				Placebo once nightly		57 ± 7	NR	NR	NR	
Pavlovich 2013	2006-2007	Single institution/USA	Men who chose to undergo nsRP who satisfied the following criteria: aged < 65 years, untreated prostate cancer < cT2b, biopsy	Nightly sildenafil 50 mg with on-demand placebo	Intervention: 12 months Washout: 4 weeks Follow-up: 13 months	54.3 (range 2-63)	4.7 (range 0.6-14)	6: 41 (82.0%) 7: 9 (18.0%)	T1c: 37 (74.0%), T2a: 13 (26.0%)	

Table 1. Baseline characteristics *(Continued)*

			Gleason score < 8, baseline IIEF-EF score ≥ 25/30, no PDE5I use, and presence of a steady sexual partner	On-demand silde-nafil 50 mg (maxi-mum 6 tablets/ month) with nightly placebo		53.6 (range 40-64)	5.1 (range 0.8-9.0)	6: 42 (84. 0%)/7: 8 (16.0%)	T1c: 40 (80.0%) ; T2a: 10 (20.0%)

ADT: androgen deprivation therapy; ED: erectile dysfunction; EF: erectile function; IIEF-EF: International Index of Erectile Function - Erectile Function domain; n: number of participants; NA: not applicable; NR: not reported; nsRP: nerve-sparing radical prostatectomy; PDE5I: phosphodiesterase Inhibitor 5 inhibitor; PSA: prostate-specific antigen; RT: radiotherapy; SD: standard deviation; SEP: Sexual Encounter Profile.

[a]Intervention started within 1 month after surgery in all included studies except Montorsi 2008 (14 days after surgery) and Montorsi 2014 (starting date of intervention: not defined).

Table 2. Participants disposition of included studies

Study	Intervention (s) and comparator (s)	Screened/ eligible (n)	randomised (n)	Analysed (effi-cacy; n)[a]	Analysed (safety; n)	Finishing trial (n (%))[b]
Aydogdu 2011	Tadalafil 20 mg/ day, 3 days/week	85/74	NR	32	NR	32
	No treatment		NR	33	NR	33
	Total		**74**	**65**	-	**65**
Kim 2016	Daily sildenafil 50 mg	100/97	49	47	47	37
	On-demand sildenafil 100 mg		48	47	47	37
	Total		**97**	**94**	**94**	**74**

Table 2. Participants disposition of included studies (*Continued*)

McCullough 2010	Daily sildenafil citrate 50 mg	227/212	73	59	NR	59
	Daily intraurethral alprostadil 125 µg (dose titration 250 µg)		139	97	NR	97
	Total		**212**	**156**	-	**156**
Montorsi 2008	Daily vardenafil 5-10 mg	997/628	210	143	207	137
	On-demand vardenafil 5-20 mg		208	149	204	141
	Placebo		210	153	206	145
	Total		**628**	**445**	**617**	**423**
Montorsi 2014	Daily tadalafil 5 mg	583/423	139	139	139	98
	On-demand tadalafil 20 mg		143	142	143	112
	Placebo		141	141	141	105
	Total		**423**	422	**423**	**315**
Pace 2010	Daily sildenafil 50 mg or 100 mg	NR/40	20	20	NR	20
	No treatment		20	20	NR	20
	Total		**40**	**40**	-	**40**
Padma-Nathan 2008	Daily sildenafil 100 mg	238/125	41	28	41	28
	Daily sildenafil 50 mg		41	23	40	23
	Placebo		43	25	42	25
	Total		**125**	**76**	**123**	**76**

Table 2. Participants disposition of included studies *(Continued)*

Pavlovich 2013	Daily sildenafil 50 mg with on-demand placebo	102/100	50	36	50	36
	On-demand sildenafil 50 mg (maximum 6 tablets/ month) with daily placebo		50	38	50	38
	Total		**100**	**74**	**100**	**74**
Grand Total			**1699**	**1307**	**1357**	**1223**

n: number of participants; NR: not reported.

[a] The number of participants in erectile function outcome.

[b] The number of participants finishing the trial at the end of the washout period or open-label treatment.

APPENDICES

Appendix 1. MEDLINE (via OvidSP)

1. Alprostadil/
2. "Prostaglandin E1".tw
3. alprostadil.tw
4. sildenafil.tw
5. viagra.tw
6. tadalafil.tw
7. cialis.tw
8. vardenafil.tw
9. levitra.tw
10. "penile rehabilitation".tw
11. "erect$ rehabilitation".tw
12. "vacuum therapy".tw
13. "vacuum erection device$".tw
14. VED.tw
15. "vacuum constriction device$".tw
16. VCD.tw
17. exp Phosphodiesterase 5 Inhibitors/
18. (Phosphodiesterase adj1 "5 Inhibit$").tw
19. (Phosphodiesterase adj1 "V Inhibit$").tw
20. (PDE5 OR PDE-5 OR "PDE 5") adj1 inhibit$.tw
21. PDE5-I.tw

22. Muse$.tw
23. ICI.tw
24. "intracavernosal injection$".tw
25. OR/1-24
26. exp Erectile Dysfunction/
27. "erectile dysfunction".tw
28. "erectile function".tw
29. ED.tw
30. impoten$.tw
31. poten$.tw
32. ((sex or sexual$) adj3 (function$ or dysfunc$ or satisf$ or problem$ or symptom$ or arous$ or activ$ or rehabilitation OR "quality of life")).tw
33. OR/26-32
34. exp Prostatectomy/
35. prostatectom$.tw
36. RP.tw
37. OR/34-36
38. exp Prostatic Neoplasms/
39. "prostat$ cancer".tw
40. "prostat$ neoplasm$".tw
41. CaP.tw
42. OR/38-41
43. 37 AND 42
44. 25 AND 33 AND 43

Appendix 2. MEDLINE via Embase

1. prostaglandin E1/
2. "Prostaglandin E1".tw
3. alprostadil.tw
4. sildenafil.tw
5. viagra.tw
6. tadalafil.tw
7. cialis.tw
8. vardenafil.tw
9. levitra.tw
10. "penile rehabilitation".tw
11. "erect$ rehabilitation".tw
12. "vacuum therapy".tw
13. "vacuum erection device$".tw
14. VED.tw
15. "vacuum constriction device$".tw
16. VCD.tw
17. exp Phosphodiesterase V Inhibitors/
18. (Phosphodiesterase adj1 "5 Inhibit$").tw
19. (Phosphodiesterase adj1 "V Inhibit$").tw
20. ((PDE5 OR PDE-5 OR "PDE 5") adj1 inhibit$).tw
21. PDE5-I.tw
22. Muse$.tw
23. ICI.tw
24. "intracavernosal injection$".tw
25. OR/1-24

26. exp Erectile Dysfunction/
27. "erectile dysfunction".tw
28. "erectile function".tw
29. ED.tw
30. Impotence/
31. impoten$.tw
32. poten$.tw
33. ((sex or sexual$) adj3 (function$ or dysfunc$ or satisf$ or problem$ or symptom$ or arous$ or activ$ or rehabilitation OR "quality of life")).tw
34. OR/26-33
35. exp Prostatectomy/
36. Prostatectom$.tw
37. RP.tw
38. OR/35-37
39. exp prostate tumor/
40. "prostat$ cancer".tw
41. "prostat$ neoplasm$".tw
42. CaP.tw
43. OR/39-42
44. 38 AND 43
45. 25 AND 34 AND 44

Appendix 3. The Cochrane Library via Wiley

1. MeSH descriptor: [Alprostadil] explode all trees
2. "Prostaglandin E1":ti,ab,kw
3. alprostadil:ti,ab,kw
4. sildenafil:ti,ab,kw
5. viagra:ti,ab,kw
6. tadalafil:ti,ab,kw
7. cialis:ti,ab,kw
8. vardenafil:ti,ab,kw
9. levitra:ti,ab,kw
10. "penile rehab*":ti,ab,kw
11. "erect* rehab*":ti,ab,kw
12. "vacuum therapy":ti,ab,kw
13. "vacuum erection device*":ti,ab,kw
14. VED:ti,ab,kw
15. "vacuum constriction device*":ti,ab,kw
16. VCD:ti,ab,kw
17. MeSH descriptor: [Phosphodiesterase 5 Inhibitors] explode all trees
18. (Phosphodiesterase next "5 Inhibit*"):ti,ab,kw
19. (Phosphodiesterase next "v Inhibit*"):ti,ab,kw
20. ((PDE5 or PDE-5 or "PDE 5") next inhibit*):ti,ab,kw
21. (PDE5-I):ti,ab,kw
22. muse*:ti,ab,kw
23. ICI:ti,ab,kw
24. "intracavernosal injection*":ti,ab,kw
25. #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 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26. MeSH descriptor: [Erectile Dysfunction] explode all trees
27. (erect* near/3 (dysfunction or function* or capacity or failure)):ti,ab,kw

28. ED:ti,ab,kw
29. impoten*:ti,ab,kw
30. poten*:ti,ab,kw
31. ((sex or sexual*) near/3 (function* or dysfunc* or satisf* or problem* or symptom* or arous* or activ* or rehabilitation or "quality of life")):ti,ab,kw
32. #26 or #27 or #28 or #29 or #30 or #31
33. MeSH descriptor: [Prostatectomy] explode all trees
34. Prostatectom*:ti,ab,kw
35. rp:ti,ab,kw
36. #33 or #34 or #35
37. MeSH descriptor: [Prostatic Neoplasms] explode all trees
38. "prostat* cancer":ti,ab,kw
39. "prostat* neoplasm*":ti,ab,kw
40. CaP:ti,ab,kw
41. #37 or #38 or #39 or #40
42. #36 and #41
43. #25 and #32 and #42

CONTRIBUTIONS OF AUTHORS

YP: drafted the protocol, undertook data collection, analysis and drafted the final review.

JHJ: undertook data collection, analysis and drafted the final review.

MS: conceptualised the review topic and drafted the protocol.

SO: developed and ran the search strategy.

CB: developed and ran the search strategy.

JB: undertook data collection,

PD: conceptualised the review topic, drafted the protocol and provided oversight.

DECLARATIONS OF INTEREST

YP: none.

JHJ: none.

MS: none.

SO: none.

CB: none.

JB: none

PD: none.

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- Minneapolis VAMC and UMN Department of Urology, USA.
Protected research time

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review was based on a published protocol with differences as described below (Philippou 2016).

- We removed the comparison of on-demand PDE5 versus placebo/no treatment as on-demand dosing is not an established method of penile rehabilitation.

- We divided time points into short-term and long-term instead of the time points outlined in the protocol of six, 12 and 24 months. Short-term time points were 12 months or less and long-term time point were greater than 12 months.

NOTES

We have based parts of the 'Methods' section of this protocol on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which has been modified and adapted for use by Cochrane Urology.