# VA Drug Class Review: Phosphodiesterase Type 5 Inhibitors

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## Introduction[1-9]

It is the purpose of this drug class review to compare the three commercially available phosphodiesterase type 5 (PDE5) inhibitors in the treatment of male erectile dysfunction (ED). The comparison will include measures of efficacy, safety, pharmacokinetics and pharmacodynamics parameters, patient satisfaction and quality of life, pharmacoeconomics, drug interactions, and convenience of use. Other medications used to treat ED will not be a part of this review.

Table 1. Phosphodiesterase Type 5 Inhibitors available in the U.S.

| Generic name | Brand (Manufacturer) | Strength & Formulations/package size | FDA approval date, approval category, & earliest patent expiration |
|---|---|---|---|
| Sildenafil | Viagra (Pfizer) | 25, 50, 100 mg unscored tablets | March 27, 1998<br>1P, March, 27, 2012 |
| Vardenafil | Levitra (Bayer Corporation) | 2.5, 5, 10, 20 mg unscored tablets in bottles of 30. | August 19, 2003<br>1S, August 19, 2008 |
| Tadalafil | CIALIS (Lilly ICOS, LLC) | 5, 10, 20 mg unscored tablets in bottles of 30. | November 21, 2003<br>1S, November 21, 2008 |

Erectile dysfunction is defined as the consistent or recurrent inability to attain or maintain an erection sufficient for satisfactory intercourse or other sexual expression. The Massachusetts Male Aging Study, a population-based study of 1709 men, using a self-administered, structured interview found the prevalence of ED to be 52% for men between the ages of 40 to 70 years and 67% for men 70 years and older. A follow-up study calculated the annual incidence to be 26 new cases per 1000 man-years. Twenty-seven percent of men 70-79 years in Olmstead County, MN had complete ED. An 11% prevalence of ED in men aged 40 to 59 years was calculated in the 1992 National Health and Social Life Survey.

Causes of ED are often categorized as organic (vasculargenic and neurogenic causes) or psychological. Several risk factors have been identified for ED, the most significant being aging although ED is not an inevitable consequence of aging. Other risk factors include diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, conditions associated with endothelial dysfunction, trauma (either localized or to the spinal chord), medications, and depression. Cigarette smoking and chronic alcohol abuse have been associated with ED. Surgeries such as radical prostatectomy and lumbarectomy can result in ED.

## Methods

Computerized databases, including MEDLINE were searched for literature on the pharmacokinetics, pharmacodynamics, safety and efficacy of the PDE5 inhibitors. Evidence based resources such as Cochrane were searched using the same criteria. Clinical trials and meta-analysis were included in this review. Only articles published in English were considered.

## Pharmacology[1-3, 9]

The release of nitric oxide by nerves and endothelial cells in the penis in response to sexual stimulation results in the formation of cyclic guanosine monophosphate (cGMP). The increase in cGMP results in the relaxation of smooth muscles in the corpus cavernosum, leading to an inflow of blood, which can produce an erection. Phosphodiesterase type 5 is the predominant PDE isozyme in penile tissue and is responsible for the metabolism of cGMP. All the PDE5 inhibitors selectively inhibit PDE5, thus preventing the breakdown of cGMP and enhancing or restoring the natural erectile response.

Other types of PDE, 1 – 11, are found through out the body and provide a number of different functions (see Table 2). The 3 PDE5 inhibitors differ in their selectivity as shown in Table 3. The

inhibition of PDE6 by sildenafil is believed to be the mechanism of visual disturbances reported in 3% to 12% of men. Sildenafil should be used with caution in men with retinitis pigmentosa.

Table 2. Tissue Location and Function of the PDE5 Isozymes

| PDE Isozyme | Tissue Location | Function |
|---|---|---|
| PDE1 | Heart, vascular smooth muscle, brain | Unknown |
| PDE2 | Potentiates platelet inhibition | Unknown |
| PDE3 | Heart, blood vessels | Cardiac conductivity, smooth muscle relaxation |
| PDE4 | Pulmonary | Airway smooth muscle relaxation |
| PDE5 | Penis | Inhibits platelets, smooth muscle relaxation |
| Rod PDE6<br>Cone PDE6 | Retina | Phototransduction |
| PDE7A | Unknown | Unknown |
| PDE8A | Unknown | Unknown |
| PDE9A | Unknown | Unknown |
| PDE10A | Unknown | Unknown |
| PDE11A | Heart, pituitary, testes | Possible effects on sperm maturation and motility |

$IC_{50}$ values and selectivity ratios of the PDE inhibitors by PDE isozyme (Source: Keating, et al. Drugs 2003)

Table 3. $IC_{50}$ Values and Selectivity Ratios for the PDE5 Inhibitors by PDE Isozyme

| PDE Isozyme | $IC_{50}$ value, nmol/L | | | Selectivity ratio vs. PDE5 | | |
|---|---|---|---|---|---|---|
| | Sildenafil | Vardenafil | Tadalafil | Sildenafil | Vardenafil | Tadalafil |
| PDE1 | 281 | 70 | >30,000 | 80 | 500 | >4450 |
| PDE2 | >30,000 | 6200 | >100,000 | >8570 | 44,290 | >14,800 |
| PDE3 | 16,200 | >1000 | >100,000 | 4630 | >7140 | >14,800 |
| PDE4 | 7680 | 6100 | >100,000 | 2190 | 43,570 | >14,800 |
| PDE5 | 3.5 | 0.14 | 6.74 | 1 | 1 | 1 |
| Rod PDE6<br>Cone PDE6 | 37<br>34 | 3.5<br>0.6 | 1260<br>1300 | 11<br>10 | 25<br>4 | 187<br>193 |
| PDE7A | 21,300 | >30,000 | >100,000 | 6090 | >214,000 | >14,800 |
| PDE8A | 29,800 | >30,000 | >100,000 | 8510 | >214,000 | >14,800 |
| PDE9A | 2610 | 581 | >100,000 | 750 | 4150 | >14,800 |
| PDE10A | 9800 | 3000 | >100,000 | 2800 | 21,200 | >14,800 |
| PDE11A | 2730 | 162 | 37 | 780 | 1160 | 5 |

$IC_{50}$ = concentration required to inhibit 50% of PDE activity. Values for PDE1-6 determined using native human enzyme. Values for PDE7A-11A determined using recombinant human enzyme.

Pharmacokinetics & Pharmacodynamics

The pharmacokinetic and pharmacodynamic parameters of the PDE5 inhibitors are shown in Tables 4 and 5. While their absolute bioavailability is less or equal to 40% (tadalafil's is unknown) the clinical implication is that both vardenafil and tadalafil can be taken without regard to meals. All three agents are metabolized to some extent by the CYP3A4 isozyme, with a fraction of sildenafil also metabolized by CYP2C9. Both sildenafil and vardenafil have active metabolites. All three agents are primarily excreted via the fecal route with varying percentages eliminated renally. Sildenafil and vardenafil have similar half-lives, and onset and duration of action. Tadalafil has a slower onset of action and longer duration of action, which is attributed to its longer half-life.

Table 4. Pharmacokinetics of PDE5 Inhibitors

| Agent | Absolute Bioavailability | Protein Binding | Metabolism | Active Metabolite | Half-life | Excretion |
|---|---|---|---|---|---|---|
| Sildenafil | 40% | 96% | CYP3A4 and 2C9 | Yes | 4 hrs | 80% fecal<br>13% renal |
| Vardenafil | 15% | 95% | CYP3A4 | Yes | 4 hrs | 91%-95 % fecal; ~2-6% renal |
| Tadalafil | ND | ND | CYP3A4 | No | 17.5 hrs | ~61% fecal<br>~36% renal |

ND - Not determined

Table 5. Pharmacodynamics of PDE5 Inhibitors in Erectile Dysfunction

| Agent | Effect of Food | Onset of Action (median) | Duration of Action |
|---|---|---|---|
| Sildenafil | High fat decreases rate of absorption, delaying | 27 minutes | 4 hours |

| | | | |
|---|---|---|---|
| | Tmax to 60 minutes and decreasing Cmax 29% | | |
| Vardenafil | High fat meal decreases Cmax 18%-50% | 26 minutes | 4 hours |
| Tadalafil | No effect | 45 minutes | 36 hours |

## Dosing

Table 6a. Recommended Doses for the PDE5 Inhibitors by Patient Population

| Patient Type | Sildenafil | Vardenafil | Tadalafil |
|---|---|---|---|
| No restrictions | 50 mg 1 hour before sexual activity. Range: 25 – 100 mg | 10 mg ~1 hour before sexual activity. Range: 5 – 20 mg | 10 mg prior to sexual activity. Range 5 – 20 mg |
| Age > 65 years | Initial: 25 mg | Initial: 5 mg | No dose adjustment |
| Hepatic Impairment | Initial: 25 mg | Initial: 5 mg | Mild – moderate impairment: Maximum: 5 mg<br>Severe impairment: Not recommended |
| Renal Impairment | CrCl<30 mL/min. Initial: 25 mg | No dose adjustment | Maximum: 10 mg |
| CYP3A4 inhibitor | Initial: 25 mg | Drug and dose specific:<br>^CYP 3A4 inhibitors<br>Ritonavir 2.5 mg/72h<br>Indinavir 2.5 mg/24h<br>Ketoconazole 400 mg/day 2.5 mg/24h<br>Itraconazole 400 mg/day 2.5 mg/24h<br>Ketoconazole 200 mg/day 5.0 mg/24h<br>Itraconazole 200 mg/day 5.0 mg/24h<br>Erythromycin 5.0 mg/24h | Maximum: 10 mg |

^These recommendations are from vardenafil's labeling and dose adjustments may be appropriate for other CYP3A4 inhibitors.

## Drug Interactions[1-3,10]

Since all three PDE5 inhibitors are metabolized by CYP3A4, there is potential that their clearance may be inhibited or induced by other drugs affecting this isozyme.

- When used by patients taking CYP3A4 inhibitors such as ritonavir, ketoconazole, and itraconazole it is recommended that tadalafil 10 mg be taken no more than every 72 hours.
- The dose of vardenafil should not exceed 2.5 mg or 5 mg in a 24 - 72 hour period depending on the inhibiting agent and its dose.
- Sildenafil's recommended starting dose is 25 mg for men taking potent CYP3A4 inhibitors such as erythromycin, ketoconazole, intraconazole, ritonavir, and amprenavir.

All three agents are contraindicated in men taking nitrates. Studies assessing tadalafil and vardenafil taken with 0.4 mg sublingual nitroglycerin in middle aged men found significant decreases in blood pressure and increases in heart rate for the 24 hour period following the last dose of PDE5 inhibitor. The use of nitrates is to be avoided for at least 24 and preferable 48 hours following a dose of sildenafil or vardenafil. Nitrates are to be avoided for a minimum of 48 hours after a dose of tadalafil.

The labeling for their interactions with alpha-blockers varies and is shown in Table 6.

Table 6. Concomitant Administration of PDE5 Inhibitors with Alpha-blockers[a]

| PDE5 Inhibitor | Labeling | Drug Interaction | Recommendations |
|---|---|---|---|
| Sildenafil | Precaution | Symptomatic hypotension with sildenafil 50 mg or 100 mg plus an alpha-blocker (doxazosin 4 mg); sildenafil 25 mg with doxazosin 4 mg reduced SBP and DBP 7 mm Hg | Sildenafil 50 mg or 100 mg should not be taken within 4 hours of an alpha-blocker; 25 mg may be taken at any time. |
| Vardenafil | Precaution | Significant hypotension (standing SBP <85 mm Hg) with vardenafil 10 mg or 20 mg taken simultaneously or 6hrs after terazosin 10 mg; also occurred with simultaneous administration of tamsulosin 0.4 mg and 6 hrs post dose[b] | Patients should be on a stable dose of alpha-blocker or vardenafil prior to the start of the other agent. Start with 2.5 or 5 mg of vardenafil dose and titrate dose based on response and tolerability. |
| Tadalafil | Precaution | Significant augmentation of BP lowering effect with tadalafil 20 mg plus doxazosin 8 mg; no clinically significant BP changes with tadalafil 10 mg and 20 mg plus tamsulosin 0.4 mg | Patients should be on a stable dose of alpha-blocker or tadalafil prior to the start of the other agent. Start with the lowest dose and titrate dose based on response and |

| | | | |
|---|---|---|---|
| | | | tolerability. |

[a]Unknown if recommendations apply to patients on an alpha-blocker in combination with other antihypertensive medications and a PDE5 inhibitor

[b]Vardenafil 10 mg plus terazosin 10 mg: 6 of 8 subjects had a SBP <85 mm Hg; vardenafil 20 mg plus terazosin 10 mg: 2 of 9 subjects had a SBP <85 mm Hg; vardenafil 10 mg plus terazosin 10 mg (post 6 hrs): 7 of 28 subjects had a SBP < 85 mm Hg; vardenafil 10 mg plus tamsulosin 0.4 mg: 2 of 16 subjects had a SBP <85 mm Hg; vardenafil 20 mg plus tamsulosin 0.4 mg (post 6 hrs): 1 of 24 subjects had a SBP <85 mm Hg.

## Efficacy and Safety

Assessment and Outcome Measures

The International Index of Erectile Dysfunction (IIEF) has been the main measure used in clinical trials to assess the efficacy of the PDE5 inhibitors. The IIEF is a validated, self-administered 15-question, questionnaire that assesses erectile function, orgasmic function, sexual desire, satisfaction with intercourse, and overall sexual satisfaction. Questions are answered on a scale of 0 (no attempt), 1 (almost never or never) to 5 (almost always). The scores of questions 1 through 5 and question 15 are frequently summed (range 1 – 30) and reported as the erectile function domain score. Men who score 0 to 10 are rated as having severe ED, those scoring 11 to 25 as mild to moderate ED, and men scoring 26 to 30 are not considered to have ED. Treatment efficacy is also assessed by evaluating Questions 3 and 4 separately, which ask the man about frequency he was able to penetrate his partner and the frequency he was able to maintain an erection after penetration in the preceding 4-weeks, respectively.

Patients in some clinical trials were asked to keep Sexual Encounter Profile (SEP) diaries to record their sexual experiences. The changes from baseline to endpoint in the mean proportions of "yes" responses to questions 2 (SEP-Q2) and 3 (SEP-Q3), respectively are often used as co-primary efficacy outcome measures. SEP-Q2 asks, "Were you able to insert your penis into your partner's vagina? (yes or no)," while SEP-Q3 asks, "Did your erection last long enough to have successful intercourse? (yes or no)." A frequently used secondary outcome is a global assessment question (GAQ) "Has the treatment you have been taking improved your erections? (yes or no)." In clinical trials, the GAQ is reported as the percent of subjects with a "yes" response at the study's endpoint. Other secondary outcome measures are the mean IIEF Intercourse Satisfaction score and the overall mean IIEF Satisfaction score.

Some clinical trials have also questioned the subject's partner regarding efficacy and satisfaction. Unfortunately, low response rates limit the interpretation of these findings.

Populations Studied

The PDE5 inhibitors pivotal trials enrolled men whose erectile dysfunction's origin was due to organic, psychogenic or both causes. Studies enrolling men with a specific cause of ED or co-morbidity have been conducted to determine their efficacy and safety in these patients (Table 7)

Table 7. PDE5 Inhibitors Erectile Dysfunction Studies: Subpopulations

| Agent | Coronary Artery Disease | Diabetes Mellitus | Post radiation therapy | Post radical retropubic prostatectomy | Spinal Cord Injury | Psychogenic Or Depression | Drug-induced sexual dysfunction |
|---|---|---|---|---|---|---|---|
| Sildenafil | X | X | X | X | X | X | X |
| Vardenafil | X | X | | X | X | X | |
| Tadalafil | | X | | X | | | |

**Sildenafil**: Meta-analysis and Systematic Reviews[11-12]

The one published meta-analysis – systematic review identified for the PDE5 inhibitors pertained only to sildenafil (Fink et al. 2002). The review's protocol originally appeared in the Cochrane Database of Systematic Reviews (Fink et al, 1999). Twenty-seven trials met inclusion criteria and involved 6659 men. None of the trials were comparisons of sildenafil to other active treatments for ED. The authors considered the percentage of successful sexual intercourse attempts to be the primary outcome measure. This percentage was also calculated excluding failed attempts reported due to reasons other than an insufficiently or long-lasting erection. Other outcomes included the percentage of participants achieving successful intercourse at least once during the treatment; the percentage of participants reporting improvement in erectile function, with improvement possibly but not necessarily indicating the ability to reliably achieve successful intercourse; and responses to questions 3 and 4 of the IIEF.

Compared to placebo, sildenafil produced a "large and statistically significant improvement in erectile function." The mean percentage of successful sexual intercourse attempts (primary outcome) was 57% with sildenafil and 21% with placebo (weighted mean difference (WMD), 33.7%; 95% CI, 29.2-38.2). The percent of men who reported at least one successful sexual intercourse attempt while on sildenafil was 83% compared to 45% of men while taking placebo (weighted relative benefits increase (RBI), 1.8; 95% CI, 1.7-1.9). An improvement in erections was reported by 78% of men while taking sildenafil compared to 25% of men taking placebo (RBI, 3.1; 95% CI, 2.7-3.5).

After excluding failed sexual intercourse attempts for reasons other than an insufficiently hard or long-lasting erection, 66% of attempts following sildenafil and 25% of attempts following placebo were successful, respectively (WMD, 39.4; 95% CI, 35.6-43.2).

For men taking sildenafil, weighted mean end-of-treatment score for IIEF question 3 (the erection was sufficient to penetrate one's partner) was 3.8 compared to 2.3 while taking placebo (WMD, 1.4; 95% CI, 1.3-1.5). The authors interpreted this finding that, on average, men taking sildenafil were able to sufficiently penetrate their partner much more that half of the time compared to much less than half of the time after taking placebo. A similar interpretation was offered for IIEF question 4 (ability to maintain an erection during intercourse) where the mean closeout scores were 3.6 after taking sildenafil compared to 2.1 following placebo (WMD, 1.5; 95% CI, 1.4-1.6).

Efficacy outcomes were stratified by the dose of sildenafil for the parallel-group, fixed-dose studies. The mean percentages of successful sexual intercourse were 43% and 17%, respectively, for 25 mg sildenafil vs. placebo (WMD, 26; 95% CI, 18-35); 50% and 14% for 50 mg sildenafil vs. placebo (WMD, 36; 95% CI, 30-42); and 51% vs. 14% for sildenafil 100 mg vs. placebo (WMD, 36; 95% CI 31-42). The percentage of men with at least one successful sexual intercourse attempt during treatment was 82% for sildenafil 25 mg and 53% for placebo (RBI, 1.5; 95% CI 1.2-1.9); 81% for sildenafil 50 mg and 43% for placebo (RBI, 1.8; 95% CI, 1.5-2.3); and 82% for sildenafil 100 mg and 43% for placebo, (RBI, 1.9; 95% CI, 2.7-3.8). The percentage of men who reported improvement in erections was 66% for sildenafil 25 mg vs. 29% for placebo (RBI, 2.2; 95% CI, 1.9-2.6); 76% for sildenafil 50 mg vs. 27% for placebo (RBI, 2.8; 95% CI, 2.3-3.4); and 82% for sildenafil 100 mg vs. 25% for placebo (RBI, 3.2; 95% CI, 2.7-3.8). Table 8 displays the efficacy of sildenafil vs. placebo from parallel group, flexible dose prn trials stratified by demographic characteristics, severity and origin of ED, and co-morbid conditions.

Table 8. Erectile Improvement and Intercourse Success: Sildenafil vs. placebo

| Group Parameter | Mean % of Successful Attempts per participant | | ≥1 Successful Attempt During Treatment | | Self-reported Improvement in Erections | |
|---|---|---|---|---|---|---|
| | S vs. P | WMD (95% CI) | S vs. P | RBI (95% CI) | S vs. P | RBI (95% CI) |
| ≥65 years | 46% vs. 14% | 31 (24-38) | 74% vs. 36% | 2.0 (1.6-2.4) | 69% vs. 18% | 3.4 (2.7-4.2) |
| Asian men | 61% vs. 24% | 37 (31-42) | 87 % vs. 49% | 1.7 (1.6-1.9) | 86% vs. 34% | 2.5 (2.2-2.8) |
| Black men | 53% vs. 19% | 34 (16-51) | 78% vs. 31% | 2.3 (1.3-3.9) | 67% vs. 28% | 1.9 (1.3-2.8) |
| Severe ED | 47% vs. 11% | 34 (26-42) | 74% vs. 26% | 2.8 (2.1-3.7) | 67% vs. 15% | 4.2 (3.5-5.1) |
| HTN | 59% vs. 16% | 33 (27-40) | 75% vs. 39% | 1.9 (1.6-2.2) | 68% vs. 21% | 3.1 (2.6-3.7) |
| Diabetes | 44% vs. 16% | 27 (20-34) | 70% vs. 34% | 2.0 (1.6-2.3) | 63% vs. 19% | 3.0 (2.5-3.7) |
| Psychogenic ED | 66% vs. 29% | 38 (32-44) | 91% vs. 61% | 1.4 (1.2-1.6) | 87% vs. 38% | 2.1 (1.7-2.5) |
| Ischemic Ht. Dis. | 42% vs. 14% | 24 (2-46) | 69% vs. 32% | 1.9 (1.3-2.7) | 63% vs. 20% | 2.6 (1.8-3.8) |
| Depression | 58% vs. 24% | 25 (4-47) | 86% vs. 43% | 1.8 (1.1-2.9) | 79% vs. 20% | 3.4 (2.4-4.7) |
| Periph. Vasc. Dis. | 57% vs. 13% | 39 (18-59) | 49% vs. 88% | 1.8 (0.9-3.6) | 70% vs. 14% | 3.0 (1.7-5.5) |
| Radical Prostat. | 25% vs. 3% | 24 (5-43) | 47% vs. 14% | 2.9 (1.1-7.3) | 48% vs. 10% | 3.8 (1.6-9.5) |
| *Spinal Cord Inj. | 53% vs. 8% | 45 (39-51) | 81% vs. 26% | 3.2 (2.4-4.2) | 83% vs. 12% | 7.2 (4.7-10.9) |

*Data from a crossover, flexible dose trial.
WMD – Weighted mean difference
RBI – Weighted relative benefits increase

Men were less likely to drop out of clinical trials when randomized to sildenafil and equally likely to drop out due to an adverse event or laboratory abnormality compared to men randomized to placebo (Table 9). Men taking sildenafil reported adverse events more often, however, these events were generally mild to moderate in severity. The authors concluded that sildenafil was more effective in the treatment of ED and was well tolerated compared to placebo

Table 9. ADE: Meta-analysis

| Event | Sildenafil (%) | Placebo (%) | RRI (95% CI) |
|---|---|---|---|
| Dropout, any reason | 7 | 14 | 0.6 (0.5-0.9) |
| Dropout, ADR or lab. Abnormality | 1.3 | 1.2 | 1.3 (0.7-2.3) |
| ≥1 ADR reported | 48 | 36 | 1.4 (1.3-1.6) |
| Headache | 11 | 4 | 2.6 (1.8-3.7) |
| Flushing | 12 | 2 | 5.8 (3.4-10.0) |
| Dyspepsia | 5 | 1 | 3.8 (2.2 – 6.6) |
| Visual Disturbance | 3 | 0.8 | 3.1 (1.8-5.4) |
| Angina or Chest pain<br>-only men with IHD | 0.8<br>2.4 | 0.5<br>0.4 | p=.08<br>p=.06 |
| MI | 0.1 | 0.2 | NA |
| *Death | 0.1 | 0.1 | NA |

*All deaths occurred more than 7 days after the last treatment dose.
ADR – Adverse drug reaction
IHD – Ischemic heart disease
MI – Myocardial infarction

Sildenafil and the Psychiatric Patient[13,14]

Sildenafil's efficacy has been studied as treatment for antidepressant-associated sexual dysfunction (AASD). In a prospective, parallel-group, randomized, double-blind, placebo-controlled trial, investigators studied 90 men who met DSM-IV criteria for AASD whose depression was in remission and dose of antidepressant had been stable for at least 6-weeks. Fluoxetine, paroxetine, citalopram and sertraline accounted for 88% of antidepressant treatment. Subjects were randomized to sildenafil or placebo at a flexible dose beginning at 50 mg which could be increased to 100 mg for 6-weeks. Outcomes were assessed using the Clinical Global Impression Scale for Sexual Function (CGI-SF), the IIEF, the Arizona Sexual Experience Scale (ASEX), and the Massachusetts General Hospital-Sexual Functioning Questionnaire (MGH-SFQ). Subjects' baseline sexual complaints were not mutually exclusive and included erectile dysfunction (86.7%), arousal problems (>87.8%), libido problems (64.4%), ejaculatory delay (69.9%), anorgasmia (21.1%), and other ejaculation and/or orgasm problems (5.5%). Data were included for 89 of the 90 subjects in the final analysis using the last observation carried forward.

Ninety-three percent of subjects took at least one dose of study medication and 85% completed the 6–week protocol. Of the men who took sildenafil, 54.5% were much or very much improved according to the CGI-SF compared to 4.4% of men in the placebo group ($p<.001$). Sildenafil showed superior efficacy to placebo on the total IIEF score, questions 3 and 4, as well as the domains of erectile function, orgasmic function, intercourse and overall satisfaction. Only the sexual desire domain was not statistically different between the sildenafil and placebo groups. Compared to placebo, sildenafil's efficacy was superior based on the total ASEX (self-rated) and MGH-SFQ (clinician rated) scores and in all of their domains (sexual desire, arousal, erectile function, orgasm ability, and overall satisfaction). The number of sexual attempts per 2-week interval did not differ between the groups: sildenafil, 5.3 versus placebo, 4.5. Adverse effects were more common in men taking sildenafil compared to placebo: headache (40.5% vs. 9.8%), dyspepsia (7% vs. 0), flushing (16.7% vs. 2.4%), visual disturbances (11.9% vs. 4.9%), nasal congestion (11.9% vs. 2.4%), palpitations (4.8% vs. 0%), restlessness/anxiety (0% vs. 19.5%), and insomnia (9.5% vs. 4.9%). The investigators concluded that sildenafil improved erectile and sexual function in men with AASD and that such improvement may increase adherence to antidepressant therapy.

In a study designed to determine whether the presence of depression affects erectile dysfunction treatment response and whether effective treatment of erectile dysfunction affect co-morbid depression and quality-of-life symptoms, investigators enrolled men seeking treatment for erectile dysfunction who also met DSM-IV criteria for depressive disorder not otherwise specified (Depression, NOS). Men meeting inclusion and exclusion criteria were enrolled in this 12-week, double-blind, placebo-controlled, flexible dose trial were randomized to either sildenafil 50 mg or matching placebo. Subjects completed self-report questionnaires and were interviewed by a psychiatrist at baseline and weeks 8 and 12. Outcomes were assessed using the Hamilton depression scale (HAM-D), the Clinical Global Impression (CGI) improvement scale, the Beck Depressive Inventory (BDI), IIEF, the Life Satisfaction Checklist, and by asking two global questions: 1) Did treatment improve your erection? 2) Did treatment improve your ability to have sexual intercourse? An intent-to-treat analysis included all men who took at least one dose of study medication and who had at least one assessment for efficacy.

A total of 152 men were randomized (sildenafil=74, placebo=78) and took one dose of study medication; 136 had at least one post randomization efficacy assessment and 125 men (82.2%) completed the study (sildenafil=65, placebo=60). The final dose of sildenafil was 100 mg and 50 mg for 79.2% and 19.4% of men, respectively, (one man took 25 mg) compared to 97.3% in the placebo group taking "100 mg". A comparison of baseline to endpoint scores found the sildenafil group with significantly greater improvement in IIEF total score, questions 3 and 4, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction than men in the placebo group ($p<.001$ for all measures). Men taking sildenafil reported improved erections, 90.9%, and ability to have sexual intercourse, 89.4%, compared to the placebo group, 11.4% and 12.9%, respectively. Nearly 73% of men in the sildenafil group were considered treatment responders compared to 14.3% who received placebo.

Improvement in depressive symptoms was associated with improvement in erectile function regardless of treatment assignment. Mean HAM-D and BDI scores declined, 10.6 and 10.7, respectively in treatment-responsive men. These decreases were significantly greater than those in men who did not respond to treatment, 2.3 and 3.7, respectively ($p<.001$). Changes in IIEF questions 3 and 4, and erectile function scores were significantly correlated with changes in HAM-D scores for all men. Response criteria

for depression were met by a greater percentage of men considered treatment responders than non-responders as measured by the HAM-D, 75.9% vs. 14.1% ($p<.001$), and CGI, 82.8% vs. 7.7%. Improvement in quality of life measures for life as a whole, sexual life, partnership relationship, social contacts, leisure situation, vocational situation and financial situation were significantly higher among treatment responders than non-responders. Adverse effects were experienced by 47.3% in the sildenafil group and 12.8% in the placebo group. The authors concluded that sildenafil was efficacious for erectile dysfunction in men with mild-to-moderate depressive illness. An improvement in depressive symptoms and quality of life was associated with an improvement in erectile dysfunction.

## Vardenafil[15-18]

Table 10. Vardenafil (V) Trials

| Study | Dose | Mean IIEF domain Endpt. | Mean IIEF domain Change | IIEF-Q3 Endpt. | IIEF-Q3 Change | IIEF-Q4 Endpt. | IIEF-Q4 Change | %GAQ Endpt. |
|---|---|---|---|---|---|---|---|---|
| Porst, et al. 2001; N-608 Phase IIb, R, DB, PC, PG, Dose finding, MC ITT n = 580 LOCF | V 5 mg, n=146 | 20.9 | 5.7** | 3.7 | 1.2** | 3.5 | 1.4** | 66%**¶ |
| | V 10 mg, n=140 | 22.1 | 8.0** | 3.9 | 1.3** | 3.6 | 1.5** | 76%** |
| | V 20 mg, n=147 | 22.8 | 9.0** | 4.0 | 1.5** | 3.8 | 1.7** | 80%** |
| | P, n = 147 | 15.6 | 1.6 | 2.7 | 0.2 | 2.5 | 0.5 | 30% |
| | | | | **SEP-Q2 Endpt.** | **SEP-Q2 Change** | **SEP-Q3 Endpt.** | **SEP-Q3 Change** | |
| Hellstrom, et al., 2002; N=805 R, DB, PC, PG, FixD, MC , 26 week trial, ITT, LOCF | V 5 mg, n=205 | 17.8 | 5.3 | 65.9%* | 23.2 | 51.7%* | 37.7 | 55.9%** |
| | V 10 mg, n=206 | 21.2 | 7.8* | 75.6%* | 30.3 | 64.7%* | 50.1 | 76.5%** |
| | V 20 mg, n=197 | 21.8 | 9.0* | 81.1%* | 40.3 | 66.7%* | 52.0 | 80.7%** |
| | P, n=197 | 14.8 | 1.2 | 51.9% | 6.3 | 32.7% | 17.9 | 22.9% |
| Goldstein, et al., 2003; N=452 Diabetic men R, PC, DB, FixD, PG, MC 12-week trial;Type 1 or 2 DM; ITT, LOCF | V 10 mg, n=153 | 17.1* | 5.9 | 61%* | NR | 49%* | NR | 57%* |
| | V 20 mg, n=149 | 19.*^ | 7.8 | 64%* | NR | 54%* | NR | 72%*^ |
| | P, n=150 | 12.6 | 1.4 | 36% | NR | 23% | NR | 13% |
| Brock, et al., 2003; N=440 men post NS-RRP, R, PC, DB, FixD, PG, MC 12 week trial, ITT, LOCF | V 10 mg, n=146 | 15.3* | 6.0* | 47%* | 26 | 37%* | 30 | 59.4%* |
| | V 20 mg, n=149 | 15.3* | 5.9* | 48%* | 30 | 34%* | 27 | 65.2%* |
| | P, n=145 | 9.2 | 0.1 | 22% | 8 | 10% | 4 | 12.5% |

R=randomized
DB=double-blind
FixD=fixed dose
ITT=intention-to-treat
NS-RRP=nerve sparing, radical retropubic prostatectomy
MC=Multicenter
PG=parallel group
PC=placebo control
LOCF=last observation carried forward
*significantly different from placebo, p<0.0001
**Least square; p<0.001 vs. placebo at endpoint
¶ p<0.01 V20 mg vs. V 5mg
^p<0.03 versus V10 mg
P=Placebo

Porst et al conducted a Phase IIb, dose-finding study to determine if the dose of vardenafil would significantly improve ED as well as vardenafil's safety profile across the three doses in a large number of men with ED (Table 10). Men between the ages of 21 – 70 years with a 6 month or longer history of ED were eligible. Men with diabetes mellitus, spinal cord injury, radical prostatectomy, significant coronary heart disease, using nitrates, or with hepatitis B and/or C or hypogonadal testosterone concentrations were excluded. Prior use of sildenafil was allowed provided the subject had experienced a positive response. Outcome efficacy was assessed using the IIEF domains, and Q 3 and Q4 in particular, the Fugl-Meyer Quality of Life Questionnaire, and the GAQ. Subjects kept a record of adverse events noted over the 12-week study period. All subjects completed a 4-week run-in period prior to being randomized to vardenafil 5 mg, 10 mg, 20 mg or placebo. Subjects were instructed to take the study medication on demand (1 hour prior to sexual intercourse), but not more often than once daily.

The primary outcome variables, IIEF Q3 and Q4, and percent responding "yes" to the GAQ are shown in Table 10. All three doses of vardenafil showed significant improvement at 12 weeks over baseline and placebo (p<.001), with no difference from baseline for placebo. Mean change in IIEF erectile

function (IIEF EF) domain scores improved significantly for all three doses of vardenafil compared to the change from baseline for placebo ($p<0.001$). The change in IIEF EF domain score for vardenafil 20 mg was significantly greater than vardenafil 5 mg ($p<0.05$). All other IIEF domain scores also improved significantly in each vardenafil-dose group compared to baseline and compared to the changes for the placebo group. The percent of men replying "Yes" to the GAQ in each of the vardenafil groups was significantly greater than placebo and the percentage of the vardenafil 20 mg group was statistically significantly greater than the 5 mg group (Table 10). During weeks 8 to 12, men in all three vardenafil groups reported an intercourse success rate of ≥70% compared to 39.5% in the placebo group ($p<0.001$); the baseline rate ranged from 24% to 29% for the four groups. Analysis of the quality of life scale found a significant improvement only in the responses to the question about sex life satisfaction in all 3 vardenafil groups compared to placebo ($p<0.001$) after 12 weeks of treatment.

Adverse events predictable for the PDE5 inhibitors were mostly dose-related (Table 11). None of the adverse events considered serious were attributed to treatment and no significant cardiovascular changes were identified.

Table 11. Adverse Events: Vardenafil and Placebo

| Adverse Event | Placebo (%) n = 152 | V 5mg (%) n = 157 | V 10 mg (%) n = 141 | V 20 mg (%) n = 150 |
|---|---|---|---|---|
| Headache | 6 (4) | 10 (7) | 12 (8.5) | 23 (15) |
| Rhinitis | 5 (3) | 7 (5) | 4 (3) | 11 (7) |
| Flushing | 1 (1) | 15 (10) | 16 (11) | 17 (11) |
| Dyspepsia | 0 | 1 (1) | 4 (3) | 10 (7) |
| Leading to study drop out | 2 (1) | 7 (5) | 2 (1) | 1 (1) |

The efficacy and safety of vardenafil was determined in a Phase III pivotal trial (Hellstrom, et al, Table 10). A total of 1311 men were screened with 805 being randomized to one of four treatment arms: placebo or vardenafil 5mg, 10 mg, or 20 mg. The study's inclusion criteria included being at least 18 years of age, having experienced erectile dysfunction for more than 6 months, and at 50% or greater failure rate on at least 4 sexual intercourse attempts during the 4-week baseline period. Exclusion criteria included but were not limited to the following: hypoactive sexual desire, s/p radical prostatectomy, ED secondary to spinal chord injury, unstable angina, retitinitis pigmentosa, uncontrolled atrial tachycardia, poorly controlled diabetes, history of hypotension or postural hypotension, hypertension, or if in the past 6-months the subject had experienced a MI, stroke, ischemia on ECG, or life-threatening arrhythmia. Subjects were allowed to have taken sildenafil (71% had) provided it had not been taken within 7 days of screening. The etiology of erectile dysfunction in was organic (>50% in each treatment arm), psychogenic (≥7%), and mixed (≥33%).

Baseline mean EF domain score for all subjects was consistent with moderate ED. Across the treatment arms 30%-45% had severe ED, 22%-37% had moderate ED, 21%-26% had mild-moderate ED, and 5%-8% had mild ED.

Improvements in the primary efficacy scores were dose-related (See Table 10). EF domain scores for vardenafil 10 mg and 20 mg groups were significantly greater than in the 5 mg vardenafil group ($p<0.01$ and $p<0.001$, respectively). The percent of subjects improving their EF domain scores to normal (≥26) were 2 to 4 times greater in the vardenafil treatment arms compared to placebo (See Table 12)

Table 12. Percent of subjects returning to normal ED (EF domain score ≥26) by baseline EF Domain

| Baseline EF Domain | Placebo | V 5mg | V 10 mg | V 20 mg |
|---|---|---|---|---|
| Mild (22-25) | 21.4% | 63.6% | 88.7% | 78.6% |
| Mild-Moderate (17-21) | 16.7% | 44% | 54.9% | 47.4% |
| Moderate (11-16) | 17.2% | 36.6% | 50.8% | 50% |
| Severe (≤10) | 4.0% | 14.3% | 25.7% | 39.5% |

A dose-response relationship was also noted in the percent of subjects stating that treatment improved their erection over the past 4 weeks. All active treatment arms were "significantly greater" than placebo (See Table 10).

Overall, 37% of men discontinued treatment following randomization; 10% due to insufficient therapeutic response. A larger percentage of men taking placebo discontinued overall and due to insufficient therapeutic effect (Table 13). Commonly reported adverse events are shown in Table 14.

Table13. Discontinuation Rates by Treatment Arm

| Treatment Arm | Percent Discontinuing | Percent Discontinuing Due to Insufficient Therapeutic Effect | Percent Discontinuing Due to an ADE |
|---|---|---|---|
| Placebo | 54% | 20% | 2% |
| Vardenafil 5 mg | 38% | 13% | 4% |
| Vardenafil 10 mg | 27% | 5% | 3% |
| Vardenafil 20 mg | 30% | 5% | 8% |

Table 14. Incidence of Treatment-emergent Adverse Events Occurring in >5% of Any of the Four Treatment Arms and Greater Than Placebo

| Adverse Event | Placebo (%) n = 182 | V 5mg (%) n = 193 | V 10 mg (%) n = 199 | V 20 mg (%) n = 188 |
|---|---|---|---|---|
| Headache | 8 (4) | 19 (10) | 44 (33) | 40 (21) |
| Rhinitis | 9 (5) | 17 (9) | 27 (14) | 32 (17) |
| Flushing | 0 | 9 (5) | 21 (10) | 24 (13) |
| Dyspepsia | 1 (<1) | 2 (1) | 8 (4) | 12 (6) |
| Sinusitis | 2 (1) | 10 (5) | 6 (3) | 9 (5) |
| Accidental injury | 5 (3) | 11 (6) | 7 (4) | 8 (4) |
| Flu syndrome | 2 (1) | 10 (5) | 5 (3) | 3 (2) |

Goldstein et al. conducted a double-blind, placebo-controlled, fixed-dose, parallel-group multicenter Phase III study to assess vardenafil's efficacy, safety, and tolerability in men with Type 1 or 2 diabetes mellitus and erectile dysfunction. Subjects were included if they were more than 18 years old, erectile dysfunction had been present in the previous 6 months, and their HbA1c was $\leq$ 12%. Exclusion criteria included ED as a result of radical prostatectomy, primary hypoactive sexual desire, or spinal cord injury. Previous use of sildenafil was permitted provided it had not been discontinued due to significant side effects or subject dissatisfaction; 55% - 60% of subjects had previously used sildenafil.

A total of 452 men were randomized to placebo, or vardenafil 10 mg or 20 mg. An organic etiology was the most frequent cause of ED in 80%-83% of men in each group. At baseline, men with severe ED (IIEF EF domain <11) accounted for 49%-58% of men in each group; with another 20%-26% considered to have moderate severity ED (IIEF EF domain 11-16). At least 86% of subjects in each group had type 2 diabetes. Hypertension was a comorbidity in 46%-57% of men per group.

The primary efficacy measures all showed significant improvement in men receiving vardenafil 10 mg and 20 mg versus placebo (Table 10). The degree of improvement differed significantly between 10 mg and 20 mg groups on change in IIEF domain score and percent GAQ at 12 weeks.

Table 15. Successful Intercourse Rates at 12 weeks by ED Severity

| Baseline Severity | Placebo | V 10 mg | V 20 mg |
|---|---|---|---|
| Severe | 11% | 34% | 40% |
| Moderate | 21% | 53% | 60% |
| Mild-Moderate | 53% | 70% | 72% |
| Mild | 47% | 72% | 75% |

There was no correlation between the relationship of HgA1c and response to vardenafil as measured on the SEP3 ($R^2$=0.0042, p=0.44) indicating that there was no relationship between glycemic control and response to vardenafil. The percent of subjects reporting successful intercourse rates with HgA1c in the >6% to <8% and >8% were 20% and 23% in the placebo group and 50% and 54% for vardenafil 20 mg group, respectively.

For men with type 1 diabetes, least squares mean subject response for success rates in maintenance of erection to successful intercourse were 10% for placebo, 48% for vardenafil 10 mg and 65% for vardenafil 20 mg ($p \leq 0.005$ for both vardenafil groups versus placebo).

The mean per subject success rates for maintenance of erection to successful intercourse were placebo, 22%; vardenafil 10 mg, 42%; and vardenafil 20, 49% in sildenafil-naive subjects. Success rates were not significantly different from the subjects who'd taken sildenafil previously: placebo, 20%; vardenafil 10 mg, 48%; and vardenafil 20 mg, 55%.

The rate of subject discontinuation due to insufficient response or adverse effects, and the frequency of adverse events occurring in ≥5% of each treatment group is shown in Table 16.

Table 16. Discontinuation and Adverse Rates

| Event | Placebo | Vardenafil 10 mg | Vardenafil 20 mg |
|---|---|---|---|
| Discontinued due to insufficient response | 5 (3%) | 3 (2%) | 0 |
| Discontinued due to adverse event | 2 (1%) | 4 (3%) | 5 (3%) |
| Headache | 10 (7%) | 20 (13%) | 16 (11%) |
| Flushing | 1 (<1%) | 14 (9%) | 14 (10%) |
| Rhinitis | 7 (5%) | 8 (5%) | 15 (10%) |
| Sinusitis | 1 (<1%) | 2 (1%) | 9 (6%) |
| Accidental injury | 4 (3%) | 12 (8%) | 3 (2%) |

## Tadalafil[19-21]

Table 17. Tadalafil (T) Trials

| Study | Dose | Mean IIEF Erectile Function | | SEP-Q2 | | SEP-Q3 | | %GAQ | Mean IIEF Intercourse Satisfaction | | Mean IIEF Overall Satisfaction | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Endpt. | Change | Endpt. | Change | Endpt. | Change | Endpt | Endpt. | Change | Endpt. | Change |
| Brock, et al, 2002 | T 2.5mg, n=74 | 16.6 | 3.2* | 56% | 15%^ | 37% | 20%* | 42%* | 7.8 | 1.6 | 5.8 | 0.8 |
| | T 5 mg, n=151 | 17.7 | 4.6^ | 57% | 16%^ | 40% | 22%^ | 50%^ | 8.5 | 1.6^ | 6.1 | 1.3^ |
| | T 10 mg n=321 | 21.1 | 6.5^ | 73% | 24%^ | 58% | 34%^ | 67%^ | 9.3 | 2.6^ | 6.7 | 1.8^ |
| | T 20 mg, n=258 | 23.9 | 7.9^ | 80% | 27%^ | 70% | 39%^ | 81%^ | 10.5 | 3.4^ | 7.4 | 2.4^ |
| | P, n=308 | 15.1 | 0.6 | 48% | 2% | 31% | 6% | 35% | 7.4 | 0.8 | 5.2 | 0.5 |
| de Tejada, et al., 2002 N=216, Type I or II diabetic men R, DB, PC, PG, FixD, MC trial; ITT | T 10mg, n=73 | NR | 6.4^ | NR | 22%^ | NR | 28.4%^ | 56%^ | | | | |
| | T 20 mg, n=72 | | 7.3^ | | 23%^ | | 29.1%^ | 64%^ | | | | |
| | P, n=71 | | 0.1 | | -4% | | 1.9% | 25% | | | | |
| Porst, et al, 2003, N=348 R, DB, PC, PG, MC, 8-wk trial to evaluate tadalafil's efficacy at 24 and 36 hrs post dose. | T 20 mg at 24 h | | | | | 60.9% | | | | | | |
| | T 20 mg at 36 hr | | | | | 64.1% | | | | | | |
| | P at 24 hr | | | | | 35.2% | | | | | | |
| | P at 36 hr | | | | | 36.8% | | | | | | |

R=randomized
DB=double-blind
FixD=fixed dose
ITT=intention-to-treat
NS-RRP=nerve sparing, radical retropubic prostatectomy
MC=Multicenter
PG=parallel group
PC=placebo control
LOCF=last observation carried forward
*significantly different from placebo, p<0.05
^significantly different from placebo, p<0.001

Brock et al published an integrated analysis of five, 12-week, randomized, double-blind, placebo controlled trials comparing fixed doses of tadalafil (2.5, 5, 10 and 20 mg) to placebo in 1112 men with ED (Table 17). All trials used a 4-week treatment free run-in period to establish baseline severity prior to randomization. Subjects were to take the study medication as needed prior to intercourse without regard to food or alcohol. Men 18 years and older with at least a 3 month history of mild to severe ED were eligible. Exclusion criteria included patients unable to have an erection following radical prostatectomy or pelvic surgery, with penile deformity or implant, history of myocardial infarction, coronary artery disease, CVA, or spinal cord trauma, and/or clinically significant renal or hepatic failure. Also excluded were men treated with nitrates, antiandrogens or cancer chemotherapy. Outcome measures included the IIEF, SEP Q2 and Q3, and GAQ.

The etiology of ED was organic (61%), psychogenic (9%), and mixed (31%). At baseline, ED was considered mild (41%), moderate (23%), and severe (36%) in severity. Hypertension and diabetes were frequent co-morbid conditions, 30% and 21%, respectively. Nine hundred ninety-five (89%) men completed treatment. Men randomized to tadalafil reported significant improvement in three primary outcome variables compared to placebo; this was true for all four doses of tadalafil. Significant improvements in secondary outcome measures were found for doses of tadalafil 5 mg and greater compared to placebo. For all primary and secondary outcome measures there was greater change from baseline as the dose of tadalafil increased (Table 17).

A significant dose-response relationship in mean change in IIEF erectile function domain scores from baseline to endpoint was found for all 3 severities of ED at baseline. This relationship was particularly notable for tadalafil doses 5 mg and greater, and in men with a baseline ED severity of moderate or severe (Tables 18 & 19). The frequency of adverse events are shown in Table 20.

Table 18. Distribution of IIEF Severity at Baseline and in Men with Normal EF at 12-weeks

Percent of Subjects at Baseline/Endpoint

| Outcome | Placebo | T 2.5 mg | T 5 mg | T 10 mg | T 20 mg |
|---|---|---|---|---|---|
| IIEF Severity at Baseline | | | | | |
| • Mild (17-30) | 39 | 37 | 31 | 40 | 52 |
| • Moderate (11-16) | 24 | 22 | 22 | 26 | 20 |
| • Severe (1-10) | 37 | 42 | 47 | 33 | 28 |
| Normal Erectile Function at Endpoint (IIEF ≥26) | 11 | 21* | 23^ | 40^ | 59^ |

*p<0.05 compared to placebo
^p<0.001 compared to placebo

Table 19. Percent of Successful Intercourse Attempts by Time After Dose

| Time After Dose | Percent of Successful Intercourse Attempts (SEP-Q3) |
|---|---|
| ≤ 30 mins. | 59 |
| > 30 mins - ≤ 4 Hrs | 73 |
| > 4 Hrs - ≤ 12 Hrs | 80 |
| >12 Hrs - ≤ 24 Hrs | 80 |
| >24 Hrs - ≤ 36 Hrs | 79 |

Table 20. Adverse Events for Four Tadalafil Doses and Placebo

| Event | Placebo n = 308 | T 2.5 mg n = 74 | T 5 mg n = 151 | T 10 mg n = 321 | T 20 mg n = 258 |
|---|---|---|---|---|---|
| > 1 ADE | 52% | 51% | 45% | 58% | 73% |
| Discontinued due to adverse event | 1.3% | 4.1% | 0.7% | 1.6% | 3.1% |
| Headache | 6% | 7% | 11% | 12% | 21% |
| Flushing | 2% | 1% | 3% | 3% | 5% |
| Rhinitis | 4% | 5% | 4% | 6% | 5% |
| Dyspepsia | 2% | 1% | 5% | 9% | 17% |
| Back Pain | 5% | 4% | 3% | 6% | 9% |
| Myalgia | 2% | 3% | 1% | 5% | 7% |

The safety and efficacy of tadalafil on ED in men with diabetes was in studied in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Spanish men age 18 years and older with type 1 or 2 diabetes and at least a 3 month history of mild to moderate ED were enrolled. Exclusion criteria included an HgA1c >13% at screening, two or more episodes of diabetic ketoacidosis, a history of hypoglycemia, coronary artery disease, poorly controlled hypertension, congestive heart failure, and orthostatic hypotension. Men were also excluded if they were unable to have an erection after radical prostatectomy or pelvic surgery, had a penile implant, penile deformities, a history of stroke or spinal cord trauma in the past 6 months, taking nitrates, antiandrogens, or cancer chemotherapy. Primary outcome measures were the change in mean erectile function domain scores from baseline to endpoint on the IIEF and changes from baseline in the mean proportion of men answering "Yes" to SEP Q2 and Q3. Secondary outcome measures included the changes from baseline in mean scores on IIEF Q3 and Q4, and the proportion of subjects responding "Yes" on the GAQ at study endpoint.

Of the 216 subjects enrolled, 88% completed the study. Prior to randomization, all subjects completed a 4-week treatment free run-in period to establish baseline severity. More than 90% of subjects had type-2 diabetes; glycemic control was considered good (HbA1c <7%) 18.5%, fair (HbA1c 7-9.5%) 63%, and poor (HbA1c > 9.5%) 22%. Tadalafil significantly enhanced erectile function as measured on the IIEF, SEP-Q2 and-Q3 (Table 17). Subjects' glycemic control (HbA1c) did not influence the response to tadalafil versus placebo. Subjects taking antihypertensive medication appeared to respond better to tadalafil 20 mg. Tadalafil significantly improved scores from baseline to endpoint compared to placebo on the IIEFQ3 and IIEFQ4 (p<0.001), and IIEF domains for intercourse satisfaction (T10 mg p<0.001, T20

mg p=0.012), orgasmic function (T10 mg p<0.001, T20 mg p=0.014), and overall satisfaction (p<0.001). Tadalafil was more likely to result in a >5 point increase in erectile function domain score compared to placebo: ~44% for T 10 mg, 56% for T 20 mg, and 13% for placebo (p<0.001). Greater percentages of men receiving tadalafil 10 mg or 20 mg had positive response to the GAQ, 56% and 64%, respectively, compared to placebo, 25% (p<0.001).

Of the adverse events reported, only the incidence of dyspepsia was significantly different for between the treatment groups (Table 21). Two subjects experienced a myocardial infarction during the trial: one randomized to placebo, the other to tadalafil 20mg, but had yet to take a dose. No other serious adverse effects or changes in ECG, laboratory values or vital signs were noted.

Table 21. Table Percent of Subjects Reporting Adverse Events

| Event | Placebo n = 71 | T 10 mg n = 73 | T 20 mg n = 72 | p-value |
|---|---|---|---|---|
| Discontinued due to lack of response | Not stated | 4% | 3% | Not tested |
| Discontinued due to adverse event | 1% | 1% | 5% | Not tested |
| ≥ 1 ADE | 31% | 40% | 44% | >0.05 |
| Headache | 3% | 10% | 8% | >0.05 |
| Flushing | 0 | 3% | 4% | >0.05 |
| Flu syndrome | 4% | 4% | 4% | >0.05 |
| Dyspepsia | 0 | 11% | 11% | 0.005 |
| Back Pain | 1% | 1% | 6% | >0.05 |
| Myalgia | 1% | 6% | 4% | >0.05 |

The investigators concluded that in men with diabetes and ED, tadalafil consistently enhanced erectile function and significantly improved their ability to achieve and maintain an erection.

Tadalafil's effectiveness in the treatment of ED 24 and 36 hours after dosing was established in a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial in 348 men. Following a 4-week run-in phase to establish baseline measures, men were randomized to tadalafil 10 mg or 20 mg, or placebo. The treatment arm was divided into two 4-week periods for which subjects were given 2 doses of study medication for each period. During one study period, subjects were instructed to use both doses during the study period by taking one dose before sexual activity, but waiting ~24 hours before attempting sexual intercourse. During the second study period, they were instructed to wait ~36 hours before attempting sexual intercourse. There was an 8 to 10 day washout between study periods. Subject inclusion and exclusion criteria were similar to those used by other tadalafil clinical trials. The sole outcome measure was the percent "Yes" responses to SEP-Q3.

Based on IIEF scores the severity of ED was mild for 40% of men in each treatment group; moderate, 25% in the placebo and 26% in the tadalafil groups; and severe in 35% in the placebo and 34% in the tadalafil groups. At 24 and 36 hours post dosing, a significantly greater proportion of intercourse attempts were successful in the tadalafil 20 mg group compared to placebo, p<0.001 (Table 22).

Table 22. Percent of Successful Intercourse Attempts at 24 and 36 hours post Tadalafil or Placebo

| Study Drug | Successful Intercourse Attempts (number of attempts) at 24 ± 2 Hrs | at 36 ± 2 Hrs |
|---|---|---|
| Tadalafil 20 mg, n = 175 | 52.9% (227) | 59.2% (223) |
| Placebo, n = 173 | 36.8% (247) | 35.2% (212) |

Adverse events were more frequent in the tadalafil group: headache 8%, flushing 6%, dyspepsia 5%, and myalgia 3%. Only two patients in the placebo group reported adverse events, headache in both cases.

Use of PDE5 Inhibitors by Men with Heart Disease[22-24]

Sildenafil has been studied in men with New York Heart Association Class II or III heart failure to determine its efficacy in treating ED, safety, and whether it improves depressive symptoms or quality-of-life measures. Erectile dysfunction response was assessed using the IIEF, depressive symptoms were measured using the Beck Depression Index (BDI) and the Center for Epidemiologic Studies-Depression

Scale (CES-D), and the Minnesota Living With Heart Failure Questionnaire (LihFE) assessed quality of life. Participants were allowed to continue all existing medications through out the trail. Persons were excluded if they had symptomatic hypotension or SBP < 80 mm Hg at baseline. Thirty-five subjects were randomized to either placebo or sildenafil 50 mg treatment arms for 6-weeks before being crossed-over to the other treatment arm. Prior to the start of the first treatment arm, all subjects participated in a safety protocol during which they received 50 mg of sildenafil followed by a 5-hour observation period including ambulatory monitoring of their blood pressure and heart rate. Baseline erectile dysfunction was severe with an average (SEM) IIEF EF Domain score of 9±1.
All 35 subjects completed the protocol. Erectile function had significantly improved by week 4 ($p<.001$) as measured by IIEF score for men taking sildenafil regardless of the randomization sequence. While on sildenafil, men reported improved scores on the BDI, CES-D, and LihFE scales. For all 3 scales, men who received sildenafil initially improved followed by their worsening when crossed over to placebo. Those who received placebo initially did not note a change in scale scores until they crossed over to sildenafil; after which they too noted a similar improvement.

In the four hours following a 50 mg dose of sildenafil, mean heart rate and blood pressure did not change significantly. A small, insignificant decrease in blood pressure was noted 60 minutes after a 50 mg dose of sildenafil. At no time did the mean arterial blood pressure decrease by more than 10%. Patients did not report any adverse effects.

It was the investigators' conclusion that sildenafil 50 mg was safe and effective for the treatment of ED in patients with NYHA Class II or III heart failure. Furthermore, sildenafil, presumably by improving sexual satisfaction, relieved depressive symptoms and consequently an improvement in perceived quality of life.

The safety and efficacy of sildenafil was studied in men with erectile dysfunction and stable coronary artery disease in a 12-week, randomized double-blind, placebo-controlled, flexible dose study. One hundred fifty-one men were randomized to placebo or sildenafil 50 mg; whose doses could be adjusted to 25 mg or 100 mg based on response. Men taking nitrates or CYP3A inhibitors, who were hypotensive, with uncontrolled hypertension, high cardiac risk, unstable angina, hypertrophic obstructive cardiomyopathy or moderate-to-severe stenosis, or who had taken previously taken sildenafil were excluded. Primary outcome measures were Questions 3 and 4 of the IIEF. Secondary outcome measures included the remainder of the IIEF, the Life Satisfaction Checklist (LSC), the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITs), 2 global assessment questions "Has treatment improved your erection?" and "Has treatment improved your ability to have sexual intercourse?" and the intercourse success rate. Partners were also requested to complete to the Partner Questionnaire and the Partner EDITS.

Compared to baseline values, men randomized to sildenafil reported a significant improvement in the frequency of penetration (IIEF Q3), $p=0.0058$, and the frequency with which they maintained erections after penetration (IIEF Q4), $p=0.0003$, at the end of treatment (least-squares mean scores). Significant differences between sildenafil and placebo in secondary outcome measures were also found including IIEF domains for erectile function, orgasm function, intercourse satisfaction, and overall satisfaction; both global assessment questions; intercourse satisfaction; and in mean scores for 10 of the 11 EDITS items. Compared to placebo, men taking sildenafil had significantly higher mean scores on the LSC pertaining to sexual life ($p=0.0186$). Too few partners agreed to participate to allow a statistical analysis of the Partner Questionnaire and Partner EDIT. Commonly reported adverse events are shown in Table 23.

Table 23. Commonly reported adverse events by men with CAD.

| Adverse Event | Placebo, n = 74 | Sildenafil, n = 74 |
|---|---|---|
| Headache | *1 (1.3%) | *6 (8.1%) |
| Chest pain | 2 (2.6%) | ^4 (5.4%) |
| Hypertension | 1 (1.3%) | 4 (5.4%) |
| Flushing | 0 | #6 (8.1%) |
| Dyspepsia | 4 (5.3%) | 2 (2.7%) |
| Leg cramps | 0 | 3 (4.1%) |
| Respiratory tract infection | 2 (2.6%) | 4 (5.4%) |
| Nasal congestion | 0 | *2 (2.7%) |
| Abnormal vision | *1 (1.3%) | *1 (1.4%) |

*All thought to be treatment related
^One case thought to be treatment related
#Five cases thought to be treatment related

Only one subject in the sildenafil group experienced cardiovascular effects attributed to sildenafil, which resolved by reducing the dose from 50 mg to 25 mg. One subject in the placebo group reported angina. The Canadian Cardiovascular Society functional classification of angina criteria did not change for 94% of the sildenafil group and 97% of the placebo group. Angina scores increased for 3 men taking sildenafil and 2 taking placebo. The investigators concluded that men with stable coronary artery disease, provided they do not require nitrates, could safely take sildenafil without additional cardiovascular risk.

Vardenafil's effect on the cardiovascular response to exercise in men with stable coronary artery disease has been studied using a randomized, double-blind, placebo-controlled, crossover, single-dose multicenter design. The effect of vardenafil 10 mg (orally) and placebo on symptom-limited treadmill exercise time, first awareness of angina or time to ST-segment depression ≥1 mm change from baseline during treadmill exercise using the Bruce protocol, and at rest and during exercise blood pressure and heart rate served as outcome measures. Men were not required to have erectile dysfunction to participate. Subjects received placebo during the run-in screen to verify exertional angina or its equivalent at exercise. A 5- to 21-day washout period took place between the two randomized arms. Exercise testing and baseline (resting) measurements were performed one hour after study drug administration. Forty-one of the 53 men screened were randomized and completed the study. Of these, 39 subjects were considered valid per protocol.

No subject experienced treatment-emergent, clinically relevant changes in vital signs. Mean outcome variable data are shown in Table 24. There was not a significant difference between vardenafil and placebo in mean total treadmill time or in mean time to first awareness of angina. Vardenafil significantly prolonged the mean time to ST-segment depression of ≥1 mm compared to placebo. An analysis of subjects with angina and ≥1 mm ST-segment depression did not find a significant difference in mean total treadmill time or time to first awareness of angina between vardenafil and placebo, but did find that vardenafil significantly prolonged the mean time to ST-segment depression. Mean differences between vardenafil and placebo with respect to systolic and diastolic blood pressure were significant at rest and during peak exercise. The mean difference in heart rate was only significant at rest.

Table 24. Cardiovascular Outcomes at Rest and During Exercise

| Variable (SD) | Vardenafil 10 mg | Placebo | P value |
|---|---|---|---|
| Mean total treadmill time, seconds | 433 (109) | 427 (105) | 0.394 |
| Mean time to 1st awareness of angina | 291 (123) | 292 (110) | 0.594 |
| Mean time to ST-segment depression ≥1 mm change | 381 (108) | 334 (108) | 0.0004 |
| Mean SBP, rest | 129 (18) | 136 (17) | <0.05 |
| Mean SBP, exercise | 165 (22) | 156 (28) | <0.05 |
| Mean DBP, rest | 76 (10) | 81 (11) | <0.05 |
| Mean DBP, exercise | 76 (22) | 83 (19) | <0.05 |
| Mean HR, rest | 73 (12) | 70 (12) | <0.05 |
| Mean HR, exercise | 131 (22) | 129 (20) | >0.05 |

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate

Adverse events reported during the study were more common with vardenafil (vs. placebo) and consistent with those of its drug class: any event (24% vs. 2%), facial flushing (12% vs. 0), headache (7%

vs. 0), tachycardia (2% vs. 0), and dizziness (2% each). The investigators concluded that vardenafil did not impair the ability of men with coronary artery disease to exercise at a level equal to or greater than that attained during sexual intercourse.

PDE5 Inhibitors After Radical Retropubic Prostatectomy[25-28]

The efficacy and safety of all three PDE5 inhibitors have been studied in men with ED after radical retropubic prostatectomy. Two published flexible dose, open-label trials of sildenafil in this patient population were reviewed. The starting dose was 50 mg and could be increased if there was an insufficient response. In the first trial, 84 men were prospectively studied after requesting a prescription for sildenafil. Patients were assessed after at least 6 doses using the IIEF as well as general questions on the effectiveness of sildenafil, side effects and dose. Comparison of the mean change from baseline and after sildenafil should a significant improvement in the IIEF domains for erectile function, intercourse satisfaction, orgasmic function as well as overall score and response as measured by IIEF Q3 and Q4 (frequency of penetration during intercourse and frequency of maintenance of erection during intercourse). The degree of nerve sparing was found to be an important predictor for sildenafil response. Erections and ability for intercourse improved in 58% and 46% of men with both nerves intact, 57% and 39% in men with one nerve intact, and 20% and 10% when neither nerve was spared, respectively. Adverse effects experienced included flushing (33%), headache (27%), nasal congestion (19%), heartburn (10%), and visual changes (10%).

In the second trial, 53 out of 65 men completed the IIEF. This study also found that the presence of neurovascular bundle preservation significantly predicted the response to sildenafil. Seventy-one percent of men who'd had a bilateral nerve sparing procedure had a positive response compared to 80% who'd had a unilateral nerve sparing procedure, and 6% who'd had a nonnerve sparing procedure. Adverse effects experienced included headache (21%), flushing (8%), nasal congestion (6%), and visual changes (6%).

Vardenafil's efficacy and safety in men with ED after unilateral or bilateral nerve sparing radical retropubic prostatectomy was studied in a prospective, randomized, double-blind, placebo controlled, fixed dose (10 or 20 mg), parallel group study (Table 10). A total of 440 men participated, although 25% discontinued prematurely over the course of the 12-week study, with an insufficient response being the first or second most common reason in all three groups. Efficacy was assessed with the IIEF, the SEP2 and SEP3 questions, and the GAQ. Previous sildenafil use was reported by ~80% of participants, with 96% having experienced some degree of improvement.

At the study's endpoint, both doses of vardenafil were significantly superior to placebo for all measures of efficacy ($p<0.0001$). Erections were reported to be improved by 65% and 60% of men assigned vardenafil 20 mg and 10 mg, respectively. Response to vardenafil was also dependent on the severity of ED at baseline, although all levels of severity improved with both doses of vardenafil. The most frequently reported adverse effects with both doses of vardenafil were headache, flushing, rhinitis, sinusitis, dyspepsia and nausea.

The efficacy and safety of tadalafil 20 mg in men who'd had a bilateral nerve sparing radical retropubic prostatectomy was studied in a randomized, double-blind, placebo controlled, parallel group, multicenter 12-week trial. Efficacy measures included the IIEF, SEP 2 ("Were you able to insert your penis into your partner's vagina?" and SEP 3 ("Did you erection last long enough for you to have successful intercourse?", the GAQ and EDITS scores. A total of the 303 men were randomized (2:1 ratio), 161 assigned to tadalafil and 76 to placebo completed the study. Eight percent of the tadalafil group discontinued due to a lack of therapeutic response compared to 9.8% of the placebo group. Men receiving tadalafil reported greater improvement on all measures of efficacy ($p<0.001$) compared to placebo. Sixty-two percent of all men randomized to tadalafil and 71% of men with evidence of postoperative tumescence randomized to tadalafil reported an improved erection, compared to 23% and 24%, respectively, of men taking placebo ($p<0.001$).

One or more adverse events was experienced by 26.5% of the placebo group and 52% of the tadalafil group ($p<0.001$). Headaches were more common with tadalafil than placebo (21% vs. 6%, $p<0.001$) as were dyspepsia (13% vs. 1%, $p<0.001$), and myalgia (6.5% vs. 0, $p=0.006$).

Adverse Events

In addition to the information on adverse events already presented along with the clinical trials, Table 25 presents a composite of adverse events reported in the package inserts of each of the PDE5 inhibitors.

Table 25. Composite of Adverse Events as Listed in the Package Insert

| | Percentage (%) of Patients with Reported Event in the Package Insert | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Adverse Event** | **Placebo N=734** | **Sildenafil N=725** | **Placebo N=1199** | **Vardenafil N=220** | **Placebo N=476** | **$T_{5mg}$ N=151** | **$T_{10mg}$ N=394** | **$T_{20mg}$ N=635** |
| Any event | ** | ** | 33 | 53 | ** | ** | ** | ** |
| Headache | 4 | 16 | 4 | 15 | 5 | 11 | 11 | 15 |
| Flushing | 1 | 10 | 1 | 11 | 1 | 2 | 3 | 3 |
| Rhinitis/nasal Congestion | 2 | 4 | 1 | 11 | 1 | 2 | 3 | 3 |
| Dyspepsia | 2 | 7 | 1 | 4 | 1 | 4 | 8 | 10 |
| Accidental Injury | ** | ** | 2 | 3 | ** | ** | ** | ** |
| Sinusitis | ** | ** | 1 | 3 | ** | ** | ** | ** |
| Flu Syndrome | ** | ** | 2 | 3 | ** | ** | ** | ** |
| Dizziness | 1 | 2 | 1 | 2 | ** | ** | ** | ** |
| Increased CK | ** | ** | 1 | 2 | ** | ** | ** | ** |
| Nausea | ** | ** | 1 | 2 | ** | ** | ** | ** |
| UTI | 2 | 3 | ** | ** | ** | ** | ** | ** |
| Abnormal Vision | 0 | 3 | ** | ** | ** | ** | ** | ** |
| Diarrhea | 1 | 3 | ** | ** | ** | ** | ** | ** |
| Rash | 1 | 2 | ** | ** | ** | ** | ** | ** |
| Back Pain | ** | ** | ** | ** | 3 | 3 | 5 | 6 |
| Myalgia | ** | ** | ** | ** | 1 | 1 | 4 | 3 |

*Non arteritic ischemic optic neuropathy (NAION)*[29]

On July 8, 2005 the FDA issued a statement approving label changes for all three PDE5 inhibitors that reflect the reporting of a small number of cases of NAION reported postmarketing. It is not possible at this time to determine causality of PDE5 inhibitors and NAION since other factors associated with NAION such as underlying anatomic or vascular risk factors, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Men who experience visual changes or loss of vision in one or both eyes are advised to stop the medication and contact their doctor or healthcare provider immediately.

Table 26. Cost of PDE5 Inhibitors

| PDE5 Inhibitor | Strength | VA Price per Tablet, $ |
|---|---|---|
| Sildenafil | 25 mg | 5.99 |
| | 50 mg | 5.99 |
| | 100 mg | 5.99 |
| Vardenafil | 2.5 mg | 2.58 |
| | 5 mg | 2.58 |
| | 10 mg | 2.58 |
| | 20 mg | 2.58 |
| Tadalafil | 5 mg | 6.13 |
| | 10 mg | 6.32 |
| | 20 mg | 6.32 |

## Summary and Recommendations

The PDE5 inhibitors have all been shown to be safe and effective in the treatment of erectile dysfunction. More data is available for sildenafil, which has been on the market the longest. The pharmacology of these

agents differs minimally. Sildenafil has the most cross-reactivity with PDE-6, which is believed to be responsible for visual disturbances, and should not be taken with a high fat meal. Tadalafil has the most cross-reactivity with PDE-11, which may contribute to back pain/myalgia in a small percentage of patients. Tadalafil's half-life is longer which is presumable responsible for its longer duration of action which some patients will find convenient. Their safety and efficacy has been studied in patients with varying origins of their ED using the same or similar outcome measures. Given that there are no direct head-to-head comparisons between the agents, it is difficult to draw conclusions whether one agent is superior to the others. All three agents have demonstrated a dose-response relationship and are efficacious in all levels of ED severity. The patient population the least responsive was men who'd had a radical retopubic prostatectomy during which neither nerve was spared. Therefore, it would appear that the agents are of similar efficacy until proven otherwise.

From a safety perspective, all three agents share similar drug interactions involving CY3A4 inhibitors and a contraindication in the use of nitrates. While all three interact with alpha-blockers and in their approved labeling the interaction is considered a Precaution . The adverse events frequently reported in clinical trials are similar for all three agents including headache, flushing, rhinitis, and dyspepsia; these too appear to be dose-related. Again, without direct comparisons, it is difficult to state that one is better tolerated than the others.

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