Clinical Monograph for Drug Formulary Review: Erectile Dysfunction Agents

HELEN ELOISE CAMPBELL, BS, PharmD

ABSTRACT

BACKGROUND: Significant advances in the pharmacologic treatment of erectile dysfunction (ERD) have occurred in recent years, most notably the introduction of sildenafil, the first oral selective phosphodiesterase type 5 (PDE5) inhibitor, in 1998. Sildenafil quickly gained acceptance by the medical community and the public because of its broad efficacy for different types of ERD and its ease of use. Two PDE5 inhibitors, vardenafil and tadalafil, have since joined sildenafil to compete in the ERD market. A review was conducted by the Drug Information Service of a pharmacy benefits manager (PBM) to determine the relative merits and place in therapy of commonly used ERD drugs as part of drug formulary management process and decision making by the Pharmacy & Therapeutics (P&T) committee.

OBJECTIVE: To provide readers with a comprehensive clinical monograph on ERD drugs written from a managed care perspective.

METHODS: The PBM clinical monograph is designed to provide health plans with an evidence-based review of drugs, therapeutic classes, and disease states with a managed care focus. For each therapeutic class or disease review, an extensive and thorough literature search of MEDLINE is conducted for efficacy, safety, effectiveness, and humanistic and economic data. Drug/disease-state databases (UptoDate online, MICROMEDEX), U.S. Food and Drug Administration clinical reviews, key Internet sites, medical/pharmacy-related news sites, clinical guidelines, and AMCP dossiers are also reviewed. Formulary drug monographs prepared by the Drug Information Service of the PBM include a critical analysis and summary of disease-oriented and patient-oriented clinical outcomes, effectiveness, and humanistic data. Additional data considered and included in the formulary review process are clinical attributes, patent expirations/generic competition, off-label or pending indications, and pharmacoeconomic data.

RESULTS: Despite the lack of head-to-head comparative studies, all 3 PDE5 inhibitors appear to have equivalent efficacy in the treatment of general ERD and ERD associated with diabetes and postprostatectomy. Sildenafil has additional efficacy data in the management of ERD associated with spinal cord injury and antidepressant medications. Tadalafil has the longest duration of action (up to 36 hours); this feature can be both beneficial (greater sexual spontaneity) or possibly detrimental (greater exposure to drug, delayed adverse events). All 3 PDE5 inhibitors appear to be generally well tolerated and have similar contraindications and warnings. However, vardenafil is the only PDE5 inhibitor with a cardiac conduction precaution. Alprostadil products are recommended in current ERD guidelines as second-line therapy for those who have not responded or cannot take the oral PDE5 inhibitors. Overall, higher clinical efficacy rates are achieved with intracavernous than with transurethral administration.

CONCLUSION: A large amount of clinical efficacy and safety data has been published since the market launch of sildenafil in 1998. Sildenafil has the greatest body of efficacy and safety evidence. No comparative studies have been conducted with any of the PDE5 inhibitors. Differences in study populations, primary end points, and measurement tools make comparisons difficult. However, all PDE5 inhibitors appear to be roughly equivalent in efficacy, with minor differences in adverse event profiles. Until more comparative data are available, economic considerations will be a significant factor in choosing ERD products for formulary inclusion.

KEYWORDS: Erectile dysfunction, Sildenafil, Vardenafil, Tadalafil, Drug monograph, Outcomes-based formulary, Evidence-based medicine

EDITORS’ NOTE: This article contains the information presented in nearly identical facsimile to the Pharmacy and Therapeutics (P&T) committee for the pharmacy benefit manager (PBM) and its health plan clients. Only the cost data have been updated, and the P&T committee sees actual cost and utilization data for the PBM during its deliberations. Part of the purpose of this article is to present for readers an example of the information that is actually reviewed in contemporary P&T processes in managed care today.

1. Introduction

Erectile dysfunction (ERD) has been defined as the persistent (lasting at least 6 months) inability to attain and maintain erection sufficient to permit satisfactory sexual performance. Although ERD is not a life-threatening disorder, it has a profound impact on the quality of life of those who suffer from it. ERD increases progressively with age, but it is not an inevitable consequence of aging. Other age-related conditions may increase the risk of developing ERD.

Based on the Massachusetts Male Aging Study, the probability of ERD of any degree is 40% among 40-year-old men and 70% among 70-year-old men. Many diseases—and many medications—may lead to erectile dysfunction. Therefore, an individual evaluation and identification of the underlying causes as well as a reduction in polypharmacy and a substitution of medications should be some of the first approaches in the management of ERD.

Significant advances in the pharmacologic treatment of ERD have occurred in recent years, most notably the introduction in 1998 of sildenafil, the first oral selective phosphodiesterase type 5 (PDE5) inhibitor. Sildenafil quickly gained acceptance by the medical community and the public because of its broad efficacy for different types of ERD and its ease of use. Recent guidelines published by the European Association of Urology and the American Association of Clinical Endocrinologists include sildenafil as first-line pharmacologic therapy in the treatment of ERD when nonspecific therapy is appropriate.

Author

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### II. Overview of ERD

#### Pathophysiology

Penile erection depends on one or two main mechanisms: reflex erection or psychogenic erection. It is a hemodynamic event regulated by the relaxation of the arterial and corporal smooth muscle. The penis consists of paired erection chambers (corpora cavernosa) that are filled with erectile tissue (corporal sinusoids) composed of smooth muscles. Relaxation of the smooth muscle of the corpora cavernosa is mediated by the release of acetylcholine by the parasympathetic nerves. Acetylcholine causes the endothelial cells to release a non-androgenic, noncholinergic carrier of relaxation signal—nitric oxide. Nitric oxide may stimulate guanylate cyclase to produce cyclic guanosine monophosphate (cGMP), therefore causing a relaxation of the trabecular smooth muscle. Penile erection is a result of neurally mediated increased arterial inflow into the corporal bodies and an increased amount of oxygen that stimulates nitric oxide synthesis by cavernosal nerves and endothelium, along with a decrease or cessation of venous outflow.2,7

The corporal smooth muscle is contracted when the penis is flaccid. The contraction is due to the presence of a normally present adrenergic tone. Smooth muscle relaxation occurs with erection. There are a number of other receptors in penile smooth muscle, including those responsive to vasoactive intestinal polypeptide, dopamine, histamine, prostaglandin, and various others.5-7

#### Etiology and Risk Factors of ERD

Vascular disease is the most common etiology of ERD in elderly men. The risk of vascular ERD increases with smoking, hypercholesterolemia, and diabetes. In addition, many diseases, such as diabetes, stroke, and Parkinson’s disease, can cause autonomic dysfunction. This can impair the penile arterial vasodilatation, maintaining the vascular constriction, and therefore preventing erection. Furthermore, a number of medications have been associated with ERD. Medications that inhibit cholinergic properties, such as antidepressants, antipsychotics, and antihistamines, block parasympathetic-mediated penile artery vasodilatation and trabecular smooth muscle relaxation.8 Causes contributing to ERD may be related to a number of disorders, which are listed in Table 2.

ERD is clearly a symptom of many conditions, and certain risk factors have been identified, some of which may be preventable. Diabetes mellitus, hypogonadism, hypertension, vascular disease, high cholesterol or low-density lipoprotein cholesterol, alcohol ingestion, depression, lack of sexual knowledge, poor sexual techniques, and many chronic diseases have all been identified as risk factors. In addition, age is a strong indirect risk factor because it may be associated with increased likelihood of direct risk factors. Smoking is another indirect risk factor that may increase the effects of other risk factors, such as hypertension or vascular disease. Knowledge of the risk factors can guide patients to prevention strategies.9-10

Two PDE5 inhibitors, vardenafil and tadalafil, have joined sildenafil to compete in the ERD market. However, PDE5 inhibitors do not work for all patients, and some individuals may have contraindications that preclude their use. Other first-line options include the use of vacuum devices or investigational oral drugs such as oral yohimbine, trazodone, phenolamine, and, in Europe, sublingual apomorphine. Efficacy data is sparse and conflicting for the off-label use of trazodone, yohimbine, and phentolamine in the treatment of hypogonadism.4

U.S. Food and Drug Administration (FDA)-approved agents recommended as second-line alternatives in ERD guidelines include intracavernosal alprostadil therapy (direct delivery of the drug to the erectile chambers) and transurethral alprostadil delivery (direct delivery to the urethra) (Table 1).

This monograph will present a short overview of the etiology, risk factors, pathophysiology, and diagnosis of ERD. The focus of this monograph will be an evaluation of pharmacology, pharmacodynamics, pharmacokinetics, clinical efficacy, and the safety of the pharmacologic treatments that are approved by the FDA for the management of ERD.

Testosterone injection, oral tablets, gels, and transdermal systems are indicated for the treatment of ERD associated with hypogonadism. The review of testosterone preparations for the treatment of hypogonadism will be the subject of a separate monograph.

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### TABLE 1

<table>
<thead>
<tr>
<th>Type of Disorder</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Atherosclerosis, penile Raynaud’s phenomenon, cardiovascular disease, diabetes</td>
</tr>
<tr>
<td>Neurological</td>
<td>Spinal cord damage, cerebrovascular accident</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy, diabetic autonomic neuropathy</td>
</tr>
<tr>
<td>Hormonal/endocrine</td>
<td>Hypogonadism, hyperthyroidism, hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>(poorly controlled diabetes)</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Performance anxiety, depression</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Pelvic radiation, lumbar sympathectomy, prostatectomy</td>
</tr>
<tr>
<td></td>
<td>Renal transplant, spinal cord resection</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Diuretics, sympatholytics, nonselective beta-blockers, alpha-blockers, direct vasodilators, calcium channel blockers, antidepressants, antipsychotics, anxiolytics, opioids, cimetidine</td>
</tr>
</tbody>
</table>

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</table>
Diagnosis of ERD

ERD may be associated with several abnormalities of the endocrine, neurological, and vascular system. Thus, an appropriate evaluation of all men with ERD should include a medical and sexual history, physical exam, psychosocial evaluation, and appropriate laboratory studies.3

Endocrine evaluation includes hemoglobin A1C, a morning serum testosterone, prolactin, luteinizing hormone, and follicle-stimulating hormone (FSH) levels. Other tests, such as complete blood count, urinalysis, creatinine, lipid profile, fasting blood sugar, and thyroid function may be indicated to exclude an unrecognized underlying systemic disease. Neurologic causes may be associated with a history of diabetes, spinal injury, or cerebrovascular accident; a detailed medical history will be essential to identify them. In addition, nocturnal penile tumescence testing may be useful when a primary psychogenic ERD is suspected. An erectile response to an intracavernosal injection of pharmacological test dose of a vasodilatory agent, such as papaverine or PGE1, indicates adequate arterial and veno-occlusive function. For patients who favor noninvasive treatments, such as the oral PDE5 inhibitors, pharmacological injection, intraurethral suppository, or vacuum constrictor devices, no further diagnostic tests are necessary. On the other hand, for patients with unsatisfactory response, penile implant surgery or further diagnostic tests may be appropriate.3

III. Pharmacology/Pharmacodynamics

FDA-Approved Therapy

Alprostadil (Caverject, Edex, and MUSE)

Prostaglandin E1 (alprostadil) is one of the prostaglandins, naturally occurring acidic lipids with a variety of pharmacological effects, including vasodilatation, inhibition of platelet aggregation, and stimulation of intestinal and uterine smooth muscle. It acts by relaxing the trabecular smooth muscles of the corpus cavernosum and increasing the diameter of cavernous arteries, and this leads to erection. In animal studies, the degree and duration of cavernous smooth muscle relaxation appears to be dose dependent.11-13

PDE5 Inhibitors (Sildenafil, Vardenafil, and Tadalafil)

The mechanism of penile erection involves relaxation of the corpus cavernosal smooth muscle. This occurs through release of nitric oxide during sexual stimulation, which results in increased concentrations of cGMP. Sildenafil, vardenafil, and tadalafil are all competitive inhibitors of the type 5 cGMP-specific PDE5 enzyme.14-16 The result is an enhancement of the effect of nitric oxide secondary to a decrease in degradation of cGMP. PDE5 inhibitors have no effect in the absence of sexual stimulation.

There are 11 families of phosphodiesterase isoenzymes that have been identified in mammalian tissue. While PDE1 through 6 have been extensively studied, PDE7 through 11 have been recently discovered, and thus less is known regarding their distribution and function in the human body.

Sildenafil, vardenafil, and tadalafil are all more selective for the PDE5 isoenzyme than for all other PDE isoenzymes. However, degrees of selectivity vary among the agents, depending on the isoenzyme in question. As illustrated in Table 3, sildenafil is 80 times more selective for PDE5 than for PDE1, but greater than 80 times more selective for PDE6, an isoenzyme heavily concentrated in the retina of the eye.17,18 In contrast, tadalafil is greater than 700 times more selective for PDE5 than for the PDE6 isoenzyme. This selectivity ratio pattern may explain why the side effect of blue-tinged vision or changes in blue-green color discrimination is reported with sildenafil but is
not expected to occur with tadalafil use. On the other hand, tadalafil is only 14 times more selective for the PDE5 than the PDE11 isoenzyme than sildenafil and vardenafil, which have much higher selectivity ratios. The low selectivity ratio of tadalafil for PDE11, an isoenzyme heavily concentrated in the testes and skeletal muscle, led investigators to conduct safety studies to ascertain what effect tadalafil would have on spermatogenesis. However, 6-month, daily-dosing, placebo-controlled studies with 10 and 20 mg/day of tadalafil produced no clinically relevant effect on spermatogenesis as measured by sperm count and sperm morphology and motility. Additionally, no effect was observed on hormones related to spermatogenesis (luteinizing hormone, FSH, testosterone) with chronic tadalafil use.19

Hemodynamic Effect

The PDE5 inhibitors all work as vasodilators. Because PDE5 is found in the smooth muscle of the systemic arteries and veins, these agents all have potential to interact with the cardiovascular system. Since many men with ERD also have coexisting hypertension, diabetes, and cardiovascular disease, significant hemodynamic effects from PDE5 inhibitor use could be clinically important. Table 4 summarizes the hemodynamic changes seen with the PDE5 inhibitors in normal healthy volunteers and patients with coronary artery disease. All 3 agents produce minor changes in systolic and diastolic blood pressure, but these changes do not alter response to exercise testing. Careful analysis of population data and vardenafil, sildenafil, and tadalafil clinical data do not show an increase in serious cardiac events associated with PDE5 inhibitor use.15,20-24

All PDE5 inhibitors are contraindicated with concomitant administration of nitrates because significant hypotension can result. Sildenafil, vardenafil, and tadalafil are also contraindicated for use with alpha-blockers for the same reason. One exception to this rule is that tadalafil can be safely administered with tamsulosin 0.4 mg daily.14-16

Effect on Cardiac Conduction

Vardenafil in therapeutic (10 mg) and supratherapeutic (80 mg) doses produced increases in the QT interval similar to that of 400 mg of moxafloxacin. While the clinical impact of these changes is unknown, the coadministration of vardenafil with Class IA and Class III antiarrhythmic medications should be avoided. Patients with congenital QT prolongation should also avoid vardenafil use.15

IV. Pharmacokinetics

The pharmacokinetics of the ERD agents are summarized in Table 5. Sildenafil and vardenafil reach peak plasma concentrations at about 1 hour after administration; tadalafil reaches peak concentrations at 2 hours. Although not well studied, efficacy data for all 3 PDE5 inhibitors indicate that onset of action is earlier (17 to 40 minutes) than when peak serum concentrations are reached.25-28 Although all 3 PDE5 inhibitors vie for the claim of earliest onset, only well-designed comparative studies will help answer the question of which agent is the fastest acting. There are no studies that directly compare the onset, duration, or overall efficacy of the PDE5 inhibitors. Unlike sildenafil and vardenafil, peak serum concentrations of tadalafil are not affected by a high-fat meal.14-16 All 3 PDE5 inhibitors undergo extensive hepatic metabolism and require some dosage adjustment with hepatic dysfunction. The most striking difference between tadalafil, vardenafil, and sildenafil is the long half-life of tadalafil (17.5 hours). This long half-life translates into a prolonged duration of action for tadalafil (up to 36 hours), earning it the name of “le weekend” drug in France.
The bioavailability of intracavernous administration of alprostadil has not been studied. The absorption with transurethral administration of alprostadil appears to be biphasic, with 80% of the dose being absorbed within 10 minutes. The onset of action after intracavernous injection is within 2 to 5 minutes of administration. The onset of action after transurethral administration is slower, at about 5 to 10 minutes. Following intracavernous and transurethral administration of alprostadil, the drug is either metabolized locally or cleared from the penis into the systemic circulation and then metabolized by the lungs. The mean peripheral plasma concentrations are not significantly greater than baseline levels of endogenous alprostadil. The metabolites are excreted primarily by the kidney. Within 24 hours following administration, about 90% of the dose was excreted in urine, and the remaining 10% was excreted in feces. The effect of age, gender, and renal or hepatic failure on the pharmacokinetics of alprostadil has not been evaluated. However, patients with pulmonary disease may have reduced ability to clear the drug because of pulmonary first-pass metabolism of prostaglandin E1.

### V. Clinical Trials

#### Table Organization

The clinical efficacy of the PDE5 inhibitors and intracavernous and transurethral alprostadil are summarized in Tables 6 through 9. The tables are organized in the following manner:

- Pivotal placebo-controlled trials in the general ERD population (Table 6)
- Pivotal placebo-controlled studies in special populations: subjects with ERD associated with diabetes, postprostatectomy, spinal cord injury, depression, and antidepressant use (Table 7)
- Comparative clinical studies (Table 8)
- Efficacy in ERD patients who have failed previous drug therapy (Table 9)

#### Considerations in the Interpretation of ERD Drug Trials

There are no head-to-head studies comparing the efficacy of one PDE5 inhibitor with another. While it may be tempting to compare the efficacy results seen with tadalafil and vardenafil with sildenafil, this practice is fraught with error since studies may have differing designs, study populations (age, ERD etiology, ERD severity, comorbidity, prior ERD drug use), and outcomes measures.

#### Outcomes Measures Used in ERD Drug Trials

There are several primary and secondary efficacy measures commonly used in ERD clinical studies. The most common included the International Index of Erectile Function (IIEF), Sexual Health Inventory for Men (SHIM), Sexual Encounter Profile (SEP) Diary, and global assessment questions. A brief definition of each measurement tool is provided.

#### International Index of Erectile Function (IIEF)

The IIEF is a validated self-administered questionnaire used to assess therapeutic efficacy of ERD therapy. It is comprised of 5 domains:

1. Erectile function (Questions 1-5 and 15, total maximum score of 30; score of 26 = normal erectile function; 22-25 = mild ERD; 17-21 = mild-to-moderate ERD; 11-16 = moderate ERD; and 1-10 = severe ERD). Of the ERD domain questions, 2 questions are often isolated as separate outcomes measures. The questions are: “When you attempted intercourse, how often were you able to penetrate your partner?” (IIEF question 3) and “During sexual intercourse, how often were you able to maintain your erections?” (IIEF question 4).
2. Libido
3. Orgasmic function
4. Sexual satisfaction
5. Overall satisfaction

IIEF outcomes may be reported in a variety of ways: change...
IIEF erectile function domain Q.3 (penetration) and Vardenafil significantly improved all IIEF domain scores vs. placebo

Headache, blurry vision, and dyspepsia were the most common events. 48% of the men on sildenafil had at least 1 adverse event compared with placebo.

Additional analyses were conducted to assess efficacy in the following subgroups: age 65 years, Asians, African Americans, severity of ERD, HTN, vascular disease, diabetes, depression, or psychogenic ERD, history of radical prostatectomy, and spinal cord disorders. While degree of efficacy varied among subgroups, all sildenafil participants had significantly higher efficacy measures than the respective placebo groups.

% improvement in erections: vardenafil 65%-85% vs. placebo 28%, RBI 3.1 (CI, 2.7-3.8)

% vaginal penetration: vardenafil 65%-80% vs. placebo 52%, P<0.001

% maintenance of erection: vardenafil 50%-65% vs. placebo 32%, P<0.001

% improvement in erections: vardenafil 65%-85% vs. placebo 28%, P<0.001

Comments:

- 30%-45% of patients in each treatment group had severe ERD at baseline.
- Efficacy increased with increasing vardenafil dose.

Results:

- All dosage levels of vardenafil significantly improved IIEF scores and global efficacy as compared with placebo.
- 50 mg (76% vs. 27%; WMD 2.8; CI, 2.3-3.4)
- 100 mg (82% vs. 25%; WMD 3.2; CI, 2.7-3.8)

Design and baseline characteristics:

- MC, R, PC, fixed-dose study
- Mean age: 52 years
- Ethnicity: white 70%, African American 5%
- Baseline ERD severity: mild 26%-28%, moderate 34%-37%, severe 32%-36%
- Prior sildenafil use: 50% or placebo x 12 weeks

Results:

- Mean % successful intercourse: 25 mg (43% vs. 17%; WMD 26; CI, 18-35)
- 50 mg (50% vs. 14%; WMD 36; CI, 30-42)
- 100 mg (51% vs. 14%; WMD 36; CI, 31-42)

Comments:

- Mean % successful intercourse: 57% vs. 21%, WMD 34% (CI, 29-38)
- % improvement in erection: 78% vs. 25%, RBI 3.1 (CI, 2.7-3.5)
- IIEF Q.3 scores: 3.8 vs. 2.3, WMD 1.4, CI, 1.3-1.5
- IIEF Q.4 scores: 3.6 vs. 2.1, WMD 1.5, CI, 1.4-1.6

Results:

- Flexible-dose design: sildenafil vs. placebo
- Mean % successful intercourse: 57% vs. 21%, WMD 34% (CI, 29-38)
- % improvement in erection: 78% vs. 25%, RBI 3.1 (CI, 2.7-3.5)
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- 48% of the men on sildenafil had at least 1 adverse event compared with 36% of men on placebo (RRI 1.4, CI 1.3-1.6)
- Most common events were headache (11%), flushing (12%), dyspepsia (5%), and visual disturbances (3%)
- Differences in angina or cardiac chest pain did not reach statistical significance nor did rates of myocardial infarction or death.

Results:

- Efficacy increased with increasing vardenafil dose.
- 50 mg (76% vs. 27%; WMD 2.8; CI, 2.3-3.4)
- 100 mg (82% vs. 25%; WMD 3.2; CI, 2.7-3.8)

Design and baseline characteristics:

- MC, R, PC, 4-arm, parallel group, fixed-dose study
- Mean age: 57 years
- Etiology of ERD: organic 59%, psychogenic 8%, mixed 33%
- Duration: 6 years
- Comorbidities: HTN 37%, diabetes 18%
- Prior sildenafil use: 71%, no sildenafil failures

Drug regimen and duration:

- Vardenafil 5 mg (N = 205), 10 mg (N = 206), 20 mg (N = 197); placebo (N = 197)
- Duration: 26 weeks

Outcomes measures: IIEF erectile function domain Q.3 (penetration) and Q.4 (maintenance of erection), global efficacy Q.1

Results:

- All dosage levels of vardenafil significantly improved IIEF scores and global efficacy as compared with placebo.
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TABLE 6  Erectile Dysfunction Placebo-Controlled Studies: General Population (continued)

Comments:
• Compared with placebo, tadalafil significantly improved all efficacy outcomes.
• High placebo response rate reflects higher proportion of subjects with mild ERD at study entry.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and baseline characteristics</th>
<th>Drug regimen and duration</th>
<th>Outcomes measures:</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linet36 (1993) Intracavernous Alprostadil vs. Placebo N = 296</td>
<td>MC, DB, R, parallel design, fixed-dose study</td>
<td>Caverject (intracavernous alprostadil) 2.5 mcg (N = 57), 5.0 mcg (N = 60), 10 mcg (N = 62), 20 mcg (N = 58), placebo (N = 59)</td>
<td>clinical evaluation of erection quality, RigiScan evaluation of erection quality</td>
<td>No response to placebo by either clinical or RigiScan evaluation. Men responding with full erection ranged from roughly 20% (2.5 mcg dose) to 50% (20 mcg dose) by either clinical or RigiScan assessment.</td>
<td>Prolonged erections occurred in 5 men; in 2 men, the erections lasted 4 hours or more. Mean duration of erection was related to dose. Penile pain was reported by 23% of the men on intracavernous alprostadil.</td>
</tr>
<tr>
<td>Albrecht abstract37 (1997) Intracavernous Alprostadil vs. Placebo N = 233</td>
<td>PC, DB, MC, crossover study</td>
<td>In-office dose titration phase: Study 1 (N = 85) Edex (intracavernous alprostadil) 1 mcg-20 mcg or placebo Home phase: Study 2 (N = 158) Intracavernous alprostadil 1 mcg-40 mcg or placebo Study 1 responders continued with the home phase; patients continued on optimal dose for 1 week then crossed over to alternate treatment.</td>
<td>erection adequate for successful intercourse (physician and patient assessments)</td>
<td>Study 2. Home phase % adequate erections: intracavernous alprostadil 73%-74% vs. placebo 7%-13% Median time to erection: intracavernous alprostadil 10 minutes Median duration of erection: intracavernous alprostadil 59 minutes</td>
<td>Average intracavernous alprostadil dose not reported; little information provided in this abstract.</td>
</tr>
<tr>
<td>Hellstrom38 (1996) Transurethral Alprostadil vs. Placebo N = 68</td>
<td>MC, DB, PC study</td>
<td>MUSE (transurethral alprostadil) 125 mcg, 250 mcg, 500 mcg, or 1,000 mcg; placebo Duration: 2-4 weeks</td>
<td>erection assessment scale, % attainment full erection, % adequate erection for intercourse</td>
<td>75.4% of alprostadil patients attained full erection on at least 1 occasion vs. 12.7% on placebo. 49% of alprostadil patients achieved adequate erection for intercourse on at least 1 occasion.</td>
<td>Prolonged erection (4-6 hours): intracavernous alprostadil 3% vs. placebo 0.4% Bleeding: intracavernous alprostadil 6% vs. placebo 3% Pain: intracavernous alprostadil 31% vs. placebo 9%</td>
</tr>
<tr>
<td>Padma-Nathan39 (1997) Transurethral Alprostadil vs. Placebo N = 1,511</td>
<td>MC, DB, PC study</td>
<td>MUSE (transurethral alprostadil) 125 mcg-1,000 mcg 3 month, at-home phase (transurethral alprostadil responders) Transurethral alprostadil (N = 485), placebo (N = 511)</td>
<td>erection assessment scale (score 4 or 5 considered a response), patient diary, % patients with at least 1 successful intercourse</td>
<td>In-clinic phase: 66% of men had at least 1 erection adequate for intercourse. At-home phase: transurethral alprostadil vs. placebo; erections resulting in intercourse: 65% vs. 19%, P&lt;0.001</td>
<td>Efficacy was similar regardless of age or ERD etiology. 11% of subjects reported mild penile pain. No reports of priapism. Hypotension occurred in 3% of alprostadil treated patients.</td>
</tr>
</tbody>
</table>

CI = confidence interval; DB = double blind; ERD = erectile dysfunction; HTN = hypertension; IIEF = International Index of Erectile Function; MC = multicenter; MUSE = Medicated Urethral System for Erection; PC = placebo controlled; Q = question; R = randomized; RBI = relative benefit increase; RRI = relative risk increase; SEP = Sexual Encounter Profile; WMD = weighted mean difference.

IIEF Question 3 or SEP Question 2: “When you attempted intercourse how often were you able to penetrate your partner?” IIEF Question 4 or SEP Question 3: “During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?”; global efficacy question 1: “Did treatment improve your erections”; global efficacy question 2: “Did treatment improve your ability to have sexual intercourse?”

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### Table 7: Erectile Dysfunction Placebo-Controlled Studies: Special Populations

#### Rendell\(^40\) (1999) Sildenafil vs. Placebo in Diabetic Population  \(N = 268\)

**Design and baseline characteristics:**
- MC, R, DB, PC, flexible-dose-escalation study
- Patient age: mean age 55 years; 21% \(\geq\) 65 years
- Comorbid conditions: type 1 diabetes 19%, type 2 diabetes 81%, HTN 53%, ischemic heart disease 26%
- ERD type (all patients): organic 96%, mixed 4%
- Duration: 5.3-5.8 years

**Drug regimen and duration:**
- Sildenafil (\(N = 136\))
  - 25 mg-100 mg as needed but no more than once daily
- Placebo (\(N = 132\))
  - Duration: 12 weeks

**Outcomes measures:** mean % successful intercourse, global efficacy (improvement in erections), IIEF score Q.3, IIEF score Q.4, IIEF erectile domain

**Results:**
- Mean % successful intercourse: Sildenafil vs. placebo
  - 48% vs. 12%, \(P < 0.001\)
- % improvement in erections: Sildenafil vs. placebo
  - 3.2 vs. 2.0, \(P < 0.001\)

#### Boulton\(^41\) (2001) Sildenafil vs. Placebo in Diabetic Population  \(N = 219\)

**Design and baseline characteristics:**
- MC, R, DB, PC study
- Mean age: 59 years
- Comorbidities: type 2 diabetes

**Drug regimen and duration:**
- Sildenafil (\(N = 110\))
  - 25 mg-100 mg as needed but no more than once daily
- Placebo (\(N = 109\))
  - Duration: 12 weeks

**Outcomes measures:** global efficacy (improvement in erections), IIEF score Q.3, IIEF score Q.4, IIEF erectile domain

**Results:**
- Mean % successful intercourse: Sildenafil vs. placebo
  - 3.42 vs. 1.86, \(P < 0.001\)
- % improvement in erections: Sildenafil vs. placebo
  - 2.9 vs. 1.6, \(P < 0.001\)

#### Stuckey\(^42\) (2003) Sildenafil vs. Placebo in Diabetic Population  \(N = 188\)

**Design and baseline characteristics:**
- MC, R, DB, PC, flexible-dose-escalation study
- Mean age: 48 years
- Etiology of ERD: type 1 diabetes
- Comorbidities: HTN 32%, cardiovascular disease 36%

**Drug regimen and duration:**
- Sildenafil (\(N = 95\))
  - 25 mg-100 mg as needed but no more than once daily
- Placebo (\(N = 93\))
  - Duration: 12 weeks

**Outcomes measures:** global efficacy (improvement in erections), IIEF score Q.3, IIEF score Q.4, IIEF erectile domain

**Results:**
- % improvement in erections: Sildenafil vs. placebo
  - 56% vs. 10%, \(P < 0.001\)

(Continued on next page)
TABLE 7  Erectile Dysfunction Placebo-Controlled Studies: Special Populations (continued)

**Outcomes measures:** IIEF erectile domain, SEP Q.2 (penetration), SEP Q.3 (successful intercourse), global efficacy (improvement in erections and improvement in sexual activity)

**Results:**
- Tadalafil vs. placebo
  - Improvement in IIEF score
    - 6.4-7.3 vs. 0.1, *P*<0.001
    - SEP Q.3: 28-29% vs. 1.9%, *P*<0.001
    - SEP Q.2: 22% vs. no response, *P*<0.001
  - Improvement in erections and sexual activity
    - 50%-64% vs. 25%, *P*<0.001

**Comments:** Response rates are lower in this study; however, >72% of subjects had severe ERD by IIEF scores at study entry.

**Tadalafil vs. Placebo in Postprostatectomy ERD**

**N = 91**

**Design and baseline characteristics:**
- Open-label, retrospective study
- Mean age: 62 years
- ERD etiology: post radical prostatectomy
- Prostatectomy types: bilateral nerve sparing 58%, unilateral nerve sparing 13%, non-nerve sparing 29%

**Drug regimen and duration:**
- Sildenafil 50 mg-100 mg (N = 91)
- Trial of 6-8 tablets

**Outcomes measures:** IIEF erectile domain, IIEF Q.3, Q.4, Cleveland Clinic postprostatectomy questionnaire

**Results:**
- IIEF responders: bilateral nerve sparing 72%, unilateral nerve sparing 50%, non-nerve sparing 15%

**Comments:**
- Patients took an average of 6-8 doses of sildenafil.
- Higher response rates with bilateral nerve-sparing procedures

**Raina** (2003)  **Sildenafil in Postprostatectomy ERD**  **N = 48**

**Design:**
- Open-label, retrospective, 3-year follow-up of sildenafil responders from the Zippe**44** (2000) study
- Mean age: 62 years
- ERD etiology: post radical prostatectomy
- Prostatectomy types: bilateral nerve sparing 58%, unilateral nerve sparing 13%, non-nerve sparing 29%

**Drug regimen and duration:**
- Sildenafil 50 mg-100 mg (N = 48)
- Trial of 6-8 tablets

**Outcomes measures:** SHIM (measures erectile functioning)

**Results:**
- At 3 years, 71% of original sildenafil responders were still responders. Of the 71% responders, 31% increased the sildenafil dose from 50 mg to 100 mg.

**Comments:**
- Drop-out rate was 27%.
- Half of the discontinuations were from return of natural erections, 5 from loss of efficacy, and 1 from death of spouse.

**Zagaja** (2000)  **Sildenafil in Postprostatectomy ERD**  **N = 120**

**Design:**
- Open-label, retrospective study
- Age: <55 years 23%, 56-65 years 54%, >65 years 23%
- ERD etiology: post radical prostatectomy
- Prostatectomy types: bilateral nerve sparing 49%, unilateral nerve sparing 34%, non-nerve sparing 17%

**Drug regimen:**
- Sildenafil 50 mg-100 mg (N = 120)

**Results:**
- Response rates by age
  - Bilateral nerve sparing
    - Age <55 years: 80%
    - Age ≥55 years: 40%
  - Unilateral nerve sparing
    - Age 56-65 years: 45%
    - Age >66 years: 33%

**Non-nerve sparing: no response**

**Comments:** Highest response rates with younger age and bilateral nerve-sparing procedure.

**Brock** (2003)  **Vardenafil vs. Placebo in Postprostatectomy ERD**  **N = 440**

**Design and baseline characteristics:**
- R, DB, PC, parallel group, fixed-dose study
- Patient age: 60 years
- ERD type: post prostatectomy, 73% had bilateral nerve-sparing procedures
- ERD severity: moderate 12%-19%, mild-moderate 11%-14%
- Comorbidities: HTN 29%-32%, hypercholesterolemia 21%, depression 1%-7%, past smoker 46%-55%
- Prior sildenafil use: 80%

**Drug regimen and duration:**
- Vardenafil 10 mg (N = 146)
- Vardenafil 20 mg (N = 149)
- Placebo (N = 145)
- Duration: 12 weeks

**Outcomes measures:** IIEF erectile function domain scores, SEP Q.2 (penetration), SEP Q.3 (successful intercourse), global efficacy (improvement in erections)

**Results:**
- Global efficacy-improvement
  - 60%-65% vs. 13%, *P*<0.001
  - Improvement in SEP Q.3 by baseline ERD severity
    - Mild-moderate 70%-74% vs. 48%
    - Moderate 32%-67% vs. 19%
    - Severe 24%-28% vs. 4%

**Comments:** Patients with mild ERD at study entry had the highest response rates.

**Data on file, Eli Lilly and Company**

**JMCP**  **Tadalafil vs. Placebo in Postprostatectomy ERD**  **N = 303**

**Design and baseline characteristics:**
- MC, R, DB, PC, parallel group, fixed-dose study
- Mean age: 60 years
- Etiology of ERD: bilateral nerve-sparing prostatectomy
- ERD severity: severe ERD 63%

**Drug regimen and duration:**
- Tadalafil 20 mg (N = 201)
- Placebo (N = 102)
- Duration: 12 weeks

**Outcomes measures:** IIEF erectile function domain scores, SEP Q.2 (penetration), SEP Q.3 (successful intercourse), global efficacy (improvement in erections)

**Results:**
- Global efficacy-improvement
  - 60%-65% vs. 13%, *P*<0.001
  - Improvement in IIEF scores by baseline ERD severity
    - Mild-moderate 25%-26% vs. 16%
    - Moderate 19%-23% vs. 13%
    - Severe 11%-13% vs. 7%

**Comments:** Patients with mild ERD at study entry had the highest response rates.

(Continued on next page)
TABLE 7 Erectile Dysfunction Placebo-Controlled Studies: Special Populations (continued)

<table>
<thead>
<tr>
<th>Results:</th>
<th>Tadalafil vs. placebo</th>
<th>SEP Q.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in IIEF</td>
<td>54% vs. 32%, P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>5.3 vs. 1.1, P&lt;0.001</td>
<td>SEP Q.3</td>
<td></td>
</tr>
<tr>
<td>41% vs. 19%, P&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comments:</th>
<th>All patients had bilateral nerve-sparing procedures, which are associated with a higher treatment success rate than unilateral or non-nerve-sparing procedures.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adverse events included headache, dyspepsia, myalgia, back pain, nasal congestion, flushing, and fatigue.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Sildenafil vs. Placebo in the Spinal Cord Injury Population N = 178</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design and baseline characteristics:</td>
<td>R, DB, PC, 2-way crossover, flexible-dose-escalating study</td>
</tr>
<tr>
<td>Mean age:</td>
<td>38 years</td>
</tr>
<tr>
<td>Etiology of ERD:</td>
<td>post-SCI</td>
</tr>
</tbody>
</table>

| Drug regimen and duration: | Sildenafil 50 mg-100 mg or placebo for 6 weeks then crossover to placebo or sildenafil for an additional 6 weeks |
| Duration: | 6 weeks on each treatment |
| Median 8.3 doses of sildenafil |

| Outcomes measures: | global efficacy question (improvement of erections), % of successful intercourse attempts, IIEF erectile function domain Q.3 (penetration) and Q.4 (erection maintenance) |

<table>
<thead>
<tr>
<th>Results:</th>
<th>Sildenafil vs. placebo % of successful intercourse attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of erections</td>
<td>55% vs. 0%, P&lt;0.001</td>
</tr>
<tr>
<td>78% vs. 4%, P&lt;0.0001</td>
<td>Significant improvement in scores for IIEF Q.3 and Q.4 for sildenafil vs. placebo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comments:</th>
<th>Most common adverse events were headache, facial flushing, nasal congestion, dyspepsia, and visual disturbances.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Significant improvement persisted even when patients with no residual erectile function at baseline were included.</td>
</tr>
<tr>
<td></td>
<td>Response to sildenafil for subjects with SCI is comparable to response seen in ERD subjects with other comorbid conditions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Sildenafil vs. Placebo in Patients With Depression N = 152</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design and baseline characteristics:</td>
<td>MC, R, DB, PC, flexible-dose-escalating study</td>
</tr>
<tr>
<td>Mean age:</td>
<td>56 years</td>
</tr>
<tr>
<td>Etiology of ERD:</td>
<td>major depressive disorder (untreated)</td>
</tr>
<tr>
<td>Duration of ERD:</td>
<td>5.7 years</td>
</tr>
<tr>
<td>Severity of depression:</td>
<td>mild 61%, moderate 35%, severe 4%, mean HAM-D score 16.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results:</th>
<th>Sildenafil vs. placebo % of successful intercourse attempts</th>
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</thead>
<tbody>
<tr>
<td>Improvement of erections</td>
<td>55% vs. 0%, P&lt;0.001</td>
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<tr>
<td>78% vs. 4%, P&lt;0.0001</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Sildenafil vs. Placebo in Patients With Depression N = 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design and baseline characteristics:</td>
<td>R, PC, DB, parallel group, flexible-dose study</td>
</tr>
<tr>
<td>Mean age:</td>
<td>45 years</td>
</tr>
<tr>
<td>Etiology of ERD:</td>
<td>secondary to SSRI antidepressant treatment</td>
</tr>
<tr>
<td>Subjects in remission from depression</td>
<td>Mean SSRI use: 27 months</td>
</tr>
</tbody>
</table>

| Drug regimen and duration: | Sildenafil 25 mg-100 mg (N = 74) |
| Placebo (N = 78) |
| Duration: | 12 weeks |

| Outcomes measures: | global efficacy questions, IIEF erectile domain function, treatment response: yes to global efficacy questions 1-2 and score ≥21 on erectile dysfunction domain of IIEF questionnaire |
| HAM-D: Beck Depression inventory; life satisfaction checklist |

<table>
<thead>
<tr>
<th>Results:</th>
<th>Sildenafil vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in CGI-SF (primary measure)</td>
<td>54.5% vs. 44.4%, P&lt;0.001</td>
</tr>
<tr>
<td>IIEF erectile function and other overall satisfaction measures were significantly improved for sildenafil subjects vs. placebo</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comments:</th>
<th>Mean depression scores remained constant and were consistent with remission.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Headache, dyspepsia, flushing, nasal congestion, palpitations, insomnia, and abnormal vision were most frequent adverse events.</td>
</tr>
</tbody>
</table>

CGI-SF = Clinical Global Impression-Sexual Function; DB = double blind; ERD = erectile dysfunction; HAM-D = Hamilton Depression Scale; HTN = hypertension; IIEF = International Index of Erectile Function; MC = multicenter; PC = placebo controlled; Q = question; R = randomized; SCI = spinal cord injury; SEP = Sexual Encounter Profile; SHIM = Sexual Health Inventory for Men; SSRI = selective serotonin reuptake inhibitor.

IIEF Question 3 or SEP Question 2: “When you attempted intercourse how often were you able to penetrate your partner?” IIEF Question 4 or SEP Question 3: “During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?”; global efficacy question 1: “Did treatment improve your erections?”; global efficacy question 2: “Did treatment improve your ability to have sexual intercourse?”
in IIEF score from baseline, normalization of IIEF erectile function domain, mean improvement in erectile function score, and percentage improvement over baseline, to name a few.

**Sexual Health Inventory for Men (SHIM)**

The SHIM is an abbreviated version of the IIEF questionnaire and was designed to allow a more rapid diagnosis of ERD and assignment of ERD severity. The instrument has 6 questions, with a maximum score of 30. ERD is present if the SHIM score is 21 or less. The SHIM primarily measures erectile function, and was designed to allow a more rapid diagnosis of ERD and assessment of ERD severity. The instrument has 6 questions, with a maximum score of 30. ERD is present if the SHIM score is 21 or less. The SHIM primarily measures erectile function, and it does not address measures of orgasmic function, libido, and satisfaction.

**Sexual Encounter Profile (SEP) Diary**

Assessments of individual sexual encounters are provided by SEP diaries. The SEP diary is intended to be an immediate-recall diary of encounters. The diaries contain 6 questions for the patient and 4 questions for the partner. SEP questions 2 and 3 are very similar to questions 3 and 4 of the IIEF erectile dysfunction domain. However, the SEP questions are answered yes or no while the IIEF questions are assigned a numerical score.

**Global Assessment or Global Efficacy Questions**

Global assessment or efficacy questions are often used as secondary outcomes measures. The 2 most common questions are: “Did this treatment improve your erections?” and “Did treatment improve your ability to have sexual intercourse?”

**Clinical Efficacy Summary**

**General ERD Population: PDE5 Inhibitors**

Sildenafil, vardenafil, and tadalafil significantly improve IIEF erectile function domain scores and improve erection quality as compared with placebo in large, double-blind, randomized, controlled trials in the general ERD population. There are several outcomes measurements reported in ERD clinical studies,
**TABLE 9** Miscellaneous Studies: Failed Previous Erectile Dysfunction Therapy

<table>
<thead>
<tr>
<th>Description</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edex (Intracavernous Alprostadil) in Sildenafil Failures</td>
<td>134</td>
</tr>
<tr>
<td>Shabsigh56 (2000)</td>
<td></td>
</tr>
</tbody>
</table>

Design and baseline characteristics:
- MC, open-label study
- Mean age: 59 years
- Etiology of ERD: organic 92%-98%

Dosage regimen and duration:
- Subjects treated with sildenafil 5 mg-100 mg for 4 weeks (N = 134)
- Nonresponders or partial responders (N = 67) with IIEF score of 3 or less given intracavernous alprostadil and titrated in-office until response (up to 40 mcg)
- 6 weeks of treatment with on demand intracavernous alprostadil

Outcomes measures: IIEF erectile domain scores, SEP Q.2 (penetration), SEP Q.3 (maintenance of erection for successful intercourse), global assessment Q.1 (improvement of erections)

Results:
- Vardenafil vs. placebo SEP Q.3: 17.6 vs. 10.5, P < 0.001
- SEP Q.2: 62.3% vs. 29.9%, P < 0.001
- Improvement in erections: 61.6% vs. 14.7%, P < 0.001

Comments:
- Most common adverse events were headache, dyspepsia, nasal congestion, and flushing.

**Outcomes measures**: IIEF Q.3 (penetration) and Q.4 (maintenance of erection for successful intercourse), erectile response score (physician and patient assessment)

**Results**:
- In-office phase
  - Mean dose of intracavernous alprostadil 28 mcg
  - 94% of patients were able to achieve an adequate erectile response as per physician assessment.
- At-home phase
  - 88% of intracavernous alprostadil subjects in 6-week at-home phase had erections adequate for intercourse.
  - 89% and 85% of patients had an improvement of 1 or more in IIEF score for Q.3 and Q.4, respectively.

Comments:
- Most frequent adverse events with intracavernous alprostadil were pain, paresthesias, and influenza-like symptoms.
- Subjects were considered to be sildenafil “failures” even if they had adequate response for 50% of all attempts.

**Outlines of key studies**

- **Engel57 1998**
  - MUSE (Transurethral Alprostadil) in ICI PGE1, Papaverine or Phentolamine Failures (N = 452)
  - Design and baseline characteristics:
    - PC, DB, retrospective study
    - Included some ERD patients not responsive to ICI of alprostadil (PGE1), 95/452; papaverine or phentolamine
  - Mean age: 60 years
  - Dosage regimen and duration:
    - In-office phase
      - Titration to response with 125 mcg-1,000 mcg of transurethral alprostadil
    - At-home phase
      - 3 months treatment with transurethral alprostadil or placebo
  - Outcomes measures: Physician and patient assessment of erection, patient diaries
  - Results:
    - 58% of patients previously unresponsive to ICI PGE1 achieved an adequate erection at least once during the in-office phase.
    - 47% of this group reported at least 1 successful intercourse during the at-home phase vs. 12% for placebo.
  - Most efficacy measures were significantly higher for transurethral alprostadil than placebo.
  - Comments:
    - Number of placebo administrations was much lower than the number of transurethral alprostadil administrations
    - Penile pain was the most common adverse event (7.8%)

- **Carson55 (2003)**
  - Vardenafil in Sildenafil Failures (N = 463)
  - Design and baseline characteristics:
    - DB, MC, PC, flexible-dose study
    - ERD severity: moderate to severe
    - Sildenafil failures defined as failure with sildenafil on at least 4 of 6 attempts with at least 1 failure at the 100 mg dosage level
  - Drug regimen and duration:
    - Vardenafil 10 mg (N = 231); titration to 5 mg or 20 mg could occur at 4 week intervals
    - Placebo (N = 226)
    - Duration: 12 weeks
  - Outcomes measures: IIEF erectile domain scores, SEP Q.2 (penetration), SEP Q.3 (maintenance of erection for successful intercourse), global assessment Q.1 (improvement of erections)
  - Results:
    - Vardenafil vs. placebo SEP Q.3: 46% vs. 16%, P < 0.001
    - SEP Q.2: Improvement in erections: 61.6% vs. 14.7%, P < 0.001
  - Comments:
    - Most common adverse events were headache, dyspepsia, nasal congestion, and flushing.

- **Shabsigh56 (2000)**
  - Edex (Intracavernous Alprostadil) in Sildenafil Failures (N = 134)
  - Design and baseline characteristics:
    - MC, open-label study
    - Mean age: 59 years
    - Etiology of ERD: organic 92%-98%
  - Dosage regimen and duration:
    - Subjects treated with sildenafil 5 mg-100 mg for 4 weeks (N = 134)
    - Nonresponders or partial responders (N = 67) with IIEF score of 3 or less given intracavernous alprostadil and titrated in-office until response (up to 40 mcg)
    - At-home phase
      - 6 weeks of treatment with on demand intracavernous alprostadil
  - Outcomes measures: IIEF erectile domain scores, SEP Q.2 (penetration), SEP Q.3 (maintenance of erection for successful intercourse), global assessment Q.1 (improvement of erections)
  - Results:
    - IIEF scores: 17.6 vs. 10.5, P < 0.001
    - SEP Q.2: 62.3% vs. 29.9%, P < 0.001
  - Comments:
    - Most frequent adverse events were pain, dyspepsia, nasal congestion, and flushing.

but perhaps the most meaningful improvement to the patient is the rate of successful intercourse. In a meta-analysis of 14 randomized, placebo-controlled, flexible-dose studies, the subjects on sildenafil 25 mg to 100 mg had a successful intercourse rate of 57% as compared with a rate of 21% with placebo. In general, higher sildenafil doses were associated with higher efficacy rates. Also included in the meta-analysis were additional analyses examining efficacy in subgroups stratified by age, race, ERD baseline severity, and ERD etiology. Sildenafil was as efficacious in the Asian and African American subjects as in the 25 mg, 50 mg, and 100 mg dose, respectively, as compared with the placebo group, which had rates of 14% to 17%. Combined data from 2 fixed-dose sildenafil studies showed a successful intercourse rate of 43%, 50%, and 51% for the 25 mg, 50 mg, and 100 mg dose, respectively, as compared with the placebo group, which had rates of 14% to 17%. Combined data from 2 fixed-dose sildenafil studies showed a successful intercourse rate of 43%, 50%, and 51% for
whites, who comprise the majority of subjects in ERD studies. While the rate of successful intercourse varied depending on age, ERD severity, and ERD etiology, sildenafil use resulted in significantly greater rates for each subgroup as compared with placebo.\textsuperscript{31}

In one large, randomized, fixed-dose study, vardenafil, at doses ranging from 5 mg to 20 mg, was able to produce a significantly greater rate of erections adequate for intercourse—50% to 65%—compared with a placebo rate of 32%, which is higher than the reported placebo average of 20%. The high placebo rate seen in this study is intriguing because 30% to 45% of subjects were classified by investigators as having severe ERD. An increase in efficacy was seen with increasing vardenafil dose.\textsuperscript{19} Vardenafil significantly improved IIEF erectile function domain scores as compared with placebo regardless of patient age, ERD etiology, or baseline ERD severity.\textsuperscript{33}

In an integrated analysis of 5 multicenter, double-blind, randomized, fixed-dose studies, tadalafil 2.5 mg, 5 mg, 10 mg, and 20 mg resulted in significantly higher rates of successful intercourse, 36%, 42%, 61%, and 75%, respectively, compared with a placebo rate of 32%.\textsuperscript{34} Another multicenter, double-blind, randomized, fixed-dose study compared the duration of efficacy of 20 mg tadalafil with placebo.\textsuperscript{35} At 24 hours postadministration, a 53% rate of successful intercourse attempts was reported in the tadalafil group compared with a 29% rate in the placebo group. Tadalafil remained significantly more efficacious than placebo at 36 hours postdose, with a rate of 59% compared with 28%.\textsuperscript{35} The results of this study confirm the long duration of tadalafil, which would be anticipated from its prolonged half-life of 17 hours.

No comparative studies have been done to assess relative efficacy of any one PDE5 inhibitor to another. Until large comparative studies prove otherwise, the efficacy of these products seems roughly equivalent; however, direct comparisons of efficacy and safety should not be made, given the many variables present in populations studied and outcomes measures used.

**General ERD Population: Alprostadil**

Intracavernous and transurethral administration of alprostadil, while not usually considered first-line therapy, is also effective in the management of ERD in the general population. In alprostadil studies, efficacy is most often measured by physician and patient assessment of erection quality. In one large, multicenter, randomized, fixed-dose study, intracavernous administration of alprostadil at doses of 2.5 mcg, 5 mcg, 10 mcg, and 20 mcg resulted in 20%, 30%, 35%, and 50%, respectively, of men achieving full erections.\textsuperscript{36} The mean duration of erection was 37 minutes, and the duration was related to dose. Five men had prolonged erections; in 2 men, the erections lasted 4 hours or more. Penile pain was reported by 23% of intracavernous alprostadil subjects. In a 6-month self-injection extension of the study, the intracavernous alprostadil responders reported being able to have intercourse after the injections 94% of the time.\textsuperscript{38} In another placebo-controlled crossover study, intracavernous alprostadil 1 mcg to 40 mcg resulted in 73% to 74% of erections deemed adequate for intercourse (patient assessment) as compared with rates of 7% to 13% for placebo.\textsuperscript{37} The median duration of erection was 59 minutes, and prolonged erections lasting 4 to 6 hours were noted in 3% of subjects taking intracavernous alprostadil. The average intracavernous alprostadil dose was not reported in this study. Penile pain and bleeding were other common adverse events.\textsuperscript{39}

Transurethral alprostadil was significantly more effective than placebo in 2 double-blind, placebo-controlled studies.\textsuperscript{38,39} In these studies, using transurethral alprostadil doses ranging from 125 mcg to 1,000 mcg, the rates of erections deemed adequate for intercourse were 49% to 66%. In the at-home phase of one of the studies, transurethral alprostadil resulted in a successful intercourse rate of 65% compared with a placebo rate of 19%. Incidence of penile pain ranged from 9% to 19%, hypotension was 3%, and there were no reports of priapism or prolonged erections.\textsuperscript{38,39}

Two open-label studies compared the efficacy of transurethral alprostadil versus intracavernous alprostadil. In one study, the intracavernous alprostadil product was an extemporaneous preparation\textsuperscript{53}; in the other, the Edex preparation was used.\textsuperscript{54} In both studies, intracavernous injections of alprostadil resulted in significantly higher erectile assessment scores or IIEF erectile function domain scores as compared with transurethral alprostadil. In one study, transurethral alprostadil was better tolerated with a lower discontinuation rate due to penile pain\textsuperscript{54}; however, the other study reported similar rates of penile pain and a marked patient preference for injection over transurethral therapy.\textsuperscript{54}

**General ERD Population: Failures on Previous ERD Therapy**

One open-label, multicenter study reported that intracavernous alprostadil, in doses up to 40 mcg, was effective in failures with sildenafil therapy. In this study, sildenafil failures had a score of 1.2 or less on the IIEF erectile domain questions 3 and 4. A score of 1 means that sildenafil was almost never or never effective. Use of intracavernous alprostadil resulted in the IIEF scores improving by 2.75 to 2.63 points for 85% to 90% of patients. Penile pain was present in 30% of all intracavernous alprostadil subjects.\textsuperscript{36}

One open-label, multicenter study examined the efficacy of vardenafil 5 mg to 20 mg in the treatment of ERD in 134 patients determined to be unresponsive to sildenafil. Unresponsiveness was defined as failure with sildenafil on at least 4 out of 6 attempts, with at least one of those attempts at the 100 mg dosage level. Sildenafil failures were randomized to receive either vardenafil (N = 231) or placebo (N = 226) for a treatment period of 12 weeks. Vardenafil use resulted in significantly higher IIEF erectile domain scores than placebo.
and higher rates of maintenance of erection sufficient for intercourse (46% vardenafil versus 16% placebo; \( P < .001 \)). Overall, 62% of vardenafil subjects stated that their erections were improved compared with 15% of those in the placebo group.37

**Special Populations**

**Diabetes**

Several double-blind, placebo-controlled studies have been performed to evaluate the efficacy of sildenafil, vardenafil, and tadalafil in the management of ERD associated with type 1 and type 2 diabetes.30-44 No direct comparative studies have been performed to assess relative efficacy of one PDE5 inhibitor to another. However, well-designed studies have reported the following rates of successful intercourse: sildenafil 48% versus placebo 12%; vardenafil 49% to 54% versus 23%; tadalafil 28% to 29% versus 1.9%.44 The lower success rate seen with tadalafil may be due to the high percentage (72%) of patients with severe ERD enrolled in the study.

**Postprostatectomy**

As with diabetes, several clinical studies have assessed the efficacy of all of the currently available PDE5 inhibitors in the management of ERD postprostatectomy. In this patient population, response to treatment is dependent on subject age, baseline ERD severity, and the type of prostatectomy surgery. In general, bilateral nerve-sparing surgery is associated with the best chance for response with non-nerve-sparing procedures having the lowest response to therapy. However all PDE5 inhibitors are potentially effective in the management of postprostatectomy ERD.31-40

**Post-Spinal-Cord Injury**

Of the PDE5 inhibitors, only sildenafil has been studied in the management of ERD resulting from spinal cord injury. This patient population differs not only in the etiology of ERD but also in age since the average spinal cord injury patient in clinical studies is much younger (38 years) as compared with the ERD patient in the general population (56 years). In one randomized, placebo-controlled crossover study in 178 spinal cord injury patients, doses of sildenafil 50 mg to 100 mg resulted in an intercourse success rate of 55% versus 0% for placebo. Thus, success rates for sildenafil in ERD secondary to spinal cord injury approach rates seen in subjects with other comorbid conditions.30

**Depression**

One double-blind, placebo-controlled study has evaluated the efficacy of sildenafil in the management of ERD in patients with depression. Most patients in this study had a diagnosis of mild or moderate major depression and were not treated with antidepressants. Sildenafil 25 mg to 100 mg or placebo was given for 12 weeks. At the end of the study, significantly more patients on sildenafil than placebo (73% versus 14%) had a treatment response as defined by IIEF erectile function treatment response questions and positive responses to 2 global efficacy questions. Successful treatment was also associated with an improvement in Hamilton Depression scores and quality-of-life measures.31 Sildenafil was more effective than placebo (55% versus 4.4%; \( P < .001 \)) in improving Clinical Global Impression-Sexual Function scores in a study with 90 patients with ERD secondary to treatment with selective serotonin reuptake inhibitor antidepressants. All patients were in remission from major depression and remained on antidepressants during treatment with sildenafil for 6 weeks.32

**Effectiveness Studies**

Overall, in controlled clinical studies, sildenafil has an efficacy rate of roughly 60% in the broad ERD population.31 However, in the real-world setting, refill rates for sildenafil are not as high as would be expected. Of patients tracked for 1 year, only 52% filled a second prescription during that 12-month period and 31% filled greater than 7 prescriptions.39 In another study, patients in a clinic were followed for 2 years to evaluate their response to sildenafil.39 Two surveys were conducted. The first survey went to 200 men who had recently been given a prescription for sildenafil. Of these 200 men, only 151 (75%) actually tried the drug. Of those who tried the drug, an overall success rate of 74% was reported. The most common doses used were 50 mg (n = 88) and 100 mg (n = 61). While 38% of patients reported side effects, none discontinued therapy from drug intolerance. Two years later, a second survey was sent out; only 82 patients participated. Of those patients, 17% discontinued because of loss of efficacy and 20% needed to increase their dose by 50 mg. There was no correlation between frequency of use and the need to increase the dose. While the authors concluded that tachyphylaxis to sildenafil was responsible for study results, it is not clear if this is the case.39 Other reasons for reduced effect over time could have included psychological factors as well as worsening of underlying comorbid conditions, especially progressive vascular disease or poorly controlled diabetes.

Efficacy results in controlled clinical studies are rarely, if ever, duplicated in the real-world setting, and the experience with ERD is no different. However, McCullough et al. did report on several studies designed to identify and improve success rates with sildenafil therapy.60 The intensive disease management approach utilized in one of the studies yielded impressive results. Overall, 55% of men not previously successful with sildenafil became successful after intensive reeducation and counseling, which included regular follow-up visits with information as to how to take the drug, titration to maximum dose, and a minimum trial of 8 attempts for efficacy assessment. Controlling risk factors for ERD as recommended in current treatment guidelines also was a successful strategy, although
men with only 1 risk factor were more likely to respond to intervention than men with multiple risk factors.60

### VI. Adverse Events

#### PDE5 Inhibitors

Tadalafil, sildenafil, and vardenafil were well tolerated in clinical studies with headache, flushing, and dyspepsia occurring as the most common adverse events. There are no comparative safety data to compare rates of common adverse events, but based on the rates seen in placebo-controlled studies, there appears to be little difference in safety profiles for these most commonly reported events. Discontinuations secondary to adverse events were low for all 3 PDE5 inhibitors, ranging from 1% to 5%. Changes in color vision, which has been reported with sildenafil use, are less frequent with vardenafil and rarely reported with tadalafil. However, tadalafil does seem to be associated with more reports of myalgia and back pain than vardenafil or sildenafil. The muscle aches and back pain usually occur within 12 to 24 hours after tadalafil administration and resolve within 48 hours. Approximately 0.5% of patients discontinued tadalafil because of back pain or myalgia.14-16

### Serious Cardiac Events

Cardiac mortality rates in the tadalafil clinical study database (N > 4,000 subjects) are consistent with the expected rate in a male population. Across all studies, the incidence rate of myocardial infarction was 0.43 per 100 patient years in the tadalafil-treated patients compared with 0.6 per 100 patient years in the placebo-treated population, which was also consistent with the incidence rate observed with an age-standardized male population.61

The cardiac safety of sildenafil has been extensively studied.

### TABLE 10 PDE5 Inhibitors: Selected Adverse Events Occurring >2% in Placebo-Controlled Studies14-16

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Sildenafil/Placebo (%)</th>
<th>Vardenafil/Placebo (%)</th>
<th>Tadalafil/Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16/4</td>
<td>15/4</td>
<td>11-15/5</td>
</tr>
<tr>
<td>Flushing</td>
<td>10/1</td>
<td>11/1</td>
<td>4-10/1</td>
</tr>
<tr>
<td>Rhinitis/nasal congestion</td>
<td>4/2</td>
<td>9/3</td>
<td>2-3/1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7/2</td>
<td>4/1</td>
<td>4-10/1</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>3/0</td>
<td>&lt;2</td>
<td>Rare, 1 episode reported</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>NR</td>
<td>3/1</td>
<td>NR</td>
</tr>
<tr>
<td>Increased creatinine kinase</td>
<td>NR</td>
<td>2/1</td>
<td>NR</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>NR</td>
<td>3/2</td>
<td>NR</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2/1</td>
<td>2/1</td>
<td>NR</td>
</tr>
<tr>
<td>Back pain</td>
<td>&lt;2</td>
<td>&lt;2</td>
<td>3-6/3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>&lt;2</td>
<td>&lt;2</td>
<td>1-4/1</td>
</tr>
<tr>
<td>NR = not reported.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 11 Selected Adverse Events: Intracavernous and Transurethral Alprostadil11-13

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Caverject (Intracavernous Alprostadil) (%)</th>
<th>Edex (Intracavernous Alprostadil) (%)</th>
<th>MUSE (Transurethral Alprostadil) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local side effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site ecchymosis</td>
<td>2</td>
<td>4</td>
<td>NR</td>
</tr>
<tr>
<td>Injection site hematoma</td>
<td>3</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>Penile edema</td>
<td>1</td>
<td>2</td>
<td>NR</td>
</tr>
<tr>
<td>Penile fibrosis</td>
<td>3</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>Penile pain</td>
<td>37</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>Penile rash</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Penis disorder</td>
<td>3</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>Prolonged erection</td>
<td>4</td>
<td>4 *</td>
<td>0.3</td>
</tr>
<tr>
<td>Priapism</td>
<td>0.4</td>
<td>&lt;1†</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Testicular pain</td>
<td>NR</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Urethral bleeding—minor</td>
<td>NR</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Urethral burning</td>
<td>NR</td>
<td>NR</td>
<td>12</td>
</tr>
<tr>
<td><strong>Systemic side effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>NR</td>
<td>2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>2</td>
<td>NR</td>
<td>4</td>
</tr>
</tbody>
</table>

* Erections lasting 4 to 6 hours. † Not listed, but < 1% rate of erections lasting >6 hours. NR = not reported.
Pooled results from 53 clinical studies indicated no difference between the incidence of death or myocardial infarction in men with ERD receiving sildenafil or placebo.62 In a United Kingdom study, 5,601 patients with ERD showed no evidence of increased risk of myocardial or ischemic heart disease during the first 4.9 months of sildenafil therapy.63 This low risk is supported by open-label safety data from subjects who have been taking sildenafil for up to 4.5 years.64

Vardenafil has been shown to prolong the cardiac conduction as evidenced by a prolonged QT interval at therapeutic and supratherapeutic doses (Section VII, Contraindications/Precautions).15

Intracavernosal and Transurethral Alprostadil
The type and degree of side effects reported in the 2 intracavernous alprostadil formulations are very similar.11-13 No controlled comparative studies are available that directly compared the adverse event rates of these 2 products. As might be expected from a penile injection, local side effects (ecchymosis, hematoma, edema, pain) are prominent with both. Transurethral alprostadil is also associated with a significant occurrence of penile pain, urethral burning, and bleeding. The 2 comparison studies that compared transurethral alprostadil with intracavernous alprostadil injections had conflicting results regarding penile pain and discontinuations due to adverse events.53,54 Prolonged erection or, in some cases, priapism, can occur with intracavernous alprostadil and transurethral alprostadil.11-13

VIII. Contraindications/Precautions
The contraindications, warnings, and precautions for sildenafil, tadalafil, and vardenafil are extremely similar (Table 12). Of note, vardenafil in therapeutic (10 mg) and supratherapeutic doses...
(80 mg) doses produced increases in the QT interval similar to that of 400 mg of moxifloxacin. While the clinical impact of these changes is unknown, the coadministration of vardenafil with Class IA and Class III antiarrhythmic medications should be avoided. Patients with congenital QT prolongation should also avoid vardenafil use.\textsuperscript{15}

The contraindications, warnings, and precautions for intracavernosal and transurethral products are exactly the same with one exception. Transurethral alprostadil should not be used for sexual intercourse with a woman who is...
pregnant or could become pregnant, unless the couple uses a condom barrier. This precaution is based on animal data that showed embryotoxic effects when alprostadil was administered as a subcutaneous bolus to pregnant female rats (transurethral alprostadil product information). Table 13 lists the contraindications, warnings, and precautions as stated in intracavernous and transurethral alprostadil product information.11-13

### VIII. Drug/Food Interactions

Drug and food interactions with PDE5 inhibitors are presented in Table 14.

### IX. Use in Pregnancy/Nursing

Transurethral alprostadil should not be used for sexual intercourse with a woman who is pregnant or could become pregnant, unless the couple uses a condom barrier.13

Vardenafil, sildenafil, and tadalafil are listed as Pregnancy Category B drugs. While no evidence of fetal or embryonic toxicity was found in animal studies, there are no adequate and well-controlled trials of vardenafil, sildenafil, or tadalafil in pregnant women.14-16

In animal studies, tadalafil and vardenafil were secreted into the milk of lactating rats at concentrations 2.4-fold (tadalafil) and 10-fold (vardenafil) greater than found in the plasma. It is not known if these agents are excreted in human breast milk. There is no information on sildenafil and lactation.14-16

### X. Indications/Dosing

The indications, usual adult dose, and dose for special populations for all FDA-approved ERD drugs are listed in Tables 15 and Table 16.11-16

### XI. Conclusion

All 3 PDE5 inhibitors have significant efficacy in the treatment of general ERD and ERD associated with diabetes and post-prostatectomy. Placebo-controlled trials have also shown sildenafil to have efficacy for patients with ERD associated with depression and spinal cord injury.

There are no head-to-head clinical studies comparing the efficacy and safety of sildenafil with vardenafil or tadalafil. Sildenafil has by far the highest number of controlled studies confirming its safety and efficacy and is recommended as first-line ERD therapy when a nonspecific therapy is appropriate. The PDE5 inhibitors differ in their duration of action. Sildenafil and vardenafil seem to have similar duration of action of about
4 hours, while tadalafil has a duration of action of up to 36 hours. This prolonged duration of action may be a significant advantage for tadalafil since it could allow for increased sexual spontaneity. However, from a side-effect standpoint, it may not be an advantage to have prolonged levels of tadalafil in the systemic circulation.

Tadalafil, sildenafil, and vardenafil have similar common and nonserious adverse events. Yet, tadalafil does have a higher rate of myalgias and back pain that can take several hours to resolve. Vardenafil and especially tadalafil seem to have less propensity for visual changes. However, vardenafil does produce changes in cardiac conduction at therapeutic doses.

<table>
<thead>
<tr>
<th>Decision Criteria</th>
<th>Sildenafil</th>
<th>Vardenafil</th>
<th>Tadalafil (Intracavernous Alprostadil)</th>
<th>Caverject (Intracavernous Alprostadil)</th>
<th>Edex (Intracavernous Alprostadil)</th>
<th>MUSE (Transurethral Alprostadil)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effectiveness outcomes</strong></td>
<td>Refill rate lower than would be expected from controlled clinical studies; real-world success rate optimized by education, follow up, and management of ERD risk factors</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Efficacy outcomes: POEM</td>
<td>Onset 30-40 minutes</td>
<td>Onset 30-40 minutes</td>
<td>Onset 16-40 minutes</td>
<td>Onset 5-20 minutes</td>
<td>Onset 5-20 minutes</td>
<td>Onset 5-10 minutes</td>
</tr>
<tr>
<td></td>
<td>Duration 4 hours</td>
<td>Duration 4 hours</td>
<td>Duration up to 36 hours</td>
<td>Long duration of erection</td>
<td>Long duration of erection</td>
<td>Offers an alternative if first-line agents fail or are contraindicated</td>
</tr>
<tr>
<td></td>
<td>57% successful intercourse</td>
<td>50%-65% successful intercourse</td>
<td>53%-70% successful intercourse</td>
<td>Offers an alternative if first-line agents fail or are contraindicated</td>
<td>Lower efficacy rate than injectable products</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Improved quality of life</td>
<td>Efficacy in sildenafil nonresponders</td>
<td>Enhanced spontaneity</td>
<td>85%-90% erections adequate for intercourse</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DOE</strong></td>
<td>Most extensive efficacy data in widest patient population of all ERD agents</td>
<td>Improved IIEF scores and other ERD measures compared with placebo</td>
<td>Improved IIEF scores and other ERD measures compared with placebo</td>
<td>Improved erectile assessment scale scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Improved IIEF scores and other ERD measures compared with placebo</td>
<td></td>
<td></td>
<td>Improved erectile assessment scale scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Headaches, flushing, rhinitis, dyspepsia</td>
<td>Headaches, flushing, rhinitis, dyspepsia</td>
<td>Headaches, flushing, rhinitis, dyspepsia</td>
<td>Injection site hematoma, ecchymosis, edema, penile fibrosis risk, penile pain, prolonged erection, and hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blue vision color change 3%</td>
<td>Infrequent reports of visual changes &lt;2%</td>
<td>Rare reports of visual changes</td>
<td>Injection site hematoma, ecchymosis, edema, penile fibrosis risk, penile pain, prolonged erection, and hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Most extensive safety data</td>
<td>Prolongs QT interval</td>
<td>More frequent myalgias and back pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical attributes</strong></td>
<td>Ease of use</td>
<td>Ease of use</td>
<td>Requires initial titration in physician office</td>
<td>Requires initial titration in physician office</td>
<td>Requires initial titration in physician office</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recommended as first-line in ERD guidelines</td>
<td>Less frequent administration</td>
<td>Limited to 3 times a week</td>
<td>Limited to 3 times a week</td>
<td>Can be used twice in 24 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmacokinetics not affected by a high-fat meal</td>
<td>Penile injections necessary</td>
<td>Penile injections necessary</td>
<td>No needles or syringes to dispose of or transport</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DOE = disease-oriented evidence; ERD = erectile dysfunction; IIEF = International Index of Erectile Function; POEM = patient-oriented evidence that matters.
**TABLE 18** | Outcome Terms in Evidence-Based Medicine
---|---
**Term** | **Definition**
---|---
Disease-oriented evidence (DOE) | Refers to surrogate markers associated with a specific-disease state such as blood pressure reduction or glucose and cholesterol lowering
Patient-oriented evidence that matters (POEM) | Refers to clinical events associated with a disease such as myocardial infarction, stroke, and death
Effectiveness | Evaluation of beneficial effects of a treatment when assessed under the usual conditions of clinical practice, also referred to as efficacy measured in a real-world setting

**TABLE 19** | Comparative Costs for Erectile Dysfunction Agents
---|---
**Agent** | **Cost per Average or Usual Dose ($)***
---|---
Intracavernous alprostadil injection (Caverject) | 29.50
Intracavernous alprostadil injection (Edex) | 29.00
Transurethral alprostadil insert (MUSE) | 22.00
Sildenafil (Viagra) | 9.00
Vardenafil (Levitra) | 9.20
Tadalafil (Cialis) | 8.90

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* Cost obtained from www.drugstore.com on December 26, 2004, for a single dose, based on the average doses used in clinical studies or the usual dose in the package insert.

**Note:** In actual deliberations, the P&T committee is provided with the WellPoint Pharmacy Management national net cost per claim for the most recent calendar quarter available.

This could be especially significant if vardenafil is coadministered with CYP3A4 inhibitors because these drugs interfere with vardenafil metabolism.

Injectable or transurethral alprostadil remains recommended second-line therapy if first-line therapy is ineffective or contraindicated. Injectable alprostadil results in a quicker onset and a higher success rate than transurethral alprostadil, but it may also have a higher rate of prolonged erections or priapism.

Table 17 contains the clinical summary grid that compares and contrasts effectiveness, efficacy, safety, and clinical attributes of the 6 products currently used for the treatment of ERD. Table 18 lists definitions of some of the outcomes terms used in the clinical summary grid. Table 19 contains the comparative costs for a single dose of the ERD agents discussed in this study.

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**REFERENCES**
Clinical Monograph for Drug Formulary Review: Erectile Dysfunction Agents