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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Phosphodiesterase Type 5 Inhibitors for Penile Rehabilitation Post Radical Prostatectomy: A Review of Clinical Effectiveness and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Context and Policy Issues

One in seven Canadian men are expected to be diagnosed with prostate cancer in their lifetime, making it the most common cancer in men.[1] Prostate cancer is the third most common cause of cancer death in Canadian males, accounting for 10% of all male cancer deaths.[1] Radical prostatectomy (RP) is one of several interventions to treat cancer that is confined to the prostate gland.[2] Between 2006 to 2013, there were between 7,262 to 8,684 RP procedures performed annually across Canada.[2] Where RP is indicated, it can be performed using either an open surgical approach or via a minimally invasive (robotic or laparoscopic) technique.[3] Depending on the degree of prostate cancer, RP may be further defined as bilateral nerve-sparing, unilateral nerve-sparing, or non-nerve-sparing.[3,4] Erectile dysfunction (ED) is a common complication post-RP.[4]

Many factors influence the incidence and severity of post-operative ED, including patient age, tumor stage, pre-operative potency, type of surgery (nerve-sparing versus non-nerve-sparing), length of time following surgery, and the experience of the surgeon.[3,5] The frequency of erectile dysfunction reported after RP also depends upon the definition of ED and the source of information.[3] The incidence of erectile dysfunction (ED) immediately after RP is virtually 100%, with any recovery of erectile function requiring as long as 18 to 24 months.[4] Post-RP ED may take up to four years to resolve, with as many as 20% to 80% of patients never returning to normal erectile function.[5] The incidence of complete ED has been reported to range from 26% to 100%, while partial ED ranges from 16% to 48%.[5] Few men experience potency that is as good post-operatively as compared with pre-operatively, and potency is increasingly defined as erection with the aid of phosphodiesterase 5 inhibitors (PDE-5Is).[4]

Penile rehabilitation after RP is defined as any intervention with the intent of re-establishing pre-operative erectile function, and includes the isolated or combined use of PDE-5Is, intracavernous injection, vacuum erectile device therapy, and the use of intraurethral drugs.[6] PDE-5Is work by allowing blood flow to the penis, which may be impaired by neurologic injury due to RP. As the neurapraxia resolves, the penis becomes increasingly responsive to PDE-5Is.[4] It has also been hypothesized that patients with ED post-RP might benefit from chronic inhibition of PDE-5 to protect against structural changes that could contribute to ED.[7]

A 2010 CADTH Rapid Response report concluded that treatment with sildenafil or vardenafil administered daily for 36 to 48 weeks following radical prostatectomy was effective for prevention of ED.[8] This conclusion was based on one systematic review (SR), and CADTH stated that more evidence was needed to determine the optimal timing of treatment, dosage, and duration.

The objective of this Rapid Response report is to evaluate the efficacy of PDE-5Is for penile rehabilitation following RP, and to identify evidence-based guidelines associated with penile rehabilitation following RP.

Research Questions

1. What is the clinical effectiveness of phosphodiesterase type 5 inhibitors (PDE-5Is) for the treatment of adults requiring penile rehabilitation post radical prostatectomy?

2. What are the evidence-based guidelines associated with penile rehabilitation post-radical prostatectomy in adults?

Key Findings

Evidence from five systematic reviews suggests that phosphodiesterase type 5 inhibitors (PDE-5Is) are more efficacious than placebo or no PDE-5Is for post-radical prostatectomy penile rehabilitation. There is either limited or conflicting evidence to demonstrate improved efficacy with longer-term versus shorter-term treatment, or with regular dosing compared with on demand dosing. No significant differences were observed for higher versus lower dosages, or for early versus late post-surgical PDE-5I use. No statistically significant differences in efficacy between sildenafil, vardenafil, avanafil or tadalafil were reported. All of the SRs reported significantly more adverse events in the PDE-5I arm than in the placebo arm, regardless of dose, PDE-5I agent, or administration protocol. The side effects were generally described as mild, and included headache, flushing, dyspepsia, and rhinitis. Evidence from a single randomized controlled trial (RCT) demonstrated no significant differences between regular and on demand sildenafil dosing. Evidence from another RCT suggested that tadalafil once daily was more efficacious than both tadalafil on demand and placebo in improving general and drug-assisted erectile function (EF), shortening the length of time to EF recovery, preserving penile length and reducing the absence of morning erections, and improving treatment satisfaction and quality of life. All of the included studies were limited by potentially inadequate treatment durations. The guidelines recommended PDE-5Is to treat ED post-radical prostatectomy, but the strength of the recommendation was not provided, and the recommendations were often based on evidence that was conflicting, dated, or of low-quality.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between July 1, 2010 and July 26, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Male adults requiring penile rehabilitation post radical prostatectomy
Intervention	Q1: Phosphodiesterase type 5 inhibitors (PDE-5Is: sildenafil, tadalafil, and vardenafil) Q2: Pharmacotherapy (e.g., PDE-5Is, injectable formulations, Muse suppositories [alprostadil urethral suppository]); Medical devices (e.g., vacuum erection devices), Combination therapy (e.g., pharmacotherapy used with medical device(s), etc.)
Comparator	Q1: Phosphodiesterase 5 inhibitors (PDE-5Is: sildenafil, tadalafil, and vardenafil), including different doses or dosing regimens; Placebo; No treatment Q2: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., increased quality of life, for example as measured by the following scales: International Index of Erectile Function [IIEF] Score, normal spontaneous erection, sexual intercourse completion rates, etc.) and safety Q2: Guidelines (standard of treatment)
Study Designs	Health Technology Assessments (HTAs), Systematic Reviews (SRs), Meta-Analyses (MAs), Randomized Controlled Trials (RCTs), Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Primary studies that evaluated PDE-5I agents other than sildenafil, tadalafil, and vardenafil were excluded. All SRs that evaluated sildenafil, tadalafil, or vardenafil were included, even if they also included primary studies evaluating other PDE-5I agents. Articles described as SRs were excluded if all of the included PDE-5I studies were captured in a single SR published at a later date. Primary studies were excluded if they were captured in an included SR.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR,[9] randomized studies were critically appraised using the Downs and Black checklist,[10] and guidelines were assessed with the AGREE II instrument.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 584 citations were identified in the literature search. Following screening of titles and abstracts, 538 citations were excluded and 46 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 36 publications were excluded for various reasons, while 14 publications met the inclusion

criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

A summary of the characteristics of the included SRs and MAs, RCTs, and guidelines are presented below, and in Appendix 2, Tables A1, A3, and A4. Overlap of studies included in the included SRs is shown in Appendix 2, Table A2.

Study Design

Five systematic reviews with meta-analyses were identified, with each including six,[12] seven,[13] eight,[5,14] and 14 RCTs.[15] The search dates varied across SRs, searching from database inception up to August 2016 for the most recently published SR,[14] and the SRs were published between 2014 to 2017. There was considerable overlap across the RCTs included in the SRs, as can be seen in Appendix 2, Table A2.

One RCT was identified.[16] Additionally, four publications[7,17-19] reporting post-hoc analyses or secondary outcomes for the a second RCT study population were identified. The primary analysis of this RCT was captured in the included systematic reviews.

Four evidence-based guidelines were identified, published in 2014,[20] 2015,[21] 2016,[22] and 2017.[23]

Country of Origin

All five of the included SRs were published by lead authors from China.[5,12-15] The primary studies included in the SRs, some of which were multi-centre RCTs, were conducted in a wide variety of countries including Canada, USA, UK, Belgium, Spain, Korea, Italy, Germany, South Africa, Australia, France, Australia, and Turkey.

The RCT[16] was conducted in the USA. Four publications[7,17-19] reported post-hoc analyses or secondary outcomes for a multi-centre RCT that was conducted in nine European countries and Europe.

Two of the guidelines were from the Program for Evidence-Based Care (PEBC) at Cancer Care Ontario (CCO) in Canada,[21,22] one was from the National Institute for Health and Care Excellence (NICE) in the UK,[20] and one was from a lead author in Italy for the International Consultation on Sexual Medicine.[23]

Patient Population

The population in all five included SRs was men with erectile dysfunction (ED) following unilateral or bilateral nerve-sparing radical prostatectomy (NSRP) with age (where reported) ranging from 18 to 75 years.

The population in the RCT included 94 men with ED following NSRP, mean age 54 years, being treated at a military centre.[16] The publications reporting post-hoc or secondary outcomes from a multicentre RCT included 423 men with ED following NSRP, mean age 57.9 years.[7,17-19]

The four guidelines each included a section on ED after radical prostatectomy. The overall purpose of the included guidelines was to provide recommendations on the diagnosis and management of prostate cancer,[20] follow-up care and psychosocial needs of survivors of

prostate cancer,[21] interventions to address sexual problems in people with cancer,[22] and sexual rehabilitation after treatment for prostate cancer.[23]

Interventions and Comparators

All of the included SRs[5,12-15] included studies that evaluated various doses of vardenafil, tadalafil, and sildenafil, either on demand (PRN) or regularly administered, compared with either placebo or no PDE-5I. Four of the five SRs[5,12,13,15] also evaluated avanafil PRN, 100 or 200 mg compared with placebo. In addition, one SR[14] compared sildenafil 50 mg once a day (OAD), with sildenafil 50 mg PRN. Treatment duration was reported for all five SRs and ranged from 1.5 to thirteen months.

The RCT[16] evaluated 50 mg sildenafil nightly compared with placebo. Both groups were allowed up to six tablets of sildenafil 100 mg PRN per month. The four publications reporting post-hoc or secondary outcomes for a second RCT evaluated tadalafil 5 mg OAD compared with placebo or tadalafil 20 mg PRN.[7,17-19]

All four guidelines included a recommendation on PDE-5Is.[20-23]

Outcomes

All five of the included SRs[5,12-15] reported the International Index of Erectile Function (IIEF) scores, usually with an erectile function (EF) subgroup of six questions, the IIEF-EF, as well as adverse events (sometimes referred to as treatment emergent adverse events or TEAEs). Three SRs[5,12,13] reported Sexual Encounter Profile (SEP) scores, including SEP-2 (successful vaginal penetration) and SEP-3 (successful intercourse).Two SRs[5,13] reported Global Assessment Questionnaire (GAQ) scores. One SR[13] reported the treatment discontinuation rate.

The RCT[16] reported return to normal EF as assessed by a device measuring nocturnal penile rigidity (RigiScan), and IIEF scores. Four publications reported post-hoc or secondary outcomes for a second RCT study population.[7,17-19] One post-hoc analysis[17] reported on returning back to the pre-surgery IIEF-EF level. Another publication[19] reported time to EF-recovery (defined as an IIEF-EF ≥ 22). Another study[18] reported on secondary outcomes including quality-of-life (QoL) and treatment satisfaction, as measured by changes in the Expanded Prostate Cancer Index Composite (EPIC-26), the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS), and the Self-Esteem and Relationship (SEAR) questionnaires. One publication[7] reported stretched penile length (SPL), as well as SEP-1 (some erection or enlargement of the penis), SEP- 2 and SEP-3 scores, and a Standardized Morning Erection Question (SMEQ).

Follow-up

Follow-up was not reported for any of the included SRs.[5,12-15] Treatment duration ranged from 1.5 to 13 months.

The RCT[16] evaluated erectile function at two weeks, then three, six, nine, and 12 months post-operatively, with a final assessment made at 13 months, following a one month drug washout.

The four publications reporting on a second RCT study population reported nine months of double-blind treatment (DBT), followed by a six-week drug-free washout (DFW), followed by a three-month open-label treatment (OLT).[7,17-19] Follow-up was reported at the end of each treatment interval for most of the four publications.

Summary of Critical Appraisal

A summary of the critical appraisal is presented below and in Appendix 3, Tables A5, A6, and A7.

Systematic Reviews and Meta-Analyses

All five SRs[5,12-15] provided an a priori research question although no research protocol was referenced. Duplicate study selection and data extraction was conducted for three SRs,[5,13,15] but was not reported in one SR,[12] and one SR[14] reported duplicate data extraction but not duplicate study selection. A comprehensive literature search was performed in all five SRs. The status of publication was used as an inclusion criteria in two SRs[5,15] but was not reported in the others.[12-14] A list of included studies was provided for all five SRs, but none included a list of excluded studies. The characteristics of the included studies were provided for all five SRs. The scientific quality of the included studies was assessed and documented, and used appropriately in forming conclusions, for all five SRs.[5,12-15] The methods used to combine the studies were appropriate in all SRs, although heterogeneity was assessed but not reported for one SR.[13] Two studies did not observe any heterogeneity in the included trials.[12,14] Two SRs[5,15] employed a random effects model due to high heterogeneity in the observed trials. The likelihood of publication bias was assessed and not detected in three SRs[12,14,15] but was not reported in two.[5,13] A conflict of interest statement was provided for all SRs with all authors declaring none, but was not reported for the RCTs included within the SRs.

Potential issues that could introduce bias in the RCTs included in the SRs were reported in several of the studies. Many of the RCTs included in the SRs were determined by the authors to lack allocation concealment.[13-15] One SR noted that withdrawals and dropouts were poorly reported.[14] In many cases, the preoperative erectile function of patients was unclear.[13] The treatment period varied considerably across studies, and this could impact treatment effectiveness.[13]

Randomized Controlled Trials

The single RCT evaluating sildenafil[16] clearly described the main outcomes to be measured, the characteristics of the included patients, the intervention of interest, the distribution of potential confounders in each intervention group, and the main findings. Characteristics of patients lost to follow-up were reported, with similar drop-put rates in both groups. Actual probability values were reported. Patients and outcome assessors were blinded, follow-up was the same for all patients, and the statistical tests used to assess the main outcomes appeared to be appropriate. Compliance was monitored and reported as 95.9% The outcome measures used appeared to be accurate. The patients in the treatment and control groups were recruited from the same population and all patients appeared to be recruited over the same time period. The patients were randomized and the intervention assignment was concealed to patients and health-care staff. Adequate adjustment for confounding occurred with intention to treat analysis. Losses to follow-up and reasons for treatment discontinuation were detailed for both treatment arms, and ITT analysis was conducted, but it is not clear how missing data was accounted for.[16]

Limitations this RCT[16] included not clearly describing the aim of the study, and not providing estimates of random variability for the main outcomes. As well, adverse events were not reported. Some issues with external validity were noted as it was unclear if the patients asked to participate in the study, or included in the study, were representative of the entire population of interest. In addition, the care setting was a military hospital and was

probably not representative of the treatment that the majority of patients would receive. There were unplanned subgroup analyses reported, and the authors reported that the study was potentially under-powered given that target enrollment figures were not met. Finally, there was not a pure placebo arm given investigator concerns that patients should have some access to treatment.[16]

Four publications reported post-hoc analysis or secondary outcomes for the same RCT evaluating tadalafil and varied in their reporting of the RCT data; more details may have been available in the parent RCT or in the supplementary tables.[7,17-19] For all four publications there was a clear description of the aim of the study, the main outcome measures, the intervention of interest, and the main findings.[7,17-19] The characteristics of the included patients and distributions of principle confounders were provided in all but one publication.[17] Estimates of random variability were provided for the main outcomes for all but one publication.[17] Actual probability values were not reported for two publications.[17,19] Based on the four publications, the parent RCT was conducted in care settings that were probably representative of the treatment the majority of patients would receive.[7,17-19] In addition, the study subjects and outcome assessors were blinded to the intervention. The length of follow-up appears to be the same for all patients (although follow-up was not reported at the end of all three treatment periods in all four publications), the statistical tests used to assess the main outcomes appeared to be appropriate, and the outcome measures used appeared to be accurate. Patients in the different arms were recruited from the same population, and were randomized to treatment groups. The study appeared to be sufficiently powered. The four publications did not report adverse events, compliance, allocation concealment, and loss to follow-up.[7,17-19] It is not known whether the patients asked to participate in the study were representative of the entire population of interest. It is not clear whether the patients who were willing to participate were representative of the entire population of interest. All four publications were either post-hoc analyses or reporting on secondary outcomes.[7,17-19] Finally, the RCT was industry funded, and the authors themselves noted that treatment duration may have been too short for optimal penile rehabilitation.

Guidelines

Four evidence-based guidelines were identified that addressed ED after RP.[20-23] For all included guidelines, the overall objective was specifically described. The health questions covered by the guidelines were specifically described for only one guideline.[20] All four guidelines described the population to whom the guideline is meant to apply, and the target users of the guideline. The guideline development group appears to have included individuals from all relevant professional groups in all but one guideline, in which professional groups were not reported.[23] One guideline[20] appeared to seek out the views and preferences of the target population. Systematic methods were used to search for evidence for all four guidelines, however, two guidelines[22,23] did not describe the criteria for selecting the evidence. A limited description of the strengths and limitations of the body of evidence was provided for one guideline,[23] but was more clearly described in the others.[20,21,21] Three guidelines clearly described the methods for formulating the recommendations.[20-22] All four guidelines have considered the health benefits, risks, and side effects in formulating the recommendations, and all four provide an explicit link between the recommendations and the supporting evidence.[20-23] All four guidelines had been externally reviewed by experts prior to publication. A procedure for updating the guideline was described in all but one guideline.[23]

For all guidelines, the recommendations are specific and unambiguous, the different options for the management of ED were clearly presented, and key recommendations were easily identifiable.[20-23] Two guidelines[21,23] did not describe barriers or facilitators to their application. One guideline[23] provided a 'shareable roadmap" tool for putting the recommendation into practice, while another guideline[20] provided advice. The other two guidelines[21,22] did not offer tools or advice for putting the guidelines into practice. The potential resource implications of applying the recommendations were not considered for two guidelines.[21,23] Only one guideline[23] presented monitoring or auditing criteria. All four guidelines contained conflict of interest statements, and the funding sources were readily identified or disclosed.[20-23]

One 2014 guideline included a 2008 recommendation on PED-5Is after RP that was not updated.[20] One guideline reported that research surrounding management options was lacking, and based at least some recommended management options on the clinical standard or expert opinion.[21] Lower-quality of evidence supported at least some of the recommendations in two guidelines.[22,23]

Summary of Findings

A summary of the findings of the included studies is presented below and in Appendix 4, Tables A8, A9, and A10.

What is the clinical effectiveness of phosphodiesterase type 5 (PDE-5Is) for the treatment of adults requiring penile rehabilitation post radical prostatectomy?

Erectile Function as Measured by the IIEF-EF

PDE-5Is Versus Placebo or No PDE-5Is

All five SRs reported significant improvements in the IIEF-EF scores as compared with placebo or no PDE-5Is.[5,12-15] Two SRs noted that this improvement remained significant in both the short (≤ 6 months) and long term (> 6 months).[12,14]

Short-Term Versus Long-Term Treatment Duration

One SR[14] reported that long-term use of PDF-5Is (> 6 months) improved IIEF-EF scores significantly in comparison with short-term (≤ 6 months) treatment duration. However, another SR[12] reported that similar IIEF-EF scores were observed for both long-term and short-term treatment durations, and one other SR[5] reported a non-significant trend of more responsiveness to PDE-5I with longer treatment duration.

Regular Versus PRN Regimen

One SR[14] reported that OAD PDE-5Is significantly improved IIEF-EF scores as compared with placebo in the short (≤ 6 months) and the long term (> 6 months). However, no significant differences were found between PRN and placebo in the short term (≤ 6 months, long-term studies not available). No significant differences were observed between the PRN and OAD regimens over the long term (> 6 months, short-term studies not available).[14] Two other SRs[5,12] also reported no differences in IIEF scores between the OAD and PRN treatment regimens.

One SR[15] reported that the efficacy of regular use (daily use and 3 times per week) was comparable with PRN as compared with placebo.[15] However, statistically significant differences favouring the regular regimen were observed when results were pooled for the

four studies comparing dosing regimen.[15] In addition, significant differences favoring three times per week treatment were identified compared with PRN.[15]

Comparisons Between PDE-5Is

One SR[15] that included both OAD and PRN PDE-5I regimens conducted a network MA and rated sildenafil treatment as the most efficacious treatment, followed by vardenafil, avanafil and tadalafil. However, none of the comparisons reached statistical significance. Another SR[5] also reported a nonsignificant trend that sildenafil had a tendency to appear more efficacious than others, followed by vardenafil, avanafil and tadalafil.

Dosage Comparisons

One SR[5] pooled the results from three studies that had dosage subgroups (vardenafil 10 mg vs 20 mg, sildenafil 50 mg vs 100 mg and avanafil 100 mg vs 200 mg) and reported a non-significant trend that higher doses seemed to be more effective.

Early Post-Operative PDE-5I Use and Late Post-Operative Use

One SR[12] reported no significant differences in IIEF scores for either early (≤4 weeks) or late (≥6 months) commencement of PDE-5Is use post-operatively.

Return to Baseline EF after DFW

One RCT[17] reported that tadalafil OAD started within six weeks after RP improved drug-assisted EF, but had no effect on unassisted EF (as measured by return to pre-surgery IIEF scores) following treatment cessation after 9 months.

Time to EF-Recovery (IIEF-EF ≥ 22)

One RCT[19] reported that time to recovery of erectile function (defined as an IIEF-EF score of ≥ 22) was 5.8 months (range 4.9 to 9.2) for OAD tadalafil versus 9.0 months (range 5.5 to 9.2) for the PRN group, and 9.3 months (range 9.0 to 9.9) for placebo. Data could only be provided for 25% of the study group (those who had achieved IIEF-EF scores ≥ 22 during the study period).

Erectile Function as Measured by the Sexual Encounter Profile (SEP-1, SEP-2, SEP-3)

The three SRs[5,12,13] that provided Sexual Experience Profile (SEP-2 and SEP-3) scores reported significant improvements in both SEP-2 and SEP-3 scores in the PDE-5Is group relative to controls.

One SR[13] reported that relative efficacies of the various PDE-5Is drug strategies (OAD versus PRN) could not be assessed due to insufficient data.

One RCT[7] reported significant increases in SEP-1, SEP-2 and SEP-3 scores for patients randomized to tadalafil OAD, both at the end of DBT and OLT. The percent “yes” responses to SEP-1 at the end of DBT had also significantly increased for patients randomized to tadalafil PRN (OLT not reported). Younger patients aged <61 years were more likely to answer SEP-1 and SEP-2 questions with “yes” than older patients. At the end of DBT, the percentage of “yes” responses to SEP-3 had increased significantly with tadalafil OAD vs placebo but not with tadalafil PRN. After all patients had received three months of OLT with tadalafil OAD, the percentage of SEP-3 “yes” responses had increased in all treatment groups, with no significant differences across groups.

Global Assessment Questionnaire (GAQ)

Two SRs[5,13] that provided GAQ scores reported significantly higher scores in the PDE-5I group as compared with controls.

Discontinuation Rate

One SR[13] reported the discontinuation rate. In the PDE-5Is group, the rate was 5.29% in the PDE-5Is group, and 2.84% in the placebo group. The difference was statistically significant.

Treatment Emergent Adverse Events (TEAEs)

PDE-5Is Versus Placebo

All of the SRs reported significantly more treatment emergent adverse events (TEAEs) in the PDE-5I arm than in the placebo arm.[5,12-15] One SR[14] reported incidence rates of TEAEs in the PDE-5Is and placebo groups of 59.63% and 48.37%, respectively, and this difference was statistically significant. Similarly, another SR[13] reported an incidence of TEAEs in the PDE-5Is group of 56.44% versus 40.63%, in the placebo group, a difference that was statistically significant. Another SR[15] reported significantly more TEAEs were found in both regular (daily or three times per week), and PRN groups as compared with placebo.

In one SR,[14] headache, flushing, dyspepsia, and rhinitis were some of the most common adverse events reported. One SR[15] reported that headache was the most common side effect with regular or PRN PDE-5Is as compared with placebo (15.8% vs. 10%) along with flushing (15.8% vs. 10%). Another SR reported TEAE rates for headache (12.08%), dyspepsia (6.76%) and flushing (6.52%), which were significantly less likely to occur with placebo. One SR[13] reported headache, flushing, dyspepsia and rhinitis, all of which were described as mild.

Regular Use versus PRN

One SR[14] reported that TEAEs in the OAD group were not significantly different from those seen in PRN group. Another SR[15] reported that no significant differences were found between either regimen (daily, three times/week) and on-demand use as compared with placebo. Regular use (OAD or three times a week) was not associated with higher proportion of patients suffering side effects when compared with PRN.[14,15]

Comparisons Across PDE-5Is

One SR[15] with network MA of tadalafil, vardenafil, sildenafil, and avanafil reported that tadalafil and vardenafil might be relatively optimal choices in terms of patients presenting with TEAEs.

Stretched Penile Length (SPL) and Standardized Morning Erection Question (SMEQ)

One RCT[7] reported that tadalafil OAD was associated with a significantly greater retention of penile length as compared with placebo (least square mean difference: 4.1 mm). The same RCT reported that significantly fewer patients in the tadalafil OAD group had an absence of morning erections as measured by the SMEQ.

QoL as Measured by EPIC-26 and Treatment Satisfaction as Measured by EDITS and SEAR

EPIC sexual domain scores improved significantly with tadalafil OAD versus placebo at the end of DBT, but not with tadalafil PRN versus placebo. The difference between groups was no longer significant at the end of OLT. Treatment satisfaction (EDITS total scores) increased significantly in both tadalafil groups when compared with placebo at the end of DBT. At the end of OLT, improvement was only significant for tadalafil OAD versus placebo (P = 0.035). No significant treatment group differences were observed for SEAR.

What are the evidence-based guidelines associated with the treatment of penile rehabilitation post radical prostatectomy in adults?

One 2017 guideline[23] reported conflicting data as to whether penile rehabilitation with PDE-5Is improves recovery of spontaneous erections, and also indicated that the data are inadequate to support any specific regimen as optimal for penile rehabilitation. However, the authors suggested that treatment with PRN PDE-5Is is better than doing nothing for the patient, although the baseline condition is rarely recoverable.[23]

One 2014 guideline from the National Institute for Health and Care Excellence (NICE) included a section on managing adverse events after radical treatment of prostate cancer, that was originally published in 2008 and not updated.[20] NICE recommended that men be offered early and ongoing access to specialist ED services, and that men with prostate cancer who experience loss of erectile function should be offered PDE-5Is to improve their chance of spontaneous erections.[20] NICE also recommended that men should be offered vacuum devices, intraurethral inserts or penile injections, or penile prostheses as an alternative If PDE-5Is fail to restore erectile function or are contraindicated.

Two guidelines from the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO) included sections on managing ED after prostate cancer therapy.[21,22] Both recommended PDE-5Is be used to help men with ED, with one guideline[21] recommending that PDE-5Is be used as first-line treatment. One guideline[21] recommended that men who do not respond to PDE-5Is should be referred to a urologist or penile rehabilitation programs, and both guidelines [21,22] recommend that alternate interventions should be offered, such as a vacuum erectile device (VED), a medicated urethral system for erection, or intracavernosal injection. One guideline[21] includes placement of penile prostheses as an alternative penile rehabilitation strategy. One guideline[22] suggested a benefit to initiating the use of any of the above interventions earlier after cancer treatment rather than later.

Limitations

The primary limitation of the included SRs was the limited amount of data for some outcomes (such as comparisons across PDE-5I agents) and inadequate treatment duration in the included studies. Treatment duration varied considerably, ranging from 1.5 to 13 months in the RCTs included in the SRs, and it has been suggested that rehabilitation analyses should ideally be performed 18 to 24 months after NSRP.[17] Some of the conflicting evidence reported from the included SRs may be explained by the potential for confounding due to study design issues. At least three SRs noted that most included RCTs did not report allocation concealment.[13-15] In one SR, the preoperative erectile function of patients in two studies was unclear, meaning that it is not clear whether the ED resulted from RP.[13]

Of the two RCTs included in this RR, one RCT evaluating tadalafil and one RCT evaluating sildenafil, the tadalafil study was limited by treatment and follow-up periods that may have been too short for full assessment of EF recovery, and was industry funded. The sildenafil

study was underpowered, and was also of limited treatment duration, and lacked a pure placebo arm.

The main limitation of the included guidelines was that the strength of the recommendations was not reported. Additionally, one recommendation was out of date,[20] and some were based on low-quality evidence, such as expert opinion and observational studies.[22,23]

Conclusions and Implications for Decision or Policy Making

Evidence from five SRs[5,12-15] suggests that PDE-5Is are more efficacious than placebo or no PDE-5Is for post-RP penile rehabilitation. There is conflicting evidence to demonstrate improved efficacy with longer-term (> 6 months) treatment duration as compared with short-term (≤ 6 months). There is very limited and conflicting evidence to support a benefit with regular dosing (OAD or three times per week) as compared with PRN. No significant differences were observed for higher versus lower dosages, or for early (≤4 weeks) versus late (≥6 months) post-RP PDE-5I use. No statistically significant differences were observed with respect to efficacy or safety between sildenafil, vardenafil, avanafil and tadalafil.

All of the SRs[5,12-15] reported significantly more TEAEs in the PDE-5Is arm than in the placebo arm. The side effects were generally described as mild, and included headache, flushing, dyspepsia, and rhinitis. No differences in TEAEs were observed with regular dosing versus PRN, and no significant differences were observed across the different PDE-5I agents. One SR reported higher treatment discontinuation rates in the treatment group, which is probably related to the higher rates of TEAEs in that group.

One RCT[16] reported that there was no evidence to support a therapeutic benefit of nightly sildenafil use compared to PRN sildenafil dosing for treatment of post-RP ED. However, this study may have been under-powered and lacked a pure placebo arm (both groups were allowed sildenafil PRN).

Four publications[7,17-19] reported post-hoc analyses or secondary outcomes on the same RCT study population administered tadalafil OAD or PRN compared with placebo. Overall, these studies showed that tadalafil OAD was more efficacious than tadalafil PRN and placebo in improving drug-assisted EF and EF generally, shortening the length of time to EF recovery, preserving penile length and morning erections, and improving treatment satisfaction and QoL.

Optimal assessment of EF recovery may have been limited by potential inadequate treatment durations of the available evidence.

Three guidelines[20-22] recommended PDE-5Is to treat ED post-RP, with one guideline[21] recommending that PDE-5Is be used as first-line treatment. One guideline,[23] citing conflicting data to support the efficacy of PDE-5Is, stated that they were better than doing nothing. Three guidelines[20-22] recommended that men be offered vacuum devices, intraurethral inserts or penile injections, or penile prostheses as an alternative if PDE-5Is failed to restore erectile function or were contraindicated. One guideline[22] suggested a benefit to initiating the use of any of the ED interventions earlier after cancer treatment rather than later. Two guidelines[20,21] recommended that men be referred to specialist ED services, penile rehabilitation services, or a urologist for ED issues. The strength of recommendations in the included guidelines was not reported.

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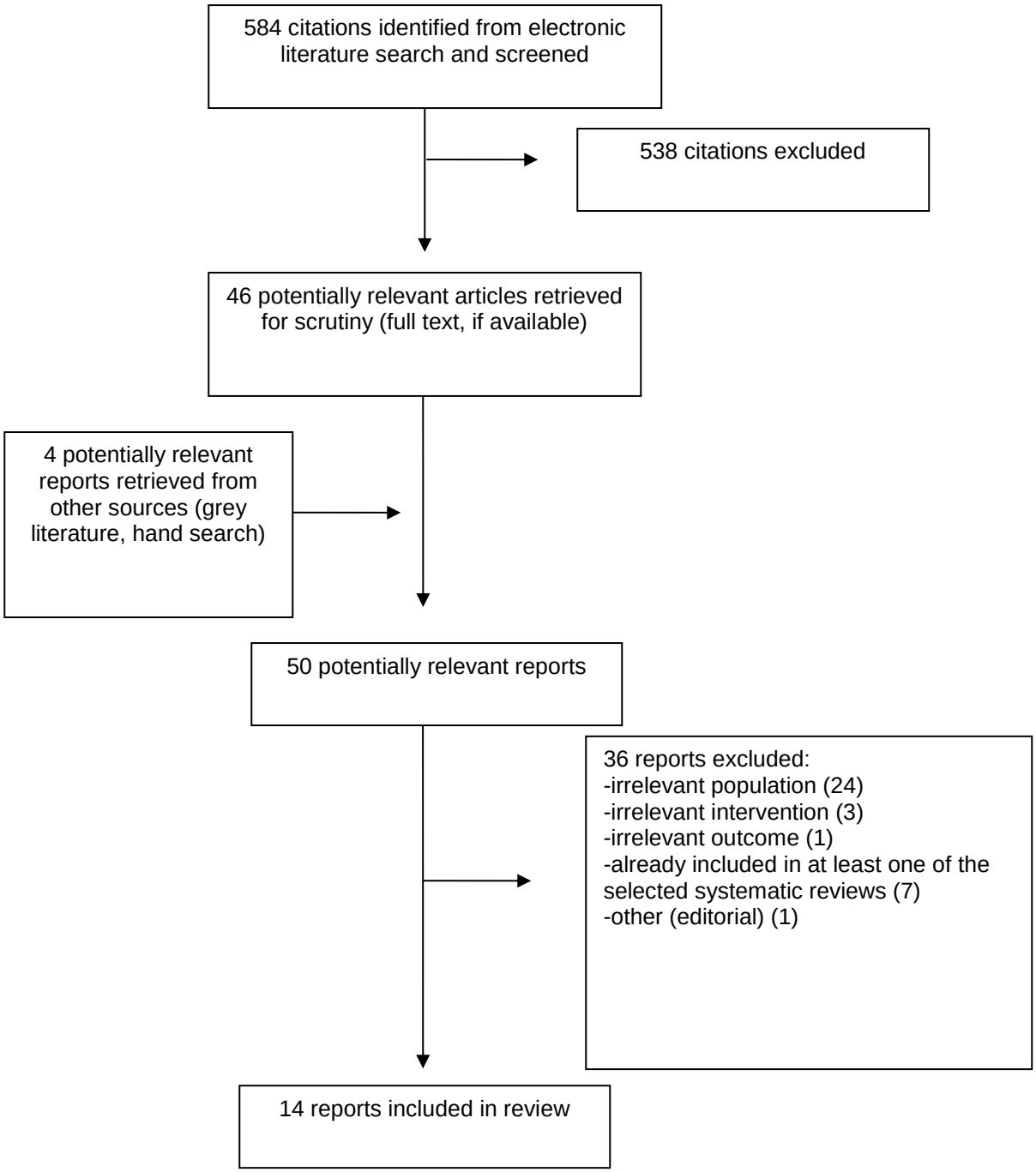
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table A1: Characteristics of Included SRs and MAs

First Author, Publication Year, Country Study Design Electronic Searches, and Search Range	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention	Comparator(s)	Outcome(s) Length of Follow-up
Tian et al, 2017[14] **China** **MA** **Search dates: Inception (assumed) to August 2016.** **PubMed, EMBASE, and MEDLINE**	N = 8 RCTs Various countries	N = 1806 NSRP patients with ED after NSRP; Median age 54 to 67.9 Sample size experimental group: 12 to 207 patients Sample size control group: 12 – 206 patients	Vardenafil: dose ranging from 5 to 10 mg OAD, or 10 mg PRN, n = 2 studies Tadalafil: dose ranging from 5 to 20 mg OAD or 20 mg PRN, n = 4 studies Sildenafil: 50 to 100 mg OAD, n = 1 study sildenafil 50 mg OAD (n = 1 study)	Placebo Sildenafil 50 mg PRN	IIEF-EF TEAEs Follow-up: NR Treatment duration: 1.5 to 13 months
Qiu et al, 2016[15] **China** **MA** **Search date: from 1998 to June 2016** **PubMed, Embase, Cochrane Library**	N = 14 RCTs Various countries	N = 3,175 patients with ED after unilateral NSRP (24%) or bilateral NSRP (76%). Mean patient age: 18 to 75 years (median 24 to 77). Open surgery (53%), conventional laparoscopy (34%), Robot-assisted laparoscopy (13%)	Vardenafil (n = 4 studies): 5 to 10 mg OAD, 10 to 20 mg PRN Sildenafil (n = 4 studies): 25 to 100 mg OAD; 50 mg PRN Tadalafil (n = 5 studies): 5 to 20 mg OAD or 20 mg 3 times per week; 20 mg PRN Avanafil (n = 1 study): 100 mg or 200 mg PRN	Placebo or no PDE-5Is	IIEF scores TEAEs Treatment duration: from 3 to 13 months.

First Author, Publication Year, Country Study Design Electronic Searches, and Search Range	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention	Comparator(s)	Outcome(s) Length of Follow-up
Cui, et al, 2016[12] **China** **MA** **Medline (1966 to June 2014), Embase (1974 to June 2014) and Cochrane Controlled Trials Register**	N = 6 RCTs Various countries	N = 1678 patients with ED after NSRP Median age: 56 to 69 years	Tadalafil: 20 mg PRN (n = 1 study), 5 mg OAD (n = 1 study), 5 mg OAD or 20 mg PRN (n = 1 study) Sildenafil 50 mg OAD (n = 1 study) Vardenafil: 10 mg OAD or PRN (n = 1 study) Avanafil 100 mg PRN (n = 1 study)	Placebo	IIEF-EF SEP-2 SEP-3 AEs headache, dyspepsia and flushing Follow-up: NR Treatment duration: 3 months to 12 months
Li et al, 2014[13] **China** **MA** **Search dates: Inception (presumed) to March 2014** **PubMed, EMBASE and Cochrane Central Register of Controlled Trials**	N = 7 RCTs Various countries	N = 2,655 ED NSRP patients Intervention, (n = 1770) or placebo (n = 885)	Vardenafil 10/20 mg PRN (n = 2 studies); 10 mg OAD or PRN (n = 1 study) Tadalafil 20 mg PRN (n = 1 study); 5 mg OAD or 20 mg PRN (n = 1 study) Sildenafil 50/100 mg OAD (n = 1 study) Avanafil 100/200 mg PRN (n = 1 study) OAD and PRN, various doses	Placebo	IIEF-EF GAQ SEP-2, SEP-3 TEAEs discontinuation rate. Follow-up: NR Treatment duration: 12 weeks to 9 months
Wang et al; 2014[5] **China** **MA**	N = 8 RCTs Various countries	N = 2018 ED NSRP patients	Vardenafil 10 mg OAD or flexible dose PRN (n = 1 study); 10 or 20 mg PRN (n = 1 study)	Placebo or no PDE-5Isls	IIEF SEP-2, SEP-3 GAQ

First Author, Publication Year, Country Study Design Electronic Searches, and Search Range	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention	Comparator(s)	Outcome(s) Length of Follow-up
Cochrane Library (June 2013), PubMed (1966-June 2013), Embase (1984-June 2013), AMED (1985-June 2013), CINAHL (1966-June 2013) and the National Health Service Research Register (1990-June 2013)			Tadalafil 20 mg OAD (n = 1 study); 20 mg PRN (n = 1 study) Avanafil 10 or 20 mg, PRN (n = 1) Sildenafil 50 or 100 mg OAD (n = 1 study); 25 mg OAD 100 mg PRN		AEs Follow-up: NR Treatment duration: 3 months to 13 months

ED = erectile dysfunction; GAQ = Global Assessment Questionnaire; IIEF-EF = International Index of Erectile Function-Erectile Function; MA = meta-analysis; NR = not reported; NSRP = nerve-sparing radical prostatectomy; OAD = once a day; PDE-5i = phosphodiesterase type 5 inhibitors; PRN = pro-re-nata (on demand); RCT = randomized controlled trial; SEP = Sexual Encounter Profile; TEAE = treatment-emergent adverse events

Table A2: Overlap Between Included Systematic Reviews

Primary Study Author, Publication Year	Systematic Review Author, Publication Year				
	Tian, 2017[14]	Qiu, 2016	Cui, 2016	Li, 2014	Wang, 2014[5]
Ajay, 2005		*			
Aydogdu, 2011		*			*
Andreas, 2012		*			
Bannowsky, 2008		*			*
Bannowsky, 2012	*				
Brock, 2003		*		*	*
Canat, 2015	*	*			
Cavallini, 2005					*
Francesco, 2004		*			
Francesco, 2014		*			

Primary Study Author, Publication Year	Systematic Review Author, Publication Year				
	Tian, 2017[14]	Qiu, 2016	Cui, 2016	Li, 2014	Wang, 2014[5]
Gianna, 2010		*			
Montorsi, 2004	*		*	*	*
Montorsi, 2008	*	*	*	*	*
Montorsi, 2014	*		*	*	
Mulhall, 2013		*	*	*	*
Nehra, 2005				*	
Padma-Nathan, 2008	*	*	*	*	*
Pavlovich, 2013	*	*			
Seo, 2014	*	*	*		

Table A3: Characteristics of Included RCTs

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention	Comparator(s)	Outcome(s) Length of Follow-up
Kim et al., 2016[16] **USA**	RCT	N = 94 men with nerve-sparing RP Normal erectile function prior to RP Mean age: 54 years	50 mg sildenafil nightly (n = 47) All patients were allowed 100 mg sildenafil PRN (6 pills per 30 days)	Placebo (n = 47) All patients were allowed 100 mg sildenafil PRN (6 pills per 30 days)	Return to normal erectile function as measured by: RigiScan IIEF-EF Follow-up: 2 weeks, then at 3, 6, 9, 12, and 13 months
Mulhall et al, 2016[17] **Moncada, 2015[19]** **Brock, 2015[7]** **Patel, 2015[18]** **9 European countries and Canada** **(multiple publications reporting on different outcomes or post-hoc analyses of Montorsi, 2014, which was included in 3 SRs)**	RCT (multi-centre)	N = 423 adult men, aged <68 years at the time of nerve-sparing RP Subjectively unimpaired EF No history of any use of erectogenic medications or aids IIEF-EF >/= 22 at Pre-surgery baseline visit	Tadalafil OAD 5 mg (n = 139) Treatment started within 6 weeks after RP	tadalafil PRN 20 mg (n = 142) placebo (n = 141) Followed by 6-week DFW and 3-month OLT with tadalafil OAD for all	Follow-up: DBT: 9 months; DFW: 6 weeks OLT: 3 months <u>Mulhall</u> EF-recovery: Returning back to the pre-surgery IIEF-EF-level at the end of DBT, DFW, and OLT. <u>Moncada</u> Time to EF-recovery (defined as IIEF-EF ≥ 22)

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention	Comparator(s)	Outcome(s) Length of Follow-up
					Brock SPL SEP-1, SEP-2, SEP-3 SMEQ Patel EPIC-26 EDITS SEAR

DBT = double-blind treatment; DFW = drug-free washout; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; EPIC-26 = Changes in Expanded Prostate Cancer Index Composite; IIEF = International Index of Erectile Function; OAD = once a day; OLT = open-label treatment; PRN = pro-re-nata (on demand); RCT = randomized controlled trial; SEAR = Self Esteem and Relationship questionairres; SMEQ = Standardized Morning Erection Question; SPL = stretched penile length

Table A4: Characteristics of Included Guidelines

First Author, Guideline Society or Institute, Year, Country	Objective	Target Users	Methodology
Guidelines			
Salonia et al, 2017[23] **Fourth International Consultation for Sexual Medicine (ICSM 2015)** **Italy**	*"To provide the International Consultation for Sexual Medicine (ICSM) 2015 recommendations concerning management strategies for post-RP erectile function impairment and to analyze post-RP sexual dysfunction other than erectile dysfunction."*	*Patients who wish to continue to be sexually active after RP.*	*"…a literature search for English-language original and review articles published up to August 2016 was performed using Google and the National Library of Medicine's PubMed database."*
Barbera et al;[22] **PEBC, CCO, 2016** **Canada**	*"To examine effective strategies/interventions to manage sexual function side effects as a result of cancer diagnosis and/or treatment with the aim of decreasing distress, and improving quality of life for cancer survivors and their partners."*	*"Healthcare practitioners such as oncologists, radiation therapists, urologists, gynaecologists, primary care providers, surgeons, nurses, physiotherapists, social workers, counsellors, psychologists and psychiatrists."*	*"This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders. The PEBC uses the AGREE II framework as a methodological strategy for guideline development. The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base."*

First Author, Guideline Society or Institute, Year, Country	Objective	Target Users	Methodology
Matthew et al;[21] **PEBC, CCO, 2015** **Canada**	*"… is to develop recommendations that address psychosocial issues, sexual health, fatigue, urinary health, and bowel health outcomes associated with treatment for prostate cancer."*	*1) "Prostate cancer patients who have undergone curative-intent treatment are the target population for this guideline."* *2) "This guideline is targeted for radiation oncologists specializing in prostate cancer, family physicians, urologists, nurses, allied health professionals, and any other care provider involved in follow-up care of prostate cancer."*	*An electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases for existing systematic reviews on the follow-up care of curatively treated prostate cancer patients. OVID was searched from 2000 to week 32 of 2014. In addition, websites/databases of specific guideline developers and systematic review producers were also searched."*
NICE;[20] **NCCC[24]** **2014** **UK**	"*This guideline covers diagnosing and managing prostate cancer in secondary care. It offers information on the best way to diagnose and identify different stages of the disease, and how to manage adverse effects of treatment. It includes recommendations on follow-up in primary care for men with diagnosed prostate cancer."*	*1) Health professionals* *2) Men diagnosed with prostate cancer, their families and carers.*	*"The following databases were searched: The Cochrane Library; Medline and Premedline 1946 onwards; Excerpta Medica (Embase) 1974 onwards; Web of Science [specifically Science Citation Index Expanded; (SCI-EXPANDED) 1899 onwards and Social Sciences Citation Index (SSCI) 1956 onwards], System for Information on Grey Literature In Europe (SIGLE) 1980–2005; Biomed Central 1997 onwards."*

CCO = Cancer Care Ontario; NCCC = National Collaborating Centre for Cancer; NICE = National Institute for Clinical Excellence; PEBC = Program for Evidence-Based Care

Appendix 3: Critical Appraisal of Included Publications

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR

AMSTAR Checklist[9]	Tian, 2017[14]	Qiu, 2016(8)	Cui, 2016[12]	Li, 2014[13]	Wang, 2014[5]
1. Was an a priori design provided	Yes; no protocol referenced	Yes; no protocol referenced	Yes; no protocol referenced	Yes; no protocol referenced	Yes; no protocol referenced
2. Was there duplicate study selection and data extraction	Data extraction: Yes Study selection: NR	Yes	NR	Yes	Yes
3. Was a comprehensive literature search performed	Yes	Yes	Yes	Yes	Yes
4. Was the status of publication used as an inclusion criteria?	NR	Yes	NR	NR	Yes
5. Was a list of studies (included and excluded) provided.	Included but not excluded	Included but not excluded	Included but not excluded	Included but not excluded	Included but not excluded
6. Were the characteristics of the included studies provided	Yes	Yes	Yes	Yes	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	Yes	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes	Yes	Yes
9. Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes	Yes
10. Was the likelihood of publication bias assessed?	Yes	Yes	Yes	NR	NR
11. Was the conflict of interest included?	Yes for SR; Not for included studies	Yes for SR; Not for included studies	Yes for SR; Not for included studies	Yes for SR; Not for included studies	Yes for SR; Not for included studies

Table A6: Strengths and Limitations of Included RCTs using Downs and Black

Strengths	Limitations
Kim 2016[16]	
Reporting The main outcomes to be measured are clearly described. The characteristics of the included patients are clearly described. The intervention of interest is clearly described.	**Reporting** The aim of the study was not clearly described. Estimates of random variability were not provided for the main outcomes. Adverse events were not reported.

Strengths	Limitations
The distributions of potential confounders in each intervention group of the patients were described. The main findings were described. Characteristics of patients lost to follow-up were reported. Actual probability values were reported. **Internal Validity - Bias** Patients were blinded to intervention. Outcome assessors were blinded. Follow-up was the same for all patients. The statistical tests used to assess the main outcomes appeared to be appropriate. Compliance was monitored and reported as 95.9% The outcome measures used appeared to be accurate. **Internal Validity – Confounding** The patients in the treatment and control groups were recruited from the same population. All patients appeared to be recruited over the same time period. The patients were randomized. The intervention assignment was concealed to patients and health-care staff. Adequate adjustment for confounding occurred with intention to treat analysis. Losses to follow-up were taken into account.	**External Validity** It is unclear if the patients asked to participate in the study were representative of the entire population of interest It is unclear if the patients included in the study were representative of the entire population of interest. The care setting was probably not representative of the treatment the majority of patients would receive. **Internal Validity - Bias** Unplanned subgroup analyses were reported. **Internal Validity – Confounding** The study was under-powered.
Mulhall 2016[17]	
Reporting The aim of the study was clearly described. The main outcomes to be measured are clearly described. The characteristics of the included patients are clearly described. The intervention of interest is clearly described. The main findings of the study are clearly described. External Validity It appears that the care settings were probably representative of the treatment the majority of patients would receive. Internal Validity The study subjects were blinded to intervention. Outcome assessors were blinded. Length of follow-up appears to be the same for all patients. The statistical tests used to assess the main outcomes appeared to be appropriate. The outcome measures used appeared to be accurate Internal Validity – Confounding Patients in the different arms were recruited from the same population. The patients were randomized to treatment groups. The study appeared to be sufficiently powered. Intention to treat analysis was performed.	Reporting A list of confounders is not provided. Estimates of random variability were not provided for the main outcomes. Adverse events were not reported. Loss to follow-up was not reported. Probability values were not reported. External validity This was a post-hoc analysis of an already published RCT Compliance was not reported. It is not known whether the patients asked to participate in the study were representative of the entire population of interest. It is not clear whether the patients who were willing to participate were representative of the entire population of interest Internal Validity – Confounding Allocation concealment was not reported. Loss to follow-up was not reported.

Strengths	Limitations
Brock 2015[7]	
Reporting The aim of the study was clearly described. The main outcomes to be measured are clearly described. The characteristics of the included patients are clearly described. Estimates of random variability were provided for the main outcomes. Actual probability values were reported. The intervention of interest is clearly described. A list of potential confounders is provided. The main findings of the study are clearly described. External Validity It appears that the patients asked to participate in the study were representative of the entire population of interest It appears that the care settings were probably representative of the treatment the majority of patients would receive. Internal Validity The study subjects were blinded to intervention. Outcome assessors were blinded. Length of follow-up appears to be the same for all patients. The statistical tests used to assess the main outcomes appeared to be appropriate. The outcome measures used appeared to be accurate Internal Validity – Confounding Patients in the different arms were recruited from the same population. The patients were randomized to treatment groups. Potential confounding factors were included in the analysis. Intention-to-treat analysis was performed. The study appeared to be sufficiently powered.	Reporting Adverse events were not reported. Loss to follow-up was not reported. External validity It is not known whether the patients asked to participate in the study were representative of the entire population of interest. It is not clear whether the patients who were willing to participate were representative of the entire population of interest This was a post-hoc analysis of an already published RCT Compliance was not reported. Internal Validity – Confounding Allocation concealment was not reported. Loss to follow-up was not reported.
Moncada 2015[19]	
Reporting The aim of the study was clearly described. The main outcomes to be measured are clearly described. The characteristics of the included patients are clearly described. Estimates of random variability were provided for the main outcomes. The intervention of interest is clearly described. A list of confounders is provided. The main findings of the study are clearly described. External Validity It appears that the care settings were probably representative of the treatment the majority of patients would receive Internal Validity The study subjects were blinded to intervention. Outcome assessors were blinded. Length of follow-up appears to be the same for all patients. The statistical tests used to assess the main outcomes appeared to be appropriate. The outcome measures used appeared to be accurate	Reporting Adverse events were not reported. Loss to follow-up was not reported. Probability values were not reported for time to return to EF External validity It is not known whether the patients asked to participate in the study were representative of the entire population of interest. It is not clear whether the patients who were willing to participate were representative of the entire population of interest This was a post-hoc analysis or an already published RCT Compliance was not reported. Internal Validity – Confounding Allocation concealment was not reported.

Strengths	Limitations
Internal Validity – Confounding Patients in the different arms were recruited from the same population. The patients were randomized to treatment groups. Intention-to-treat analysis was performed. The study appeared to be sufficiently powered.	
Patel 2015[18]	
Reporting The aim of the study was clearly described. The main outcomes to be measured are clearly described. The characteristics of the included patients are clearly described. Estimates of random variability were provided for the main outcomes. The intervention of interest is clearly described. A list of confounders is provided. Actual probability values were reported. The main findings of the study are clearly described. External Validity It appears that the patients asked to participate in the study were representative of the entire population of interest It appears that the care settings were probably representative of the treatment the majority of patients would receive Internal Validity The study subjects were blinded to intervention. Outcome assessors were blinded. Length of follow-up appears to be the same for all patients. The statistical tests used to assess the main outcomes appeared to be appropriate. The outcome measures used appeared to be accurate Internal Validiy – Confounding Patients in the different arms were recruited from the same population. The patients were randomized to treatment groups. Intention-to-treat analysis was performed. The study appeared to be sufficiently powered.	Reporting Adverse events were not reported. Loss to follow-up was not reported. External validity It is not clear whether the patients who were willing to participate were representative of the entire population of interest This was a post-hoc analysis or an already published RCT Compliance was not reported. Internal Validity – Confounding Allocation concealment was not reported.

Table A7: Strengths and Limitations of Included Guidelines using AGREE

Strengths	Limitations
ICSM: Sexual rehabilitation after treatment for prostate cancer[23]	
• The overall objective of the guideline was specifically described. • The population to whom the guideline is meant to apply was specifically described, and the target users of the guideline are clearly defined. • Limited systematic methods were used to search for evidence • A limited description of the strengths and limitations of the body of evidence was provided	• The health questions covered by the guidelines were not specifically described • It is not clear whether the guideline development group included individuals from all relevant professional groups • It does not appear that the views and preferences of the target population were sought • Criteria for selecting evidence were not provided • The methods for formulating the recommendations were

Strengths	Limitations
• The health benefits, risks, and side effects have all been considered in formulating the recommendations • There was an explicit link between the recommendations and the supporting evidence • The guideline appears to have been peer-reviewed • The recommendations were specific and unambiguous. • The different options for the management of ED were clearly presented • Key recommendations were easily identifiable • The guideline provides a shareable roadmap for addressing sexual dysfunction after RP • The guideline authors stated that no funding was received • The guideline authors included a statement indicating no conflict of interest • The different options for the management of ED were clearly presented • Key recommendations were easily identifiable	not clearly described • No procedure for updating the guideline was provided • The guideline does not describe barriers or facilitators to its application • The potential resource implications of applying the recommendations were not considered • The guideline does not present monitoring or auditing criteria
PEBC, CCO: Interventions to address sexual problems in people with cancer[22]	
• The overall objective of the guideline was specifically described. • The population to whom the guideline is meant to apply was specifically described, and the target users of the guideline were clearly defined. • The guideline development group appears to have included individuals from all relevant professional groups • Systematic methods were used to search for evidence • The strengths and limitations of the body of evidence are clearly described • The methods for formulating the recommendations are clearly described • The health benefits, side effects, and risks have been considered in formulating the recommendations • There is an explicit link between the recommendations and the supporting evidence • The guideline has been externally reviewed by experts prior to its publication • A procedure for updating the guideline is provided • The recommendations are specific and unambiguous • The different options for the management of ED were clearly presented • Key recommendations were easily identifiable • The guideline described barriers or facilitators to its application • The potential resource implications of applying the recommendations were considered • Conflict of interest declaration were made available, and funding sources were easily identified	• The health questions covered by the guidelines were not specifically described • It does not appear that the views and preferences of the target population were sought • Criteria for selecting the evidence were not clearly described. • The guideline provided limited advice and no tools on how the recommendations could be put into practice. • The guideline does not present monitoring or auditing criteria

Strengths	Limitations
PEBC, CCO: Follow-up care and psychosocial needs of survivors of prostate cancer[21]	
• The overall objective of the guideline was specifically described. • The population to whom the guideline is meant to apply was specifically described, and the target users of the guideline were clearly defined. • The population to whom the guideline is meant to apply is specifically described, and the target users of the guideline are clearly defined • The guideline development group appears to have included individuals from all relevant professional groups • Systematic methods were used to search for evidence, with clearly described criteria for selecting evidence • The methods for formulating the recommendations were clearly described. • The health benefits, side effects and risks were considered in formulating the recommendations • There is a link between the recommendations and the supporting evidence • The guideline has been externally reviewed by experts prior to its publication • A procedure for updating the guideline was provided • The recommendations are specific and unambiguous • Different options for the management of ED were described. • Key recommendations are easily identifiable • The funding body was easily identified, and a conflict of interest statement was included.	• The health questions covered by the guidelines were not specifically described • It does not appear that the views and preferences of the target population were sought • The strengths and limitations of the body of evidence were not clearly described • The guideline provided no advice and no tools on how the recommendations could be put into practice. • The guideline did not provide any detail on facilitators or barriers to adoption • The guideline does not present monitoring or auditing criteria • The potential resource implications of applying the recommendations were not considered
NICE/NCCC: Prostate cancer: diagnosis and management20,24	
• The overall objective of the guideline was specifically described. • The health questions covered by the guidelines are specifically described • The population to whom the guideline is meant to apply is specifically described, and the target users of the guideline are clearly defined. • The guideline development group includes individuals from all relevant professional groups • Systematic methods were used to search for evidence, with clearly described criteria for selecting evidence • The guideline provides advice and tools on how the recommendations can be put into practice • The potential resource implications of applying the recommendations have been considered • The strengths and limitations of the body of evidence are clearly described • The methods for formulating the recommendations are clearly described • The health benefits, side effects, and risks have been considered in formulating the recommendations	The recommendation for PDE-5Is after RP has not been updated since 2008.

Strengths	Limitations
• There is an explicit link between the recommendations and the supporting evidence • The guideline has been externally reviewed by experts prior to its publication • A procedure for updating the guideline is provided • Key recommendations are easily identifiable, specific and unambiguous • Competing interests of guideline development group members have been recorded and addressed • The funding body is easily identified • The guideline presented monitoring or auditing criteria • The guideline provided advice and tools on how the recommendations could be put into practice. • The guideline provided detail on facilitators or barriers to adoption • The guideline presents monitoring or auditing criteria • The potential resource implications of applying the recommendations were considered	

CCO = Cancer Care Ontario; ED = erectile dysfunction; ICSM = International Consultation for Sexual Medicine; NCCC = National Collaborating Centre for Cancer; NICE = National Institute for Clinical Evidence; PEBC = Program for Evidence-Based Care

Appendix 4: Main Study Findings and Author's Conclusions

Table A8: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusion
Tian, 2017[14]	
IIEF-EF PDE-5Is improve IIEF-EF significantly as compared with placebo in the short (</= 6 months) and long term (> 6 months): MD: 2.26, 95% CI, 1.45–3.08, *P* < 0.00001; MD: 4.5, 95% CI, 3.6–5.4, *P* < 0.00001) Long-term use of PDF-5Is (> 6 months) can improve IIEF-EF significantly in comparison with short-term use of PDF-5Is (</= 6 months) (MD: 3.9, 95% CI, 3.01–4.8, *P* < 0.00001). OAD PDF-5Issignificantly improved the IIEF-EF compared to placebo in short and long term (MD: 4.08, 95% CI, 3.2–4.97, *P* < 0.00001, and MD: 4.74, 95% CI, 3.79–5.69, *P* < 0.00001). No significant differences were found between PRN and placebo (</= 6months). MD: 2.64, 95% CI, -0.87 to 6.14, *P* = 0.14, and between PRN and OAD group (> 6 months) MD: -0.58, 95% CI, -9.86 to 8.74, *P* = 0.91 Differences between PDE-5I agents not reported. **TEAEs** Incidence rate of TEAEs in PDF-5Isand placebo groups was 59.63% and 48.37%, respectively. Headache, flushing, dyspepsia, and rhinitis were some of the most common adverse events. There were more TEAEs in PDF-5Isgroup in comparison with placebo. OR: 1.55, 95% CI, 1.26–1.91, *P* < 0.0001 TEAEs in OAD group were not significantly different from those seen in PRN group. OR: 1.05, 95% CI, 0.78 to 1.4, *P* = 0.77	*Our meta-analysis suggests that PDE-5Is are efficient and safe for treatment of ED after NSRP, and we should choose regular regimen for short term and regular or on-demand regimen for long term. Further high-quality RCTs are needed to validate this result. (*p. 411)
Qiu, 2016[15]	
IIEF Score PDE-5Is Compared with Placebo PDF-5Is demonstrated significant improvement over placebo: MD 4.89, 95% CI 4.25–5.53, *P* < 0.001 Subgroup analysis: The efficacy of regular use (daily use and 3 times/week) was comparable with on-demand as compared with placebo: MD 4.66, 95% CI, 3.54–5.79, *P* < 0.001; MD 5.13, 95% CI, 2.55–7.71; MD 4.99, 95% CI 4.17–5.81, *P* < 0.001	*In summary, this systematic review suggested that PDE5-Is were safe and efficacious in the treatment of ED after NSRP. Using network meta-analysis, sildenafil seems to be the most efficiency with a slightly higher rate of TEAEs, followed by vardenafil, avanafil and tadalafil, whereas tadalafil had the lowest TEAEs. Direct comparisons between regular and on-demand delivery of PDE5-Is demonstrated statistically significant difference. Given its better outcomes and decreased incidence of TEAEs, regular use of tadalafil seems to be a reasonable management option in the treatment of ED after*

Main Study Findings	Author's Conclusion
IIEF: Regular treatment versus PRN 4 studies (834) patients assessing the efficiency of different method of PDE-5Is, follow-up ranging from 9 to 13 months Statistically significant differences favouring the regular group were reported: MD 3.28, 95% CI, 1.67-4.89, *P* < 0.001. Significant differences favoring 3 times/week treatment were identified compared with PRN. MD 4.09, 95% CI, 1.23–6.95, *P* = 0.005 No significant differences between PDE-5I agents were found. **TEAEs.** Significant differences were reported with regular (daily or three times per week), and PRN use as compared with placebo: RR 1.22, 95% CI, 1.10–1.37, *P* = 0.0003; RR 2.29, 95% CI, 1.40–3.77, *P* = 0.001 Regular use was not associated with higher proportion of patients suffering side effects when compared with PRN: RR 1.02, 95% CI, 0.90–1.16, *P* = 0.72 Stratified by the disparate dosing methods, no significant differences were found between either regimen (daily, three times/week) and on-demand use: RR 0.99, 95% CI, 0.87–1.12, *P* = 0.88; RR 1.68, 95% CI, 0.88–3.24, *P* = 0.12 Headache was the most common side effect with regular or PRN PDE-5Is as compared with placebo:(15.8% vs. 10%) along with flushing (15.8% vs. 10%)	*NSRP in PCa patients who wished to regain sexual function. (p. 9)*
Cui et al, 2016[12]	
IIEF (n = 4 studies) SMD: 4.04, 95% CI, 2.87–5.22, P < 0.00001 favouring PDE-5Is over placebo **Subgroup Analysis** No comparison between PDE-5Is agents was performed. **Early Post-Operative PDE-5I Use (≤4 weeks) and Late Post-Operative Use (≥6 months)** Both groups favoured PDE-5I use similarly over placebo: SMD: 3.97, 95%CI, 1.78 to 6.16, *P* = 0.0004 (early) and SMD = 4.07, 95% CI, 2.68 to 5.47, *P* < 0.00001 (late). **OAD Versus PRN** IIEF score improved similarly in both groups favouring PDE-5I over placebo: SMD: 4.07, 95% CI, 2.68 to 5.47, *P* < 0.00001 (PRN) and SMD: 3.97, 95% CI, 1.78–6.16, *P* = 0.0004 (OAD)	*"This meta-analysis indicates that PDE5 inhibitors to be an effective and well-tolerated treatment for ED after BNSRP. Further high-quality, prospective studies are required to confirm this observation." (p. 27)*

Main Study Findings	Author's Conclusion
Duration of Therapy Similar results in IIEF-EF scores were observed for long-term (> 6 months) versus short term (</= 6 months) PDE-5I treatment duration favouring PDE-5Is over placebo: SMD: 4.07, 95% CI, 2.68–5.47, *P* < 0.00001 (short-term) and SMD: 3.97, 95% CI, 1.78–6.16, *P* = 0.0004 (long-term) **SEP-2 and SEP-3** (n = 2 studies) OR: 14.87, 95% CI, 4.57–48.37, *P* < 0.00001 (SEP-2) and 6.47, 95% CI was 3.00–13.98, *P* < 0.00001 (SEP-3) favouring PDE-5Is over placebo **AEs** Specific adverse events with PDE-5 inhibitors included headache (12.08%), dyspepsia (6.76%) and flushing (6.52%), which were significantly less likely to occur with placebo. **Headache** (n = 6 studies) OR: 2.86, 95% CI, 1.87–4.39, *P* < 0.00001 **Dyspepsia** (n = 4 studies) OR: 4.86, 95% CI, 2.28–10.36, *P* < 0.0001 **Flushing** (n = 3 studies) OR: 5.64, 95% CI, 1.99–16.01, *P* = 0.001	
Li et al, 2014[13]	
IIEF 3 studies (vardenafil, n = 1, and tadalafil, n = 3) PDF-5Isgroup improved significantly when compared with placebo: MD: 4.35, 95% CI, 3.42–5.29; *P* < 0.00001 **GAQ** 3 studies (Vardenafil, tadalafil and avanafil) A significantly higher proportion of patients in PDE-5Is group responded positively. RR: 3.50, 95% CI, 2.31–5.31; *P* < 0.00001 **SEP-2 and SEP-3** 6 studies, 2 classes of PDF-5Is (vardenafil and tadalafil) PDF-5Iswas associated with a significantly greater change in SEP-2 as compared with placebo, MD:	*In summary, our results showed that PDE5-Is significantly improved the erectile function in patients with post-NS-RP ED. Although adverse events commonly occurred in patients, the low discontinuation rate revealed that the safety profile was acceptable. Therefore, PDE5-Is are recommended for the treatment of post-NSRP ED. Patients should be informed of the possible adverse events. (p. 5)*

Main Study Findings	Author's Conclusion
21.49, 95% CI, 16.36–26.63; *P* < 0.00001, and SEP-3: MD: 17.01, 95% CI, 8.46–25.56; *P* < 0.0001 Relative efficacies of these drugs or drug strategies (OAS versus PRN) could not be assessed due to insufficient data. **TEAEs** Incidence of TEAEs: PDE-5Is (56.44%); Placebo (40.63%) Most frequently reported adverse events: headache, flushing, dyspepsia and rhinitis, all of which were mild. TEAEs in PDE-5Is group were significantly more than that in the placebo group: RR 1.42, 95% CI, 1.21–1.65; *P* < 0.0001. **Discontinuation Rate** PDF-5Is(5.29%); placebo (2.84%) Discontinuation rate was significantly more in PDF-5Isgroup than in the placebo group; RR 1.87, 95% CI, 1.16–2.99; *P* < 0.01	
Wang et al, 2014[5]	
IIEF (n = 6 studies) MD: 5.63, 95% CI, 4.26 to 6.99, *P* < 0.00001 in favor of the PDE-5Is arm. **Subgroup Analysis** No statistical significance was observed for various subgroup analyses, including treatment duration, treatment delivery (PRN versus OAD), or PDE-5I agent administered **SEP-2** (n = 4 studies) RR: 1.63, 95% CI, 1.18 to 2.25, *P* = 0.003 favouring the PDE-5Is group when compared to controls. **SEP-3** (n = 5 studies) RR: 2.00, 95% CI, 1.27 to 3.15 favouring the PDE-5Is group when compared to controls. **GAQ** (n = 3 studies) RR 3.53, 95% CI, 2.68 to 4.67 favouring the PDE-5Is arm when compared to placebo.	*PDE5-Is were determined as efficacious and well tolerated for treatment of ED subsequent to BNSRP and early initiation of treatment is recommended. Also our subgroup analysis showed a trend that higher dose, longer course of treatment, on-demand dosing and mild ED are associated with greater responsiveness to PDE5-Is. Additionally, direct comparisons among various PDE5-Is were not available and indirect comparison made in current review found a trend that sildenafil was more effectiveness than the others. Statistical significance for these trends could not be obtained in the subgroup analysis, probably due to insufficient patient numbers. Therefore, to provide sound practical advice for the use of of PDE5-Is for post-BNSRP ED, such as when to initiate treatment, what dosage to use, duration of treatment, selection criteria and which drug is most efficacious, more clinical trials are required. A high degree of heterogeneity was observed in the studies analyzed. Therefore, we recommend close attention to trial design and determination of more objective outcome measurements in future studies.(p. 9)*

Main Study Findings	Author's Conclusion
AEs N = 6 studies reported the number of AEs, of which 531 of 891 patients suffered an AE in the PDE-5Is arm compared to 191 of 450 in controls: RR 2.11 (95% CI 1.66 to 2.67, *P* < 0.00001. Among the AEs, headache was the most frequent event reported. Other common AEs were flushing, dyspepsia and upper respiratory tract complaints.	

AE = adverse event; CI = confidence interval; GAQ = Global Assessment Questionairre; MD = mean difference; PDE-5i = phosphodiesterase type 5 inhibitors; IIEF-EF = International Index of Erectile Function-Erectile Function; MA = meta-analysis; NSRP = nerve-sparing radical prostatectomy; OAD = once a day; OR = odds ratio; PDE-5I = phosphodiesterase type 5 inhibitor; PRN = pro-re-nata (on demand); RCT = randomized controlled trial; RR = relative risk; SEP = Sexual Encounter Profile (question 1 or 2); SMD = standard mean difference; TEAE = treatment-emergent adverse events

Table A9: Summary of Findings of Included RCTs

Main Study Findings	Author's Conclusion
Kim 2016[16]	
RigiScan (rigidity measurement device) Return to normal erectile function was 40% of patients in the treatment arm and 40% of patients in the placebo arm at 13-month follow-up, *P* = 1.0 No statistically significant differences were observed at any point during follow-up. **IIEF-EF** Return to normal erectile function was 29.0% (treatment arm) versus 32.4% (placebo arm) at any point during follow-up, P = 0.79 No statistically significant differences were observed at any point during follow-up.	*In conclusion, in this prospective, randomized, placebo-controlled clinical trial, there was no evidence to support a therapeutic benefit of nightly sildenafil use compared to on-demand dosing for treatment of post-prostatectomy ED. This finding was confirmed with both subjective questionnaires, as well with the RigiScanTM device. Evaluation of the patterns of recovery indicates a significant decrease in function based on RigiScanTM immediately after surgery with rate of recovery to normal EF tapering off at around 9 months. Further evaluation with longer follow-up, other PDE5 inhibitors, and investigation into the role of race/ethnicity on post-treatment EF, is warranted to better understand patterns of recovery with penile rehabilitation. (p. 31)*
Mulhall 2016[17]	
Percentage of Patients with IIEF Scores Back to Baseline* **P* values not reported **<u>After 9 months of DBT:</u>** Tadalafil OAD: 22.3% Tadalafil PRN: 11.3% Placebo: 7.8% **<u>After 6 weeks DFW:</u>** Tadalafil OAD: 12.2% Tadalafil PRN: 9.2% Placebo: 11.4%	*In summary, changing the definition of EF recovery from IIEF-EF ≥ 22 to the more strict definition of "returning back-tobaseline IIEF-EF" had no major impact. Treatment with tadalafil OAD started early after nsRP improved drug-assisted EF, but had no effect on unassisted EF following treatment cessation after 9 months. (p. 682)*

Main Study Findings	Author's Conclusion
After 3 months OLT in each group: Tadalafil OAD: 23 Tadalafil PRN: 24.6 Placebo: 19.9	
Brock 2015[7]	
SPL Greater retention of SPL was observed with tadalafil OAD versus placebo at the end of DBT: LSmean: 95% CI difference OAD versus placebo, 4.1 mm [0.4 to 7.8 mm]; *P* = 0.032). No significant effects on SPL were found for tadalafil PRN vs placebo. **SEP-1 and SEP-2** Significantly increases in both SEP-1 and SEP-2 for tadalafil OAD versus placebo at the end of DBT (*P* = .008) and OLT (*P*= .029 Significant increases in SEP-1 only for PRN at the end of DBT for tadalafil PRN versus placebo (*P* = .038) Younger patients (aged <61 years) were more likely to answer SEP1 and SEP2 questions with "yes" than older patients (61 to 68 years; LSmean difference for SEP1: 11.3%, 95% CI, 4.0 to 18.5; SEP2: 8.2%, 95% CI, 1.3 to 15.0. **SEP-3** SEP-3 at the end of DBT increased significantly with tadalafil OAD vs placebo but not with tadalafil PRN (*P* = .019) After all patients had received 3 months of OLT with tadalafil OAD, SEP-3 had increased in all treatment groups. **Standard Morning Erection Question** Absence of morning erection was reported by 34.2% of patients on tadalafil OAD, 50.0% on tadalafil PRN, and 56.5% on placebo (*P* = .045)	*Our data show a significant protective effect of tadalafil OAD treatment on penile length, associated with accelerated EF recovery as observed by consistent improvements in IIEF-EF, SEP1-3, and recovery of morning erections. Taken together, these effects suggest that tadalafil OAD treatment, if started early, may contribute to protection from structural cavernosal changes after nsRP. This new information may be an important point for physicians to discuss with men undergoing nsRP and interested in preserving penile length and function.* (p. 1096)
Moncada 2015[19]	
IIEF-EF ≥22 at some point during DBT: with OAD, PRN, and placebo was 29.5, 23.9, and 18.4 %, respectively. DBT was too short to achieve EF-recovery (IIEF-EF ≥ 22) in >50 % of patients; median time to EF recovery was non-estimable. Time for 25 % of patients to achieve EF-recovery (95 % CI) was	*In conclusion, patients taking tadalafil OAD (but not those taking PRN) significantly shortened the time to EFrecovery during DBT when compared with placebo. No statistically significant difference in time to EF-recovery was observed between younger and older patients. These data suggest that tadalafil OAD, if started early, may accelerate EF-recovery post-nsRP.* (p. 1037)

Main Study Findings	Author's Conclusion
5.8 (4.9 - 9.2) months for OAD versus 9.0 (5.5 - 9.2) and 9.3 (9.0 - 9.9) months for PRN and placebo, respectively.	
Patel 2015[18]	
EPIC At the end of DBT, EPIC sexual domain-scores improved significantly with tadalafil OAD versus placebo: 9.6, 95% CI, 3.1 to 16.0; *P* = 0.004 Comparisons of PRN versus placebo at end of DBT, and comparisons of tadalafil OAD and PRN versus placebo after OLT were not significant. In older patients (61-68 years); age-by-treatment (*P* ≤ 0.1), EPIC urinary incontinence domain-scores also improved significantly with tadalafil OAD versus placebo. Overall treatment effect across all visits, 8.3, 95% CI, 0.4 to 16.1; *P* = 0.040. In older patients (61-68 years), EPIC urinary incontinence domain scores improved significantly with tadalafil OAD versus placebo. Overall treatment effect across all visits: 8.3, 95% CI, 0.4 to 16.1, *P* = 0.040). **EDITS** Treatment satisfaction increased significantly in both tadalafil groups. EDITS total-scores increased significantly with OAD (*P* = 0.005) and PRN (*P* = 0.041) versus placebo during DBT At the end of OLT, improvement was significant for tadalafil OAD versus placebo only (*P* = 0.035). SEAR No significant differences were observed for SEAR.	*Chronic dosing of tadalafil started early after nsRP increases and accelerates EF recovery [9,20] and also improves patients' QoL. The improvement of urinary incontinence facilitated by tadalafil OAD specifically in elderly patients may contribute to this effect on QoL.(p. 9)*

DBT = double-blind treatment; DFW = drug-free washout; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; EPIC-26 = Changes in Expanded Prostate Cancer Index Composite; IIEF = International Index of Erectile Function; LSmean = least-squares mean; nsRP = nerve sparing radical prostatectomy; OAD = once a day; OLT = open-label treatment; PRN = pro-re-nata (on demand); RCT = randomized controlled trial; SEAR = Self Esteem and Relationship questionairres; SMEQ = Standardized Morning Erection Question; SPL = stretched penile length

Table A10: Summary of Guideline Recommendations

Lead Author; Guideline Society or Institute	Year	Recommendation	Strength of Recommen-dation	Quality of Evidence (Assessed by Guideline Authors)
Salonia et al,[23] **Fourth International Consultation for Sexual Medicine (ICSM 2015)** **Italy**	2017	*"There are conflicting data as to whether penile rehabilitation with phosphodiesterase type 5 inhibitors (PDE-5Is) improves recovery of spontaneous erections"* *"The data are inadequate to support any specific regimen as optimal for penile rehabilitation*."	Grade of recommendation: A Grade of recommendation: C	Level of evidence: 1 Level of evidence: 3
Barbera et al;[22] **PEBC, CCO** **Canada**	2016	*"It is recommended that phosphodiesterase type 5 inhibitor (PDE-5I) medications be used to help men with erectile dysfunction."* *"Men who do not respond to PDE-5I Medications should consider alternate interventions such as a vacuum erectile device (VED), medicated urethral system for erection, or intracavernosal injection."* *"There may be some benefit to initiating the use of any of the above interventions earlier after cancer treatment rather than later."*	NR	Low to High
Matthew et al;[21] **PEBC, CCO** **Canada**	2015	*"Men may be prescribed PDE5 inhibitors as first line treatment.* *Men who do not respond to PDE5 inhibitors will need more advanced treatments and should be referred to a urologist.* *Men may be referred to penile rehabilitation programs, which include PDE5 inhibitors, vacuum constriction devices, intracorporal or intraurethral therapy, or placement of penile prostheses."*	NR	NR: *"Research surrounding management options is lacking.* *Included management options are based on the clinical standard in Ontario or expert opinion of the Prostate Cancer Follow-up Expert Panel."*
NICE;[20] NCCC[24] **UK**	2014	**Managing adverse effects of radical treatment** *"Ensure that men have early and ongoing access to specialist erectile dysfunction services." [2008, amended 2014]* . *"Offer men with prostate cancer who experience loss of erectile function*	NR	*Qualifying statement: "There was GDG consensus to support making this recommendation."* *Qualifying statement: "Evidence from*

Lead Author; Guideline Society or Institute	Year	Recommendation	Strength of Recommen-dation	Quality of Evidence (Assessed by Guideline Authors)
		phosphodiesterase type5 (PDE5) inhibitors to improve their chance of spontaneous erections."[2008] *"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."[2008]*		*randomised trials has shown a clinical benefit for intervention with PDE5 inhibitors."* *Qualifying statement: "This recommendation is based on evidence from observational studies."*

CCO = Cancer Care Ontario; NCCC = National Collaborating Centre for Cancer; NICE = National Institute for Clinical Excellence; NR = not reported; NSRP = nerve-sparing radical prostatectomy; PDE-5I = phosphodiesterase type 5 inhibitor; PEBC = Program for Evidence-Based Practice.