PDE-5 Inhibitor Therapy for Erectile Dysfunction Secondary to Nerve-Sparing Radical Retropubic Prostatectomy

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The majority of patients receiving therapy for erectile dysfunction (ED) following post–radical retropubic prostatectomy (RRP) are treated with phosphodiesterase (PDE)-5 inhibitors, which seem to have variable efficacy in this population. So far, the only head-to-head trials with PDE-5 inhibitors have been in general ED patients and not in post-RRP patients. Both vardenafil and tadalafil failed to meet statistical noninferiority to sildenafil in head-to-head trials. To date, only sildenafil has demonstrated efficacy in the prevention of post–nerve-sparing RRP ED. The selection of a PDE-5 inhibitor requires consideration of the patient's sexual activity pattern as well as the drug's efficacy and its ability to meet the patient's expectations. In this regard, sildenafil continues to account for almost 70% of PDE-5 inhibitor prescriptions in the United States.

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Erectile dysfunction (ED) following radical prostatectomy is immediate, with profound effects on nocturnal, morning, and psychogenic erections.[1-3] The etiology of the immediate loss of nocturnal erections, though debated by experts in the past, appears to be related to intraoperative neurapraxia. There is little evidence of arterial injury during radical prostatectomy.[4] Over time, there does

appear to be recovery of nocturnal activity that corresponds with an increase in natural erectile function.[1] The recovery of erectile function is indeed slow, requiring up to 18 to 24 months. This is consistent with a slowly resolving neurapraxia.[5]

Comparative Phosphodiesterase-5 Inhibitor Efficacy for Therapy and Novel Prevention Strategies

The majority of patients treated for post–radical retropubic prostatectomy (RRP) ED are treated with phosphodiesterase (PDE)-5 inhibitors; this review focuses on this class of oral agents. As neurapraxia resolves, the trabecular smooth muscle becomes increasingly responsive to sildenafil, as would be expected given that the mechanism of sildenafil and the other PDE-5 inhibitors is dependent on the production of nitric oxide from the nerve endings. Success with a PDE-5 inhibitor in the first 6 months following RRP, however, can be expected to be very low.[6]

With increasingly accurate predictors of localized disease, most patients will know with some degree of certainty before the surgery whether or not they will have a bilateral, unilateral, or non–nerve–sparing procedure.[7,8] Patients assume that bilateral nerve sparing is synonymous with preservation of potency, not realizing that few men are as potent postoperatively as they were preoperatively, and the term *potent* is increasingly defined in terms of response to PDE-5 inhibitors.[5]

In a nonrandomized, open-label, mixed-dose, nonconsecutive study of sildenafil in a highly selected population of 91 men taking sildenafil after RRP, Zippe and colleagues[9] reported a 72% (38/53) rate of erections satisfactory for intercourse (vaginal penetration) in patients with bilateral nerve-sparing surgery versus 50% (6/12) in men with unilateral procedures. At 3 years, 31 of the original 91 (72% of the 43 patients who had returned the surveys) were still responding to sildenafil. Of these 31 respondents, 10 (32%) had increased their dose from 50 to 100 mg. The drop-out rate was 27%. Six of 12 discontinued because of the return of natural erections, 5 because of a loss of efficacy, and 1 because of the death of his spouse.[10]

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In a double-blind, mixed-dose, placebo-controlled study, vardenafil was examined in 440 men after unilateral and bilateral nerve-sparing procedures, starting at 6 months post surgery, well before maximum nerve recovery. In this study, 70% of men had severe ED.[11] In this highly selected population, intercourse success rates (Sexual Encounter Profile Question 3 [SEP3] outcomes) were 37% for the 10 mg vardenafil group, 34% for the 20 mg vardenafil group, and 10% for placebo. Sildenafil nonresponders were excluded from the studies, and more than 50% of the men were at least partial responders to sildenafil prior to entry.

Tadalafil was studied in a double-blind, placebo-controlled, fixed-dose manner in a group of 303 men (mean age, 60 years) with preoperative normal erectile function (by surgeon's history) who had undergone a bilateral nerve-sparing RRP 12 to 48 months prestudy. These highly selected men were randomized (2:1) to tadalafil 20 mg only (n = 201) or placebo (n = 102). The mean rate of successful intercourse attempts at the end of treatment was 41% for the tadalafil 20 mg group, with a 19% placebo-response rate.[12] Eighty percent of the men were previous sildenafil users.

To date, the only head-to-head trials with PDE-5 inhibitors have been in general ED patients and not in post-RRP patients. There are no signals that, despite careful patient selection and the exclusion of sildenafil nonresponders, either vardenafil or tadalafil offers advantages over sildenafil in the treatment of ED in the nerve-sparing RRP patient.

ED Prevention by Sildenafil in the Nerve-Sparing RRP Patient

Padma-Nathan and colleagues[1] reported the results of a randomized, placebo-controlled study examining the benefits of nightly administration of sildenafil during the postoperative period for the return of normal function at 48 weeks following a bilateral nerve-sparing RRP. This study included 76 men with normal preoperative erectile function—defined as a combined score of > 8 for questions Q3 and Q4 of the International Index of Erectile Function (IIEF) and normal nocturnal penile tumescence (NPT) testing (10 continuous minutes of $\geq$ 55% base rigidity)—who were scheduled to undergo a bilateral nerve-sparing RRP performed by an experienced surgeon.

Four weeks post surgery, patients were randomized to either sildenafil (50 mg, n = 23; 100 mg, n = 28) or placebo (n = 25) and entered into a 36-week, double-blind treatment period with drug administration every

night prior to sleep. Erectile function was assessed 8 weeks after discontinuation of drug treatment (week 48 post surgery) by the question, "Over the past 4 weeks, have your erections been good enough for satisfactory sexual activity?" and by IIEF and NPT assessments. Responders were defined as those having a combined score of ≥ 8 for IIEF Q3/4 and a positive response to the above question.

Forty-eight weeks after bilateral nerve-sparing RRP, 14 of 51 patients (27%) receiving sildenafil demonstrated return of spontaneous erectile function, compared with 1 of 25 (4%) in the placebo group ($P = .0156$). Postoperative NPT assessments were supportive. No serious treatment-related adverse events (AEs) were reported; 2 patients discontinued because of treatment-related AEs. Nightly administration of sildenafil for 9 months post nerve-sparing RRP thus significantly increased the return of spontaneous erections by 700% compared with placebo, and was well tolerated. Sildenafil may improve oxygenation at the time of nocturnal erections, endothelial function, and/or neuronal regeneration. These results support the consideration of this treatment regimen as an adjunct to nerve-sparing RRP.

Would a longer-acting PDE-5 inhibitor provide additional benefit? This is very unlikely. The mechanism of drug effect in this nightly prevention strategy is thought to be through nitric oxide release during phase 4 and REM sleep. Sildenafil appears to have a duration that is sufficient to cover 8 to 12 hours of sleep. Thus there is no theoretical advantage to a longer-acting PDE-5 inhibitor in this prevention strategy. Moreover, the mechanism of action here may be related to nonvascular effects, including improvement in endothelial function and/or neuronal regeneration or neuroprotection, that to date have been demonstrated only with sildenafil. It should be noted that, unlike treatment of ED, prevention is associated with a single chance at success, and to date only sildenafil has been studied in this prevention modality.

A Urologic Focus on PDE-5 Inhibitor Efficacy and Safety Differentiations

The introduction of sildenafil citrate has dramatically altered the management of ED. There is a significant body of data, including a field experience in more than 25 million men, supporting its efficacy and safety, and it has a well-documented cardiovascular profile.[13-16] Tadalafil and vardenafil have recently been approved in the United States by the Food and Drug Administration (FDA). Although pharmacologically members of the same class of drugs, these new molecules have different chemical, pharmacokinetic, efficacy, and safety profiles.[13,14,16,17]

In head-to-head trials, neither tadalafil nor vardenafil reached statistical noninferiority to sildenafil for treating ED.

Potency, Selectivity, Cardiovascular Profile, and General Safety

Like sildenafil, vardenafil and tadalafil are PDE-5 inhibitors. Biochemical potency is described by the IC_{50}—the concentration of enzyme inhibitor needed to inhibit 50% of the activity of the enzyme. This is a test tube measure, and the IC_{50} of all 3 drugs is within the range of 1 to 10 nmol/L.[18] Clinical efficacy does not seem to be different within this potency range. In fact, in head-to-head trials, neither tadalafil nor vardenafil reached statistical noninferiority to sildenafil.[13,14,19]

Selectivity is the differential ability to inhibit PDE-5, as opposed to the other 10 members of the PDE family. In addition to their PDE-5 inhibitory activity, both sildenafil and vardenafil seem to inhibit PDE-6 at high doses. Although PDE-6 inhibition is associated with transient visual disturbances, data on sildenafil indicate that this inhibition is not associated with significant acute or chronic effects in men with normal visual function or in men with macular degeneration, treated glaucoma, or nonproliferative diabetic retinopathy.[16,20] Tadalafil does not inhibit PDE-6. However, it has been shown to inhibit PDE-11, a dual-substrate (cyclic guanosine monophosphate [cGMP] and cyclic adenosine monophosphate [cAMP]) enzyme found in the anterior pituitary, testes, prostate, cardiac myocytes, and cells of the conducting system of the heart.[16,21] The localization and the molecular functional role of PDE-11 are clear. However, the functional significance of pharmacologic PDE-11 inhibition is unknown and unclear. The mechanism of the increased incidence of myalgia seen with tadalafil remains controversial. The FDA label for tadalafil has implicated PDE-11A inhibition as the mechanism of myalgia observed with this PDE-5 inhibitor,[13,16] though another explanation may be related to prolonged PDE-5 inhibition in skeletal muscle. The effect of PDE-11 inhibition on seminal parameters and gonadal and pituitary gonadotropins in normal volunteers is modest or insignificant, but the impact on sperm function is less clear. Furthermore, the safety of tadalafil on testicular function in the hypogonadal or subfertile

male has yet to be established. More importantly, the effects of PDE-11 inhibition on cardiac contractility (inotropism) and myocardial oxygen consumption are completely unknown and have not been studied to date in humans or animals, in vitro or in vivo.

Indications and Contraindications

At present, PDE-5 inhibitors are approved only as on-demand (not chronic or daily dosing) therapy for the treatment of ED. All PDE-5 inhibitors are absolutely contraindicated in men receiving organic nitrates. The greatest period of risk for an interaction between a PDE-5 inhibitor and a nitrate may be at 1 hour postdosing of sildenafil and 48 hours postdosing of tadalafil.[22,23]

Pharmacokinetics and Pharmacodynamics

Several common pharmacokinetic parameters can be measured and quantified that describe the distribution and availability of a PDE-5 inhibitor. The bioavailability, maximum plasma concentration (C_{max}), time required for attaining C_{max} (T_{max}), and time required for elimination of one-half of the inhibitor from plasma ($t_{1/2}$) are all important pharmacokinetic properties. Bioavailability is the ultimate percentage of an orally administered drug that is found in the circulation as a percentage of injected dose. It is a reflection of absorption and the effects of first-pass hepatic metabolism. Lower bioavailability can affect inter- and intrapatient variability of efficacy and may result in drug–drug interactions. Sildenafil has 40% bioavailability versus 15% for vardenafil. Sildenafil and vardenafil have broadly similar T_{max}, but the C_{max} of vardenafil is significantly lower than that of either of the other 2 inhibitors. This might be expected based on the lower bioavailability. Onset of activity is faster for sildenafil and vardenafil than it is for tadalafil. The range of T_{max} for tadalafil is broad (30 minutes to 6–12 hours), and so many patients find it to be associated with a very slow onset of action. Sildenafil has the fastest onset of action of any PDE-5 inhibitor, and it may be effective as quickly as within 14 minutes in 35% of responders and within 20 minutes in more than half of all responders.[24] The duration of action is probably about 3 half-lives of a PDE-5 inhibitor. The half-life of sildenafil is 3 to 5 hours; therefore, sildenafil efficacy may be seen 8 to 12 hours beyond administration. The $t_{1/2}$ of tadalafil is considerably longer than that of the other 2 PDE-5 inhibitors—17.5 hours for men under 60 and 21 hours for men over 60 years of age.[25] The extended exposure to tadalafil (overall 105 hours, or 5 half-lives, in men over 60 years of age and 87.5 hours in men under 60 years of age) is associated with a greater exposure to AEs and possibly other effects, particularly cardiovascular, including nitrate interactions. Tadalafil's clinical efficacy has been studied only up to 36 hours post dosing.[26] It is expected that clinical efficacy may be seen in a significant number of patients for up to 3 half-lives post dosing—that is, 60 hours or longer. Both sildenafil and vardenafil seem to have a food effect (delayed C_{max}) when high-fat (50%) meals are consumed.[27–29] Tadalafil, although not demonstrating a food interaction, is much more slowly absorbed and therefore has a longer T_{max} than the other PDE-5 inhibitors; thus the absence of a food interaction has little clinical advantage in this case.[25]

Comparative Efficacy and Safety

Vardenafil has demonstrated efficacy in general, diabetic, and postprostatectomy ED.[14,15,30,31] Tadalafil has demonstrated efficacy in the same population.[16,32] However, in head-to-head trials performed and made public initially by the European Medicines Evaluation Agency and, more recently, by the FDA, tadalafil's SBA (summary basis for approval) indicates that neither tadalafil nor vardenafil met statistical noninferiority criteria compared with sildenafil.[13,19]

The pivotal tadalafil studies were not performed in the United States. They included men from Asia, Australia, and Canada.[32] However, the FDA did request studies in the United States, and 2 such studies (at academic and community centers) were performed with 20 mg tadalafil versus placebo. The results are presented in the tadalafil USPI.[16] These studies included 402 men ages 21 to 87 years (78% white, 14% black, and 7% Hispanic). The intercourse success rates (SEP3) were 50% for 20 mg tadalafil versus 25% for placebo in a predominantly academic-center study, and 64% for 20 mg tadalafil versus 23% for placebo in a predominantly community center–based study.[16]

In general, all PDE-5 inhibitors have similar AEs as a result of PDE-5 inhibition—headaches, flushing, and dyspepsia (PDE-5 inhibition in lower esophageal sphincter with resultant gastroesophageal reflux). However, myalgia—back pain and pain in the extremities—is seen predominantly with tadalafil.[16,19] Myalgia (back pain and/or pain in the limbs) may occur with tadalafil in about 12% of men in at-home studies.[16,19] Myalgia was indicated to be severe in $< 5\%$ of men.[16] This myalgia, although clinically indistinguishable from that seen with certain statins, is not associated with rhabdomyolysis and is not life threatening.

The α-blocker interactions distinguish the new members of the class; both vardenafil and tadalafil are contraindicated in men receiving any α-blocker (with 1 exception). Despite

only minor QT prolongation (< 10 msec), the label indicates that vardenafil should be "avoided in patients with congenital QT prolongation or in those taking class IA (eg, quinidine or procainamide) or class III (eg, amiodorone, sotalol) antiarrhythmic medications."[15]

Conclusions

PDE-5 inhibitors have variable efficacy in the postprostatectomy population. As yet, the only head-to-head trials with PDE-5 inhibitors have been in general ED and not in post-RRP patients. These head-to-head trials demonstrated the failure of either vardenafil or tadalafil to meet statistical noninferiority to sildenafil. To date, there are no signs that, despite careful patient selection and the exclusion of sildenafil nonresponders, either vardenafil or tadalafil is as effective as sildenafil in the nerve-sparing radical prostatectomy patient, and only sildenafil has demonstrated efficacy in the prevention of post–nerve-sparing RRP ED. One should remember that this strategy is a primary prevention approach, and given just "one shot at primary prevention," it should be evidence based. Only sildenafil is supported by evidence.

The comparative pharmacology and clinical profile of the 3 PDE-5 inhibitors are indeed unique, despite similarities to the native substrate of PDE-5, cGMP. Importantly, selection of a PDE-5 inhibitor will require consideration of the specifics of the sexual activity pattern of a patient and his partner. PDE-5 inhibitor utilization will most likely be determined by efficacy and the ability to meet patients' expectations. In this regard, sildenafil continues to account for almost 70% of the PDE-5 inhibitor prescriptions in the United States.[33] ■

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Main Points

- As neurapraxia resolves following nerve-sparing radical retropubic prostatectomy (RRP), the trabecular smooth muscle becomes increasingly responsive to sildenafil. One might expect this result given that the mechanism of sildenafil and the other phosphodiesterase (PDE)-5 inhibitors is dependent on the production of nitric oxide from the nerve endings. Success with a PDE-5 inhibitor in the first 6 months following RRP, however, can be expected to be very low.
- The effects of PDE-11 inhibition on cardiac contractility (inotropism) and myocardial oxygen consumption are completely unknown and have not been studied to date in humans or animals, in vitro or in vivo.
- At present, PDE-5 inhibitors are approved only as on-demand (not chronic or daily dosing) therapy for the treatment of ED. All PDE-5 inhibitors are absolutely contraindicated in men receiving organic nitrates.
- Vardenafil has demonstrated efficacy in general, diabetic, and post-prostatectomy ED. Tadalafil has demonstrated efficacy in the same population. However, in head-to-head trials performed and made public initially by the European Medicines Evaluation Agency and, more recently, by the Food and Drug Administration, tadalafil's summary basis for approval indicates that neither tadalafil nor vardenafil met statistical noninferiority criteria compared with sildenafil.

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