Collaborative Review – Prostate Cancer

Phosphodiesterase Type 5 Inhibitors in Postprostatectomy Erectile Dysfunction: A Critical Analysis of the Basic Science Rationale and Clinical Application

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Abstract

Context: Erectile dysfunction (ED) after radical prostatectomy (RP) has a significant negative impact on a patient's health-related quality of life. Phosphodiesterase type 5 inhibitors (PDE5-Is) have recently been utilized not only as a treatment of ED in this population but also as a preventive strategy in penile rehabilitation programs.

Objective: To elucidate the pathophysiologic mechanisms of post-RP ED, to assess the need for rehabilitation following surgery, and to analyze the basic scientific evidence and clinical applications of PDE5-Is for the prevention and treatment of ED.

Evidence acquisition: A systematic review of the literature using Medline, Cancerlit, and the Cochrane Library was conducted for the period between January 1997 and June 2008 using the keywords erectile dysfunction, radical prostatectomy, and phosphodiesterase inhibitors. Efficacy and safety of PDE5-Is in the randomized, placebo-controlled trials are evaluated in this review, and the limitations of the remaining studies are also discussed.

Evidence synthesis: Post-RP ED has many factors. Cavernosal nerve injury induces pro-apoptotic factors (ie, loss of smooth muscle) and pro-fibrotic factors (ie, an increase in collagen) within the corpora cavernosa. Cavernosal changes may also be attributed to poor oxygenation due to hemodynamic changes. Experimental data support the concept of cavernosal damage and suggest a protective role for daily dosages of a PDE5-I; however, similar data have not yet been replicated in humans. Penile rehabilitation programs are common in clinical practice, but there is no definitive evidence to support their use or the best treatment strategy. PDE5-Is are efficacious and safe in young patients with normal preoperative erectile function who have undergone bilateral nerve-sparing radical prostatectomy. On-demand use of a PDE5-I may be at least as efficacious as daily use. PDE5-I use in penile rehabilitation programs is not supported by rigorous level 1 evidence-based medicine.

Conclusions: PDE5-Is are an efficacious and safe treatment for post-RP ED in properly selected patients. The experimental results on the protective role of daily dosages of PDE5-Is, while robust, have not been replicated in humans. With current human data, the role of a PDE5-I alone as a rehabilitation strategy is unclear and deserves further investigation.

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1. Introduction

Radical prostatectomy (RP) is a commonly used treatment for localized prostate cancer in patients with a life expectancy of at least 10 yr [1]. The number of RPs has been increasing annually, and currently many patients are treated at younger ages [2]. Erectile dysfunction (ED) is the most common complication in these patients, having a significant negative impact on patients’ health-related quality of life and well-being [3]. Erectile function may take up to 4 yr to return, even in younger men with normal preoperative potency who have undergone bilateral nervesparing radical prostatectomy (BNSRP) [4–6]; however, 20–80% of these patients may never return to normal erectile function [7].

The advent of phosphodiesterase type 5 inhibitors (PDE5-Is) revolutionized ED treatment with an average success rate of 60–70% in the general ED population [8]. Nevertheless, these rates are significantly lower and vary considerably in post-RP ED patients [7]. New insights into the pathophysiology of post-RP ED have led to the development of penile rehabilitation strategies. These new strategies are promising, but they are still controversial due to the lack of strong evidence [9].

2. Evidence acquisition

This review aims to elucidate the current knowledge on the pathophysiologic mechanisms of post-RP ED, to assess the need for penile rehabilitation following surgery, and to analyze the basic science rationale of PDE5-I as well their clinical applications for the prevention and treatment of post-RP ED. A systematic review of the literature using Medline, Cancerlit, and the Cochrane Library was conducted for the period between January 1997 and June 2008. An electronic search was conducted that included all English-language studies using the keywords erectile dysfunction, radical prostatectomy, and phosphodiesterase inhibitors. Only full-text articles were included and analyzed.

3. Evidence synthesis

3.1. Pathophysiology of postprostatectomy erectile dysfunction

ED becomes clinically evident immediately after RP. This pattern is associated with nerve injury to the corpora cavernosa during surgery. Even in BNSRP, some trauma to the nerves, known as neuropraxia, is inevitable due to their anatomical proximity to the prostate. Commonly hypothesized causes of post-RP ED include nerve traction/percussion, thermal damage due to electrocautery use, nerve ischemia due to vascular injury, and local inflammatory effects associated with surgical trauma [10].

Neuropraxia results in loss of daily and nocturnal erections associated with persistent cavernous hypoxia. There are in vitro and animal in vivo data supporting the concept that penile hypoxia results in collagen accumulation, smooth-muscle apoptosis, and fibrosis due to transforming growth factor beta 1 (TGF-β1) production, while prostaglandin E1 (PGE1) and cyclic adenosine monophosphate (cAMP) production, which suppresses TGF-β1-induced collagen synthesis, are inhibited under hypoxic conditions [11–16]. Furthermore, synthesis of endothelin-1 (ET-1; a potent constrictor of penile smooth muscle and a profibrotic peptide) is increased by TGF-β1 and prolonged hypoxia [17]. This vicious cycle leads to ED because of veno-occlusion of the corpus cavernosum and to permanent ED (Fig. 1). Müller et al [18] studied the effect of hyperbaric oxygen therapy (HBOT) in rats with cavernous nerve injury. Rats treated with hyperbaric oxygen had higher ratio of intracavernosal pressure (ICP) to mean arterial pressure (MAP) and higher levels of penile nerve growth factor (NGF) and endothelial nitric oxide synthase (eNOS) compared with the control group. (No data are presented on oxygen saturation or pO2 levels.) Although there was a trend toward improvement in the ratio of smooth muscle to collagen with

Fig. 1 – The vicious cycle of post-radical prostatectomy erectile dysfunction.
HBOT, these data did not reach a statistically significant difference. Therefore, cavernosal oxygenation as a treatment strategy remains a controversial subject.

There is evidence that cavernosal nerve injury induces proapoptotic factors (ie, loss of smooth muscle) and profibrotic factors (ie, an increase in collagen) within the corpora cavernosa [19]. Based on this theory, smooth-muscle fibrosis and atrophy observed in cavernosal tissue may be due to the ablation by neural trauma of certain key growth factors produced by the cavernosal nerves and to the production of cytokines and reactive oxygen species by the damaged nerve axons [20,21]. The cavernosal tissue counteracts this process through the endogenous induction of the inducible isoform of nitric oxide synthase (iNOS) and its second messenger, cyclic guanosine monophosphate (cGMP). This theory provides the rationale for the administration of a PDE5-I after RP. The immunophilin ligand FK506 has been reported to exert a neuroprotective effect, preserving penile erections in rats as early as 1 d following a partial nerve-crush injury [22]. Further support is provided by recent data showing that FK506 reduces the degree of ED following cavernous injury in the rat model and results in the following: improved ICP/MAP, restored iNOS staining, reduced apoptosis, preserved cavernosal architecture, and decreased oxidative stress-associated tissue damage through upregulation of the antioxidant enzyme glutathione peroxidase (GPX) [23–25].

In a small study, which included 19 post-RP patients, a significant decrease in the elastic fibers and smooth-muscle fibers and a significant increase in the collagen content were reported in the late (12 mo) postoperative period compared with both the early (2 mo) postoperative period and the preoperative period [26]. These structural alterations clinically result in veno-occlusive dysfunction. The incidence of venous leakage increases in proportion to the time interval after surgery, supporting these pathophysiologic mechanisms as the cause of the leakage and providing the rationale for early penile rehabilitation before penile fibrosis occurs. In a landmark study, Montorsi et al [27] showed that penile rehabilitation with intracavernous alprostadil is associated with venous leakage in 17% of the treated patients compared with 53% of patients in the control group. Furthermore, Mulhall et al [28] reported that postoperative venous leakage increased from 14% at 4 mo to 35% between 9 mo and 12 mo.

In addition to the fundamental role of cavernous nerve preservation during RP, there is evidence that arterial insufficiency contributes to the pathophysiology of ED. Mulhall et al [28] reported that the incidence of arterial insufficiency was 59% after RP, not related to postoperative time. Arterial insufficiency is attributed to damage of the lateral and apical accessory pudendal arteries (APAs) during surgery. The prevalence of damaged APAs ranges from 4% to 75%, being higher in laparoscopic RP and after cadaveric dissection or use of arteriography [29,30]. Rogers et al [31] reported that preservation of APAs may be associated with better recovery of sexual function (93% vs 70%) and shorter interval to recovery (6 mo vs 12 mo). McCullough et al [32], in a penile duplex Doppler study with 174 patients after nerve-sparing radical prostatectomy (NSRP), found a low incidence of arterial insufficiency (19%), questioning the clinical importance of APAs.

These pathophysiologic mechanisms may lead to progressive penile shortening. Four studies reported

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Mean age, yr (range)</th>
<th>Type of surgery (%)</th>
<th>Assessment of preoperative EF using IIEF</th>
<th>Patients with decrease in penile stretched length (%)</th>
<th>Penile shortening</th>
<th>Time after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraiman et al [33]</td>
<td>100</td>
<td>60.6 (47–74)</td>
<td>BNSRP (90)</td>
<td>No</td>
<td>NA †</td>
<td>NA †</td>
<td>Mean: 9.4 mo (range: 1.7–27.6) 3 mo</td>
</tr>
<tr>
<td>Munding et al [34]</td>
<td>31</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>71</td>
<td>0.5–4 cm</td>
<td>3 mo</td>
</tr>
<tr>
<td>Savoie et al [35]</td>
<td>63</td>
<td>59.1 (42–76)</td>
<td>BNSRP (74.6)</td>
<td>No</td>
<td>68</td>
<td>0.5–5 cm</td>
<td>3 mo</td>
</tr>
<tr>
<td>Gontero et al [36]</td>
<td>126</td>
<td>65.4 (SD: 6.7)</td>
<td>BNSRP or UNSRP (39.7)</td>
<td>Yes</td>
<td>100</td>
<td>2.3 cm at 12 mo after surgery, peak change at catheter removal</td>
<td>No shortening</td>
</tr>
<tr>
<td>Briganti et al [37]</td>
<td>33</td>
<td>56.5 (50–65)</td>
<td>BNSRP (100)</td>
<td>Yes</td>
<td>No shortening</td>
<td>No shortening</td>
<td></td>
</tr>
</tbody>
</table>

BNSRP = bilateral nerve-sparing radical prostatectomy; UNSRP = unilateral nerve-sparing radical prostatectomy; IIEF = International Index for Erectile Function; EF = erectile function; SD = standard deviation; NA: not available.

† Penile shortening was recorded as time from surgery increased.
various shortening rates [33–36], while one study reported no significant change in penile length [37]. These studies are not methodologically comparable (Table 1). Major concerns include the age of the patients, the preoperative erectile function assessed by the International Index for Erectile Function (IIEF), the preservation or neurovascular bundles (bilateral or unilateral), and the time of the postoperative measurement. Patients recovering early potency may be protected from fibrosis which leads to penile shortening.

3.2. Is it possible to predict erectile function after radical prostatectomy?

The successful recovery of erections following RP has been revolutionized by the nerve-sparing technique described by Walsh [38]. It is well established that BNSRP is associated with higher rates of postoperative potency in the range of 50–90% [3,5,39]. Several technical tips and modifications have been described to further improve outcome, such as the intraoperative magnification, the intrrafascial technique, and the preservation of the nerve fibers on the ventral parts of the prostate [30,40–44]. Laparoscopic and robotic-assisted approaches appear to be associated with results that are at least equivalent [7,45–47]. These techniques have been described to improve potency rates, but this has yet to be proven with a methodologically sound, head-to-head comparative study. It must be emphasized that the definition of potency in post-RP studies is unique for the ED literature because almost all studies include the patients that responded to treatment with PDE5-Is as potent.

In addition to the use of the improved BNSRP technique, age and preoperative erectile function are important in predicting postoperative erectile function [5,39,48–50]. In all of the aforementioned studies, potency rates of about 70–90% are to be expected in patients 50–60 yr old, declining to <50% in patients >70 yr. Preoperative erectile function, however, is a critical factor. Recovery of erections cannot be expected in a man with ED preoperatively, despite a "perfect" technique or a young age. The importance of proper assessment of preoperative erectile function must be emphasized. Validated instruments, such as the IIEF, should be used before and after RP to document changes in potency status [51,52].

3.3. Do we need penile rehabilitation programs?

The etiology of ED after RP is multifactorial and includes neurogenic and vasculogenic factors. Even with meticulous nerve-sparing technique, the commonly associated neuropaxia may take as long as 4 yr to resolve [4,7]. During this period, cavernosal fibrosis, penile shortening, and venous leakage may become evident. These pathophysiologic changes are not reversible, and response to pharmacotherapy will be suboptimal or absent. Post-RP ED is a common problem, with reported rates of 26–100% for complete ED and 16–48% for partial ED [53]. This wide range can be explained by the differing manners of assessment in clinical trials, which can be difficult to interpret and inconsistent: (a) there are substantial differences in the surgical technique; (b) patient selection criteria, including age and comorbidities, differ substantially; and (c) most studies do not use validated tools to evaluate potency, while many estimate postoperative potency rate by including those patients responding to PDE5-Is [8].

The aim of a penile rehabilitation program is to preserve the functional smooth-muscle content of the corpus cavernosum during the neuropraxia period. The crucial questions are, therefore, how to rehabilitate and when to rehabilitate. Emerging data from animal studies suggest that rehabilitation is possible [19–21,54,55]. Several clinical trials support the use of intracavernosal injections, PDE5-Is, intraurethral alprostadil, vacuum constriction devices (VCD), combination treatments, and neuromodulatory therapy in penile rehabilitation programs [9,27,55–60]. The major criticisms of these studies include retrospective design, absence of control group, nonrandomized nature, small patient number, and short term of follow-up [55]. PDE5-Is and intracavernosal injections are more commonly used in rehabilitation programs than are other treatment options [55,61]. Regular use is proffered, starting as early as possible (from the day of catheter removal or during the first month after surgery), although there are no approved guidelines. Bannowsky et al [62] suggested that the selection of PDE5-I in rehabilitation programs should only be based on the presence of nocturnal tumescence documented by the Rigiscan device (Timm Medical Technologies, Inc, Eden Prairie, MN). To support this hypothesis, Bannowsky et al treated 23 patients with preserved nocturnal erections with nightly doses of sildenafil 25 mg per day for 52 wk and compared them with a control group of 18 patients [63]. The mean IIEF question 5 (IIEF-5) score decreased from 20.8 to 14.1 in the sildenafil group and from 21.2 to 9.3 in the control group (p < 0.001). In the sildenafil group, 47% of patients achieved and maintained a penile erection sufficient for vaginal intercourse, compared with 28% in the control group.
With additional doses of sildenafil (50–100 mg) on demand, this baseline potency was increased to 86% overall potency in the sildenafil group versus 66% in the control group. Currently, there are no studies comparing rehabilitation programs, and there is no evidence to support one particular program over another.

3.4 Basic science rationale of phosphodiesterase type 5 inhibitors in postprostatectomy erectile dysfunction

PDE5-Is increase cGMP levels which, in turn, exert an antifibrotic action on the cavernous tissue. The production of cGMP is dependent on nitric oxide (NO). Since the production of NO by the neuronal nitric oxide synthase (nNOS) is impaired after surgery, NO is produced mainly from the induction of iNOS and eNOS. Long-term use of a PDE5-I may amplify the depressed NO signaling pathway that inhibits hypoxia-associated fibrosis.

Several experimental studies support this theory (Table 2). In four studies, sildenafil has been shown to (1) improve or normalize the ratio of smooth-muscle to collagen, (2) increase smooth-muscle replication, (3) reduce the apoptotic index, (4) preserve endothelial integrity (preserving platelet endothelial cell adhesion molecule-1 [CD31] and eNOS expression), (5) increase GPX levels (an antioxidant enzyme), and (6) decrease nitrotyrosine (NT) levels (an oxidative stress marker) [21,24,64,65]. In three studies, tadalafil has been shown to (1) normalize the ratio of smooth muscle to collagen; (2) increase smooth muscle replication; (3) reduce the apoptotic index; (4) normalize endothelin B (ETB) expression; and (5) increase the phosphorylation of the two survival-associated kinases, Akt and extracellular signal-regulated kinase 1/2, but tadalafil did not rescue the neurectomy-induced underexpression of nNOS and eNOS [54,66,67]. Finally, vardenafil has been shown, in one study, to increase iNOS and to proliferate cellular nuclear antigen expression (smooth-muscle cell replication), with normalization of the ratio of smooth muscle to collagen and without effecting the

### Table 2 – Basic scientific data on the role of phosphodiesterase type 5 inhibitors (PDE5-Is) in the cavernous nerve injury animal model (rats)

<table>
<thead>
<tr>
<th>Study</th>
<th>PDE5-I</th>
<th>Dosage</th>
<th>Functional results</th>
<th>Structural results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrini et al [20]</td>
<td>Vardenafil</td>
<td>30 mg/l of drinking water for 45 d</td>
<td>Normalized the dynamic infusion cavernosometry drop rate</td>
<td>Increased iNOS; increased smooth muscle replication; normalized ratio of smooth muscle to collagen; no effect in apoptotic index Normalized ETB expression; almost normalized ratio of smooth muscle to collagen; absence of hypoxyprobe labeling in smooth muscle cells; did not rescue the neurectomy-induced hypoxia-expression of nNOS and eNOS</td>
</tr>
<tr>
<td>Vignozzi et al [66]</td>
<td>Tadalafil</td>
<td>2 mg/kg per day in drinking water for 3 mo</td>
<td>NA</td>
<td>Normalized ETB expression; almost normalized ratio of smooth muscle to collagen; did not rescue the neurectomy-induced hypoxia-expression of nNOS and eNOS</td>
</tr>
<tr>
<td>Ferrini et al [65]</td>
<td>Sildenafil</td>
<td>20 mg/kg per day in drinking water for 45 d</td>
<td>Normalized the dynamic infusion cavernosometry drop rate</td>
<td>Improved ratio of smooth muscle to collagen; reduced apoptotic index Increased GPX levels; decreased NT levels</td>
</tr>
<tr>
<td>Lagoda et al [24]</td>
<td>Sildenafil</td>
<td>20 mg/kg every 8 h SC for 7 d</td>
<td>Improved ICP/MAP ratios</td>
<td>Normalized ratio of smooth muscle to collagen; increased smooth muscle replication; normalized apoptotic index</td>
</tr>
<tr>
<td>Kovanecz et al [21]</td>
<td>Sildenafil</td>
<td>20 mg/kg per day in drinking water for 45 d</td>
<td>Normalized dynamic infusion cavernosometry</td>
<td>Protected ratio of smooth muscle to collagen; preservation of CD31 and eNOS expression; reduced apoptotic index</td>
</tr>
<tr>
<td>Kovanecz et al [54]</td>
<td>Tadalafil</td>
<td>5 mg/kg per day retrolingually for 45 d</td>
<td>Normalized the low response to papaverine</td>
<td>Decreased apoptotic cells; increased Akt and extracellular signal-regulated kinase 1/2</td>
</tr>
<tr>
<td>Mulhall et al [64]</td>
<td>Sildenafil</td>
<td>20 mg/kg per day SC for 28 d</td>
<td>Improved ICP/MAP ratios</td>
<td>Protected ratio of smooth muscle to collagen; preservation of CD31 and eNOS expression; reduced apoptotic index</td>
</tr>
<tr>
<td>Lysiak et al [67]</td>
<td>Tadalafil</td>
<td>1.3 g/day for 20 d via oral gavage</td>
<td>NA</td>
<td>Protect ratio of smooth muscle to collagen; preservation of CD31 and eNOS expression; reduced apoptotic index</td>
</tr>
</tbody>
</table>

iNOS = inducible nitric oxide synthase; eNOS = endothelial nitric oxide synthase; nNOS = neuronal nitric oxide synthase; SC = subcutaneously; ICP (AUC) = intracavernosal pressure (area under the curve); ICP/MAP = intracavernosal pressure/mean arterial pressure; ETB = endothelin B; GPX = glutathione peroxidase; NT = nitrotyrosine; NA = not available.
apoptotic index. All of the previously mentioned animal studies were based on cavernosal nerve resection or crush (without removal of the rat prostate). It is not clear whether the results might be different if the prostate and seminal vesicles had been removed from these rats [55].

Can the results of these studies be applied to humans? The answer is unknown. There are only two human studies assessing cavernosal tissue before and after treatment. Schwartz et al [68] assessed the effect of sildenafil on the intracorporal smooth-muscle content of patients after RP. Twenty-one previously potent volunteers received sildenafil 50 mg or sildenafil 100 mg, respectively, every other night for 6 mo beginning on the day of catheter removal. Cavernosal biopsy was performed before incision for RP and under local anesthesia 6 mo later. In the sildenafil 50 mg group, there was no statistically significant change in mean smooth-muscle content (51.5% vs 52.7%), while in the sildenafil 100 mg group there was a statistically significant increase in mean smooth-muscle content 6 mo after surgery (42.8% vs 56.9%, p < 0.05). Iacono et al [69] reported that the percentage of connective tissue and the elastic fiber count did not differ significantly before and after RP in 21 patients treated with sildenafil citrate (sildenafil citrate 50 mg, 3 times per week for 2 mo). However, there was no placebo group in these two studies, and the effect on the return of potency is unknown.

3.5. Clinical applications of phosphodiesterase type 5 inhibitors as prophylactics in post–radical prostatectomy patients

The earlier application of pharmacologic regimens aimed at preventing cavernosal hypoxia after RP. Montorsi et al [27] showed in a prospective, randomized trial in a small group of patients that early postoperative administration of alprostadil injections significantly increased the recovery rate of spontaneous erections after BNSRP. Mulhall et al [56] showed in a nonrandomized study in a group of BNSRP patients who had not responded to sildenafil that a pharmacologic penile rehabilitation protocol that included sildenafil and intracavernosal injections of alprostadil resulted in higher rates of spontaneous functional erections and sildenafil response 18 mo after surgery. The efficacy of nightly doses of sildenafil in post-BNSRP patients was investigated in a prospective, two-center, randomized, double-blind, parallel-group, placebo-controlled study with 76 patients [60]. Sildenafil 50 mg, sildenafil 100 mg, or placebo was administered every night for a total of 36 wk, followed by an 8-wk washout. Treatment started 4 wk after surgery. The a priori end point was return of preoperative erectile function as measured by a combined score of ≥8 for IIEF-3 and IIEF-4 and a positive response to “Were erections good enough for satisfactory sexual activity?” after the 8-wk washout and without any erectogenic aids. Normalization of spontaneous erectile function occurred in only 4% of the placebo group (n = 1 of 25) versus 27% (n = 14 of 51, p = 0.0156) of the sildenafil group. This study demonstrated that at 48 wk, surgery alone was inferior to surgery plus a rehabilitative regimen that included a PDE5-I. Though the differences in treatment versus placebo achieved statistical significance, the relatively low numbers enrolled in this study weaken the strength of the result. In a subanalysis with 54 patients, there appeared to be a dose-dependent improvement in nocturnal penile tumescence and rigidity (NPTR) using the Rigiscan device in the treatment group with little improvement in the placebo over their postoperative nadir (Fig. 2) [58]. This is the only randomized, placebo-controlled study that presents objective and non-questionnaire-based data on the possible value of penile rehabilitation with the PDE5-Is.

Gallo et al [70] assessed time-dependent vardenafil response in 40 men treated with vardenafil on demand following RP (22 patients underwent BNSRP and 18 patients underwent unilateral nerve-sparing radical prostatectomy [UNSRP]). All patients were treated with vardenafil 20 mg on demand for 6 mo, using the drug at least three times per week (before sexual intercourse). Responders were given vardenafil on demand for an additional 6 mo. The authors reported statistically significant improvement of the IIEF-5 score compared with the baseline, but no further improvement was noticed at 9 mo and at 12 mo. However, this study provides limited information because it lacked a control group and because the definition of on-demand treatment and the number of vardenafil treatments were not reported.

Montorsi et al [71], in a prospective randomized, double-blind, double-dummy, multinational, multicenter, parallel-group study, assessed the efficacy of on-demand versus nightly dosages of vardenafil versus placebo in 628 patients after BNSRP with normal preoperative erectile function. The study was done at 87 centers across Europe, Canada, South Africa, and the United States. Dropout rates were 31%, 35%, and 33% in the placebo, nightly vardenafil, and on-demand vardenafil groups, respectively. Erectile function and sexual intercourse completion rates improved significantly in both treatment arms compared to placebo during the initial double-blind period. IIEF erectile function domain scores ≥22
were 24.8%, 32.0%, and 48.2% for the placebo, vardenafil nightly, and vardenafil on-demand groups, respectively, and Sexual Encounter Profile question 3 (SEP-3) rates of positive response were 25.0%, 34.5%, and 45.9% for the placebo, vardenafil nightly, and vardenafil on-demand groups, respectively, \( (p = 0.0001) \). During the single-blind, washout phase and the open-label, on-demand phase, no statistically significant differences were observed in IIEF or SEP-3 scores among groups. Unlike the sildenafil study \[60\], this study did not show that either on-demand vardenafil or nightly vardenafil was more effective in improving erectile function and sexual intercourse completion rates than placebo after the 8-wk washout period. The advantage of the treatment arms over placebo was also not sustained in the open-label phase. This is the largest randomized, placebo-controlled clinical trial of PDE5-I in post-RP ED published so far. The contrasting results between the sildenafil and vardenafil studies may be secondary to the surgical site selection, agent used, dosing schedule, the dosages used, and the differing end points. Neither study addresses long-term return of function. These results may prompt reconsideration of the current clinical practice of prescribing a PDE5-I after RP.

\[3.6.\] Treatment

Response rates to sildenafil after NSRP range from 10% to 76% (the higher rates reported after BNSRP), while the response rates after non–nerve-sparing RP (NNSRP) ranged from 0% to 15% \[72–86\] (Table 3). There is considerable heterogeneity between these studies, and there are no data currently available from multicenter, randomized, placebo-controlled trials designed specifically to address efficacy of sildenafil in post-RP ED \[87\]. The response to sildenafil has been shown to improve as time passes. The best response rates were recorded 1 yr after surgery. The patient’s penile vascular status assessed by duplex penile Doppler ultrasonography within 6 mo after RP is correlated with the response to sildenafil. Ohebshalom et al reported that 72% (23/32) of patients with normal vascular status responded to sildenafil compared with 43% (34/79) of patients with abnormal vascular status \( (p = 0.03) \) \[88\]. Furthermore, most patients required titration to the highest recommended dose (100 mg). The adverse-event profile was typical for sildenafil, while discontinuation rates due to adverse events were similar to the general ED population.

Another randomized, multi-institution, 12-wk study compared the effects of sildenafil 100 mg on-demand in combination with acetyl-L-carnitine 2 g per day and propionyl-L-carnitine 2 g per day to
sildenafil 100 mg on demand and to placebo in 96 patients seeking treatment for their ED after surgery [89]. All patients had undergone a BNSRP 5 mo to 2 yr before treatment (average time after surgery: 1.3 yr, 1.1 yr, 1.2 yr, respectively). The mean post-treatment IIEF erectile function domain scores were 27.3 in the combination group, 21.7 in the sildenafil group, and 11.7 in the placebo group, with no discernible placebo treatment effect. Improvement was also reported in the sexual intercourse satisfaction, orgasm, and general sexual well-being domains of the IIEF; however, no specific statistical data were provided beyond a statement that improvement was significant. The rationale of this combination is poorly supported by the possibly antifibrotic activity of carnitines.

The efficacy and safety of vardenafil was assessed in a 12-wk, multicenter, prospective, randomized, double-blind, placebo-controlled, fixed-dose, parallel group study including 34 centers in the United States, 24 centers in Canada, and a total of 440 men [90]. BNSRP and UNSRP were performed in 73% and 27% of patients, respectively. The mean age of the patients was 60 yr, 61 yr, and 60 yr in the placebo, vardenafil 10 mg, and vardenafil 20 mg groups, respectively. Nonresponders to sildenafil and patients who discontinued sildenafil due to adverse events were excluded from this study. Patients had undergone RP a mean of 1.7 yr (range: 0.4–5.1 yr) before entering the study. The mean IIEF erectile function domain scores after treatment were 15.3, 15.3, and 9.2 for the vardenafil 10 mg, vardenafil 20 mg, and placebo groups, respectively ($p < 0.0001$). The mean rates of positive response to SEP-2 were 47%, 48%, and 22% of patients using vardenafil 10, vardenafil 20 mg, and placebo, respectively, and the mean rates of positive response to SEP-3 were 37%, 34%, and 10% of patients using vardenafil 10, vardenafil 20 mg, and placebo, respectively ($p < 0.0001$). Both vardenafil dosages appeared to be less effective in patients who underwent UNSRP and in patients with increased ED severity at baseline (no statistical data

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**Table 3 – Clinical data on sildenafil treatment for post–radical prostatectomy erectile dysfyunction**

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<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Type of surgery (No.)</th>
<th>Efficacy tool</th>
<th>Response rates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong et al [72]</td>
<td>198</td>
<td>BNSRP (188) NNSRP (10)</td>
<td>EDITS score 1 or 2 in Q1 and Q2 (n = 80)</td>
<td>54-60 after 18-24 mo</td>
</tr>
<tr>
<td>Jarow et al [73]</td>
<td>77</td>
<td>Not specified</td>
<td>IIEF-5, satisfaction (single five-scale question)</td>
<td>Mean IIEF-5 score: 10.8 ± 9.2 Satisfaction: 35 (score 4 or 5)</td>
</tr>
<tr>
<td>Lowentritt et al [74]</td>
<td>84</td>
<td>BNSRP (37) NNSRP (10)</td>
<td>IIEF-4</td>
<td>42</td>
</tr>
<tr>
<td>Marks et al [75]</td>
<td>14</td>
<td>NSRP (9)</td>
<td>IIEF-3 and IIEF-4</td>
<td>NSRP: 40</td>
</tr>
<tr>
<td>Blander et al [76]</td>
<td>72</td>
<td>Unknown</td>
<td>IIEF-3 and IIEF-4</td>
<td>NSRP: 0</td>
</tr>
<tr>
<td>Feng et al [77]</td>
<td>53</td>
<td>BNSRP (21) NNSRP (17)</td>
<td>Erection sufficient for intercourse (single question)</td>
<td>31</td>
</tr>
<tr>
<td>McMahon et al [82]</td>
<td>13</td>
<td>Not specified</td>
<td>IIEF-4</td>
<td>31 (score 4 or 5)</td>
</tr>
<tr>
<td>Zagaja et al [79]</td>
<td>170</td>
<td>BNSRP (59) NNSRP (20)</td>
<td>Erection adequate for intercourse in &gt;50% of attempts</td>
<td>BNSRP: 53</td>
</tr>
<tr>
<td>Zippe et al [78]</td>
<td>91</td>
<td>BNSRP (53) NNSRP (26)</td>
<td>Ability for sexual intercourse (CCPP questionnaire)</td>
<td>BNSRP: 72</td>
</tr>
<tr>
<td>Baniel et al [83]</td>
<td>59</td>
<td>Not specified</td>
<td>Erection sufficient for vaginal intercourse</td>
<td>20</td>
</tr>
<tr>
<td>Martinez-Jabaloyas et al [84]</td>
<td>17</td>
<td>NNSRP (17) BNSRP (18)</td>
<td>SHIM IIEF-4 (n = 33) BNSRP: 62</td>
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<tr>
<td>Ogura et al [85]</td>
<td>43</td>
<td>NNSRP (4) BNSRP (21)</td>
<td>SHIM</td>
<td>6</td>
</tr>
<tr>
<td>Raina et al [81]</td>
<td>174</td>
<td>BNSRP (104) NNSRP (42)</td>
<td>SHIM</td>
<td>BNSRP: 62</td>
</tr>
<tr>
<td>Shimizu et al [86]</td>
<td>13</td>
<td>BNSRP (8) NNSRP (5)</td>
<td>Erection sufficient for penetration</td>
<td>BNSRP: 100</td>
</tr>
</tbody>
</table>

N = total number of post-RP ED patients treated with sildenafil; BNSRP = bilateral nerve-sparing radical prostatectomy; UNSRP = unilateral nerve-sparing radical prostatectomy; NNSRP = Non–nerve-sparing radical prostatectomy; NSRP = nerve-sparing radical prostatectomy; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; IIEF = International Index of Erectile Function; IIEF-4 = IIEF question 4; IIEF-5 = IIEF question 5; SHIM = Sexual Health Inventory for Men (IIEF-5); CCPP = Cleveland Clinic Post Prostatectomy questionnaire.
An extended analysis reported that the vardenafil 10 mg and vardenafil 20 mg doses were significantly superior to placebo for the IIEF domains for intercourse satisfaction, orgasmic function, overall satisfaction with sexual experience, and satisfaction rate with erection hardness ($p < 0.0009$ compared to placebo) [91]. Adverse events were consistent with those previously reported for vardenafil in the general ED population, and the discontinuation rates were 1–4% across study groups. Further analysis has been provided by a Cochrane review (Fig. 3) [92].

![Figure 3](image)

**Fig. 3** – Efficacy of vardenafil 10 mg and vardenafil 20 mg after bilateral nerve-sparing radical prostatectomy (BNSRP) and unilateral nerve-sparing radical prostatectomy (UNSRP) compared to placebo. The x-axis shows the weighted mean difference and 95% CI for (a) International Index of Erectile Function (IIEF) erectile function (EF) domain and (b) Sexual Encounter Profile question 3 (SEP3). Data are from Brock et al [90] and Miles et al [92]. The right part of the graph (right to the vertical line) supports the use of vardenafil in terms of efficacy while the left part supports the use of placebo (no efficacy).
The efficacy and safety of tadalafil was assessed in a multicenter, prospective, randomized, double-blind, placebo-controlled study conducted in 38 sites in the United States, Canada, and Europe, and they included 303 men [93]. All patients had undergone a BNSRP and had been treated with tadalafil 20 mg or placebo, and they were between 12 mo and 48 mo postoperative at the time of the study. Preoperative IIEF scores were not available. The mean ages of the patients were 59.8 yr and 59.6 yr in the placebo group and the tadalafil 20 mg group, respectively. The mean post-treatment IIEF erectile function domain scores were 17.7 and 13.3 in the treatment group versus the placebo group, respectively; the mean rates of positive response to SEP-2 were 53.9% and 32.4% in the treatment group versus the placebo group, respectively; and the mean rates of positive response to the SEP-3 were 40.5% and 19.4% in the treatment versus placebo group, respectively (p < 0.001). Normal erectile function (IIEF-EF domain score ≥26) was attained by 24% versus 4% in the treatment group versus the placebo group, respectively (p < 0.001), while the mean Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) scores were 58% and 34% in the treatment group versus the placebo group, respectively (p < 0.001). The 4% placebo normalization of erectile function is similar to that seen in the placebo group of the rehabilitation study with sildenafil [60]. No unexpected adverse event was recorded, and the discontinuation rate due to adverse events was 5.5% (2% in the placebo group, p = 0.231). Further analysis has been provided by a Cochrane review (Figs. 3 and 4) [92].

PDE5-Is may be combined with intraurethral alprostadil to salvage oral therapy failures [94,95]. Major criticism for both of these studies includes the small number of patients included and the non-randomized, placebo-controlled design. PDE5-Is may also be combined with intracavernosal alprostadil [96,97]. However, only one study was prospective, crossover, and placebo-controlled [97], while the number of patients treated was also low. Combination treatment may be a treatment alternative in a carefully selected subgroup of patients, but larger, properly designed trials are necessary to assess efficacy and safety.

4. Conclusions

Data from limited clinical studies show that PDE5-Is are efficacious in the treatment of post-RP ED.
While experimental evidence suggests that PDE5-Is can prevent smooth-muscle apoptosis and fibrosis related to ED after RP in the animal model, these findings have not yet been replicated in humans. Therefore, their use in penile rehabilitation programs remains controversial. More prospective, randomized, placebo-controlled studies are needed to firmly establish efficacy of PDE5-Is in rehabilitation programs. Much like breast reconstruction after mastectomy for breast cancer, the treatment of ED after RP has a tremendously positive impact on quality of life for the patient and his partner. We should properly counsel patients preoperatively and offer medical treatment based on the currently available data. Ultimately, the patient will decide to seek and accept treatment, but optimally both he and his partner should be involved in the decision-making process.

Author contributions: Konstantinos Hatzimouratidis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Montorsi, Hatzichristou, Hatzimouratidis.

Acquisition of data: Hatzimouratidis.

Analysis and interpretation of data: Hatzimouratidis.

Drafting of the manuscript: Hatzimouratidis.

Critical revision of the manuscript for important intellectual content: Montorsi, Hatzichristou, Mulhall, Burnett, McCullough.

Statistical analysis: None.

Obtaining funding: None.

Administrative, technical, or material support: Hatzimouratidis.

Supervision: Montorsi, Hatzichristou, Mulhall, Burnett, McCullough.

Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Francesco Montorsi, Dimitrios Hatzichristou, John Mulhall, Arthur Burnett, and Andrew McCullough are consultants/investigators of Bayer-Glaxo-SmithKline, Lilly-ICOS, and Pfizer.

Funding/Support and role of the sponsor: None.

References


