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*Technology Assessment Program*

Report No. 11

# Treatment Options for Male Erectile Dysfunction:
## A Systematic Review of Published Studies of Effectiveness


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# Treatment Options for Male Erectile Dysfunction: A Systematic Review of Published Studies of Effectiveness

## EXECUTIVE SUMMARY

### Purpose

This report was written in response to a request to VA's Technology Recommendations Panel (TRP) regarding treatment options for male erectile dysfunction (ED). The TRP, a national committee, is "responsible for the evaluation of health care technologies and for preparing recommendations regarding the use of such technologies" (TRP Charter, unpublished, 1997). The Health Services Research and Development Service, Management Decision and Research Center Technology Assessment Program commissioned the review on behalf of the TRP.

The intent of this report is to update and expand information from the 1996 American Urological Association Clinical Guidelines Panel on Erectile Dysfunction: Summary Report on the Treatment of Organic Erectile Dysfunction. The current report relies primarily on results from randomized controlled trials of treatment for ED published from January 1995-January 1999. It also includes results from additional sources including patient preference studies, post marketing reports, product inserts and FDA announcements. It focuses on new FDA-approved therapies for ED of greatest clinical and resource significance to the VA, i.e. oral sildenafil (*Viagra*); intraurethral alprostadil (*MUSE*); and intracavernous injections of alprostadil (*Caverject*).

### Background

ED is defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance (Anon, 1993). The prevalence of ED increases with age and comorbid conditions such as diabetes, heart disease, hypertension, neurologic and psychiatric conditions, smoking and some surgical therapies. ED, while not life threatening, can result in withdrawal from sexual intimacy and reduced quality of life. ED is common, accounting for 525,000 physician visits in 1985. Nearly 10% of men aged 40-70 have reported complete ED and 52% some degree of dysfunction. If these findings are extrapolated to male veteran users of the VA medical system then an estimated 1.7 million veterans may have some degree of ED.

The treatment of ED (without evidence of hypogonadism) includes a number of options that are generally viewed by patients, partners and providers as effective in initially restoring erectile function: vacuum constriction devices, penile prosthesis implantation, vasoactive drug injection and oral therapies. However, for many treatments there is a high rate of treatment cessation. Therefore, efforts to optimize treatment should target improvements not only in physiologic/clinical measures of erectile function but also patient/partner satisfaction and preference. The NIH Consensus Statement on Impotence encourages physicians to try the least invasive treatment first. The ideal treatment is effective, useful 'on demand,' free of toxicity and side effects, easy to administer (oral or topical) and affordable.

### Key Findings

- ED is a common condition that results in reduction in quality of life. The number of men seeking help is likely to increase with enhanced awareness of ED and of its treatment options.

- ED is associated with chronic illnesses and medications used to treat these illnesses. Psychological or relationship issues often coexist. Therefore, a wide range of health care providers must be aware of ED and knowledgeable about the etiologies of ED and its treatment options.

- Diagnosis of ED has been comprehensively reviewed by the Office of Health Technology Assessment (OHTA) of the Agency for Health Care Policy and Research (AHCPR, 1990).

- In patients with psychogenic ED, psychosexual counseling may be useful. Currently available effective treatments for primarily organic ED include vacuum constriction devices, intraurethral (IU) (alprostadil) and intracavernosal (IC) vasoactive drug injection therapy (alprostadil monotherapy; papaverine plus phentolamine; and a combination of all three agents), surgical implantation of a penile prosthesis and oral medications (sildenafil and yohimbine).

- A patient/partner goal directed approach is important to educate the patient/partner about the advantages and disadvantages of the commonly used treatments.

- Most patients desire a convenient, noninvasive therapy that preserves intimacy by causing minimal or no interruption of events leading to sexual intercourse, even if this therapy has lower efficacy (i.e. prefer oral treatments).

- The table on page iv summarizes results of studies reviewed for this report with the results published by the American Urological Association Consensus Panel on treatment of ED.

- Inconsistent or lack of clinically relevant reported outcomes, lack of long term follow-up or comparisons with active treatments, and selection bias of enrolled patients limit study results.

- Compared to other therapies, studies of sildenafil and intraurethral alprostadil involved the most patients, were of greatest duration and used standardized, validated outcome measures.

- Only two controlled studies, involving a small number of participants, evaluated at-home use of intracavernous drug injection or vacuum constriction therapy to assess outcomes. Results were qualitatively pooled with data from the 1996 AUA report. The 1996 AUA report supplied the data on penile prosthetic implants.

**VA guideline: *The Primary Care Management of Erectile Dysfunction***

- VA's Pharmacy Benefits Management Strategic Healthcare Group, with the Medical Advisory Panel, produced a guideline, *The Primary Care Management of Erectile Dysfunction (June, 1999)*. After further internal review and approval, the guideline will be available at http://www.dppm.med.va.gov.

- The guideline generally concurs with the results of this systematic review. However, it does not recommend the use of yohimbine and reflects concerns that the literature on sildenafil (*Viagra*) does not represent the drug's use inVA's population of elderly men with multiple co-morbidities and multiple medications. The guideline authors believe that the VA population may experience a greater risk of adverse effects than would be reflected in the rates of adverse events reported in the currently available literature.

## Executive Summary of Treatments for Erectile Dysfunction †

| TREATMENT TYPE/ TRADE NAME DOSE | COST* | RESPONSE/EFFICACY | SUCCESS RATE (%) | DROP OUT RATE (%) | NNT†† | PRIMARY ADVERSE EVENT(S) | (%) |
|---|---|---|---|---|---|---|---|
| ***Mechanical Devices*** | | | | | | | |
| **Vacuum Constriction** | | Return to intercourse | ~75 | 25 (short term) | NA | Discomfort/pain | 19 |
| | | Patient/partner satisfaction | | | | | |
| e.g. *ErecAide* | $174 | | | | | | |
| ***Surgery*** | | | | | | | |
| **Penile Prosthesis Implantation** | $4300-8200 | Functional prosthesis enabling intercourse | 82-95 | | ~1 | Device failure | 5-18 |
| | | Patient/partner satisfaction | 54-95 | | | Discomfort/pain | 2-14 |
| ***Vasoactive Drug Injection Therapy*** | | | | | | | |
| **Alprostadil/ PGE1** | | Return to intercourse | 77 | | NA | Pain | 20 |
| e.g. *Caverject* | $26.52 | Patient/partner satisfaction | 70-89 | | | Bleeding/hematoma | 3 |
| 10 or 20 mg prn (6/month) | | | | | | Prolonged erection | 3 |
| ***Intraurethral Drug Therapy*** | | | | | | | |
| **Alprostadil** | | Return to intercourse | 40 | 9 | 3.50 | Penile pain | 33 |
| *MUSE* | $73.86 | **Erections sufficient for intercourse: attempts | 51 | | 2.47 | Urethral pain | 12 |
| 500 mcg prn (6/month) | | | | | | Vaginal burning | 6 |
| ***Oral Drug Therapy*** | | | | | | | |
| **1. Sildenafil** | | Erections sufficient for intercourse: attempts | 47 | 9 | 3.51 | Headaches | 18 |
| *Viagra* | $31.38 | Improvement in erections | 70 | | 1.96 | Visual disturbances | 4 |
| 25, 50 or 100 mg prn (6/month) | | | | | | | |
| Note: There have been 130 confirmed deaths possibly associated with sildenafil (FDA, November 25, 1998) | | | | | | | |
| **2. Yohimbine §** | | Responders to treatment | 48 | 13 | 3.94 | Includes HTN, anxiety | 17 |
| e.g. *Yocon, Yohimex* | $2.00 | | | | | | |
| 5.4 mg t.i.d. | | | | | | | |
| **3. Phentolamine §** | | Erections sufficient for intercourse: attempts | 29 | 0 | NS | Includes headache | 3 |
| *Vasomax* | $ NA | | | | | | |
| 20, 40, 60 or 80 mg prn | | | | | | | |
| **4. Trazodone §** | | Improvement in erections | 36 | 19 | NS | Primarily sedation | 26 |
| *Desyrel* | $0.75 | | | | | | |
| 50 mg qd | | | | | | | |

† Based on randomized controlled trials (RCTs) except mechanical devices. Not all RCTs provided information.

†† NNT=Number Needed to Treat (an estimate of the # of patients who need to receive treatment in order to obtain the measured outcome in one patient).

* Based on costs in the VA medical system (per month, where applicable). Costs for penile prosthesis implantation includes first six months follow-up care and are based on 1996 HCFA data.

** Based on a randomized trial that included men who achieved an erection during an initial dosing phase of alprostadil. Men responding (65%) were then randomized to alprostadil or placebo

§ Currently not FDA approved for the treatment of erectile dysfunction

NS= Not significantly different than placebo

NA= Not available

**Treatment Considerations**

The following treatment considerations for ED apply to the standard patient. This patient is defined as a man who develops ED after a well-established period of normal erectile function, whose ED is primarily due to organic causes rather than psychological or relationship issues, and who has no evidence of hypogonadism or hyperprolactinemia.

- The patient and, when possible, his partner should be fully informed in an unbiased manner about treatment options, their relative benefits and potential complications.

- Treatment options should incorporate issues related to patient/partner preferences, coexisting illnesses and medications, treatment side effects, costs and efficacy.

- Based on available data, acceptable treatment options for ED include:
  1. Vacuum constriction devices
  2. Oral therapy with sildenafil
  3. Oral therapy with yohimbine
  4. Intraurethral drug injection therapy with alprostadil
  5. Intracavernous drug injection therapy with: alprostadil + phentolamine + papaverine; phentolamine + papaverine; or alprostadil alone
  6. Surgical implantation of a penile prosthesis

- Treatment options have marked differences in costs, contraindications, side effects, and patient acceptability profiles.

- Randomized trials directly comparing treatment options have not been performed, making evaluation of relative treatment efficacy, safety and patient/partner preference difficult.

- Baseline characteristics and the number of male veterans with ED are not known. It is likely that veterans are older, have a greater number of coexisting medical conditions (depression, smoking and possibly vascular disease and diabetes) and have more severe ED than reported in randomized trials. The efficacy, safety and patient/partner preference of treatments for ED in veterans are not known.

- Formal cost-benefit analyses have not been conducted. However, if one fifth of the estimated 1.7 million veterans with ED were treated with sildenafil it would cost almost $100,000,000 per year. Cost estimates for treatment of identical numbers of veterans with IU or IC alprostadil are higher. However, the availability of oral medications like sildenafil are most likely to result in the greatest increase in the number of veterans requesting and utilizing treatments for ED.

**Research Recommendations**

- Research is needed to develop new therapies for ED which are convenient, effective, noninvasive, safe and ultimately less expensive

- Randomized trials directly comparing treatment options for ED in veterans or comparable populations using clinically relevant endpoints of treatment efficacy and adverse effects, and patient-centered outcomes such as patient/partner preferences and quality of life, will enable a more informed evaluation of treatments for ED within the veteran population.

- Subgroup analyses may be useful for determining if particular patient groups are better treated with specific therapies.

- Results from comparative randomized trials should be incorporated in cost-effectiveness analyses to help guide the efficient allocation of VA health care resources for the treatment of ED.

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# I. INTRODUCTION AND BACKGROUND

## A. Purpose

This report was written in response to a request from the Management Decision and Research Center (MDRC) Technology Assessment (TA) Program to provide information about treatment options for male erectile dysfunction (ED). The MDRC TA Program commissioned the review on behalf of VHA's national Technology Recommendations Panel (TRP). The TRP is a collaboration between headquarters and the networks and is "responsible for the evaluation of health care technologies and for preparing recommendations regarding the use of such technologies" (TRP Charter, unpublished, 1997).

The purpose of this report is to perform a systematic review of the literature and, where possible, a quantitative meta-analysis to evaluate efficacy and safety of therapeutic options for male ED. The report will update and expand on information in the 1996 American Urological Association (AUA) Clinical Guidelines Panel on Erectile Dysfunction: Summary Report on the Treatment of Organic Erectile Dysfunction (Montague, 1996). This report focuses on new therapies for ED of greatest relevance regarding clinical and resource utilization to the VA medical system: oral sildenafil (Viagra), intraurethral alprostadil (MUSE) and intracavernous injections of alprostadil (Caverject).

Any therapeutic recommendations in this report are only one component of a comprehensive approach to the care of patients with ED. An initial evaluation should include a thorough medical and sexual history, a focused physical exam, and a limited laboratory investigation as guided by clinical findings. Patients with a sizeable psychogenic component to their ED may benefit from psychosexual counseling (Wagner, 1998). Those with ED secondary to medications may be helped by a change in their drug regimen. While this review does not exclude studies which do not document a multi-faceted approach to ED, it is targeted at patients with acquired ED that is primarily organic in nature and not of gonadal origin.

## B. Male Erectile Dysfunction (ED)

ED is defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance. (Anon, 1993). Physiologically, a sexually stimulated erection is a vascular process mediated by the autonomic nervous system. Initially, psychogenic stimuli (e.g. sensations of sexual arousal) experienced in the central nervous system (CNS) act in concert with sensory stimuli from the penis. Nonadrenergic, noncholinergic nerve endings and endothelial cells release nitric oxide (NO) to stimulate the autonomic nervous system. NO, acting through a second messenger pathway involving cyclic guanosine monophosphate (cGMP), produces trabecular smooth muscle relaxation and helicine artery dilation. This facilitates increased flow of blood into the sinusoidal spaces of the cavernous bodies. Elevated pressure in the cavernous bodies compresses the draining venules against the tunica albuginea and thereby prevents venous outflow. Engorged with this trapped blood, the penis becomes sufficiently rigid for coitus (Anon, 1993; Christ, 1995).

In this manner, normal erectile function relies on the coordination of psychological, neurological, endocrine, vascular and muscular factors. Therefore, problems with any one of these elements--secondary to medical or psychiatric illness, psychogenic stress, or a drug side effect--may contribute to ED. Most cases of ED are thought to be multifactorial.

Though estimates of the prevalence of ED vary depending on the criteria used for diagnosis and the population surveyed, the Massachusetts Male Aging Study (MMAS), a community based cross-sectional study of men 40 to 70 years old, found a combined prevalence of minimal, moderate and complete impotence to be 52%. Further, they found that increased age, diabetes, heart disease, hypertension, current cigarette smoking, and depression were independent risk factors for ED. (Feldman, 1994) Data from the government's 1992 National Health and Social Life Survey found the percentage of men having trouble achieving or maintaining an erection was 7% among men ages 18 to 29, 9% among men in their 30's, 11% among men in their 40's, and 18% among men ages 50 to 59. Analysis of survey data also found that sexual dysfunction, including erectile dysfunction, is highly associated with negative experiences in sexual relationships and overall well-being as well as poor physical health (Laumann, 1999).

In 1998 approximately 3.4 million veterans (95.5% male) used the VA medical system (VA HSR&D data). If the MMAS data were extrapolated to this population, an estimated 1.7 million veterans would have some degree of ED. However, this may underestimate veteran morbidity given that nearly 40 percent of veterans are 65 or older, an age group with a higher expected rate of ED. Also, compared to US males in general, veterans may have a higher prevalence of other risk factors for ED. They have higher rates of smoking (Feigelman, 1994; Klevens, 1995; Patrick, 1990) and depression (Patrick, 1990), while comparative data on the prevalence of diabetes, heart disease and hypertension are less clear (Rogot, 1989; Patrick, 1990). In addition, because only a fraction of all veterans eligible for VA health care services currently uses the system (Ashton, 1998), there is potential for a much larger number of VA users with ED.

While ED is not a life-threatening condition, it is associated with a significant reduction in quality of life (Litwin, 1998; Jonler, 1995; Jackson, 1998; Fugl-Meyer, 1997). However, it is not clear to what degree this reduced quality of life is due to factors such as increased age and associated comorbidities.

In any case, as the US population ages it is likely that the prevalence of ED will increase. In addition, heightened public awareness of this condition, increased expectations for sexual function even at advanced ages, and the availability of new therapeutic options are all likely to increase the number of patients presenting with ED and requesting treatment.

## C. Treatment Recommendations by the AUA ED Guidelines Panel

In 1996 the American Urological Association published a report on the treatment of organic ED (AUA 1996). Following a systematic review of the literature on treatment of ED published

between January 1979 and December 1994, including both randomized controlled trials and less rigorously designed studies, the authors of this report listed five potential therapies:

- Oral medications;
- Vacuum constriction devices;
- Intracavernous vasoactive drug injection therapy;
- Penile prosthesis implantation, and;
- Venous and arterial surgery.

For each treatment modality the report presented probability estimates for efficacy and adverse effects outcomes (Table 1).

1. **Oral Medications**

   The only oral medication addressed in detail was yohimbine. Its possible effect on erection may be related to its peripheral parasympathetic (cholinergic) stimulation as well as to its antagonism of both central and peripheral presynaptic alpha-2 adrenergic receptors (anon, 1997; Yocon® product insert). Its antagonism of the adrenergic receptors in penile vascular and corporal smooth muscle may facilitate erections by relaxing these tissues and enhancing arterial inflow. Its effect on erectile function may also be related to its actions on dopaminergic and vaso-intestinal polypeptidic receptors. (Ernst, 1998) However, based on 4 studies, fewer than 25% of patients allocated to yohimbine were satisfied, not excluding a pure placebo effect.

   In the absence of adequately sized, randomized, placebo-controlled trials, additional oral therapies, including phentolamine, trazodone and pentoxifylline, as well as the topical vasoactive drugs minoxidil and nitroglycerin, were described as investigational.

2. **Vacuum Constriction Devices (VCD)**

   To use a VCD a patient first places a plastic cylinder over his penis. Then he uses a vacuum pump to remove air from the cylinder, generating negative pressure around the penis. This draws blood into the penis, causing it to become rigid. After removal of the vacuum, rigidity is maintained by application of an elastic band or other constriction device around the base of the penis. Constriction may be safely maintained for 30 minutes (Amer. Urological Assoc., 1996). In 20 studies, VCDs produced patient satisfaction in approximately 75% of patients. However, in twenty-two studies, 25% of VCD users discontinued therapy. Adverse effects were generally minor, consisting of local petechiae and ecchymoses, though 18% complained of penile pain. The most common complaint by users was the need to interrupt sexual activity to employ the device.

3. **Intracavernous Injections (IC)**

   Intracavernous injection involves the administration with a small needle syringe of one or more vasoactive compounds directly into the corpora cavernosa. This therapy may produce a more normal-like erection than VCDs, but is associated with more serious adverse effects including hypotension, tachycardia and liver dysfunction. Erections may be painful or dangerously prolonged. Other adverse effects include the development of penile

nodules, plaques or fibrosis.

Phentolamine, papaverine and alprostadil (prostaglandin $E_1$ or $PGE_1$), alone and in combination, were the medications studied in the AUA report.

Phentolamine, an alpha-adrenergic receptor antagonist and smooth muscle relaxant, was described as "seldom" effective when used as monotherapy, though no studies were cited.

Papaverine may effect erectile function by causing relaxation of vascular smooth muscle. It acts directly on the muscle itself, not via its innervation. Limited data were available on papaverine monotherapy. One study found 67% patient satisfaction, but two studies suffered 64% dropouts, possibly related to the high frequency of adverse events. These included penile pain in 18%; prolonged erections in 9%; and corporal nodules, plaques or fibrosis in 9%. Its current product labeling contraindicates its intracorporal injection for the treatment of ED because of the frequency of persistent priapism (Anon, 1998).

Alprostadil induces erection by relaxation of penile trabecular smooth muscle and dilatation of cavernosal arteries. This augments arterial inflow of blood, expanding the corporal sinusoids and impeding venous outflow, thereby producing penile rigidity. While data were sparse, monotherapy produced greater than 70% return to intercourse and patient satisfaction. However, in four studies nearly 35% of treated patients dropped out. While alprostadil was less likely than papaverine to produce prolonged pharmacologic erections (3%), corporal fibrosis or systemic side effects (0.1% and 1.9% respectively), it was more likely than other vasoactive drugs to cause pain during injection or diffuse penile pain during erection (23%).

There were many studies of patients treated with papaverine/phentolamine combination therapy. Return to intercourse and patient satisfaction exceeded 70% while frequency of adverse events were: prolonged erections 6%; fibrosis 6%; systemic side effects 2.9%; and local discomfort/pain 17%. These studies had more than 30% dropouts and were not placebo controlled.

Finally, there were limited data to evaluate papaverine/phentolamine/alprostadil combination therapy. One study demonstrated 78% return to intercourse. Adverse events were reported in 2 studies. The combined incidence of penile pain was 3.5%, prolonged erections occurred in 3.5% and fibrosis in 2.7% of patients. Dropout rate was 15% and studies were not placebo controlled.

**4. Penile Prosthesis Implantation**

There are two types of penile prostheses. Each involves surgical insertion of a rod or chamber inside the penis. The simplest type of prosthesis is a semirigid but malleable rod. This functions by making the corpora cavernosa rigid. The other type of prosthesis is hydraulic. A hydraulic prosthesis contains a fluid-filled reservoir, a pump and two inflatable cylinders. There are one-piece, two-piece and three-piece designs. All produce penile

rigidity when one manually squeezes the pump and transfers the fluid from the reservoir to the cylinders. A man with a prosthesis can create an erection any time he wishes. However, in the event of mechanical failure, erosion or infection, another surgery is usually required to correct the problem.

Because any functional prosthesis is adequate for intercourse, penile prostheses had the highest rates for return to intercourse among treatments for ED. Nevertheless, patients were not uniformly satisfied. Multiple retrospective studies found patient satisfaction rates between 53% and 95%. Following surgery, mechanical device failure occurred in 5-18% of patients; infection and erosion rates were each 1-3%.

**5. Venous or Arterial Surgery**

Venous surgery is directed at correcting corporovenous occlusive dysfunction or venous leak. This problem occurs when there is incomplete closure of venous outflow from the penis, preventing full tumescence and penile rigidity. Surgical technique involves the resection and/or ligation of penile veins. (Amer. Urological Assoc., 1996) Based on data from 1801 patients in 43 patient groups, venous surgery had an estimated probability for return to intercourse and for patient satisfaction of 43%. However, these short-term improvements often were not maintained.

Arterial surgery generally involves the anastamosis of the inferior epigastric artery, the femoral artery or a saphenous vein graft to either one or both dorsal penile arteries, central arteries of the corpora cavernosa or the deep dorsal vein of the penis. Nineteen studies, involving 713 patients receiving arterial surgery, found 60% return to intercourse.

Postoperative complication rates for both surgeries were high, 17% for venous surgery and 21% for arterial surgery. Both surgeries were considered investigational.

**6. Ideal Therapy**

Two studies on patient preferences in treatments for ED showed that restoration of erectile function was not the patients' only concern. When the success of an intervention was defined as the ability to achieve and maintain erections adequate for penetrative sexual intercourse, penile prostheses were the most successful therapy (85-94%), followed by intracavernous injections (78-85%), VCD (55-63%), and then oral medications (28-41%). However, at least 70% of patients chose oral medications as their first choice therapy (Hanash, 1997; Jarow, 1996). When these studies were performed sildenafil and IU alprostadil were not available.

An ideal treatment for ED should have many or all of the following features:

- free of toxicity and side effects
- effective, regardless of etiology, severity or duration of ED, or age of patient
- noninvasive
- easy to use and useful "on demand"
- affordable

# II. METHODS FOR THE SYSTEMATIC REVIEW

## A. Identification of Studies

One aim of this report was to update and expand information from the 1996 American Urological Association (AUA) Clinical Guidelines Panel on Erectile Dysfunction: Summary Report on the Treatment of Organic Erectile Dysfunction. Therefore, this report relies primarily on results from randomized trials of treatment for ED published from January 1995-January 1999. Studies concerning the efficacy and adverse effects of treatments for erectile dysfunction were initially identified by conducting a systematic review of the relevant literature. We searched the MEDLINE®, HealthSTAR®, Current Contents®, EMBASE® and Cochrane computer databases for the period January 1995 through January 1999. The primary search terms were the MESH heading *impotence* and the keyword *erectile dysfunction* with the subheadings *therapy*, *drug therapy*, *surgery* and *disease management*. This result was combined with *clinical trials*, *controlled trials*, *randomized controlled trials*, *meta-analyses*, *guidelines*, *academic or systematic reviews* and *multi-center studies*. Only articles in English were considered. In addition, bibliographies of retrieved articles were reviewed, and journals and AUA national meeting abstracts from 1995-1998 were hand searched. Unpublished data available on the FDA internet web site were screened.

## B. Inclusion Criteria for the Systematic Review

Randomized controlled trials (RCT) are the most scientifically valid method for assessing treatment efficacy. Therefore, assessments of treatment effect in this report are based on RCT. To maximize clinical relevance, this review includes only studies reporting outcomes of importance to patients, such as success of intercourse or patient satisfaction. Longer-term studies were considered to provide more clinically relevant evidence than single dose studies.

Trials were eligible if they were:

- randomized
- compared an active treatment for ED with placebo or an active control
- evaluated outcomes of importance to patients (i.e. success of intercourse or satisfaction)
- at least 7 days in duration or involved administration of multiple treatment doses (i.e. single dose studies excluded)

Summary descriptions of individual trial characteristics, interventions and results are provided in Appendices 1-9. A list of randomized trials included in this report is provided as Appendix 10.

## C. Assessment of Adverse Events and Patient Preferences

Because randomized controlled trials are generally not the best source for evaluating adverse events and patient preferences, we included results on these outcomes from patient preference studies, post-marketing reports, product inserts and FDA Medwatch announcements.

## D. Data Extraction

For eligible studies, information on study characteristics, patient demographics, inclusion and exclusion criteria, dropouts, treatment efficacy and adverse effects, were extracted in a standardized fashion by two reviewers onto pretested data abstraction forms. Completed forms were reviewed for discrepancies by the lead author; discrepancies found were then resolved by discussion among all authors

Treatment efficacy outcomes extracted included:

- percent of intercourse attempts which were successful, averaged across all subjects in a treatment group;
- percent of subjects achieving successful intercourse at some time during treatment;
- percent of subjects reporting improvement in erectile function, with improvement possibly but not necessarily indicating successful intercourse;
- scores to questions 3 and 4 of the International Index Erectile Function (IIEF) questionnaire:
    - IIEF scoring scale: 0=(no attempts); 1=(almost never/never); 2=(much less than half the time); 3=(about half the time); 4=(much more than half the time); 5=(almost always/always).
    - IIEF question 3: "When you attempted intercourse were you able to penetrate your partner?"
    - IIEF question 4: "During intercourse how often were you able to maintain an erection after penetration?"

All results were reviewed by the lead author and discrepancies resolved by group discussion.

## E. Data Synthesis

When pooling data was appropriate, weighted risk ratios (RR), risk differences and their 95% confidence intervals were calculated using RevMan 3.0 software (Update Software, 1996) for dichotomous variables. The Number Needed to Treat (NNT) is a useful measure of treatment effectiveness. It provides an estimate of the number of patients that need to receive treatment in order to obtain the measured outcome. For example, if the measured outcome is "improvement in erections" then the NNT gives the number of men who need to receive treatment in order that one man experiences an improvement in his erections. The NNT for different outcomes along with their respective 95% confidence intervals were calculated as: "1/Risk Difference". Not all trials reported outcome data in a consistent fashion, limiting pooling of findings in some cases (Cochrane Review Group Handbook, 1997).

Results were tested for heterogeneity at a significance level of $p < 0.1$. If evidence of heterogeneity existed then a random effects model was utilized. Such a model provides a more conservative estimate of treatment effects and yields wider confidence intervals. When heterogeneity was not present, a fixed effects model was used to combine data. Critical issues

in homogeneity include similarities in the methodology, participants, interventions and outcome variables of each trial. An intention to treat analysis was utilized. The denominator included all participants randomized to treatment at baseline and the numerator included the number completing the trial and showing improvement or a "successful outcome."

## III. PUBLISHED FINDINGS

### A. Oral/Transdermal Therapies

#### 1. Sildenafil (Viagra) (Tables 2a-d; Figures 1a-e; Appendices 1a-d)

##### a. Description

Physiologically, a sexually stimulated erection involves release of nitric oxide (NO) in the corpus cavernosum. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation and allowing inflow of blood and penile engorgement. Sildenafil enhances the effect of NO by selectively inhibiting phosphodiesterase type 5, the enzyme responsible for degradation of cGMP in the corpora cavernosa. Sildenafil rarely produces erections in the absence of sexual stimulation and does not enhance libido or normal erectile function.

Sildenafil, in doses of 25 mg, 50 mg or 100 mg, is taken orally one hour before desired sexual activity. Its peak effect occurs 30-120 minutes after administration. It is recommended that patients not use more than one dose of sildenafil per day.

Sildenafil was approved for use in the treatment of ED by the FDA on March 25, 1998. Since that time more than 6 million prescriptions have been dispensed (FDA 11/25/98).

##### b. Characteristics of Studies (Appendix 1a-d)

Fifteen studies involving 4081 subjects met eligibility criteria. All were randomized, double blind and placebo controlled. Study size ranged from 12 to 532 subjects. All except for the smallest study were multi-center trials. Enrolled subjects had been referred for treatment of ED. One study was 1 week in duration, five were 4-8 weeks, six were 12 weeks and three were either 24 or 26 weeks. Common study inclusion criteria were: age > 18 years; ED > 3-6 months duration; and involvement in a stable heterosexual relationship > 6 months. All studies had extensive exclusion criteria. The most common were: endocrine or gonadal etiology of ED; uncontrolled hypertension or hypotension; recent cardiac events (MI, CHF exacerbation, unstable angina or life-threatening arrhythmia); active peptic ulcer disease; and the need for anti-coagulants or nitrates. Three studies were published in peer reviewed journals. The remaining data were provided by the drug manufacturer (Pfizer) and available on the FDA web site.

##### c. Demographics of Patients

| | |
|---|---|
| Subjects | N=4081 |

| | |
|---|---|
| Age (mean yrs) | 55.6 |
| Duration of ED (mean yrs) | 4.9 |
| Baseline Severity of ED * | |
| Mean score IIEF question 3 | 2.0 |
| Mean score IIEF question 4 | 1.6 |
| Etiology of ED (%) | |
| Organic/Vascular | 52.1 |
| Psychogenic | 21.1 |
| Mixed | 26.0 |
| Comorbidities (%) | |
| Diabetes Mellitus | 15.3 |
| Spinal Cord Injury | 5.0 |
| Radical Prostatectomy | 15.3 |

* The International Index Erectile Function (IIEF) is scored: 0=(no attempts); 1=(almost never/never); 2=(much less than half the time); 3=(about half the time); 4=(much more than half the time); 5=(almost always/always).
IIEF question 3: "When you attempted intercourse were you able to penetrate your partner?"
IIEF question 4: "During intercourse how often were you able to maintain an erection after penetration?"

On average, men enrolled in these studies had a mean age of 56 years and mean baseline erectile function "adequate for intercourse much less than half the time." Mean duration of ED was approximately 5 years. Greater than half of men had ED due to organic/vascular causes while 21% of cases were psychogenic and one-quarter had a mixed etiology. In studies that reported comorbidities, 15% of subjects had diabetes, 5% spinal cord injury and 15% had undergone a radical prostatectomy for treatment of prostate cancer.

## d. Effectiveness Outcomes

### 1) Overall Effectiveness

Sildenafil produced a large and statistically significant improvement in ED when compared with placebo. The results were consistent across studies, outcome measures and special populations (Tables 2a-d and Figures 1a-c).

In data taken from subjects' diary/event logs, "success of sexual intercourse attempts," probably the most relevant clinical outcome, was 46.5% for sildenafil versus 19.5% for placebo (RR=2.94; 95%CI=2.26-3.82. NNT=3.5; 95%CI = 2.8-4.1). "Successful sexual intercourse"or at least one successful intercourse attempt during treatment was reported in 81.7% of men receiving sildenafil and 52.4% receiving placebo (RR=1.56; 95%CI=1.35-1.81). In response to the question: "Did treatment improve your erections," 70.0% of sildenafil treated patients answered affirmatively compared to 19.6% of placebo treated patients (RR=3.59; 95%CI=2.97-4.35. NNT=2.0; 95% CI = 1.8-2.3).

Sildenafil was superior to placebo based on subjects' responses to IIEF Q3 and Q4 at study completion, the primary outcome for many studies. Overall, the

subjects' mean follow-up Q3 scores were 2.2 for placebo and 3.6 for sildenafil. This indicated that on average sildenafil provided "erections sufficient to penetrate one's partner" about half to much more than half the time (compared to much less than half the time for placebo). For Q4 the mean follow-up scores were 1.9 for placebo and 3.4 for sildenafil indicating that the "maintenance of erections during intercourse" was possible greater than half the time for sildenafil and much less than half the time for placebo. Summary statistical comparisons were not possible for the overall IIEF scores, but individual study differences were statistically different in favor of sildenafil.

**2) Effectiveness in Special Populations**

Compared to the overall results, sildenafil provided similar effectiveness in subjects with spinal cord injuries (Table 2c) and psychogenic ED (Table 2b) as measured by "improvement" in erections. There were no data available regarding erections sufficient for intercourse. Sildenafil was less effective in men with diabetes compared with the overall group as defined by "improved erections" (DM = 54.4% versus overall = 70.0%) and "successful attempts at intercourse" (DM = 30.3% versus 48.0%) (Table 2d). Nevertheless, because response to placebo was much lower in diabetics (possibly indicating a more severe or multifactorial disease process), the RR for sildenafil versus placebo for "total successful intercourse attempts" was high (RR=4.23; 95%CI=3.74-4.78). Still, the NNT to achieve this outcome was greater for patients with diabetes than overall (4.3 versus 3.5).

According to a pooled subgroup analysis reported in one abstract, sildenafil produced significantly better erections than placebo, as assessed by response to IIEF Q3 and Q4, in both subjects < 65 and in those $\geq$ 65 years old. Another analysis reported by the manufacturer, which pooled subjects with a history of radical prostatectomy, suggested that for these subjects response to sildenafil was less than that seen overall (43% reported improvement) but still greater than with placebo (15%). Information in the product insert suggested that most subjects had improved erections regardless of baseline severity of ED and that this difference was greater in sildenafil treated subjects than placebo subjects at all levels of ED severity. However, this appears to be a post-hoc analysis based on only one of many measures of treatment outcome and includes only a fraction of subjects for whom this particular outcome was assessed.

**e. Adverse Events**

About 10% of enrollees withdrew from studies. This drop out rate was similar in both the sildenafil and placebo groups and did not vary significantly between studies (RR=0.82 for sildenafil; 95%CI=0.65-1.05) (Table 2; Figure 1c). Adverse events were generally mild and transient and were experienced by 49.7% of sildenafil treated patients compared to 13.4% of placebo treated patients (RR=3.60; 95%CI=1.64-7.89) (Table 2; Figure 1d). In special populations, the frequency of any adverse events was similar to that seen overall (Tables 2a-c). The most common event was headache,

experienced by 18.3% of all sildenafil patients versus 4.2% of placebo patients (RR=4.01, 95%CI=2.60-6.20). Visual disturbances, flushing and dyspepsia were also experienced significantly more often in the sildenafil treated group.

Post-marketing data reported to the FDA indicate that since late March 1998, when sildenafil received FDA approval, through mid-November 1998 there have been 130 confirmed deaths possibly associated with sildenafil. Seventy-two of these patients had cardiovascular events and 27 died during or immediately following intercourse. Most of these patients had risk factors for heart disease and 16 had taken nitrates (FDA 11/25/98). It is not possible to determine from post-marketing reports whether the cardiovascular events are directly related to sildenafil, to sexual activity, to patients' underlying disease, or to a combination of these factors. Sildenafil is contraindicated in men taking nitrate preparations of any kind at any time. Also, caution should be exercised when considering use in patients with active coronary ischemia untreated with nitrates, patients with congestive heart failure and borderline low blood pressure, patients on multi-drug, anti-hypertensive regimens and in patients with hepatic or renal disease (American College of Cardiology, 1998).

Updated FDA labeling further advises that sildenafil not be used in men for whom sexual activity is inadvisable due to their underlying cardiovascular status, or in men who could be adversely affected by transient decreases in blood pressure. Patients with retinitis pigmentosa and those who had suffered a heart attack, stroke or life-threatening arrythmia within the past six months were excluded in the clinical trials for sildenafil and prescribing sildenafil for these patients should be done with caution (FDA 11/25/98).

**f. Cost**

The cost to the VA for sildenafil (Viagra) is estimated to be $5.23 per pill (25, 50 or 100 mg) or $31.38 for 6 pills/month.

**2. Yohimbine (Yocon, Yohimex, Aphrodyne, Erex) (Table 3; Fig. 2; Appendix 2)**

**a. Description**

Yohimbine may induce erection by its peripheral parasympathetic (cholinergic) stimulation as well as its antagonism of both central and peripheral presynaptic alpha-2 adrenergic receptors. (Anon, 1997; Yocon® product insert). Its antagonism of the adrenergic receptors in penile vascular and corporal smooth muscle may relax these tissues, enhance arterial inflow and thereby produce penile engorgement. Its effect on erectile function may also be related to actions on dopaminergic and vaso-intestinal polypeptidic receptors (Ernst, 1998).

Yohimbine is taken orally, generally at a dose of 5.4 mg three times per day.

Yohimbine has been used as a treatment for ED for many years. More than 1.3 million prescriptions were written in 1997 (Spivack, 1998). Yohimbine has not received FDA approval for treatment of ED.

**b. Characteristics of Studies (Appendix 2)**

Nine studies met eligibility criteria, six of which had appeared previously in a meta-analysis of yohimbine for treatment of ED (Ernst, 1998). Eight of the studies were randomized, double blind and placebo controlled. The other was randomized and used an active control group. Study size ranged from 11 to 100 subjects. Three studies were 2-4 weeks in duration, while the other six were 7-10 weeks. Inclusion and exclusion criteria were varied between studies. All studies were published in peer reviewed journals. There was a tenth placebo controlled study which met all eligibility criteria but, because it combined trazodone with yohimbine in the active treatment arm, it could not be used to evaluate the effect of yohimbine alone.

**c. Demographics of Patients**

Collectively, the eligible studies included 469 subjects. Among the studies which provided patient age data, the range of the mean age was 43-61 years. Too few studies provided information regarding duration of ED, baseline severity of ED or associated comorbidities to calculate overall estimates. In regard to etiology of ED, some studies included only subjects with a psychogenic etiology, others were limited to subjects with an organic etiology and others gave no information.

**d. Effectiveness Outcomes**

The studies employed generally different questionnaires to ascertain from subjects their improvements in erections or sexual function. When these results were converted into "response" or "nonresponse" to treatment, and combined across the different studies, 47.6% of subjects randomized to yohimbine had a response to active therapy compared to 24.9% with placebo (RR=1.91; 95%CI=1.30-2.82, NNT = 3.9; 95% CI=2.7-7.1 (Table 3, Fig. 2)

**e. Adverse Events**

In the 3 studies which reported drop outs, 13.7% occurred in the yohimbine group and 0% in the placebo group. Five studies reported comparative data on adverse events. These indicated that 16.9% of yohimbine subjects experienced one or more adverse event versus 4.8% of placebo subjects (RR=2.78; 95% CI=1.40-5.56). Adverse events included elevation of blood pressure, anxiety, dizziness, chills, headache, sweating, tachycardia, GI disturbances, urinary frequency and rash. Yohimbine should not be used in geriatric, psychiatric, cardiac or renal patients, or in men with a history of gastric or duodenal ulcer (Anon, 1997).

**f. Cost**

The cost to the VA for yohimbine = $2.00 per 100 tablets (one month therapy).

**3. Phentolamine (Vasomax) (Table 4; Appendix 3)**

**a. Description**

Phentolamine is an alpha-adrenergic receptor antagonist. Antagonism of adrenergic

receptors in penile vascular and corporal smooth muscle may relax these tissues, enhance arterial inflow and thereby produce a penile erection.

As an oral agent, phentolamine is available in 20-80 mg doses. It is to be administered 15-30 minutes prior to desired sexual activity. The manufacturers of oral phentolamine (Vasomax) are currently seeking FDA approval for its use in treatment of ED.

**b. Characteristics of Studies**

Three studies met eligibility criteria (Appendix 3). One was a study of 40 subjects published in a peer reviewed journal, while two others, containing 293 and 459 subjects respectively, appeared together in an abstract. All were double blind and placebo controlled. One indicated a random assignment of treatment group while the other two did not mention randomization. Subjects in the small study received 3 doses of treatment. The two larger studies did not specify treatment duration but appeared to be multiple dose studies. Inclusion and exclusion criteria were stated only in the peer reviewed study. Inclusions were ED duration < 3 years and involvement in a stable partnership. Exclusions were psychogenic ED, erectile success during placebo run-in phase, diabetes and significant cardiovascular or neurologic disease.

**c. Demographics of Patients**

The studies did not provide data on subjects' ages, duration of ED, etiology of ED or presence of comorbid conditions. The 2 studies reported in the abstract only included subjects with "minimal ED" while the third study gave no information on the baseline severity of subjects' ED.

**d. Effectiveness Outcomes**

In data taken from subject diary/event logs, "success of sexual intercourse attempts," probably the most relevant clinical outcome, was 28.9% for phentolamine versus 13.4% for placebo (RR=2.17; 95%CI=0.82-5.71. NNT=4.9; 95%CI=3.8-7.1) (Table 4). When a subject's response to treatment was defined as an improvement of $\geq$ 1 point in erectile domain score (sum of IIEF questions 2-5; possible scoring range 0-20) 38.8% of phentolamine treated subjects improved compared to 18.5% with placebo (RR=2.10; 95%CI=1.62-2.73).

**e. Adverse Events**

One study reported comparative data on adverse events. 3.3% of phentolamine treated subjects versus 0.0% of placebo subjects experienced any event. Adverse events seen in the studies included headaches, facial flushing and nasal congestion.

**4. Trazodone (Desyrel) (Table 5; Figure 3; Appendix 4)**

**a. Description**

Trazodone is indicated for the treatment of depression. It selectively inhibits serotonin re-uptake in the brain but its most important action with respect to erection may be its antagonism of alpha-2 adrenergic receptors (Eardley, 1998). Antagonism of these receptors in penile vascular and corporal smooth muscle may relax these tissues,

enhance arterial inflow and thereby produce erection. Trazodone has not been FDA approved for treatment of ED.

**b. Characteristics of Studies/Patients**

Four studies met eligibility criteria (Appendix 4). All were randomized and placebo controlled. Except for the study that used hypnotic suggestion as an active control group the studies were double blinded. Study size ranged from 51-100. Study duration ranged from 4-16 weeks. Inclusion and exclusion criteria were not uniform: one study included only subjects with ED of >3 months duration; two included only subjects without an organic cause for ED; and the third excluded subjects with severe kidney or liver disease and those using anti-hypertensives, psychoactive drugs or any medication which may influence erectile function. Three of the studies were published in peer reviewed journals while the other was published as an abstract. The mean age in the three studies reporting subject age ranged from 38-65 years. No data were given on baseline severity of ED and little data were given with regard to etiologies of ED and subject comorbidities.

**c. Effectiveness Outcomes**

The main clinical outcome in these studies was subject-reported "improvement in erections." (Table 5) Pooled data using a random effects model demonstrated no significant difference between trazodone and placebo (35.7% versus 22.2%), though the confidence intervals were wide and could not exclude a clinically important response to trazodone (RR=1.56; 95%CI=0.78-3.10) (Figure 3).

**d. Adverse Events**

There was an increased risk for trazodone treated subjects to experience an adverse event compared with placebo treated subjects (24.4% versus 10.0%; RR=2.14; 95%CI=1.00-4.58). Common adverse events were sedation, fatigue, dizziness, headache, dry mouth and nausea. There were no reports of priapism in these small studies.

**5. Aminophylline+Isosorbide Dinitrate+Co-Dergocrine (Appendix 5)**

**a. Description**

The three agents contained in this cream are vasodilators with different mechanisms of action, each of which is thought to effect erectile function by improving arterial blood flow to the penis. When it is applied in a thin layer to the glans penis and the penile shaft 15 minutes before desired sexual activity, the cream enhances a sexually stimulated erection. This therapy is not currently FDA approved for treatment for ED.

**b. Characteristics of Studies/Patients**

One randomized, double blind crossover study comparing active cream with placebo cream met eligibility criteria and was published in a peer reviewed journal (Appendix 5). Duration of treatment was one week in each arm. The study involved 36 subjects with a mean age of 48 years, mean duration of ED of 3.3 years and a mixture of psychogenic and organic etiologies of ED.

**c. Effectiveness Outcomes**

In data taken from questionnaires completed by subjects, erectile response and subject satisfaction with treatment were assessed. The subject's best response during the week was used in the statistical analysis. Erectile response was graded as "full erection, which implies successful intercourse" in 58.3% of subjects randomized to active cream compared with 8.3% randomized to placebo cream ($p<0.001$).

**d. Adverse Events**

No adverse events observed.

**6. Buflomedil Transdermal Electromotive Administration (Appendix 6)**

**a. Description**

Buflomedil is a vasoactive drug with alpha-adrenergic activity and possibly beneficial rheological properties. Transdermal absorption of the drug is accelerated by use of an electrode-drug receptacle attached to the patients.

**b. Characteristics of Studies/Patients**

One study, published as a meeting abstract, met eligibility criteria (Appendix 6). It was randomized, patient-blind, parallel group involving 25 subjects with ED associated with ischemic heart disease and generalized vasculopathy. Subjects received treatment twice weekly for 6 weeks. Study follow-up was 6 months.

**c. Effectiveness Outcomes**

In interview data, "satisfactory intercourse" was reported by 54% of subjects randomized to active therapy at 1 month and by 62% of these subjects at 3 months (versus 17% and 8% in the placebo subjects). Follow-up data at 6 months were available for only 60% of the subjects, with 38% of subjects randomized to active therapy reporting "satisfactory intercourse" compared with 29% of subjects randomized to placebo.

**d. Adverse Events**

No data given.

## B. Intraurethral Alprostadil (MUSE) (Table 6; Figures 4a-b; Appendices 8a-c)

**1. Description**

Alprostadil, or prostaglandin $E_1$, causes relaxation of the corpora cavernosa and vascular smooth muscle. In the penis this augments arterial inflow of blood, expanding the corporal sinusoids and impeding venous outflow, thereby producing penile rigidity. To reduce systemic effects of therapy the alprostadil MUSE system involves the placement of a medicated pellet in the tip of a hollow plastic applicator, which is then inserted into the urethra. The pellet is injected into the urethra by depressing a button on the applicator. Injection following urination facilitates application, enhances absorption and may reduce

penile pain. The drug is absorbed directly across the urethral lining into the corpus spongiosum and corpora cavernosa.

Intraurethral alprostadil is available in 125µg, 250µg, 500µg and 1000µg doses. The onset of effect is within 5-10 minutes after administration and the duration of effect is approximately 30-60 minutes (MUSE product insert). It is recommended that patients not use more than one application of intraurethral alprostadil per day.

Intraurethral alprostadil (MUSE) was FDA approved for treatment of ED in November 1996. Since that time more than 1.2 million prescriptions have been dispensed. (Spivack, 1998).

## 2. Characteristics of Studies (Appendices 8a-c)

Two studies were included in the analysis. Both were multi-center, randomized, double blind, placebo controlled, parallel group studies. They screened 1511 and 249 subjects respectively, but only enrolled responders to open-label, in-clinic intraurethral alprostadil into their double blind phases (66% of those screened). Both studies were 3 months in duration. Study inclusion criteria were: involvement in a stable heterosexual relationship; and inability to achieve a spontaneous erection sufficient for intercourse at any time within the preceding 3 months (i.e. severe ED at baseline). Exclusion criteria were not given for one study but included poorly controlled diabetes, unstable angina, CHF or recent acute MI in the other study. Both studies were published in peer reviewed journals.

## 3. Demographics of Patients

| Subjects† | N=1155 |
|---|---|
| Age (mean yrs) | 60.9 |
| Duration of ED (mean yrs) | 4.2 |
| Baseline Severity of ED | See below |
| Etiology ED/ Comorbidities (%) | |
| Vascular | 29.8 |
| Surgery/Trauma | 30.2 |
| Diabetes Mellitus | 17.4 |
| Other | 21.4 |
| Previous therapy for ED (%) | 55.4 |

† Includes only those subjects who enrolled in the double blind phase of the 2 trials.

On average, men enrolled in these studies had a mean age of 61 and “severe” ED of approximately 4 years duration. While no subjects were able to achieve an erection adequate for intercourse at baseline, 60.4% could achieve partial erections and only those screened who responded to intraurethral alprostadil administered in clinic were enrolled in the studies. The etiology of ED was reported to be vascular in 30% of subjects, surgery/trauma in 30%, diabetes in 17% and ‘other’ 21% of subjects.

Patients enrolled in the intraurethral alprostadil studies were about 5 years older (61 versus 56) and appeared to have more severe baseline ED than men enrolled in sildenafil studies.

## 4. Effectiveness Outcomes (Table 6 and Figures 4a-b)

### a. Overall Effectiveness

Intraurethral alprostadil produced a large and statistically significant improvement in erectile dysfunction when compared with placebo. In data taken from the diary/event logs of enrolled subjects (i.e. those who responded to intraurethral alprostadil during screening), "successful sexual intercourse," probably the most relevant clinical outcome, occurred in 50.5% of attempts in patients randomized to versus 10.1% of attempts in patients randomized to placebo (RR=5.01; 95%CI=4.59-5.47. NNT=2.5; 95%CI=2.4-2.6) (Table 6, Figure 4). In addition, within enrolled subjects, 61.3% in the alprostadil group were able to have sexual intercourse at least once during 3 months of treatment compared with 16.5% in the placebo group (RR=3.59; 95%CI 2.97-4.34. NNT=2.3; 95%CI=2.0-2.5) (Table 6, Figure 4a). Assuming that subjects who failed to respond in clinic would not have experienced return to intercourse had they been randomized, this suggests that approximately 40% of screened subjects responded to intraurethral alprostadil with return to intercourse versus an approximately 11% response to placebo (RR=3.53; 95%CI 2.89-4.31. NNT=3.5; 95%CI=3.08-4.04).

### b. Effectiveness in Special Populations

Effectiveness in men having ED following radical prostatectomy was less than that in the overall group (Costabile, 1998). "Erections sufficient for intercourse" were reported in 70% of these men (n= 384) who received "in-clinic" test doses of alprostadil. During the 3 month home treatment phase of "in-clinic responders" 57.1% of post prostatectomy patients receiving alprostadil had intercourse at least once versus 6.6% on placebo. In comparison, 67.8% of the overall group of "in-clinic responders" reported intercourse at least once during the 3 month home treatment phase versus 23.1% on placebo. Assuming that subjects who failed to respond in clinic would not have experienced return to intercourse had they been randomized, approximately 40.1% of post prostatectomy patients screened responded to intraurethral alprostadil. This result is similar to that seen overall. Two-thirds of post prostatectomy men used 500 or 1000ug alprostadil. In the 70% of post prostatectomy patients who responded to test doses of alprostadil, 570 of 1368 applications (41.7%) produced erections sufficient for sexual intercourse.

## 5. Adverse Events (Table 6)

Nearly twice as many men assigned to intraurethral alprostadil dropped out (8.7%) compared to placebo patients (RR=1.83; 95%CI=1.19-2.80). Systemic adverse events were uncommon. Penile pain occurred in 32.7% of alprostadil patients compared with 3.3% of placebo patients (RR=9.52; 95%CI=5.94-15.25). Urethral pain occurred in 12.1% of alprostadil patients compared with 4.1% in the placebo group (RR=5.82; 95%CI=2.36-14.33). In addition, partner adverse events such as vaginal itching or burning were more likely in partners of men receiving alprostadil than partners of men receiving

placebo (5.8% versus 0.8%; RR=7.36; 95%CI=2.60-20.83). However, serious cardiac events were rare and were less common in subjects treated with alprostadil than in subjects given placebo (RR=0.52 for alprostadil versus placebo; 95%CI=0.15-1.67).

Adverse events were higher in the subgroup of men receiving alprostadil following radical prostatectomy (n=270). Penile pain was reported by 38.9% of men receiving alprostadil versus 1.5% on placebo while 18.3% reported urethral pain/burning versus 4.4% receiving placebo.

**6. Cost**

The cost to the VA for intraurethral alprostadil = $12.31 per intraurethral injection (500 µg) or $73.86 for 6 injections per month.

## C. Intracavernous Injections

### 1. Alprostadil (Caverject) (Table 7a-b; Appendices 9a-b)

#### a. Description

Alprostadil, or prostaglandin E1, induces erection by relaxation of penile trabecular smooth muscle and dilatation of cavernosal arteries. This augments arterial inflow of blood, expanding the corporal sinusoids and impeding venous outflow, thereby producing penile rigidity.

Intracavernosal alprostadil is administered directly into the corpora cavernosa by injection with a small needle syringe. It is dosed at 10µg or 20µg. Erection occurs within 5 to 20 minutes and dose may need to be titrated to limit duration of effect to less than 1 hour. Intracavernosal alprostadil (Caverject) was FDA approved for use in treatment of ED in July 1995.

#### b. Characteristics of Studies

Since January 1995 there have been no published studies on intracavernosal alprostadil that met all of the eligibility criteria (i.e. randomized, placebo or active controlled, have a duration of treatment of 7 days or longer and assess clinically relevant outcomes) (Appendices 9a-b). One study, published in a peer reviewed journal, was double blinded and randomized subjects between two active treatments administered in a clinic setting, intracavernosal alprostadil or intracavernosal moxisylate. Within each arm, subjects had their dose titrated to achieve a response, the adequacy of the erection for intercourse as assessed by the investigator. Another study, only partially complete and published as an abstract, was a nonblinded, randomized, actively controlled study of at-home intracavernous alprostadil versus intraurethral alprostadil. Various doses of each treatment were compared. Duration of the study was not given. Listed outcomes included subject treatment preference and quality of erections as assessed by subject. In addition, there were 6 single dose studies which were either placebo or active controlled. For the single dose studies, all treatments were administered in the clinic setting, most often by the investigator. The most clinically relevant outcome measures were investigator assessment of the adequacy of penile rigidity for intercourse and subjects' rating of erection quality.

Study size ranged from 22 to 296 subjects. The most common study inclusion criterion was ED > 4 to 6 months duration but this wasn't uniform. No single criterion merited exclusion in all studies. Several studies excluded subjects with an endocrine etiology of ED and 3 excluded those with either uncontrolled hypertension or a recent episode of unstable angina or MI.

### c. Demographics of Patients †

| | Multiple dose studies only [1] | Including single dose studies |
|---|---|---|
| Subjects | N=201 | N=869 |
| Age (mean yrs) | 53.7 | 54.3 [2] |
| Duration of ED (mean yrs) | 4.4 | 2.5 [3] |
| Etiology of ED (%) [4] | | |
| Organic/Vascular | 26 | 47 |
| Psychogenic | 47 | 30 |
| Mixed | 28 | 23 |

† Table includes data from all studies in which one arm was IC alprostadil monotherapy.
[1] Of 2 multiple dose studies only 1 provided demographic data in addition to study size.
[2] Data based on 7 studies.
[3] Data based on 3 studies.
[4] Data based on 1 multiple dose study and 3 single dose studies.

### d. Effectiveness Outcomes/Adverse Events

Three studies compared intracavernous alprostadil with placebo and looked at the frequency with which treatment produced penile rigidity thought to be adequate for vaginal penetration, with adequacy determined by Rigiscan or subject/investigator palpation. All found a statistically significant difference in treatments favoring alprostadil.

A fourth study was designed as an open-label parallel group comparison of six at-home treatments of intracavernous alprostadil or intracavernous moxisylate. Outcomes included “percent successful sexual attempts” and “percent of subjects with erectile success” and it favored alprostadil by a significant difference. Alprostadil was associated with more pain during and after erection.

A study comparing three different formulations of intracavernous alprostadil found no differences between them. Another study compared alprostadil with alprostadil+lidocaine in a group of men who had previously experienced penile pain with alprostadil. It found a significant improvement in penile rigidity (investigator palpation) and a reduction in penile pain in the alprostadil+lidocaine group. Preliminary results reported from a study comparing intracavernous alprostadil with intraurethral alprostadil were difficult to interpret. As presented, they suggested that subjects were more satisfied by, and preferred treatment with, the intracavernous injections. However, results were not uniform and not all dose comparisons were presented.

When alprostadil monotherapy was compared with a combination of papaverine+phentolamine there did not appear to be any difference between treatments in terms of efficacy, but penile pain occurred in 35% of alprostadil subjects versus 15% of those receiving combination therapy. Last, when alprostadil was compared with an intracavernous combination of alprostadil+phentolamine+papaverine, the combination therapy was significantly more effective and resulted in a much lower frequency of penile pain (13% versus 41%).

**e. Cost**

The cost to the VA for alprostadil (Caverject) = $4.42 per intracavernous injection (10 or 20 mg) or $26.52 for 6 injections per month.

**2. Alprostadil + Phentolamine + Papaverine (Trimix) (Table 1; Appendices 9a-b)**

**a. Description**

The mechanism for each of these drugs has been described earlier. Their combination may produce a synergism of their unique actions on erectile function while minimizing side effects by allowing smaller doses of each individual agent. The limited available data at the time of the 1996 AUA report suggested that this combination had a success rate equivalent to alprostadil alone, with a lower incidence of painful erections and lower cost (Amer. Urological Assoc., 1996) (Table 1).

**b. Characteristics of Studies/Demographics of Patients**

Subsequent to the 1996 AUA report there have been no published studies involving this Trimix combination therapy that met all of the eligibility criteria. There are 4 randomized, actively controlled studies. In one, the combination therapy was compared with VCD. This study enrolled 50 subjects, with a mean age of 62.3 years and mean duration of ED of 3.3 years. Each treatment was used at least 15 times. No quantitative data on erectile success was reported but patient satisfaction "with the sexual experience" was significantly higher with the injection therapy. Three single dose trials compared this combination therapy with other intracavernous treatment regimens: alprostadil monotherapy (N=32); phentolamine + papaverine combination therapy (N=20); and atropine + alprostadil + phentolamine + papaverine combination therapy (N=230) respectively. Inclusions and exclusions were limited and differed between studies. Outcome was generally adequacy of erection for penetrative sexual intercourse as assessed by investigator palpation.

| | Multiple dose study only | Including single dose studies |
|---|---|---|
| Subjects | N=50 | N=332 [1] |
| Age (mean yrs) | 62.3 | 55.5 [1] |
| Duration of ED (mean yrs) | 3.3 | 2.8 [2] |
| Etiology of ED (%)[3] | | |
| Vascular | 30 | 60 |
| Surgical | 26 | Not given |
| Diabetes Mellitus | 18 | Not given |
| Neurologic | - | 15 |
| Other | 14 | 25 |

[1] Data based on 4 studies.
[2] Data based on 3 studies.
[3] Data based on 1 multiple dose study and 1 single dose study.

**c. Effectiveness Outcomes/Adverse Events**

Using "adequacy of erection for intercourse" as assessed by the subject or investigator, Trimix therapy was superior to alprostadil alone (50% versus 22%; $p<0.05$) and to the phentolamine + papaverine combination (73% versus28%; $p<0.05$). There was no

significant difference when atropine was added to the triple mixture; both produced "full erection" in 45.6% of subjects.

Penile pain was significantly less with the triple mixture compared with alprostadil monotherapy (13% versus 41%; $p<0.05$), similar to the atropine augmented mixture (53.8% for triple mixture versus 50.0%; p=NS) and greater than that with phentolamine + papaverine (15% for triple mixture versus 0%; p=NS).

**3. Phentolamine + Papaverine (Table 1; Appendix 9a)**

**a. Description**

The mechanism for these drugs has been described earlier. Their combination may produce a synergism of their actions on erectile function while lessening side effects by allowing smaller doses of each agent.

As indicated in the 1996 AUA report there were many studies of patients treated with papaverine/phentolamine combination therapy prior to 1995. Results are limited by lack of placebo controls and the greater than 30% drop out rate. Nevertheless, these studies showed a "return to intercourse" and "patient satisfaction" exceeding 70%. Frequent adverse events included: prolonged erections 6%; fibrosis 6%; and local discomfort/pain 17%. This suggested an efficacy similar to IC alprostadil but an increased frequency of priapism and fibrosis or plaques (Amer. Urological Assoc., 1996) (Table 1).

**b. Characteristics of Studies/Demographics of Patients**

Since 1995 no published studies involving this combination therapy met all of the eligibility criteria. There have been two randomized, controlled, double blind, single dose crossover studies. In one, IC phentolamine + papaverine was compared with placebo and with IC alprostadil monotherapy. This study enrolled 60 subjects, with a mean age of 58 years. Subjects' ED duration had to be > 6 months, and those whose ED was secondary to spinal cord injury, radical pelvic surgery, or those previously treated with IC therapy were excluded. The second study compared IC phentolamine + papaverine with IC Trimix therapy. It enrolled 20 subjects with a mean age of 58. No inclusions or exclusions were given. Outcome in both studies was "adequacy of erection for penetrative sexual intercourse" as assessed by investigator palpation.

**c. Effectiveness Outcomes/Adverse Events**

Double therapy was as effective as alprostadil monotherapy (57% versus 50%; p=NS) but less effective than the triple mixture (28% versus 73%; $p<0.05$). Penile pain appeared to be less in phentolamine + papaverine than in alprostadil alone (15% versus 35%) as well as compared to the triple mixture (0% versus 15%; p=NS).

## D. Treatments Under Development

Apomorphine is a non-narcotic dopamine receptor agonist that is used in the treatment of

Parkinson's disease. The mechanism by which it may effect erectile function is not known. When used for the treatment of ED, apomorphine is taken sublingually prior to desired sexual activity. Apomorphine appeared to be effective in one large study which assessed firmness of erections in response to therapy. (Padma-Nathan, 1998) (Appendix 7)

However, there are no data to date assessing clinical outcomes such as intercourse success. Neither apomorphine nor the previously described treatments, yohimbine, and oral phentolamine, is FDA approved for treatment of ED. Clinical trials are ongoing involving the latter two agents as well as a host of others. The following table lists some additional oral and topical preparations for treatment of ED under development or awaiting FDA approval (Love and Sansone, 1998).

| | Status | Route (Company) |
|---|---|---|
| **Centrally Acting Agents** | | |
| α-adrenergic antagonists | | |
| Atipamezole | Phase I | Oral (Farmos Orion) |
| Deacetyl moxisylyte HCl | Clinical | Intracavernous (IRCEBA) |
| Delequamine HCl | Phase III | Oral (Roche Bioscience) |
| Phentolamine mesylate | Phase III | Oral (Zonagen) |
| Dopaminergic agonists | | |
| Apomorphine | Phase III | Oral (Pentech) |
| **Peripherally Acting Vasoactive Agents** | | |
| Alprostadil gel | Phase I/II | Transdermal (Macrochem) |
| Alprostadil liposomal | Phase I/II | Intrameatal (Harvard Scientific) |
| Alprostadil patch | Development | Transdermal (Therapeutic Discovery) |
| Papaverine patch | Preclinical | Transdermal (PharmaPatch) |
| Papaverine gel | Phase I/II | Transdermal (Pharmedia) |
| **Miscellaneous** | | |
| Melanotan II | Phase I | Subcutaneous (Univ.of Arizona) |

## IV. DISCUSSION

Erectile dysfunction, while not life threatening, is a common condition that can result in withdrawal from sexual intimacy and reduced quality of life. ED is associated with chronic illnesses and medications used to treat these illnesses. Psychological or relationship issues often coexist and can contribute to, or result from, ED. Therefore, a wide range of health care providers must be aware of ED and knowledgeable about the etiology of ED and its treatment options. Advocates of particular ED treatments have suggested that peer-reviewed published randomized trial reports may exaggerate the costs and adverse events associated with these treatments. Other sources of drug safety data (e.g., drug company press releases or the FDA Web page) that are not peer-reviewed may provide more biased data and, therefore, were not extensively used in this report.

This report estimates potential costs to VHA for providing Viagra and other treatments using sets of reasonable assumptions about ED prevalence, dosage and frequency of use. Literature searches conducted in the course of this systematic review discovered no published economic analyses of ED treatments. In the absence of data collected specifically for cost estimation and of rigorously conducted

economic analyses with sensitivity analyses, other sets of assumptions may be equally reasonable and would lead inevitably to different aggregate cost estimates. Thus, postulating or hypothesizing as to a true net cost-utility or cost-benefit ratio at this time could be incorrect in either direction.

The prevalence of ED increases with age and comorbid conditions such as diabetes, heart disease, hypertension, neurologic and psychiatric conditions, smoking and some surgical therapies. Because these conditions are highly prevalent in patients treated within VA, ED is likely to be a major and increasingly important health care issue both in terms of quality of life as well as resource utilization. If results from non-VA population based studies are extrapolated to male veteran users of the VA medical system, an estimated 1.7 million veterans may have some degree of ED. The number of men seeking help is likely to increase with enhanced awareness of ED and its increased treatment options.

Advocates of particular ED treatments have suggested that men seeking these treatments may have undiscovered underlying serious diseases, which cause ED, diagnosed and treated. The availability of ED treatments could thus contribute to improving health care quality and possibly to improving population health. This hypothesis remains untested; its validity would rely on the extent to which early intervention in these diseases does lead to improved outcomes.

The treatment of ED (without evidence of hypogonadism) includes a number of options that are generally viewed by patients, partners and providers as effective in initially restoring erectile function: vacuum constriction devices, penile prosthesis implantation, vasoactive drug injection and oral therapy. However, for many treatments there is a high rate of treatment cessation. Therefore, efforts to optimize treatment should target improvements not only in physiological/clinical measures of erectile function but also patient/partner satisfaction and preference. The NIH Consensus Statement on Impotence encourages physicians to try the least invasive procedure first. The ideal treatment is effective, useful "on demand," free of toxicity and side effects, easy to administer (oral or topical) and affordable.

**Summary of findings**

The results of this systematic review, in conjunction with those published by the American Urological Association Consensus Panel on treatment for erectile dysfunction, indicate that:

- A patient/partner goal directed approach is important to educate the patient/partner about the advantages and disadvantages of the commonly used treatments.

- Most patients desire a convenient, noninvasive therapy that preserves intimacy by causing minimal or no interruption of events leading to sexual intercourse even if this therapy has lower efficacy (i.e. prefer oral treatments).

- In patients with psychogenic ED, psychosexual counseling may be useful.

- **Vacuum constriction devices, intraurethral (alprostadil) and intracavernosal vasoactive drug injection therapy** (alprostadil; papaverine+phentolamine; and a combination of all three agents), **surgical implantation** of a penile prosthesis and **oral medications** (sildenafil and yohimbine) are effective treatments for primarily organic ED.

- Report findings are limited by the inconsistency or lack of reported outcomes, lack of long-term follow-up or comparisons with other active therapies, and selection bias of enrolled patients. Compared to studies of other therapies, studies of **sildenafil and intraurethral alprostadil** involved the most patients and were of greatest duration.

  1. **Vacuum constriction devices** provide a "return to intercourse" and "patient/partner satisfaction rate" of about 75%. Adverse events include discomfort/pain in 19%, likely contributing to the short-term drop out rates of 25%.

  2. In the AUA report, **vasoactive drug injection therapy with alprostadil (IC)** provided "return to intercourse" in approximately 77% of subjects and "patient/partner satisfaction rate" in 70-89%. Subsequent studies assessed for the current report indicate "adequacy of penile rigidity for intercourse" in 22-81% of subjects. Considering both sets of studies, adverse events included: pain in 23-40% and prolonged erection or priapism in 3-5%. Drop out rates were 12-35%.

  3. **Intraurethral drug injection therapy with alprostadil (MUSE)** provides a "return to intercourse rate" of about 40% (65.4% of men who responded to an initial dose of MUSE) versus 11% placebo. It provided "erections sufficient for sexual intercourse" in 50.5% of intercourse attempts within this group of men. Adverse events included: penile pain = 33%, urethral pain = 12% and partners' vaginal burning/itching = 6%. Drop out rates are high, occurring in almost one-third of men receiving transurethral alprostadil.

  4. **Surgical implantation** of penile prostheses provided a functional prosthesis, enabling intercourse in 82-95% of patients. Patient/partner satisfaction ranged from 54% for semirigid devices to greater than 95% for mechanical devices. Adverse events included: discomfort/pain 2-14%; infection 3%; device failure 5-18%; and prosthesis erosion 1-4%.

  5. **Oral therapy with sildenafil** (25-100 mg one hour before sexual stimulation) provided "erections sufficient for sexual intercourse" in 47% of intercourse attempts compared with 20% in men randomized to placebo (RR = 2.9; 95% CI = 2.3-3.8; NNT = 3.5). "Improvement in erections" were noted in 70% of men randomized to sildenafil versus 20% of men randomized to placebo (RR = 3.6; 95% CI = 3.0-4.4; NNT = 2.0). Men are more likely to report improved erections with 50 or 100 mg of sildenafil than with 25 mg.

     Most men enrolled in studies had mild to moderate ED. Results have been comparable in subgroups of men with ED of psychogenic etiology (76% versus 29% noted improvement in erections) or spinal cord injury (78% versus 11%), but lower in men with diabetes (54% versus 10%; RR = 5.5; 95% CI = 3.2-9.5). Sildenafil resulted in "erections sufficient for sexual intercourse" in only about 30% of attempts in men with diabetes.

     With sildenafil, adverse events are generally mild and transient with 10% of men discontinuing medications in short term studies. Headaches and visual disturbances were reported in 18%

and 4% of men taking sildenafil. In the first 8 months since FDA approval over 6 million prescriptions were dispensed (80% to men older than 50 years of age). One hundred thirty deaths following intercourse have been reported as possibly associated with sildenafil. Sildenafil is contraindicated in men taking nitrate preparations of any kind at any time. Also, caution should be exercised when considering use in patients with active coronary ischemia untreated with nitrates, patients with congestive heart failure and borderline low blood pressure, patients on multi-drug, anti-hypertensive regimens and in patients with hepatic or renal disease (American College of Cardiology, 1998).

6. **Oral therapy with yohimbine** (5.4 mg t.i.d.) appears to provide moderate improvement in erectile function. "Response to treatment" has been reported in 48% versus 25% on placebo (RR = 1.9; 95% CI = 1.3-2.8; NNT = 3.9). Adverse events occurred in 17% of men on yohimbine and included elevated blood pressure, anxiety, headache and tachycardia. The drop out rate was 14%. Yohimbine should not be used in geriatric, psychiatric, cardiac or renal patients, or in men with a history of gastric or duodenal ulcer.

7. **Oral therapy with trazodone** was not shown to be effective for treatment of ED but the confidence intervals cannot exclude a clinically important "improvement" in ED.

8. **Oral therapy with phentolamine** has been evaluated in few patients. "Successful intercourse attempts" were reported in 29% of men taking phentolamine versus 13% on placebo (RR = 2.2; 95% CI = 0.8-5.7). While phentolamine was not statistically superior to placebo, clinically important effects cannot be ruled out. Adverse events were mild and occurred in 3% of subjects, and the drop out rate was 3%. It does not have current FDA approval for ED treatment.

- Government costs for treatment options for erectile function vary dramatically:

1. vacuum constriction device (Erec-aide) = $174.25
2. alprostadil (Caverject) = $4.42 per IC injection (10 or 20 mg) ($26.52 for 6 injections/month)
3. alprostadil (MUSE) = $12.31 per IU injection (500 µg) ($73.86 for 6 injections/month)
4. surgical implant = $4300-$8200 (surgical procedure plus six months of follow-up care)
5. sildenafil (Viagra) = $5.23 per pill (50 or 100 mg) ($31.38 for 6 pills/month)
6. yohimbine (Yocon)= $2.00 per 100 tablets (one month therapy)

**VA guideline: The Primary Care Management of Erectile Dysfunction**

VA's Pharmacy Benefits Management Strategic Healthcare Group, along with the Medical Advisory Panel, produced a guideline – *The Primary Care Management of Erectile Dysfunction - June, 1999* (Ogden, 1999). After further internal review and approval, the guideline will be available at http://www.dppm.med.va.gov.

The guideline generally concurs with the results of this systematic review, and also highlights the research needs outlined above. Its authors did not include yohimbine among possible treatment options, and felt strongly that Viagra should not be used without restrictions in the VA population until additional

research confirms its efficacy and safety in elderly men with multiple comorbidities who take multiple concurrent medications.

## V. CONSIDERATIONS FOR TREATMENT AND FUTURE RESEARCH

The following considerations for treatment of erectile dysfunction apply to the standard patient. This patient is defined as a man who develops erectile dysfunction after a well-established period of normal erectile function, whose erectile dysfunction is primarily due to organic rather than psychological or relationship issues and who has no evidence of hypogonadism or hyperprolactinemia.

- ED is a common condition that results in reduction in quality of life. The number of men seeking help is likely to increase with enhanced awareness of ED and treatment options.

- ED is frequently associated with chronic illnesses and medications used to treat these illnesses. Psychological or relationship issues often coexist. A wide range of health care providers must be aware of ED and knowledgeable about its etiologies and treatment options.

- The patient and, when possible, his partner should be fully informed in an unbiased manner about recommended treatment options, their relative benefits and potential complications.

- Based on the available data acceptable treatment options for men with ED include:
  - Vacuum constriction devices
  - Oral therapy with sildenafil
  - Oral therapy with yohimbine
  - Intraurethral drug injection with alprostadil
  - Intracavernous drug injection therapy: phentolamine + papaverine + alprostadil; phentolamine + papaverine; or alprostadil alone
  - Surgical implantation of a penile prosthesis

- Randomized trials directly comparing treatment options have not been performed making evaluation of relative treatment efficacy, safety and patient/partner preferences difficult.

- Baseline characteristics of male veterans with ED are not known. It is likely that veterans are older, have a greater number of coexisting psychological (e.g. depression) and medical conditions and have ED that is more severe than reported in randomized trials. The efficacy, safety and patient/partner preference of treatments for ED in veterans is not known.

- Treatment options have marked differences in costs, contraindications, side effects and patient acceptability profiles. Formal cost benefit analyses have not been conducted. However, if one fifth of the estimated 1.7 million veterans with ED were treated with sildenafil it would cost almost $100,000,000 per year. Cost estimates for treatment with IU or IC alprostadil are higher. However, the availability of sildenafil is most likely to provide the greatest increase in the number of veterans requesting and utilizing treatment for ED.

**Suggestions for further research**

This assessment concludes that a range of treatment options for men with ED of primarily organic origin is available. While the options vary in their side effects, patient and partner acceptability and costs, all of those approved by the FDA for this indication, i.e. oral sildenafil (*Viagra*); intraurethral alprostadil (*MUSE*); and intracavernous injections of alprostadil (*Caverject*), have been shown in well-designed research to be effective in initially restoring erectile function.

The currently available literature does not reflect the use of the available treatment options, specifically sildenafil (*Viagra*), in VA's population of elderly men with multiple comorbidities, taking multiple concurrent medications. The risk of adverse events with Viagra may be higher in the VA population than is reported in the published literature. Additional research, which could correct deficits in the existing research-based knowledge foundation highlighted by this systematic review, is presented below:

- Research is needed to develop new therapies for ED that are convenient, effective, noninvasive, safe and ultimately less expensive.

- Long term, randomized clinical trials incorporating clinically relevant and patient-centered criteria are needed to directly compare the performance of available treatment options.

- Randomized trials directly comparing treatment options for ED, in veterans or comparable populations, using clinically relevant endpoints of treatment efficacy and adverse effects, as well as patient-centered outcomes such as patient/partner preferences and quality of life, will enable a more informed evaluation of treatments for ED within veterans.

- Subgroup analyses may be useful for determining if particular patient groups are better treated with specific therapies.

- Results from comparative randomized trials should be incorporated in cost-effectiveness analyses to help guide the efficient allocation of VA health care resources for the treatment of ED.

## VI. ONGOING RANDOMIZED TRIALS

There are several ongoing randomized trials to assess the efficacy of different oral therapies for ED. Manufacturers for oral phentolamine (Vasomax) and apomorphine have submitted requests for FDA approval. Adequate data for analysis (particularly for apomorphine) were not available for this review. Additional randomized trials of sildenafil are assessing long-term efficacy as well as the effectiveness of sildenafil in men with a wide range of etiologies and severity of ED.

Randomized trials have been initiated to enhance the efficacy and reduce the side effects of intraurethral alprostadil. One study uses a penile constriction device in addition to intraurethral alprostadil to enhance drug absorption and prevent "venous leak." Other studies are combining the alpha-blocker prazosin with alprostadil to reduce penile pain. Updated reviews to evaluate new therapies for ED are encouraged.

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## VIII. TABLE 1 [adapted from AUA Clinical Guidelines Panel on Erectile Dysfunction (D. K. Montague, et al. J Urol; 156:2007-2011; 1996)]

| OUTCOMES OF TREATMENTS | | VACUUM DEVICES | | VENOUS/ARTERIAL SURGERY | | | |
|---|---|---|---|---|---|---|---|
| | | G / P[1] | VCD | G / P[1] | Venous | G / P[1] | Arterial |
| Return to intercourse | Median: | 18 | .757 | 43 | .433 | 19 | .603 |
| | 95% CI: | 1943 | .668-.828 | 1801 | .378-.488 | 713 | .538-.664 |
| Patient Satisfaction[2] | Median: | 20 | .763 | 11 | .438 | 11 | .738 |
| | 95% CI: | 859 | .686-.826 | 515 | .357-.522 | 245 | .660-.803 |
| Partner Satisfaction | Median: | 7 | .742 | 1 | .319 | 0 | No |
| | 95% CI: | 218 | .582-.867 | 72 | .222-.435 | 0 | Data |
| Dropout | Median: | 22 | .253 | | | | |
| | 95% CI: | 1072 | .218-.291 | | | | |
| Systematic adverse events[3] | Median: | | | | | | |
| | 95% CI: | | | | | | |
| Local adverse events[4] | Median: | 18 | .095 | | | | |
| | 95% CI: | 884 | .054-.150 | | | | |
| Discomfort / Pain | Median: | 20 | .188 | 6 | .216 | 1 | .192 |
| | 95% CI: | 2481 | .135-.254 | 156 | .116-.346 | 11 | .040-.467 |
| Prolonged erection / priapism | Median: | | | 8 | .028 | 1 | .077 |
| | 95% CI: | | | 218 | .001-.059 | 15 | .007-.272 |
| Fibrosis / nodules / plaques | Median: | | | | | | |
| | 95% CI: | | | | | | |

1. G = Number of groups/treatment arms P = Number of patients
2. Patient satisfaction groups for venous and arterial surgery include only those patients able to return to intercourse
3. Systemic adverse events include hypotension, tachycardia, vasovagal response, liver dysfunction, flushing and dizziness
4. Local adverse events include petechiae, ecchymoses, hematomas, abrasions and discomfort on ejaculation
5. Nonmalleable semirigid prostheses are no longer available

**Table 1 (continued)**

| OUTCOMES OF TREATMENTS | | PROSTHESES | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | G / P[1] | Semirigid[5] | G / P[1] | Malleable | G / P[1] | Mechanical (nonhydraulic) | G / P[1] | Hydraulic | G / P[1] | Multicomponent hydraulic |
| Return to intercourse | Median: | **Intercourse is possible with any functional prosthesis** | | | | | | | | | |
| | 95% CI: | | | | | | | | | | |
| Patient satisfaction[2] | Median: | 3 | .533 | 8 | .833 | 2 | .957 | 5 | .644 | 12 | .889 |
| | 95% CI: | 80 | .302-.754 | 254 | .773-.880 | 73 | .877-.992 | 177 | .539-.737 | 1953 | .838-.925 |
| Partner satisfaction | Median: | 2 | .540 | 2 | .789 | 1 | .986 | 1 | .581 | 4 | .879 |
| | 95% CI: | 43 | .270-.795 | 37 | .567-.932 | 16 | .857-.999 | 12 | .312-.820 | 478 | .746-.959 |
| Discomfort / pain | Median: | 2 | .144 | 4 | .102 | 1 | .019 | 2 | .087 | 5 | .025 |
| | 95% CI: | 212 | .044-.315 | 145 | .030-.233 | 63 | .002-.072 | 118 | .012-.269 | 983 | .001-.050 |
| Prolonged erection / priapism | Median: | | | | | | | | | | |
| | 95% CI: | | | | | | | | | | |
| Infection | Median: | 6 | .025 | 9 | .033 | 2 | .024 | 12 | .038 | 36 | .025 |
| | 95% CI: | 695 | .015-.038 | 465 | .019-.051 | 89 | .005-.070 | 1051 | .028-.051 | 5133 | .021-.029 |
| Mechanical device failure | Median: | 2 | .062 | 7 | .046 | 2 | .069 | 6 | .183 | 26 | .096 |
| | 95% CI: | 181 | .033-.103 | 476 | .031-.069 | 89 | .029-.134 | 355 | .146-.227 | 2225 | .084-.109 |
| Prosthesis erosion | Median: | 2 | .012 | 6 | .039 | 1 | .009 | 2 | .025 | 21 | .011 |
| | 95% CI: | 262 | .003-.030 | 242 | .019-.067 | 26 | .000-.091 | 125 | .007-.063 | 2396 | .008-.016 |
| Surgical complications | Median: | 0 | No data | 0 | No data | 0 | No data | 1 | .299 | 3 | .055 |
| | 95% CI: | 0 | | 0 | | 0 | | 107 | .220-.392 | 531 | .038-.077 |

1. G = Number of groups/treatment arms P = Number of patients
2. Patient satisfaction groups for venous and arterial surgery include only those patients able to return to intercourse
3. Systemic adverse events include hypotension, tachycardia, vasovagal response, liver dysfunction, flushing and dizziness
4. Local adverse events include petechiae, ecchymoses, hematomas, abrasions and discomfort on ejaculation
5. Nonmalleable semirigid prostheses are no longer available

**Table 1 (continued)**

| OUTCOMES OF TREATMENTS | | ORAL DRUG THERAPY | | | | VASOACTIVE DRUG INJECTION THERAPY | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | G / P[1] | Yohimb. | G / P[1] | Placebo | G / P[1] | Pap Mono | G / P[1] | Pap/ Phent | G / P[1] | $PGE_1$ | G / P[1] | P/P/P |
| Return to intercourse | Median: | 4 | .247 | 0 | No data | 1 | .999 | 10 | .714 | 3 | .771 | 1 | .781 |
| | 95% CI: | 445 | .188-.317 | 0 | | 20 | .883-1.000 | 672 | .588-.821 | 77 | .642-.872 | 146 | .706-.841 |
| Patient satisfaction[2] | Median: | 4 | .247 | 3 | .112 | 1 | .674 | 12 | .776 | 2 | .706 | 0 | No data |
| | 95% CI: | 445 | .188-.317 | 110 | .051-.202 | 144 | .593-.745 | 1112 | .666-.864 | 19 | .442-.898 | 0 | |
| Partner satisfaction | Median: | 0 | No data | 0 | No data | 0 | No data | 1 | .976 | 1 | .886 | 0 | No data |
| | 95% CI: | 0 | | 0 | | 0 | | 172 | .946-.992 | 10 | .619-.989 | 0 | |
| Dropout | Median: | 0 | No data | 0 | No data | 2 | .640 | 17 | .309 | 4 | .346 | 2 | .158 |
| | 95% CI: | 0 | | 0 | | 195 | .533-.734 | 2074 | .227-.407 | 253 | .098-.667 | 262 | .067-.295 |
| Systemic adverse advents[3] | Median: | 2 | .067 | 0 | No data | 4 | .070 | 8 | .029 | 6 | .019 | 0 | No data |
| | 95% CI: | 297 | .044-.102 | 0 | | 452 | .046-.104 | 635 | .017-.043 | 639 | .008-.036 | 0 | |
| Local adverse advents[4] | Median: | | | | | 1 | .040 | 9 | .147 | 4 | .098 | 0 | No data |
| | 95% CI: | | | | | 136 | .013-.089 | 1045 | .077-.242 | 287 | .057-.151 | 0 | |
| Discomfort / pain | Median: | | | | | 3 | .189 | 9 | .171 | 9 | .233 | 2 | .035 |
| | 95% CI: | | | | | 377 | .101-.303 | 1059 | .076-.306 | 856 | .175-.304 | 262 | .011-.081 |
| Prolonged erection / priapism | Median: | | | | | 10 | .093 | 19 | .061 | 14 | .031 | 3 | .035 |
| | 95% CI: | | | | | 997 | .049-.156 | 2084 | .043-.085 | 1191 | .017-.053 | 490 | .011-.080 |
| Fibrosis / nodules / plaques | Median: | | | | | 2 | .093 | 14 | .062 | 4 | .001 | 2 | .027 |
| | 95% CI: | | | | | 117 | .002-.452 | 1371 | .035-.099 | 332 | .000-.008 | 262 | .002-.110 |

1. G = Number of groups/treatment arms P = Number of patients
2. Patient satisfaction groups for venous and arterial surgery include only those patients able to return to intercourse
3. Systemic adverse events include hypotension, tachycardia, vasovagal response, liver dysfunction, flushing and dizziness
4. Local adverse events include petechiae, ecchymoses, hematomas, abrasions and discomfort on ejaculation
5. Nonmalleable semirigid prostheses are no longer available

# IX. TABLE 2: ORAL DRUG THERAPY: SILDENAFIL VERSUS PLACEBO

## Table 2A: All Causes of Erectile Dysfunction†

| OUTCOME OF TREATMENTS | Sildenafil | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|
| | # Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| Patient overall assessment of treatment : "Did treatment improve your erections" | 1905 | 2729 | 70.0 | 308 | 1575 | 19.6 | 15 | 3.59<br>2.97-4.35 |
| Sexual Intercourse: Diary/Event Log: Total successful attempts | 25159 | 54135 | 46.5 | 6651 | 34101 | 19.5 | 5 | 2.94<br>2.26-3.82 |
| Sexual Intercourse - Diary/Event Log: success by subjects | 949 | 1161 | 81.7 | 418 | 797 | 52.4 | 5 | 1.56<br>1.35-1.81 |
| Dropouts: All causes* | 161 | 1781 | 9.0 | 98 | 917 | 10.7 | 8 | 0.82<br>0.65-1.05 |
| Dropouts: Treatment related | 7 | 812 | <1 | 2 | 465 | <1 | 3 | 1.65<br>0.28-9.63 |
| **ADVERSE EVENTS** | Sildenafil | | | Placebo | | | | |
| | # Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| All adverse events: | 400 | 805 | 49.7 | 94 | 704 | 13.4 | 5 | 3.60<br>1.64-7.89 |
| Headache | 115 | 627 | 18.3 | 22 | 526 | 4.2 | 4 | 4.01<br>2.60-6.20 |
| Visual disturbances | 27 | 615 | 4.3 | 3 | 514 | < 1 | 3 | 6.46<br>1.92-21.76 |
| Other (flushing, dyspepsia, rhinitis, urinary tract infection,) | 164 | 491 | 33.4 | 21 | 394 | 5.3 | 3 | 4.27<br>1.30-14.04 |
| Deaths** - (Most had risk factors for heart disease) | 130: 16 had taken NTG or other nitrate medicine/27 died immediately following intercourse | | | | | | | |

* For some studies, dropouts estimated from discontinuation rates; ** From U.S. Food and Drug Administration, November 25, 1998.
† Not all studies provided information

## Table 2B: Wholly or Substantially Psychogenic Erectile Dysfunction

| **OUTCOME OF TREATMENTS** | SILDENAFIL | | | PLACEBO | | | | |
|---|---|---|---|---|---|---|---|---|
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| Patient overall assessment of treatment : "Did treatment improve your erections" | 306 | 405 | 75.6 | 74 | 253 | 29.2 | 4 | 2.52<br>2.08-3.07 |
| Sexual Intercourse: Diary/Event Log:<br>Total successful attempts | | | | | | | | |
| Sexual Intercourse - Diary/Event Log: success by subjects | | | | | | | | |
| Dropouts: All causes* | 1 | 44 | 2.3 | 1 | 44 | 2.3 | 1 | 1.00 |
| Dropouts: Treatment related | | | | | | | | |
| **ADVERSE EVENTS** | SILDENAFIL | | | PLACEBO | | | | |
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| All adverse events | 6 | 12 | 50.0 | 5 | 12 | 41.6 | 1 | 1.20<br>0.50-2.88 |
| Headache | 1 | 12 | 8.3 | 0 | 12 | 0.0 | 1 | - |
| Visual disturbances | | | | | | | | |
| Other (flushing, dyspepsia, rhinitis, urinary tract infection) | | | | | | | | |

* For some studies, dropouts estimated from discontinuation rates

## Table 2C: Erectile Dysfunction Caused By Spinal Cord Injury

| **OUTCOME OF TREATMENTS** | SILDENAFIL | | | PLACEBO | | | | |
|---|---|---|---|---|---|---|---|---|
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| Patient overall assessment of treatment : "Did treatment improve your erections" | 160 | 205 | 78.0 | 22 | 205 | 10.7 | 2 | 7.27<br>4.87-10.86 |
| Sexual Intercourse: Diary/Event Log:<br>Total successful attempts | | | | | | | | |
| Sexual Intercourse - Diary/Event Log: success by subjects | | | | | | | | |
| Dropouts: All causes* | 8 | 205 | 3.9 | 5 | 205 | 2.4 | 2 | 1.60<br>0.54-4.73 |
| Dropouts: Treatment related | | | | | | | | |
| **ADVERSE EVENTS** | SILDENAFIL | | | PLACEBO | | | | |
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| All adverse events | 94 | 178 | 52.8 | 50 | 178 | 28.1 | 1 | 1.88<br>1.43-2.47 |
| Headache | | | | | | | | |
| Visual disturbances | | | | | | | | |
| Other (flushing, dyspepsia, rhinitis, urinary tract infection) | | | | | | | | |

* For some studies, dropouts estimated from discontinuation rates

## Table 2D: Erectile Dysfunction Caused By Diabetes Mellitus

| **OUTCOME OF TREATMENTS** | SILDENAFIL | | | PLACEBO | | | | |
|---|---|---|---|---|---|---|---|---|
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| Patient overall assessment of treatment : "Did treatment improve your erections" | 74 | 136 | 54.4 | 13 | 132 | 9.8 | 1 | 5.52<br>3.22-9.47 |
| Sexual Intercourse: Diary/Event Log:<br>Total successful attempts | 1439 | 4746 | 30.3 | 270 | 3763 | 7.2 | 1 | 4.23<br>3.74-4.78 |
| Sexual Intercourse - Diary/Event Log: success by subjects | 71 | 136 | 52.2 | 25 | 132 | 18.9 | 1 | 2.76<br>1.87-4.06 |
| Dropouts: All causes* | 5 | 136 | 3.7 | 11 | 132 | 8.3 | 1 | 0.44<br>0.16-1.24 |
| Dropouts: Treatment related | | | | | | | | |
| **ADVERSE EVENTS** | SILDENAFIL | | | PLACEBO | | | | |
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| All adverse events | 22 | 136 | 16.2 | 1 | 132 | < 1 | 1 | 21.35<br>2.92-156.16 |
| Headache | 15 | 136 | 11.0 | 2 | 132 | 1.5 | 1 | 7.28<br>1.70-31.22 |
| Visual disturbances | 5 | 136 | 3.7 | 1 | 132 | < 1 | 1 | 4.85<br>0.57-40.99 |
| Other (flushing, dyspepsia, rhinitis, urinary tract infection) | | | | | | | | |

* For some studies, dropouts estimated from discontinuation rates

## X. TABLE 3: ORAL DRUG THERAPY: YOHIMBINE VERSUS PLACEBO: All causes of erectile dysfunction†

| **OUTCOME OF TREATMENTS** | Yohimbine | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| Positive drug response or responders to drug treatment | 133 | 277 | 47.6 | 67 | 269 | 24.9 | 8 | 1.91<br>1.30-2.82 |
| Dropouts: All causes | 16 | 128 | 12.5 | 4 | 128 | 3.1 | 4 | 2.14<br>0.28-16.17 |
| Dropouts: Treatment related | 18 | 131 | 13.7 | 0 | 131 | 0.0 | 3 | |
| **ADVERSE EVENTS (1)** | Yohimbine | | | Placebo | | | | |
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| All events:* | 32 | 189 | 16.9 | 9 | 188 | 4.8 | 5 | 2.78<br>1.40-5.56 |

*In some studies, numbers calculated from percentages. Includes HTN, anxiety, dizziness, chills, headache, sweating, tachycardia, GI disturbances, increased frequency of urination, rash, loss of antiepileptic action of phenytoin

†Not all studies provided information

## XI. TABLE 4: ORAL DRUG THERAPY: PHENTOLAMINE VERSUS PLACEBO: All causes of erectile dysfunction

| **OUTCOME OF TREATMENTS** | Phentolamine* | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| Number of patients reporting success or responding to treatment | 190 | 489 | 38.8 | 56 | 303 | 18.5 | 2** | 2.10<br>1.62-2.73 |
| Sexual Intercourse:<br>Total successful attempts | 26 | 90 | 28.9 | 4 | 30 | 13.4 | 1 | 2.17<br>0.82-5.71 |
| Dropouts: All causes | 0 | 30 | | 0 | 10 | | | |
| Dropouts: Treatment related | | | | | | | | |
| **ADVERSE EVENTS (1)** | Phentolamine* | | | Placebo | | | | |
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| All events: (headaches, facial flushing or nasal congestion)† | 1 | 30 | 3.3 | 0 | 10 | | 1 | |

* Pooled doses of 20, 40, 60 and 80 mg.

** Includes information from AUA meeting abstract (2 multi-center trials. The first was a placebo-controlled, parallel group, double-blind design (40, 80mg or placebo); the second, a placebo-controlled crossover design of a fixed dose (40mg) vs. placebo. A responder was considered any patient whose endpoint International Index of Erectile Function domain score improved by at least one clinical dysfunction class and who met the criteria for at least mild-to-moderate dysfunction at endpoint.

† Abstract indicated sides effects <10% occurrence.

## XII. TABLE 5: ORAL DRUG THERAPY: TRAZODONE VERSUS PLACEBO: All causes of erectile dysfunction

| **OUTCOME OF TREATMENTS** | Trazodone | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| Positive drug response or responders to drug treatment* | 44 | 123 | 35.8 | 28 | 126 | 22.2 | 4 | 1.56<br>0.78-3.11 |
| Dropouts: All causes | 8 | 57 | 14.0 | 8 | 62 | 12.9 | 2 | 1.12<br>0.45-2.81 |
| Dropouts: Treatment related | 8 | 57 | 14.0 | 3 | 62 | 4.8 | 2 | 2.62<br>0.79-8.63 |
| **ADVERSE EVEVTS (1)** | Trazodone | | | Placebo | | | | |
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| All events: ** | 19 | 78 | 24.4 | 8 | 80 | 10.0 | 3 | 2.14<br>1.00-4.58 |

*Two studies also included 2 additional treatment arms: Aydin (1996) testosterone and hypnosis. For improvement in sexual function success rates for hypnosis and testosterone were 80% and 60%, respectively,
compared to a 67% success rate for trazodone.; and Kurt (1994) ketanserin and mianserin. Positive response rates for ketanserin and mianserin were 19% and 32%, respectively, compared to a 65% success rate for
trazodone.

## XIII. TABLE 6: INTRAURETHRAL THERAPY: ALPROSTADIL VERSUS PLACEBO: All causes of erectile dysfunction†

| OUTCOME OF TREATMENTS | Alprostadil | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| **Note: 2 studies (Padma-Nathan, Williams) included only men who achieved an erection sufficient for intercourse (EAS* score of 4 or 5) during an initial dosing phase of alprostadil. The men who responded were then randomized to alprostadil or placebo.** | | | | | | | | |
| Sexual Intercourse: Diary/Event Log: Total successful attempts | 2875 | 5696 | 50.5 | 500 | 4957 | 10.1 | 2 | 5.01 4.59-5.47 |
| Return to Sexual Intercourse: at least once during three-month treatment | 345 | 563 | 61.3 | 101 | 592 | 17.1 | 2 | 3.59 2.97-4.34 |
| Dropouts: All causes | 49 | 563 | 8.7 | 28 | 592 | 4.7 | 2 | 1.83 1.19-2.80 |
| **ADVERSE EVENTS**** | Alprostadil | | | Placebo | | | | |
| | #Events | Totals | % | # Events | Totals | % | # Studies | RR (95%CI) |
| Penile pain | 159 | 486 | 32.7 | 17 | 511 | 3.3 | 2 | 9.52 5.94-15.25 |
| Urethral pain | 59 | 486 | 12.1 | 21 | 511 | 4.1 | 2 | 5.82 2.36-14.33 |
| Female partner adverse events: (vaginal burning/itching) | 28 | 486 | 5.8 | 4 | 511 | 0.8 | 1 | 7.36 2.60-20.83 |
| Serious Cardiac Adverse Events ‡ | 5 | 564 | <1 | 10 | 592 | 1.7 | 1 | 0.52 0.15-1.67 |

* Erection Assessment Scale (3=full erection, 4=erection sufficient for intercourse, 5=rigid erection).
** Urogenital system only. All other AEs (nervous system, respiratory ≤ 5%.
‡ Of the 15 serious cardiac adverse events, one was considered by the investigator to be "possibly" drug related.
† Not all studies provided information

# XIV. TABLE 7: INTRACAVERNOUS THERAPY (IT)

## TABLE 7A: Prostaglandin E1 (Alprostadil/PGE1) versus moxisylate chlorhydrate (MC), transurethral alprostadil (TA) and vacuum device (VD): all causes of erectile dysfunction

| OUTCOME OF TREATMENTS | PGE1 | | | MC | | | TA and VD |
|---|---|---|---|---|---|---|---|
| | # Events | Totals | % | # Events | Totals | % | |
| Erectile response/investigator rated: "erection adequate for intercourse" | 61 | 75 | 81 | 37 | 81 | 46* | Treatment preference: IT 64% vs. TA 36%** |
| Erectile response: subjects reporting at least 1 rigid erection | 58 | 75 | 77 | 37 | 81 | 46* | Treatment preference: IT 57% vs. VD† 27% |
| Erectile response: Buckling Test (at least 1 positive test)†† | 56 | 75 | 75 | 32 | 81 | 40* | Partner preference: IT 50% vs. VD 27% |
| Dropouts | 1 | 75 | 1 | 8 | 81 | 9 | IT vs. VD<br>6 did not complete study |

| ADVERSE EVENTS‡ | PGE1 | | | MC | | | TA and VD§ | | |
|---|---|---|---|---|---|---|---|---|---|
| | # Events | Totals | % | # Events | Totals | % | # Events | Totals | % |
| Penile pain | 28 | 75 | 37 | 14 | 81 | 17.3 | | | |
| Prolonged erection (> 2 hours) | 4 | 75 | 5 | 0 | 81 | | | | |
| Priapism | 0 | 75 | | 0 | 81 | | 1 (IT vs. VD) | 50 | 2 |
| Other (bleeding, hematoma) | 2 | 75 | 2.7 | 2 | 81 | 2.5 | | | |

* $p<0.001$ versus MC.
** Abstract data (ongoing study, 45 enrolled - 22 have completed follow-up)
† IT therapy versus VD contained PGE1+ papaverine + phentolamine
†† Number of patients with 3 consecutive buckling tests, alprostadil = 40/75 (53%) versus MC = 13/81 (16%), $p<0.001$.
‡ For office period only versus MC. Penile pain includes pain during injection, during and after erection.
§ Adverse events reported as "bruising, injury or skin changes sufficient to stop or decrease treatment" IT = 9%, VD = 16%. No adverse events information available for IT vs. TA.

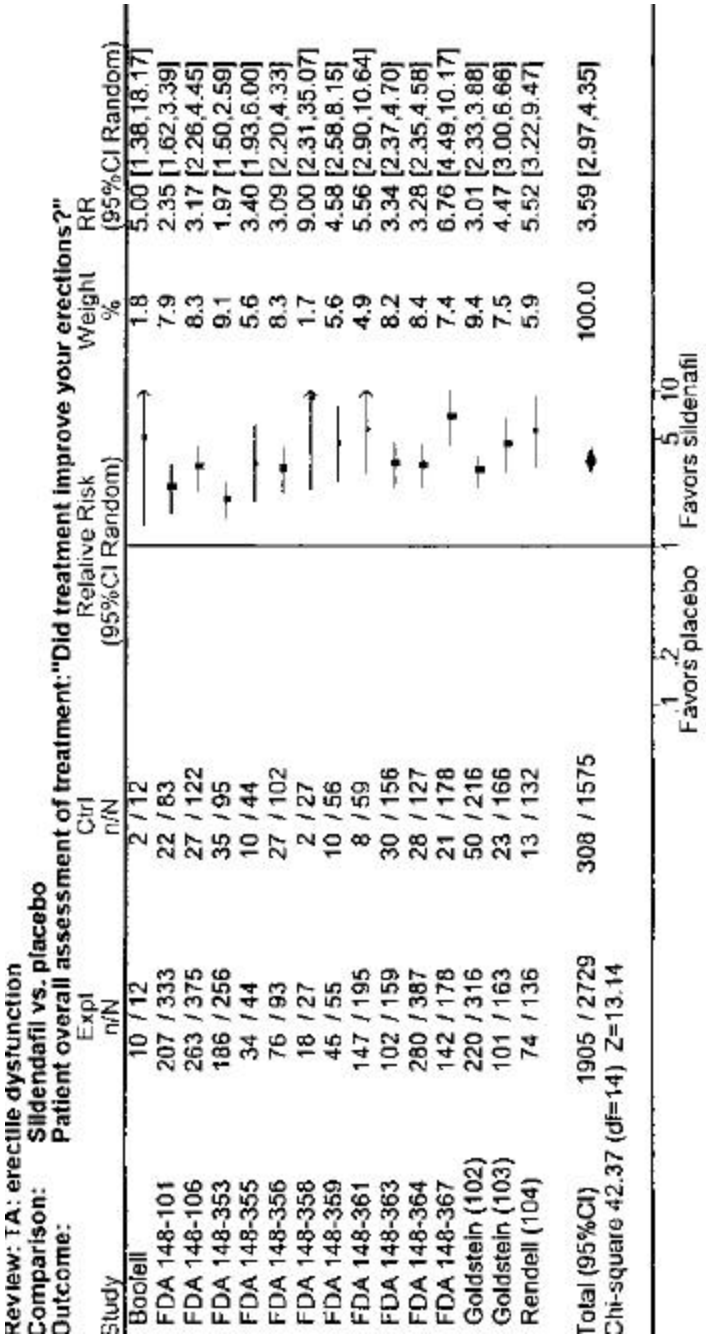
**TABLE 7B: (single-dose) Prostaglandin E1 (Alprostadil/PGE1) versus COMBINATION THERAPY†, or versus placebo: all causes of erectile dysfunction**

| **OUTCOME OF TREATMENTS** | PGE1 alone | | PGE1+PAP+PHEN | | PAP+PHEN | | Placebo | |
|---|---|---|---|---|---|---|---|---|
| | # E/T†† | SR%‡ | # E/T | SR% | # E/T | SR% | # E/T | SR% |
| Erectile response: Clinical evaluation or investigator rated (EAS score of 4 or 5, erections "allowing penetration, "full" or "adequate" erections) | 84/237**a***<br>12-23/45**b**<br>30/60**c**<br>7/32**d**<br><br><br>6/25**f** | 16-52**<br>27-51**<br>50<br>22<br><br><br>24 | <br><br><br>16/32**d**<br>52/114**e**<br>52/114**e**§ | <br><br><br>50<br>46<br>46 | <br><br>34/60**c** | <br><br>57 | 0/59**a**<br>0/45**b**<br>0/60**c** | |
| Erectile response: Rigiscan (rigidity ≥ 70%) | 78/237**a**<br>17-25/45**b** | 22-50**<br>38-56** | | | | | 0/59**a**<br>0/45**b** | |
| Dropouts: All causes | 3/25 | 12 | 2/230 | <1 | | | | |
| **ADVERSE EVENTS** | PGE1 alone | | PGE1+PAP+PHEN | | PAP+PHEN | | Placebo | |
| **(pooled for all studies)** | # E/T | % | # E/T | % | # E/T | % | # E/T | % |
| Penile pain | 120/424<br>10/25§§ | 28<br>40 | 64/166<br>61/114§ | 39 | | | 0/342 | |
| Prolonged erection | 14/297 | 5 | 2/20 | 10 | 12/80 | 15 | | |
| Priapism | 1/237 | <1 | | | | | | |
| Other (bleeding, hematoma) | 1/45 | 2 | | | | | | |

††E/T=Event/Totals. Events calculated from provided percentages for some studies.
‡SR=success rate
* letters matching to corresponding control group
** percent ranges for escalating doses
§ active-control contained 0.075mg atropine
§§ active-control 1% lidocaine
† PAP=Papaverine, PHEN=Phentolamine

## XV. FIGURE 1: Sildenafil versus placebo

### A. Patient overall assessment of treatment: "Did treatment improve your erections?"

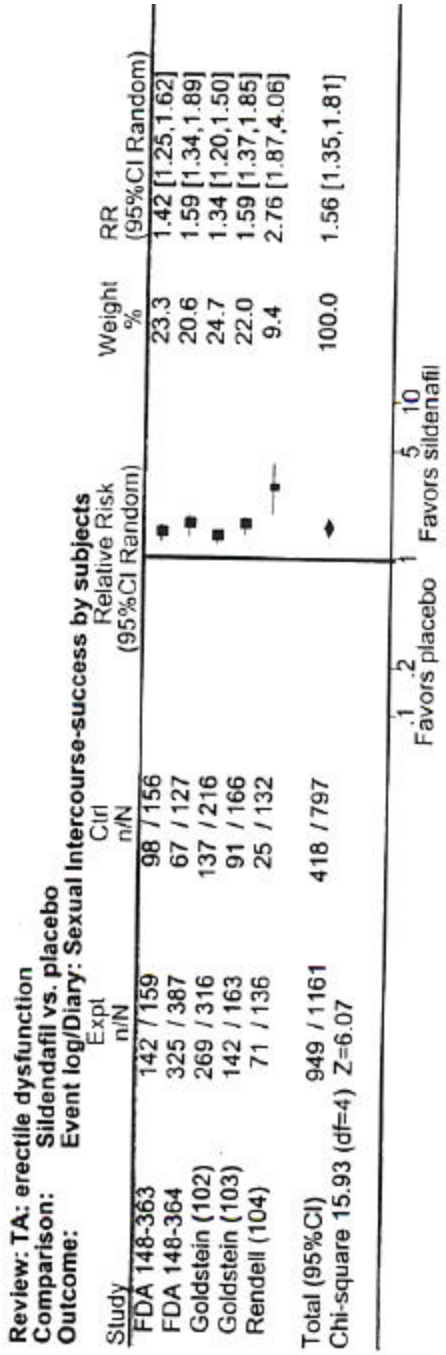


**B. Event log/diary: sexual intercourse - total successful attempts**

**Review: TA: erectile dysfunction**
**Comparison: Sildendafil vs. placebo**
**Outcome: Event log/Diary: Sexual Intercourse-TOTAL successful attempts**

| Study | Expt n/N | Ctrl n/N | Relative Risk (95%CI Random) | Weight % | RR (95%CI Random) |
|---|---|---|---|---|---|
| FDA 148-363 | 5284 / 8978 | 1780 / 6984 | | 20.2 | 2.31 [2.21,2.41] |
| FDA 148-364 | 5322 / 12567 | 481 / 3705 | | 19.9 | 3.26 [2.99,3.55] |
| Goldstein (102) | 10322 / 21873 | 3388 / 14004 | | 20.3 | 1.95 [1.89,2.02] |
| Goldstein (103) | 2792 / 5971 | 732 / 5645 | | 20.0 | 3.61 [3.35,3.88] |
| Rendell (104) | 1439 / 4746 | 270 / 3763 | | 19.5 | 4.23 [3.74,4.78] |
| Total (95%CI) | 25159 / 54135 | 6651 / 34101 | | 100.0 | 2.94 [2.26,3.82] |
| Chi-square 411.74 (df=4) Z=8.04 | | | | | |

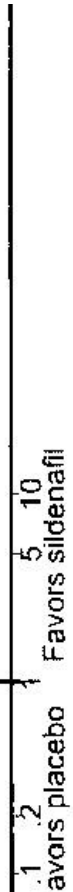
## C. Event log/diary: sexual intercourse - success by subjects



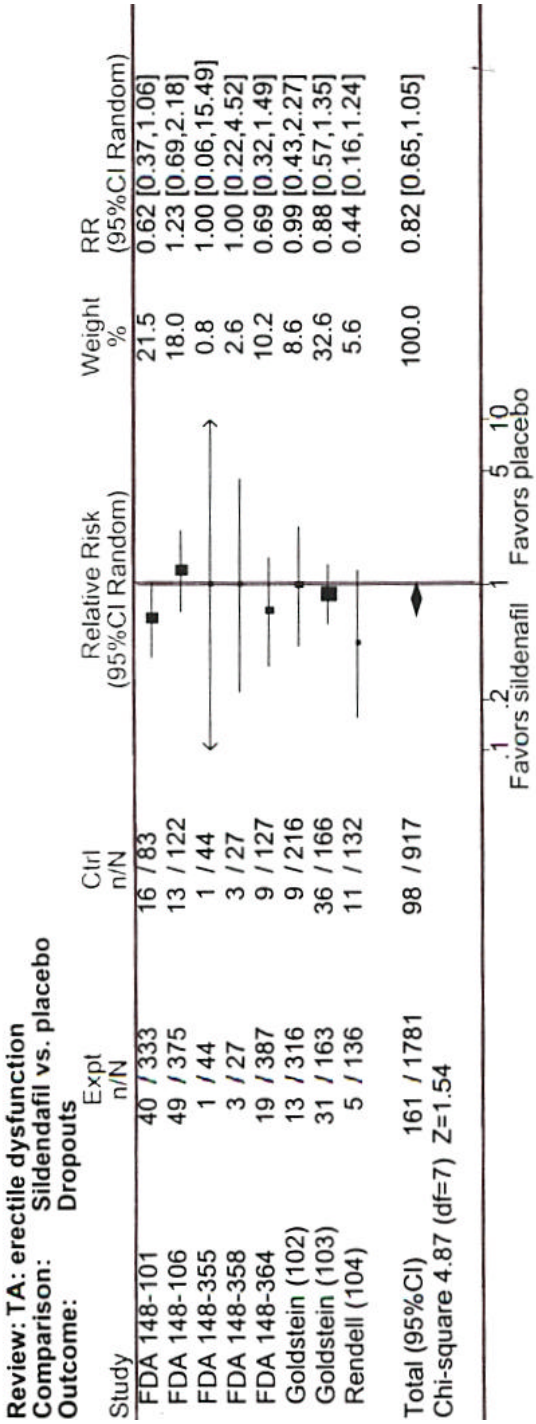
## D. Adverse events: mild and transient

**Review: TA: erectile dysfunction**
**Comparison: Sildendafil vs. placebo**
**Outcome: Adverse events: mild and transient (headache, dyspepsia, flushing, rhinitis, visual disturbance)**

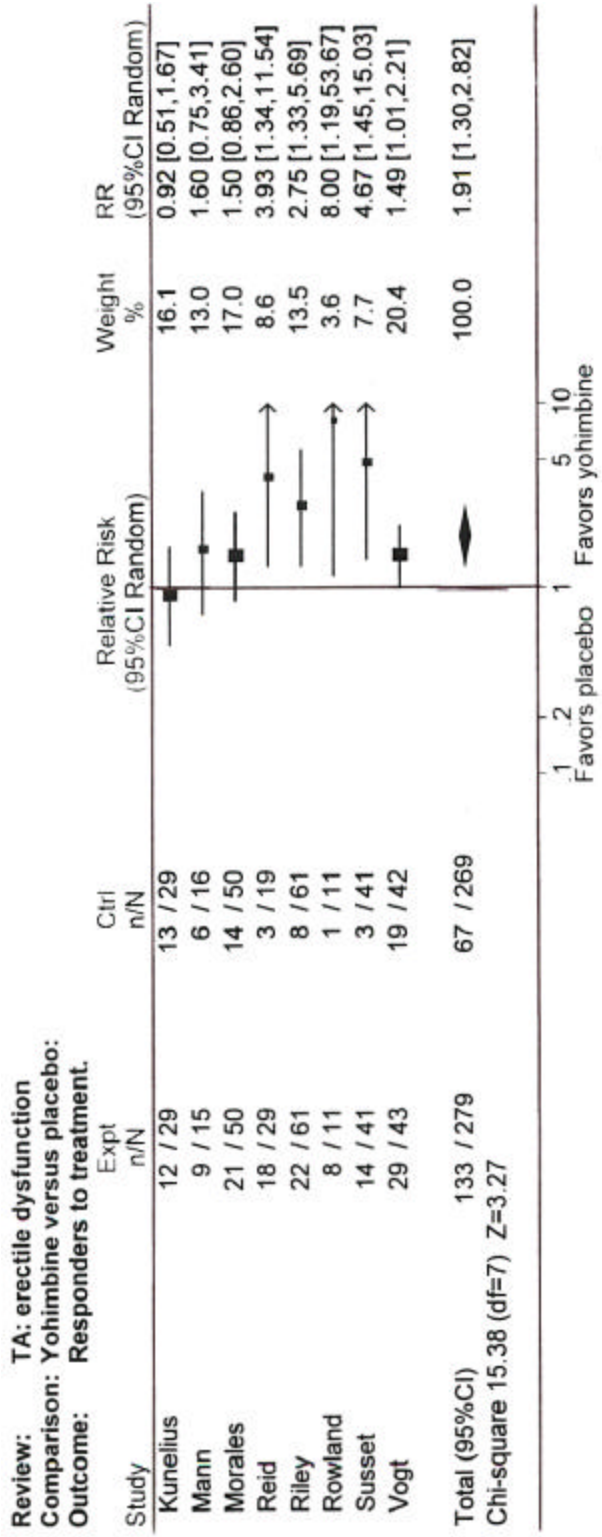
| Study | Expl n/N | Ctrl n/N | RR (95%CI Random) | Weight % | RR (95%CI Random) |
|---|---|---|---|---|---|
| Boolell | 5 / 12 | 5 / 12 | | 18.6 | 1.00 [0.39,2.58] |
| FDA 148-367 | 94 / 178 | 50 / 178 | | 24.8 | 1.88 [1.43,2.47] |
| Goldstein (102) | 198 / 316 | 25 / 216 | | 24.1 | 5.41 [3.71,7.90] |
| Goldstein (103) | 81 / 163 | 13 / 166 | | 22.8 | 6.35 [3.68,10.94] |
| Rendell (104) | 22 / 136 | 1 / 132 | | 9.7 | 21.35 [2.92,156.16] |
| Total (95%CI) | 400 / 805 | 94 / 704 | | 100.0 | 3.60 [1.64,7.89] |
| Chi-square 41.42 (df=4) Z=3.20 | | | | | |



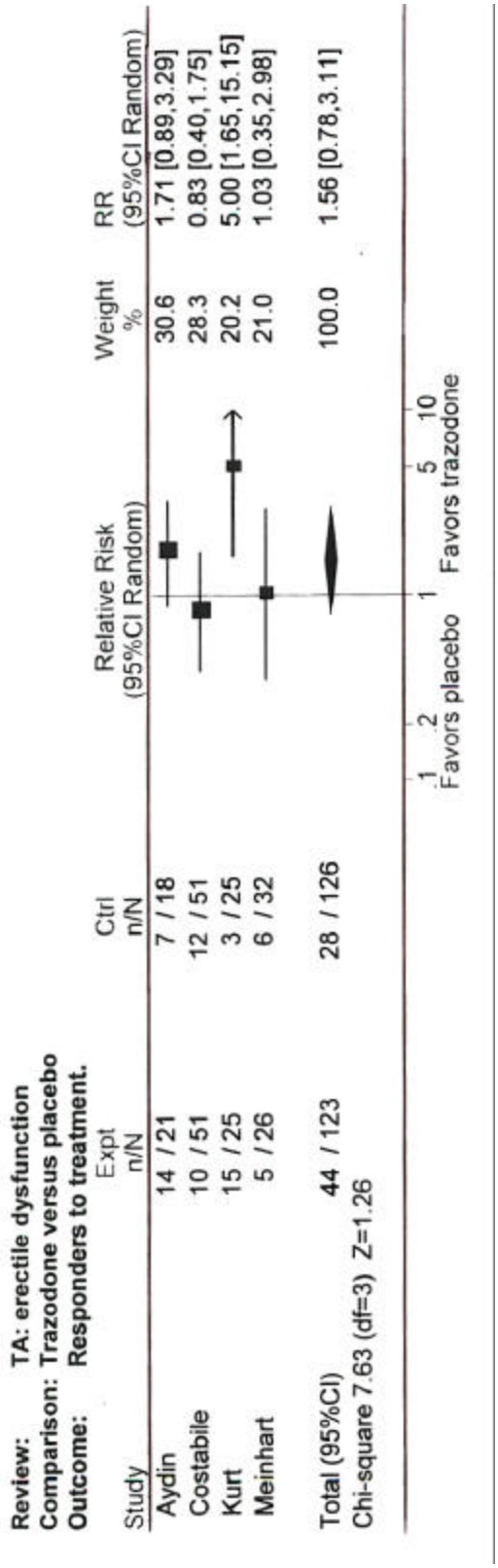
## E. Dropouts


Review: TA: erectile dysfunction
Comparison: Sildendafil vs. placebo
Outcome: Dropouts
Study
Expl n/N
Ctrl n/N
Relative Risk (95%CI Random)
Weight %
RR (95%CI Random)
FDA 148-101 40 / 333 16 / 83 21.5 0.62 [0.37,1.06]
FDA 148-106 49 / 375 13 / 122 18.0 1.23 [0.69,2.18]
FDA 148-355 1 / 44 1 / 44 0.8 1.00 [0.06,15.49]
FDA 148-358 3 / 27 3 / 27 2.6 1.00 [0.22,4.52]
FDA 148-364 19 / 387 9 / 127 10.2 0.69 [0.32,1.49]
Goldstein (102) 13 / 316 9 / 216 8.6 0.99 [0.43,2.27]
Goldstein (103) 31 / 163 36 / 166 32.6 0.88 [0.57,1.35]
Rendell (104) 5 / 136 11 / 132 5.6 0.44 [0.16,1.24]
Total (95%CI) 161 / 1781 98 / 917 100.0 0.82 [0.65,1.05]
Chi-square 4.87 (df=7) Z=1.54
.1 .2 1 5 10
Favors sildenafil
Favors placebo

## XVI. FIGURE 2: Yohimbine versus placebo: Responders to treatment

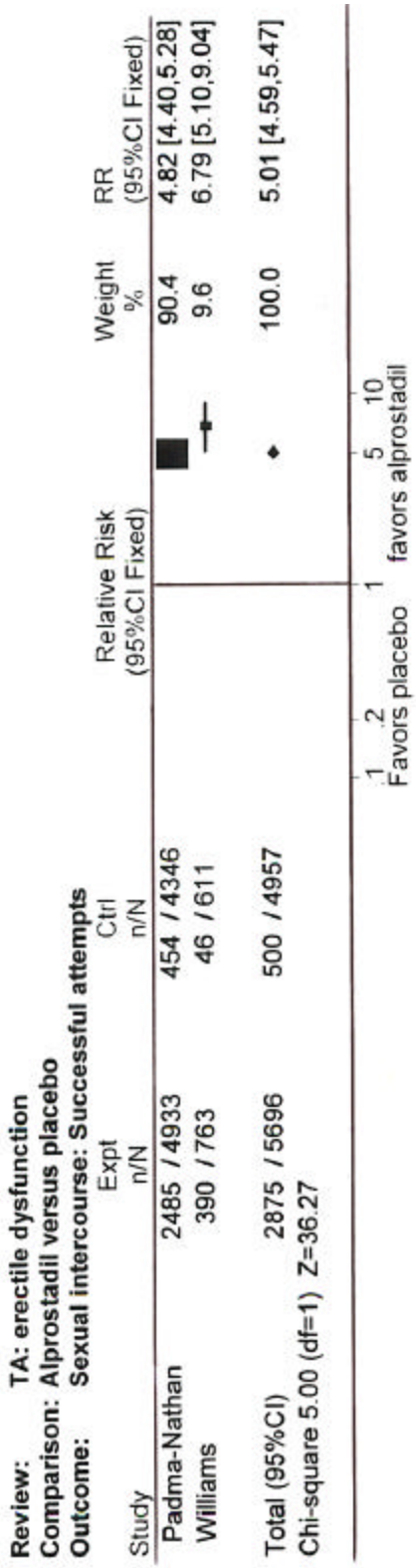


## XVII. FIGURE 3: Trazodone versus placebo: Responders to treatment

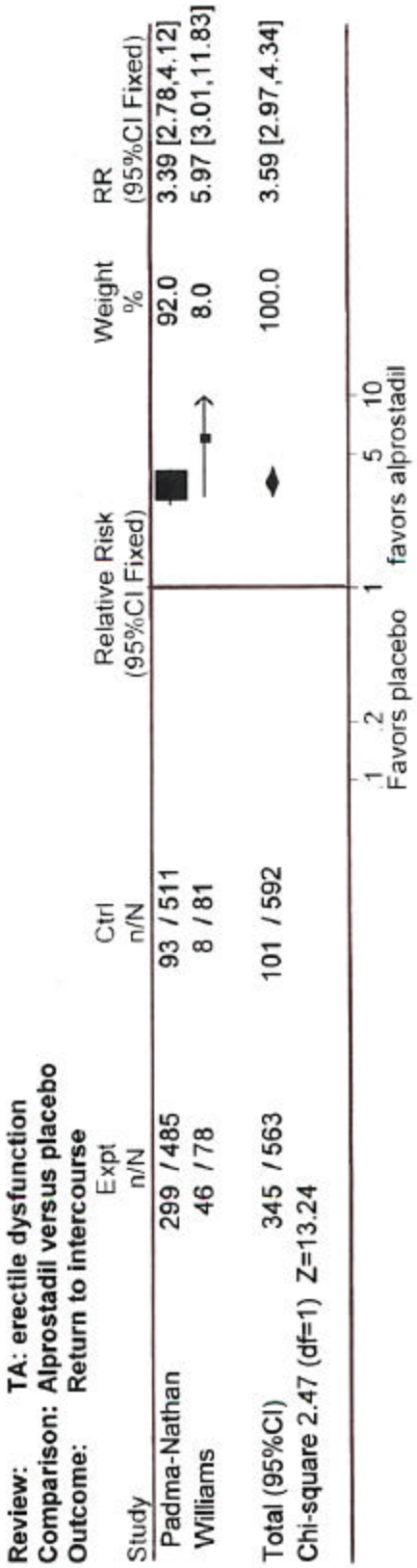


## XVIII. FIGURE 4: Alprostadil versus placebo

### A. Sexual intercourse: Successful attempts



## B. Return to intercourse



# XIX. APPENDIX 1: Oral Sildenafil for Treatment of Erectile Dysfunction (ED)

## A. Peer-reviewed RCTs only

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Goldstein (1998)**<br><br>This paper included a dose-response and a dose-escalation study. The dose-response study was previously reported in **Padma-Nathan (1998) Abstract 911** and on FDA web site as **Pfizer 148-102.** | DOSE-RESPONSE STUDY<br>**Sildenafil** 25, 50, 100mg or placebo, taken 1 hr prior to sexual activity. | DOSE-RESPONSE STUDY<br>Multi-center, randomized, double blind, placebo-controlled, fixed-dose, parallel group, dose-response study.<br><br>Duration: 24 weeks<br><br>Drop-outs<br>Overall 67 — Randomized n=532<br>Placebo 36 — n=216<br>Sildenafil 31 — n=316<br><br>A 4 week treatment-free run-in period preceded randomization. Of 604 subjects screened, 532 were randomized, and 465 had complete follow- | DOSE-RESPONSE STUDY<br>*Inclusions:*<br>In stable heterosexual relationship >6 months; ED ≥6 months; age ≥18<br>*Exclusions:*<br>Penile anatomical defect; primary diagnosis of sexual disorder; poorly controlled DM; use of nitrate therapy; spinal cord injury; hematologic, renal or hepatic disease; stroke or MI within 6 months; major psychiatric disorder not controlled with treatment; active PUD; history of alcohol or drug abuse.<br>*Age, mean yrs (range):*<br>Placebo 57 (20-79)<br>Sildenafil 58 (24-87)<br>*Duration of ED (mean yrs):*<br>Placebo 3.2<br>Sildenafil 3.2<br>*Etiology of ED(%):*<br>Placebo / Sildenafil<br>Organic 77 / 78<br>Psychogenic 10 / 9<br>Mixed 13 / 13<br>*Comorbid conditions (%):*<br>Placebo / Sildenafil<br>HTN 26 / 30<br>IHD 8 / 8<br>LIPID 16 / 19<br>DM 15 / 13 | DOSE-RESPONSE STUDY<br>Erectile function assessed at baseline and at 24 weeks through questions 3 and 4 of the International Index of Erectile Dysfunction (IIEF) and a global assessment question (GAQ). The IIEF was scored from 1=(never or rarely successful) to 5=(always or almost always successful); 0=(no attempts).<br><br>*IIEF Q3: When you attempted intercourse were you able to penetrate your partner?* — final rating mean ± SE<br>Sildenafil 100mg * 4.0 ± 0.2<br>Sildenafil 50mg 3.5 ± 0.2<br>Sildenafil 25mg 3.2 ± 0.2<br>Placebo 2.2 ± 0.2<br><br>*IIEF Q4: During intercourse how often were you able to maintain erection after penetration?* — final rating mean ± SE<br>Sildenafil 100mg * 3.9 ± 0.2<br>Sildenafil 50mg 3.5 ± 0.2<br>Sildenafil 25mg 3.1 ± 0.2<br>Placebo 2.1 ± 0.2<br><br>*GAQ: Has the treatment you have been taking the past 4 weeks improved your erections?(% yes)*<br>Sildenafil 100mg * 84 | DOSE-RESPONSE STUDY<br>*Headache(%):*<br>Sildenafil 22<br>Placebo 6<br>*Flushing(%):*<br>Sildenafil 20<br>Placebo 1<br>*Dyspepsia(%):*<br>Sildenafil 10<br>Placebo 1<br>*Rhinitis(%):*<br>Sildenafil 5<br>Placebo 2<br>*Visual disturbance(%):*<br>Sildenafil 6<br>Placebo <1 |

ED=erectile dysfunction
PVD=peripheral vascular disease
HTN=hypertension
IHD=ischemic heart disease
STD=sexually transmitted disease
RP=radical prostatectomy
BP=blood pressure
PUD=peptic ulcer disease
MI=myocardial infarction
ECG=electrocardiogram
DE=depression
DM=diabetes mellitus
CAD=coronary artery disease
ASA=aspirin
LIPID=hyperlipidemia
NSAID=nonsteroidal anti-inflammatory drug

## Appendix 1A (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Goldstein (1998) cont.**<br><br>This paper included a dose-response and a dose-escalation study. The dose-escalation study was previously reported on the FDA web site as **Pfizer 148-103.**<br><br>‡Information taken from Pfizer 148-103. | | | *Previous treatment for ED:*‡<br>Drug Non-drug<br>Overall "about half" "about 9%" | Sildenafil 25mg 56<br>Placebo 25<br><br>*(p<0.001 for treatment effect) | |
| | DOSE-ESCALATION STUDY<br>**Sildenafil** initiated at 50mg or placebo. Dose taken 1 hr before sexual activity. Dose could be doubled or halved during follow-up based on therapeutic response or adverse effects. | DOSE-ESCALATION STUDY<br>Multi-center, randomized, double blind, placebo-controlled, parallel group, flexible dose-escalation study.<br><br>Duration: 12 weeks<br><br>Drop-outs<br>Random-ized<br>Overall n=329 22<br>Placebo n=166 13<br>Sildenafil n=163 9<br><br>A 4 week treatment-free run-in period preceded randomization. Of 368 subjects screened, 329 were randomized, and 307 had complete follow-up.‡<br><br>Analysis was by intention to treat. | DOSE-ESCALATION STUDY<br>*Inclusions/Exclusions:*<br>See Dose-Response study above.<br>*Age, mean yrs (range):*<br>Placebo 59 (31-81)<br>Sildenafil 60 (26-79)<br>*Duration of ED, mean yrs (range):*<br>Placebo 4.7 (0.6-26)‡<br>Sildenafil 5.0 (0.5-26)‡<br>*Etiology of ED(%):*<br>Placebo Sildenafil<br>Organic 63 55<br>Psychogenic 16 14<br>Mixed 22 31<br>*Comorbid conditions(%):*<br>Placebo Sildenafil<br>HTN 28 24<br>IHD 8 15<br>LIPID 14 15<br>DM 11 8<br>RP 11 9<br>*Previous treatment for ED:*‡<br>Drug Non-drug<br>Overall "about 56%" "about 11%" | DOSE-ESCALATION STUDY<br>Erectile function assessed at baseline and at 12 weeks through questions 3 and 4 of the International Index of Erectile Dysfunction (IIEF), a global assessment question (GAQ) and evaluation of subjects' event logs. The IIEF was scored from 1=(never or rarely successful) to 5=(always or almost always successful); 0=(no attempts).<br><br>*IIEF Q3: When you attempted intercourse, were you able to penetrate your partner?* final rating mean ± SE<br>Sildenafil * 3.9 ± 0.1<br>Placebo 2.3 ± 0.1<br>*IIEF Q4: During intercourse how often were you able to maintain erection after penetration?* final rating mean ± SE<br>Sildenafil * 3.6 ± 0.1<br>Placebo 1.8 ± 0.1<br>*GAQ: Has the treatment you have been taking the past 4 weeks improved your erections? (% yes)*<br>Sildenafil * 74<br>Placebo 23<br>*In the last 4 wks, % of intercourse attempts which were successful:*<br>Sildenafil * 69<br>Placebo 22<br>*(p<0.001 for treatment effect)<br><br>Subgroup analysis of responses to IIEF questions 3 and 4, based on etiology of ED, indicated significant | DOSE-ESCALATION STUDY<br>*Headache(%):*<br>Sildenafil 18<br>Placebo 4<br>*Flushing(%):*<br>Sildenafil 18<br>Placebo 1<br>*Dyspepsia(%):*<br>Sildenafil 6<br>Placebo 2<br>*Rhinitis(%):*<br>Sildenafil 5<br>Placebo 1<br>*Visual disturbance(%):*<br>Sildenafil 2<br>Placebo 1 |

## Appendix 1A (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Boolell (1996)**<br><br>This paper reported a two phase study. The first phase was only a single dose study and will not be detailed here. Data from this paper was previously reported in **Boolell (1996) Abstract 739**. | PHASE 2<br>**Sildenafil** 25 or placebo. | OVERALL<br>Randomized, double blind, placebo controlled, crossover studies.<br><br>N=12<br>(100% completed)<br><br>PHASE 2<br>7 day duration, fixed once daily dose, 2-way crossover study (washout ≥3 days).<br><br>There was ≥7 day washout between phases 1 and 2. | OVERALL<br>*Inclusions:*<br>Outpatients referred for treatment of ED; no established organic cause for ED; ages 18-70.<br>*Exclusions:*<br>DM; HTN; alcohol abuse.<br>*Age, mean yrs (range):*<br>Overall 47.9 (36-63)<br>*Duration of ED, mean yrs (range):*<br>Overall 3.4 (1.5-10)<br>*Previous treatment for ED:*<br>50% had used intracavernous papaverine | PHASE 2<br>Erectile function assessed through evaluation of subjects' 7-day diary of at-home erectile success.<br><br>*Total # of erections sufficient for penetrable intercourse, mean (±95%CI):*<br>Sildenafil 6.1 (3.2-11.4)<br>Placebo 1.3 (0.5-2.7)<br><br>*% of men with improvement in erectile activity:*<br>Sildenafil * 83<br>Placebo 17<br><br>*(p<0.05 for treatment vs placebo) | PHASE 2<br>*"Mild and transient...adverse events" including headache, dyspepsia and pelvic musculoskeletal pain(%):*<br>Sildenafil 50<br>Placebo 42<br>*Severe headache(%):*<br>Sildenafil 8<br>Placebo 0 |

## B. Pfizer data (from FDA)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **148-101/101B** | **Sildenafil** 5, 25, 50, 100mg or placebo | Multi-center, randomized, double blind, placebo-controlled, fixed-dose, parallel group, dose-response study.<br><br>Duration: 24 weeks<br><br>A 4 week treatment-free run-in period preceded randomization.<br><br>523 subjects screened, 416 randomized, 359 with complete follow-up.<br><br>Random-ized / Drop-outs<br>Overall n=416 57<br>Placebo n=83 19%<br>Sildenafil n=333 12%<br>5mg n=86 na<br>25mg n=82 na<br>50mg n=83 na<br>100mg n=82 na | *Inclusions:*<br>Heterosexual relationship >6 months; ED >6 months; age >18<br>*Exclusions:*<br>Penile anatomical defect; suspected STD; use of estrogens, anti-androgens, nitrates, anti-coagulants or psychotropic drugs; spinal cord injury; hematologic, renal or hepatic disease; stroke/MI within 6 months; life-threatening CAD/arrhythmia; migraine/ cluster headache; depression/major psychiatric disorder; active PUD; bleeding disorder; postural hypotension; BP<90/50 or >160/95; experimental drug use within 4 wks; alcohol/drug dependence.<br>*Age, mean yrs (range):*<br>Placebo 58 (36-79)<br>Sildenafil 5mg 58 (26-80)<br>Sildenafil 25mg 57 (32-79)<br>Sildenafil 50mg 56 (35-73)<br>Sildenafil 100mg 59 (37-79)<br>*Duration of ED (mean yrs):*<br>Placebo 5.1<br>Sildenafil 5mg 5.1<br>Sildenafil 25mg 4.2<br>Sildenafil 50mg 3.8<br>Sildenafil 100mg 4.9<br>*Etiology of ED(%):*<br>Organic / Psycho-genic / Mixed<br>Placebo 76 7 17<br>Sildenafil 5mg 80 5 15<br>Sildenafil 25mg 70 12 18<br>Sildenafil 50mg 70 7 23<br>Sildenafil 100mg 74 10 16<br><br>*Comorbid conditions (%):*<br>HTN IHD DM PVD RP<br>Placebo 33 7.2 14 0 3.6<br>Sildenafil 5mg 31 4.7 15 0 7.0<br>Sildenafil 25mg 30 6.1 8.5 2.4 3.7<br>Sildenafil 50mg 34 8.4 18 1.2 2.4<br>Sildenafil 100mg 38 6.1 20 1.2 4.9 | Treatment response assessed at 8 and 24 weeks through patient response to the question, "How often were you able to get an erection?" Rating scale was from 1=(never or rarely successful) to 5=(always or almost always successful); 0=(no attempts).<br><br>8 Wks* / 24 Wks*<br>Placebo 2.1 2.1<br>Sildenafil 5mg 2.7 2.7<br>Sildenafil 25mg 3.1 2.9<br>Sildenafil 50mg 3.5 3.1<br>Sildenafil 100mg 3.7 3.6<br><br>*(p<0.0001) | No information given. |

ED=erectile dysfunction
HTN=hypertension
ECG=electrocardiogra
STD=sexually transmitted disease
IHD=ischemic heart disease
ASA=aspirin
MI=myocardial infarction
DM=diabetes mellitus
BP=blood pressure
CAD=coronary artery disease
PVD=peripheral vascular disease
DE=depression
PUD=peptic ulcer disease
RP=radical prostatectomy
NSAID=nonsteroidal anti-inflammatory

## Appendix 1B (contined)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Rendall (1999)**<br><br>This paper was previously reported on the FDA web site as<br>**Pfizer 148-104**<br><br>‡Information obtained from personalcorres pondence with V Mascoli at | **Sildenafil** 25-100mg or placebo, taken 1 hr before sexual activity. | Multi-center, randomized, double blind, placebo-controlled, parallel group, flexible dose escalation study in **men with a history of DM**. Treatment initiated at Sildenafil 50mg or placebo but could have been increased or decreased during follow-up.<br><br>Duration: 12 weeks<br><br>A 4 week treatment-free run-in period preceded randomization.<br><br>Of 355 subjects screened, 268 were randomized, and 252 had complete follow-up.<br><br>Overall N=268<br>Placebo N=132<br>Sildenafil N=136<br><br>Intention to treat analysis performed on all subjects with a baseline measurement. | *Inclusions:*<br>ED >6 months; DM typeI >5 yrs or DM type2 >2 yrs; DM under stable control ≥3 months; heterosexual relationship >6 months<br>*Exclusions:*<br>Penile anatomical deformity; other sexual disorder; elevated prolactin; low free testosterone; major, uncontrolled psychiatric disorder; alcohol or drug abuse; major hematologic, renal or hepatic disorder; spinal cord injury; uncontrolled DM, active diabetic retinopathy, serious hypoglycemia with 6 months, severe autonomic neuropathy, ketoacidosis within 3 yrs, DM secondary to pancreatic damage/Cushing's disease/acromegaly; stroke or MI within 6 months; heart failure, unstable angina, ECG ischemia or life-threatening arrhythmia within 6 months; BP <90/50 or >170/100; active PUD or bleeding disorder; any clinically significant laboratory abnormality; need for anticoagulants, nitrates, androgens or trazadone; need for ASA/NSAIDS and a history of PUD; unwillingness to cease use of other therapy for ED; other experimental drug use within 3 months; retinitis pigmentosa.<br>*Age, mean yrs (range):*<br>Placebo 57 (27-79)<br>Sildenafil 57 (33-76)<br>*Duration of ED, mean yrs (range):*<br>Placebo 5.8 (0.6-22)<br>Sildenafil 5.0 (0.5-26)<br><br>*Etiology of ED (%):*<br>Organic / Psycho-genic / Mixed<br>Placebo 96 / 0 / 4<br>Sildenafil 95 / 0 / 5<br><br>*Comorbid conditions (%):*<br>HTN / IHD / DM / PVD / RP<br>Placebo 51 / 25 / 100 / 7.6 / 7.6<br>Sildenafil 53 / 27 / 100 / 3.7 / 4.4<br><br>*Previous treatment for ED (%):*<br>Any / Non-drug<br>Overall 38 / 11 | Erectile function assessed at baseline and at 12 weeks through questions 3 and 4 of the International Index of Erectile Dysfunction questionnaire (IIEF), a global assessment question (GAQ) and evaluation of subjects' event logs. The IIEF was scored from 1=(never or rarely successful) to 5=(always or almost always successful); 0=(no attempts).<br><br>*IIEF Q3: When you attempted intercourse were you able to penetrate your partner?*<br>final mean rating<br>Sildenafil* 3.2<br>Placebo 2.0<br><br>*IIEF Q4: During intercourse how often were you able to maintain erection after penetration?*<br>final mean rating<br>Sildenafil * 2.9<br>Placebo 1.6<br><br>*GAQ: Has the treatment you have been taking the past 4 weeks improved your erections?(% answering 'yes')*<br>Sildenafil† 57<br>Placebo 10<br><br>*% of intercourse attempts which were successful:*<br>Sildenafil 30<br>Placebo 7.2<br><br>*% of subjects with successful attempts:*<br>run-in / double blind | ‡*Emergent adverse events(%):*<br>Sildenafil 57<br>Placebo 33<br>‡*Emergent adverse events which were "treatment related"(%):*<br>Sildenafil 16<br>Placebo 1<br><br>‡Events included headache, dyspepsia, flushing, abnormal vision and urinary tract infection.<br><br>Incomplete data is available for the open-label extension to this study. |

## Appendix 1B (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **148-106** | **Sildenafil** 50, 100, 200mg or placebo, taken 1 hr before sexual activity. | Multi-center, randomized, double blind, placebo-controlled, fixed-dose, parallel group, dose-response study.<br><br>Duration: 12 weeks<br><br>A 4 week treatment-free run-in period preceded randomization.<br><br>Of 582 subjects screened, 497 were randomized, and 436 had complete follow-up.<br><br>Random- ized / Drop- outs<br>Overall n=497 61<br>Placebo n=122 na<br>Sildenafil n=333 na<br>50mg n=127 na<br>100mg n=124 na<br>200mg n=124 na | *Inclusions:*<br>Heterosexual relationship >6 months; ED >6 months; age >18<br>*Exclusions:*<br>Penile anatomical defect; other sexual disorder; elevated prolactin; low free testosterone; uncontrolled DM or diabetic retinopathy; need for androgens, anti-coagulants, nitrates or trazadone; spinal cord injury; major hematologic, renal or hepatic disease; stroke or MI within 6 months; heart failure, unstable angina, ECG ischemia or life-threatening arrhythmia within 6 months; major, uncontrolled psychiatric disorder; active PUD or bleeding disorder; BP<90/50 or >170/100; any clinically significant laboratory abnormality; need for ASA/NSAIDs and a history of PUD; unwillingness to cease other therapy for ED; experimental drug use within 3 months; alcohol or drug abuse; retinitis pigmentosa.<br>*Age, mean yrs (range):*<br>Placebo 57 (25-79)<br>Sildenafil 50mg 60 (39-80)<br>Sildenafil 100mg 58 (24-80)<br>Sildenafil 200mg 58 (21-79)<br><br>*Duration of ED, mean yrs (range):*<br>Placebo 5.2 (0.5-26)<br>Sildenafil 50mg 5.5 (0.5-34)<br>Sildenafil 100mg 5.6 (0.5-37)<br>Sildenafil 200mg 5.2 (0.5-23)<br><br>*Etiology of ED(%):* Organic / Psycho-genic / Mixed<br>Placebo 59 14 27<br>Sildenafil 50mg 62 18 19<br>Sildenafil 100mg 58 16 26<br>Sildenafil 200mg 53 18 29<br><br>*Concomitant conditions (%):* HTN / IHD / DM / PVD / DE<br>Placebo 27 17 18 4.9 7.4<br>Sildenafil 50mg 22 15 22 3.9 5.5<br>Sildenafil 100mg 30 16 12 3.2 4.9<br>Sildenafil 200mg 21 15 17 0.8 4.8 | Erectile function assessed at baseline and at 12 weeks through questions 3 and 4 of the International Index of Erectile Dysfunction questionnaire (IIEF), a global assessment question (GAQ) and evaluation of subjects' event logs. The IIEF was scored from 1=(never or rarely successful) to 5=(always or almost always successful); 0=(no attempts).<br><br>*IIEF Q3: When you attempted intercourse, were you able to penetrate your partner?* final mean rating<br>Sildenafil 200mg * 3.5<br>Sildenafil 100mg 3.7<br>Sildenafil 50mg 3.5<br>Placebo 2.2<br><br>*IIEF Q4: During intercourse how often were you able to maintain erection after penetration?* final mean rating<br>Sildenafil 200mg * 3.4<br>Sildenafil 100mg 3.6<br>Sildenafil 50mg 3.2<br>Placebo 1.7<br><br>*GAQ: Has the treatment you have been taking the past 4 weeks improved your erections?(% yes)*<br>Sildenafil 200mg 80<br>Sildenafil 100mg 82<br>Sildenafil 50mg 70<br>Placebo 25<br><br>*% of intercourse attempts which were successful:*<br>Sildenafil 200mg 49 | No information given. |

## Appendix 1B (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **148-353** | **Sildenafil** 10, 25, 50mg or placebo, taken once daily. | Multi-center, randomized, double blind, placebo controlled, parallel group, dose-response study in **men with purely or partly psychogenic ED**.<br><br>Duration: 4 weeks<br><br>A 2 week treatment-free run-in period preceded randomization.<br><br>Of 404 subjects screened, 351 were randomized, and 317 have complete follow-up.<br><br>Overall n=351<br>Placebo n=95<br>Sildenafil 10mg n=90<br>Sildenafil 25mg n=85<br>Sildenafil 50mg n=81 | *Inclusions:*<br>Age >18; ED >3 months duration; in a heterosexual relationship.<br>*Exclusions:*<br>Advanced vascular or neurological ED; regular use of nitrates, anticoagulants, major tranquilizers, estrogens or antiandrogens; high prolactin or low testosterone; major hematologic, renal or hepatic disease; history of stroke, bleeding disorder or active PUD; postural hypotension or BP<90/50 or >170/110; experimental drug use within 3 months; alcohol abuse; blood donation within 1 month; HBsAg positivity; significant abnormalities at screening or inadequate compliance during screening;<br>*Age, mean yrs (range):*<br>Placebo 53 (26-70)<br>Sildenafil 10mg 52 (28-70)<br>Sildenafil 25mg 53 (24-70)<br>Sildenafil 50mg 52 (26-69)<br><br>*Duration of ED, mean yrs (range):*<br>Placebo 4.3 (0.3-40)<br>Sildenafil 10mg 4.7 (0.4-30)<br>Sildenafil 25mg 4.5 (0.3-30)<br>Sildenafil 50mg 4.5 (0.3-23)<br><br>*Etiology of ED (%):*<br>Organic / Psycho-genic / Mixed<br>Placebo 0 / 54 / 46<br>Sildenafil 10mg 0 / 59 / 41<br>Sildenafil 25mg 0 / 61 / 39<br>Sildenafil 50mg 0 / 59 / 41<br><br>*Comorbid conditions (%):*<br>HTN / DM / RP<br>Placebo 14 / 1.1 / 2.1<br>Sildenafil 10mg 8.9 / 3.3 / 3.3<br>Sildenafil 25mg 18 / 3.5 / 2.4<br>Sildenafil 50mg 12 / 1.2 / 2.5 | Erectile function assessed at 4 weeks through a global assessment question (GAQ) and a question about treatment preference.<br><br>*GAQ: Has the treatment you have been taking the past 4 weeks improved your erections? (% yes) **<br>Placebo 39<br>Sildenafil 10mg 64<br>Sildenafil 25mg 79<br>Sildenafil 50mg 88<br><br>*Proportion of subjects interested in continuing treatment (% yes)**<br>Placebo 51<br>Sildenafil 10mg 78<br>Sildenafil 25mg 84<br>Sildenafil 50mg 91<br><br>* (p<0.0001) | No information given. |

## Appendix 1B (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **148-355** | **Sildenafil** 25-75mg or placebo, taken once daily. | Multi-center, randomized, double blind, placebo controlled, two-way crossover study (washout period not specified).<br><br>Duration: 4 weeks<br><br>A 3 week treatment-free run-in period preceded randomization.<br><br>47 screened, 44 randomized, and 43 had complete follow-up. | *Inclusions:*<br>Age >18; ED of no established organic cause; ED >6 months; ability to attain an erection under some circumstances during a treatment-free run-in period.<br>*Exclusions:*<br>Advanced neurological or vascular cause of ED; history of alcohol abuse; regular use of nitrates, anticoagulants or ASA; need for antidepressants or major tranquilizers; history of asthma, eczema or drug hypersensitivity; family history of bleeding disorder, active PUD or migraines; significant abnormality on screening exam or lab test; experimental drug use within 4 months; recent or planned blood donation; HBsAg positivity.<br>*Age, mean yrs:*<br>Overall 53<br>*Duration of ED, yrs:*<br>Overall "about 3 years"<br>*Etiology of ED:*<br>No information given<br>*Concomitant conditions:* | *Mean number of erections/week adequate for penetration:*<br>Placebo 1.4<br>Sildenafil 4.2<br><br>*Mean number of erections/week adequate for penetration that were sexually stimulated:*<br>Placebo 0.8<br>Sildenafil* 2.4<br><br>*(p<0.0001) | No information given. |
| **148-356**<br><br>This study consisted of a 2 week single-blind run-in period, then a 16 week open-label dose titration phase, then an 8 week double blind phase. Only the last phase is detailed here. | **Sildenafil** 10-100mg or placebo. | Multi-center, randomized, double blind, placebo controlled, parallel group, titrated dose study in **men with purely or partly psychogenic ED**.<br><br>Duration 8 weeks.<br><br>292 subjects were screened, 233 randomized, 205 entered the double blind phase, and 202 completed all phases.<br><br>During open-label phase all subjects began treatment with Sildenafil 10mg. Dose was increased or decreased as indicated by effectiveness and tolerability. In double blind phase subjects were randomized to placebo or their optimum dose as determined | *Inclusions:*<br>Age 18-70; ED >3 months; ability to attain at least erection within 4 weeks of screening.<br>*Exclusions:*<br>Known vascular, neurological, endocrine or anatomical causes for ED; regular use of nitrates, anticoagulants, major tranquilizers, estrogens, antiandrogens or other drugs possibly causing ED; elevated prolactin or low free testosterone; history of major hematologic, renal or hepatic disease; history of stroke, subarachnoid hemorrhage, bleeding disorder or PUD; postural hypotension or BP <90/50 or >170/110; poorly controlled DM or DM possibly contributory to ED; experimental drug use within 3 months; alcohol abuse; recent or planned blood donation; clinical depression.<br>*Age, mean yrs:*<br>Overall 54<br>*Duration of ED, mean yrs:*<br>Overall 4.9<br>*Etiology of ED (%):*<br>Organic 0<br>Psychogenic 40<br>Mixed 60<br>*Concomitant conditions:*<br>No information given | Erectile function assessed at 8 weeks through a global assessment question (GAQ), a question about treatment preference, and evaluation of subjects' event logs.<br><br>*GAQ: Has the treatment you have been taking the past 4 weeks improved your erections?(% yes)*<br>Sildenafil 82<br>Placebo 26<br><br>*Proportion of subjects interested in continuing treatment (% yes)*<br>Sildenafil 85<br>Placebo 40<br><br>*Mean number of erections/week sufficient for intercourse:*<br>Sildenafil 1.4<br>Placebo 0.5 | No information given. |

## Appendix 1B (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **148-358**<br><br>This study consisted of 2 phases. Phase 1 was a single-dose study and will not be detailed here. | **Sildenafil** 50mg or placebo. | Multi-center, randomized, double blind, placebo controlled, two phase study in **men with a history of spinal cord injury**.<br><br>PHASE 2: Fixed dose, at home, parallel group study of 4 weeks duration.<br><br>34 subjects were screened, 27 randomized, and 24 had complete follow-up. | *Inclusions:*<br>Age 21-49; spinal cord injury ≥6 months; ability to achieve erection in response to a vibrator.<br>*Exclusions:*<br>Penile anatomical defect; vascular or endocrine etiology for ED; drugs associated with ED; major hematologic, renal or hepatic dysfunction; DM; history of stroke, subarachnoid hemorrhage, bleeding disorder or PUD; spinal cord injury above T5-6 level; postural hypotension or BP <90/50; regular use of nitrates or anticoagulants; experimental drug use within 3 months; alcohol abuse; recent or planned blood donation; other "serious...conditions apt to interfere with participation."<br>*Age, mean yrs:*<br>Overall 33<br>*Duration of ED, mean yrs:*<br>Overall 6<br>*Etiology of ED:*<br>Spinal cord injury presumed to be contributory or causitive of ED in all patients.<br>*Comorbid conditions:*<br>No information given. | Erectile function assessed at 4 weeks through a global assessment question (GAQ), a question about treatment preference, and evaluation of subjects' event logs.<br><br>*GAQ: Has the treatment you have been taking improved your erections?(% yes)*<br>Sildenafil 75<br>Placebo 7<br><br>*Proportion of subjects interested in continuing treatment (% yes)*<br>Sildenafil 67<br>Placebo 15<br><br>*% of intercourse attempts which were successful:*<br>Sildenafil 67<br>Placebo 38 | No information given. |
| **148-359** | **Sildenafil** 25-50mg or placebo. | Multi-center, randomized, double blind, placebo controlled, parallel group, flexible dose study.<br><br>Duration: 12 weeks<br><br>A 2-4 week treatment-free run-in period preceded randomization. Subjects were randomized to Sildenafil 25mg or placebo. Then, the dose could be increased or decreased during follow-up as indicated by efficacy or side effects.<br><br>127 subjects were screened, 111 randomized, and 97 had complete follow-up. | *Inclusions:*<br>Age >18; ED >6 months; stable heterosexual relationship >6 months.<br><br>*Exclusions:*<br>Erectile success ≥ 2/3 of time during run-in period; advanced vascular, neurological, endocrine or anatomical causes for ED; regular use of nitrates or anticoagulants; history of major hematologic, renalor hepatic disease; history of stroke, subarachnoid hemorrhage, bleeding disorder or PUD; experimental drug use within 3 months; alcohol or drug dependence; recent or planned blood donation; significant abnormalities on screening labs or physical exam.<br>*Age, mean yrs:*<br>Overall 56<br>*Duration of ED, mean yrs:*<br>Overall 4.5<br>*Etiology of ED (%):*<br>Organic 21<br>Psychogenic 40<br>Mixed 39<br>*Comorbid conditions:* | Erectile function assessed at 12 weeks through a global assessment question (GAQ).<br><br>*GAQ: Has the treatment you have been taking improved your erections?(% yes)*<br>Sildenafil 81<br>Placebo 18 | No information given. |

## Appendinx 1B (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **148-361** | **Sildenafil** 50, 100, 200mg or placebo | Multi-center, randomized, double blind, placebo controlled, parallel group, fixed dose study.<br><br>Duration: 12 weeks<br><br>A 2 week treatment-free run-in period preceded randomization.<br><br>277 subjects were screened, 254 randomized, and 241 had complete follow-up.<br><br>Placebo n=59<br>Sildenafil 50mg n=62<br>Sildenafil 100mg n=66<br>Sildenafil 200mg n=67 | *Inclusions:*<br>Age >18; ED >6 months; in heterosexual relationship >6 months.<br>*Exclusions:*<br>Penile anatomical deformities; other sexual disorders; spinal cord injury; poorly controlled DM or diabetic retinopathy; major hematologic, renal or hepatic dysfunction; history of stroke or MI within 6 months; major psychiatric disorder; alcohol or drug abuse; history of bleeding disorder or PUD; heart failure, unstable angina or life-threatening arrhythmia; postural hypotension or BP <90/50 or >170/110; clinically significant abnormalities on screening; use of drugs associated with ED; regular use of nitrates or anticoagulants; other impediments to study; use of other treatments for ED; experimental drug use within 3 months; recent or planned blood donation.<br><br>*Age, mean yrs (range):*<br>Placebo 60 (44-74)<br>Sildenafil 50mg 57 (32-74)<br>Sildenafil 100mg 57 (34-77)<br>Sildenafil 200mg 58 (38-75)<br><br>*Duration of ED, mean yrs:*<br>Placebo 4.9<br>Sildenafil 50mg 5.8<br>Sildenafil 100mg 5.1<br>Sildenafil 200mg 5.1<br><br>*Etiology of ED (%):*<br>Organic / Psycho-genic / Mixed<br>Placebo 49 / 8 / 41<br>Sildenafil 50mg 48 / 5 / 47<br>Sildenafil 100mg 52 / 5 / 44<br>Sildenafil 200mg 46 / 10 / 43<br><br>*Previous treatment for ED (%):*<br>Overall 56 | Erectile function assessed at baseline and at 12 weeks through questions 1, 3 and 4 of the International Index of Erectile Dysfunction questionnaire (IIEF) and a global assessment question (GAQ). The IIEF was scored 1=(never or rarely successful) to 5=(always or almost always successful) with 0=(no attempts).<br><br>*IIEF Q1: How often were you able to get an erection during sexual activity?*<br>final mean rating<br>Sildenafil 200mg * 3.9<br>Sildenafil 100mg 3.8<br>Sildenafil 50mg 3.8<br>Placebo 2.1<br><br>*IIEF Q3: When you attempted intercourse, were you able to penetrate your partner?*<br>final mean rating<br>Sildenafil 200mg * 3.7<br>Sildenafil 100mg 3.7<br>Sildenafil 50mg 3.4<br>Placebo 1.9<br><br>*IIEF Q4: During intercourse how often were you able to maintain erection after penetration?*<br>final mean rating<br>Sildenafil 200mg * 3.6<br>Sildenafil 100mg 3.5<br>Sildenafil 50mg 3.2<br>Placebo 1.7<br><br>*GAQ: Has the treatment you have been taking improved your erections?(% yes)* | No data given for double blind portion of study. Incomplete data is available for its open-label extension. |

## Appendix 1B (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **148-363** | **Sildenafil** 25-100mg or placebo, taken 1 hr prior to sexual activity | Multi-center, randomized, double blind, placebo controlled, parallel group, flexible dose escalation study.<br><br>Duration: 26 weeks<br><br>A 4 week treatment-free run-in period preceded randomization.<br><br>387 subjects were screened, 315 randomized, and 307 had complete follow-up.<br><br>Placebo n=156<br>Sildenafil n=159 | *Inclusions:*<br>Age >18; ED >6 months; in a heterosexual relationship >6 months.<br>*Exclusions:*<br>Penile anatomical deformity; other sexual disorder; elevated prolactin; low free testosterone; major, uncontrolled psychiatric disorder; history of alcohol or drug abuse; history of major hematologic, renal or hepatic disorder; ED following spinal cord injury; uncontrolled DM or diabetic retinopathy; stroke or MI within 6 months; heart failure, unstable angina, ECG ischemia, or life-threatening arrhythmia within 6 months; BP <90/50 or >170/100; active PUD or bleeding disorder; any clinically significant baseline lab abnormality; need for anticoagulants, nitrates, androgens or trazadone; need for ASA or NSAIDs and a history of PUD; unwillingness to cease use of other treatment for ED; other experimental drug use within 3 months; retinitis pigmentosa.<br><br>*Age, mean yrs (range):*<br>Placebo 54 (23-82)<br>Sildenafil 55 (24-77)<br><br>*Duration of ED, mean yrs (range):*<br>Placebo 5.1 (1-27)<br>Sildenafil 4.8 (1-35)<br><br>*Etiology of ED(%):*<br>Organic / Psycho-genic / Mixed<br>Placebo 30 / 32 / 35<br>Sildenafil 29 / 31 / 38<br><br>*Concomitant conditions (%):*<br>HTN / IHD / DM / RP / DE<br>Placebo 19 / 6.4 / 15 / 12 / 4.5<br>Sildenafil 21 / 13 / 16 / 10 / 8.2<br><br>*Previous treatment for ED (%):*<br>Overall 71 | Erectile function assessed at baseline, 12 weeks, and 26 weeks, through questions 3 and 4 of the International Index of Erectile Dysfunction questionnaire (IIEF), a global assessment question (GAQ) and evaluation of subjects' event logs. The IIEF was scored from 1=(never or rarely successful) to 5=(always or almost always successful); 0=(no attempts).<br><br>*IIEF Q3: When you attempted intercourse, were you able to penetrate your partner?*<br>Mean ratings<br>12wks / 26wks<br>Sildenafil 3.5* / 3.7*<br>Placebo 2.2 / 2.2<br><br>*IIEF Q4: During intercourse how often were you able to maintain erection after penetration?* Mean ratings<br>12Wks / 26Wks<br>Sildenafil 3.5* / 3.6*<br>Placebo 2.1 / 2.1<br><br>*GAQ: Has the treatment you have been taking the past 4 weeks improved your erections?(% yes)*<br>12 Wks / 26 Wks<br>Sildenafil 82† / 80†<br>Placebo 22 / 23<br><br>*% of intercourse attempts which were successful over 26 weeks of treatment:*<br>Sildenafil 59<br>Placebo 25<br><br>*% of subjects with successful attempts:*<br>run-in / double blind<br>Sildenafil 38 / 89<br>Placebo 33 / 63<br><br>*(p<0.0001) | No information given. |

## Appendix 1B (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **148-364** | **Sildenafil**<br>25, 50, 100mg or placebo, taken 1 hr prior to sexual activity | Multi-center, randomized, double blind, placebo controlled, parallel group, fixed dose study.<br><br>Duration: 12 weeks<br><br>A 4 week treatment-free run-in period preceded randomization.<br><br>564 subjects were screened, 514 randomized, and 484 had complete follow-up.<br><br>Placebo<br>n=127<br>Sildenafil 25mg<br>n=128<br>Sildenafil 50mg<br>n=132<br>Sildenafil 100mg<br>n=127 | *Inclusions:*<br>Age >18; ED >6 months; in a heterosexual relationship >6 months.<br>*Exclusions:*<br>Penile anatomical defect; other sexual disorder; elevated prolactin; low free testosterone; major, uncontrolled psychiatric disorder; history of alcohol or drug abuse; history of major hematologic, renal or hepatic disorder; ED following spinal cord injury; uncontrolled DM or diabetic retinopathy; stroke or MI within 6 months; heart failure, unstable angina, ECG ischemia, or life-threatening arrhythmia within 6 months; BP <90/50 or >170/100; active PUD or bleeding disorder; any clinically significant baseline lab abnormality; need for anticoagulants, nitrates, androgens or trazadone; need for ASA or NSAIDs and a history of PUD; unwillingness to cease use of other treatments for ED; other experimental drug use within 3 months; retinitis pigmentosa.<br><br>*Age, mean yrs (range):*<br>Placebo 55 (20-77)<br>Sildenafil 25mg 55 (19-74)<br>Sildenafil 50mg 57 (30-76)<br>Sildenafil 100mg 56 (25-79)<br><br>*Duration of ED, mean yrs (range):*<br>Placebo 5.0 (0.6-30)<br>Sildenafil 25mg 4.5 (0.5-30)<br>Sildenafil 50mg 4.6 (0.5-40)<br>Sildenafil 100mg 5.0 (0.5-30)<br><br>*Etiology of ED(%):*<br>Organic / Psycho-genic / Mixed<br>Placebo 46 / 29 / 24<br>Sildenafil 25mg 44 / 28 / 28<br>Sildenafil 50mg 41 / 36 / 23<br>Sildenafil 100mg 39 / 35 | Erectile function assessed at baseline and at 12 weeks through questions 3 and 4 of the International Index of Erectile Dysfunction questionnaire (IIEF), a global assessment question (GAQ) and evaluation of subjects' event logs. The IIEF was scored from 1=(never or rarely successful) to 5=(always or almost always successful); 0=(no attempts).<br><br>*IIEF Q3: When you attempted intercourse, were you able to penetrate your partner?*<br>final mean rating<br>Sildenafil 100mg* 3.8<br>Sildenafil 50mg 3.7<br>Sildenafil 25mg 3.2<br>Placebo 2.2<br>*IIEF Q4: During intercourse how often were you able to maintain erection after penetration?*<br>final mean rating<br>Sildenafil 100mg* 3.6<br>Sildenafil 50mg 3.4<br>Sildenafil 25mg 3.0<br>Placebo 2.0<br><br>*GAQ: Has the treatment you have been taking the past 4 weeks improved your erections?(% yes)* †<br>Sildenafil 100mg 86<br>Sildenafil 50mg 78<br>Sildenafil 25mg 67<br>Placebo 24<br><br>*% of intercourse attempts which were successful:*<br>Sildenafil 100mg 46<br>Sildenafil 50mg 43<br>Sildenafil 25mg 38<br>Placebo 13<br><br>*% of subjects with successful attempts:*<br>run-in / double blind<br>Sildenafil 100mg 31 / 82<br>Sildenafil 50mg 33 / 91<br>Sildenafil 25mg 42 / 79<br>Placebo 32 / 53<br><br>*(p-value <0.0001 for linear trend by dose)<br>†(" highly statistically significant")<br><br>A subgroup analysis was performed for IIEF questions 3 and 4 based on etiology, | No information given. |

## Appendix 1B (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **148-367** | **Sildenafil** 50-100mg or placebo, taken 1 hr prior to sexual activity | Multi-center, randomized, double blind, placebo controlled, flexible dose, two-way crossover study in **men with a history of spinal cord injury**.<br><br>A 4 week treatment-free run-in period preceded randomization.<br><br>Two 6 week treatment periods were separated by 2 week washout.<br><br>Within each treatment period, subjects initiated at Sildenafil 50mg or placebo. Dose could be doubled or halved during follow-up depending on efficacy or adverse effects.<br><br>183 subjects were screened, 178 randomized, and 168 had complete follow-up. | *Inclusions:*<br>Age >18; ED >6 months; in a heterosexual relationship >6 months; ED caused by spinal cord injury.<br>*Exclusions:*<br>Penile anatomical defect; other sexual disorder; elevated prolactin; low free testosterone; major, uncontrolled psychiatric disorder; history of alcohol or drug abuse; history of major hematologic, renal or hepatic disorder; uncontrolled DM or diabetic retinopathy; stroke or MI within 6 months; heart failure, unstable angina, ECG ischemia, or life-threatening arrhythmia within 6 months; BP <90/50 or >170/100; active PUD or bleeding disorder; any clinically significant baseline lab abnormality; need for anticoagulants, nitrates, androgens or trazadone; need for ASA or NSAIDs and a history of PUD; unwillingness to cease use of other treatments for ED; other experimental drug use within 3 months; retinitis pigmentosa.<br><br>*Age, mean yrs (range):*<br>Placebo first 38 (19-63)<br>Sildenafil first 38 (21-61)<br><br>*Duration of ED, mean yrs (range):*<br>Placebo first 10.3 (0.7-35)<br>Sildenafil first 11.7 (0.7-38)<br><br>*Etiology of ED(% of men):*<br>ED was secondary to spinal cord injury in all subjects.<br><br>*Comorbid conditions (%):*<br>HTN IHD DM DE RP<br>Placebo first 4.5 2.2 0 5.6 1.1<br>Sildenafil first 3.4 1.1 1.1 3.4 1.1<br><br>*Previous treatment for ED (%):* | Erectile function assessed at baseline and at end of each 6 week treatment period through questions 3 and 4 of the International Index of Erectile Dysfunction questionnaire (IIEF) and a question about subject treatment preference. The IIEF was scored from 1=(never or rarely successful) to 5=(always or almost always successful); 0=(no attempts).<br><br>*IIEF Q3: When you attempted intercourse, were you able to penetrate your partner?*<br>final mean rating<br>Sildenafil * 3.8<br>Placebo 2.2<br><br>*IIEF Q4: During intercourse how often were you able to maintain erection after penetration?*<br>final mean rating<br>Sildenafil * 3.6<br>Placebo 1.7<br><br>*Subject's preference for a treatment (%):*<br>Sildenafil 74<br>Placebo 4<br>No preference 22<br><br>*(p-value <0.0001)<br><br>Analyses also were done for each of the above endpoints in the subgroup of subjects with some residual erectile function at baseline. For IIEF questions 3 and 4, there were highly statistically significant differences favoring Sildenafil over placebo (p<0.0001). Regarding treatment preference, of 145 such subjects 77% preferred Sildenafil (n=111), 5% placebo (n=7), and 19% (n=27) had no preference. | ‡*Emergent adverse effects (%):*<br>Sildenafil 55<br>Placebo 29<br><br>‡Adverse events included headache, dyspepsia, flushing, abnormal vision and urinary tract infection. Severe adverse events made up 11% of the total. |

## C. Abstracts

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Lue (1997) Abstract 701** | **Sildenafil** 5, 25, 50, 100mg or placebo | Multi-center, randomized, double blind, placebo controlled, parallel group, fixed dose study.<br><br>Duration: 8 wks<br><br>N=416<br><br>A 2-4 wk single-blind, placebo run-in period preceded randomization. | *Etiology of ED (%):*<br>Organic 73<br>Psychogenic 9<br>Mixed 18 | Erectile function assessed at baseline and at 8 weeks through questions 3 and 4 of the International Index of Erectile Dysfunction (IIEF) and a global assessment question (GAQ). The IIEF was scored from 1=(never or rarely successful) to 5=(always or almost always successful); 0=(no attempts).<br><br>*IIEF Q3: When you attempted intercourse, were you able to penetrate your partner? (mean final rating):*<br>Placebo 2.00<br>Sildenafil 5mg 2.69<br>Sildenafil 25mg 2.93<br>Sildenafil 50mg 3.28<br>Sildenafil 100mg 3.69<br><br>*IIEF Q4: During intercourse how often were you able to maintain erection after penetration? (mean final rating):*<br>Placebo 2.05<br>Sildenafil 5mg 2.40<br>Sildenafil 25mg 2.95<br>Sildenafil 50mg 3.32<br>Sildenafil 100mg 3.60<br><br>*GAQ: Has the treatment you have been taking the past 4 weeks improved your erections? (% 'yes'):*<br>Placebo 27.7<br>Sildenafil 5mg 47.7<br>Sildenafil 25mg 60.9<br>Sildenafil 50mg 72.9 | For each adverse effect the data was reported as range of percent of men experiencing the effect among all five treatment groups.<br><br>Headache 2.4-11<br>Dyspepsia 0-8.5<br>Vasodilation 0-8.5<br>Diarrhea 0-4.9 |
| **Gingell (1997) Abstract 738**<br>The data from this study is detailed in Appendix 1b under the study name, **148-353**, and will not be given here. | | | | | |
| **Eardley (1996) Abstract 737** | **Sildenafil** 25-75mg or placebo | Randomized, double blind, placebo controlled, flexible dose, 2-way crossover (washout not specified).<br><br>Duration: 28 days<br><br>N=42<br>(88% follow-up)<br><br>Analysis was not intention to treat | *Age, mean yrs (range):*<br>Overall 53 (34-70)<br>*Duration of ED, mean yrs (range):*<br>Overall 3 (0.5-10) | *Subjects reporting improved erections(%):*<br>Sildenafil * 92<br>Placebo 27<br>*Partners reporting improved erections (%):*<br>Sildenafil * 91<br>Placebo 19<br>*Over the 28 days of treatment, how many erections did you have which were sufficient for penetrative sexual intercourse? mean (95%CI):*<br>Sildenafil * 18.4 (14-24.3)<br>Placebo 5.6 (4.1-7.4) | "The most commonly reported adverse events were headache, dyspepsia and muscle aches which were mild and transient." |

## D. Pooled Subgroup Studies

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Wagner (1998) Abstract 912** | **Sildenafil** 25, 50, 100 mg or placebo, taken 1 hr before sexual activity | Pooled subgroup analysis of **men ≥65 years and <65 years old** from eight multi-center, double blind, placebo controlled, either fixed or flexible dose studies.<br><br>Duration: 12 weeks | No information given. | Erectile function assessed at baseline and at 12 weeks through questions 3 and 4 of the International Index of Erectile Dysfunction (IIEF). The IIEF was scored from 1=(never or rarely successful) to 5=(always or almost always successful); 0=(no attempts).<br><br>*IIEF Q3: When you attempted intercourse, were you able to penetrate your partner? (mean rating):*<br><br><65 years baseline final >65 years baseline final<br>* Sildenafil (n=1328) 2.0 3.5 * Sildenafil (n=448) 1.6 3.2<br>Placebo (n=700) 1.9 2.1 Placebo (n=229) 1.8 1.8<br><br>*IIEF Q4: During intercourse how often were you able to maintain erection after penetration? (mean rating):*<br><br><65 years baseline final >65 years baseline final<br>* Sildenafil (n=1326) 1.7 3.3 * Sildenafil (n=442) 1.4 3.0<br>Placebo (n=695) 1.6 1.8 Placebo (n=229) 1.4 | No information given. |
| **Pfizer data. Personal communication with V. Mascoli.** | **Sildenafil** or placebo; doses not specified | Pooled subgroup analysis of **men with a history of radical prostatectomy** from several clinical trials.<br><br>N=140 | *Inclusions:*<br>Subjects with ED participating in one of Pfizer trials who have a history of radical prostatectomy (RP).<br><br>No other information given. | Erectile function assessed at baseline and final follow-up through questions 3 and 4 of the International Index of Erectile Dysfunction (IIEF) and a global assessment question (GAQ). The IIEF was scored from 1=(never or rarely successful) to 5=(always or almost always successful); 0=(no attempts).<br><br>*GAQ: Has the treatment you have been taking the past 4 wks improved your erections?(% 'yes'):* Sildenafil 43<br>Placebo 15<br><br>*IIEF Q3: When you attempted intercourse, were you able to penetrate your partner?*<br>*IIEF Q4: During intercourse how often were you able to maintain erection after penetration?*<br><br>Subjects on Sildenafil had higher scores than did those on placebo. However, subjects with a history of RP had significantly lower scores | No information given. |

## XX. Appendix 2: Yohimbine for the Treatment of Erectile Dysfunction (ED): controlled trials (from Ernst and Pittler, J. Urol., Vol 159, 433-436)

| References | Trial Design | No. Pts., ED etiology, mean age | Treatment | End Point | Result (%) | Adverse events (frequency %, type) |
|---|---|---|---|---|---|---|
| Morales | Randomized controlled trial (RCT), placebo-controlled (PC), double blind (DB), partial crossover | N=100<br>organic impotence<br>56 years | Yohimbine HCl 6 mg. capsules 3/day or identical placebo capsules x 10 wks | Report of treatment by pt. and partner | Positive drug response<br>Yohimbine 43%<br>Placebo 28% | Not reported |
| Reid | RCT, PC, DB, partial crossover | N=48<br>psychogenic impotence<br>18-70 years | Yohimbine HCl 6 mg. or placebo 3/day x 10 wks | Self-reported improvement | Improvement<br>Yohimbine 62%<br>Placebo 16% | Not reported |
| Riley | RCT, PC, DB, crossover | N=61<br>chronic erectile impotence of mixed etiology | Yohimbine HCl 5.4 mg. or identical placebo 3/day for a first/second 8-wk period | Score on penile erectility and interest in sex | Good stim. Erection<br>Yohimbine 37%<br>Placebo 13%<br>($p<0.05$) | Drug grou (10)<br>Placebo (5), HTN, contraindicated phenytoin rash |
| Susset | RCT, PC, DB, crossover | N=82 (12 dropouts)<br>any kind of erectile impotence<br>61 years | Yohimbine HCl 5.4 mg. or identical placebo 4/day increasing to 8/day for 4 wks. | Derogatis sexual functioning inventory, penile brachial index, daytime arousal test | Full or partial response<br>Yohimbine 34%<br>Improvement placebo (3 pts.) | Drug group (21), anxiety, dizziness, ↑ urination, chills, headache |
| Mann | RCT, PC, DB | N=31 (1 dropout)<br>erectile dysfunction due to organic or non-organic etiology<br>43 years | Yohimbine HCl 5 mg. 3/day or placebo for 7 wks. | Clinical Global Impression Scale pos. penile rigidity | Nonorganic erectile dysfunction improvement was significantly better<br>Yohimbine 60%<br>Placebo 40% | Drug group 919) placebo (16), sweating, agitation, anxiety, headache, tachycardia, GI disturbances |
| Vogt | RCT, PC, DB | N=86 (5 dropouts)<br>erectile dysfunction without detectable cause<br>53 years | Yohimbine HCl 10 mg. 3/day or placebo for 8 wks. | Subjective result pos. penile rigidity (by polysonography) | Positive Drug response<br>Yohimbine 71%<br>Placebo 45% | Drug group (30)<br>Placebo (10) |

## Appendix 2 (continued)

| References | Trial Design | No. Pts., ED etiology, mean age | Treatment | End Point | Result (%) | Adverse events (frequency %, type) |
|---|---|---|---|---|---|---|
| Rowland | RCT, PC, DB, crossover | N=11<br>Erectile dysfunction<br>49 years | Yohimbine 3/day 5 mg./10 mg. For a first/second 2-wk period or identical placebo | Inventory of sexual functioning nocturnal penile tumescence waking erectile assessment | Positve drug response<br>Yohimbine 73%<br>Placebo 9% | Drug group (27),<br>Diarrhea, ↑ urination, lack of energy |
| Kunelius | RCT, PC, DB, crossover | N=29 (2 dropouts)<br>Mixed-type impotence<br>47 years | Yohimbine HCL 36mg./day or identical placebo x two 25-day treatment courses | Self-reported improvement and penile tumescence and rigidity (Rigiscan) | Positive drug response<br>Yohimbine 44%<br>Placebo 48% | Drug group (7),<br>HTN, severe palpitation |
| Knoll | RCT, crossover | N=20<br>Vasculogenic impotence<br>47 years | Yohimbine HCL 5.4 mg. + isoxsuprine 10 mg. 3/day versus 400 mg. Pentoxifylline 3/day x two 2-month treatment courses | Asessment by sexual questionnaire and duplez ultrasonography | Positive drug response<br>Yohimbine 50%<br>Active control (30-40%) | Drug group (20)<br>Active control (10)<br>Insomnia, dyspepsia |
| Montosori | RCT,PC, DB, partial crossover | N=63 (8 dropouts)<br>Psychogenic impotence<br>42.5 years | Yohimbine HCl 5 mg. 3/day + Trazodone 50 mg. 1/day versus placebo x 8 wks. Men on placebo were then crossed over to the combination therapy. | Reported improvement (patient and partner) | Positive drug response<br>Yoh. + Traz. 71%<br>Placebo 22% | Drug group (11)<br>Placebo (4)<br>Dizziness, gastric intolerance, restlessness and agitation |

# XXI. Appendix 3: Oral Phentolamine (Vasomax) for the treatment of Erectile Dysfunction

| Study Name | Doses | Study Design | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| Goldstein (1998)<br>J Urol<br>159 (suppl) : 240<br>meeting abstract<br>#919 | **ZON-301**<br><br>Phentolamine (Vasomax): 40, 80 mg or placebo<br><br>**ZON-300**<br><br>Phentolamine (Vasomax): 40 mg or placebo | **ZON-301**<br><br>Placebo-controlled, parallel group, double blind<br><br>**ZON-300**<br><br>Placebo-controlled, crossover, double blind | Men with "minimal erectile dysfunction of broad-spectrum etiology" | Assessment instrument:<br>IIEF score<br><br>Responder = IIEF score improved by ≥ one clinical dysfunction class and mild-to-moderate dysfunction at endpoint<br><br>**ZON-301**<br><br>intervention (n) % responders<br>placebo (148) 16<br>40 mg (152) 37<br>80 mg (159) 45<br><br>[p < 0.001 (CMH, controlling for investigator)]<br><br>**ZON-300**<br><br>intervention (n) % responders<br>placebo (145) 21<br>40 mg (148) 34 | **Adverse effects:**<br>40 mg phentolamine:<br>< 10% occurrence of headaches, facial flushing, nasal congestion. |

## Appendix 3 (continued)

| Study Name | Doses | Study Design | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| Becker (1998)<br>J Urol<br>159: 1214 - 1216 | Phentolamine (Vasomax): 20 mg, 40 mg, 60 mg; placebo. | Randomized, prospective, double blind, placebo-controlled<br><br>Evaluation phase:<br>Patients were given an in-office test to evaluate drug tolerance (dropouts were not stated).<br><br>Single-blinded placebo phase:<br>Patients given 3 placebo tablets. Instructed to attempt an erection. Patients achieving an erection sufficient for vaginal penetration were excluded.<br><br>Study phase:<br>Three doses of placebo, 20 mg, 40 mg or 60 mg phentolamine, instructed to attempt intercourse on three occasions.<br><br>Patients completed detailed diaries on the effect and side effects of the medications.<br><br>Inclusions: history of ED for less than 3 years; tolerance to the study medication; stable partnership.<br><br>Exclusions: severe psychogenic etiology of disease; achieving 1 erection sufficient for vaginal penetration during placebo; | N = 40<br><br>Patients were randomized to either 20 mg, 40 mg, or 60 mg phentolamine or placebo (n = 10 for each group)<br><br>Responders:<br>Mean age = 48<br>Age range = 26 - 70 | Assessment instrument:<br>full erections sufficient for vaginal penetration.<br><br>**Percentage of patients reporting success:**<br><br>Dose % patients<br>placebo 20<br>20 mg 30<br>40 mg 50<br>60 mg 40<br><br>**Successful attempts at intercourse:**<br><br>Dose % success<br>placebo 13.4<br>20 mg 20.0<br>40 mg 30.0<br>60 mg 36.7 | **Adverse effects:**<br><br>stuffy nose = 1 patient |

# XXII. Appendix 4: Trazodone for the Treatment of Erectile Dysfunction (ED)

| References | Trial Design | No. Pts. Sample (mean age) | Treatment | End Point | Result (%) | Adverse events (frequency %, type) |
|---|---|---|---|---|---|---|
| Costabile† | Randomized controlled trial (RCT), double blind (DB), placebo-controlled (PC), crossover | N=51<br>65 years | Trazodone 50 mg. q.h.s. or placebo x 3 months | Self-reported improvement and Index of Sexual Satisfaction score (ISS) | Improved erection drug (19) versus placebo (24) (p=ns) | Drowsiness (31), fatigue (19) and dry mouth (1) |
| Meinhart | RCT, DB, PC | N=69 (11 dropouts)<br>54 years | Trazodone 50 mg. 3/day or placebo x4 weeks | Self-reported improvement, tumescence and rigidity (Rigiscan) | Pos. response drug (19) versus placebo (19) | Drug group (35) placebo group (19) sleepiness, headache, dizziness, nausea |
| Aydin | RCT, PC and active-controlled (AC) | N=79<br>Non-organic etiology | Trazodone (T) 150 mg./day or placebo or testosterone undecanoate (TES) 120 mg./day x16 weeks or hypnotic suggestion (HS) x1 session/3 days per week decreasing to 1 session per month by the 6 month follow-up period | Reported improvement (patient and partner) | Pos. response (T) (67), placebo (39), TES (60), HS (80) | T group (5) sedation |
| Montosori | RCT, DB, PC, partial crossover | N=63 (8 dropouts)<br>Psychogenic impotence<br>42.5 years | Yohimbine HCL 5 mg. 3/day + Trazodone 50 mg. 1/day versus placebo x8 weeks. Men on placebo were then crossed over to the combination therapy | Reported improvement (patient and partner) | Pos. response drug (50) versus placebo (11) | Drug group (11) placebo (4) dizziness, gastric intolerance, restlessness and agitation |
| Kurt | RCT, DB, PC and AC | N=100 (15 dropouts)<br>Non-organic etiology<br>47 years | Trazodone (T) to mg. 3/day or placebo or Ketanserin (K) 20 mg. 2/day or mianserin (M) 10 mg. 3/day x 30 days | Reported improvement (patient) | Pos. response (t) (65), placebo (14), (K) (19), (M) (32) | T group: priapism (n=1), severe sedation (n=1), xerostomia (n=2), blurred vision (n=1)<br>K group: veritgo (n=1), fatigue (n=1)<br>M group: severe sedation (n=2)<br>Placebo: nausea (n=2) |

†Abstract

# XXIII. Appendix 5: Aminophylline + Isosorbide Dinitrate + Co-Dergocrine

| Study Name | Doses | Study Design | Participants | Outcomes |
|---|---|---|---|---|
| **Gomaa** (1996)<br>BMJ 312:1512-5 | Topical cream (2 g): aminophylline (3%), isosorbide dinitrate (0.25%), co-dergocrine mesylate (0.05%)<br><br>Placebo gel | Randomized, double blinded, placebo-controlled, crossover<br><br>Patients supplied 7 doses active cream or placebo (1 dose daily X week), then crossover for a week. | N = 36<br><br>Median age (years) = 48<br>Age range = 31 – 65<br><br>Median duration of ED = 39 mo. (range = 5-72)<br><br>Etiology of ED (n)<br>Psychogenic = 9<br>Neurogenic = 8<br>Arterial insuffic. = 7<br>Venous leakage = 4<br>Psychogenic with minor organic disorder = 8<br><br>Inclusions:<br>Men with ED<br><br>Exclusions:<br>Hypotension, glaucoma | Assessment instruments<br>Questionnaires measured erectile response and patient satisfaction on a 7-point scale. Erectile responses recorded as full erection (adequate for successful intercourse), partial erection (adequate for penetration but not intercourse), tumescence (inadequate for penetration), or no response. The best response during the week was used in the analyses.<br><br>Active (N = 36) / Placebo (N = 36)<br>Full: 21 (58.3%) / 3 (8.3%)<br>Partial: 2 (5.6%) / -<br>Tumesc.: 2 (5.6%) / -<br>None: 11 (30.6%) / 33 (91.7%)<br><br>**Response by etiology**<br><br>Psychogenic (n = 9)<br>Active / Placebo<br>Full: 8 (88.9%) / 3 (33.3%)<br>Partial: - / -<br>Tumesc.: - / -<br>None: 1 (11.1%) / 6 (66.7%)<br><br>Neurogenic (n = 8)<br>Active / Placebo<br>Full: 4 (50%) / -<br>Partial: 1 (12.5%) / -<br>Tumesc.: 1 (12.5%) / -<br>None: 2 (25%) / 8 (100%)<br><br>Atrerial insufficiency (n = 7)<br>Active / Placebo<br>Full: 2 (28.6%) / -<br>Partial: 1 (14.3%) / -<br>Tumesc.: 1 (14.3%) / -<br>None: 3 (42.9%) / 7 (100%)<br><br>Venous leakage (n = 4)<br>Active / Placebo<br>Full: 1 (25%) / -<br>Partial: - / -<br>Tumesc.: - / -<br>None: 3 (75%) / 4 (100%)<br><br>Mixed (n = 8)<br>Active / Placebo<br>Full: 6 (75%) / - |

# XXIV. Appendix 6: Buflomedil Transdermal Electromotive Administration

| Study Name | Doses | Study Design | Participants | Outcomes |
|---|---|---|---|---|
| **Bergamaschi** (1996)<br>J Urol<br>155(suppl):497A<br>meeting abstract #744 | Transdermal electromotive administration (EMDA) – buflomedil<br><br>EMDA – saline (placebo)<br><br>1.5 – 2.0 mA current through electrode-drug receptacle attached to the penis ( 2 X/week for 6 weeks) | Randomized, placebo-controlled, parallel group, patient-blinded | N = 25<br><br>Etiology of ED<br>Impotence associated with ischemic heart disease and generalized vasculopathy.<br><br>Active group: n = 13<br><br>Placebo group: n = 12 | Satisfactory intercourse<br><br>Active / Placebo<br>1 mo 7/13 (54%) 2/12 (17%)<br>3 mo 8/13 (62%) 1/12 (8%)<br>6 mo 3/8 (38%) 2/7 (29%)<br><br>No side effects were reported by patients. |

# XXV. Appendix 7: Apomorphine

| Study Name | Doses | Study Design | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Padma-Nathan** (1998) J Urol 159(suppl):241 meeting abstract #920 | Apomorphine (sublingual): 2 mg, 4 mg, 6 mg, or placebo | Randomized, double blinded, placebo-controlled, crossover<br><br>Patients randomized to 1 of 3 doses vs. placebo | N = 457<br><br>Inclusions<br>ED with no major organic component | Assessment instrument<br>Percent attempts resulting in an erection firm enough for intercourse<br><br>Apomorphine / Placebo<br>Dose (n = unknown) (n = unknown)<br>2 mg 45.8% 32.2%<br>4 mg 52.0% 35.0%<br>6 mg 59.6% 34.2%<br><br>(P < .001) | Mild to moderate nausea:<br><br>Dose % reporting<br>2 mg 2.1%<br>4 mg 19.5%<br>6 mg 39.0%<br>placebo up to 4.9%<br><br>Severe nausea:<br><br>Dose % reporting<br>2 mg 0%<br>4 mg 0%<br>6 mg 2.7%<br>placebo 0% |

# XXVI. Appendix 8: Intraurethral Alprostadil for the Treatment of Erectile Dysfunction (ED)

## A. Peer reviewed RCTs

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Padma-Nathan (1997)** | Alprostadil<br>125 µg, 250 µg, 500 µg, 1000 µg or placebo | Multi-center, randomized, double blind, placebo controlled, parallel group study.<br><br>Duration: 3 months<br><br>In an initial open-label dosing phase, subjects received up to four escalating doses of active therapy in clinic. Those who responded with either an "erection sufficient for intercourse" or "full rigidity" were eligible for the double blind phase. In the double blind phase subjects were randomized to placebo or to the dose to which they had responded during the dosing phase.<br><br>1511 subjects participated in the dosing phase, 996 achieved an adequate erectile response and enrolled in the double blind phase, 961 of these reported results of at least one administration and were included in analysis of efficacy, and 873 had complete follow-up.<br><br>Dosing phase n=1511<br>Random-ized / Drop-outs<br>Double blind n=996 123<br>Alprostadil n=485 na<br>Placebo n=511 na | Inclusions:<br>In a stable, monogamous, heterosexual relationship; unable to achieve a spontaneous erection sufficient for intercourse at any time within the preceding 3 months; responder to active therapy administered in an escalating dose-finding study phase<br>Exclusions:<br>History of urethral stricture or obstruction; indwelling urethral catheter; anuria; history of penile implant or penile surgery; sickle cell disease; paraplegia or quadriplegia; CHF, unstable angina, or recent acute MI; poorly controlled DM; hypogonadism with inadequate testosterone therapy; marked baseline lab abnormality.<br>*Age, mean yrs (range):*<br>Dosing phase 61 (27-88)<br>Double blind phase<br>Alprostadil 62 (38-84)<br>Placebo 61 (30-83)<br>*Duration of ED, mean yrs (range):*<br>Dosing phase 4.25 (0.025-44)<br>Double blind phase<br>Alprostadil 4.0 (0.025-44)<br>Placebo 4.08 (0.025-30)<br>*Primary Etiology of ED (%):*<br>VaD S/T DM Other<br>Dosing phase 28.7 29.6 20.6 21.0<br>Double blind phase<br>Alprostadil 28.9 31.8 18.8 20.6<br>Placebo 28.4 31.1 19.2 21.3<br>*Previous treatment for ED (%):*<br>Dosing phase 55.3 | Outcomes given only for the double blind phase of the study.<br><br>*Return to intercourse (% reporting sexual intercourse at least once during 3 month treatment):*<br>Alprostadil * 64.9<br>Placebo 18.6<br><br>*% of intercourse attempts which were successful:*<br>Alprostadil * 50.4<br>Placebo 10.4<br><br>* (p<0.001)<br><br>Subgroup analysis for return to intercourse question, performed by etiology of ED, age group of subject, indicated a significant treatment effect vs placebo (p<0.001). | Adverse events given only for the double blind phase of the study.<br><br>*Penile pain (%):*<br>Alprostadil 32.7<br>Placebo 3.3<br>*Minor urethral trauma (%):*<br>*Alprostadil 5.1*<br>*Placebo 1.0*<br>*Urinary tract infection (%):*<br>Alprostadil 0.2<br>Placebo 0.6<br>*Dizziness (%):*<br>Alprostadil 1.9<br>Placebo 0.2<br>*Hypotension (%):*<br>Alprostadil 0<br>Placebo 0.2 |

ED=erectile dysfunction
S/T=surgery/trauma
MI=myocardial infarction
UTI=uniry tract infection
DM=diabetes mellitus
VaD=vascular disease

## Appendix 8A (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Williams (1998)** | Alprostadil 125µg, 250µg, 500 µg, 1000 µg or placebo | Multi-center, randomized, double blind, placebo-controlled, parallel group study<br><br>Duration: 3 months<br><br>In an initial open-label dosing phase, subjects administered up to four escalating doses of Alprostadil at home. Those who responded with either an "erection sufficient for intercourse" or "full rigidity" were eligible for the double blind phase. In the double blind phase, subjects were randomized to placebo or to their "most comfortable, effective dose" of Alprostadil from the dosing phase.<br><br>249 subjects entered an open-label dosing phase (125-1000µg), 159 achieved a sufficient erectile response and were enrolled in the double blind phase, 140 reported results of at least one administration and were included in analysis of efficacy, and 117 had complete follow-up.<br><br>Dosing phase n=249<br>Random- Drop-<br>ized outs<br>Double blind n=159 42 | *Inclusions:*<br>Age >18 yrs; ED of primarily organic etiology; inability to achieve an erection sufficient for intercourse without therapy during the 3 months before study entry; in a stable, monogamous, heterosexual relationship.<br>*Exclusions:*<br>None given.<br>*Age, mean yrs (range):*<br>Dosing phase 56.5 (25-78)<br>Double blind phase<br>Alprostadil 57.3 (25-78)<br>Placebo 57.3 (26-77)<br>*Duration of ED, mean mos (range):*<br>Dosing phase 58.3 (3-644)<br>Double blind phase<br>Alprostadil 59.6 (3-644)<br>Placebo 63.3 (4-417)<br>*Primary Etiology of ED (%):*<br>VD S/T DM Other<br>Dosing phase 30 23 17 31<br>Double blind phase<br>Alprostadil 33 24 18 24<br>Placebo 41 21 15 24<br>*Previous treatment for ED (%):*<br>Dosing phase 50<br>Double blind phase<br>Alprostadil 51<br>Placebo 54 | Outcomes given only for the double blind phase of the study.<br><br>*Return to intercourse (% reporting sexual intercourse at least once during 3 month treatment):*<br>Alprostadil * 69<br>Placebo 11<br><br>*% of intercourse attempts which were successful:*<br>Alprostadil 51<br>Placebo 7.5<br><br>* (p<0.001)<br><br>Subgroup analysis for return to intercourse question, performed by etiology of ED, age, duration of ED, history of previous treatment for ED and capability of achieving partial tumescence prior to treatment, indicated a significant treatment effect vs placebo (p<0.05). | Outcomes given only for the double blind phase of the study.<br><br>*Urethral pain/burning (%):*<br>Alprostadil 6<br>Placebo 0<br>*Penile pain (%):*<br>Alprostadil 5<br>Placebo 1<br>*Testicular pain (%):*<br>Alprostadil 3<br>Placebo 0<br>*Minor urethral spotting/bleeding (%):*<br>Alprostadil 1<br>Placebo 1<br>*"Prolonged erection" (%):*<br>Alprostadil 1<br>Placebo 0<br>*Dizziness (%):*<br>Alprostadil 3<br>Placebo 0 |

## Appendix 8A (continued)

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Peterson (1998)** | Alprostadil<br>125 µg<br>250 µg<br>500 µg<br>1000 µg<br><br>Prazosin<br>250 µg<br>500 µg<br>1000 µg<br>2000 µg<br><br>**Alprostadil/prazosin**<br>125/250 µg<br>125/500 µg<br>250/250 µg<br>250/500 µg<br>250/1000 µg<br>500/500 µg<br>500/1000 µg<br>500/2000 µg<br>1000/1000 µg<br><br>**Placebo** | Randomized-crossover, double blind, placebo-controlled (partial block, factorial design trial)<br><br>**Initial study visit:**<br>Patients self-administered a test dose of alprostadil under supervision. Those who tolerated the medication and demonstrated a measurable response continued to the study.<br><br>**Partial block, factorial design trial:**<br>Each patient self-administered 7 randomly-ordered, blinded doses (2 a/p combinations, 2 prazosin doses, 2 alprostadil doses and 1 placebo) in the clinic in a 2 to 4-week period.<br><br>Active medication assigned in triads: a/p combination and single-agent components of the combination. Placebo dose was 1 of first 4 systems given, and high doses (500 or 1000 µg) alprostadil alone or in combination as the last 3 doses. | Inclusions: stable, monogamous marital relationship; inability to achieve a spontaneous erection sufficient for intercourse within 3 months before study.<br><br>Exclusions: waking or early morning erections with sufficient tumescence for vaginal penetration within 3 months before study entry; urethral stricture or obstruction; anuria; penile implant; indwelling urethral catheter of previous penile surgery; sickle cell disease; paraplegia or quadriplegia; congestive heart failure; unstable angina or acute myocardial infarction; poorly controlled DM; use of investigational treatments other than intracavernous injections; epilepsy; vasculitis; life expectancy 6 months; morbid obesity.<br><br>N = 234<br><br>Mean age = 60.0 ± 10.0<br>Age range = 26.8 - 81.5<br><br>Mean duration of ED = 47.7 months<br><br>*Concomitant conditions (%):*<br>vascular disease = 39.3%<br>surgery/trauma = 24.8%<br>diabetes mellitus = 17.9%<br>other = 17.9%<br><br>*Previous ED treatment (%):*<br>none = 39.7%<br>counseling = 9.4%<br>hormonal treatment = 18.8%<br>cavernous injection = 33.3%<br>band therapy = 4.3%<br>vacuum pump = 18.4%<br>other = 2.6% | **Assessment instruments:**<br>Erection Assessment Scale (EAS) -<br>1 = no response<br>2 = some enlargement<br>3 = full enlargement<br>4 = erection sufficient for intercourse<br>5 = rigid erection<br><br>Visual Analogue Scale (VAS) -<br>couples assessed penile response:<br>0 = no effect<br>100 = rigid erection<br><br>**EAS score = 3, 4 or 5**<br>A125 = 32.6%<br>A250 = 39.1%<br>A500 = 51.8%<br>A1000 = 23.6%<br>P2000 = 12.7%<br>A125/P500 = 45.6%<br>A250/A500 = 53.2%<br>A500/P2000 = 58.9%<br>placebo = 2.7%<br><br>**EAS score = 4 or 5**<br>A125 = 14.1%<br>A250 = 17.4%<br>A500 = 31.1%<br>P2000 = 3.0%<br>A/P (range) = 30.4 – 35.7%<br>placebo = 0.4%<br><br>**VAS Penile Response Mean (0 - 100)**<br>A (range) = 36.5 – 50.0 | **Discontinued treatment:**<br>N = 234<br>Overall dropouts = 19:<br>patient request = 4<br>noncompliance = 3<br>unrelated illness = 3<br>physician decision = 2<br>intolerable side effects = 2<br>other = 5<br><br>**Adverse effects:**<br>Penile pain -<br>A (range) = 17.0 - 23.6%<br>P (range) = 0.7 - 5.5%<br>A/P (range) = 17.0 - 31.6%<br>placebo = 1.7%<br><br>Testicular pain -<br>A (range) = 1.8 - 4.4%<br>P (range) = 0 - 1.4%<br>A/P = 1.8 - 7.7%<br>placebo = 0.4%<br><br>Urethral pain -<br>A (range) = 1.0 - 9.1%<br>P (range) = 0 - 2.1%<br>A/P (range) = 5.3 – 13.5%<br>placebo = 1.7%<br><br>Hypotension -<br>A (range) = 1.0 - 3.6%<br>P (range) = 0 - 1.8%<br>A/P (range) = 0 - 14.0%<br>placebo = 0%<br><br>Dizziness -<br>A (range) = 0 - 5.5%<br>P (range) = 0 - 0.7%<br>A/P (range) = 0 - 11.5% |

## B. Abstracts

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Costabile (1998)** | **Alprostadil**<br>(4 possible doses):<br>125mcg, 250mcg, 500mcg, 1000mcg;<br><br>or **Alprostadil/Prazosin**<br>(16 possible doses):<br>125/250mcg, 125/500mcg, 125/1000mcg,<br>125/2000mcg, 250/250mcg, 250/500mcg, 250/1000mcg, 250/2000mcg, 500/250mcg, 500/500mcg, 500/1000mcg, 500/2000mcg,<br>1000/250mcg,<br>1000/500mcg,<br>1000/1000mcg,<br>1000/2000mcg; | Multi-center, double blind, placebo controlled, crossover study. Randomization not mentioned.<br><br>Duration up to 6 months<br><br>In an initial, double blinded dosing phase, subjects received various doses of Alprostadil and Alprostadil/Prazosin combinations which they self-administered at home. Next, subjects entered a double blind, placebo controlled phase of up to 6 months duration in which they received 8-dose packs that included their selected dose from the dosing phase and interspersed placebo. | *Inclusions:*<br>Men with complete, organic ED.<br><br>*Exclusions:*<br>None given.<br><br>*Age, mean yrs* = 63<br><br>*Duration of ED, mean mos* = 34 | *DOSING PHASE*<br>% reporting sexual intercourse:<br>*Of the 70% of men who reported intercourse (n = 276), 89 succeeded with A/P only, and were not responsive to alprostadil alone.*<br><br>*PLACEBO CONTROLLED PHASE*<br>% reporting sexual intercourse during placebo controlled phase:<br>"Alprostadil alone and alprostadil/prazosin combinations each demonstrated high efficacy vs. placebo." | Adverse events were reported as % of doses, with the range for the different treatment groups given.<br>*Penile pain:* 7.6-19.8<br>*Hypotension:* 1.5-9.2 |
| **Costabile (1997)** | **Alprostadil** 125mcg, 250mcg, 500mcg, 1000mcg or placebo. | This paper is an analysis of the subgroup of subjects with a **history of radical prostatectomy** from the study listed in Table 3a under the name **Padma-Nathan (1997).**<br>Details of the study design will not be repeated here.<br><br>DOSING PHASE<br>Overall<br>n=1511 | | *Outcomes given only for the placebo controlled phase.*<br><br>*PLACEBO CONTROLLED PHASE*<br>% reporting sexual intercourse during placebo controlled phase:<br>Alprostadil * 57.1<br>Placebo 6.6<br><br>* ($p<0.001$) | "The most common adverse effect was penile pain, occurring in 39% of patients." Details of frequency of penile pain by study phase and treatment arm not given. |
| **Su (1998)**<br><br>See Appendix 9C | | | | | |
| **Padma-Nathan (1996)**<br><br>The data from this study is detailed in Appendix 8A under the study name **Padma-Nathan (1997)** and will not be detailed here. | | | | | |

## C. Peer reviewed RCTs - short-term single-dose studies

| Study Name | Dose | Study Design, Duration and Size | Participants | Outcomes | Adverse Events |
|---|---|---|---|---|---|
| **Hellstrom (1996)** | Alprostadil<br>125 μg, 250 μg, 500 μg, 1000 μg and placebo<br><br>Each patient recieved a medication kit containing randomly ordered doses of medication to be used at home: 1 dose of placebo and 1 each of the 4 dosages of alprostadil. The 5 doses were dispensed in a 2 to 4-week period.<br><br>[no washout period mentioned] | Randomized-crossover, double blind, placebo-controlled<br><br>Inclusions: men in a stable, monogamous marital relationship; unable to achieve a spontaneous erection sufficient for intercourse on any occasion within the previous 3 months without the aid of therapy.<br><br>Exclusions: urethral stricture; anuria, indwelling urethral catheter, or prior penile surgery; sickle cell disease; unstable angina or a recent myocardial infarction; poorly controlled diabetes mellitus or congestive heart failure; or recent use of another investigational treatment. | N = 68<br><br>[These patients were a subset of the 247 patients in Padma-Nathan (1995). Criteria for selection of subset: first 68 patients who completed an in-clinic evaluation of transurethral therapy (not based on a favorable response).]<br><br>Mean age = 58.6 ± 10.7<br>Age range = 26.8 - 76.4<br><br>Mean duration of ED = 41.3 ± 52.7 months<br><br>Concomitant conditions (n, %):<br>vascular disease = 32, 47.1%<br>surgery/trauma = 18, 26.5%<br>diabetes mellitus = 10, 14.7%<br>other = 8, 11.8% | Assessment instruments: the Erection Assessment Scale (EAS) -<br>1 = no response<br>2 = some enlargement<br>3 = full enlargement<br>4 = erection sufficient for intercourse<br>5 = rigid erection<br><br>The Visual Analogue Scale (VAS) - couples assessed penile response using the following scale:<br>0 = no effect<br>100 = rigid erection<br><br>**EAS score = 4 or 5**<br>placebo = 4.8%<br>125 μg = 19.7%<br>250 μg = 30.3%<br>500 μg = 26.7%<br>1000 μg = 31.7%<br><br>($p < 0.001$)<br><br>**Percentage of patients who had intercourse for each individual dose**<br>placebo = 12.5%<br>125 μg = 39.4%<br>250 μg = 33.3%<br>500 μg = 40.0%<br>1000 μg = 50.0%<br><br>($p \leq 0.01$)<br><br>**VAS Penile Response Mean (0 - 100)**<br>placebo = 18.4<br>125 μg = 41.8<br>250 μg = 44.2 | **Discontinued treatment:** Actual number of dropouts was not reported. "For patients exiting the study prior to completion of the dosing sequence, all validly collected measurements were included in the analysis, but no data extrapolation was performed."<br><br>**Adverse effects:**<br>*Penile pain or discomfort* = ranged from 9.1% (125 μg) to 18.3% (1000 μg) [none reported in association with placebo]<br><br>*Prolonged erection / sustained engorgement* = 3 episodes reported by the same patient<br><br>*Dizziness* = 1 patient<br><br>*Sweating* = 1 patient<br><br>*Minor urethral trauma* = 1 patient |