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PrescQIPP
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Tadalafil once daily

This bulletin focuses on tadalafil once daily. It provides the rationale for the choice of phosphodiesterase type 5 (PDE5) inhibitor if one is needed. It also recommends reviewing the treatment of current patients on comparatively expensive tadalafil products (i.e. generic 2.5mg strength and Cialis® branded products) with a view to switching to better value treatments, where clinically appropriate. Information on options for dose conversion in support of the change and potential switch savings are provided.

The PrescQIPP bulletin on 'Male sexual dysfunction' discusses the general use of PDE5 inhibitors in treating ED and makes recommendations regarding their prescribing in primary care. This bulletin focuses specifically on the use of PDE5 inhibitors for indications where tadalafil once daily might be considered.

The use of PDE5 inhibitors for the treatment of pulmonary arterial hypertension is not within the scope of this bulletin.

Recommendations

Erectile dysfunction

- Do not choose tadalafil once daily for treating ED on the assumption of favourable efficacy. Evidence suggests that tadalafil 5mg once daily has a similar efficacy to tadalafil 10mg or 20mg taken on-demand for ED.
- Choose the PDE5 inhibitor with the lowest acquisition cost (currently generic sildenafil), unless it is clinically unsuitable.
- Note that the price of some strengths of generic tadalafil has fallen to a level comparable with generic sildenafil (see table 1). This can make it a favourable alternative where sildenafil is not tolerated or is unsuccessful. Be aware that men who do not meet the NHS criteria for tadalafil should be offered a private prescription.
- For patients identified as non-responders to a PDE5 inhibitors it is important to re-counsel on proper use. Where appropriate, it may be worth trying a different PDE5 inhibitor as there is limited data to suggest that some patients might respond better to one PDE5 inhibitor than to another.
- Consider switching to generic sildenafil (or other low cost PDE5 inhibitor) for men receiving comparatively expensive PDE5 inhibitors such as tadalafil 2.5mg once daily or Cialis® branded products, where clinically appropriate.
- Periodically reassess the appropriateness of continued daily use of tadalafil in line with anticipated use by the patient. The product licence only supports consideration of daily dosing in men who anticipate frequent use (at least twice weekly).

Recommendations

Use after radical prostatectomy

- Men with prostate cancer should have early and ongoing access to specialist ED services. Those who experience loss of erectile function should be offered PDE5 inhibitors to improve their chance of spontaneous erections, in line with NICE guidance.
- All of the available PDE5 inhibitors are licensed for treating ED and can be prescribed on an NHS prescription after prostatectomy. None however, are specifically licensed for prevention of long term ED or penile rehabilitation after prostatectomy.
- Guidelines from expert bodies advocate early initiation of pro-erectile treatment after radical prostatectomy.
- There is a good scientific rationale for the use of PDE5 inhibitors for penile rehabilitation after radical prostatectomy and a number of randomised controlled trials (RCTs) and meta-analysis have investigated this subject. However the clinical evidence has limitations and is conflicting.
- In the absence of robust evidence favouring a particular PDE5 inhibitor treatment regimen, local policy makers may advocate choosing a lower cost option where clinically appropriate. Consultation with local stakeholders including urology specialists is needed.
- Organisations considering a review of prescribing should ensure that the process and switching methodology is agreed locally by all key stakeholders including GPs, urology specialists and other relevant healthcare professionals.

Background

Tadalafil once daily is an item is poor value for money compared with available alternatives. This is particularly relevant to the 2.5mg strength and Cialis® branded products, which are many times more expensive than generic sildenafil or other strengths of generic tadalafil.

Rationale for restricting or avoiding once daily tadalafil

Erectile dysfunction and other indications for PDE-5 inhibitors

Four PDE5 inhibitors are licensed in the UK for the treatment of ED: avanafil, sildenafil, tadalafil and vardenafil.[1] ED has been defined as the persistent inability to attain and/or maintain an erection sufficient for sexual performance.[2] Erectile dysfunction is a very common disorder with a prevalence that increases steeply with age.[3] Where pharmacotherapy is indicated, PDE5 inhibitors are a first line treatment.[2,3]

All PDE5 inhibitors can be taken on demand for ED (i.e. prior to anticipated sexual activity) up to a maximum of once per day. Tadalafil (10mg or 20mg) should be taken at least 30 minutes prior to sexual activity, sildenafil approximately 60 minutes prior, vardenafil 25 to 60 minutes prior and avanafil 15 to 30 minutes prior.[1,4-7] Tadalafil has also been found to be suitable for once daily administration. It has a half-life of 17.5 hours.[4] This is approximately four times longer than sildenafil or vardenafil, and up to three times longer than avanafil.[5-7] Steady state tadalafil plasma concentrations are reached after approximately five days.[4] Avanafil, sildenafil and vardenafil are not licensed for continuous daily administration.[5-7]

Tadalafil once daily (2.5mg and 5 mg tablets) is licensed for ED in adult males. The product information states that in men who anticipate a frequent use of tadalafil (i.e. at least twice weekly) a once daily regimen with the lowest doses of tadalafil might be considered suitable, based on patient choice and the physician's judgement. In these patients, the recommended dose is 5mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5mg once a day based on

individual tolerability. The appropriateness of continued use of the daily regimen should be reassessed periodically.[4] This gives a potential advantage in that ED therapy could be taken without regard to timing of sexual activity, but conversely it does promote continuous use of a medication where it may not be necessary.

The tadalafil 5mg daily dose of tadalafil is also licensed for benign prostatic hyperplasia in adult men.[4]

PDE5 inhibitors have also been used with the aim of preserving erectile tissue health and maximising erectile function recovery after radical prostatectomy.[8] ED is a common complication after radical prostatectomy experienced by 25-75% of men.[3] The main pathophysiological mechanism behind this is considered to be damage to the cavernosal nerves and vascular injury, which can be affected even after nerve-sparing surgery.[8] This has led to the development of penile rehabilitation programmes, often using PDE5 inhibitors (including tadalafil), which aim to improve long-term erectile function after nerve-sparing surgery.[8] The intention is to promote re-oxygenation of the tissue in order to maximise the potential for cavernosal nerve repair and reduce penile fibrosis.[8,9] None of the available PDE5 inhibitors are specifically licensed for prevention of long term ED or penile rehabilitation after prostatectomy.[4-7]

National guidance

Erectile dysfunction

Since 1999 the provision of PDE5 inhibitors on NHS prescriptions in England has been subject to certain restrictions.[10,11] In 2014 the regulations were amended to remove the requirement for prescribers to restrict NHS prescribing of generic sildenafil to men with ED who meet defined criteria. Changes were also made to how those with severe distress can access treatment. The changes include the following:

- The availability of generic sildenafil tablets on the NHS 'for any person with ED, regardless of cause' does **not** apply.
- The other PDE5 inhibitors - branded sildenafil (e.g. Viagra®), vardenafil, tadalafil and avanafil can only be prescribed for those who meet NHS criteria (see below*). If a person does not meet these criteria, a private prescription can be offered.
- Patients who suffer severe distress as a result of ED can be treated in primary care. Where pharmacological treatment is also required, and a PDE5 inhibitor is suitable, generic sildenafil should be offered. Patients with severe distress for whom generic sildenafil is not effective or not tolerated, can be referred to secondary care for treatment and ongoing prescribing.[12]

*NHS criteria for provision of pharmacological treatment of ED on the NHS, excluding generic sildenafil, remain. These are:

- Patients suffering from any of the following:
  - Diabetes
  - Multiple sclerosis
  - Parkinson's disease
  - Poliomyelitis
  - Prostate cancer
  - Severe pelvic injury
  - Single gene neurological disease
  - Spina bifida
  - Spinal cord injury.
- Patients receiving treatment for renal failure by dialysis.

- Patients who have had the following surgery:
  - Prostatectomy
  - Radical pelvic surgery
  - Kidney transplant.
- Patients who were receiving NHS prescriptions for one of these drugs on 14th September 1998.[13]

Note that an enlarged prostate alone is not included in the clinical conditions list.

The changes were made following a significant reduction in the price of sildenafil after the expiry of patent protection for Viagra® in 2014. The restrictions continue to apply to branded Viagra® and other ED therapies such as alprostadil, avanafil, tadalafil and vardenafil. It should be noted that despite generic versions of tadalafil and vardenafil becoming available (resulting in varying degrees of price reduction) the restrictions have not been removed from these medicines at present.

Advice around the quantity of medication to prescribe remains unchanged at one treatment per week, based on research evidence in the 40-60 year age range. The prescribing doctor can prescribe more than one dose a week if it is considered clinically appropriate.[10]

Restrictions also apply to the prescribing of PDE5 inhibitors in Wales, Scotland and Northern Ireland. The same criteria for provision of pharmacological treatment of ED on the NHS apply as in England.[13-15] However, there are some notable differences to the guidance for Wales, Scotland and Northern Ireland:

- The availability of generic sildenafil tablets on the NHS 'for any person with ED, regardless of cause' does **not** apply.
- Avanafil is not listed as an option for prescribing where the NHS criteria are met.[13-15]
- The arrangements for prescribing in cases of severe distress vary.[15]

NICE has not published a clinical guideline on the management of ED, although some NICE guidelines make recommendations about identifying and managing ED in specific patient groups. NICE guidance states that, unless contraindicated, PDE5 inhibitors should be offered to men with isolated ED and type 1 diabetes (NG17) or considered to treat problematic ED in men with type 2 diabetes (NG28).[16,17]

NICE guidance on the diagnosis and management of men with prostate cancer (NG131) states that those having radical treatment or starting androgen deprivation therapy should have access to specialist ED services. Further, it states that men with prostate cancer who experience loss of erectile function should be offered PDE5 inhibitors to improve their chance of spontaneous erections.[18]

None of the NICE guidelines above discuss choice of PDE5 inhibitor or dosage regimens, other than to recommend that the PDE5 inhibitor with the lowest acquisition cost should be chosen (which is stated in both the type 1 and type 2 diabetes guidelines).[16,17] Generic sildenafil remains the lowest cost PDE5 inhibitor, although the difference compared with generic tadalafil has reduced (for most, but not all strengths - see costs on page 9).

Guidelines on the management of ED are available from the British Society for Sexual Medicine (BSSM) and from the European Association of Urologists. Both guidelines recommend PDE5 inhibitors as a first-line treatment.[2,3] This is due to their proven efficacy and safety both in non-selected populations of men with ED and in specific sub-groups (e.g. men with diabetes and those who have had a prostatectomy).[2]

Neither guideline specifies a first-line choice PDE5 inhibitor and both note the general lack of robust comparative data available.[2,3]

European guidance discusses the use of tadalafil once daily as an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be temporally linked. They advise periodic reassessment of the appropriateness of the continuous use of a daily regimen.[3]

The All Wales Medicines Strategy Group produced guidance on prescribing for ED in 2012. They recommended that once-daily preparations should only be considered in patients who anticipate frequent use of single dose preparations (i.e. at least twice- weekly) and that it should be based on the clinician's judgement.[19]

In 2009 the Scottish Medicines Consortium (SMC) accepted tadalafil 2.5mg and 5mg tablets for use in NHS Scotland for regular once daily administration in patients with ED responding to an on-demand regimen of tadalafil who anticipate frequent use (at least twice weekly). They stated that at this level of on-demand use, the low dose regular regimen would be expected to be cost-neutral overall. The SMC also stated that tadalafil represents an alternative to other PDE5 inhibitors, primarily for patients for whom the longer duration of action represents a significant advantage.[20] Since this decision was made, both sildenafil and tadalafil have become available generically at a greatly reduced cost, although a cost disparity is still apparent, particularly with regard to tadalafil 2.5mg. Twenty eight days treatment with tadalafil 2.5mg costs £30.31, compared with £1.93 for tadalafil 5mg.[13]

Present-day price comparisons of different PDE5 inhibitor options must therefore take these price changes into consideration (see costs on page 9). The costs of PDE5 inhibitor treatments must also be considered in context with second and third-line treatments, which are often more expensive, can be more invasive and involve referral to a specialist. Further information on such treatments is available in the PrescQIPP bulletin on 'Male sexual dysfunction'.

General prescribing points on PDE5 inhibitor

When initiating PDE5 inhibitors it is important to give clear instructions on their use. The most common causes of incorrect drug use are:

- Failure to use adequate sexual stimulation.
- Failure to use an adequate dose.
- Failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.[3]

Where treatment is unsuccessful it is important to re-counsel on proper use.[2,3] It is also worth checking that they have been using a licensed medication as there is a large counterfeit market in PDE5 inhibitors.[3]

Clinical strategies if the PDE5 inhibitor is being correctly used include:

- Optimal treatment of concurrent diseases and frequent re-evaluation for new risk factors.[2,3]
- Treatment of concurrent hypogonadism[2,3] (refer to endocrinology).[21]
- Trying a different PDE5 inhibitor.[2] Limited data suggest that some patients might respond better to one PDE5 inhibitor than to another.[3]
- More frequent dosing regimens. This could be achieved within the licence of any of the PDE5 inhibitors approved for ED by using them more frequently for anticipated sexual activity. It could also involve daily dosing of tadalafil 5mg, which the BSSM guideline authors state might be useful for the many couples that find on-demand therapy totally unacceptable.[2]

The BSSM advice that patients be exposed to a minimum of four (preferably eight) of the highest tolerated dose of at least two drugs (taken sequentially, not concurrently) with adequate sexual stimulation. Patients should be followed up, ideally within six weeks of commencing therapy.[2]

More information about PDE5 inhibitors and their use can be found in the PrescQIPP bulletin on 'Male sexual dysfunction'.

Prevention of long-term ED or penile rehabilitation after prostatectomy

NICE guidance states that men with prostate cancer who experience loss of erectile function should be offered PDE5 inhibitors to improve their chance of spontaneous erections.[18] NICE highlighted the need for further research into the timing and effectiveness of treatments for ED after all treatments for prostate cancer.[22]

Guidelines from the BSSM discuss a number of studies investigating early use of daily PDE5 inhibitors after radical prostatectomy. They recommend that pro-erectile therapy should be prescribed as early as possible after radical prostatectomy although specific drug treatment recommendations for this group are not made.[2] The authors refer to the availability of UK consensus recommendations for the treatment of post-surgical ED, published by a group of experts in 2014.[9] These recommendations, which consider data from a literature review along with recommendations from an expert panel, advocate early initiation of PDE5 inhibitor after nerve-sparing surgery, but not after non-nerve sparing surgery. Various PDE5 inhibitor dosing options are outlined, including daily dosing, on-demand dosing or a combination of both, with or without concurrent vacuum erection device use.[9]

Guidance from the European Association of Urology similarly discusses the rationale and evidence for penile rehabilitation. They recommend that pro-erectile treatments should start at the earliest opportunity after radical prostatectomy/pelvic surgery and other curative treatments for prostate cancer but acknowledge the evidence supporting this recommendation is weak. Furthermore, they state that data are inadequate to support the use of any specific regimen for penile rehabilitation after radical prostatectomy.[3]

Benign prostatic hyperplasia (BPH)

Generic and branded tadalafil 5mg once daily are the only PDE5 inhibitor licensed for treating the signs and symptoms of BPH. It should be noted that the 2.5mg dose of tadalafil is not licensed for this indication as efficacy has not been demonstrated.[4,23-25]

NICE guidance on the management of lower urinary tract symptoms (LUTS) in men (CG97) states that PDE5 inhibitors should not be offered solely for the purpose of treating LUTS in men, except as part of a RCT. The current evidence for PDE5 inhibitors in this indication includes men with LUTS and ED. Therefore the standing Committee that updated the guideline in 2015 decided that it was not appropriate to make a recommendation about the routine use of PDE5 inhibitors in clinical practice. They stated that more evidence is needed to enable a recommendation to be made on the use of PDE5 inhibitors in all men with LUTS, including those without ED.[26] Surveillance of CG97 in 2019 identified new evidence in relation to tadalafil and LUTS,[27] including a Cochrane review.[28] A decision to update CG97 was made but the section on drug treatment (including tadalafil) was not recommended for updating as the new evidence was considered unlikely to change guideline recommendations.[27]

In 2013 a NICE Technology Appraisal on the use of tadalafil for the treatment of symptoms associated with BPH was terminated due to non-submission of supporting evidence from the manufacturer.[29] The Scottish Medicines Consortium and the All Wales Medicines Strategy Group were also unable to recommend tadalafil for this indication for the same reason.[30,31] Use of daily tadalafil for this indication is not considered further here.

Clinical Effectiveness

Erectile dysfunction

Randomised placebo-controlled trials of individual PDE5 inhibitors have shown them to be effective interventions for ED.[3,32,33] The paucity of meaningful head-to-head trials of PDE5 inhibitors in ED makes assessment of comparative efficacy difficult. In their 2022 guideline update, the European Association

of Urology acknowledge this evidence gap, stating that to date, no data are available from double or triple-blind multicentre studies comparing the efficacy and/or patient preference for the most-widely available PDE5 inhibitors (sildenafil, tadalafil, vardenafil, and avanafil).[3]

Data from several systematic reviews with meta-analysis are available.[34-39] They are comprised mostly of placebo-controlled trials, although some head-to-head studies are included. Two of these reviews indicate similar efficacy for sildenafil, tadalafil and vardenafil,[34,36] whilst others suggest greater efficacy with some pairwise comparisons.[35,37-39] Such suggestions should be interpreted cautiously due to limitations of the data, and in the absence of good quality comparative trials.[35,40-42]

The European Association of Urology note that two of the network meta-analyses suggest that ED patients who prioritise high efficacy should use sildenafil 50mg whereas those who optimise tolerability should initially use tadalafil 10mg.[3,38,39]

The current evidence therefore remains compatible with the approach recommended in NICE guidance of selecting the PDE5 inhibitor with the lowest acquisition cost unless there are clinical reasons to prefer another.[16,17]

To support the hypothesis that low dose, once daily tadalafil may be a safe and effective treatment in men with ED, initial randomised placebo-controlled trials investigating tadalafil 2.5mg and 5mg daily versus placebo (n=287, 24 weeks), and 5mg and 10mg daily versus placebo (n=268, 12 weeks) were undertaken.[43] A third study (n=298, 12 weeks) exclusively enrolled men with type 1 or type 2 diabetes and randomised them to treatment with tadalafil 2.5mg or 5mg daily or placebo.[44] The primary efficacy end points in the studies were the International Index of Erectile Function (erectile function domain) (IIEF-EF) to assess the severity, and the number of 'yes' responses to the Sexual Encounter Profile (SEP) Questions 2 (successful penetration) and 3 (successful intercourse). In all three studies tadalafil significantly and clinically improved erectile function as measured by the three primary efficacy measures.[43,44]

Head-to-head comparisons of on-demand and once daily therapies were not conducted in these studies.[43,44] It was noted that the efficacy associated with once daily tadalafil 5mg in the studies with a mixed population was consistent with those of historical on-demand studies evaluating tadalafil 10mg and 20mg.[43] The results of an integrated analysis that pooled data from tadalafil on-demand and once-daily placebo-controlled studies support this observation.[45] However, there remains a lack of robust head-to-head data from double-blind RCTs comparing on-demand tadalafil treatment with a daily dose of 2.5mg or 5mg of tadalafil in the general ED population.

Use after radical prostatectomy

A Cochrane review (updated in 2018) investigating penile rehabilitation for postprostatectomy ED is available.[8] It included eight RCTs with 1699 participants across three comparisons (two of which are discussed here). The individual studies included in the review were relatively small (largest n=628). Treatment duration varied between eight weeks and 12 months, with follow up of between 48 weeks and 24 months. Primary outcomes included self-reported potency and erectile function measured by validated questionnaires. Key findings were:

- Scheduled PDE5 inhibitors (e.g. daily or twice a week) versus placebo or no treatment, may have little or no effect on short-term (up to 12 months) self-reported potency and short-term erectile function as assessed by a validated questionnaire. No long-term data was located for these outcomes.
- For scheduled PDE5 inhibitors versus on-demand PDE5 inhibitors, daily PDE5 inhibitor appears to result in little to no difference in both short-term and long-term (greater than 12 months) results for either self-reported potency or erectile function.

The findings of the review were based on mostly very-low and some low-quality evidence, so are very uncertain. The quality of the evidence was downgraded due to study limitations (such as risk of bias), indirectness and imprecision.[8]

The authors concluded that penile rehabilitation strategies consisting of scheduled PDE5 inhibitor use following radical prostatectomy may not promote self-reported potency and erectile function any more than on-demand use. They state that this underscores concern that scheduled use may have no advantage over on-demand use in this context, but likely increase the costs of treatment. They call for better quality research on rehabilitation strategies focused on patient-important outcomes.[8]

The Cochrane review authors note that their findings appear to be at odds with several other systematic reviews on this subject. They cite several reviews that have reported significant improvements in the IIEF-EF scores with PDE5 inhibitors as compared with placebo or no treatment. One potential reason they propose for the apparent discrepancy relates to differences in study inclusion criteria. For a study to be included in the Cochrane review, 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 PDE5 inhibitor, the same dose and dosing schedule should have been used. This was to ensure a fair comparison was being made, which the authors consider to be a critical methodological aspect of their review. They state that several other published reviews chose to include all existing trials for a given comparison irrespective of whether they provided a fair comparison at the time of outcome assessment.[8]

A number of other meta-analyses have addressed the use PDE5 inhibitors as supportive therapy to rehabilitate erectile function after nerve-sparing radical prostatectomy. Those that pre-date the Cochrane review include four meta-analyses published in 2016 and 2017.[46-49] They mostly included studies comparing PDE5 inhibitors in various dosing regimens to placebo or no treatment. As in the Cochrane review, the individual studies were relatively small individually with a treatment duration of up to 13 months. There was considerable overlap in the studies included in all the above meta-analyses but none included exactly the same mix of studies.

In contrast with the Cochrane review, the findings of the meta-analyses by Cui 2016, Qiu 2016 and Tian 2017 generally favoured PDE5 inhibitors. They reported statistically significant improvements in the IIEF-EF scores with PDE5 inhibitors as compared with placebo or no treatment.[46,48,49] It should be noted that these three studies were amongst those whose methodology was questioned by the Cochrane review authors, as discussed above.

The fourth meta-analysis made a distinction between the use of PDE5 inhibitors for drug-assisted recovery of erectile function and the rehabilitative effect of PDE5 inhibitors on drug-unassisted erectile function recovery.[47] The primary assessment measures were:

- Whether drug-assisted erectile function recovery was achieved after PDE5 inhibitor treatment.
- Whether erectile function recovery was influenced by PDE5 inhibitor treatment modality (on-demand vs. daily) or by PDE5 inhibitor half-life or PDE5 inhibitor active ingredients and time from surgery to the prescription of PDE5 inhibitors.
- Whether PDE5 inhibitors have a rehabilitative effect on erectile function by measuring unassisted recovery of erectile function. 'Unassisted recovery of erectile function' refers to recovery of spontaneous erectile function subsequent to completion of a course of PDE5 inhibitors.

They found PDE5 inhibitors to be effective in achieving drug-assisted recovery of erectile function. On-demand treatment with PDE5 inhibitors was significantly better than daily treatment in recovering drug-assisted erectile function. This effect was maintained even when the drugs were stratified according with half-life. Tadalafil was equally effective when used both on-demand and daily. The pooled data did not demonstrate a beneficial effect of PDE5 inhibitor use on recovery of drug-unassisted erectile function.[47]

At least five further meta-analyses (four include a systematic review) on this subject have been published since the Cochrane review.[50-54] All are supportive of PDE5 inhibitors in this setting, reporting favourable results for at least some PDE5 inhibitor regimens compared with placebo. Although

published more recently, the meta-analyses are generally not based on newer studies and mainly include the same primary studies that appear in the earlier meta-analyses discussed above, or other studies from that period. An exception to this is the inclusion of a more recent RCT (published 2018, n=120) comparing early vs. delayed initiation of sildenafil in the meta-analysis by Motlagh 2021.[52]

Several of the meta-analyses discussed above suggest greater efficacy with particular treatment regimens. Some found regular dosing to be more effective than on demand dosing,[48,52] with others concluding the opposite.[47,50] Some meta-analyses suggest the evidence favours a specific drug but they do not all concur in their choice.[47,48,50,52] No head-to-head data comparing the different drugs is included in any of the meta-analyses, so such comparisons are indirect.

Several of the meta-analyses above include other interventions for ED after radical prostatectomy, such as alprostadil and vacuum erection devices. Although not discussed here, other treatments for ED are included in the PrescQIPP bulletin on 'Male sexual dysfunction'.

Evidence summary

- PDE5 inhibitors are an effective intervention for ED.[3,32,33]
- It is unclear if efficacy for ED varies between PDE5 inhibitors as the results of systematic reviews differ:[34-39]
  - Some reviews indicate similar efficacy for sildenafil, tadalafil and vardenafil,[34,36]
  - Others suggest greater efficacy with some pairwise comparisons.[35,37-39]
  - Two network meta-analyses suggest sildenafil 50mg for those who prioritise high efficacy and tadalafil 10mg initially for those who optimise tolerability.[38,39]
  - Data from double or triple-blind multicentre comparative trials are lacking.[3]
- Data from placebo-controlled studies suggests that tadalafil 5mg once-daily has a similar efficacy to tadalafil 10mg or 20mg given on-demand.[43,45] However, there remains a lack of robust head-to-head data from double-blind RCTs in men with ED to confirm this.
- There is a good scientific rationale for the use of PDE5 inhibitors for penile rehabilitation after radical prostatectomy and a number of RCTs and meta-analysis have investigated this subject. However, a Cochrane review raises concerns about the quality of the available evidence and the methodology of a number of other meta-analyses on this subject.[8]
- Despite considerable overlap in the studies included in meta-analyses investigating PDE5 inhibitors after radical prostatectomy, their findings are sometimes conflicting.
- The meta-analyses mostly favour PDE5 inhibitors after radical prostatectomy.[46,48-54]
- However, benefits were not observed where meta-analyses focused specifically on rehabilitative effects on erectile function after completion of a course of PDE5 inhibitors (i.e. no improvement in drug-unassisted erectile function)[47] or when comparing daily PDE5 inhibitors with on demand use, placebo or no treatment.[8]
- Whilst the current evidence does not agree on a rehabilitative effect on erectile function after completion of a course of PDE5 inhibitors, it is supportive more generally of the use of PDE5 inhibitors for ED after radical prostatectomy.
- It is not possible to reliably conclude which regimens offer the best treatment outcomes after radical prostatectomy based on the current clinical evidence.

Costs

There is a significant difference in cost between the 2.5mg dose of tadalafil once daily and other available PDE5 inhibitors, particularly generic sildenafil. The cost difference for the 5mg dose of tadalafil one daily is much less pronounced. Table 1 below illustrates the costs.

Table 1. PDE5 inhibitor costs per month based on four doses per month or 28 doses of tadalafil 2.5mg and 5mg once daily

PDE5 inhibitor	Pack size	Cost per 28 days based on four doses a month or once daily dosing of tadalafil[13,14,55]
Sildenafil 25mg	4	£0.77 (£1.01 Scotland)
Sildenafil 50mg	4	£0.83 (£1.03 Scotland)
Sildenafil 100mg	4	£0.90 (£1.08 Scotland)
Tadalafil 10mg	4	£0.96 (£0.96 Scotland)
Tadalafil 20mg	4	£1.07 (£1.07 Scotland)
Tadalafil 5mg *daily dose*	28	£1.93 (£1.95 Scotland)
Vardenafil 5mg	4	£6.35
Vardenafil 20mg	4	£5.06 (£6.12 Scotland)
Avanafil 50mg (Spedra®)	8	£9.85
Vardenafil 10mg	4	£10.68
Avanafil 50mg (Spedra®)	4	£10.94
Viagra Connect® (sildenafil) 50mg tablets	8	£10.94
Viagra Connect® (sildenafil) 50mg tablets	4	£12.50
Avanafil 100mg (Spedra®)	8	£13.13
Viagra Connect® (sildenafil) 50mg tablets	2	£13.74
Avanafil 100mg (Spedra®)	4	£14.08
Levitra® (vardenafil) 10mg	4	£14.78
Viagra® (sildenafil) 25mg tablets	4	£16.59
Viagra® (sildenafil) 25mg tablets	8	£16.60
Avanafil 200mg (Spedra®)	8	£19.70
Viagra® (sildenafil) 50mg tablets	4	£21.27
Viagra® (sildenafil) 50mg tablets	8	£21.27
Avanafil 200mg (Spedra®)	4	£21.90
Viagra® (sildenafil) 100mg tablets	8	£23.50
Viagra® (sildenafil) 100mg tablets	4	£23.50
Levitra® (vardenafil) 20mg	4	£24.30
Cialis® (tadalafil) 20mg	4	£28.88
Cialis® (tadalafil) 10mg	4	£28.88
Cialis® (tadalafil) 20mg	8	£28.88
Tadalafil 2.5mg *daily dose*	28	£30.31
Cialis® (tadalafil) 5mg *daily dose*	28	£54.99
Cialis® (tadalafil) 2.5mg *daily dose*	28	£54.99

Note: A variety of dosage regimens (both 'on-demand' and regular) have been used after radical prostatectomy, several of which fall outside the examples in Table 1. Regular regimens in clinical trials are not limited to the use of tadalafil 5mg daily, and have included a variety of drugs and doses, e.g. tadalafil 20mg three times a week, sildenafil 50mg daily. Such regimens would result in costs higher than those listed in Table 1, which uses four doses per month for comparison (other than for tadalafil daily). Ensure that the dosing frequency used locally is factored in when comparing the costs of different regimens.

Prescribing review and switching options

Local policy should outline which PDE5 inhibitors should be prescribed and the indications for which they can (and cannot) be NHS prescribed. For unlicensed indications, such as penile rehabilitation after prostatectomy, consideration as to who initiates, continues and reviews treatment is also needed. This information should be easily accessible to prescribers, e.g. stated in the local medicines formulary.

See the PrescQIPP bulletin on 'Male sexual dysfunction' and associated resources for an audit on PDE5 inhibitors.

Organisations considering a review of prescribing should ensure that the process and switching methodology is agreed locally by all key stakeholders including GPs, urology specialists and other relevant health professionals.

For erectile dysfunction:

- **New patients – sildenafil**
  Commence on the PDE5 inhibitor with the lowest acquisition cost (currently generic sildenafil) unless it is clinically unsuitable.
- **Sildenafil is not tolerated or successful**
  The price of some strengths of generic tadalafil has fallen to a level comparable with generic sildenafil (see table 1). This can make it a favourable alternative where sildenafil is not tolerated or is unsuccessful. Be aware that men who do not meet the NHS ED criteria for tadalafil should be offered a private prescription.
- **Patient is on a comparatively expensive PDE5 inhibitor**
  Consider switching to generic sildenafil (or a low cost tadalafil product if this is more suitable) for men receiving PDE5 inhibitors that are comparatively expensive, where clinically appropriate. Comparatively expensive PDE5 inhibitors include tadalafil 2.5mg daily and all branded prescribing (see table 1 for full list of costs).
- **Dose to prescribe when switching**
  The lack of head-to-head studies means that a pragmatic approach to choosing comparable doses will be needed when switching. Unless a lower starting dose is indicated, prescribers may prefer to switch to sildenafil 50mg. Titrate the dose up or down according to the response and tolerability, in accordance with the product information for sildenafil.[5]
- **Patient factors**
  It is important to undertake case by case reviews and consider all relevant patient factors. This includes previously tried treatments. If more costly PDE5 inhibitors are being used successfully after failure of lower cost options, the medication costs should be considered in context with second and third-line treatments. These are often more expensive, can be more invasive and involve referral to a specialist.

For use after radical prostatectomy:

- For penile rehabilitation after prostatectomy, the clinical evidence has limitations and is conflicting. In the absence of robust evidence favouring a particular treatment regimen, local policy makers may advocate choosing a lower cost regimen i.e. one based on generic sildenafil or generic tadalafil (excluding tadalafil 2.5mg), where clinically appropriate. Consultation with local stakeholders including urology specialists is needed.
- A variety of dosage regimens have been used after radical prostatectomy, several of which fall outside the examples in Table 1. Ensure that the dosing frequency is factored in when comparing the costs of different regimens.
- The quantity of PDE5 inhibitor required per month for patients after radical prostatectomy will depend on the regimen(s) agreed locally. They are likely to require more than the limited quantities,

(e.g. four doses per month) that GPs are accustomed to prescribing for ED. The regulations allow for more than one dose a week to be prescribed if it is considered clinically appropriate.[10] GPs should be supported in this by ensuring that local guidance is clear regarding dosing and recommended quantities. Guidance on how long this phase of treatment should last, i.e. at what point treatment should revert to usual care for ED, should also be included.

For LUTS:

- Review the treatment of men receiving a PDE5 inhibitor solely for the purpose of treating LUTS (only tadalafil 5mg daily is licensed), unless it is as part of an RCT. Prescribers should use their judgement when considering whether to continue tadalafil 5mg where there is a perceived benefit and treatment is well tolerated. The 2.5mg dose is not licensed for this indication so should not be used.

Costs and savings

Based on prescribing data from NHSBSA (December 2022 to February 2023) and Public Health Scotland (November 2022 to January 2023).

Generic tadalafil once daily 2.5mg costs £30.31 for 28 days treatment. Branded Cialis® tablets (both 2.5mg and 5mg strengths) are more expensive, costing £54.99 for 28 days.

Generic tadalafil 5mg is less costly (£1.93 (£1.95 Scotland) for 28 days), but still costs more than on demand generic sildenafil 25-100mg (£0.77-£0.90 (£1.01-£1.08 Scotland) for 4 doses) or on demand generic tadalafil 10-20mg (£0.96-£1.07 for four doses). [13,14,55]

Table 2 illustrates tadalafil tablets used for once daily dosing (generic and Cialis® brand 2.5mg and 5mg tablets) prescribed as a percentage of all PDE5 inhibitors, annual costs and 12 months cost avoidance figures by switching to an on-demand PDE5 inhibitor costing <£1.50 per 28 days for England, Wales and Scotland. Cost avoidance figures are also expressed as cost avoidance per 100,000 population.

Table 2. Tadalafil for daily use cost and saving figures

Tadalafil for daily dosing	England	Wales	Scotland
Percentage of all PDE5 inhibitor prescriptions	5.1%	11.6%	10.3%
Annual cost	£1,415,804	£195,768	£239,604
12 months cost avoidance by switching to PDE5 inhibitors costing <£1.50 per 28 days	£1,345,014	£185,979	£227,623
Savings per 100,000 population by switching to PDE5 inhibitors costing <£1.50 per 28 days	£2,460		

Summary

Tadalafil once daily (2.5mg and 5mg tablets) is licensed for ED in men who anticipate a frequent use of tadalafil (i.e. at least twice weekly).[4] This gives a potential advantage in that ED therapy could be taken without regard to timing of sexual activity. However, the available evidence does not suggest that taking tadalafil on a daily basis gives better results compared with on-demand treatment in the general ED population.[43,45] This should be considered in the context of treatment costs, with the 2.5mg strength of tadalafil costing approximately 40 times more than treatment with generic sildenafil on-demand.[13] Branded tadalafil (Cialis® 2.5mg and 5mg) is even more expensive,[55] and should be reviewed where possible.

The current clinical evidence does not agree on a rehabilitative effect on erectile function after completion of a course of PDE5 inhibitors (including tadalafil once daily) post-radical prostatectomy,[8,47] and no PDE5 inhibitor is licensed specifically for this purpose.[4-7] However the evidence is supportive more generally of the use of PDE5 inhibitors for ED after radical prostatectomy.[46-54]

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Additional PrescQIPP resources

Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-322-tadalafil-once-daily/
Implementation tools	
Data pack	https://data.prescqipp.info/?pdata.u/#/views/B322_Tadalafiloncedaily/FrontPage?:iid=1

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