

Erectile Dysfunction Following Radical Retropubic Prostatectomy

Epidemiology, Pathophysiology and Pharmacological Management

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Abstract

Radical prostatectomy has been the time-honoured and standard treatment option for prostate cancer. Erectile dysfunction (ED) is one of the common quality-of-life issues following radical prostatectomy. The recovery of potency following radical prostatectomy varies from 16% to 86%. Although major modifications in surgical technique appear to be promising, the reported ED rates are still high. The time period required for the recovery of erectile function after surgery varies from 6 to 24 months. During this period of neuropraxia lack of natural

erections produces cavernosal hypoxia. This cavernosal hypoxia has been implicated as one of the most important factors in the pathophysiology of ED. Cavernosal hypoxia predisposes to cavernosal fibrosis, ultimately producing venous leak and long-term ED. Interruption of this cascade of events has been the major challenge for physicians. Physicians have several options available for the treatment of ED. However, oral treatment options have quickly become established as first-line treatment options. Sildenafil has been most extensively studied in the radical prostatectomy population. In patients who do not respond to oral therapy alone, standard treatment options (intracavernosal injections, vacuum constriction devices and intraurethral alprostadil) are useful. Use of penile prostheses is one of the oldest treatment options available for the treatment of ED but is used only as a last resort. Initial attempts to promote the earlier recovery of erectile function appear to be promising. However, further confirmatory studies are essential. The roles of gene transfer and growth factors are still in experimental stages. In this review we discuss the epidemiology, pathophysiology and treatment options available for ED following radical prostatectomy.

Prostate cancer is the most common solid cancer diagnosed and treated in men.^[1] Radical prostatectomy (RP) has been the 'gold standard' treatment for organ/specimen-confined prostate cancer for several decades.^[2] Urinary incontinence and erectile dysfunction (ED) are the two most important quality-of-life issues reported following radical retropubic prostatectomy. Improvement in surgical techniques has significantly reduced postoperative incontinence rates. However, most urologists still report ED as a significant long-term postoperative complication of RP.^[2,3] As a result, many patients seek alternative treatments such as prostate brachytherapy or external beam radiotherapy.^[4]

In the past, ED following RP was not an overwhelming concern, as most prostate cancers were detected in older men.^[5] However, with the advent of prostate specific antigen (PSA) screening, which began in the late 1980s, prostate cancer is now detected at early stages in young men. Because quality of life is a major issue in these young patients, researchers have begun to focus on the pathophysiology and prophylaxis of ED following RP.

1. Epidemiology

The incidence of ED after RP ranges between 40% and 85% at centres of excellence.^[3,6] While an individual surgeon's experience and technique remain the dominant variables in the outcome, several

other factors also affect postoperative ED, including the patient's age, preoperative sexual function and coexisting medical diseases.

Walsh and Donker^[7] first introduced nerve-sparing surgery in 1982. They reported potency rates of 86% in patients after bilateral nerve-sparing RP,^[3] which was higher than reported in previous studies: in most series, the incidence varied from 53% to 86%.^[8,9] However, not all large series reported excellent potency rates. In fact, many series reported rates ranging from 11% to 20%. The reasons for low potency rates are often a result of the inclusion of multisurgeon series and data from non-nerve-sparing surgeries,^[10,11] as well as nonuniformity of data collection. Potency rates can also vary depending on the qualitative difference used to distinguish partial and full erections, the percentage of rigid erections/ attempts, and the duration of vaginal intercourse.

Age and preoperative potency status significantly influence recovery of erectile function. Most series report higher (59–82%) potency in patients <60 years of age compared with older patients (36–57%).^[6,8,11,12] Age also correlates with preoperative potency status, which influences recovery of erectile function. Geary et al.^[13] and Rabbani et al.^[11] reported that preoperative erectile status significantly affects recovery of spontaneous erections.

Potency rates in most studies are reported after a follow-up of 12–24 months. Long-term (>5 years) potency reports are limited in the literature. To

address this issue, the Prostate Cancer Outcome Study recently evaluated sexual function at 60 months' follow-up.^[14] At that point, 55% of participants reported an inability to achieve any erections, and only 28% had erections firm enough for intercourse. However, the proportion reporting adequate erections significantly increased from the figure of 22% noted at 24 months ($p = 0.003$). The degree of sexual bother also decreased between 24 and 60 months. The study demonstrated that with long-term follow-up, the return of natural erections increases while sexual bother decreases. However, this study comprised multisurgeon series, which is reported to influence potency rates following RP. Similarly, a study performed by our institution also found an increase in the return of natural erections with long-term follow-up (4% at 1 year vs 23% at 5 years).^[15]

2. Pathophysiology of Erectile Dysfunction (ED) Following Radical Prostatectomy (RP)

The role of cavernosal smooth muscle in normal erections was demonstrated in the early 1980s.^[9] Since then, it has been well established that normal smooth muscle content and function are essential for initiation and maintenance of erections. Cavernous smooth muscle function and integrity depend on neurogenic, vascular and psychological factors. Neurovascular factors – either alone or in combination – appear to play a key role in the pathophysiology of ED in a majority of cases.

Several authors have implicated vascular compromise as one of the important causes of ED following RP. While it is well known that damage to the neurovascular bundle can cause cavernosal arterial insufficiency, Breza et al.^[16] reported that accessory pudendal arteries are often the major blood supply in selected cases. This group hypothesised that damage to these arteries might be the main cause of ED. However, this opinion was not universally accepted. In 1995, Polascik and Walsh^[17] reported that accessory pudendal arteries were identified in only 4% of cases (33/835). This study found that attempts to preserve accessory pudendal arteries increased intraoperative bleeding from the dorsal vein complex without significantly improving potency rates (preservation vs nonpreservation: 67% vs 50%). However, this study was criticised because

it included a very small percentage of men who underwent vascular preservation. Therefore, the study may have been inadequately powered to detect statistically significant differences.

Recently, revisiting their database in 2004, Rogers et al.^[18] for Dr Walsh reported that preservation of the accessory pudendal artery was associated with a significant increase in potency rates. They also noticed that the time needed for recovery of spontaneous erection was significantly less in the vascular preservation group. However, this difference was not evident when the vascular pedicle was not identified at the time of surgery. They concluded that preservation of the accessory pudendal artery at the time of surgery (if identified) may favourably influence sexual function.

In a small series in 1996, Mulhall and Greydon^[19] reported that arterial insufficiency is seen in almost all patients with ED after RP. In a later publication with a larger study population, these investigators noted arterial insufficiency in 56% of the study population who underwent RP.^[20] These two studies highlighted that arterial insufficiency is an important factor in ED following RP. Further refinement in surgical techniques is essential to limit the degree of arterial insufficiency.

Historically, collagen accumulation (fibrosis) has been reported as the most probable cause of ED in patients with penile arterial insufficiency.^[10-12] However, the exact mechanism of collagen accumulation in patients with penile hypoxia has not been established. Penile hypoxia was reported to induce transforming growth factor (TGF)- β_1 in cavernosal smooth muscle, which has been implicated in collagen deposition.^[21] Later studies reported that prostaglandin E₁ (PGE₁) decreases TGF β_1 -induced collagen synthesis.^[22] These initial reports have shown that penile hypoxia is a key factor in collagen deposition in hypoxic cavernosal muscle and that PGE₁ reduces the expression of TGF β_1 . This opened a new era of interest in the field of pharmacological prevention of ED following RP.

After nerve-sparing RP, patients may still experience postoperative impairment of natural erections. This damage is inevitable despite the best efforts of the most experienced surgeons. The time period required for the recovery of natural erectile function varies from 6 to 24 months.^[3,23] Because the penile

tissues receive little oxygen during this time, persistent penile hypoxia occurs.^[24] Hypoxia in a consistently flaccid penis may induce fibrosis. This was observed in animal models after cavernous neurectomy, which was associated with an increase in collagen production.^[25,26] Similarly, Iacono et al.^[27] from Italy studied changes in penile biopsy before and after RP (2 months and 12 months) in humans. Compared with preoperative biopsies, postoperative biopsies showed a significant decrease in elastic fibres and smooth muscle content and a significant increase in collagen content. These studies have further confirmed that neuropraxia as a result of transient cavernous nerve damage and arterial insufficiency plays a central role in cavernosal fibrosis.

Cavernosal fibrosis produced over time as a result of persistent penile hypoxia has been shown to increase the incidence of veno-occlusive dysfunction. De Luca et al.^[28] followed patients after RP for an average of 2.5 years and found that the prevalence of veno-occlusive dysfunction was 5%. Thus, veno-occlusive dysfunction also appears to play an important role in ED following RP. In 2002, Mulhall and Graydon^[19] reported that the incidence of venous leak increases with the postoperative time interval (14% at 4 months vs 35% at 9–12 months). Similarly, Montorsi et al.^[29] in 1997 reported that the incidence of venous leak was much higher in their control group (no treatment) compared with the treatment group (alprostadil injections three times/week), i.e. 53% versus 17%. The literature supports the notion that postoperative venous leak increases with time after surgery and that early treatment may reduce its incidence.

In summary, ED after RP is multifactorial in aetiology. Psychological and neurovascular factors are among the most important factors in ED after RP. Penile hypoxia results from two important factors: neuropraxia and altered vascular factors. It is well established that penile hypoxia is the most important precipitating factor in the formation of cavernosal fibrosis. The formation of cavernosal fibrosis with subsequent venous leak has been implicated as the most important cause of long-term ED after RP.

3. Pharmacological Management of ED Following RP

Treatment of ED is one of the rapidly developing fields of medicine. Researchers have made great strides in understanding the complex neural and vascular pathways that are essential for normal erection. Recent advances in the understanding of the physiology of erection, and of the pathophysiology of ED and its interaction with central and peripheral neurotransmitters, have led to the development of new medications. The discovery that nitric oxide acts as a neurotransmitter in cavernosal tissue has been the major breakthrough in the management of ED. Today, physicians have several options available to treat ED.

Current treatment options can be divided into pharmacological and nonpharmacological agents. Pharmacological agents can be further divided according to their route of administration: oral, intracavernosal or intraurethral (table I).

3.1 Mechanism of Action of Various Pharmacological Agents

Penile erection is a complex phenomenon mediated by interactions between various neurovascular, hormonal and psychological factors. The integration between central and peripheral phenomena is essential for producing a normal erection. The vast major-

Table I. Classification of treatment options for erectile dysfunction following radical prostatectomy

1. Pharmacological agents
a. oral
i. PDE5 inhibitors (sildenafil, tadalafil and vardenafil)
b. intracavernosal injections
i. prostaglandin E ₁ (alprostadil)
ii. papaverine
iii. phentolamine
iv. mixtures (Trimix, Bimix) ^a
c. intraurethral alprostadil (MUSE)
d. apomorphine (intranasal, oral)
2. Nonpharmacological agents
a. vacuum constriction device
3. Combination treatments
4. Penile prosthesis

a Commonly used, but not approved.

MUSE = medicated urethral system for erection; **PDE5** = phosphodiesterase-5.

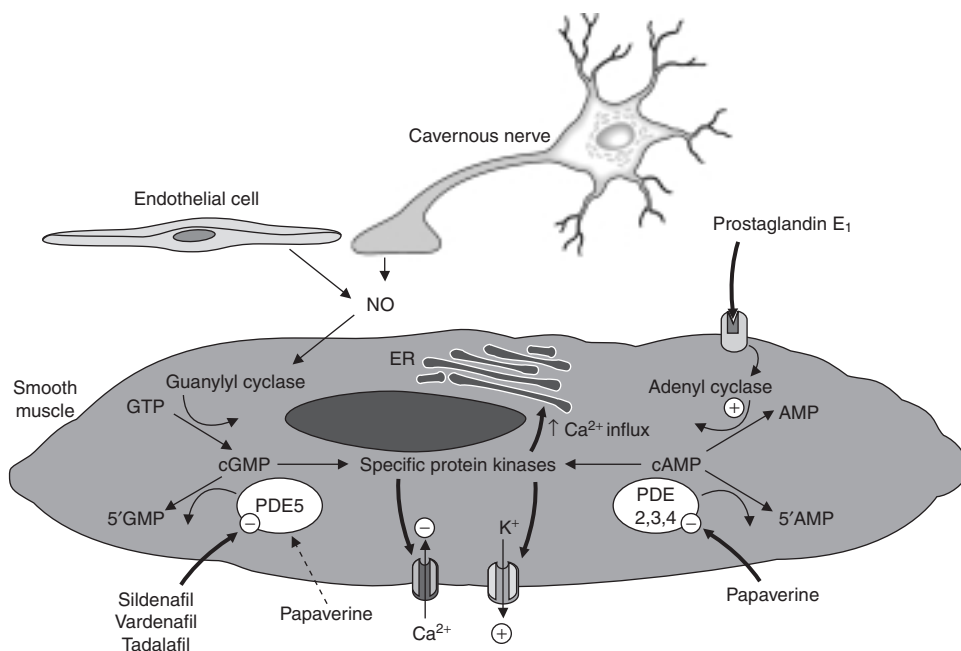


Fig. 1. Mechanism of action of drugs used for the treatment of erectile dysfunction. Oral phosphodiesterase-5 (PDE)-5 inhibitors (sildenafil, vardenafil and tadalafil) decrease cyclic guanosine monophosphate (cGMP) inactivation. Prostaglandins act through adenylyl cyclase. Adenylyl cyclase increases the cyclic adenosine monophosphate (cAMP) concentration. cAMP and cGMP stimulate protein kinases which decrease the calcium concentration. **ER** = endoplasmic reticulum; **GTP** = guanosine triphosphate; **NO** = nitric oxide.

ity of currently available medications act through a peripheral mechanism.

Nitric oxide is a nonadrenergic, noncholinergic mediator which increases cyclic guanosine monophosphate (cGMP) concentration by stimulating guanyl cyclase (figure 1). cGMP activates intracellular protein kinases, which open potassium channels and close calcium channels, thereby leading to hyperpolarisation of smooth muscle. This ultimately produces smooth muscle relaxation and erection. cGMP is inactivated by phosphodiesterase-5 (PDE)-5 enzyme, which is inhibited by PDE5 inhibitors (sildenafil, vardenafil and tadalafil).

An alternative mechanism of erection is mediated by adenylyl cyclase. Adenylyl cyclase increases the intracellular cyclic adenosine monophosphate (cAMP) concentration. cAMP stimulates specific protein kinases, which produce an effect that is similar to that of cGMP. This pathway is stimulated by PGE₁, papaverine and phentolamine.

3.2 Oral Medications

3.2.1 Sildenafil

Sildenafil was the first PDE5 inhibitor approved by the US FDA, in 1998, for the treatment of ED. This drug has been extensively investigated in the general and RP population. The introduction of sildenafil and subsequent PDE5 inhibitors revolutionised the treatment of ED after RP to the extent that these drugs are now used as first-line treatment options after RP. PDE5 inhibitors increase the cGMP concentration in cavernosal muscle and produce smooth muscle relaxation. The overall efficacy of sildenafil in ED following RP varies from 51% to 57% in the literature.^[30,31]

The Cleveland Clinic was one of the first groups to investigate the role of sildenafil in the RP population. In an initial study involving a small RP population, we found that 12/15 patients who underwent bilateral nerve-sparing RP responded to sildenafil.^[32] In a later update in a larger population, we found that 52% (48/91) of post-RP patients respond-

ed to sildenafil. Patients who underwent bilateral nerve-sparing surgery had a better response than patients who underwent unilateral or non-nerve-sparing surgery.^[32] The efficacy in our study was similar to that reported in other studies in the literature. In a 3-year follow-up study, we re-evaluated the 43/48 patients who returned our questionnaire. Of these 43 patients, 31 (72%) still continued to use sildenafil. This study suggested that most patients who initially respond to sildenafil continue to use the drug long-term.^[33]

5-Year Efficacy of Sildenafil Citrate

More recently, we completed a 5-year follow-up on our post-RP patients who were using sildenafil for the treatment of ED.^[34] We identified 68 patients with ED who were initial sildenafil responders following RP. Using a self-administered questionnaire, we found that 31/68 (45.6%) were still responding to sildenafil at 5 years, but 37/68 (54.4%) were not satisfied with the results and had either discontinued the drug (17/37, 46%), switched to another therapy (8/37, 21.6%) or used sildenafil in combination with another therapy (12/37, 32.4%). More specifically, 17/37 (46%) discontinued the treatment because of loss of interest in sex (5/17, 30%), cardiovascular co-morbidities (5/17, 30%), change in personal circumstances (4/17, 23%), adverse effects (2/17, 11%) or loss of libido (1/17, 6%). The most common adverse effects at 5 years were headache (4/25, 16%), flushing (2/25, 8%) and blurred vision (2/25, 8%). The vast majority (21/25, 85%) of patients who were still responding to sildenafil at 5 years had bilateral nerve-sparing procedures. In summary, at 5

years, nearly half of initial sildenafil responders continued to do well. However, 54.4% of the patients discontinued the drug (25%), switched to another erectaid (11.8%), or used sildenafil as part of combination therapy (17.6%). The major reasons for discontinuation were cardiovascular co-morbidities (30%) and loss of interest in sex (30%).^[34]

Factors Affecting the Efficacy of Sildenafil

We also evaluated the factors affecting the efficacy of sildenafil, which are also predictors of satisfactory outcome of sildenafil treatment for ED following RP. In our study, we identified four factors that were significantly associated with a successful outcome: the presence of at least one neurovascular bundle, preoperative Sexual Health Inventory for Men (SHIM or International Index for Erectile Function [IIEF]-5) score ≥ 15 , age ≤ 65 years, and interval from RP to drug use > 6 months ($p < 0.001$).^[35] These findings have been supported by other reports in the literature (table II). Zagaja et al.,^[36] reviewing the Dr Brendler series, reported that the response to sildenafil depends on the age of the patient. These investigators found that patients who were < 55 years of age and who underwent bilateral nerve-sparing surgery had a better response than patients who were 55–65 years of age and those who were > 65 years of age (80% vs 45% vs 33%, respectively).

Interestingly, our group noticed that 15% of patients who underwent non-nerve sparing surgery responded to sildenafil. This was not observed by Zagaja et al.^[36] or Ogura et al.,^[30] who found that no patients who underwent non-nerve-sparing RP re-

Table II. Summary of studies evaluating response to sildenafil after radical prostatectomy

Study	No.	Response to sildenafil (%) [no.]			
		BNS	UNS	NNS	overall
Zippe et al. ^[32]	91	71.7 (38/53)	50 (6/12)	15.4 (4/26)	52.7 (48/91)
Zagaja et al. ^[36]	120/170	52.5 (31/59)	9.8 (4/41)	0 (0/20)	29 (35/120)
Age (years):					
<55 (n = 28)		80 (12/15)	40 (4/10)	0 (0/3)	
55–65 (n = 65)		45 (17/38)	0 (0/21)	0 (0/6)	
>65 (n = 27)		33 (2/6)	0 (0/10)	0 (0/11)	
Feng et al. ^[31]	53	71.5 (15/21)	80 (12/15)	5.9 (1/17)	52.8 (28/53)
El-Galley et al. ^[37]	25				52 (13/25)
Raina et al. ^[34]	174	76 (79/104)	53.5 (15/28)	14.2 (6/42)	57 (100/174)
Ogura et al. ^[30]	33/43	62.5 (10/16)	53.8 (7/13)	0 (0/4)	51.5 (17/33)

BNS = bilateral nerve-sparing; **NNS** = non-nerve-sparing; **UNS** = unilateral nerve-sparing.

Table III. Percentage distribution of adverse effects of sildenafil in different studies

Study	Headache (%)	Visual changes/dizziness (%)	Flushing (%)	Nasal congestion (%)	Dyspepsia (%)
Zippe et al. ^[32]	28.6	8.8	21.9	5.4	6.5
Zagaja et al. ^[36]	12	6	6	2	1
Feng et al. ^[31]	21	6.3	8.3	6.3	0
Raina et al. ^[33]	24	8.6	14.5	3	5.6
Ogura et al. ^[30]	21	6	8	6	0

sponded to sildenafil. It was unclear whether the 15% response rate in our patients was due to a placebo effect, unrecognised residual nerve tissue, or to a non-neurogenic mechanism.

Currently, the only contraindication to the use of sildenafil is the use of nitroglycerin or nitrate-containing compounds, which may cause hypotension. The most common adverse effects of sildenafil reported are transient headaches (12–28.6%), flushing (6–21.9%), visual changes/dizziness (6–8.6%), dyspepsia (1–6.5%) and nasal congestion (2–6.3%) [table III]. However, the discontinuation rate with these adverse effects is only 5%.^[32]

3.2.2 Tadalafil

Tadalafil is a newly approved long-acting PDE5 inhibitor that has been shown to be effective, safe and well tolerated in the treatment of ED. Its long-half-life and the fact that food does not delay its absorption are two important advantages (table IV). Tadalafil significantly improves erectile function and is well tolerated at 10mg and 20mg doses. Padma-Nathan et al.^[38] reported that on-demand tadalafil significantly improved erectile function compared with placebo in the general population.

Montorsi et al.^[42] evaluated the efficacy of tadalafil for an RP population in a randomised, double-blind, placebo-controlled multicentre study. They included 303 men (mean age 60 years) with normal preoperative erectile function who had undergone bilateral nerve-sparing RP. The interval between the surgery and initiation of tadalafil varied from 12 to 48 months. The patients were randomised (2 : 1) to tadalafil (n = 201) or placebo (n = 102). Patients receiving tadalafil reported a greater improvement in all primary endpoints (changes in IIEF domain score, percentage of positive responses to sexual encounter profile questions 2 and 3) and secondary endpoints (global assessment questionnaire and ED inventory of treatment) [$p < 0.001$],

compared with placebo. Patients randomised to the tadalafil group also reported a significant improvement in the mean IIEF erectile function domain score ($p < 0.001$) versus placebo. For all randomised patients who received tadalafil, the mean percentage of successful penetration attempts was 54%, and the mean percentage of successful intercourse was 41%. In a subgroup of patients who showed some postoperative tumescence, these values increased to 69% and 52%, respectively. The most commonly reported adverse effects were headaches (21%), dyspepsia (13%) and myalgia (7%). This large randomised controlled trial demonstrated that tadalafil is efficacious and well tolerated in post-RP patients.

3.2.3 Vardenafil

Vardenafil is another newly approved PDE5 inhibitor that has been shown to be effective for the treatment of ED. *In vitro* studies have revealed that vardenafil is more potent than sildenafil and tadalafil in inhibiting the PDE5 enzyme.^[43] However, this greater *in vitro* potency may not be translated to humans, as other factors such as pharmacokinetics may influence the therapeutic efficacy of the drug (table IV).

In a randomised, placebo-controlled, double-blind, multicentre trial by Brock et al.,^[44] 440 men with ED were randomised 0.5–5 years after nerve-sparing radical retropubic prostatectomy to receive vardenafil 10 or 20mg or placebo as needed for 12 weeks. IIEF erectile function domain scores at baseline were approximately 9.1, indicating that the population generally had severe ED. Treatment with vardenafil significantly improved these scores (15.3 for both treatment groups versus 9.2 in the placebo group, $p = 0.0001$). Furthermore, the responder rate on the improved erectile function global assessment questionnaire (GAQ) and successful penetration and intercourse rates were all significantly greater after 12 weeks' treatment with vardenafil 10 or 20mg

Table IV. Pharmacological properties of phosphodiesterase-5 inhibitors

Properties	Sildenafil ^[36,39]	Vardenafil ^[40]	Tadalafil ^[41]
Food delays absorption	Yes	Yes	No
Peak plasma levels	30–60 min	40–60 min	2h
Duration of action (h)	4–6	4	17.5
Dose (mg)	50–100	10–20	10–20

compared with placebo ($p = 0.0001$). Seventy-one percent of the study population underwent bilateral nerve-sparing RP, while the remaining 29% underwent unilateral nerve-sparing RP. The response rate on the GAQ in those patients who had undergone the bilateral nerve-sparing procedure was significantly better with the 20mg dose than with the 10mg dose, and both doses were significantly better than placebo in this subgroup (71%, 60% and 12%, respectively; $p = 0.0001$ for all three comparisons). Adverse effects consisted of mild to moderate headache, flushing and rhinitis. This study demonstrated that vardenafil was efficacious and well tolerated in an RP population.

In a recent update, Nehra et al.^[45] reported that vardenafil 10 and 20mg were significantly superior to placebo in IIEF domains for intercourse satisfaction, orgasmic function and overall satisfaction with sexual experience ($p < 0.0009$). The satisfaction rate with erection hardness was also significantly improved compared with placebo ($p < 0.0001$). The discontinuation rates were 21% for the vardenafil group and 33% for the placebo group. The most common reasons for discontinuation in the vardenafil group were lack of efficacy and withdrawn consent, and the most common reason in the control group was lack of efficacy. The most common adverse effects of vardenafil were headaches and rhinitis. The discontinuation rates due to adverse effects were higher in the vardenafil group than in the placebo group (3–4% vs 1%). In this study, vardenafil was shown to significantly improve sexual experience and patient satisfaction following nerve-sparing RP.

Our centre recently conducted a prospective study comparing the efficacy and adverse effects of all three oral PDE5 inhibitors (sildenafil, vardenafil and tadalafil).^[46] We included 46 men with ED following bilateral nerve-sparing RP who previously responded to sildenafil 100mg. Baseline (without

any treatment) and sildenafil SHIM scores were obtained for all patients, who were given tadalafil 20mg for 5 weeks, then vardenafil 20mg for 5 weeks. All patients had a 1-week washout period between drugs, and the sequence of drug use was allocated randomly. All patients completed the SHIM questionnaire, gave reasons for discontinuation and provided an adverse effect profile. Thirty-nine of 46 patients completed a 5-week trial of each PDE5 inhibitor; 5 patients discontinued because of adverse effects and 2 patients were lost to follow-up. The mean SHIM scores were 18.2 ± 1.26 for sildenafil, 17.6 ± 1.4 for tadalafil and 17.9 ± 1.9 for vardenafil. Patients with pretreatment (baseline) SHIM scores <10 preferred sildenafil, while patients with SHIM scores >10 preferred tadalafil. Of the total 46 patients, 23 (50%) still preferred sildenafil, 14 (30%) preferred tadalafil and 9 (20%) preferred vardenafil. The most frequent adverse effects reported with sildenafil were headaches ($n = 4$), flushing ($n = 3$) and visual disturbances ($n = 1$). The most frequent adverse effects with tadalafil were backache ($n = 5$), headache ($n = 3$), and flushing ($n = 1$). Headache ($n = 6$) and flushing ($n = 2$) were the two most commonly reported adverse effects with vardenafil. None of the patients discontinued sildenafil because of adverse effects whereas three patients discontinued tadalafil because of backache and one discontinued vardenafil because of headaches. Overall, all three PDE5 inhibitors appeared to be equally effective in treating patients with ED after RP.

Future randomised, double-blind trials alternating the use of the three currently available PDE5 inhibitors are required to establish whether a single agent is better than the others in treating ED following RP. However, it appears that individual selection of the best drug will vary based on its efficacy and adverse effects.

3.3 Nonoral Agents

3.3.1 Intracavernosal Injections

Intracavernosal injections were introduced 2 decades ago as a treatment for ED. Today, even with the availability of oral therapy, intracavernosal injection remains one of the most important treatment options. These injections bypass the need for effective neural transmission from the cavernosal endothelial cells and are effective even in patients with organic vasculogenic ED, which is a major advantage. Papaverine was the first substance studied extensively in the 1980s. It is a nonspecific PDE inhibitor that increases cAMP and cGMP.^[46,47] Another vasoactive agent – phentolamine – is a direct α -adrenoceptor antagonist. However, phentolamine alone produces rigid erections in only a small percentage of cases, and is therefore commonly used in combination with other agents.^[47] A third vasoactive agent – alprostadil – is a synthetic analogue of PGE₁ and has gained wider acceptance because of its effectiveness and lower incidence of adverse effects.^[48] However, in patients with significant vasogenic impotence, the most commonly used medication is a mixture of all three drugs (PGE₁, papaverine and phentolamine). This three-drug mixture, which is referred to as Trimix, was first introduced in 1991. These drugs act through different mechanisms synergistically to produce a maximal erectogenic effect and to minimise the adverse effects of individual agents.

The lower dose of PGE₁ used in Trimix often decreases the pain component compared with the higher PGE₁ dose that is used in monotherapy to produce a similar effect.^[49,50] This may have a crucial impact on long-term compliance with injections, which appears to be a significant issue. When reviewing our database at the Cleveland Clinic Foundation, we could identify only 102 patients who were using these injections on a long-term

basis. Of these, 69 (68%) achieved and maintained erections sufficient for satisfactory vaginal intercourse, and 48% (49/102) were continuing injections long-term. The major reasons for discontinuation were insufficient erections (18/53, 33%) and preference for oral therapy (17/33, 32%). Including patients with a preference for oral therapy (n = 17), loss of partner (n = 4) and return of natural erections (n = 1), 71 (70.6%) were compliant for a mean period of 3.7 years with injections. In our database, the majority of patients using intracavernosal injections switched to oral therapy or otherwise discontinued injections because they were cumbersome and inconvenient.^[50]

Despite having a high degree of therapeutic efficacy (more than 85%), patients do not readily accept penile injections, and dropout rates in many series have exceeded 40% (table V).^[51] Evaluation of the reasons for discontinuation showed that 10–20% stopped injections because of unsatisfactory erections, 14% because of pain and 2–5% because of penile fibrosis and corporal plaque.^[51]

3.3.2 Intraurethral Alprostadil

Intraurethral alprostadil represents an alternative method of delivering PGE₁ into erectile tissue.^[55] Using the medicated urethral system for erection (MUSE), a pellet containing alprostadil is delivered into the male urethra and absorbed by the cavernosal tissue through vascular communications from the corpus spongiosum. In 1997, Padma-Nathan et al.^[56] reported that MUSE has an overall efficacy of 44%. However, similar results were not consistently reported in subsequent series. Costabile et al.^[57] later reported that their overall success rate with MUSE was 40%. Intraurethral MUSE is associated with the following disadvantages: urethral discomfort, low response rate and inconsistent efficacy.^[58]

Reviewing our experience with MUSE in post-RP patients, we found that 55% (30/54 patients)

Table V. Efficacy and discontinuation rates with intracavernosal injections

Study	Follow-up (years)	Efficacy (%)	Discontinuation (%)	Major reasons for discontinuation
Dennis and McDougal ^[52]	1	85	55	Not stated
Mulhall et al. ^[53]	3	75	31	Cost, lack of education and loss of partner
Purvis et al. ^[54]	2	87	58	Lack of efficacy, cost and discomfort
Raina et al. ^[50]	3.7	68	52	Lack of efficacy and preference for oral therapy

achieved and maintained erections sufficient for sexual intercourse while using MUSE, and 48% (26/54) continued therapy long-term. A total of 28 patients (52%) discontinued treatment after a mean use of 8 ± 1.4 months. The reasons for discontinuation were insufficient erections ($n = 16$), switch to other ED therapy ($n = 4$), natural return of erections ($n = 4$), and urethral pain and burning ($n = 4$). Excluding patients who preferred other therapies and return of natural erections ($n = 8$), the compliance with MUSE was 63%.^[59]

MUSE provides an important alternative treatment option, especially in post-RP patients who do not respond to oral therapy and who are not willing to perform penile injections or use vacuum constriction devices.

3.3.3 Vacuum Constriction Devices

Vacuum constriction devices were first introduced in the early 1980s for the treatment of ED and gained major acceptance among urologists in the early 1990s. These devices create a vacuum around the penis, drawing blood into the corpora cavernosa. Constricting rings are placed at the base of the penis, preventing venous outflow and affording tumescence while the bands are in place.^[60] These devices are an important option for clinicians who treat ED. Current models are safe and can be used by patients with mixed aetiologies and risk factors. The rigidity achieved is sufficient for vaginal penetration and intercourse in a very high percentage of cases; efficacy ranges from 60% to 80% in various reports.^[61] However, lack of spontaneity, difficult mechanics and complications have led to high discontinuation rates.

Vacuum constriction devices can be used as a treatment option in patients who do not respond to oral therapy and who are not willing to use injections.

3.4 Combination Therapy

The introduction of oral PDE5 inhibitors generated great enthusiasm and interest because of their high compliance rates. However, many studies in the literature reported a percentage of users who either had a suboptimal response or did not respond to these drugs.^[23,36] Similarly, a percentage of the population using standard treatment options (intra-

cavernosal injection, intraurethral alprostadil and vacuum constriction devices) also reported suboptimal responses. A recent area of interest is the use of combination therapy for ED following RP when individual therapies are associated with suboptimal responses or are ineffective. Management of ED with a combination of available treatment modalities appears to be synergistic by virtue of their different mechanisms of action. Also, use of combination therapy may avoid the need for invasive treatment modalities such as penile prostheses for some patients with ED.

3.4.1 Sildenafil plus Vacuum Constriction Devices After RP

In a general population with ED, Chen et al.^[62] in 2004 reported that a combination of sildenafil and a vacuum constriction device resulted in greater satisfaction, as documented by a significant improvement in IIEF scores, compared with either agent alone. This study demonstrated that this combination treatment might be a reasonable option in patients who are not satisfied with either agent alone.

We assessed the effectiveness of combining sildenafil with a vacuum constriction device in men who were unsatisfied with the results of the vacuum constriction device alone.^[63] Thirty-one post-RP patients (mean follow-up 4.5 months) were instructed to take sildenafil 100mg 1–2 hours prior to vacuum constriction for sexual intercourse. Patients used combination therapy for a minimum of five attempts prior to assessment with the SHIM IIEF5 and a visual analogue scale to gauge rigidity. The effects of combination therapy on the total IIEF5 score and penile rigidity scores were assessed. Of the 31 patients, 7 (22%) had no improvement with the addition of sildenafil and discontinued the drug, whereas 24 (77%) reported improved penile rigidity and sexual satisfaction. In these 24 patients, the IIEF5 score showed significant improvement in each domain, and patients reported that sildenafil enhanced their erections most of the time. Rigidity scores on a scale of 0–100 with vacuum device use alone averaged 55% (23–85%) for men and 59% (26–90%) for their partners. With the addition of sildenafil, these scores increased to 76% for men and 82% for their partners. Thirty percent (7/24) reported return of natural erections at 18 months using combination therapy,

and 5/7 said this was sufficient for vaginal penetration.

Thus, addition of sildenafil to vacuum constriction improved sexual satisfaction and penile rigidity in patients unsatisfied with vacuum constriction alone.

3.4.2 Medicated Urethral System for Erection (MUSE) plus Sildenafil After RP

cAMP and cGMP are two secondary messenger proteins that mediate smooth muscle relaxation in different pathways. PDE5 inhibitors such as sildenafil act indirectly and require sexual stimulation and endogenous nitric oxide production to activate the cGMP pathway and be effective. In contrast, agents such as PGE₁ act directly on the trabecular smooth muscle, binding to specific receptors and increasing cAMP synthesis. Thus, combination therapy that induces both cAMP- and cGMP-mediated vasodilatation may be more efficacious in the salvage of patients who desire noninvasive therapy but in whom single-treatment modalities fail.

A study conducted by Nehra and Kulaksizoglu^[64] demonstrated that the combination of sildenafil (100mg) and intraurethral PGE₁ (1000µg) salvaged a refractory population of men with ED. Similarly, Mydlo et al.^[65] in 2000 reported that 60/65 patients who were unsatisfied with sildenafil or MUSE alone responded to combination treatment, with a significant improvement in IIEF5 scores. However, the populations in both studies had diverse aetiologies, including vascular, neurogenic and postoperative ED patients.

We have examined the effectiveness of MUSE-sildenafil combination therapy in 23 patients who were unsatisfied with sildenafil alone for ED following RP.^[66] Of these patients, 4 (17%) had no improvement with the addition of MUSE and discontinued the drug, whereas 19 (83%) reported improved penile rigidity and sexual satisfaction. In these 19 patients, the IIEF5 score significantly improved in each domain, and patients reported that their erections were sufficient for vaginal penetration 80% of the time. Rigidity scores on a scale of 0–100 with sildenafil alone averaged 38% (23–53%) for men and 46% (26–67%) for their partners. With the addition of MUSE, the average scores increased to 76% for men and 62% for their partners. Thus, addition of MUSE to sildenafil ther-

apy improved sexual satisfaction and penile rigidity in patients unsatisfied with sildenafil alone.

3.4.3 Intracavernosal Injections plus PDE5 Inhibitors

Adding an intracavernosal injection may be useful in oral PDE5 inhibitor nonresponders, as reported by several authors. Shabsigh et al.^[67,68] reported that intracavernosal injections are effective in 88% of patients with ED who do not respond to sildenafil alone.

Repeated intracavernous PGE₁ injections have been reported to upregulate nitric oxide synthase expression in an animal model.^[69] Recently, the effectiveness of combination treatment in an RP population was demonstrated by Mydlo et al.^[70] Of the 34 patients in their study, 32 continued the treatment and 2 discontinued it because of pain associated with penile injections. Of the 32 patients, 22 (68%) reported significant improvement in all domains of their SHIM scores compared with sildenafil or vardenafil alone. After a mean follow-up of 7 months, 36% (8/22) discontinued use of the injections because of improvement in response to oral PDE5 inhibitors. The remaining patients continue to use the injections on a regular basis.

Intracavernosal injections in combination with oral therapy are a useful treatment when oral agents alone are ineffective.

3.5 Other Agents

Apomorphine is a dopamine D₁/D₂ receptor antagonist that acts on the CNS. Several trials have reported that apomorphine is effective in the treatment of ED in the general population. It is administered sublingually 20 minutes prior to expected sexual activity. At the approved doses of 2mg and 3mg, apomorphine induces a significantly higher percentage of erections than placebo. At the 2–3mg dose the main adverse effect of nausea was acceptable at a rate of 4.7%.^[71] A multicentre study by Mulhall et al.^[72] reported that sublingual apomorphine in heterosexual men with ED increased the number of attempts at intercourse from a mean of 12.7% at baseline to 38.3%. These clinical trials show that apomorphine is an effective alternative treatment option for ED at the approved dose of 2–3mg.

However, the role of apomorphine in the treatment of ED following RP has yet to be established.

4. Role of Pharmacological Agents in Prophylaxis of ED Following RP

There is a growing interest among urologists regarding the role of early prophylaxis against ED following RP. The rationale behind the use of early prophylaxis is to prevent cavernosal hypoxia during neuropraxia. This ultimately prevents the formation of cavernosal fibrosis and subsequent venous leak. This concept was first reported in 1997 by Montorsi et al.,^[29] who used intracavernosal injection of PGE₁. However, no further confirmatory studies followed because of penile pain and fear of injections. Recently, there has been growing interest in the use of oral PDE5 inhibitors for prophylaxis against ED following RP.

4.1 Role of Oral Medications in ED Prophylaxis

Recently, Schwarz et al.^[73] analysed cavernosal smooth muscle content in a post-prostatectomy population. A total of 40 patients were included in the study. A first cavernosal biopsy was performed at the time of surgery. Patients were advised to take sildenafil 50mg (group 1, n = 20) or 100mg (group 2, n = 20) every other night. After 6 months' follow-up, 11 of 20 patients in group 1 and 10 of 20 patients in group 2 underwent a second biopsy. At 6 months, group 2 (100mg) patients had significantly more smooth muscle content in the second biopsy (56.85%) compared with the first biopsy (42.82%; $p < 0.05$). However, in group 1 (50mg), no significant difference in smooth muscle content was observed between the first and second biopsy (51.2% vs 51.7%, $p > 0.05$). The investigators concluded that early use of sildenafil (50mg) following RP appears to preserve smooth muscle content, and at doses of 100mg increases the smooth muscle content.

Use of sildenafil for early recovery of erectile function was first reported by Padma-Nathan et al.,^[74] who conducted a randomised controlled study in 76 men (oral sildenafil daily [50mg, n = 23; 100mg, n = 28], placebo, n = 25) with normal preoperative erectile function who underwent nerve-sparing RP. Sildenafil was given for 36 weeks in the

study group. After 48 weeks' (~11 months') follow-up, 14 of 51 (27%) patients receiving sildenafil experienced a return of spontaneous erections compared with 1 of 25 (4%) in the placebo group. This study revealed that oral daily sildenafil increased the return of erections 7-fold compared with placebo and that the treatment was well tolerated. However, this study has been criticised because the return of spontaneous erections in the placebo group was only 4%, which is very low compared with rates reported in other series in the literature. Further multicentre randomised studies are ongoing to investigate the potential benefit of daily sildenafil following radical RP.

Recently, Gallo et al.^[75] from Italy evaluated the role of vardenafil in recovery of erectile function following pelvic urological surgeries (RP and cystectomy). After 6 months, vardenafil users reported a 12.9-point increase in mean IIEF5 scores in the bilateral nerve-sparing RP group, an 8.0-point increase in the unilateral nerve-sparing RP group, and an 11.3-point increase in the nerve-sparing radical cystectomy group. This study showed that vardenafil is well tolerated and effective in the recovery of erectile function in patients undergoing pelvic urological surgery. However, lack of a control group may be a limiting factor in this study.

4.2 Role of Early MUSE in ED Prophylaxis

We recently evaluated the use of early MUSE after RP at the Cleveland Clinic Foundation.^[76] Of 91 patients, 56 received early MUSE and 35 (control group) did not receive any early treatment. Patients in the early MUSE group received 125µg 3 times per week for the first 6 weeks. Overall, in the MUSE group, 27% (15/56) achieved natural erections sufficient for sexual intercourse at 6 months. The MUSE discontinuation rate was 32% (18/56). In the control group, 13/35 (37%) resumed sexual activity, 4/13 (30.7%) had natural erections sufficient for vaginal penetration, and 9/13 (69.3%) were dissatisfied with their erections and used oral therapy/erectoids as adjuvant treatments. Overall, in the control group, 11% (4/35) achieved natural erections sufficient for satisfactory sexual intercourse at 6 months.

In our experience, early MUSE therapy following RP increased the frequency of sexual activity, increased the incidence of spontaneous erections

sufficient for intercourse and appeared to shorten the neuropraxia period.

4.3 Role of Early Intracavernosal Injection in ED Prophylaxis

Montorsi et al.^[29] from Milan, Italy, first reported their experience of using intracavernous injections for preservation of erectile function in 1997. Of a total of 30 patients who underwent nerve-sparing RP, 15 were randomised into group 1 (PGE₁ injections three times per week for 12 weeks) and another 15 into group 2 (observation without erectaids). The mean dose of PGE₁ was 8µg (4–14µg). At 6 months, 67% of patients in the injection group reported a return of spontaneous erections sufficient for satisfactory intercourse compared with 20% in the observation group.

We recently re-examined the role of early intracorporeal injections, using a lower dose of PGE₁ (4µg two to three times per week) commenced 2 weeks after RP, combined with oral sildenafil 50 mg/day.^[77] We reduced the injection dose to 4µg to obtain partial erections with minimal, if any, pain. We included a total of 18 patients in this study. Our goal was to achieve a compliance rate >90%. Further dose modifications have been made to achieve this goal. After a mean follow-up of 6 months (2–8 months), 17/18 patients were sexually active: 8 (45%) patients were using injections alone and 9 (55%) patients were using the combination of injections and sildenafil.^[77] In this follow-up period, 10/18 (56%) patients achieved spontaneous partial erections, but could not have sexual intercourse. One patient was sexually inactive because of significant incontinence. Our initial response with PGE₁ was very encouraging, but 50% of our patients needed sildenafil to be sexually active with our low-dose PGE₁ programme. This oral dependence prompted us to use 30 units of low-dose Trimix (1mL = 100 units of low Trimix, which contains PGE₁ 5.88µg, phentolamine 0.59mg and papaverine 17.65mg, taken 2–3 times per week); this achieved comparable sexual activity without sildenafil. Early low-dose Trimix can produce more efficacious erections than early low-dose PGE₁. All patients using low-dose Trimix were sexually active without sildenafil, and after a mean follow-up of 4 months (3–9 months), one patient had partial natural erec-

tions. Overall, when all patients on early injections (18 PGE₁ and 4 low-dose Trimix) were combined, all 22 (100%) patients were compliant at 6 months, 96% (21/22) remained sexually active and 50% (11/22) regained natural erections.

We conclude from our early injection data that high compliance can be achieved if good counselling education is performed at the time of the initial dose and proper dose modifications are made on the basis of efficacy and adverse effects profile. A good early injection programme should facilitate early sexual intercourse in addition to stimulating an earlier return of natural erections.

5. Penile Prostheses

Use of a penile prosthesis is one of the oldest treatment options available for impotence. In 1972, the first rod prosthesis was introduced, which was soon replaced by inflatable devices.^[78] Gerstenberger et al.^[79] in 1979 reported 75% satisfaction rates with use of a penile prosthesis. McLaren et al.^[80] reported that 83% of men were satisfied with the results of implant surgery. Advances in prosthesis design and implantation techniques have resulted in increased device survival. The 5-year actuarial survival rates free of mechanical failure range from 86.2% to 93.6%, whereas patient satisfaction ranges from 83% to 85% and partner satisfaction rates range from 70% to 76%.^[81] Prosthesis infection is the major concern after surgery, with rates ranging from 1.7% to 1.8%.^[82]

Penile prosthesis was a reliable invasive treatment option for ED. With the availability of effective non-invasive treatment options, it is no longer the first-line treatment option. However, penile prosthesis is considered an important option for patients who do not respond to medications and devices, and for those who are not willing to use such treatment options.

6. Future Directions

Current research is beginning to focus on nitric oxide donors, which increase nitric oxide synthesis in the cavernosal bodies. NCX 4050 (a drug belonging to a new class of nitric oxide donors) increases guanyl cyclase activity and produces smooth muscle relaxation in both human and rabbit cavernosal

models.^[83] Recently, Kalsi et al.^[84] reported that NCX 911, a nitric oxide-releasing PDE5 inhibitor, produced relaxation of the cavernosal smooth muscle by increasing endogenous nitric oxide. These two agents may be promising future options for patients with impaired nitric oxide release from the endothelium. However, the efficacy of these agents needs to be confirmed in human studies.

The role of growth factors in the treatment of ED is another exciting area of interest. Vascular endothelial growth factor has shown some promise in animal experiments conducted by Lee et al.^[85] However, the efficacy and safety of growth factors need to be evaluated in human trials before they can be used in routine clinical practice.

7. Practice-Based Treatment Algorithm for ED Following RP

ED following RP is multifactorial in aetiology, and it is difficult to predict the appropriate treatment choice for any individual patient. The treatment decision for ED following RP depends on preoperative erectile function status, duration of ED following surgery, the type of surgery (nerve-sparing or non-nerve-sparing) and the age of the patient. Standard treatment options (intracavernosal injection, vacuum constriction device and MUSE) form the first-line treatment options following RP during the period of neuropraxia. When ED persists for 6 months to 1 year, patients should be treated with oral PDE5 inhibitors. PDE5 inhibitors are effective in 52–72% of patients with bilateral nerve-sparing RP. Intracavernosal injections are reasonable treatment alternatives for patients who are not responding to oral therapy or who have contraindications to oral therapy. Intracavernosal injections have high efficacy rates ranging from 60% to 90%. In patients who are not responding to oral agents and who are not willing to use penile injections because of pain and/or fear, the vacuum constriction device may be a reasonable treatment option. In patients who do not respond to oral medication and who are not willing to try injections or a vacuum constriction device (because of a lack of spontaneity or because of petechiae at the base of penis), MUSE can be a reasonable option. Recently, combination therapy

has become an important treatment option. Combination therapy with oral PDE5 inhibitors and non-oral treatments (injections, vacuum constriction devices or MUSE) is useful for salvaging erectile function in patients who do not respond to individual agents. Penile prosthesis is the final invasive treatment option: success rates range from 70% to 90%.

8. Summary

ED is a common complication after RP. Even with major advances in surgical techniques, ED rates are still high. Currently, we have several options available for the treatment of ED after RP. Oral therapy using PDE5 inhibitors (sildenafil, vardenafil and tadalafil) is associated with good compliance. However, lack of efficacy results in considerable attrition. Unless there is functioning nerve tissue to stimulate nitric oxide release, none of the PDE5 inhibitors will be effective. Standard treatment options such as intracavernosal injections, vacuum constriction devices and MUSE appear to be effective. However, compliance is the major problem with these treatment modalities.

The pathophysiology of ED after RP is multifactorial, with neurovascular factors being most important. Neuropraxia in combination with vascular insufficiency produces penile hypoxia. Prolonged periods of penile hypoxia induce penile fibrosis, which further aggravates ED by increasing the incidence of venous leak. There is growing interest in interrupting this cascade of events by decreasing penile hypoxia in the early postoperative period. Early evidence using intracavernosal injections for this hypothesis is promising. While early daily sildenafil appears to improve natural erections, it does not promote early sexual activity. Our data indicate that all three non-oral options (injections, MUSE and vacuum constriction devices) promote frequent sexual activity in the first year, when neuropraxia sets in. Only early pharmacological stimulation appears to improve the return of natural erections and shorten the period of neuropraxia. These early rehabilitation strategies may become part of routine practice in the management of ED following RP.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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