Daily vs. on-demand PDE-5 inhibitors for management of erectile dysfunction following treatment for prostate cancer

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Summary

- Erectile dysfunction (ED) is extremely common following treatment for prostate cancer, since the available treatments (radical prostatectomy, androgen deprivation therapy, radiotherapy) can cause physical trauma, vascular changes and endocrine changes, all of which can have a negative impact on erectile function.

- Standard management for ED involves prescription of PDE5 inhibitors such as sildenafil or tadalafil. These treatments are effective in men with ED due to treatment for prostate cancer, but there is some debate as to the most appropriate treatment regimen. UK clinical practice guidelines recommend either once daily or on-demand PDE5 inhibitors, or some combination of the two.

- Some brands of tadalafil are licensed for daily use at low doses. Sildenafil is not licensed for daily use, and has a much shorter half-life than tadalafil (3-5 hours vs. 17.5 hours).

- There is limited evidence comparing daily and on-demand treatment regimens.

- Three systematic reviews (with extensive overlap in included trials) and one additional double-blind RCT provide evidence in men who have undergone radical prostatectomy. Both daily and on-demand use of PDE5 inhibitors produced improvements in erectile function compared to baseline.

- One meta-analysis pooled data for several PDE5 inhibitors and found that on-demand use was associated with a higher probability of erectile function recovery than daily use (ratio of OR 1.8, 95% CI 1.4 to 2.4, p<0.0001). This effect disappeared when data for tadalafil alone were examined; there was no data for sildenafil.

- There was no other evidence of any difference in outcomes between daily and on-demand use of any PDE5 inhibitor. There was no evidence comparing sildenafil with tadalafil.

- Only one small phase II trial provided evidence in men who had received radiotherapy. It found no difference in outcomes between tadalafil 5 mg daily and 20 mg on-demand.

- Adverse effects reported were in line with the known ADR profile of the PDE5 inhibitors, and included flushing, headache, nasal congestion and dyspepsia. No new safety concerns were identified.

- Daily use of PDE5 inhibitors is more expensive than on-demand use. Sildenafil is currently less costly than tadalafil. However, tadalafil came off patent relatively recently and the Drug Tariff price may change in coming months.
Introduction and background

Erectile dysfunction is common in the general population, affecting around half of men aged 40 to 70 at some stage.\(^1\) Usual management involves a combination of lifestyle factors (e.g. weight loss, smoking cessation, reduced alcohol intake, increased exercise, reduced bicycle use) and pharmacological intervention. The first-line option for pharmacological management is an on-demand PDE5 inhibitor such as sildenafil, tadalafil, vardenafil, or avanafil. The PDE5 inhibitors are generally well tolerated and are effective regardless of the cause or severity of ED. Around 75% of men benefit from treatment.

Prostate cancer is one of the most common cancers in the UK, and is the most common in men. Around 26% of cancer diagnoses in men in the UK are prostate cancer. The incidence increases with age, but around 25% of cases occur in men younger than 65. Incidence and mortality rates are higher in men of African and Caribbean origin than in white Caucasians.

Treatment for prostate cancer is determined by the stage of disease at diagnosis. In some cases active surveillance or watchful waiting may be appropriate; however, in more advanced disease intervention is required. Several of the commonly-used treatments for both localised and metastatic prostate cancer may result in erectile dysfunction (ED):

- Radical prostatectomy (removal of the entire prostate) – trauma to erectile tissue, damage to nerves, and fibrosis can all affect erectile function. Use of modern nerve-sparing prostatectomy techniques means that erectile function can be preserved, however most men will still experience some degree of erectile dysfunction
- Radiotherapy, including external beam radiotherapy – radiation can cause damage to vascular structures of the penis, leading to ED. Arterial insufficiency may take time to develop, and ED can manifest in this patient group at any time from several months up to two years after treatment.
- Androgen deprivation therapy (ADT) – reduction in testosterone levels can lead to a loss in sexual interest and reduced erectile function, particularly when testosterone levels are reduced to <10% of the normal range.

In all cases, psychological or relationship factors may contribute to ED.

There are four oral PDE5 inhibitors licensed for treatment of ED in the UK; sildenafil, tadalafil, vardenafil, or avanafil. Sildenafil and tadalafil are available as generics, while vardenafil (Levitra\(^\circledR\), Bayer) and avanafil (Spedra\(^\circledR\), A Menarini Farmaceutica) are still protected by patents.

Daily sildenafil or tadalafil have been used in clinical practice in some areas for men who have undergone treatment for prostate cancer. However evidence for better outcomes compared with as-needed dosing is limited, so it is unclear whether daily use is cost-effective.

There are concerns over whether sildenafil is suitable for daily use since it has a short half-life of 3-5 hours.\(^2\) When used as treatment of pulmonary arterial hypertension the recommended dose schedule is 20 mg three times daily, which suggests that once daily dosing is not sufficient to maintain a continuous drug effect.\(^3\)
In contrast, tadalafil has a half-life of around 17.5 hours and some brands are licensed for daily use in men who expect to use tadalafil at least twice weekly (e.g. Cialis®). In these cases the lowest daily dose of 5 mg is recommended, and 10 mg or 20 mg tablets should not be used.

This document will review the evidence for daily versus on-demand use of sildenafil and tadalafil in men with ED resulting from treatment for prostate cancer.

**Guidance and related advice**

NICE published guidance on the diagnosis and management of prostate cancer in January 2014. The guidance includes advice management of sexual dysfunction following radical treatment:

- Ensure that men have early and ongoing access to specialist erectile dysfunction services.
- Offer men with prostate cancer who experience loss of erectile function phosphodiesterase type 5 (PDE5) inhibitors to improve their chance of spontaneous erections.
- If PDE5 inhibitors fail to restore erectile function or are contraindicated, offer men vacuum devices, intraurethral inserts or penile injections, or penile prostheses as an alternative.

NHS England recently published guidance on items which should not be routinely prescribed in primary care. Tadalafil 10 mg & 20 mg tablets, when given daily for the treatment of ED, were included on the list. No routine exceptions were identified.

Two UK practice guidelines were published in 2013 and 2014, covering management of ED following surgery, radical radiotherapy and androgen deprivation therapy. The recommendations were made based on a survey of UK clinicians and the clinical practice of the authors.

**Post-surgery**

The guidance notes that PDE5 inhibitors are not generally useful for men who have non-nerve sparing surgery. The following treatment pathway is suggested for men undergoing nerve-sparing surgery:

- Sildenafil 25 mg/tadalafil 5 mg nightly for 2 weeks prior to surgery
- First line post-surgery, to continue for 12 weeks or as long as needed:
  - Low dose PDE5 inhibitor daily, plus high dose on demand or once weekly PDE5 inhibitor OR
  - On demand PDE5 inhibitor only OR
  - PDE5 inhibitor daily or every 3 days.
  - Psychosexual therapy and counselling and use of a vacuum erection device for 5-10 minutes daily may be considered as an adjunct to PDE5 inhibitors.
- Second line: add vacuum erection device, intracorporeal injections or transurethral alprostadil may be added to therapy.
• Third line: intracorporeal injection should be trialled, followed by penile prosthesis if injections fail.

The guidance notes that combination therapy is usually the most cost-effective, and recommends giving consideration to this approach first line (e.g. PDE5 inhibitor plus vacuum erection device). Similarly, it recommends considering daily PDE5 inhibitor therapy, particularly during initial management. It is acknowledged that evidence is lacking for superiority of daily vs. on-demand PDE5 inhibitor treatment.

**Post-radiotherapy or androgen-deprivation therapy**

The first-line recommendation for all men is to employ practical measures such as exercise, lifestyle advice, and pelvic floor exercises. Treatment approach then varies slightly depending on the clinical situation.

In men with low libido due to ADT:

- Psychosexual therapy and counselling, with or without:
  - High dose on-demand PDE5 inhibitor, with or without low dose daily PDE5 inhibitor, OR
  - On-demand PDE5 inhibitor only OR
  - On-demand or daily PDE5 inhibitor use for 12 weeks, or as long as needed
  - Consider adding vacuum erection device for 10 minutes

In men with ED due to radiotherapy:

- Early initiation of PDE5 inhibitors:
  - High dose on-demand PDE5 inhibitor, with or without low dose daily PDE5 inhibitor, OR
  - On-demand PDE5 inhibitor only OR
  - On-demand or daily PDE5 inhibitor use for 12 weeks, or as long as needed
  - Consider adding vacuum erection device for 10 minutes

Consider initiating PDE5 inhibitors soon after the start of RT/ADT, or within 3-6 months of treatment at least. All patients should be reviewed after 3 months, with referral to specialist ED clinic if necessary. Second line options for addition to PDE5 inhibitors include intracavernosal or transurethral alprostadil. Penile implants may be considered third line.

In summary, the first line pharmacological option for all patients is at least 12 weeks treatment with a PDE5 inhibitor, on either a daily or on-demand schedule or a combination of the two.

**Current practice in the NTAG region**

Ten clinical specialists across the NTAG region were approached to request information on how ED in men with prostate cancer is currently managed. One specialist responded.
In summary, the specialist reported that all men will experience ED post-prostatectomy. All men are given sildenafil 50 mg on alternating days to prevent tissue hypoxia; those who wish to pursue improved sexual function continue this for at least 12 months. Since PDE5 inhibitors are used for more than supporting sexual function, all men benefit from their use.

Prescription of a PDE5 inhibitor is very much on a case-by-case basis, with daily use considered for men who are distressed by lack of spontaneity. Around half of men will benefit from a PDE5 inhibitor alone, but many will also use a vacuum device. All treatment options are available as needed, including psychosexual counselling, alternative PDE5 inhibitor, vacuum devices, topical alprostadil, and intracavernosal injections.

Clinical efficacy: Post radical prostatectomy

Meta-analyses

Several systematic reviews and meta-analyses have examined the evidence for use of PDE5 inhibitors following radical prostatectomy.

Limoncin et al conducted a meta-analysis which included randomised controlled trials (RCTs) in men who had undergone bilateral nerve-sparing radical prostatectomy and who experienced ED after surgery. All trials compared PDE5 inhibitors to placebo, and those which used a combination of PDE5 inhibitor plus other treatment were excluded. The primary objectives were to determine whether used of PDE5 inhibitors results in drug-assisted recovery of erectile function, and whether dosing (daily vs. on-demand) affects recovery of erectile function.

Seven RCTs were included, enrolling a total of over 2,300 men. Trials were generally at low risk of bias, as measured by the Cochrane Risk of Bias Tool. Treatment durations ranged from 3 to 12 months, and all four currently available PDE5 inhibitors were assessed. Participants were relatively young (mean ages ranged from 54 to 60 years) and around 22% had a cardiovascular co-morbidity such as hypercholesterolaemia or hypertension.

Meta-analysis found that men treated with PDE5 inhibitors were more likely to have a significant recovery of erectile function than those who received placebo (odds ratio [OR] 2.4, 95% CI 1.9 to 3.0). Recovery was defined as an IIEF-EF score of ≥22 in most studies (see appendix 1).

Data for tadalafil, avanafil and vardenafil were pooled to compare the effectiveness of daily vs. on-demand dosing. Both regimens performed significantly better than placebo. On-demand use of any PDE5 inhibitor was associated with a higher probability of erectile function recovery than daily use (ratio of OR 1.8, 95% CI 1.4 to 2.4, p<0.0001). However, response rates for tadalafil were similar in both the daily and on-demand analyses (One-demand OR 2.4, 95% CI 1.5 to 4.0; daily use OR 2.2, 95% CI 1.2 to 4.0).

There was no difference between daily and on-demand used of PDE5 inhibitors for the number of patients answering yes question 3 of the sexual encounter profile (SEP3, ability to maintain an erection long enough to have successful sexual intercourse, see appendix 1) (ratio of OR 1.3, 95% CI 0.8 to 1.9, p=0.6). Again, response rates for tadalafil were similar in the daily and on-demand groups (OR 1.9 for both).
No data were available for sildenafil for these outcomes.

Cui et al performed another systematic review and meta-analysis, including data from six RCTs. Inclusion criteria were similar to those discussed above, and there was therefore substantial overlap in the included trials. Characteristics of the included trials were similar to those discussed above. Included trials were all of high quality, as assessed using the Jadad scale.

Pooled data for all four drugs showed that PDE5 inhibitors produced greater changes in the IIEF-EF score than placebo (standardised mean difference 4.0, 95% CI 2.9 to 5.2, p<0.001). When analysed by treatment regimen, PDE5 inhibitors significantly improved the IIEF-EF score in both the on-demand and once-daily treatment groups (standardised mean difference vs. placebo = 4 in both groups, p<0.001). There was no further analysis of on-demand vs. once-daily dosing, and there was insufficient data to make comparisons for either tadalafil or sildenafil individually.

Wang et al performed a third systematic review and meta-analysis, including data from eight RCTs. Inclusion criteria were similar to those discussed above, and there was again substantial overlap in included trials. Three of the included RCTs were not included in either of the reviews discussed above, while the remaining five were included in either one or both. Trials assessing all of the licensed PDE5 inhibitors were included, with durations ranging from 3-12 months. The methodological quality of the included trials was variable, as assessed by the Cochrane Risk of Bias Tool. Five trials had a low risk of bias overall, but three had a high or unclear risk of bias in three or four of the six domains assessed.

PDE5 inhibitors produced significantly larger changes in IIEF scores than placebo (mean difference 5.6, 95% CI 4.3 to 7.0, p<0.001). Men who received PDE5 inhibitors were also more likely to answer “yes” to question 2 of the SEP (ability to achieve penetration, see appendix 1) (risk ratio 1.6, 95% CI 1.2 to 2.3, p=0.003) and question 3 of the SEP (risk ratio 2.0, 95% CI 1.3 to 3.2, p=0.003).

The mean difference in IIEF versus placebo was 4.7 (95% CI 3.2 to 6.2) in patients who received daily PDE5 inhibitors, and 5.6 (95% CI 4.7 to 6.5) in those on an on-demand regimen. There was no statistical significance between these two groups (p=0.5) and no data were presented for individual drugs.

**Randomised controlled trial**

One additional double-blind RCT has been published since these systematic reviews were performed. Kim et al recruited 100 men with localised prostate cancer who underwent nerve-sparing radical prostatectomy at a single centre in the USA. Men with known cardiovascular disease, significant renal or hepatic impairment, or bleeding disorders were excluded.

Participants were randomised to receive either nightly sildenafil 50 mg or a matching placebo, and men in both groups were given six additional tablets of sildenafil 100 mg every 30 days to be used as-needed. The study therefore compared daily plus PRN use to PRN use only. The primary outcome was penile rigidity, as measured
using the RigiScan® device, which uses contractile loops at the base and tip of the penis to assess rigidity. Patients were given a RigiScan device to use at home, and training on how to use it. RigiScan produces a score from 0-100%. A normal RigiScan within 30 days prior to prostatectomy was required before enrolment into the study. The IIEF-EF was used as a secondary outcome, with scores >21 considered to represent treatment success.

There were no statistically significant differences in return to normal erectile function between treatment arms at any point. After 13 months, 40% of men in both treatment arms had returned to normal erectile function (p=1.0). For the secondary outcome of IIEF-EF score, 32.4% of men in the control arm had achieved a score of >21, compared to 29.0% in the treatment arm (p=0.79). No safety outcomes were reported.

An important limitation of this study is lack of statistical power. The trial was powered to have an 80% chance of detecting an increase in RigiScan score from 50% in the placebo arm to 77% in the treatment arm, assuming recruitment of 188 men. However, only 100 men were enrolled in the study due to financial constraints. It is therefore possible that a small difference in efficacy existed, but was not detected.

Clinical efficacy: Post radiotherapy/androgen-deprivation therapy

Evidence for effectiveness of PDE5 inhibitors in men post radiotherapy or ADT is extremely limited. One small (n=52), open-label phase II RCT compared daily tadalafil 5 mg to tadalafil 20 mg on-demand.15 Participants were men treated with 3-dimensional conformal radiation therapy for prostate cancer at least 6 months before entry to the trial. All patients had normal erectile function prior to radiotherapy, defined as an IIEF-EF score ≥25, and experienced progressively worsening ED after therapy. Patients with diabetes, severe chronic renal or hepatic disease, ED due to other factors (e.g. hypogonadism) or ADT use in the preceding 6 months were excluded. Patients with any prior unsuccessful use of a PDE5 inhibitor were also excluded.

A total of 86 men were screened and 52 were randomised 1:1 to receive either two tablets of tadalafil 20 mg per week to be used on-demand, or tadalafil 5 mg daily. The on-demand group were instructed to take tadalafil 2-3 hours prior to anticipated sexual activity. The primary outcomes were the change from baseline after 1 and 3 months treatment in the IIEF-EF and the percentages of patients answer “yes” to SEP2 and SEP3.

There was no difference between treatment groups in IIEF-EF scores after 1 month or 3 months of treatment (p=0.22 and p=0.19 respectively). More patients in the daily treatment group achieved a normal IIEF-EF score (>26 points), but the difference did not reach statistical significant (87% vs. 63%, p=0.07). The number of patients answering yes to the SEP2 and SEP3 increased from baseline in both groups, but there was no significant difference between treatment groups at any time point.

Clinical efficacy: summary

Evidence comparing daily and on-demand use of PDE5 inhibitors is somewhat limited. The bulk of the available data indicates no difference in outcomes between
the two regimens. No studies directly comparing tadalafil and sildenafil in this population were identified.

**Safety**

No new safety concerns were identified in the evidence discussed above. Common adverse events included known effects of the PDE5 inhibitors, such as flushing, headache, nasal congestion and dyspepsia. PDE5 inhibitors appeared to be well tolerated in this population. No comparisons of the relative safety of daily vs. on-demand dosing were identified.

**Dosage and administration**

For management of ED, sildenafil is licensed at a dose of 50 mg as needed, approximately one hour prior to anticipated sexual activity. The dose may be titrated to response and tolerability to either 25 mg or 100 mg, on an as-needed basis. The maximum recommended frequency is once per day.

Tadalafil is licensed at a dose of 10 mg or 20 mg for use prior to anticipated sexual activity. These doses should not be used on a continuous daily basis. Where use is frequent (at least twice weekly), a daily dose of 5 mg may be considered based on patient choice and clinical judgement. The daily dose may be reduced to 2.5 mg, based on response and tolerability.

**Cost analysis**

The patents for both sildenafil and tadalafil have expired, sildenafil in 2013 and tadalafil in November 2017. As a result sildenafil is a Drug Tariff category M drug while tadalafil remains in category C, with the price based on Cialis. Several tadalafil generics have been launched and the cheapest represents a 90% discount over Cialis. The Drug Tariff category and price are likely to be updated in due course to reflect this.

The chart below shows the price per patient per year of PDE5 treatment. Treatment durations were selected based on the practice guidelines discussed above, which recommend treatment for “12 weeks or as long as needed”. Costs will be highly dependent on treatment duration. A regional clinical specialist indicated that men may require up to three years post-prostatectomy to recover from ED.

Doses were selected based on drug licensing (for tadalafil) and the doses tested in the literature (for sildenafil). Costs for branded Cialis (Drug Tariff price) and the cheapest generic tadalafil are presented for illustrative purposes. It should be noted that the price of generic tadalafil varies widely, and some brands have a list price identical to Cialis. The Drug Tariff price for tadalafil is likely to change in the coming months.

Estimates for the number of men treated in the NTAG region each year are not available. Cancer Research UK estimates that the crude rate of prostate cancer in the UK is 149.2 per 100,000. The NTAG region has a population of around 1.45 million men, so around 2165 new cases of prostate cancer would be expected each year. Cancer Research UK further estimates that around 15% of patients have
surgery to remove prostate tumours, while a further 32% have radiotherapy as part of their primary treatment.\(^{18}\)

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NB: Prices are for general comparison only and do not imply therapeutic equivalence.

* Tadalafil is in Drug Tariff Category C. The prices indicated will only apply if a generic product is prescribed by brand.

**Author’s declaration:** The author has no relevant interests to declare.
References

Appendix 1: Measures of erectile function

International Index of Erectile Function (IIEF)\textsuperscript{19}

The IIEF was developed to assess male sexual function. It can be self-administered or used in research or clinical settings. The questionnaire consists of 15 questions and asks the patient to rank each one on a scale of 0 to 5. Questions address areas such as ability to get and maintain an erection, frequency of successful intercourse, sexual desire, and overall satisfaction with the patient’s sex life and sexual relationship.

A simplified version, using only the questions relating directly to erectile function, is also sometimes used. Referred to as the IIEF-EF, this questionnaire includes questions 1-5 and 15 of the original IIEF.\textsuperscript{20}

1. How often were you able to get an erection during sexual activity?
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
15. How do you rate your confidence that you could get and keep an erection?

Since each question is scored from 0-5 the IIEF-EF produces a total possible score of 30. Scores of 22 are more are associated with the following probabilities for success:

- 81% for getting an erection
- 86% for having a firm erection
- 89% for being able to penetrate
- 67% for maintaining an erection
- 70% for maintaining an erection to completion
- 32% for erection confidence

Sexual encounter profile (SEP)

The SEP consists of a brief diary which allows patients to record satisfaction with sexual encounters. The proportion of patients answering “yes” to questions 2 and 3 is frequently used as a measure of efficacy in trials addressing ED:

- SEP2: Were you able to insert your penis into your partner’s vagina?
- SEP3: Did your erection last long enough for you to have successful intercourse?