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## **Phosphodiesterase Type 5 Inhibitor Treatment for Erectile Dysfunction in Patients with End-Stage Renal Disease Receiving Dialysis or After Renal Transplantation**

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### **Abstract**

#### Introduction

The phosphodiesterase type 5 (PDE5) inhibitors are generally well tolerated and effective for treating erectile dysfunction (ED), including in patients with significant comorbidity. Because of this benign safety profile, investigators have used PDE5 inhibitors to treat patients with ED and severe renal disease or those who have received renal transplants.

#### Aim

To assess safety and efficacy of PDE5 inhibitors in patients receiving dialysis or renal transplants.

#### Main Outcome Measures

Erectile function as assessed by the International Index of Erectile Function (IIEF) and Global Assessment Questions; adverse events (AEs).

### **Methods**

We reviewed published studies of PDE5 inhibitors in patients receiving dialysis or renal transplants.

### **Results**

In double-blind, placebo-controlled studies in patients receiving dialysis or renal transplants, sildenafil significantly improved erectile function as assessed by the IIEF, and 75–85% of patients reported improved erectile function on Global Assessment Questions; efficacy was more variable in less well-controlled studies. In >260 patients undergoing dialysis who received sildenafil in clinical studies, there were only six reported discontinuations because of AEs (headache [N = 3], headache and nausea [N = 1], gastrointestinal [N = 1], and symptomatic blood pressure decrease [N = 1]). In approximately 400 patients with renal transplants who received sildenafil, only three patients discontinued because of AEs. Vardenafil improved IIEF scores of up to 82% of renal transplant recipients in randomized, controlled studies (N = 59, total), with no reported discontinuations because of AEs. Limited data also suggest benefit with tadalafil.

### **Conclusions**

ED is common in patients undergoing renal dialysis or postrenal transplant and substantially affects patient quality of life. Sildenafil and vardenafil appear to be efficacious and well tolerated in patients receiving renal dialysis or transplant.

## Introduction

Phosphodiesterase type 5 (PDE5) inhibitors are generally well tolerated and effective for treating erectile dysfunction (ED), which is defined as the inability to attain and/or maintain a penile erection sufficient for satisfactory sexual performance [1]. Clinical trials have demonstrated success with the PDE5 inhibitor sildenafil citrate as treatment in multiple patient populations, including those with significant comorbidity [2]. Findings from >14,000 patients enrolled in sildenafil clinical trials and nearly 40,000 patients in the postmarketing safety database suggest that sildenafil has a good safety profile [3]. Because of this safety profile, many investigators have used sildenafil to treat patients with ED and severe renal disease and those who have received renal transplants, in whom ED is a common concern. In this article, we review published studies of sildenafil and other PDE5 inhibitors in these patients.

A MEDLINE search was performed on August 1, 2011 for studies that assessed treatment of ED with PDE5 inhibitors in patients on dialysis or who had received kidney transplants. Searches included “(PDE5 inhibitor) and dialysis,” “(PDE5 inhibitor) and kidney and erectile dysfunction,” and “(PDE5 inhibitor) and renal and erectile dysfunction”; the PDE5 inhibitors were sildenafil, tadalafil, and vardenafil. Studies were included if erectile function was assessed in patients on dialysis or who had received kidney transplants and had concomitant ED; imaging studies and meeting abstracts were excluded. If published manuscripts were not in English but provided an abstract in English that presented data, the study was included. References cited within retained studies were obtained when relevant.

## Renal Disease and ED

ED is observed frequently in patients with end-stage renal disease (ESRD), in patients undergoing peritoneal dialysis (PD) and hemodialysis (HD), and in patients who receive kidney transplants. Prevalence is estimated at 71% to >80% in dialysis patients [4-9]. ED substantially affects the quality of life for HD [9, 10] and posttransplant [11] patients. Renal transplantation has been reported to improve ED in some, but not all, patients [6-8, 12-19]; furthermore, de novo ED has been reported after transplantation. In most studies, approximately half of patients with renal transplants report ED [20-25].

Advanced age is almost uniformly associated with the development and persistence of ED in dialysis and transplant patients [6, 8, 9, 15, 24-27]. However, associations with other factors are less clear. ED was associated with “comorbidity” in one study [24]; although hypertension and lipid disorders have occasionally been associated with ED in these populations [28], more studies dispute these associations [14, 25, 26]. Poorer erectile function has been noted for patients receiving >1 antihypertensive drug [28]. ED appears to associate more clearly with diabetes mellitus in renally impaired patients [9, 14, 15, 25, 28]; however, it should be noted that patients with this comorbidity have been excluded from some analyses [8]. Similarly, immunosuppression with cyclosporin A has been associated with ED in some [14, 26], but not all [15], studies.

Before sildenafil, ED treatments included optimization of dialysis, reduction of anemia through administration of erythropoietin, altering medications suspected to contribute to ED, administering testosterone, using vacuum devices, intraurethral or intracavernosal vasoactive medications, penile prosthesis, and vascular surgery [29-31]. The availability of sildenafil since 1998, and subsequent PDE5 inhibitors, has provided an effective and convenient oral alternative for ED treatment.

#### Pharmacokinetics of PDE5 Inhibitors

The pharmacokinetic effects of sildenafil have been studied in healthy volunteers, in patients undergoing dialysis, and in patients who have received renal grafts (Table 1). Independent of total drug concentrations, 96% of sildenafil is bound to plasma proteins [45].

Table 1. Studies describing pharmacokinetic end points in patients with renal insufficiency or transplant

Study	N	Study type PDE5i and dose (study duration)	Age, year Mean ± SD (range)	ED duration PK end point(s) Mean ± SD (range)	Time posttransplant/on dialysis, months
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\*Healthy, N = 8; with renal impairment, N = 16

†Including one subject who discontinued and was not included in the analysis

‡Abstract in English; article in Spanish

§SIL treated

¶Not reported for the subset of men who received SIL

\*\*Abstract in English; article in Chinese

††Taken “every night 1 hour before sex 3–4 hours after taking immunosuppressant for 3 days”

‡‡Healthy, N = 12; with renal graft, N = 16

§§VAR, N = 39; placebo, N = 21

¶¶VAR, N = 20; placebo, N = 19

AUC = area under the curve; Cmax = maximal plasma concentration; CL/F = renal clearance; DBPC = double-blind, placebo-controlled; ED = erectile dysfunction; ESRD = end-stage renal disease; HD = hemodialysis; MT = mean time; NA = not applicable; NR = not reported; PDE5i = phosphodiesterase type 5 inhibitor; PK = pharmacokinetic; PRN = taken as needed; RCT = randomized, controlled trial; SD = standard deviation; SIL = sildenafil; t1/2 = half-life; Tmax = time to maximal plasma concentration; TAD = tadalafil; VAR = vardenafil

Christ et al., 2001 [32] 10 PK 42.5 (29–52) NR 43.3 (22–67) Single dose of 50 mg of SIL (24 hours post-SIL) No effect of SIL on tacrolimus (C<sub>max</sub>, T<sub>max</sub>, AUC, CL/F, MT, t<sub>1/2</sub>); tacrolimus increased C<sub>max</sub>, AUC, t<sub>1/2</sub> of SIL

Muirhead et al., 2002 [33] 24\* PK (22–72) NA NA Single dose of 50 mg of SIL (48 hours post-SIL) In patients with severe impairment, SIL CL/F significantly decreased and C<sub>max</sub> significantly increased vs. normal; two times exposure in severely impaired patients vs. normal

Christ et al., 2004 [34] 9 PK 42 (29–52) NR 42 (22–67) 25 mg of SIL/day (9 days) No significant difference in t<sub>1/2</sub> or trough level of tacrolimus with SIL

Grossman et al., 2004 [35] 15 PK 47.6 ± 12.1 (33–75)<sup>+</sup> NA ESRD for 8.2 ± 6.8 (0.4–21.8) 2 single doses of 50 mg of SIL, separated by 1 week SIL clearance by dialysis minimal (<1% in dialysate); SIL AUC unaffected by timing relative to hemodialysis (rate of absorption slightly higher postdialysis)

Prieto Castro et al., 2001 [36] 50 Open label 54 NR 20/35 25, 50, or 100 mg of SIL PRN Cyclosporine/FK506 plasma concentrations not significantly different with SIL

Cofan et al., 2002 [37]‡ 9 Pilot 50 ± 8 (38–64) NR NR/NR 50 or 100 mg of SIL PRN (7 days) Trough whole-blood concentrations of tacrolimus and cyclosporine not significantly altered by SIL

Barrou et al., 2003 [38] 50 Open label 54 ± 9 6.8 ± 5.9 years 66.6 ± 61.2/113.7 ± 82.4 (for 85.2% of patients) 50 mg of SIL PRN, adjustable to 25 or 100 mg (12 weeks) Trough blood levels of tacrolimus (N = 6) and cyclosporine (N = 33) not significantly different with SIL

Lasaponara et al., 2004 [20] 78§ Case series NR¶ NR¶ NR/NR§ 25, 50, or 100 mg of SIL PRN “No effect on immunosuppressive drug levels” (i.e., FK506 and mycophenolate mofetil)

Liu et al., 2004 [39]\*\* 53 Case series (26–50) NR >6/NR SIL NR (6 months) No interactions between SIL and cyclosporine

Russo et al., 2004 [21] 20 Open label 45.9 ± 11.1 NR 49 ± 40/57 ± 50 50 mg of SIL PRN (4 weeks) “No observed negative effects” of SIL on cyclosporine concentration

Zhang et al., 2005 [40] 65 Open label 41.6 (30–47) NR 8.6 (3–12)/2.2 years (8–3.2 years) 50 mg of SIL, adjustable to 100 mg<sup>++</sup> (unspecified) Cyclosporine trough level not significantly different than before SIL

Sharma et al., 2006 [41] 32 DBPC crossover 40 ± 8 17 ± 22 months 4.7 ± 3 years/3.5 ± 2 25, 50, or 100 mg of SIL PRN (8 weeks) AUC, C<sub>max</sub> of cyclosporine similar (N = 5), as was cyclosporine trough level

Forgue et al., 2007 [42] 28‡‡ PK (renally impaired group) 47.7 ± 9.6 (30–65) NA NR/NA Single dose of 5 or 10 mg of TAD (8 days) AUC in mild, moderate roughly twice that of healthy cohort, C<sub>max</sub> 20% higher, t<sub>1/2</sub> substantially prolonged; effects on major metabolite more pronounced

Forgue et al., 2007 [42] 16 PK (HD group) 48.1 ± 13.2 (28–74) NA “≥3 months”/NA Single dose of 5, 10, or 20 mg of TAD (13 days) AUC 2.1 times that in healthy cohort, C<sub>max</sub> 41% higher, t<sub>1/2</sub> similar; HD contributed negligibly to elimination of TAD and metabolite

Demir et al., 2006 [43] 60§§ RCT 48 ± 7.4NR 41/25 10 mg of VAR PRN, adjustable to 20 mg (4 weeks) Cyclosporine and tacrolimus concentrations not significantly different between the groups

Yang et al., 2008 [44]\*\* 39¶¶ DBPC NR NR NR/NR VAR NR (4 weeks) Cyclosporine concentrations unchanged in VAR-treated patients

Sildenafil is extensively absorbed in healthy volunteers. Mean absolute bioavailability is limited by rapid first-pass metabolism to approximately 40% [46]. Maximum plasma concentration (C<sub>max</sub>) occurs within 30–150 minutes after oral administration [47], and terminal half-life (t<sub>1/2</sub>) is ~3–5 hours [48]. Sildenafil is primarily metabolized by the hepatic cytochrome P450 (CYP) enzymes 3A4 and 2C9 [49]. Sildenafil metabolites are excreted predominantly in the feces (~80%), although a small amount (~13%) is excreted in the urine [46].

In men with mild or moderate renal impairment, sildenafil pharmacokinetics were not significantly different from those of healthy men [33]. However, in seven patients with severe renal insufficiency (creatinine clearance [CL<sub>cr</sub>] < 30 mL/minute), sildenafil clearance was significantly decreased compared with eight patients having normal renal function (CL<sub>cr</sub> > 80 mL/minute). This reduced clearance produced an increased drug exposure; values for the area under the concentration vs. time curve (AUC) and C<sub>max</sub> were approximately doubled and tripled, respectively, relative to healthy volunteers. A significant correlation was demonstrated between CL<sub>cr</sub> and apparent plasma clearance (CL/F) for sildenafil (P < 0.01): CL/F decreased with CL<sub>cr</sub>. CL<sub>cr</sub> was also significantly correlated with C<sub>max</sub> for sildenafil (P < 0.05), which increased with decreasing CL<sub>cr</sub>. No adverse events (AEs) were reported for men in this renal impairment study. Thus, the authors suggested that a lower starting dose of sildenafil (25 mg) should be considered for men with severely compromised renal function.

The effects of sildenafil on pharmacokinetic parameters were studied in men receiving dialysis for renal disease as well as men who received kidney transplants; cohorts ranged from 9 to 78 patients per study (Table 1). In a study of 15 men undergoing chronic outpatient maintenance HD who were administered sildenafil 2 hours before or 2 hours following HD, HD did not clear sildenafil (or its major metabolite, UK-103,320) [35]. ESRD in these men resulted most commonly from glomerulonephritis (N = 7), hypertension (N = 4), and diabetes (N = 3); all men had comorbid anemia and hypertension. More than 95% of the administered drug was bound to plasma protein. The extent of absorption was unaffected by HD; the ratio of geometric means of AUC was 98% (95% confidence interval, 84–116%). Mean plasma sildenafil concentrations were similar between phases, although the rate of sildenafil absorption appeared to be faster following HD. Eight patients experienced intradialytic hypotension (four patients in each phase); sildenafil did not appear to exacerbate this hypotension. Twelve patients reported 41 AEs, which were described as “expected” in HD patients. The most common AEs were asthenia (N = 5), fever (N = 4), and dizziness (N = 3); all other events occurred ≤2 times. Only fever was considered to be possibly related to treatment. No patients discontinued because of AEs. Two episodes of syncope were experienced by two different patients, but in neither case was decreased blood pressure documented.

Because sildenafil and immunosuppressive drugs (including tacrolimus and cyclosporine) share a common elimination pathway, potential interaction between these drugs and sildenafil have been studied in men with ED who have received kidney transplants.

Sildenafil 50 mg did not affect tacrolimus pharmacokinetics, including C<sub>max</sub>, time to C<sub>max</sub> (T<sub>max</sub>), AUC, CL/F, total mean time, and t<sub>1/2</sub> in 10 men with ED who received kidney transplants [32]. However, tacrolimus coadministration increased the C<sub>max</sub> (by 44%), AUC (by 90%), and t<sub>1/2</sub> (by 1.7 hours) of sildenafil compared with that observed in healthy volunteers. Kidney failure in these men resulted from chronic glomerulonephritis (N = 8), Alport syndrome (N = 1), and diabetic nephropathy (N = 1); prior and concomitant diseases included arterial hypertension (N = 10), renal anemia (N = 6), hyperlipoproteinemia (N = 3), diabetes mellitus (N = 2), secondary hyperparathyroidism (N = 1), and chronic bronchitis (N = 1). Five patients reported mild AEs: headache (N = 2), drowsiness (N = 1), gastric disorders (N = 1), and nasal congestion (N = 1). After sildenafil administration, decreases in blood pressure relative to the values with unchanged concomitant medication were observed (maximal mean changes of 27 mm Hg [range 5–50] for systolic and 20 mm Hg [11–35] for diastolic). The maximal difference in the mean arterial blood pressure was 20 mm Hg [13–37]. Thus, a starting dose of sildenafil 25 mg and possible adjustment of hypertensive drugs on the day of sildenafil use was recommended.

Nine of these patients (one patient with renal failure caused by chronic glomerulonephritis was excluded) participated in a second study that examined the effect of sildenafil 25 mg administered daily over 9 days [34]. Overall, trough levels and t<sub>1/2</sub> of tacrolimus were unchanged with this extended regimen. Half-lives were clearly prolonged in two patients, but these changes were not considered clinically meaningful. Mean arterial blood pressure was lower after sildenafil administration, although this decrease was not statistically significant. Six patients reported mild AEs: headache (N = 2), nasal congestion (N = 2), flushing (N = 1), and dyspepsia (N = 1). Two patients required dose reductions of antihypertensive drugs, and one patient had an asymptomatic rise in gamma-glutamyl transpeptidase.

Trough blood levels of tacrolimus and cyclosporine were not significantly affected by sildenafil (up to 100 mg) administration in a pilot study of nine patients receiving transplants [37] and an open-label study in 50 patients receiving transplants [38] (Table 1). Trough levels of cyclosporine were not significantly different than before sildenafil administration in an open-label study that included 65 patients who received renal transplants [40] or in a randomized, double-blind, placebo-controlled (DBPC) crossover trial of 32 renal transplant recipients [41]; AUC and C<sub>max</sub> of cyclosporine were also similar in the latter study (Table 1).

No interactions were noted between sildenafil and cyclosporine in three other open-label studies (Table 1) [21, 36, 39]. Sildenafil appears to have no effects on the pharmacokinetics of other immunosuppressive drugs, including FK506 and mycophenolate mofetil (Table 1) [20, 36].

Tadalafil is rapidly absorbed in healthy subjects, with a median T<sub>max</sub> of 2 hours; absorption is unaffected by food [50, 51]. Roughly 94% of plasma tadalafil is bound to albumin or  $\alpha$ 1-acid glycoprotein. Clearance is predominantly via hepatic metabolism by CYP3A4; approximately 36% of an oral radiolabeled dose was excreted in urine, almost completely as metabolites. Exposure in subjects with mild (CL<sub>cr</sub> 51–80 mL/minute) or moderate (CL<sub>cr</sub> 31–50 mL/minute) renal insufficiency was approximately twice that in healthy subjects and the mean C<sub>max</sub> was 20% higher [42]; a starting dose of 5 mg once daily is recommended for moderately impaired patients (maximum dose, 10 mg in 48 hours) [50]. In patients with ESRD, the mean AUC for the major metabolite (total methylcatechol glucuronide) was three times the mean for healthy subjects [42]; a 5-mg starting dose (per 72 hours) is recommended for severely impaired and ESRD patients [50].



Vardenafil is rapidly absorbed (median Tmax, 1 hour) with an absolute bioavailability of ~15%; high-fat meals reduce Cmax from 18% to 50% [52]. Vardenafil is metabolized primarily by CYP3A4, with contributions from the CYP3A5 and CYP2C9 isoforms. In men with mild renal impairment (CLcr 50–80 mL/minute), vardenafil pharmacokinetics were similar to healthy controls. In moderate (CLcr 30–50 mL/minute) and severe (CLcr < 30 mL/minute) renal impairment groups, the AUC of vardenafil was 20–30% higher compared with healthy controls. Vardenafil pharmacokinetics have not been evaluated in patients requiring dialysis; however, no significant differences in renal function or cyclosporine or tacrolimus concentrations occurred between vardenafil and placebo groups in two prospective trials in kidney transplant recipients [43, 44]. The starting dose of vardenafil was 10 mg [43] in one trial and not stated for the other [44].

### Renal Function

Renal function in graft recipients is not adversely affected by sildenafil administration. The glomerular filtration rate and filtration fraction of renal grafts were significantly increased in 10 patients who received a single 100-mg dose of sildenafil; mean ± standard deviation (SD) arterial pressure in the supine position decreased by 13.7 ± 4.2 mm Hg (P < 0.01) [53] (Table 2). Slight, transient headaches (N = 3) and facial and cervical flushing (N = 9) were reported.

Table 2. Studies examining renal function in patients posttransplant receiving sildenafil

Study	N	Study type	Age, years	ED duration	Time posttransplant/on dialysis	PDE5i and dose (study duration)	Renal function
			Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)		

\*Not reported for the subset of patients treated with SIL

†Abstract in English; article in Chinese

‡Taken “every night 1 hour before sex 3–4 hours after taking immunosuppressant for 3 days”

§VAR, N = 39; placebo, N = 21

¶VAR, N = 20; placebo, N = 19

BUN = blood urea nitrogen; DBPC = double-blind, placebo-controlled; ED = erectile dysfunction; GFR = glomerular filtration rate; NA = not applicable; NR = not reported; PDE5i = phosphodiesterase type 5 inhibitor; PK = pharmacokinetic; PRN = taken as needed; RCT = randomized, controlled trial; SD = standard deviation; SIL = sildenafil; VAR = vardenafil

Rostaing et al., 2000 [53]	10	Renal function (43–72)	NR	18–126 months/NR	Single dose of 100 mg of SIL	Significantly increased GFR and filtration fraction with SIL; significantly decreased mean arterial pressure with SIL
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Chatterjee et al., 2004 [54]	12	Pilot	42 (29–56)	NR	≥12 months/NR	50 or 100 mg of SIL once or twice weekly (12 months)	No deterioration of renal function with SIL
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Malavaud et al., 2001 [55]	11	PK	59.6 ± 2.3	(16.1 ± 2.0 months of SIL treatment)	66.8 ± 11.2 months/63.9 ± 15.5 months	Single dose of 100 mg of SIL	Significantly increased GFR, filtration fraction, and lithium clearance with SIL; significantly decreased renal vascular resistance and mean arterial pressure with SIL
Barrou et al., 2003 [38]	50	Open label	54 ± 9	6.8 ± 5.9 years*	66.6 ± 61.2 months/113.7 ± 82.4 months (for 85.2% of patients)	25, 50, or 100 mg of SIL PRN (12 weeks)	Serum creatinine increased (N = 43) with SIL
Liu et al., 2004 [39]†	53	Case series	(26–50)	NR	>6 months/NA	SIL NR (6 months)	“No significant adverse effect of SIL on the graft function”
Russo et al., 2004 [21]	20	Open label	45.9 ± 11.1	NR	49 ± 40 months/57 ± 50 months	50 mg of SIL PRN (4 weeks)	“No observed negative effects” of SIL on BUN, creatinine clearance, or blood chemistry
Zhang et al., 2005 [40]	65	Open label	41.6 (30–47)	NR	8.6 months (3–12 months)/2.2 years (8 months–3.2 years)	50 or 100 mg of SIL‡	BUN and creatinine not different than before SIL treatment
Sharma et al., 2006 [41]	32	DBPC crossover	40 ± 8	17 ± 22 months	4.7 ± 3 years/3.5 ± 2 months	25, 50, or 100 mg of SIL PRN (8 weeks)	Serum creatinine, BUN, and hemoglobin similar with and without SIL
Demir et al., 2006 [43]†	60§	RCT	48 ± 7.4	NR	41/25	10 mg of VAR PRN, adjustable to 20 mg (4 weeks)	Renal function (serum creatinine, creatinine clearance) not significantly different between placebo and VAR groups
Yang et al., 2008 [44]	39¶	DBPC	NR	NR	NR/NR	VAR NR (4 weeks)	Renal function (serum creatinine, creatinine clearance) unchanged in VAR-treated patients

In a later study from the same group [55], lithium clearance was also significantly increased in sildenafil-treated patients (N = 11), all of whom had severe ED (International Index of Erectile Function [56]-erectile function domain [57] [IIEF-EF] score < 10) and concomitant hypertension; two had type II diabetes mellitus. Significant decreases were observed in renal vascular resistance and mean arterial pressure. No additional AEs were reported and the authors concluded that no specific precautions for sildenafil use were required for transplant recipients [53, 55].

In a mixed population of kidney transplant recipients (N = 8) and patients on dialysis (N = 4), no deterioration of renal function occurred with combination therapy of sildenafil 50 or 100 mg once or twice weekly and 250 mg testosterone cypionate administered intramuscularly once per month [54]. No AEs were reported in an open-label study of 53 patients receiving kidney transplant who received sildenafil for 6 months, although the timing and methods of assessment were unclear [39].

Mean ± SD serum creatinine increased slightly from baseline (by 4.9 ± 19.5 µmol/L; P = 0.0474) in 50 transplant recipients given sildenafil 25, 50, or 100 mg as needed for 12 weeks in an open-label study [38] (Table 2). However, no effect on creatinine level was found in a second open-label study of 65 younger transplant recipients who received sildenafil 50 or 100 mg for an unspecified time period [40] or in a randomized, controlled, crossover trial of sildenafil 25, 50, or 100 mg for 8 weeks [41]. No negative effects of sildenafil on CL<sub>cr</sub> occurred in 20 patients who received sildenafil 50 mg for 4 weeks [21].

Blood urea nitrogen was also not significantly changed in two open-label studies [21, 40] and one randomized, controlled, crossover trial [41] of transplant recipients who initially received sildenafil 50 mg (Table 2). Blood chemistry [21] and hemoglobin [41] were also unchanged with sildenafil treatment.

#### PDE5 Inhibitor Efficacy and Safety in Patients Undergoing Renal Dialysis

Three controlled trials provide the strongest evidence supporting the efficacy of sildenafil for ED in patients undergoing dialysis (Table 3). A DBPC study examined 41 patients with ED (most of moderate severity) and chronic renal failure who were receiving HD for  $\geq 6$  months; patients received placebo (N = 21) or sildenafil 50 mg (N = 20) for 1 month [62]. Sildenafil treatment significantly improved IIEF scores for all domains, except Sexual Desire. The IIEF-EF score improved in 85% of sildenafil-treated patients compared with 10% of placebo-treated patients; IIEF-EF scores indicating normal erectile function ( $\geq 26$ ) were reported in 35% of patients taking sildenafil. Although moderate flushing and dyspepsia (N = 1), mild headache and dyspepsia (N = 1), and mild headache (N = 1) were reported in sildenafil-treated patients, similar AEs were observed in placebo-treated patients (headache, N = 2, and mild facial flushing, N = 1). Patients were asked not to take sildenafil on days when they were undergoing dialysis because of concerns about hypotension; additionally, patients with diabetes were excluded.

Table 3. Studies examining safety and efficacy of phosphodiesterase type 5 inhibitors in patients receiving dialysis

Study (study duration)	N	Study type	Age, years	ED duration	Time on dialysis	PDE5i	and	dose
			Efficacy end point(s)	Safety end point(s)				
			Mean $\pm$ SD (range)	Mean $\pm$ SD (range)	Mean $\pm$ SD (range)			

\*HD, N = 34; PD, N = 1

†All patients were receiving PD; only six patients completed the study (lost to follow up, N = 4; spouse unwilling/uninterested, N = 4)

‡HD, N = 13; PD, N = 2

§Patients with ED (HD, N = 25; PD, N = 12); SIL was given to 30 patients (HD, N = 20; PD, N = 10)

¶SIL, N = 20; placebo, N = 21

\*\*HD, N = 30; PD, N = 11

††All patients were receiving PD; 13 patients received SIL

‡‡HD, N = 40; PD, N = 2

§§SIL, N = 14; placebo, N = 13

AE = adverse event; DBPC = double-blind, placebo-controlled; d/c = discontinuation; ED = erectile dysfunction; GA = global assessment; HD = hemodialysis; IIEF = International Index of Erectile Function; NR = not reported; PBO = placebo; PD = peritoneal dialysis; PDE5i = phosphodiesterase type 5 inhibitor; PRN = taken as needed; SD = standard deviation; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; SIL = sildenafil; VAR = vardenafil

Jacques and Abrairs, 1999 [58] 4 Case series (37–68)NR 2 months–6 years 50 mg of SIL PRN (varying intervals) Descriptive reports, IIEF improvements in all patients No AEs described

Chen et al., 2001 [30] 35\* Open label 60.7 (47–72) 44.2 months (18–120) 61.6 months (24–44) 25, 50, or 100 mg of SIL PRN (≥6 months)

80% had IIEF total score improve ≥10 points

GA: 77% satisfied with erectile function

71% of partners satisfied with treatment

7 patients d/c for lack of efficacy

AEs in 14 patients: headache (N = 10), visual disturbance (N = 7), hypertension (N = 3), nasal congestion (N = 4), flushing (N = 4)

3 d/c for AEs (dose-related headaches)

Juergensen et al., 2001 [59] 15† Open label 56.1 ± 8.8 NR 33.4 ± 34.1 months 25, 50, or 100 mg of SIL PRN (12 weeks) 2 of 6 patients (33%) completing the study were responders by IIEF scores (increases of 100%) 1 d/c for AE (gastrointestinal)

Punzo et al., 2001 [60] 18 Open label (29–51)NR NR 25 or 50 mg of SIL (3 months) Improvement in sexual activity and desire (unclear measurement) No AEs described

Rosas et al., 2001 [61] 15‡ Open label 50.1 ± 14.1 (29–75) 67% had ED >1 year 3.9 ± 3.5 years (median 21 months) 25, 50, or 100 mg of SIL (≥4 weeks)

Significant improvement in IIEF domains of Erectile Function, Orgasmic Function, and Intercourse Satisfaction

GA: 66.7% improved erections

Headache (N = 2), flushing (N = 1), diarrhea (N = 1)

1 d/c for AE (headache and nausea)

Turk et al., 2001 [4] 37§ Open label 50 ± 10 HD: 25 ± 27 months; PD: 16 ± 16 months  
35 ± 29 months 50 or 100 mg of SIL twice a week (4-week titration period)

60% of IIEF scores (both HD and PD) >26

Significantly improved IIEF scores (both HD and PD); similar magnitude between groups

Dyspepsia (N = 2) and headache (N = 1)

Seibel et al., 2002 [62] 41¶ DBPC 46 ± 9 placebo; 49 ± 10 SIL NR 36 ± 26 months placebo;  
42 ± 31 months of SIL 50 mg of SIL PRN (1 month) Significantly improved IIEF question scores vs.  
baseline (except desire frequency and desire level) and vs. PBO (except intercourse frequency, desire  
frequency, and desire level); all domain scores (vs. baseline and PBO) except Sexual Desire domain; 85%  
improved erectile function (vs. 9.5% PBO) Moderate flushing and dyspepsia (N = 1), mild headache  
and dyspepsia (N = 1), and mild headache (N = 1) in SIL-treated patients

Yenicerio Glu et al., 2002 [63] 41\*\* Open label 48.2 ± 9.6 (28–70) HD: 2.2 ± 2.0 years; PD:  
1.4 ± 0.6 years HD: 4.4 ± 2.5 years; PD: 1.6 ± 1.4 years 25 mg of SIL PRN (4 weeks)

Significantly improved total IIEF scores (HD and PD)

Significant improvement in Fugl–Meyer life satisfaction scale

GA: erections improved in 80% HD and 82% PD patients

AEs in 17 patients (5 reported ≥1 AE), commonly flushing (N = 12), and headache (N = 7)

Blurred vision (N = 1)

1 d/c for symptomatic decrease in blood pressure

Hyodo et al., 2004 [64] 14 Open label 54.9 ± 9.3 NR 3.1 ± 3.8 25 or 50 mg of SIL  
57.1% of patients improved IIEF-5 scores to be ≥20 (diabetic patients, 38%; nondiabetic, 83%) 1  
d/c for ventricular arrhythmia and flushing

Sahin et al., 2004 [65] 51 Open label 50.6 ± 10.9 (30–73) 4.7 years (6–10) 58.2 ± 42.3  
 months (1–179 months) Single dose of 50 mg of SIL Overall response rate of 74.5% on IIEF-EF  
 Nausea (N = 2), palpitations (N = 2), flushing (N = 1), and angina (N = 1)

Mahon et al., 2005 [66] 16<sup>††</sup> Randomized, placebo-controlled crossover 53 (26–74) (6 months–7  
 years) (6 months–5 years) 50 mg of SIL PRN initially for 2 weeks, then 100 mg (4 weeks)

Significant improvement vs. baseline and placebo in IIEF domains of Erectile Function, Intercourse Satisfaction, and Overall Satisfaction; vs. baseline in Orgasmic Function

GA: 75% improved erections (vs. 28% placebo)

Headache (N = 1)

No d/c

Zamd et al., 2005 [67] 10 Open label NR NR NR 50 mg of SIL (unclear) Subjective  
 improvement in all patients No AEs

Dachille et al., 2006 [68] 42<sup>††</sup> Open label Median: 57 (34–71) 84 months (7–228 months)  
 ≥5 months 50 mg of SIL PRN for 1 week; 25, 50, or 100 mg of SIL (2 weeks) 91% response rate  
 to sildenafil (100% of PD patients) No d/c for AEs

Tas et al., 2006 [69] 16 Open label 41.2 ± 2.6 NR NR Epo + 25, 50, or 100 mg of  
 SIL PRN (12 weeks) Significantly improved IIEF scores (17.4% P < 0.05), including 8 patients with IIEF  
 ≥26; significant improvement in erection frequency, firmness, maintenance ability, and confidence;  
 intercourse enjoyment, desire level, and relationship satisfaction Headache (N = 3) and rhinitis (N = 1)  
 with SIL treatment

Turk et al., 2010 [70] 32 Randomized, head-to-head crossover 47.2 ± 10.8 ≥6 months  
 45.9 ± 48.2 months 50 mg of SIL or 10 mg of VAR once a week (4 weeks drug 1, 2 weeks  
 washout, 4 weeks drug 2) Significantly improved IIEF-5 and SF-36 scores vs. baseline in SIL and VAR  
 groups

SIL: facial flushing (N = 1), headache (N = 1), and dyspepsia (N = 2)

VAR: flushing (N = 1) and headache (N = 2)

No d/c for AEs

Ghafari et al., 2010 [71] 27§§ DBPC 46.5 ± 9.9 NR (6 months–11 years) 50–150 mg of SIL PRN Significantly improved IIEF-5 score vs. placebo; improvements occurred for all items No AEs reported

An 8-week, prospective, DBPC, crossover study randomized 16 patients undergoing PD who had severe ED (mean IIEF-EF score, 6.7) to receive 4 weeks of treatment with either placebo or sildenafil (50 mg initially, increased to 100 mg after 2 weeks, if tolerated) followed by 4 weeks of the alternate treatment [66]. In 13 patients who completed the study, comorbidities included hypertension (N = 10) and diabetes (N = 6); renal failure was caused most commonly by diabetic nephropathy (N = 4), focal segmental glomerulosclerosis (N = 3), polycystic kidney disease (N = 2), and hypertension (N = 2). Sildenafil treatment significantly improved IIEF-EF domain scores compared with baseline and placebo. IIEF Intercourse Satisfaction and Overall Satisfaction domains were also significantly improved vs. baseline and placebo for patients receiving sildenafil; the Orgasmic Function domain was significantly improved compared with baseline only. No significant improvement occurred in the Sexual Desire domain. Seventy-five percent of sildenafil-treated patients reported that their erections were improved. One patient reported a headache. Because all patients were able to correctly guess their sildenafil treatment period, the study may not have been truly blinded.

Twenty-seven patients with moderate ED who had undergone HD for ≥6 months received placebo (N = 13) or sildenafil 50–150 mg (N = 14) postdialysis in a randomized, 1-week, DBPC study [71]. IIEF-5 scores were significantly improved with sildenafil compared with placebo ( $P < 0.0001$ ) [72]; all IIEF-5 items were improved with sildenafil, whereas placebo treatment improved only penetration ability. No AEs were reported for either group.

Other open-label studies indicate that sildenafil is effective and well tolerated in patients undergoing renal dialysis (Table 3). A case series published in 1999 qualitatively described positive results in four patients undergoing dialysis (with diagnoses of diabetic glomerulosclerosis, hypertension, polycystic kidney disease, and diabetic nephropathy), receiving sildenafil 50 mg for varying intervals [58].

In 35 men with ED (mean IIEF-EF score, 10.5) on dialysis (resulting most commonly from diabetes [N = 17], glomerulopathy [N = 7], hypertension [N = 4], and nephrolithiasis [N = 3]; 25 patients had multifactorial etiology) who received sildenafil 25, 50, or 100 mg for 6 months, all IIEF domain scores and the IIEF total score were significantly improved after sildenafil treatment; 80% improved their total IIEF score ≥10 points [30]. Response to sildenafil was not correlated with any examined factor (age, etiology of ED, duration and severity of ED, prior treatments, testosterone and prolactin blood levels, and the duration and etiology of renal failure). Eight patients were not satisfied with treatment; seven were nonresponders based on total IIEF score (<10-point increase). Ten female partners were unsatisfied with treatment; seven were partners of IIEF nonresponders (0.86 correlation between patient and partner satisfaction scores). AEs were reported for 14 patients, most commonly headache (N = 10), visual disturbance (N = 7), nasal congestion (N = 4), flushing (N = 4), and hypertension (N = 3). Three patients discontinued because of AEs (dose-related headaches) despite improved IIEF scores.

Of 68 male patients on chronic PD at a single institution, 32 (47%) reported ED. Only 17 patients were interested in trying sildenafil therapy, and two of them were excluded because they were taking nitrates. Of 15 patients who agreed to try sildenafil, only six completed 12 weeks of therapy [59]. Two of the six completers had satisfactory responses (100% increases in IIEF scores) to sildenafil (50 mg, N = 1; 100 mg, N = 1); one had coexisting hypertension and diabetes mellitus, and one had hypertension and peripheral vascular disease. Four patients did not respond (IIEF scores unchanged) to doses up to 100 mg; all

nonresponders were hypertensive, two had diabetes mellitus, and one had peripheral vascular disease. Of the nine patients who did not complete the study, one patient discontinued because of gastrointestinal AEs, four received sildenafil but did not report their response or request additional medication, and another four reported that their partner was not interested in sex.

Taking sildenafil 25 or 50 mg for 3 months led to improvement in sexual activity and sexual desire in 20 patients receiving dialysis (two of whom also received renal transplant). "Very good" repercussions were noted on general and psychosocial conditions in this study [60].

Fifteen men with ED (mean IIEF-EF score, 11.4) and ESRD mostly caused by hypertension (53%) and diabetes (19%) on dialysis (N = 13 HD; N = 2 PD) received sildenafil as prescribed by their primary physician or nephrologist. Comorbid conditions in this patient group included hypertension (93%), diabetes (33%), coronary artery disease (31%), and hypercholesterolemia (23%) [61]. After  $\geq 4$  weeks, 67% believed that treatment improved their erections. Significant improvements compared with baseline were noted in the IIEF-EF score as well as IIEF Orgasmic Function and Intercourse Satisfaction domains. Of the three patients who discontinued sildenafil, only one did so because of AEs (headache and nausea). Headache (N = 2), flushing (N = 1), and diarrhea (N = 1) were also reported.

In a subset of 30 patients on dialysis (HD, N = 20; PD, N = 10) who had ED (mean IIEF-EF scores: HD, 8; PD, 10) and received sildenafil, 60% (HD, N = 12; PD, N = 6) reported IIEF-EF scores  $>26$ ; mean scores improved in both groups to a similar extent [4]. Sildenafil nonresponders (IIEF-EF  $\leq 26$ ) had significantly lower penile blood flow than responders; furthermore, IIEF-EF score changes correlated with penile blood flow. Of five diabetic patients with ED, four received sildenafil treatment; three responded to therapy. Dyspepsia (N = 2) and headache (N = 1) were described as short lasting; no patients reported hypotension.

In 41 patients with renal failure caused predominantly by hypertensive nephrosclerosis, polycystic kidney disease, or chronic glomerulonephritis and ED (mean IIEF score, 11.9), 4 weeks of sildenafil treatment improved mean erectile function scores: 20 of 30 HD and 9 of 11 PD patients had IIEF-EF scores  $>25$  [63]. Erections were improved in  $\geq 80\%$  of patients. Interestingly, when responders (IIEF-EF  $> 25$ ) and nonresponders to sildenafil were compared, all IIEF domain scores except Sexual Desire were significantly lower in nonresponders at baseline. Seventeen patients reported  $\geq 1$  AE, most commonly flushing (N = 12; 10 HD and 2 PD) and headache (N = 7; 6 HD and 1 PD). One HD patient reported blurred vision. One PD patient had a symptomatic decrease in blood pressure that led to discontinuation.

Among 14 patients undergoing dialysis (N = 13 HD; N = 1 PD) who had baseline IIEF-5 scores  $<20$ , sildenafil 25 or 50 mg improved IIEF-5 scores to  $\geq 20$  (defined as "success" in this study) in 57% [64]. There was a discrepancy in sildenafil efficacy rates between diabetic (N = 8) and nondiabetic (N = 6) patients (38% vs. 83%, respectively). One patient discontinued because of sildenafil-related AEs (flushing and arrhythmia), and two patients who were considered to be nonresponders did not attempt sexual intercourse.

A single dose of sildenafil 50 mg was administered to 51 HD patients on the day after dialysis; 34 had severe and 17 had mild-to-moderate ED. Patients had comorbid hypertension (N = 16), diabetes mellitus (N = 4), chronic obstructive respiratory disease (N = 1), and Parkinson's disease (N = 1) [65]. Although the success rate was higher in younger vs. older patients and in patients with mild-to-moderate vs. severe ED, 75% reported significant increases in IIEF-EF scores. Seven (14%) patients reported AEs, including nausea (N = 2), palpitations (N = 2), flushing (N = 1), and angina (N = 1).



In a subset of patients (N = 10) undergoing HD who reported sexual dysfunction (half of whom had sexual dysfunction before HD and half of whom developed it after HD), sildenafil 50 mg led to subjective improvement in all patients [67].

Sildenafil (initially 50 mg; adjustable to 25 or 100 mg) was compared with apomorphine in 42 patients with ED undergoing dialysis (N = 40 HD; N = 2 PD) [68]. ED was moderate in the PD patients. ED was mild, moderate, and severe in 20%, 22%, and 57% of HD patients, respectively. A single factor caused kidney failure in 19 (45%) patients (chronic glomerulopathy [N = 5], hypertension [N = 5], diabetes [N = 4], hyperthyroidism [N = 3], and hepatopathy [N = 2]), whereas 23 (55%) had multiple factors. Over 90% of patients receiving sildenafil had a therapeutic response vs. 14% of patients receiving apomorphine. No significant AEs were reported, and no AEs led to discontinuation.

Patients undergoing HD with IIEF-EF scores <26 who were unresponsive to erythropoietin or testosterone treatment (N = 16) received sildenafil 25 mg (with subsequent increases to 50 or 100 mg) in combination with erythropoietin administered subcutaneously at 50 U/kg three times per week after each dialysis session [69]. Significant improvement in IIEF-EF scores (17%; P < 0.05) was observed, with 50% of patients achieving IIEF-EF scores ≥26. Areas with significant improvement included erection frequency, firmness, maintenance ability, and confidence; intercourse enjoyment; desire level; and relationship satisfaction. Patients reported headache (N = 3) and rhinitis (N = 1) with sildenafil treatment; these were transient and did not require treatment.

Sildenafil 50 mg and vardenafil 10 mg were compared in 32 HD patients with ED (mean IIEF-5 score 13.0 before sildenafil and 12.7 before vardenafil). Kidney disease was most often of unknown etiology (53%), but common known causes included diabetes mellitus and polycystic kidney disease (13% each) [70]. Patients received alternate drug for 4 weeks, followed by a 2-week washout period and then 4 weeks of treatment with the other drug. Both drugs significantly improved IIEF-5 scores and quality of life assessed with the Medical Outcomes Study 36-Item Short-Form Health Survey instrument compared with baseline; there were no differences in improvements between groups. Similar AEs were reported in each group: facial flushing (N = 1), headache (N = 1), and dyspepsia (N = 2) were reported for sildenafil; flushing (N = 1) and headache (N = 2) were reported for vardenafil.

Few independent or new safety signals have arisen in nonsponsored studies of renal dialysis patients receiving PDE5 inhibitors. Only one case report noted significant symptomatic hypotension secondary to a 50-mg dose of sildenafil in a 49-year-old patient with an underlying diagnosis of polycystic kidney disease [73]. However, whether sildenafil was the causative agent of the hypotension was unclear [74].

Thus, in DBPC studies, PDE5 inhibitors significantly improved erectile function as assessed by the IIEF in patients undergoing dialysis. Efficacy was more variable in less well-controlled studies. Furthermore, no new or unexpected AEs occurred in the >400 dialysis patients examined in these studies.

#### Efficacy and Safety of PDE5 Inhibitors in Renal Transplant Recipients

Studies in renal transplant recipients have also shown PDE5 inhibitors to be efficacious and well tolerated (Table 4). Sildenafil was examined in a DBPC study in 32 patients with ED and stable allograft function; in this crossover study, patients were randomized to receive placebo or sildenafil 50 mg (adjustment to 25 or 100 mg was possible) for 8 weeks, followed by a 2-week washout period, and then 8 weeks on the alternate treatment [41]. In these patients, 14 had chronic glomerulonephritis, 8 had chronic interstitial nephritis, 7 had diabetic neuropathy, and 3 had other basic diseases; mean IIEF-EF score was 13. IIEF-EF, Intercourse

Satisfaction, Orgasmic Function, and Overall Satisfaction domain scores were significantly increased after sildenafil treatment, but not scores in the Sexual Desire domain. The score for only one question (relationship satisfaction) was significantly improved after placebo treatment. Significantly more patients receiving sildenafil than placebo reported improved erections (81% vs. 19%). Reported AEs with sildenafil treatment included headache (N = 5), rhinorrhea and flushing (N = 2), generalized body ache (N = 1), and visual disturbance (N = 1); the patient with visual disturbance discontinued sildenafil.

Table 4. Studies examining safety and efficacy of phosphodiesterase type 5 inhibitors in patients receiving kidney transplant

Study	N	Type of study	Age, years	ED duration	Time posttransplant/on dialysis	PDE5i and dose (study duration)	Efficacy end point(s)	Safety end point(s)
			Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)			

\*Abstract in English; Spanish article

†Hemodialysis, N = 4; posttransplant, N = 8

‡SIL treated

§Not reported for the subset of men who received SIL

¶Abstract in English; Chinese article

\*\*Taken “every night 1 hour before sex 3–4 hours after taking immunosuppressant for 3 days”

††VAR, N = 39; placebo, N = 21

‡‡VAR, N = 20; placebo, N = 19

AE = adverse event; DBPC = double-blind, placebo-controlled; d/c = discontinuation; ED = erectile dysfunction; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; ESRD = end-stage renal disease; GA = global assessment; IIEF = International Index of Erectile Function; LiSat = life satisfaction scale; NIH = National Institute of Health; NR = not reported; PDE5i = phosphodiesterase type 5 inhibitor; PRN = taken as needed; Q = question; RCT = randomized, controlled trial; SD = standard deviation; SIL = sildenafil; VAR = vardenafil

Prieto Castro et al., 2001 [36]	50	Open label	54	NR	20 months/35 months	25 or 50 mg of SIL PRN	60% satisfactory response	
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AEs in 12% of patients: facial flushing (N = 2), headache (N = 2), and visual disturbance (N = 1)

No d/c for AEs

Punzo et al., 2001 [60]	18	Open label	(29–51)NR	NR/NR	25 or 50 mg of SIL (3 months)		Improvement in sexual activity and desire (unclear measurement)	No AEs described
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Cofan et al., 2002 [37]\* 9 Open label 50 ± 8 (38–64) NR NR/NR 2 single doses of 50 or 100 mg of SIL 66% positive response (N = 6: 5 complete; 1 incomplete) Self-limited tachycardia (N = 1) and mild visual disturbances (N = 1)

Espinoza et al., 2002 [22] 28 Open label 37.6 ± 9.6 26.8 ± 15.5 months 41.8 ± 31.9 months/(ESRD: 20.1 ± 12.6 months) 50 mg of SIL (4 weeks)

92.8% response rate

Significantly improved IIEF-5

Headache (N = 28), nasal congestion (N = 16), and seasickness (N = 1)

Barrou et al., 2003 [38] 50 Open label 54 ± 9 6.8 ± 5.9 years 66.6 ± 61.2/113.7 ± 82.4 (for 85.2% of patients) 25, 50, or 100 mg of SIL PRN (12 weeks)

Significant improvement on IIEF Q3 and Q4 vs. baseline; also all domains

GA: 66% improved erections

60% EDITS Index >50 (satisfied with treatment)

LiSat sexual life and partnership relation significantly improved

AEs in 58.8% of patients, commonly headache (18%), abnormal vision (6%), abdominal pain (6%), vomiting (4%), hot flushes (4%), palpitation (4%), and creatinemia (4%)

2 d/c for AEs

3 patients withdrawn for serious AEs; 2 (angina pectoris, aggravated depression) possibly related to SIL

Chatterjee et al., 2004 [54] 12<sup>†</sup> Open label 42 (29–56) NR ≥12 months (N = 8)/NR 50 or 100 mg of SIL once or twice weekly plus testosterone (12 months)

IIEF scores increased from a median of 20 (range 16–25) to 66 (62–68)

NIH ratings improved from poor at baseline to satisfactory for all patients

No AEs

Lasaponara et al., 2004 [20] 78‡ Open label NR§ NR§ NR/NR§ 25, 50, or 100 mg of SIL Satisfactory response 31% AEs in 3 patients: facial flushing (N = 2), headache and visual disturbance (N = 1)

Liu et al., 2004 [39]¶ 53 Unclear(26–50)NR >6 months/NR SIL NR (6 months) Significantly improved all IIEF indices NR

Russo et al., 2004 [21] 20 Open label 45.9 ± 11.1 NR 49 ± 40 months/57 ± 50 months 50 mg of SIL PRN (4 weeks) Significantly improved all IIEF domains except Orgasmic Function Flushing and headache (number unclear)

Zhang et al., 2005 [40] 65 Open label 41.6 (30–47) NR 8.6 months (3–12 months)/2.2 years (8 months–3.2 years) 50 or 100 mg of SIL\*\* (unspecified) Effective in 81.54% of patients (IIEF Q3 and Q4) Headache (N = 3) and dyspepsia (N = 2)

Sharma et al., 2006 [41] 32 DBPC crossover 40 ± 8 17 ± 22 months 4.7 ± 3 years/3.5 ± 2 months 25, 50, or 100 mg of SIL PRN (8 weeks)

Significantly improved IIEF scores (including Q3 and Q4), except Sexual Desire domain

GA: 81.3% improved erections (18.7% for placebo)

Headache (N = 5), rhinorrhea and flushing (N = 2), body ache (N = 1), and visual disturbance (N = 1) with SIL

1 d/c for visual disturbance

Demir et al., 2006 [43] 60†† RCT 48 ± 7.4NR 41 months/25 months 10 mg of VAR PRN, adjustable to 20 mg (4 weeks) Significantly improved IIEF scores (all domains) Headache (N = 3), palpitations (N = 1), flushing (N = 2), and dyspepsia (N = 1)

Yang et al., 2008 [44]¶ 39‡‡ DBPC NR NR NR/NR VAR NR (4 weeks) Significantly improved IIEF scores Headache (N = 2), palpitation and flushing (N = 1), and dyspepsia (N = 1)

Vardenafil treatment was assessed in a prospective trial that randomized renal transplant recipients with ED (diagnosed using penile color Doppler ultrasonography and intracavernosal injection) and serum creatinine values < 2 mg/dL to receive vardenafil (starting dose of 10 mg, with adjustment to 20 mg possible; N = 39) or placebo (N = 21) for 4 weeks [43]. IIEF-EF scores improved from 12.8 ± 3.5 to 26.5 ± 2.4

in vardenafil-treated patients ( $P < 0.001$ ). Seven (18%) patients reported AEs (headache,  $N = 3$ ; palpitations,  $N = 1$ ; flushing,  $N = 2$ ; and dyspepsia,  $N = 1$ ).

Similar results for the efficacy, safety, and effects on graft function and immunosuppressant concentrations were observed in a 4-week randomized, DBPC study in 39 kidney transplant recipients (placebo,  $N = 19$ ; vardenafil [dose unspecified],  $N = 20$ ) with ED and serum creatinine values  $< 2$  mg/dL [44]. IIEF-EF scores improved from  $12.6 \pm 3.4$  to  $26.5 \pm 2.8$  ( $P < 0.01$ ). Four patients reported AEs (headache,  $N = 2$ ; palpitation and flushing,  $N = 1$ ; and dyspepsia,  $N = 1$ ).

Nine open-label studies have evaluated sildenafil in renal transplant recipients. Chatterjee and colleagues evaluated sildenafil (50 or 100 mg once or twice weekly) combined with testosterone replacement therapy (250 mg intramuscular monthly injections of testosterone cypionate) for 12 months in 12 patients with ED related to hypogonadism associated with a variety of reproductive hormone abnormalities and cavernosal insufficiency; eight were posttransplant and four were on HD [54]. Renal failure in this population was most commonly attributed to insulin-dependent diabetes mellitus ( $N = 3$ ), chronic glomerulonephritis ( $N = 2$ ), obstructive uropathy ( $N = 2$ ), and prune belly syndrome ( $N = 2$ ). All patients, who had severe ED at baseline and  $\geq 1$  comorbidity, responded to the testosterone and sildenafil therapy. Thus, these data suggest that the combination of testosterone and sildenafil therapy may benefit patients with both cavernosal arterial insufficiency and reproductive hormone abnormalities.

In 50 patients with ED and a functioning renal transplant, treatment with sildenafil 25, 50, or 100 mg produced a 60% satisfactory response as assessed subjectively by the patient and his partner and by the IIEF; response was unsatisfactory in 28%, and 12% did not take the medication [36]. Interestingly, nonresponders had received dialysis for a longer time than responders (means of 43 and 23 months), which may signal more advanced penile vascular disease in nonresponders. No significant differences in age or associated conditions (hypertension, diabetes, and dyslipidemia) were noted between responders and nonresponders. Six patients reported AEs, including facial flushing ( $N = 2$ ), headache ( $N = 2$ ), and visual disturbance ( $N = 1$ ); no AEs led to discontinuation.

In nine men with severe ED and stable renal function receiving sildenafil 50 or 100 mg, 67% had a positive clinical response, with 55% having a complete response [37]. Self-limited tachycardia and mild visual disturbances were each reported in one patient.

Records of 971 male renal graft recipients were reviewed in 2004, including 126 patients reporting ED during or after 1998 (the launch year of sildenafil), only 78 of whom chose to be treated [20]. Of those 78 patients, 31% had a satisfactory response to sildenafil 50 or 100 mg; 10% of patients did not take the drug after a positive test. The subset of patients who responded to sildenafil therapy had been on dialysis for a shorter time compared with the overall population (22 vs. 40 months), although there was no difference in blood pressure or prevalence of diabetes or dyslipidemia. AEs occurred in three patients: facial flushing ( $N = 2$ ) and headache and visual disturbance ( $N = 1$ ).

In a separate study, there was a 93% response rate for sildenafil 50 mg in 28 patients with ED who had received a kidney transplant, 12 of whom also had hypertension and 4 of whom were diabetic [22]. Although the final IIEF-5 score showed a significant mean increase vs. the baseline score of 13.3 points (out of 25 points, indicating mild-to-moderate ED), the mean score (20 points) was still indicative of mild ED

(mild ED scores range from 17 to 21;  $\geq 22$  indicates no ED). AEs included headaches, which were reported for all participants (N = 28), nasal congestion (N = 16), and nausea (N = 1).

In 53 men with ED who had received their kidney transplant  $\geq 0.5$  years before being treated with sildenafil for 6 months, all IIEF-5 items increased significantly; no AEs were reported [39].

Sildenafil 50 or 100 mg was administered to 65 men with kidney transplant and ED (N = 10, 32, and 23 with light, moderate, and severe ED, respectively), the majority (69%) of whom had no definite diagnosis of their primary diseases (all others had nephritis or nephrotic syndrome). Coexisting hypercholesterolemia and hypertension (N = 20), hypercholesterolemia (N = 6), and hypertension (N = 5) were noted in the cohort [40]. Eighty-two percent had a  $\geq 2$ -point improvement on IIEF questions 3 (frequency of achieving erection) and 4 (frequency of maintaining erection). Despite this improvement (and increases in the scores for other IIEF questions), 30 patients still had clinical ED (assessed by IIEF-EF score) following treatment. AEs included headache (N = 3) and dyspepsia (N = 2).

An open-label study included 50 patients with ED (mean IIEF score of 11.4) who had received kidney transplants most commonly necessitated by nondiabetic (46%) and diabetic (15%) nephropathy and polycystic disease (11%); coexisting conditions in this population included hypertension (91%), diabetes mellitus (30%), coronary insufficiency (9%), and depression (4%) [38]. Sildenafil significantly improved scores on IIEF questions 3 and 4, with 54% of patients at 12 weeks “almost always or always” or “most times” able to achieve and maintain their erections. All domains of the IIEF were significantly improved, although the magnitude of the change for Sexual Desire was the smallest. Sixty-six percent of patients reported that treatment improved their erections. Satisfaction with sexual life and partnership relation scores were significantly improved and 60% reported satisfaction with treatment. Fifty-nine percent of patients reported  $\geq 1$  AE, most of which were mild to moderate and were commonly headache (18%), abnormal vision (6%), and abdominal pain (6%). Two patients withdrew for serious AEs considered possibly related to sildenafil, angina pectoris, and aggravated depression.

Russo et al. surveyed erectile function in kidney transplant recipients and treated only a subset of patients (20 of 60 who reported mild-to-moderate ED) willing to take sildenafil [21]. IIEF domain scores were significantly improved in this subset, with the exception of Orgasmic Function. “Minimal” AEs were reported and included headache and flushing.

We recently updated our center's previous experience [20]; newer patients received any of the approved PDE5 inhibitors (sildenafil, vardenafil, and tadalafil). Of 2,372 graft recipients, 1,523 were men and 203 reported ED during or after 1998; of the 147 who chose to be treated, 41% had a satisfactory response to PDE5 inhibitors (9% refused drugs after a positive test of PDE5 inhibitor). Responders had received dialysis for a shorter time than the overall population (22 vs. 42 months, respectively). Ten patients reported AEs (facial flushing, N = 7; headache and visual disturbance, N = 3).

To summarize, in parallel with the results in patients on dialysis, PDE5 inhibitors significantly improved erectile function as assessed by the IIEF in DBPC studies in renal transplant recipients. Open-label studies also favored PDE5 inhibitor treatment, and there were few discontinuations reported in the >450 patients examined.

Clinical Recommendations

Sildenafil appeared to be efficacious and well tolerated in patients receiving kidney dialysis in three randomized, placebo-controlled studies in a total of 47 patients receiving sildenafil (N = 47 receiving placebo) and 11 open-label studies in >250 additional patients receiving sildenafil. Vardenafil appeared to be efficacious and well tolerated in patients receiving kidney transplant, showing similar efficacy and safety as sildenafil in an open-label, head-to-head study crossover study of 32 patients. Likewise, both PDE5 inhibitors showed efficacy and safety in patients who received kidney transplants. Sildenafil was assessed in one DBPC crossover study in 32 patients (as well as nine open-label studies in >300 additional patients), while vardenafil was assessed in two randomized, controlled studies with a total of 59 patients receiving drug (N = 40 receiving placebo). The relative paucity of information for vardenafil likely reflects the amount of time that it has been approved and available (2003) relative to sildenafil (1998).

The recommended starting dose of sildenafil in patients with severe renal dysfunction (i.e., CLcr < 30 mL/minute) is 25 mg [33]. No dosage adjustments are required for vardenafil in patients with mild, moderate, or severe renal function; however, the prescribing information warns that vardenafil has not been studied adequately in patients requiring dialysis and should not be used when treating these patients [52]. The recommended starting dose of tadalafil is 5 mg for moderately impaired patients (CLcr 31–50 mL/minute), and a maximum dose of 10 mg should not be exceeded in 48 hours. For severely impaired patients (CLcr < 30 mL/minute) and patients with ESRD receiving dialysis, a 5-mg dose is recommended and should not exceed 5 mg in 72 hours; once-daily treatment is not recommended in patients with CLcr < 30 mL/minute [50].

In the most rigorous studies, PDE5 inhibitors were administered as needed; open-label studies assessed medication given as needed or one to two times per week. Although daily intake of medication has not been assessed in patients receiving dialysis or transplant, generally, AEs in these patients appear similar to those reported in men with ED without kidney dysfunction (i.e., headache and flushing). However, because hypertension and hypotension have been reported, as well as ventricular arrhythmia, palpitations, and angina, warning patients to be alert for symptoms indicating changes in cardiac function is appropriate.

#### Future Studies

Current information is limited because most of the highest-quality evidence reviewed was from short-duration studies (i.e., <12 weeks). Long-term safety and the sustainability of improvements require further testing. Additionally, optimal timing of sildenafil in relation to dialysis should be established [73, 74]. Studies differed in the dosing instructions provided to patients, and adherence to recommended timing was rarely assessed. The contribution of altered hormonal status (for example, hyperprolactinemia) also deserves further investigation [4, 30, 65]. Given the efficacy and tolerability of PDE5 inhibitor for ED in men, biological rationale exists for the treatment of sexual dysfunction that occurs in women with renal dysfunction [75].

The safety and efficacy of PDE5 inhibitors in the treatment of patients who have received kidney transplants suggest that patients receiving other types of transplant who have ED might benefit from PDE5 inhibitor treatment. Indeed, better erection quality and sustainability were noted in male cardiac transplant patients from a single institution who tried sildenafil [76]. Liver transplant patients have reported benefit from sildenafil treatment [77, 78], and success has been reported with sildenafil in combination with testosterone in men receiving bone marrow transplant for hematologic malignancies [79].

## Conclusion

PDE5 inhibitors appear to be efficacious and well tolerated in patients receiving kidney dialysis or transplant. In DBPC studies, PDE5 inhibitors significantly improved erectile function. In >260 dialysis patients who received PDE5 inhibitors in clinical studies, there were only six reported discontinuations because of AEs; only three of approximately 400 patients with renal transplants who received PDE5 inhibitors discontinued because of AEs. As treatments for renal dysfunction become more successful and survival improves, improving the quality of life, including sexual concerns such as ED, becomes a priority. The safety of PDE5 inhibitors in patients with serious comorbidity suggests that ED accompanying other types of comorbidity might be safely treated with PDE5 inhibitors, though further study is necessary.

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