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Male sexual dysfunction: Management of erectile dysfunction and premature ejaculation

This bulletin reviews the place in therapy of phosphodiesterase 5 (PDE5) inhibitors, other treatments for erectile dysfunction (ED) and treatments for premature ejaculation (PE). It offers guidance and support material for organisations considering reviewing these treatments. It should be read in conjunction with Bulletin 322: Tadalafil once daily.

In England, Wales, Scotland and Isle of Man, approximately £21 million is spent annually on the prescribing of these products [NHSBSA May-Jul 23 and Public Health Scotland Jan-Apr 23]. More than 88% of this spend is attributable to PDE5 inhibitors and alprostadil.

Medicines optimisation projects can support quality improvement, value and sustainability in healthcare. In the management of male sexual dysfunction, such projects focus on appropriate treatment choices, effective use of products, minimisation of waste and the promotion of self care where appropriate.

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

Recommendations

Erectile dysfunction

PDE5 inhibitors

- Choose the PDE5 inhibitor with the lowest acquisition cost (currently generic sildenafil), unless clinically unsuitable, and give clear instructions on their use including how long between taking the dose and attempting sexual intercourse. Follow up within 6 weeks of starting treatment.
- Do not classify someone as a non-responder until they have trialed at least four (but preferably eight) doses of the highest tolerated dose with adequate sexual stimulation on each occasion.
- Consider trying a different PDE5 inhibitor in non-responders, as limited data suggests that some patients might respond better to one PDE5 inhibitor than to another. Generic tadalafil 10mg or 20mg tablets are currently the next least costly PDE5 inhibitor preparations after generic sildenafil tablets. Note that tadalafil 2.5mg strength tablets and Cialis® brand tablets are comparatively more costly PDE5 inhibitors.
- Consider advising on purchasing sildenafil or tadalafil over the counter if appropriate for the individual.

Vacuum erection assistance devices (VEDs)

- Only patients who meet NHS criteria for treatment can receive VEDs and consumables on an NHS prescription. Those not meeting NHS criteria would need to purchase these products.
- VEDs are a potential first-line option for ED, particularly in well-informed patients with infrequent sexual intercourse and in patients with comorbidities requiring non-invasive, drug-free management.

Recommendations

- When developing pathways that include VEDs, consider factors to optimise the chance of successful treatment, for example the route of supply of VEDs and consumables, such as constrictor rings, and how people will be supported, such as with initial training and ongoing assistance if needed.
- Prescribing VEDs should be undertaken by a specialist with knowledge of the appliances and in line with the service level agreement for prescribing in primary or secondary care.
- Do not add the VED pump or the consumables to repeat prescriptions.

Alprostadil

- Alprostadil treatments are a second-line option that may be considered where PDE5 inhibitors are contraindicated or ineffective and should only be initiated under a specialist.

Premature ejaculation

- Be aware that European guidance recommends pharmacotherapy with dapoxetine or lidocaine/prilocaine spray (the latter is not licensed in the UK) as a first line treatment for lifelong PE. For acquired PE addressing the underlying cause is recommended. Psychological/behavioural therapies in combination with pharmacological treatment may also be appropriate. Other local anaesthetics and off-label selective serotonin reuptake inhibitors (SSRIs) are alternative pharmacological options.
- Agree locally which treatments to offer for PE within the treatment pathway based on effectiveness, licensed use, adverse effects and cost.
- Ensure that patients are aware that local anaesthetic preparations are available without a prescription:
  - A spray licensed for PE containing lidocaine 9.6% w/w (Stud 100 Spray) is available to purchase over the counter (OTC) as a Pharmacy medicine.
  - Condoms containing benzocaine and lidocaine are commercially available.
- Be aware that dapoxetine is the only SSRI licensed for the treatment of men with a clinical diagnosis of PE and has the largest body of evidence supporting efficacy in PE, although the effects on intravaginal ejaculatory latency time (IELT) are relatively modest. The adverse effects are similar to other SSRIs, however there are additional concerns regarding orthostatic hypotension and syncope.
- Appreciate that discontinuation rates as high as 90% after two years have been reported with dapoxetine in PE and it has a high cost compared to other SSRIs.
- Explain to patients that SSRIs (except dapoxetine) are an 'off-label' use for PE so that they can make an informed decision. Document the discussion in the patient's notes. Paroxetine appears to increase IELT more than other SSRIs.
- Be aware of the risk of suicidal ideation or suicide attempts, if prescribing SSRIs to young adolescents aged 18 years or younger with PE, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation.
- Warn patients of the risk of withdrawal syndrome if SSRIs are stopped suddenly.

Erectile dysfunction

Background

Erectile dysfunction has been defined as the persistent inability to attain and/or maintain an erection sufficient for sexual performance.[1] It is a very common disorder, with a prevalence that increases

steeply with age.[2] Causes can be organic and/or psychogenic. ED can also be a drug induced side-effect of some medications e.g. antihypertensives, antipsychotics, and antidepressants.[3]

The risk factors for ED are similar to those for cardiovascular disease and include obesity, diabetes, dyslipidaemia, metabolic syndrome, hypertension, endothelial dysfunction, lack of exercise, and smoking.[3] Erectile dysfunction increases the risk of cardiovascular disease. All men with unexplained erectile dysfunction should be evaluated for the presence of cardiovascular risk factors and any identified risk should be addressed.[4]

Increasing awareness of convenient ED treatments has led to more men seeking medical help. This provides an opportunity to improve the early detection of these associated conditions and address appropriate lifestyle and risk factor modifications.[5]

Where pharmacotherapy for ED is indicated, PDE5 inhibitors are a first-line treatment[1,2] and should be considered for men not at high cardiac risk from sexual activity.[3] Four PDE5 inhibitors are licensed in the UK: sildenafil, tadalafil, vardenafil and avanafil.[4] All can be taken on demand for ED (i.e. prior to anticipated sexual activity) up to a maximum of once per day.[4] Tadalafil is also licensed for once daily administration at a dose of 5mg (reduced to 2.5mg if necessary for tolerability) in men who anticipate a frequent use of tadalafil (i.e. at least twice weekly).[6-8]

Vacuum erection devices (VEDs) are an alternative first-line treatment option. A cylinder is placed over the penis, air is pumped out with an attached manual or battery-powered pump, and the resulting penile tumescence (swelling/erection) is maintained by a constriction ring around the base of the penis. Although the principle of VEDs is simple, initial one-to-one supervised instruction is important.[1]

Potential second-line treatment options include intracavernosal alprostadil injections (Caverject® or Viridal®) or intraurethral alprostadil, medicated urethral system for erection (MUSE®).[1,3] A topical alprostadil cream (Vitaros®) is also available.[4,9] Penile prosthesis is a third-line treatment.[1,3] Second and third line treatment options may be offered after referral to a urology specialist.[3]

Compared with generic PDE5 inhibitors, the alternative treatments options for ED are often more expensive, more invasive and involve referral to a specialist.

National Guidance

The National Institute for Health and Care Excellence (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.

Guidelines on the management of ED are available from the British Society for Sexual Medicine (BSSM, published in 2017)[1] and from the European Association of Urologists (EAU, published in 2023).[2]

Before considering treatment options for ED, cardiovascular risk should be assessed and categorised. Those at low cardiovascular risk can be managed in primary care and do not need cardiac testing or evaluation before the initiation or resumption of sexual activity. Men at high cardiac risk (or intermediate cardiac risk, depending on clinical judgement) should be advised to stop all sexual activity until specialist assessment, and a decision has been made that further cardiac assessment and management is needed, or it is safe to resume sexual activity.[3]

More information on how to assess men presenting with ED can be found in a summary from the BSSM called A practical guide on managing erectile dysfunction[5] and in the Clinical Knowledge Summary for ED.[3] CKS also describes how to assess cardiovascular risk in this context.[3]

ED usually responds well to a combination of lifestyle measures and drug treatment. Lifestyle measures include (where indicated) weight loss, smoking cessation, and reducing alcohol consumption.[3]

Bicycle riding for more than three hours per week has been described as an independent risk factor for ED. It has been postulated that interaction with the saddle may produce a neuropraxia, which is usually

reversible, or vascular endothelial injury and vasculogenic ED.[1] Advise men that regularly cycle for more than three hours a week to stop cycling for a trial period. If this is not possible advise them to use a properly fitted bicycle seat and ride with the seat in a suitable position.[3]

Testosterone deficiency and lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia can also be related to ED and should be considered in the assessment of men presenting with ED. Routine investigations for men presenting with ED should include a fasting serum total testosterone.[3,4] If hypogonadism is identified treatment with testosterone supplementation may be indicated (refer to endocrinology).[1]

PDE5 inhibitors

NICE guidelines on diabetes recommend that, unless contraindicated, PDE5 inhibitors should be offered to men with isolated ED and type 1 diabetes.[10] They should be considered to treat problematic ED in men with type 2 diabetes.[11]

For men with prostate cancer, NICE guideline (NG131) states that those having radical treatment or starting androgen deprivation therapy should have access to specialist ED services. Men that experience loss of erectile function should be offered PDE5 inhibitors to improve their chance of spontaneous erections.[12]

None of the NICE guidelines above discuss the 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).[10,11] Generic sildenafil remains the lowest cost PDE5 inhibitor, although the cost difference compared with generic tadalafil has narrowed somewhat (for the generic tadalafil 5mg, 10mg and 20mg tablets, but not the 2.5mg tablets or brand version Cialis® all strengths - see costs section).[4] This can make generic tadalafil 5mg, 10mg and 20mg tablets favourable alternatives where sildenafil is not tolerated or is unsuccessful. Men who do not meet the NHS criteria for tadalafil can be advised to purchase for self care or be offered a private prescription.

Guidelines from the BSSM and the EAU recommend PDE5 inhibitors as a first-line ED treatment. Neither guideline specifies a first-line choice PDE5 inhibitor and both note the general lack of robust comparative data available.[1,2] The EAU say that the choice of drug depends on frequency of intercourse (occasional use or regular therapy, three to four times weekly) and the patient's personal experience.[2]

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.[2]

Where treatment is unsuccessful it is important to re-counsel on proper use.[1,2] It is also worth checking that the patient has been using a licensed medication as there is a large counterfeit market in PDE5 inhibitors.[2]

Potential clinical strategies for non-responders who are using the treatment correctly include:

- Optimal treatment of concurrent diseases and frequent re-evaluation for new risk factors.[1,2]
- Treatment of concurrent hypogonadism (refer to endocrinology).[1-3]
- Trying a different PDE5 inhibitor.[1] Limited data suggest that some patients might respond better to one PDE5 inhibitor than to another.[2]
- 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 (2.5mg if 5mg not tolerated), which the guideline authors state might be useful for the many couples that find on-demand therapy totally unacceptable.[1]

Before classifying a person as a non-responder, the BSSM advise that they be exposed to a minimum of four (but 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.[1]

Table 1 outlines selected pharmacokinetic and clinical comparators, including the time each PDE5 inhibitor should be taken before sexual activity and effect of food intake.

Table 1.PDE5 inhibitor selected pharmacokinetic and clinical comparators for on-demand dosing

	Sildenafil tablets[13]	Tadalafil tablets[14]	Vardenafil tablets[15]	Avanafil tablets[16]
Maximum frequency	Once daily	Once daily	Once daily	Once daily
Time taken before sexual activity	60 minutes	At least 30 minutes	25-60 minutes	Approximately 30 minutes (50mg) or 15 to 30 minutes (100mg and 200mg)[17]
Tmax (time to peak concentration)	30-120 minutes (median 60 minutes)	120 minutes (median)	30-120 minutes (median 60 minutes)	30-45 minutes (median)
Time still able to produce erection post dose	Four to five hours	Up to 36 hours	Up to four to five hours	Up to six hours (longer in some people)[18]
Effect of food intake	Rate of absorption is reduced when taken with food (mean delay in Tmax of 60 minutes)	Not affected	Rate of absorption is reduced when taken with a high fat meal (median delay in Tmax of 60 minutes)	Rate of absorption is reduced when taken with a high fat meal (mean delay in Tmax of 1.25 hours)

Tadalafil once daily (5mg and 2.5mg) is licensed for ED in men who anticipate a frequent use of tadalafil (i.e. at least twice weekly). The recommended dose is 5mg, with 2.5mg only recommended where tolerability is an issue.[6-8] The cost of treatment with tadalafil 5mg daily has greatly reduced now that generics are available. However, the generic 2.5mg strength and Cialis® brand tablets (all strengths) are comparatively expensive (see Table 2).

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).[19]

Avanafil, the newest PDE5 inhibitor, was not recommended for use within NHS Scotland. Although the pivotal studies demonstrated a statistically significant improvement in ED after administration of avanafil compared with placebo, the company did not present a sufficiently robust clinical and economic analysis.[20]

This decision contrasts with the All Wales Medicines Strategy Group, who recommended avanafil as an option for ED within NHS Wales.[21] NICE have produced an evidence summary for avanafil which states that overall, compared with placebo, avanafil 50mg, 100mg and 200mg statistically significantly improved the percentage of sexual attempts in which an erection of sufficient duration was maintained to enable successful intercourse, but it is not known how the efficacy, tolerability and safety of avanafil compares with the other PDE5 inhibitors.

NICE does not make any recommendations about whether avanafil should be used within the NHS.[22]

PDE5 inhibitor use after radical prostatectomy

PDE5 inhibitors have been used to improve long term erectile function in men after radical prostatectomy for prostate cancer (penile rehabilitation), although they are not specifically licensed for this purpose.[4,23] 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.[12] Guidelines from expert bodies advocate early initiation of pro-erectile treatment after radical prostatectomy.[1,2]

A more detailed discussion of this use of PDE5 inhibitors (including consideration of the clinical evidence) can be found in Bulletin 322: Tadalafil once daily. It recommends that, in the absence of robust evidence favouring a particular PDE5 inhibitor treatment regimen, local policy makers may advocate choosing a lower cost option (see table 2) where clinically appropriate. Consultation with local stakeholders including urology specialists is needed.

VEDs

Guidance from the BSSM and the EAU recommends VEDs as a potential first-line option for ED.[1,2] The EAU recommend them as an alternative first-line therapy in well-informed patients with infrequent sexual intercourse and in patients with comorbidities requiring non-invasive, drug-free management of ED.[2]

The EAU guidance suggests considering combination treatment with VED plus PDE5 inhibitor in refractory cases of ED, although this is based on limited data.[2]

NICE recommend offering VEDs as a treatment option for some men with ED as a side-effect of prostate cancer treatment. VEDs are an option (along with intraurethral inserts, penile injections, or penile prostheses) where PDE5 inhibitors are unsuccessful or are contraindicated.[12]

VEDs have also been used (alone or in combination with other treatments) for ED after radical prostatectomy.[1,2] The BSSM state that combined use of VEDs with PDE5 inhibitors/injection therapy may be useful post-radical prostatectomy and to salvage treatment failures.[1]

The initial cost of a VED is relatively high (see table 4) compared with generic PDE5 inhibitors. The pump devices cost between approximately £90 and £200. Consumables such as constrictor rings (costing approximately £5 - £19 per ring) are also required. Treatment failure is therefore relatively costly, however cost-effectiveness increases the longer the VED is used successfully.

The BSSM state that VEDs work best if the man and his partner have a positive attitude to them and sufficient time has been spent demonstrating their use.[1] Those developing pathways that include VEDs must consider how people will be supported, such as with initial training and ongoing assistance if needed, to optimise the chance of successful treatment.

Prescribing VEDs should be undertaken by a specialist with knowledge of the appliances, in line with the service level agreement for prescribing in primary or secondary care. VED prescribing would therefore usually fall withing the remit of the specialist service in secondary care, although some areas may have different arrangements in place.

A number of VEDs are listed in the Drug Tariff and their features vary.[24] Incorporating consultation with an expert into the patient pathway can help to ensure that the most suitable device for the individual is recommended. Where multiple options are equally suitable and the device is being prescribed on the NHS, choose the most cost-effective option.

Ongoing supply of consumables such as constrictor rings could be undertaken in primary care, where the GP is advised which products are required and the products are listed in the Drug Tariff. Neither the pump nor the consumables should be prescribed as a repeat prescription. The route of supply of VEDs and consumables should be agreed within a locally commissioned ED pathway.

Note that only patients who meet certain NHS criteria can receive VEDs and their consumables on an NHS prescription (see section on NHS prescribing).[24] Those not meeting NHS criteria would need to purchase products themselves.

Alprostadil

Alprostadil treatments are a second-line option that may be considered where PDE5 inhibitors are contraindicated or ineffective.[1,3] Intracavernosal, intraurethral and topical preparations are available. They require careful medical supervision and should be initiated under a specialist.[4]

NICE guidance on prostate cancer recommends intraurethral inserts or penile injections as potential options for those having radical treatment or androgen deprivation therapy, if PDE5 inhibitors are contraindicated or ineffective.[12]

Since 2013 alprostadil has also been available as a topical cream that is applied to the opening of the penis using an applicator.[25] Although less invasive than the alternative preparations, it still requires individual instruction by a medical professional on proper administration technique.[26] NICE have considered the efficacy and safety of alprostadil cream for ED in an evidence summary (ESNM50), but have not issued guidance on its use.[9]

Clinical Effectiveness

PDE5 inhibitors

Randomised placebo-controlled trials (RCTs) of individual PDE5 inhibitors have shown them to be effective interventions for ED.[2,22,27] The paucity of meaningful head-to-head trials of PDE5 inhibitors in ED makes assessment of comparative efficacy difficult. In their 2023 guideline update the EAU 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).[2]

Data from several systematic reviews with meta-analysis are available.[28-33] 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,[28,30] whilst others suggest greater efficacy with some pairwise comparisons.[29,31-33] Such suggestions should be interpreted cautiously due to limitations of the data, and in the absence of good quality comparative trials.[29,34-36]

The EAU guidance notes that two of the network meta-analyses above suggest that ED patients who prioritise high efficacy should use sildenafil 50mg whereas those who optimise tolerability should initially use tadalafil 10mg.[2,32,33]

The current evidence therefore remains compatible with the approach recommended in NICE guidance of selecting the PDE5 inhibitor with the lowest acquisition cost[10,11] unless there are clinical reasons to prefer another.

With respect to the different dosing regimens available for tadalafil, data from placebo-controlled studies suggests that tadalafil 5mg once-daily has a similar efficacy to tadalafil 10mg or 20mg given on-demand.[37,38] However, there remains a lack of robust head-to-head data from double-blind RCTs in the general ED population to confirm this.

VEDs

VEDs are reported to be highly effective in inducing erections regardless of the aetiology of the ED.[1] Published data report that efficacy, in terms of erections satisfactory for intercourse, is as high as 90%. Satisfaction rates vary widely, ranging from 27% to 94%.[2] Most men who discontinue VED use do so within three months. Long-term use decreases to 50 - 64% after two years.[2] It should be noted that such statements on the efficacy, satisfaction and long-term use of VEDs are based largely on older data from single-centre observational series, collection of small prospective clinical trials and commercial databases.[39]

A meta analysis investigating combination therapies for ED vs. monotherapy found that using a VED in addition to PDE5 inhibitors was associated with additional improvement in International Index of Erectile Function (IIEF) score. This result was based on limited data.[40]

The EAU suggests considering VEDs as a therapeutic alternative for ED after radical prostatectomy. This is based on a meta-analysis that showed a positive therapeutic effect with the early use of VED post-radical prostatectomy. They also note a 2021 network meta-analyses that showed combination therapy with VED and PDE5 inhibitor to offer advantages over monotherapy.[2] In both meta-analyses the data relating to VEDs were limited and came from small RCTs with some methodological limitations.[41,42]

The BSSM guidance notes a study by Raina et al which was included in the two meta-analyses above and was also considered by NICE in their evidence review for NG131 on prostate cancer.[1,12,43] It investigated the early use of VEDs after radical prostatectomy, reporting a greater mean improvement in the abridged IIEF-5 score in the intervention group compared with the group that received no erectogenic treatment.[43] As noted in the meta-analyses above, this was a small RCT (n=109) with some potential methodological limitations.[41,42]

Alprostadil

Efficacy rates with intracavernous alprostadil are reported to be high at approximately 70% or more in the general ED population[1,2] and higher in those without vascular disease.[1] An intact nerve supply is not required, so treatment can be effective after spinal cord injuries and after major pelvic surgery.[1]

Long term compliance rates can be low, with as many as 50% of patients stopping in the first two to three months. Careful counselling during the training phase and easy access to ongoing advice can improve compliance.[1]

Intraurethral alprostadil is less invasive than intracavernous injection but efficacy rates are lower. Erections sufficient for intercourse are achieved in approximately 30 - 66% of patients. Adherence to long-term therapy is in the region of 30%.[2]

In two RCTs alprostadil cream statistically significantly improved erectile function and intercourse ability compared with placebo but the average absolute benefit was modest and only 31% - 40% of men (depending on outcome considered) obtained a clinically relevant response.[9]

In their evidence summary on alprostadil cream, NICE state that the response rates for this product are less than those reported with other ED treatments. They note that this is based on indirect comparisons (which are limited by differences in study design and clinical endpoints) as there are no direct head-to-head comparisons.[9]

Regarding the use of alprostadil in penile rehabilitation after postprostatectomy, a Cochrane review investigating different treatment strategies included one study (n=156) comparing daily PDE5 inhibitor versus intraurethral alprostadil. The review authors found that, based on very low quality evidence, efficacy was comparable.[23]

Safety

There is a risk of priapism with some ED treatments.[1,3] Patients should be advised to seek immediate medical assistance for any erection lasting for more than four hours.[1]

PDE5 inhibitors

Common side-effects of PDE5 inhibitors are headache, flushing, dyspepsia, nasal congestion, dizziness, abnormal vision, back pain and myalgia. Abnormal vision has a stronger association with sildenafil, and back pain and myalgia with tadalafil.[1] Rare but serious adverse effects of PDE-5 inhibitors include:

- Non-arteritic anterior ischaemic optic neuropathy - PDE5 inhibitors are therefore contraindicated in patients who have loss of vision in one eye.

- Hearing impairment.[4]
- Priapism.[3]

Contraindications include men with cardiac disease for whom sexual activity is inadvisable. They are also contraindicated in men taking nitrates or nitric oxide donors.[6,13,15] This includes regular or intermittent use of nitrates in any form, such as:

- Organic nitrates (e.g. nitroglycerine, isosorbide mononitrate, isosorbide dinitrate).
- Other nitrate preparations used to treat angina such as nicorandil.
- Recreational drugs such as amyl nitrite ('poppers').
- Guanyl cyclase stimulators such as riociguat.[1]

Sildenafil, tadalafil, vardenafil and avanafil are all metabolised via the cytochrome P450 system (principally via CYP3A4), so interactions with drugs affecting this system must be considered.[6,13,15,16]

VEDs

VEDs are contraindicated in men with bleeding disorders or those taking anti-coagulant therapy.[1,2]

The most common adverse events include pain, inability to ejaculate, petechiae (tiny spots on the skin), bruising, and numbness.[2]

Serious adverse events are very rare, but skin necrosis has been reported.[1] To avoid this, patients should be advised to remove the constriction ring within 30 minutes.[2] Some pumps have a pressure limiter as a safety feature.

Alprostadil

Intracavernous: Adverse effects of intracavernous alprostadil include post-injection penile pain (in up to half patients after at least some of their injections). Other complications include priapism (1%) and fibrosis (2%).[2]

Systemic side effects are uncommon; the most common being mild hypotension when using higher doses.[2]

Contraindications are few but include a history of hypersensitivity to alprostadil, a risk of priapism, and bleeding disorders,[1,2] and anatomical deformation of the penis.[44]

Intraurethral: The most frequently reported adverse effect is pain in the penis. Dizziness and symptomatic hypotension are reported commonly. Priapism is uncommon.[45]

Incorrect insertion may cause urethral abrasion and minor urethral bleeding. Penile fibrosis, including angulation, fibrotic nodules, and Peyronie's disease, was reported in 3% of clinical trial patients overall.[45]

Vaginal burning/itching is a common side effect in female partners. A condom barrier should be used during sexual intercourse if the female partner is pregnant.[45]

Contraindications include those with anatomical deformities of the penis and predisposition to priapism.[45]

Topical (alprostadil cream): Common adverse effects include skin rash, urethral pain and penile burning, tingling or pain. Dizziness, syncope and hypotension are uncommon, as is prolonged erection/priapism. In clinical trials priapism occurred rarely (in 0.06–0.4% of men).[26]

Partners of alprostadil cream users can experience adverse events, most commonly vaginal irritation. The effects on male fertility and early pregnancy are not known. Use of a condom is recommended for sexual intercourse with women of childbearing age, pregnant or lactating women.[26]

Alprostadil cream is contraindicated in men with certain underlying disorders such as orthostatic hypotension, myocardial infarction and syncope, conditions that might predispose to priapism, and anatomical deformation of the penis.[26]

NHS prescribing for ED

Since 1999 the provision of ED medications on NHS prescriptions in England has been subject to restrictions.[46,47] Changes to the regulations in 2014 mean that they no longer apply to generic sildenafil (see below),[48] but they are in place for alprostadil, avanafil, tadalafil, vardenafil and Viagra®. The criteria for prescribing these medications for ED on the NHS 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.[24]

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

The same clinical criteria listed above also apply to NHS prescriptions for VEDs and constrictor rings.[24]

The prescriber must endorse prescriptions for any of these restricted items with 'SLS' in order for the pharmacy contractor to be able to dispense the product.[24]

The changes made to the regulations in 2014 mean that:

- Generic sildenafil tablets can be prescribed on the NHS for any person with ED, regardless of cause.
- The other PDE5 inhibitors (including branded sildenafil) can only be prescribed for those who meet NHS criteria listed above. 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.[48]

The changes were made following a significant reduction in the price of sildenafil after the expiry of patent protection for Viagra® in 2014.[48] 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 group. The prescribing doctor can prescribe more than one dose a week if it is considered clinically appropriate.[46]

Restrictions also apply to the prescribing of ED treatments in Wales, Scotland and Northern Ireland. The same criteria for provision on the NHS apply as described above for England.[24,49,50] However there are some notable differences to the guidance for Wales, Scotland and Northern Ireland:

- Generic sildenafil is **not** exempt from the prescribing restrictions listed in the relevant Drug Tariff.
- Avanafil is **not** listed as an option for prescribing where the NHS criteria are met.
- The arrangements for prescribing in cases of severe distress vary.[24,49,50]

Self care with PDE5 inhibitors

Two PDE5 inhibitors, Viagra® Connect and Cialis® Together are available for purchase over the counter (OTC). In 2017 the Medicines and Healthcare products Regulatory Agency (MHRA) reclassified Viagra Connect® (containing sildenafil 50mg) from a prescription only medicine (POM) to a pharmacy medicine (P).[51] It was hoped that providing another access route could help to bring a hard-to-reach group into healthcare earlier. This could also increase identification of cardiovascular disease and reduce the risk of men obtaining counterfeits via the internet.[52] Cialis® Together was reclassified to a pharmacy medicine in March 2023.[53]

A number of sildenafil 50mg products and a tadalafil 10mg product (Cialis® Together) are now available for purchase as a pharmacy medicine for use by men aged ≥18 years who have ED. Before making a supply, the pharmacist must ascertain if the OTC route is appropriate by assessing factors such as cardiovascular risk and the potential for drug interactions.

Several manufacturers of OTC sildenafil and tadalafil products have published training materials to support pharmacists in assessing suitability for this treatment as a P medicine. Materials include essential information booklets and Pharmacy checklists. These support materials can be found alongside the Summary of Product Characteristics (SPC) at www.medicines.org.uk.

When undertaking a consultation about OTC sildenafil or tadalafil, the community pharmacist should advise the patient to make an appointment with their doctor within six months for a clinical review of potential underlying conditions and risk factors associated with ED. This applies regardless of whether or not they are suitable for supply OTC.[54,55]

Purchasing OTC sildenafil or tadalafil is more expensive than obtaining it on prescription, costing approximately £5 - £6 per tablet,[56] compared to free prescriptions in Wales, Scotland and Northern Ireland or £9.65 for a prescription charge in England (for those that are not exempt from paying). However, it may be a convenient option for some men and can be included as an option in local guidance on prescribing. For example, it provides an access route to tadalafil for men who do not meet NHS funding criteria. Healthcare professionals could consider advising patients to discuss the suitability of OTC sildenafil or tadalafil with a community pharmacist, where the patient is willing and able to do so. Those not willing or able to consider OTC purchase, or not meeting the OTC licence requirements should have access to prescribed PDE5 inhibitors (where clinically appropriate).

Sources of patient information on ED

A variety of patient information resources are available which discuss what ED is and what causes it, how to seek medical help, lifestyle modifications, and treatment options:

- NHS website https://www.nhs.uk/conditions/erection-problems-erectile-dysfunction/
- SH:24 https://sh24.org.uk/sexual-health/erectile-dysfunction
- Patient website https://patient.info/mens-health/erectile-dysfunction-impotence

- British Association of Urological Surgeons website (note that the website includes a warning that some of the information provided contains graphic, medical images which individuals may find upsetting) https://www.baus.org.uk/patients/conditions/3/erectile_dysfunction_impotence/

Premature ejaculation (PE)

Background

Premature ejaculation is a poorly understood disorder and there is a lack of consensus on its definition.[57] Available definitions have the following factors in common: a measure of time-to-ejaculation, perceived issue with ejaculatory control, distress, and interpersonal difficulty related to PE.[2]

PE is described as 'lifelong' if symptoms have been present since first sexual intercourse and 'acquired' if they develop after a period of satisfactory ejaculatory function.[58] The International Society for Sexual Medicine (ISSM) and the European Association of Urologists (EAU) define PE as a male sexual dysfunction, characterised by the following:

- Ejaculation that always or nearly always occurs prior to or within about one minute of vaginal penetration (lifelong PE) **or** a clinically significant and bothersome reduction in latency time, often to about three minutes or less (acquired PE).
- Inability to delay ejaculation on all or nearly all vaginal penetrations.
- Negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.[2,57]

There is a high level of discrepancy in reported prevalence rates of PE, with some studies reporting prevalence of 20-30%. The EAU consider that the prevalence is unlikely to be as high as this, based on the relatively low number of men who seek medical help. They state that an approximate 5% prevalence of acquired PE and lifelong PE in the general population is consistent with epidemiological data indicating that around 5% of the population have an ejaculation latency of < 2 minutes.[2]

The aetiology of PE is unknown, with few data to support suggested biological and psychological hypotheses. It has been hypothesised that lifelong PE is mediated by a complex interplay of central and peripheral serotonergic, dopaminergic, oxytocinergic, endocrinological, genetic and epigenetic factors. Acquired PE may occur due to psychological problems (such as sexual performance anxiety, and psychological or relationship problems) and/or co-morbidity, including ED, prostatitis and hyperthyroidism.[2]

Diagnosis of PE is based on the patient's medical and sexual history. The subtype of PE must be established before commencing any treatment. Pharmacological and behavioural/psychological treatments have been used for PE.[2]

As serotonin has been shown to have an inhibitory role in ejaculation, research on PE treatment has focussed mainly on the use of selective serotonin reuptake inhibitors (SSRIs).[59]

National guidance

NICE have not issued guidance on managing PE. They have produced an evidence summary for dapoxetine but it does not make recommendations about whether it should be used within the NHS.[60] The Scottish Medicines Consortium (SMC) do not recommend the use of dapoxetine within NHS Scotland for PE, as the marketing authorisation holder has not made a submission to them.[61]

Current guidance on PE is available in the 2023 guidance on Male Sexual Dysfunction from the EAU.[2] The guidance recommends pharmacotherapy as first-line treatment for patients with lifelong PE. For acquired PE the initial goal is to address the underlying cause (e.g. ED, prostatitis, LUTS, anxiety and hyperthyroidism). Psychological/behavioural therapies in combination with pharmacological treatment may also be appropriate.[2]

Psychosexual interventions, whether these are behavioural, cognitive, or focused on the couple, are aimed at teaching techniques to control/delay ejaculation, gaining confidence in sexual performance, reducing anxiety, and promoting communication and problem solving within the couple. The EAU note that psychosexual interventions alone lack empirical support in PE. They advise considering them for patients who are uncomfortable with pharmacological therapy or in combination with pharmacological therapy.[2]

Dapoxetine

Dapoxetine (Priligy®) is a short acting SSRI licensed for 'on demand' treatment of PE in adult men aged 18 to 64 years. The SPC states that dapoxetine should only be prescribed to men who meet **all** the following criteria:

- An intravaginal ejaculatory latency time (IELT) of less than two minutes.
- Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the man wishes.
- Marked personal distress or interpersonal difficulty as a consequence of PE.
- Poor control over ejaculation.
- A history of PE in the majority of intercourse attempts over the prior six months.

The SPC states that dapoxetine should not be prescribed to delay ejaculation in men who have not been diagnosed with PE. The starting dose recommended in the SPC for all men is 30mg, taken as needed approximately one to three hours prior to sexual activity.[62]

Dapoxetine is the only oral medication licensed in the UK for the treatment of PE, although other treatments are used off-label for this indication. The General Medical Council advice to use a licensed medicine whenever possible should be taken into consideration.[60]

Off-label SSRIs

Other SSRIs used to treat mood disorders have been widely used 'off-label' for PE since the 1990s. Clomipramine, the most serotoninergic tricyclic antidepressant, has also been used.[2]

Previous versions of the EAU guidance stated that off-label SSRIs and clomipramine should be used daily for PE as they are not amenable to on-demand dosing.[63] However, the current guideline includes on demand SSRIs and clomipramine when referring to treatments that have consistently shown efficacy in PE.[2]

Other available guidance on PE includes older guidelines from the ISSM (2014) and a recent guideline from the American Urological Association (AUA, 2022). On the issue of dosing regimens for off-label SSRIs and clomipramine both guidelines agree that on-demand administration of clomipramine, paroxetine, sertraline, and fluoxetine three to six hours before intercourse is modestly efficacious and well tolerated but is associated with substantially less ejaculatory delay than daily treatment in most studies.[57,64]

They advise that the choice between on-demand dosing of dapoxetine (which is not licensed in the United States) or daily dosing of off-label SSRIs should be based upon the treating physician's assessment of individual patient requirements. They note preference for a daily or on demand treatment will vary between men.[57] The AUA advise that use of off-label SSRIs is favoured over clomipramine because of a better side effect profile.[64]

When dosed regularly, ejaculation delay may start a few days after drug intake, but it is more evident after one to two weeks as receptor desensitisation requires time to occur.[2]

Current EAU guidance prioritises licensed PE treatments as first line choices for lifelong PE i.e. either dapoxetine or lidocaine/prilocaine spray (for which a licensed product is available, but not in the UK –

see below).[2] This differs from a previous version of the guidance, which advised 'pharmacotherapy' first-line for lifelong PE; pharmacotherapy included either dapoxetine on demand or other off-label SSRIs or clomipramine daily.[63]

The EAU considers dapoxetine to be safer compared with clomipramine, paroxetine, fluoxetine, sertraline, and other compounds that are used for treatment of PE. However they also note data showing moderate-to-high discontinuation rate (reaching 90% after two years) with dapoxetine. Reasons for discontinuation included cost (29.9%), disappointment that PE was not curable and the on-demand nature of the drug (25%), adverse effects (11.6%), perceived poor efficacy (9.8%), a search for other treatment options (5.5%), and unknown (18.3%).[2]

Because of the risk of suicidal ideation or suicide attempts, caution is needed in prescribing SSRIs to young adolescents aged 18 years or younger with PE, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation (see safety section).[2]

Patients should be advised to avoid sudden cessation or rapid dose reduction of daily-dosed SSRIs, which may be associated with a SSRI withdrawal syndrome.[2]

Local anaesthetics

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE. Several trials support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis thereby delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation.[2]

EAU guidance recommends lidocaine/prilocaine spray as a first-line treatment option for PE, but the guidance refers to a product approved by the European Medicines Agency which is not available in the UK. They also note limited evidence for off-label use of lidocaine/prilocaine cream.[2]

In the UK, a spray licensed for PE containing lidocaine 9.6% w/w (Stud 100 Spray) is available to purchase OTC as a Pharmacy medicine.[65] Condoms containing benzocaine and lidocaine are also commercially available.[66]

Partner effects such as vaginal numbness or burning have been reported with local anaesthetic preparations, which can be avoided by using a condom.[2] Note that some products can affect the integrity of some condom materials. Local anaesthetic preparations should not be used if either partner is hypersensitive to any of the ingredients.[66]

Tramadol

The analgesic tramadol combines opioid receptor activation and serotonin and noradrenaline re-uptake inhibition. It has been used off-label for PE, and is suggested by EAU guidance as a potential on-demand alternative (to be used with caution) to on-demand SSRIs. The guidance is careful to outline that the use of tramadol has to be considered with caution since there is a lack of data on long-term safety in this setting.[2]

As an opioid there is known risk for serious side effects with tramadol such as respiratory depression and potential for addiction.[4] As a result of the increased incidence of tramadol related deaths, the Advisory Council on the Misuse of Drugs recommended that tramadol was reclassified as a Class C substance under the Misuse of Drugs Act 1971. Consequently, it has been a schedule 3 drug since June 2014.[67,68]

In summary, the lack of long-term safety data, risk of adverse effects and controlled drug status in the UK makes tramadol a less suitable choice for this unlicensed indication.

PDE5 inhibitors

If ED is present, it should be treated before PE, which may well be with a PDE5 inhibitor. Furthermore, it is possible for patients with ED to develop secondary PE caused by the anxiety associated with difficulty in attaining and maintaining an erection.[2]

There is also evidence to suggest a benefit with PDE5 inhibitors for PE where ED is not present, and the EAU recommend them as an option in PE (without ED).[2] This is an off-label use and the methodological quality of the majority of RCTs is unclear.[69]

Clinical Effectiveness

Dapoxetine

NICE ESMN40 on dapoxetine discusses a pooled analysis of 4 RCTs (n=4843) in men with PE. The analysis showed a statistically significant increase in IELT at 12 weeks with dapoxetine 30mg and 60mg 'on demand' compared with placebo 'on demand' although an increase in IELT was also seen with placebo. IELT went from 0.9 minutes in all groups to 1.9, 3.1 and 3.6 minutes respectively for placebo, dapoxetine 30 mg and dapoxetine 60 mg; p<0.001 for comparisons with placebo.[60]

The changes in IELT from baseline stated above are expressed in terms of the arithmetic mean (the mean value of the sum of values), and there is some debate as to whether the geometric mean (using an average of the log-transformation of each IELT value) is a more appropriate measure. The geometric mean tends to give more conservative results that are less affected by data outliers. In the analysis above, the geometric mean IELT increased at 12 weeks from a baseline of 0.8 minutes to 1.3, 2.0 and 2.3 and minutes with placebo, dapoxetine 30mg and dapoxetine 60mg respectively. This represents a 2.5 to 3-fold increase in geometric mean IELT compared with a 1.6-fold increase with placebo, which has been described as a relatively modest improvement.[59]

In the pooled analyses statistically significantly more men reported that their PE was 'better' or 'much better' with dapoxetine compared with placebo (30.7% and 38.3% with dapoxetine 30 mg and 60 mg respectively compared with 13.7% with placebo; p<0.001 for comparisons with placebo).[60]

In their evidence summary on dapoxetine, NICE state that men will need to balance the potential benefits with the likelihood of very common (greater than one in ten men) adverse reactions of dizziness, headache and nausea reported in the SPC.[60]

Off-label SSRIs and dapoxetine

The EAU state that several systematic reviews and meta-analyses on drug treatment show that (despite methodological problems in most studies) there remain several, well-designed, double-blind, placebo-controlled trials supporting the therapeutic effect of daily SSRIs on PE.[2]

The meta-analyses state that paroxetine is superior to fluoxetine and sertraline. Sertraline is superior to fluoxetine. Paroxetine was evaluated in doses of 20-40 mg, sertraline 25-200 mg, and fluoxetine 10-60 mg. They note limited evidence that citalopram may be less efficacious compared to other SSRIs, while fluvoxamine may not be effective.[2]

A 2021 Cochrane review assessed the effects of SSRIs for treatment of PE.[71] The review included 31 RCTs (n=8254) in which men with PE were administered SSRIs or placebo. SSRIs could be long acting (e.g. paroxetine, fluoxetine, sertraline, citalopram and fluvoxamine) or the short actingdapoxetine. Active comparator studies were not included. More than 6500 of the participants were enrolled in dapoxetine studies.

The authors concluded that SSRI treatment for PE appears to substantially improve a number of outcomes of direct patient importance such as symptom improvement, satisfaction with intercourse and perceived control over ejaculation when compared to placebo. Substantially increased adverse effect rates were reported with SSRI treatment and a small increase in treatment withdrawals due to adverse events was reported. Issues around study limitations and imprecision affected the certainty of the outcomes.[70]

The Cochrane review included studies comparing SSRIs to placebo or no treatment. The authors state that studies comparing SSRIs to other active treatments are needed, as the current evidence used to choose between the available pharmacologic agents is mostly indirect.[70]

Safety

Dapoxetine

Adverse effects of dapoxetine are similar to those of other SSRIs.[59] Nausea, headache and dizziness are very common. Orthostatic hypotension and syncope were reported in clinical trials. An orthostatic test should be performed before initiating therapy (blood pressure and pulse rate, supine and standing). Furthermore it should not be prescribed where there is a history of documented or suspected orthostatic reaction.[62]

The recommended starting dose for all patients is 30mg. The incidence and severity of adverse events is higher with the 60mg dose and it should not be initiated at this dose. Dose escalation should only be considered where the response to 30mg is inadequate and it has been well tolerated (including no orthostatic symptoms or prodromal symptoms suggestive of syncope). Drug interactions with inhibitors of CYP2D6 and CYP3A4 must also be considered.[62]

A careful appraisal of individual risk benefit should be performed after the first four weeks of treatment (or at least after six doses of treatment) to determine whether continuation is appropriate. Data regarding the efficacy and safety beyond 24 weeks are limited. Continued need and risk benefit balance should be re-evaluated at least every six months.[62]

The SPC for dapoxetine notes that antidepressants, including SSRIs, increased the risk compared to placebo of suicidal thinking and suicidality in short-term studies in children and adolescents with Major Depressive Disorder and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24.[62]

In clinical trials with Priligy® for the treatment of PE, there was no clear indication of treatment-emergent suicidality in evaluation of possibly suicide-related adverse events by the Columbia Classification Algorhythm of Suicide Assessment (C-CASA), Montgomery-Asberg Depression Rating Scale, or Beck Depression Inventory-II.[62]

Sources of patient information on PE

A variety of patient information resources are available that discuss what PE is and provide information on self help techniques and pharmacological treatments:

- NHS website
  - https://www.nhs.uk/conditions/ejaculation-problems/
  - https://www.nhs.uk/common-health-questions/sexual-health/can-premature-ejaculation-be-controlled/
- SH:24 https://sh24.org.uk/sexual-health/premature-ejaculation
- Patient website https://patient.info/mens-health/penis-problems/premature-ejaculation
- British Association of Urological Surgeons website (note that the website includes a warning that some of the information provided contains graphic, medical images which individuals may find upsetting) https://www.baus.org.uk/patients/conditions/8/premature_ejaculation/#What_should_I_do_if_I_have_premature_ejaculation_

Costs

The tables below indicate the product costs of treatments for ED and PE.

Table 2: Monthly PDE5 inhibitor costs 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 for England and Wales - Scotland where indicated[24,49,56,71]
Sildenafil 25mg	4	£0.71 / £1.01 (Scotland)
Sildenafil 50mg	4	£0.73 / £1.03 (Scotland)
Sildenafil 100mg	4	£0.79 / £1.08 (Scotland)
Tadalafil 10mg	4	£0.78 / £1.16 (Scotland)
Tadalafil 20mg	4	£0.94 / £1.28 (Scotland)
Tadalafil 5mg **daily dose**	28	£1.68 / £2.34 (Scotland)
Vardenafil 20mg	4	£3.18 / £6.12 (Scotland)
Vardenafil 5mg	4	£5.92
Avanafil 50mg (Spedra®)	8	£9.85
Vardenafil 10mg	4	£10.60
Avanafil 50mg (Spedra®)	4	£10.94
Avanafil 100mg (Spedra®)	8	£13.13
Avanafil 100mg (Spedra®)	4	£14.08
Viagra Connect® (sildenafil) 50mg tablets	8	£14.19 / £19.30 (retail price)
Viagra Connect® (sildenafil) 50mg tablets	4	£16.17 / £21.94 (retail price)
Viagra® (sildenafil) 25mg tablets	4	£16.59
Viagra® (sildenafil) 25mg tablets	8	£16.60
Viagra Connect® (sildenafil) 50mg tablets	2	£17.64 / £23.98 (retail price)
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
Cialis® (tadalafil) 20mg	4	£28.88
Cialis® (tadalafil) 10mg	4	£28.88
Cialis® (tadalafil) 20mg	8	£28.88
Tadalafil 2.5mg **daily dose**	28	£29.52
Cialis® (tadalafil) 5mg **daily dose**	28	£54.99
Cialis® (tadalafil) 2.5mg **daily dose**	28	£54.99

Table 3: Monthly cost of alprostadil preparations based on four doses per month

Products are listed by brand name as generics are not available in this category.

Product	Cost of 4 doses[71]
Caverject Dual Chamber 10 microgram injection	£29.40
Caverject vials 10 micrograms	£36.96
Caverject Dual Chamber 20 microgram injection	£38.00
Vitaros 3mg/g cream	£40.00
Viridal Duo 10 microgram injection	£40.26
MUSE 1000 micrograms urethral stick (6 pack)	£43.78
MUSE 500 micrograms urethral stick (6 pack)	£45.20
Caverject vials 20 microgram injection	£47.76
Viridal Duo 20 microgram injection	£49.08
Viridal Duo 40 microgram injection	£59.66

Table 4: Cost of VED devices

Product name	Manufacturer	Cost of pump[24]
VaxAid Hydropump V30	VaxAid Ltd	£89.50
Vetex Pump System (manual)	Vetco UK	£95.00
Pos-T-Vac (manual)	Maia Health and Beauty Ltd	£98.00
Osbon ErecAid Classic	Maia Health and Beauty Ltd	£111.82
Impulse with limiter (manual)	Genesis Medical Ltd	£119.00
Accord (manual)	Genesis Medical Ltd	£119.00
Rapport Classic	Owen Mumford Ltd	£125.93
Pos-T-Vac (battery operated)	Maia Health and Beauty Ltd	£127.00
Elite	R and G Products Ltd	£139.87
E.I.D. Erection Inducer Device	Healthcare 2000 Ltd	£149.00
Revive with limiter (battery operated)	Genesis Medical Ltd	£149.00
VED Axis	FTP Medical	£159.00
Elite Plus with gauge	R and G Products Ltd	£165.78
Elite Plus 2 with limiter	R and G Products Ltd	£165.78
SomaCorrect	iMedicare Ltd	£170.43
SomaErect Response II	iMedicare Ltd	£175.99
SomaErect Response II – XL	iMedicare Ltd	£175.99
SomaErect Touch II	iMedicare Ltd	£184.96
SomaCorrect Xtra	iMedicare Ltd	£195.90
Osbon ErecAid Esteem	Maia Health and Beauty Ltd	£202.18

Table 5: Cost of constrictor rings for VED devices

Product name	Manufacturer	Description	Cost[24]
VaxAid Erection Rings	VaxAid Ltd	Single rings available in six sizes	£5.00
Constriction Rings White C-Flex	Vetco UK	Small, medium, large	£6.50
Genesis constriction ring	Genesis Medical Ltd	Single ring available in sizes B,C,D,E,F	£7.00
Genesis 3H	Genesis Medical Ltd	Single ring available in sizes three to nine	£7.00
Constrictor ring	Maia Health and Beauty Ltd		£9.68
VED Axis Constriction ring	FTP Medical	Available as size four or size six	£10.42
Constriction Rings Mentor	Vetco UK	Medium, large	£10.00
Constriction Rings Comfort	Vetco UK	One size fits all	£10.00
Sensation Seal	FTP Medical	Available as size two or size three	£10.00
VED Axis Firma Band	FTP Medical		£13.33
VaxAid Erection Rings	VaxAid Ltd	Pack of three rings in the three smaller sizes or the three larger sizes	£15.00
Asset	Genesis Medical Ltd	Set of five different rings, loading cone, and holding cylinder for maintaining an erection	£24.00
Confidence Rings Starter pack of two rings	Healthcare 2000 Ltd	1 x regular, 1 x firm	£24.00
Confidence Rings Firm	Healthcare 2000 Ltd	2 x Firm (pink)	£29.00
Confidence Rings Regular	Healthcare 2000 Ltd	2 x Regular (natural)	£29.00
Assist Maintenance System	iMedicare Ltd		£29.55
Select Maintenance Ring Set	iMedicare Ltd	Set of three rings	£31.74
SureEase Maintenance Ring Set	iMedicare Ltd		£35.02
Ultimate (Surefit) Maintenance Ring Set	iMedicare Ltd		£37.21
Ultra Maintenance Ring Set	iMedicare Ltd		£37.21
Osborn ErecAid Constrictor ring MaxElasticity tension	Maia Health and Beauty Ltd	Pack of two rings (grey)	£37.00
Osborn ErecAid Constrictor ring Standard tension	Maia Health and Beauty Ltd	Pack of two rings (beige)	£37.00

Table 5 cont.

Product name	Manufacturer	Description	Cost[24]
Osborn ErecAid Constrictor ring High tension	Maia Health and Beauty Ltd	Pack of two rings (pink)	£37.00
ErectAssist	Mediwatch UK Ltd	Set of three retention rings, loading cone, transfer collar and lubricating gel	£23.00
Retention Rings	Mediwatch UK Ltd	Available in three sizes in pack of three retention rings. Can order pack with one of each size or three of the same size.	£21.00
Constriction rings	R and G Products Ltd	Available in five sizes in pack of five retention rings. Can order pack with one of each size or five of the same size.	£20.72
Constriction rings	R and G Products Ltd	Applicator and cone set with five different sized rings	£24.87
VaxAid Erection Rings	VaxAid Ltd	Pack of six rings with one of each size	£30.00

Table 6: Monthly cost of SSRIs based on once daily dosing (28 doses) or four doses per month for dapoxetine

SSRI	Cost per 28 days[27]
Sertraline 25mg (0.5 x 50mg tablet) (unlicensed for PE)	£0.48
Fluoxetine 20mg capsules (unlicensed for PE)	£0.95
Sertraline 50mg (1 x 50mg tablet) (unlicensed for PE)	£0.96
Sertraline 100mg (1 x 100mg tablet) (unlicensed for PE)	£1.11
Paroxetine 20mg tablets (unlicensed for PE)	£1.39
Fluoxetine 60mg capsules (unlicensed for PE)	£2.01
Sertraline 200mg (2 x 100mg tablets) (unlicensed for PE)	£2.22
Fluoxetine 40mg (1 x 40mg capsules) (unlicensed for PE)	£2.34
Paroxetine 40mg (2 x 20mg tablet) (unlicensed for PE)	£2.78
Fluoxetine 30mg (1 x 30mg capsules) (unlicensed for PE)	£2.98
Sertraline 150mg (1 x 150mg tablet) (unlicensed for PE)	£12.60
Paroxetine 40mg (1 x 40mg tablet) (unlicensed for PE)	£14.50
Fluoxetine 10mg capsules (unlicensed for PE)	£15.16
Sertraline 25mg (1 x 25mg tablet) (unlicensed for PE)	£15.63
Sertraline 200mg (1 x 200mg tablet) (unlicensed for PE)	£16.80
Dapoxetine 30mg tablets	£17.65 - £19.61*
Dapoxetine 60mg tablets	£22.95 - £25.49*

***Depending on pack size dispensed.**

Prescribing review and switching options

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

Erectile dysfunction

Local policy should outline which PDE5 inhibitors should be prescribed and the indications for which they can (and cannot) be prescribed on the NHS. 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.

PDE5 inhibitors for ED:

- **New patients – generic sildenafil**
  Commence on the PDE5 inhibitor with the lowest acquisition cost (currently generic sildenafil all strengths) unless it is clinically unsuitable.
- **If sildenafil is not tolerated or successful**
  The price of *some* strengths of generic tadalafil has fallen to a level comparable with generic sildenafil, i.e. generic tadalafil 10mg or 20mg tablets (see table 2). This can make it a favourable alternative where sildenafil is not tolerated or there is no response. 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 more costly PDE5 inhibitor**
  Consider switching to generic sildenafil (or generic tadalafil 10mg or 20mg if this is more suitable) for men receiving PDE5 inhibitors that are comparatively expensive, where clinically appropriate. Comparatively more costly PDE5 inhibitors include generic tadalafil 2.5mg daily and all branded PDE5 inhibitors (see table 2 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.[13]
- **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 may involve referral to a specialist.

PDE5 inhibitors 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 2. 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.[46] 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.

PDE5 inhibitors 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 tadalafil dose is not licensed for this indication so should not be used.

VEDs:

- Ensure prescribing of VEDs and consumables is in line with the local service level agreement. VED prescribing will usually fall within the remit of the specialist in secondary care and the consumables in primary care, but check local arrangements.
- Ensure that neither pumps nor consumables are added to the GP prescribing system as a repeat prescription. Investigate where a consumable is being ordered frequently to identify if this is appropriate.
- Ensure that consumables are only issued on prescription when the person meets the NHS criteria (prescriptions should be endorsed SLS).

Premature ejaculation

Local policy should outline which treatments can be prescribed for PE. If dapoxetine is part of the local pathway, ensure the following:

- Dapoxetine is only prescribed where there is a diagnosis of PE and all criteria for the licence are met.
- Treatment is reviewed after the first four weeks of treatment (or at least after 6 doses).
- Continued need and risk benefit are re-evaluated every six months.

Costs and savings

Data is based on prescribing data from NHSBSA (May-Jul 23) and Public Health Scotland (Jan-Apr 23).

Approximately £12million is spent annually on PDE5 inhibitors in England, Wales, Isle of Man, and Scotland.

Generic sildenafil (25mg, 50mg and 100mg) and generic tadalafil (10mg and 20mg) all cost less than £1.50 per 28 days (based on for 4 doses per 28 days). Generic tadalafil 5mg daily costs £1.68 for 28 days treatment.

All other PDE5 inhibitors are more costly, including generic tadalafil 2.5 mg daily (£29.56 for 28 days) and all branded products (up to £54.99 for 28 days).

Switching more costly PDE5 inhibitors to a PDE5 inhibitor costing <£1.50 per 28 days treatment could save £4.6million annually which equates to £6,423 per 100,000 population annually.

Approximately £8.1million is spent annually on VEDs and alprostadil and £314,028 on dapoxetine in England, Wales, Isle of Man, and Scotland.

Auditing the use of VEDs and alprostadil to ensure that prescribing meets NHS prescribing criteria and licensed use, e.g. age criteria, and deprescribing in 10% of patients could save £814,295 annually or £1,134 per 100,00 population. Auditing the use of dapoxetine to ensure that prescribing is in line with local guidance and licensed use, e.g. age criteria and deprescribing in 10% of patients could save £31,403 annually or £44 per 100,00 population.

Summary

The risk factors for ED are similar to those for cardiovascular disease, so consultations are an opportunity to identify co-morbidity and address modifiable risk factors.[3]

PDE5 inhibitors are a convenient and effective treatment for ED. Generic sildenafil is the cheapest option and the only PDE5 inhibitor without restrictions on who it can be prescribed for on an NHS prescription (in England).[24] This makes it a preferred choice where it is clinically suitable. Sildenafil and tadalafil are available for purchase for self care in patients meeting clinical criteria for OTC purchase from a pharmacy.[54,55]

Most strengths of generic tadalafil are also a lower cost option (with the exception of the 2.5mg tablet which is relatively expensive), making this a good alternative where appropriate. However not all patients will be eligible for an NHS prescription.[24]

Compared with generic PDE5 inhibitors, the alternative treatments options for ED (such as VEDs or alprostadil preparations) are often more expensive, more invasive and involve referral to a specialist. It is therefore worth ensuring that PDE5 inhibitor treatment has been used optimally before moving to an alternative.

Pharmacological treatment options for PE include local anaesthetic preparations, dapoxetine, or off-label SSRIs. When deciding which treatments to offer, local policy makers will need to consider the available evidence, potential adverse effects, licensed status and cost.

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Additional PrescQIPP resources

Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-337-male-sexual-dysfunction/
Implementation tools	
Data pack	https://data.prescqipp.info/views/B337_MaleS_dysfunction/FrontPage?%3Aembed=y&%3Aiid=2&%3AisGuestRedirectFromVizportal=y

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