

## Local Therapies to Heal the Penis: Fact or Fiction?

## Minireview

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**ABSTRACT:** Penile rehabilitation has been an area of intense study and debate over the last decade. Interest in this topic was stimulated by the observation that erectile dysfunction remained a significant problem after radical prostatectomy despite meticulous nerve-sparing technique. Smooth muscle alterations and fibrotic changes in the penis were identified as the underlying causes of penile atrophy, veno-occlusive dysfunction, and Peyronie's-like changes that were observed after surgery. Initial observations that intracavernous injection therapies used on a regular basis postoperatively resulted in improvements in the return of sponta-

neous erectile function led to the development of penile rehabilitation protocols. Chronic dosing of oral type V phosphodiesterase inhibitors is now commonly used by urologists after radical prostatectomy despite a lack of convincing evidence from randomized, placebo-controlled clinical trials. Use of local therapies to heal the penis may have applications beyond the postprostatectomy patient. This article reviews the current evidence behind penile rehabilitation therapy.

Key words: Penile rehabilitation, radical prostatectomy.

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The topic of penile rehabilitation therapy has become an area of intense interest over the last decade. Advances in basic science studies have led to the widespread acceptance of the use of oral type V phosphodiesterase (PDE-V) therapy on a chronic basis after radical prostatectomy (RP). Undoubtedly, “healing of the penis” will remain an area of intensive study and debate. Although speculative, demonstration of success of penile rehabilitation therapy may lead to future prevention strategies. The ability of a man to have spontaneous erections will always remain paramount to his sense of sexual well-being.

A central question is whether local therapies, such as PDE-V inhibitors and intracavernous or intraurethral alprostadil, can lessen or reverse the effects of causative factors for erectile dysfunction (ED). The purpose of this article is to present an overview of the scientific data

applicable to the question of whether vasoactive therapies can heal the penis.

### *A Model of Penile Injury: Penile Alterations after RP*

Interest in the topic of penile rehabilitation developed in the 1990s with the observation that ED was a significant problem for men after nerve-sparing RP (NSRRP). With refinements in the nerve-sparing technique developed by Walsh (Quinlan et al, 1991), attention shifted from the cavernous nerve to the penis and the cavernous smooth muscle. As a consequence, the most studied model of penile rehabilitation is the post-RP patient.

A basic outline of pathophysiology of injury after RP is depicted in Figure 1. During an NSRRP, microneural damage to the cavernous nerve may occur despite meticulous nerve-sparing technique. This damage may be caused by traction and manipulation of the neurovascular bundle even in an experienced surgeon's hands. The subsequent neurapraxia then results in cavernous smooth muscle injury and fibrosis. Clinical manifestations of these changes may be evident as corporal veno-occlusive dysfunction (CVOD), shrinkage and atrophy of the penis (Fraiman et al, 1999; Savoie et al, 2003), and the development of Peyronie's-like plaques and curvature (Ciancio and Kim, 2000).

### *Basic Science: Injury and Repair*

The underlying hypothesis of penile rehabilitation therapy is that local therapies can minimize penile smooth muscle alterations after nerve injury. In the

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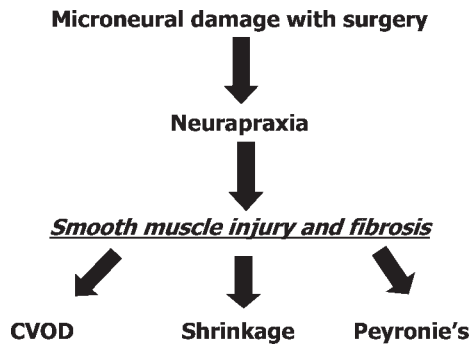


Figure 1. Nerve injury during radical prostatectomy affects penile smooth muscle and may lead to fibrotic changes. Corporal veno-occlusive dysfunction (CVOD), penile atrophy, and Peyronie's-like plaques may result.

1990s, it was recognized that denervation injury to the penis affects the cavernous smooth muscle. An analogy is that after spinal cord injury, muscles in the affected neurological distribution atrophy.

Using a rat model, Klein et al (1997) were the first to demonstrate that denervation of the penis leads to apoptosis. Using an in situ end labeling technique for the detection of DNA fragmentation, apoptosis was detected in the glans penis and corporal bodies as early as 2 days after cavernous nerve transection. The control, sham-operated rats had no evidence of apoptosis. This apoptotic process is directly related to atrophy and fibrosis.

User et al (2003), from Northwestern University, confirmed the presence of penile apoptosis as early as 1 day after cavernous nerve ablation in a rat model. The most intense staining for apoptotic cells was identified directly under the tunica albuginea. This finding may be of significance when recognizing that Peyronie's-like changes are common after RP. Penile weight decreased.

The treatments most studied for penile rehabilitation therapy after RP are alprostadil, administered intraurethral or intracavernously, and oral PDE-V inhibitors (McCullough, 2008). Alprostadil, specifically prostaglandin E-1 (PGE-1), may promote the recovery of erectile function by the promotion of cavernosal oxygenation levels. By stimulating the formation of adenylate cyclase, PGE-1 increases the concentration of cyclic adenosine monophosphate within the smooth muscle cells (Ruiz Rubio et al, 2004). In the in vitro setting, prostanoids have been shown to be protective for smooth muscle (Moreland et al, 2001).

The hypothesis is that PDE-V inhibitors promote penile rehabilitation by stimulating smooth muscle cell replacement via a cyclic guanosine monophosphate mechanism and reducing collagen synthesis via phosphokinase G activation (Kovanecz et al, 2007). If PDE-V inhibitors can induce cavernosal oxygenation in the absence of erection, they may function as endothelial protectants and preserve smooth muscle after cavernous nerve injury (Figure 2).

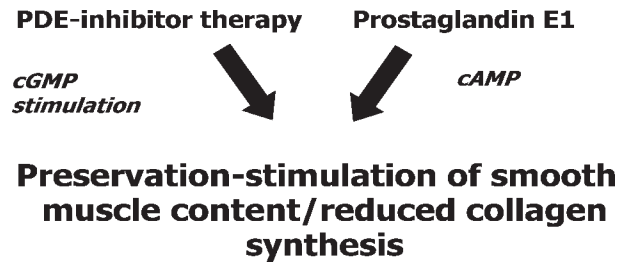


Figure 2. Possible mechanisms of therapies in protecting the cavernous smooth muscle.

Kovanecz et al (2007) have identified that this benefit is independent of the antifibrotic effects of inducible nitric oxide synthase (iNOS).

By performing percutaneous penile biopsies at the time of RP and 6 months later, Schwartz et al (2004) were the first to demonstrate that early use of sildenafil after RP may preserve intracorporeal smooth muscle content. A total of 40 potent volunteers with prostate cancer underwent RP and were divided into 2 treatment groups. Group 1 received 50 mg sildenafil every other night for 6 months starting on the day of catheter removal. Group 2 received 100 mg sildenafil using the same dosing regimen. With a follow-up on 21 men, there was no statistically significant change in mean smooth muscle content as assessed by an image analysis method preoperatively to postoperatively (51.52% and 52.67%, respectively) in group 1. However, in group 2 there was a statistically significant increase in mean smooth muscle content 6 months after RP (42.82% vs 56.85%,  $P = .05$ ; Figure 3) Average smooth muscle content is approximately 40%–50%. (Wespes et al, 1991).

Although the higher dose of 100 mg sildenafil may increase smooth muscle content, the effects on long-term return of erectile function were not determined in this

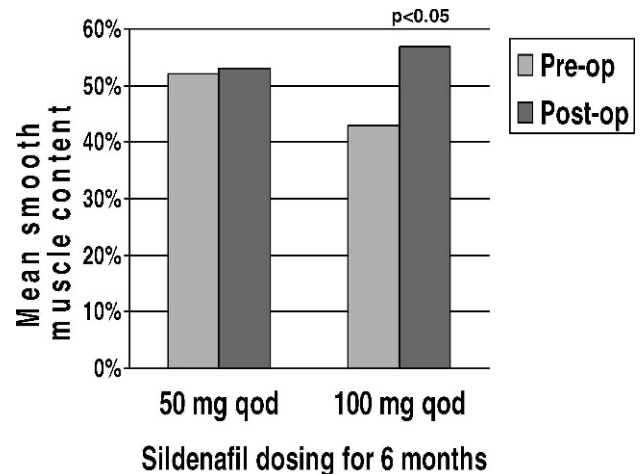


Figure 3. Sildenafil preserves intracorporeal smooth muscle after radical prostatectomy (adapted from Schwartz et al, 2004).

study. A limitation of this study was the absence of a control group. However, the findings provide a foundation for the use of PDE-V inhibitors for penile rehabilitation therapy.

In several elegant studies, Rajfer and others from the University of California, Los Angeles, demonstrated that chronic therapy with both long- and short-acting PDE-V inhibitors can prevent CVOD and underlying histological changes induced by neurapraxia (Ferrini et al, 2006, 2007; Kovanecz et al, 2007, 2008). Using a rat model of cavernous nerve transection in separate studies, male rats were administered vardenafil, sildenafil, and tadalafil for 45 days in doses 2–2.5 times higher than normally given to men for the on-demand treatment of ED.

PDE-V–treated rats had no significant increase in the penile shaft collagen content. The untreated rats had a reduction in corporal smooth muscle cell content and in the ratio of smooth muscle cells to collagen, and an increase in the apoptotic index. There were no effects of PDE-V inhibition on increased transforming growth factor  $\beta$ 1, iNOS, and xanthine oxidoreductase levels. These studies have provided important animal model documentation of the benefit of PDE-V therapy for prevention of functional and histologic changes in the penis that can occur after nerve damage.

#### *Clinical Studies of Local Therapies for Penile Rehabilitation*

Although an increasing number of studies are providing a signal that therapies for penile rehabilitation facilitate the return of spontaneous erections after RP, these publications have relatively small numbers of patients and have not yet been replicated. Reproducible large-scale, long-term, randomized double-blind placebo-controlled studies are necessary.

Montorsi et al (1997), from Milan, performed the first prospective study of pharmacologic therapy for penile rehabilitation after RP using intracavernous alprostadil injections. A total of 30 potent men with clinically localized prostate cancer underwent NSRRP. They were randomized to alprostadil injections 3 times per week for 12 weeks (group 1, 15 patients) or observation (group 2, 15 patients).

Patients were assessed 3 months after initiating treatment or placebo. Twelve of 15 men completed treatment. Of these men, 8 (67%) reported the recovery of spontaneous erection sufficient for satisfactory sexual intercourse, compared with 3 patients (20%) in the observation arm ( $P < .01$ ; Figure 4). They concluded that early use of alprostadil injections significantly increases the recovery rate of spontaneous erections after NSRRP. Notable limitations were that preoperative parameters of erectile function were not assessed and

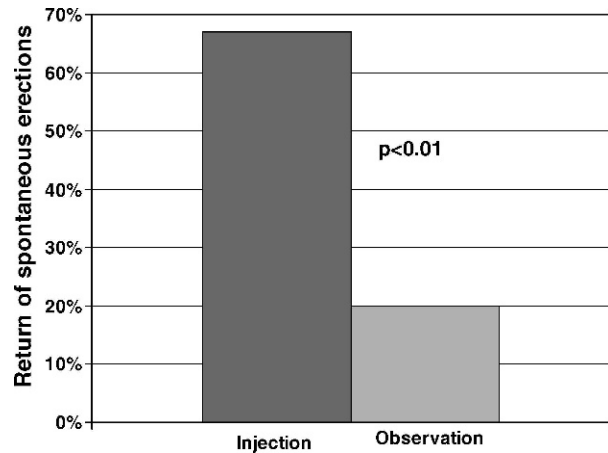


Figure 4. Intracorporeal injection therapy after radical prostatectomy: overall return of spontaneous erections (adapted from Montorsi et al, 1997).

that this study was performed before the routine use of validated questionnaires. Additionally, the short duration of follow-up limits any conclusions regarding long-term impact of therapy. Nevertheless, this study was the first clinical report to suggest a benefit of a penile rehabilitation strategy using a pharmacologic therapy.

Gontero et al (2003), from Novara, Italy, reported that earlier initiation of alprostadil injections resulted in a more rapid return of penile tumescence. Although those men starting therapy within 1 month had the best response rate, those initiating therapy within the first 3 months after a non-nerve-sparing RP also had a meaningful erectile response as assessed by color Doppler ultrasound testing.

In 2005, Mulhall et al reported on a nonrandomized study of a pharmacotherapy regimen designed to improve the return of spontaneous erections after RP. Men with functional preoperative erections who underwent RP were challenged early postoperatively with oral sildenafil. Nonresponders were switched to intracavernosal injection therapy and were instructed to inject 3 times a week. Only patients who presented within 6 months after surgery and who had been followed for at least 18 months were included.

Results were evaluable for 58 patients in the rehabilitation group and 74 in the nonrehabilitation group. At 18 months postoperatively, 52% of the rehabilitation group vs 19% of the nonrehabilitation group were capable of having medication-unassisted intercourse ( $P < .001$ ). Mean International Index of Erectile Function (IIEF) erectile function domain (EF domain) scores (rehabilitation group  $22 \pm 6$  vs nonrehabilitation group  $12 \pm 14$ ,  $P < .01$ ) and the percentage of patients with normal EF domain scores (rehabilitation 22% vs nonrehabilitation 6%,  $P < .01$ )

were significantly better in those men undergoing therapy. The percentage of patients responding to sildenafil, the time to become a sildenafil responder, and the percentage of patients responding to intracavernous injection therapy were also significantly improved in the treatment arms.

These authors concluded that a pharmacologic penile rehabilitation protocol results in higher rates of spontaneous functional erections and erectogenic drug response. This study did not contain a placebo arm and had a strong patient selection bias, because patients were allowed to select treatment or observation.

The first randomized, placebo-controlled trial of chronic PDE-V therapy for the purposes of penile rehabilitation was presented at the 2003 American Urological Association annual meeting by Padma-Nathan (Padma-Nathan et al, unpublished) as an abstract, but not as a peer-reviewed publication at that time. Four weeks postoperatively, men undergoing bilateral NSRRP were randomized to sildenafil 50 or 100 mg nightly or placebo for 36 weeks. Erectile function was assessed 8 weeks after discontinuation of drug treatment (week 48) using the IIEF questionnaire (Rosen et al, 1997) and the question "Over the past 4 weeks, have your erections been good enough for satisfactory sexual activity?" Responders were defined as those having a combined score of  $>8$  for IIEF questions 3 and 4 and positive response to the preceding question (Rosen et al, 1997).

Forty-eight weeks after bilateral NSRRP, 14 of 51 (27%) patients receiving sildenafil demonstrated return of spontaneous erectile function compared with 1 of 25 (4%) in the placebo group ( $P = .0156$ ; Figure 5). They concluded that nightly administration of sildenafil for 9 months post-NSRRP increased the return of spontaneous erections 7-fold compared with placebo. Although this study has been criticized for the seemingly low percentage (4%) of men considered responders in the placebo arm, the criteria for being considered a responder were stringent. This study represents the first placebo-controlled trial suggesting benefit of oral PDE-V therapy in improving the return of spontaneous erections (Padma-Nathan et al, 2008).

A subset of these men had nocturnal penile tumescence and rigidity (NPTR) testing performed preoperatively and at various time points postoperatively (McCullough et al, 2008). A rapid and profound reduction in nocturnal erectile function was noted in all groups. A gradual dose-dependent improvement in base and tip rigidity in the sildenafil groups, but not in the placebo group, was identified. These authors concluded that nightly sildenafil for 9 months post-bilateral NSRRP objectively improved nocturnal erections and pharmaceutically unassisted erectile func-

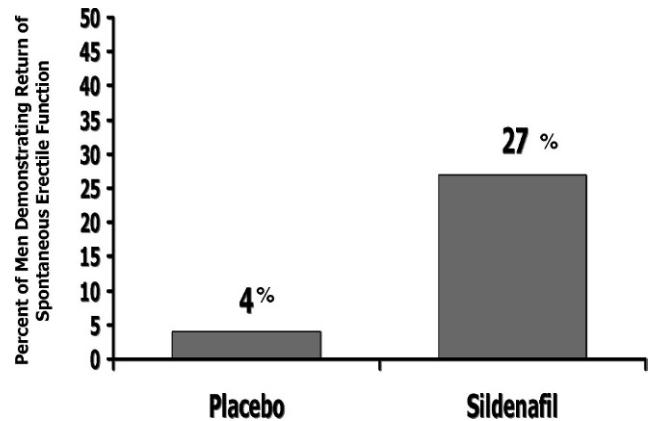


Figure 5. Improvement in erectile function postprostatectomy after nightly sildenafil (adapted from Padma-Nathan et al, unpublished). Sildenafil was administered at doses of 50 and 100 mg.

tion. The importance of this study was the objective characterization of the return of erectile function using NPTR testing.

Bannowsky et al (2008), from Germany, reported their findings of low-dose sildenafil for rehabilitating erectile function after NSRRP. Twenty-three men with preserved erectile function based on Rigiscan testing 1–2 weeks postoperatively received sildenafil 25 mg nightly vs 18 men who received placebo for 52 weeks. There was a significant difference in IIEF-5 score and time to recovery of erectile function between the groups ( $P < .001$ ), with potency rates of 86% vs 66%. The authors concluded that in cases of early penile erection, daily low-dose sildenafil leads to a significant improvement in the recovery of erectile function.

In contrast, Montorsi et al (2008) recently reported on a vardenafil trial after bilateral NSRRP. In this randomized, double-blind, double-dummy, multicenter, parallel group study, a total of 628 men were randomized to placebo, nightly vardenafil, or on-demand vardenafil for 9 months, followed by a 2-month washout period, and an optional 2-month open-label period. No statistically significant differences were observed among treatment groups in the proportion of patients with an IIEF EF score of  $\geq 22$  or in Sexual Encounter Profile, question 3, success rates after the washout period. Although on-demand dosing was efficacious, nightly vardenafil for the purpose of penile rehabilitation was not efficacious. This well-designed study provides a cautionary note for the present enthusiasm of oral PDE-V inhibitors for penile rehabilitation therapy.

Similarly, as an abstract presentation at the 2006 American Urological Association annual meeting, Montorsi et al (unpublished) reported no significant difference in erectile function between on-demand PDE5 inhibitors and daily PDE5 inhibitors as rehabilitative

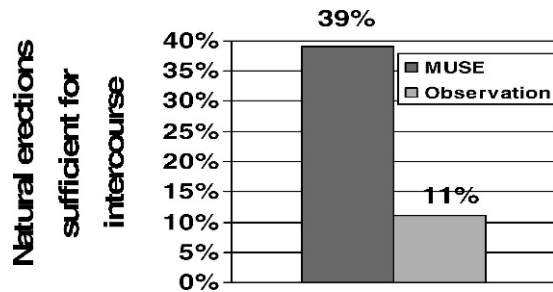


Figure 6. MUSE potentially facilitates an earlier return of erectile function after nerve-sparing radical prostatectomy (adapted from Raina et al, 2007). MUSE was administered at 125 or 250  $\mu$ g 3 times per week for 6 months. Results are expressed for those patients who completed the entire study.

treatment after bilateral NSRRP (2006). The IIEF EF domain score at the mean 12-month follow-up was  $19.5 \pm 9.4$  for on-demand use compared with  $18.3 \pm 4.0$  for use as rehabilitation. A limitation of this study was that compliance to PDE5-I as rehabilitative treatment was not reported.

Raina et al (2007), from the Cleveland Clinic, treated 56 men with intraurethral alprostadil (MUSE; Vivus Inc, Mountain View, California) at dosages of 125 and 250 mg 3 times weekly for 9 months. Treatment was initiated 3 weeks postoperatively. Overall, 68% (38/56) of patients using MUSE completed the study. In patients who continued to use MUSE, 15 of 38 (40%) reported having natural erections sufficient for vaginal intercourse. In comparison, 4 of 35 men (11%) in the observation group had natural erections sufficient for vaginal intercourse (Figure 6).

Intraurethral alprostadil would be expected to have a similar mechanism of action to intracavernous alprostadil, namely that of improved acute blood flow to the penis. Although MUSE therapy avoids the needles associated with intracavernous injections, it is notable that almost one-third of men did not complete the study. This noncompliance rate indicates that men need encouragement to continue with therapies that may not have immediate results.

Although most of the discussion has focused on the role of local therapies for penile rehabilitation therapy after RP, recent studies suggest that local therapies may improve erectile function in other disease states. Using a streptozotocin-induced diabetic rat model, De Young et al (2008), from Ontario, Canada, identified a significant increase in intracavernous pressure in rats receiving vardenafil therapy, even 20 hours after the last dose. Improved endothelial and smooth muscle cell staining were also evident with chronic vardenafil use. These findings suggest that PDE-V inhibitors may have a protective effect in this disease state.

### Where We Stand: More Fact than Fiction

At the present time, the study of penile rehabilitation is in active evolution. The body of literature suggests a beneficial role of local therapies for the restoration of erections after injury. However, although most published reports point towards improved outcomes with active treatment, nearly all studies have significant limitations. As a result, point-counterpoint debates have become common regarding this subject (Mulhall and Morgentaler, 2007).

The basic arguments supporting the role of local therapies for penile rehabilitation therapy are that 1) a mechanism for the protection of endothelial function and smooth muscle function is present, 2) animal models of chronic dosing of PDE-V inhibitors clearly demonstrate improvement in erectile response, and 3) human data with intracavernous, intraurethral, and oral PDE-V therapies point to improvement of erectile function. The counterpoint argument notes that the present human studies have significant limitations that do not permit any type of definitive conclusions regarding the benefit of therapy. However, all agree that reproducible, randomized, controlled trials whose results can be replicated are necessary to clearly define the role of penile rehabilitation therapy.

### Treatment Regimens

There is no consensus regarding the ideal regimen for penile rehabilitation therapy. Although the use of chronic dosing of PDE-V inhibitors has become accepted medical practice after surgery (Wang, 2007; Zippe and Pahlajani, 2007), there is no consistency among regimens. Monotherapy with a PDE-V inhibitor has become the most widely adopted form of therapy. Cost has been a significant barrier to greater acceptance of daily dosing of PDE-V inhibitors. Commonly used regimens often incorporate every-other-day dosing for cost-saving purposes.

The oral route of administration is intuitively easier to use than intracavernous or intraurethral forms of application. Whether combining oral PDE-V inhibitors with intracavernous or intraurethral alprostadil improves outcomes remains speculative. However, there may be advantages with combination therapy given their different mechanisms of action.

### Barriers to Treatment

Significant barriers to treatment include cost, a lack of well-designed clinical trials, poor compliance, and questions regarding duration of therapy. Even with the introduction in March 2008 of tadalafil 5 mg for once-daily use, costs of most treatment regimens are over

\$120 monthly in the United States. Although some insurers may cover 6–8 tablets monthly for use as needed, coverage of PDE-V inhibitors for the purpose of penile rehabilitation is uncommon given this off-label use. When Viagra's patent expires in 2011, the introduction of generic sildenafil may lower costs and increase affordability.

Performing a randomized, placebo-controlled trial has many challenges. First, without industry support, the cost of a 9–24-month trial can be prohibitive for a large-scale study. Recruitment of men with normal erectile function at the time of RP who are willing to participate in a placebo-controlled trial can be a lengthy process. For a sufficiently powered study, a multi-institutional trial may be required, thereby increasing cost and complexity. Industry support can introduce potential biases and limit the opportunity for direct comparative trials.

Second, differences in nerve-sparing technique and methods of reporting outcomes between surgeons can confound interpretation of results. Erectile function outcomes after nerve sparing RP vary widely. In the Padma-Nathan trial, only 4% of men had normal erectile function postoperatively, but stringent criteria for reporting were applied (Padma-Nathan et al, 2008, unpublished). In contrast, Walsh (2001) has reported a 91% potency rate after RP, but did not use validated questionnaires.

Third, as evidenced in published trials, long-term compliance with treatment can be poor. It is not uncommon for men to lose interest in sexual activity after this cancer surgery. Given the need for chronic dosing without immediate feedback on the return of erectile function, men are often easily discouraged and fall out of therapy.

#### *Questions: Practical and Theoretical*

More questions are raised as our knowledge base on this topic expands. A basic question is why PDE-V inhibition should help the return of spontaneous erections if the penis remains flaccid for prolonged periods of time postoperatively. PDE-V inhibitors do not increase blood flow to the flaccid penis. Therefore, how can benefit occur? Although rat studies demonstrate a distinct benefit, extending benefits in a rodent model to the human could be a large extrapolation.

Although the best available clinical evidence has studied sildenafil and vardenafil, which both have a half-life of 4 hours, would a longer half-life agent have theoretical benefits? Until the true value of PDE-V inhibitors in restoring erectile function is determined, comparative analysis is not possible. Interestingly, in a

follow-up to their first study (Montorsi et al, 1997), Montorsi et al (unpublished) reported that men using PDE-V inhibitors on a regular rehabilitation schedule did no better than men who used PDE-V inhibitors on demand.

The optimal time for starting penile rehabilitation has not been determined. Although it is common to start therapy 2–6 weeks postoperatively, a question is whether starting treatment preoperatively can have benefit. Rat models have demonstrated that after nerve injury, penile changes appear after as soon as 2 days.

#### *In My Practice*

I offer penile rehabilitation therapy to those patients who are motivated to pursue a 9–12-treatment course. I explain that although the basic science is compelling and the clinical studies are suggestive, I consider this field still investigational. Although use of oral PDE-V inhibitors on a regular basis after RP is popular and commonplace, the body of evidence is still limited. I offer these men a PDE-V inhibitor with every-other-day dosing starting 2–4 weeks postoperatively. I encourage them to split the highest-dose tablet for cost savings.

These men are instructed that the best return of erectile function may take 18–24 months postoperatively. They are instructed to try the highest dose of their PDE-V inhibitor before sexual activity for use on demand. I remind them that results may not be evident for over 1 year. They are cautioned that if ED, however mild, is present preoperatively, I am not optimistic about the return of erectile function.

#### *Conclusions*

Significant advances over the last decade have led to an increased understanding of the possibilities for local therapies for healing of the penis. The most studied model has been penile rehabilitation after RP. Compelling rat models demonstrate a beneficial effect of PDE-V inhibition after cavernous nerve injury. Clinical studies in men have been suggestive, but not yet conclusive, regarding the benefit of local therapies in restoring the return of spontaneous erections. Although the practice of frequent administration of PDE-V inhibitors has become a standard for urologists, a reproducible, randomized, placebo-controlled trial is necessary for more definitive conclusions. However, there are substantial logistical barriers to the completion of such a trial. If demonstration of improved erectile function can be demonstrated, prevention of ED and healing of the penis will be topics of interest. I believe that penile rehabilitation is

more fact than fiction. Progress in medicine is made in small steps, not giant leaps.

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