

Treatment Option for Erectile Dysfunction

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Erectile dysfunction (ED) is the inability to achieve and maintain an erection sufficient for satisfactory sexual activity.¹ Researchers have made great strides in understanding the complex neural and vascular pathways that are essential for normal erectile function. Investigations into smooth muscle physiology, endothelial cell function, central nervous control, and neurotransmitters such as nitric oxide (NO) and vasoactive intestinal peptide in the corpus cavernosum have led to the design, development, and use of specific pharmacological agents to recreate the normal physiology of the corpus cavernosum and restore erectile dysfunction in men who were previously termed impotent.

Several treatment options are currently available for ED. Intracavernosal injection (IC) of vasoactive drugs, transurethral vasodilators, and vacuum constriction devices (VCDs) are safe, nonsurgical treatments that have variable ranges of efficacy and satisfaction rates. All of these erectaid treatments can potentially work and can have excellent compliance in an individual patient².

The introduction of the first effective oral agent for ED treatment, sildenafil citrate, has revolutionized the management of this disorder and has significantly increased the number of men coming forward for evaluation and treatment. Sildenafil is effective in most men with erectile dysfunction (ED) in the general population including men with spinal cord injury, diabetes mellitus, and patients who have had nerve-sparing radical prostatectomy.

This paper will discuss the physiology of the normal erection and how the aforementioned treatment options can help those with ED. The paper will also review new medications that may soon be available to supplement treatment with sildenafil.

Molecular physiology of erection

Both the peripheral and central nervous systems

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play a role in the complex physiological response that leads to penile erection. Before an erection can occur, the central cavernosal arteries of the corpora cavernosa must dilate to increase blood flow to the penis. This increased blood flow combined with the production of NO from the nerve endings in the smooth muscles that form the lacunar spaces for the corpora cavernosa-produce lacunar smooth muscle relaxation.³ Once the smooth muscles have relaxed, blood flows rapidly into the lacunar spaces, increasing the volume in the corpora. This process also compresses and elongates the subtunical veins that drain the corpora cavernosa, decreasing venous outflow and increasing intracorporeal pressure. Pressure in the corpora cavernosa is supplemented by the contraction of the perineal muscles, resulting in a high-pressure rigid erection that is satisfactory for sexual activity. On a subcellular level, control of smooth muscle activity depends on intracellular calcium flux. Neurotransmitters and endothelium-derived factors influence the flow of intracellular calcium that balances penile flaccidity and rigidity.

The principal substance responsible for smooth muscle relaxation is NO.⁴ Nitric oxide is produced from the precursor L-arginine through the enzyme nitric oxide synthase (NOS). Nitric oxide subsequently diffuses into smooth muscle cells and activates the secondary neurotransmitter system guanylate cyclase, which converts guanosine triphosphate into cyclic guanosine monophosphate (cGMP). This secondary neurotransmitter activates the intracellular sodium pump system, opening potassium channels and decreasing levels of intracellular potassium, which causes smooth muscles to relax. cGMP is metabolized through enzymatic breakdown by phosphodiesterase type 5 (PDE5), which closes potassium channels, increases levels of intracellular calcium, and facilitates smooth muscle contraction.⁵ Other neurotransmitters serve as cotransmitters, including vasoactive intestinal polypeptide and prostaglandins that act through the adenylate cyclase pathway and its secondary neurotransmitter, cyclic adenosine monophosphate (cAMP).^{6,7}

Smooth muscle relaxation is counterbalanced by neurotransmitters and substances that cause the smooth muscles to contract.⁸ Levels of these agents, which are present in the healthy corpus cavernosum, may be increased by high sympathetic tone caused by physical and psychological stressors. The vasoconstrictor norepinephrine is the principal agent responsible for smooth muscle contraction. Norepinephrine is released from the sympathetic nerve endings in the corpora cavernosa and activates the alpha-1 adrenoceptors, which raise intracellular calcium and produce smooth muscle contraction.⁹ Other similar molecules may also play a role on smooth muscle contraction, including endothelin-1, prostaglandin F₂, and epinephrine. Levels of these local neurotransmitters along with central nervous system substances that can be manipulated pharmacologically have led to the revolution in the pharmacologic treatment of ED.

Standard Treatments For Erectile Dysfunction - Pre Sildenafil Era

Vacuum Constriction Device (VCD)

Vacuum constriction devices (VCD) were described as early as 1917, but did not achieve acceptance in the urologic community until the early 1980s. The VCD consists of a clear plastic cylinder, a vacuum pump, and a constriction ring. After application of a lubricant, the open end of the cylinder may be placed over the flaccid penis and compressed against the abdominal wall to create an airtight seal. Erection is achieved by creating a vacuum inside the cylinder using a pump directly connected to the cylinder or connected by tubing. After an adequate erection is achieved, a constriction band can be applied around the base of the penis to help maintain the erection. The device can then be removed and the patient can engage in intercourse with the constriction bands) maintaining the erection. The band can remain for a maximum of 30 minutes. The erection produced by this device differs from a normal erection and is thought to involve venous occlusion from the constriction band, resulting in generalized swelling of the entire penis, presumably with preservation of arterial inflow.

Numerous published reports exist that describe this treatment as very effective. These devices have been used successfully in a variety of patients with organic ED, including those patients treated for prostate cancer with either RP or radiation therapy.¹⁰ Cookson and Nadig reported long term follow-up

results in-patients treated with vacuum constriction devices. They reported long term efficacy and patient satisfaction rates of more than 80%, with statistically significant increase in the frequency of successful intercourse attempts in 79% of the patients using the device for 1 year, which were maintained in 77% beyond the first year. However, despite this excellent satisfaction in this subset of patients, the overall dropout rate was 30-40%. The primary reasons for discontinuation were bruising and petechiae 5%, pivoting at the base of the penis 6%, coldness and numbness around penis 5%, and pain related to VCD or the constriction band 10%, and decreased ability to achieve orgasm with the device 10%.¹¹

Turner and his associates did a prospective comparison of intracorporeal injection of papaverine/phentolamine and external vacuum devices in term of usage rates, effectiveness, side effects, dropout rates and impact on patient sexual and psychological functioning. Both treatments were efficacious and safely used by patients, though dropout rates were higher for the group using IC injections (60% vs 20%). There were no differences between the two treatments in sexual or psychological impact.¹²

While IC injections can reproduce a more natural and satisfactory erection, the efficacy is not 100% and the continued use of needles lends itself to 40-60% noncompliance rate after one year.¹³ For these patients, VCD may be a reasonable alternative. Gould and colleagues reported that 71% patients who failed to achieve satisfactory erections by intracavernosal injection subsequently received adequate rigidity and satisfactory erection with VCD.¹⁴ In men with preoperative ED, where recovery of function and the non-physiological erection is not a major issue, there is no disadvantage to this form of therapy¹⁵. However, VCD may be detrimental in men with intact preoperative function during the first 24 months after surgery when there is a theoretical advantage of increasing tissue oxygenation during the erection.

Although the published reports describe efficacy rates of 60% to 80%, the compliance after 1 year of activity decreases to 50 to 70%.¹⁶ Non-compliant patients typically complain of tightness or pain from the constriction ring, diminished sensation of the phallus and glans, swiveling of the base of the penis with erection, and the laborious mechanics of just using the vacuum device. In addition, there is variability in the success of using the VCD each time which leads to frustration.

A current area of interest includes the early intervention clinical protocols in the use of VCD to encourage early corporeal rehabilitation and

Table 1: Comparison between patients with nerve-sparing (NS) and non-NS RP in response to early use of VCD¹⁹

Variable	Bilateral NS (n = 25)	Unilateral NS (n = 19)	Non-NS (n = 16)
VCD for sexual intercourse	100% (25/25)	100% (19/19)	100% (16/16)
Return of natural erection with VCD at 6-9 mo	36% (9/25)	37% (7/19)	19% (3/16)
Natural, erection sufficient, for intercourse at 6-9 mo	55% (5/9)	57% (4/7)	33% (1/3)
Spouse satisfaction	52% (13/25)	57% (11/19)	57% (9/16)
IIEF Q3 (penetration frequency) pre-surgery → post-surgery → after VCD use	4.76 → .91 → 3.61	4.33 → .86 → 3.24	4.1 → .85 → 3.14
IIEF Q4 (erection, maintenance) pre-surgery → post-surgery → after VCD use	4.81 → .86 → 3.63	4.76 → .84 → 3.54	4.81 → .80 → 3.06
Total IIEF-5 score	16	15	15

All questions taken from the International Index for Erectile Function questionnaire.

Answers were scored: 0 = no intercourse, 1 = never/ almost never, 3 = sometimes, 5 = always/ almost always.

The total IIEF-5 score are calculated by totaling the response to all 5 domain of IIEF questionnaire

prevention of post surgery venoocclusive dysfunction by increasing the frequency. of tissue oxygenation. Early sexual rehabilitation after pelvic surgery may enhance earlier recovery of nocturnal erections, as treatments enhanced oxygenation of the corpora cavernosa and prevents formation of collagen and fibrosis, a cofactor in smooth relaxation and erectile function.¹⁷.

In our experience, daily use of VCD after RP (with/ without the constriction ring) to either maintain corporeal engorgement or to achieve vaginal intercourse during period of neuropraxia was associated with a high compliance rate 62/105 (60%) and few complications. Of this series, 59% of the patients at 6 months reported having sexual activity (vaginal intercourse) with the VCD at a frequency of twice/week. This level of activity in the first 6 months helped maintain the sexual interest and comfort between the couples that existed preoperatively. At a mean interval of 9 months, the early (daily) use of VCD resulted in erectile function in 32% (20/ 62) of patients, with 10 of these 20 patients (50%) having erections firm enough for vaginal penetration for an overall potency rate of 16% at 9 months. This potency rate (defined as vaginal penetration) of 16% at 9 months is not significantly different from our contemporary series (without early VCD), which had a 15% potency rate at 9 months. Our study was consistent with the study done by Wiles and his associates who reported return of nocturnal erections

in 40% of the men using VCD after an interval of 6 months, but did not report significant success at vaginal intercourse.¹⁸ Longer follow-up is need to determine if early VCD use can increase the return of both nocturnal erections and rigid erections sufficient for vaginal intercourse. It does appear that early VCD encourages early sexual activity and interest in patients (and partners) who previously were inactive for a year or more, waiting for the period of neuropraxia to resolve. This improvement in sexual satisfaction within the first year with early VCD use is apparent by the increase in IIEF scores seen at 9 months in our study (Table 1)¹⁹.

VCDs are an important option in the armamentarium for clinicians who treat erectile dysfunction. The current models seem safe and are applicable to patients with mixed etiologies and risks factors. The rigidity is sufficient for vaginal penetration and intercourse in a very high percentage of cases. The satisfaction scores are high for both patients and partners in individual circumstances, and the dropout rates and complications are less than those of IC injection.

Topical and Intraurethral alprostadil (PGE1) (MUSE)

Minidoxil, an antihypertensive agent and potassium channel opener that produces significant arterial dilatation, has been applied topically as a 2%

Table-2. Responses to the IIEF questionnaire of 19 post-prostatectomy patients before and after MUSE treatment²⁸

Questions	Mean score before surgery (± SD)	Mean score after surgery (± SD)	Mean score after MUSE (± SD)	P (Before vs. after IC therapy)
3. Frequency of penetration	4.47 ± 1.07	1.36 ± 1.42	1.94 ± 1.47	<0.001
4. Frequency of maintained erection	4.63 ± 0.59	1.31 ± 1.29	2 ± 1	<0.001
7. Frequency of satisfactory intercourse	4.94 ± 0.22	1.78 ± 1.65	2.29 ± 1.57	<0.001
Efficacy Score	14.05 ± 1.68	4.2 ± 3.45	5.94 ± 4.37	<0.001

All questions taken from the International Index for Erectile Function questionnaire.

Answers were scored: 0 = no intercourse, 1 = never/ almost never, 3 = sometimes, 5 = always/ almost always.

Efficacy score: Sum of responses to questions 3, 4, and 7. p-value by Wilcoxon rank-sum test.

solution.²⁰ Although Minidoxil produced results that were superior to placebo, satisfactory rigidity was not obtained for clinical use.

Nitroglycerine, an older established vasodilator, has been applied transcutaneously using an ointment formulation.^{21,22} A randomized, placebo-controlled, double blind trial showed that in patients who were treated with a nitroglycerine patch had a significant response. Twenty-one of 26 patients with mild ED had satisfactory erectile function. Side effects included headache and penile erythema.²³ Because topical nitroglycerine is rapidly absorbed through the vaginal mucosa, patients using transcutaneous or ointment-based nitroglycerine for ED must be advised to wear a condom during sexual activity.

A newer preparation of PGE1 in SEPA (soft enhancement of percutaneous absorption) gel has undergone early trials. McVary et al²⁴ reported that 67% to 75% of patients had an erection (compared with 17% of the controls) within 60 minutes of applying the PGE1 gel and using visual sexual stimulation. More than 75% of all men (in both placebo and PGE1 groups) reported glans discomfort.

In November 1996, intraurethral alprostadil therapy received Food and Drug Administration (FDA) approval for use in ED. This therapy currently represents as alternative method of delivering PGE1 to the erectile tissue by means of a medicated pellet. Through the medicated urethral system for erection, a pellet containing alprostadil (an analogue of prostaglandin E1) is delivered into the male urethra, which is absorbed by the cavernosal tissue through vascular communications from the corpus spongiosum. Intraurethral alprostadil, when introduced by Padma-Nathan et al in 1997, was reported to have an over all efficacy rate of 44%, but subsequent

investigations could not confirm these initially favorable results and reported significant urethral pain and burning.²⁵ Studies suggest that MUSE is much less successful in patients with erectile dysfunction caused by pelvic surgery or radical prostatectomy. Costabile and associates examined the effect of transurethral alprostadil in 384 men with erectile dysfunction after RP and reported overall success rate of 40%.²⁶ However, Palone et al. at the Cleveland Clinic reported that MUSE was effective in only 15% in men who had pelvic surgery.²⁷

More recently, the efficacy and compliance of MUSE was studied in a contemporary radical prostatectomy series at the Cleveland Clinic, using the International Index of Erectile Function questionnaire to validate responses. The results showed that MUSE was effective in 32% of patients. In this series, questions 3, 4 and 7 of the IIEF were added to get an efficiency score, and 31.6% of patients rated their response as good (Table 2). Moreover, 80% of the patients discontinued treatment, mainly because of an inadequate response or side effects. In this study, there were no statistically significant differences in the responses among different etiologic subgroups.²⁸

When intraurethral therapy is compared with IC injections, most patients who have tried intraurethral therapy (MUSE) and intracavernous injection therapy favor injections, and find that it produces a firmer erection. Porst et al compared intraurethral and intracavernosal injected PGE1 and reported a significantly higher success rate and decreased side effects with injection of PGE1 at lower doses compared with intraurethral application of PGE1.²⁹ Since the introduction of oral therapy, the use of MUSE has decreased because comparative studies show that sildenafil has better efficacy and

Table-3. Responses to the IIEF questionnaire (Qs 3, 4 and 7) and ES of 98 post-prostatectomy patients before and after IC injection treatment³⁹

Questions	Mean score before surgery (\pm SD)	Mean score after surgery (\pm SD)	Mean score after IC injection therapy (\pm SD)	P (Before vs. after IC therapy)
3. Frequency of penetration	4.78 \pm 0.62	1.45 \pm 1.53	3.91 \pm 1.52	<0.001
4. Frequency of maintained erection	4.84 \pm 0.63	1.30 \pm 1.18	3.81 \pm 1.67	<0.001
7. Frequency of satisfactory intercourse	4.79 \pm 0.77	1.44 \pm 1.38	3.61 \pm 1.67	<0.001
Efficacy Score	14.41 \pm 1.85	4.2 \pm 3.45	11.13 \pm 1.67	<0.001

All questions taken from the International Index for Erectile Function questionnaire.

Answers were scored: 0 = no intercourse, 1 = never/ almost never, 3 = sometimes, 5 = always/ almost always.

Efficacy score: Sum of responses to questions 3, 4, and 7.p-value by Wilcoxon rank-sum test.

compliance. Recently, there have been clinical research efforts to use combination therapy, sildenafil with MUSE, to improve efficacy. A study conducted by Nehra and colleagues (Rochester, MN, USA), demonstrated that a combination of sildenafil (100mg) and intraurethral prostaglandin E1 (1000 mcg) salvaged a selected population of men with ED. The use of combination therapy will open a new area of interest in the treatment for ED. Further studies are required to confirm this interesting results.³⁰

The most common complication related to intraurethral therapy is discomfort in the penis, testicles, legs, and perineal area, probably owing to the hyperalgesia related to the use of PGE1. Additional complications include warmth or burning sensation in the urethra, minor urethral bleeding and occasional leg vein swelling.

Intraurethral therapy (MUSE) is effective in selected patients and should remain in the armamentarium when considering options for erectile dysfunction. The use of the MUSE system for oral medication failures and in selective patients with unsatisfactory erection with penile prosthesis establishes a niche for this method of treatment of erectile dysfunction.

Intracavernosal (IC) Injection Therapy

Intracavernosal injection became a standard treatment for erectile dysfunction when it was introduced in the United States at the 1983 Meeting of the American Urological Association.³¹ With this therapy, patients inject drugs such as PGE1 (alprostadil) or alprostadil in combination with

papaverine and phentolamine (triple mixture) directly into the cavernosal blood vessels to obtain an erection.³² Whereas phentolamine is a direct adrenoceptor blocker, alprostadil and papaverine modulate levels of cyclic 3', 5'-adenosine monophosphatase in the cells, eventually increasing the penile blood flow by relaxing the arterial and trabecular smooth muscles.³³ By combining papaverine, phentolamine, and PGE1, the amount of each drug that is needed is less than a dose of one drug. This increases safety and decreases morbidity.³⁴

Despite having a high degree of therapeutic efficacy (more than 85%), patients do not readily accept penile injections, and dropout rates in many series have exceeded 40%.³⁵ This may be partially due to the fact that the injections cause pain in about 14% of patients and penile fibrosis in about 2% to 5% of patients. In addition, about 10% to 20% of patients have difficulty reproducing a successful injection.³⁶ Despite multiple technological attempts to devise better delivery systems, many patients continue to have both physical and emotional difficulties using a needle for any length of time.

Mulhall et al reported that 75% of 720 men in their study, which included patients with ED of all etiologies, had a good response to IC injection. They reported an attrition rate of 31% over a 38-month period; cost, penile discomfort, and patient-partner problems were the main reasons for discontinuation. Lack of efficacy was the primary reason for discontinuation in only 1 of 7 (14.2%) patients.³⁷ In a similar study, Purvis et al also found that 87% of their patient sample (which included all etiologies) were fully or partially satisfied with IC

Table-4. Comparison of IIEF-5 scores and partner satisfaction in long term intracavernous injection users who successfully switch to Sildenafil citrate⁴⁰

IIEF-5 Scores	On IC Therapy (n = 36)	Switch from IC to Sildenafil (n = 22) Successful Switch to Sildenafil (n = 15)	Combination Therapy (n = 7)
Q5, Maintenance ability	4.24	2.6	4.64
Q15, Erection confidence	3.96	2.22	4.23
Q4, Maintenance frequency	4.28	2.54	4.64
Q2, Erection firmness	4.12	2.36	4.27
Q7, Intercourse satisfaction	3.61	2.45	4.8
Total IIEF-5 Score	20.21	12.17	22.58
Partner satisfaction	71.8%	60.7%	72.8%

injections. The discontinuation rate in their study was 58% over 2 years; lack of spontaneity, penile discomfort, and cost of therapy were the main reasons for dissatisfaction. Inadequate rigidity or lack of efficacy was the primary reason for discontinuation in 18% of the patients.³⁸

Post-prostatectomy patients were treated with IC injections at the Cleveland Clinic and followed to analyze the efficacy and satisfaction rates and to document the reasons for its discontinuation using the International Index of Erectile Function (IIEF) questionnaire (Table 3).³⁹ Although the injections had considerable efficacy (mean efficacy score increased 2.7 times after use) and 68% of patients rated their erections as being "good to excellent" (Table 4), nearly 50% of the patients discontinued therapy.⁴⁰ The main reasons for discontinuation included insufficient erectile response and the fact the IC injections ultimately became an inconvenient and cumbersome procedure.

Although IC injection therapy is often not routinely advised in the early postoperative period because of penile discomfort, patient anxiety, and lack of interest, there is some evidence that "early rehabilitation" of the penis is necessary to prevent lasting dysfunction. During the period of neuropraxia that follows nerve-sparing radical prostatectomy (about 6 to 24 months), early IC injection therapy may limit the development of hypoxia-induced tissue damage and produce an overall improvement in the recovery of spontaneous erections.^{41,42} This concept is supported by a recent report by Montorsi et al, who demonstrated that immediate postoperative biweekly

IC injections of alprostadil resulted in a normal erection recovery rate at 6 months that was significantly higher than the rate among the nontreated controls (67% vs. 20%, $P < 0.01$). These subjective results were also confirmed by hemodynamic and nocturnal testing⁴³.

Further studies are required to confirm the results of these early IC injection studies and whether the 6- and 12-month potency rates are significantly better than that of age-matched controls who have undergone similar operations (stage of disease and type of nerve-sparing procedure). Early IC injections may promote more sexual activity and satisfaction but not necessarily an earlier return to potency.

The Viagra Era - 1998 and Beyond

The treatment algorithm for patients with ED improved dramatically with the availability of sildenafil citrate (Viagra, Pfizer Pharmaceutical), the first effective oral medication. Following the landmark publication by Goldstein et al in 1998,⁴⁴ sildenafil revolutionized the evaluation and treatment of ED so much so that sildenafil citrate is now the first choice of treatment for patients with ED caused by a variety of organic and psychogenic causes.⁴⁴

Data from clinical trials have demonstrated improved erectile function in patients with a cross-section of etiologies of ED. The 3 years following the launch of sildenafil have been a time of tremendous growth in information related to the mechanism of drug, its clinical efficacy and safety,

Table-5. Characteristics of 91 post-prostatectomy patients with erectile dysfunction before sildenafil citrate (Viagra) therapy⁵⁷

Patient Characteristics	Overall (n = 91)	Bilateral NS (n = 53)	Unilateral NS (n = 12)	Non-NS (n = 26)
Age (mean/yrs)	61.8	60.5	61.2	65.6
Time from surgery to Tx (median/mos)	18.4	22	14	14.5
Pre-surgery erectile status (%)				
Full	0	0	0	0
Partial	15.1	18.2	14.3	11.5
None	84.9	81.8	85.7	88.8
Able to penetrate (%)	0	0	0	0
Nocturnal erections present (%)	21	24.2	28.6	15.4

and appropriate use of the drug. Significant improvements in erectile function have been demonstrated in double-blind, placebo-controlled trials in patients with ED and underlying diabetes, cardiovascular disease, minor depression, spinal cord injury, and multiple sclerosis. Promising results have also been reported for patients treated with prostate cancer, in patients with end-stage renal failure, Parkinson's disease, and spina-bifida, and in multiple organ transplant recipients. Accounts of sildenafil use in clinical practice and post-marketing data reflect clinical trial results that found that the drug is effective in patients with a broad spectrum of ED etiologies and that its overall tolerability is good.⁴⁵

Sildenafil citrate works by transmitting NO across the neuromuscular junction of the penile smooth muscle or penile vasculature. However, the presence or absence of the neurovascular bundles greatly influences a man's ability to achieve vaginal intercourse. When non-adrenergic, non-cholinergic nerves are damaged or destroyed, transmission of NO diminishes or does not occur at all.⁴⁶ Without NO, guanylate cyclase is not activated and therefore cannot convert guanosine triphosphate into cGMP. cGMP relaxes the erectogenic smooth muscles by activating the intracellular sodium pump system, opening potassium channels and causing a decrease in intracellular potassium with resultant smooth muscle relaxation.^{47,48} Without cGMP, there is no substrate in which PDE5 can work. Hence, the PDE5 inhibitor is ineffective.

Researchers at the Cleveland Clinic were among the first to investigate the effects of this new oral medication in patients who had undergone radical prostatectomy and study the impact of the presence or absence of the neurovascular bundles.^{49,50} The study by Zippe et al⁴⁹ consisted of patients who were not able to have an erection or who had unsatisfactory

erections following radical prostatectomy. All eligible men had a complete history and physical to exclude any contraindications to the drug. Also, those who used oral, sublingual, or transdermal nitrates were excluded. A total of 91 patients were enrolled. The patients' operative reports were reviewed, and the patients were stratified as to the type of nerve-sparing procedure they underwent.

The mean age of the patients was 63.1 years, and the mean time interval from surgery to the start of sildenafil citrate was 18 months. Among the 91 patients, 53 (58.2%) had a bilateral nerve-sparing procedure, 12 (13.2%) had a unilateral nerve-sparing procedure, and 26 (28.6%) had a non-nerve sparing procedure. Patients were started on 50 mg a day; the dose was titrated to 100 mg when needed.

Before surgery, 80 patients (87.9%) were able to achieve a full erection and 9 (9.8%) were able to achieve a partial erection (Table 5). After surgery, 22 of the patients (24.2%) were able to have a partial erection and 69 (75.8%) were not able to have an erection at all. After surgery but before sildenafil use, none of the patients was able to achieve vaginal penetration. The mean time interval from radical prostatectomy to drug use was roughly greater than 1 year in all 3 subgroups.

Following treatment with sildenafil, 48 of the 91 patients responded to the drug: 38 of the 53 patients (71.7%) who had the bilateral nerve-sparing procedure, 6 of the 12 patients (50%) had the unilateral nerve sparing procedure, and 4 of the 26 patients (15.4%) had the non-nerve sparing procedure (Table 6). It was unclear whether the 15% response rate in the non-nerve-sparing group was due to placebo effect, unrecognized residual nerve tissue, or a non-neurogenic mechanism.

We individually interviewed all of the patient's spouses or partners and found that the quality of

Table-6. Comparison between patients with nerve-sparing and non-nerve-sparing prostatectomies in response to sildenafil citrate (Viagra)⁵⁷

Variable	Bilateral NS (n = 53)	Unilateral NS (n = 12)	Non-NS (n = 26)	p value
Number of doses	8	8.5	6.5	NS
Able to penetrate (%, n)	71.7 (38/53)	50 (6/12)	15.4 (4/26)	0.001
Mean duration of intercourse (mins)	10	4.5	12	
Spouse satisfaction (%, n)	66 (33/53)	41.6 (5/12)	15.4 (4/26)	
IIEF (responders)	N = 38	N=6	N=4	
Q 3 (freq. of penetration)	1.2 - 4.8	1.0 - 2.8	1.5 - 3.3	P = 0.04*
Q4 (freq of maintenance)	1.2 - 4.8	1.0 - 2.6	1.5 - 3.3	P= -0.02*
Q7 (sexual satisfaction)	1.3 - 4.2	1.2 - 2.5	1.3 - 3.0	P= -0.02*

Key: NS = nerve sparing; NSF = not significant

* Bilateral NS vs. unilateral NS/non-NS.

erection was excellent in all 48 responders and that the mean duration of intercourse ranged from 4.5 to 12 minutes. The ability to achieve vaginal penetration and the quality of the erection correlated with a spousal satisfaction rate of 80%. Only 1 % of the responding patients discontinued the medication (99% compliance).

The impact of nerve preservation and the efficacy of sildenafil was also reported by Zagaja et al⁵¹ from the University of Chicago, who showed an 80% response rate in men younger than 55 years when both nerve bundles were spared and a 40% response when one bundle was spared. However, in the 56-65 year old group, the response rate dropped to 45% in the group with two nerves spared and to 0% in those with one nerve preserved. In the older age group (> 65 years old), 33 % of the patients responded when two bundles were spared, and none of the 10 patients responded who had preservation of just one bundle. Also, in this series, sildenafil was ineffective in the first 9 months after prostatectomy.

Currently, the only contraindication to the use of sildenafil is the use of nitroglycerine or nitrate-containing compounds, which may cause hypotension. The drug is generally prescribed in either 50 or 100 mg tablets, which should be taken approximately 1 hour before intercourse. The drug requires sexual stimulation to be effective.⁵² Morales and associate summarized the side effects of sildenafil that occurred in 18 randomized, double blind placebo-controlled studies and found that 16% of patients experienced headache, 10% experienced flushing, and 7% experienced dyspepsia.⁵³ The side affects of the drug were transient, and none of the

patients discontinued the medication because of the side effects.

In a Cleveland Clinic series, the mean time interval from RP to the initiation of sildenafil was roughly 1 year in both the non nerve-sparing and nerve-sparing groups. Prospective studies have already been started to assess the efficacy of prescribing sildenafil earlier after radical prostatectomy. Montorsi and associates⁵⁴ demonstrated that in men with ED, sildenafil increases the duration and amplitude of nocturnal erection in the early postoperative period. Multicenter, placebo-controlled trials are currently underway to evaluate the benefit of receiving nightly sildenafil (50 or 100 mg) immediately after surgery in improving and expediting the return of erectile function in men after RP.^{55,56}

Our study showed that sildenafil citrate can salvage erectile function in roughly 70% of impotent, motivated patients if a bilateral nerve-sparing procedure is performed and in 50% of patients if a unilateral nerve-sparing procedure is done. Our results also suggest that urologists can initiate treatment with sildenafil at anytime after surgery and that they should not be hesitant to increase the dose to 100 mg. The potential impact of sildenafil (and its requirement for nerve tissue) should encourage urologists to continue to perform and perfect the nerve-sparing approach to give their patients the best chance of resuming sexual activity after RP.⁵⁷

Recently, there have been clinical research efforts to use combination therapy (sildenafil with MUSE) to improve efficacy. A study conducted by Nehra and colleagues³⁰ showed that a combination of sildenafil (100 mg) and intraurethral prostaglandin E1

Table-7. Three-year update of sildenafil citrate use (Ref. 61)

VARIABLES	BNS	UNS	NNS
Viagra responders	25/33(75.7%)	2/2(50%)	2/2 (50%)
Dropouts in 3 yr.	8/33(24.3%)	2/2(50%)	2/2(50%)
Return of natural erection	N=5	N=1	N=0
Lack of efficacy	N=2	N=1	N=2
Able to penetrates	18/25 (72%)	1/2 (50%)	0/2 (0%)
Total IIEF-5 score after surgery- after 1 yr - <u>after 3 yrs</u>	4.81-18.09- <u>20.49</u>	4.21-12.34- <u>15.79</u>	3.02-10.01- <u>11.39</u>
Q3 (Penetration,frequency) after surgery - after 1 yr - <u>after 3 yrs</u>	1.3-4.6- <u>4.96</u>	1.5-3.3- <u>3.3</u>	1-2.8- <u>2.6</u>
Q4 (Erection,maintenance) after-surgery - after 1 yr - <u>after 3 yrs</u>	1.2-4.6- <u>4.86</u>	1.3-3.3- <u>3.34</u>	1-2.8- <u>2.34</u>

All questions taken from the International Index for Erectile Function questionnaire.

Answers were scored: 0 = no intercourse, 1 = never/ almost never, 3 = sometimes, 5 = always/ almost always.

Efficacy score: Sum of responses to questions 3, 4, and 7.p-value by Wilcoxon rank-sum test.

(1000 mcg) salvaged erectile function in a selected sample of men with ED. The use of combination therapy will open a new area of interest in the treatment for ED. Further studies are required to confirm these interesting results.³⁰

Three-year update of sildenafil citrate efficacy and safety: Cleveland Clinic series

Data from 41 patients who responded to sildenafil therapy at 1 year after radical prostatectomy were stratified according to the type of nerve-sparing procedure: bilateral nerve sparing, unilateral nerve sparing, and non-nerve-sparing. A telephone survey was conducted during the first year of sildenafil use and repeated 3 years later. Sildenafil was prescribed at a dose of 50 mg, and increased to 100, if needed. The responses to the abridged 5-item IIEF questionnaire, the number of patients' attempts at successful intercourse, partner satisfaction, and side effects were assessed.

At 3 years, 71% (29/41) patients were still responding to sildenafil. Thirty-one percent (9/29) of these respondents had augmented their dose from 50 to 100mg. The drop out rate was 29% with 50% (6/12) discontinuing because of the return of natural erection; only 5 patients dropped out because of gradual loss of efficacy. There was no difference in the scores to the abridged IIEF item between the first and third year in either of the nerve-sparing groups (Table 7). Eighty-five percent of patients were sexually satisfied, and 95% were able to achieve and

maintain erection in more than 65% of attempts. The most common side effects at 3 years were: headache (12%), flushing (10%), and abnormal color vision (2%). No patient discontinued the drug at 3 years because of side effects. The patients that respond to sildenafil continue to show excellent long-term efficacy and compliance.⁶¹

NEW ORAL THERAPIES

A myriad of new therapeutic agents is emerging for the treatment of sexual dysfunction. A number of experimental drugs have been evaluated in phase 1 and 2 clinical studies. The closest to clinical use is apomorphine SL, which has been approved for marketing in Europe. This drug has a central mechanism of action; it is administered sublingually 20 minutes prior to expected sexual activity. At the approved doses of 2 and 3 mg, apomorphine SL has been shown to induce a significantly higher percentage of erections than placebo. At the 2 to 3 mg dose, the principal side effect of nausea was acceptable at 4.7%.

There are currently new efforts to design PDE5 inhibitors to increase potency and selectivity. Roger and colleagues⁵⁸ sequenced 3 distinct isoforms of PDE5 in human cavernosal tissue, heralding the advent of pharmacogenomics into the field of ED. Giuliano and colleagues⁵⁹ from Bicetre, France and several other European centers showed that IC351 (Cialis from Lilly ICOS LIC), a PDE5 inhibitor, significantly increased International Index of ED scores and was safe and well tolerated. The efficacy and safety of

Cialis for the treatment of ED is currently being investigated in phase 3 clinical trials. The drug significantly improved erectile function and was equally well tolerated by the 10- and 20-mg dose groups.

A phase 1 trial from Germany⁶⁰ has shown that BAY38-9456 (Vardenafil), a new potent and selective PDE5 inhibitor, is safe. The results also showed that Vardenafil potentiates NO-mediated relaxation and cGMP accumulation in human trabecular smooth muscle, supporting its use as a future therapeutic agent for the oral treatment of ED. Further clinical trials are required to assess the selectivity, pharmacokinetics, and period of responsiveness of these new drugs and their potential benefits in the treatment modality of ED.

CHOOSING THE RIGHT THERAPY: GENERAL CONSIDERATIONS

Oral pharmacotherapy is currently considered the first option for most patients with ED. Overall, patients are much happier and compliant with this treatment option. The pre-treatment options (VCD, IC injection, and MUSE) should be offered on an individual basis to patients who have undergone non nerve-sparing surgery, those who have failed oral treatment, and those awaiting the return of nerve function after a nerve-sparing radical prostatectomy.

Although IC injections can reproduce a more natural and satisfactory erection, the efficacy is not 100% and the continued use of needles lends itself to a 40% to 60% noncompliance rate after 1 year.¹³ For these patients, VCD may be a reasonable alternative. Gould and colleagues¹⁴ reported that 71 % patients who were not able to achieve satisfactory erections by IC injection subsequently received adequate rigidity and satisfactory erection with a VCD.¹⁴ In men with preoperative ED, where recovery of function and the non-physiological erection is not a major issue, there is no disadvantage to this form of therapy.¹⁵ However, VCD may be detrimental in men with intact preoperative function during the first 24 months after surgery when there is a theoretical advantage of increasing tissue oxygenation during the erection.

Turner and associates¹² prospectively compared IC injection (papaverine and phentolamine) with external VCDs in term of usage rates, effectiveness, side effects, dropout rates, and impact on patient sexual and psychological functioning. Both treatments were efficacious and safely used by patients, although dropout rates were higher for the group using IC injections (60% vs 20%). There were no differences

between the 2 treatments in sexual or psychological impact.¹²

The MUSE system is generally used in patients whose ED has failed to respond to oral therapy and for selected patients with an unsatisfactory erection with penile prosthesis. Porst et al²⁹ compared intraurethral and intracavernosal injected PGE1 and reported a significantly higher success rate and decreased side effects with injection of PGE1 at lower doses compared with intraurethral application of PGE1. When intraurethral therapy (MUSE) is compared with IC injections, most patients who have tried both treatments favor the injections and find that it produces a firmer erection.

Motivated men who fail to respond to these second line treatments or reject them as unappealing usually consider penile prosthesis implantation.

CONCLUSION

Today, physicians can offer men with ED a variety of solutions suited to their pathophysiology and personal needs. Most patients are prescribed sildenafil citrate for initial treatment. If treatment with this drug fails, second-line treatments (VCD, IC injection, and MUSE) are discussed. It is important that we realistically advise patients of the long-term efficacy and compliance of our pre-Viagra treatment options and the implications of doing a non-nerve sparing surgical procedures. Non-oral therapies should be considered in the early postoperative period to enhance sexual activity and to enhance penile oxygenation, which may prevent corporeal fibrosis. Early penile rehabilitation with IC injections or VCDs should be encouraged to increase chances for recovery of rigid erections during the neuropraxia that develops immediately following surgery. The coming century will witness many additional agents designed for patients with specific conditions causing ED. We can expect these oral agents, assisted by topical and injectable agents, to successfully restore erectile function in the majority of men suffering from ED.

REFERENCES

1. NIH Consensus Conference: Impotence. JAMA1993; 270:83-90.
2. Padma-Nathan H: Minimally invasive therapy for erectile dysfunction:., intracavernosal, oral, transdermal/transglandular and intraurethral approaches. Mulcahy JJ, Ed. In: Diagnosis and Management of Male Sexual Dysfunction. Igaku-Shoin, New York; 1997; 182-195.

3. Anderson KE, Wagner G: Physiology of penile erection. *Physiology Rev.* 1995; 75:191-236.
4. Rajifer J, Aronson WJ, Bush PA, et al: Nitric oxide as a mediator of the corpus cavernosum in response to non cholinergic non adrenergic neurotransmission. *N Eng J Med* 1992; 326: 90-94.
5. Holmquist F, Anderson KE, Fovaeus MN, Hedlund H: Potassium channel openers for relaxation of isolated erectile tissue from rabbit. *J Urol* 1990; 144: 146-151.
6. Kim YC, Kim JA, Hagan Po, Carson CC: modulation of vasoactive intestinal peptide (VIP) mediated relaxation by nitric oxide and prostenoids in the rabbit corpus cavernosum. *J Urol* 1995; 153: 807-810.
7. Iwanga T, Hanyu S, Tamaki M: VIP and other bioactive substance involved in penile erection. *Bio Med Res* 1992; 2:71-73.
8. Kerfoot WW, Schwartz LB, Hagen Po, Carson Cc: Characterization of contracting and relaxing agents in human and rabbit corpus cavernosum. *Surg Forum* 1991; 42: 688-689.
9. Kim SC, Ooh MM: Norepinephrine involvement in response to intracorporeal injection of papaverine in psychogenic impotence. *J Urol* 1992; 147: 1530-1532.
10. Dutta TC, Eid JF: Vacuum constriction devices for erectile dysfunction: a long-term, prospective study of patients with mild, moderate, and severe dysfunction. *Urology* 1999; 54: 891-893.
11. Cookson MS, Nadig PW: Long term results with vacuum constriction device. *J Urol* 1993; 149: 290-294.
12. Turner LA, Althof SE, Levine SB et al: Twelve-month comparison of two treatments for erectile dysfunction: self- injection versus external vacuum devices. *Urology* 1992; 39(2): 139-144.
13. Soderdahl DW, Thrasher JB, Hansberry KL: Intracavernosal drug-induced erection therapy versus external vacuum devices in the treatment of erectile dysfunction. *British Journal of Urology* 1997; 79: 952-957.
14. Gould JE, Switters DM, Broberick GA, deVereWhite RW: External vacuum devices: a clinical comparison with pharmacologic erections. *World J Urol* 1992; 10: 68-70.
15. Blackard CE, Borken WD, Lima JS et al: Use of vacuum tumescence device for impotence secondary to venous leakage. *Urology* 1996; 41: 225-227.
16. Sidi AA, Becher EF, Zhang G, Lewis JH: Patient acceptance of and satisfaction with an external negative pressure device for impotence. *J Urol* 1990; 144: 1154.
17. Fraiman MC, Lepor H, Telegrafi S et al: Does early treatment of erectile dysfunction after nerve sparing radical prostatectomy lead to better long term return of natural function? Society for the Study of Impotence Meeting, Cleveland OH, USA, September 15, 2000. (Abstr.)
18. Wiles PG: Successful non-invasive management of erectile impotence in diabetic men. *Br Med J (Clin Res Ed)* 1988; 296 (6616): 161-162.
19. Raina R, Zippe CD, Agarwal A et al: Early use of vacuum constriction device (VCD) following radical prostatectomy (RP) facilitates early sexual activity and potential return of erection.. Abstract submitted AUA 97th Annual meeting for May 2002.
20. Cavalini G: Minidoxil and capsacin: an association of transcutaneous active drugs for erection facilitation. *Int J Impot Res* 1994; 6: D71.
21. Heaton JPW, Morales A, Owen J, et al: Topical glyceryltermitate causes penile arterial dilation in impotent man. *J Urol* 1990; 43: 729-731.
22. Nunez BD, Anderson DC: Nitroglycerine ointment in the treatment of impotence. *J Urol* 1993; 150:1241-1243.
23. Cavalini G: Minidoxil versus nitroglycerine: prospective double blind control trial in transcutaneous erection facilitation for organic impotence. *J Urol* 1991; 146 :50-53.
24. Mc Vary KT, Polepalle S, Riggis: Topical prostaglandin E1 SEPA gel for treatment of erectile dysfunction. *J Urol* 1999; 162: 726-731.
25. Padma-Nathan H, Hellstrom WJ, Kaiser FE et al: Treatment of men with erectile dysfunction with transurethral alprostadil. *N Eng J Med* 1997; 336: 1-7.
26. Costabile RA, Govier FE, Ferrigni RG et al: Safety of transurethral alprostadil in patients with erectile dysfunction following radical prostatectomy. *J Urol* 1997; 157(4): 1424.
27. Paolone DR, Lakin MM, Ingleright BJ et al: Intraurethral alprostadil therapy at The Cleveland Clinic Foundation. Abstr- act submitted to North Central Section AUA for presentation in October, 1998.
28. Thukral M, Lakin MM, Agarwal A, Zippe CD et al: Effectiveness of MUSE for erectile dysfunction after radical prostatectomy. Abstract submitted to 74th North Central Section AUA for presentation October 29-November 4, 2000, Scottsdale Arizona.
29. Porst H: Transurethral alprostadil with MUSE versus intracavernous alprostadil: a comparative study in 103 patients with erectile dysfunction. *Int J Impot Res* 1997; 9: 187192.
30. Nehra et al: Combination of sildenafil and intraurethral prostaglandin E1 salvaged a selected population of men with ED. Abstract submitted to AUA for 95th meeting of the American Urological Association, May 2000.
31. Brindley GS: Pilot experiments on the action of drugs injected into the human corpus cavernosum penis. *Br J Pharmacol* 1986; 87:405-500
32. Stakl W, Hasun R, Marberger N: Prostaglandin E-1 in the treatment of erectile dysfunction. *World J Urol* 1990; 8: 84-86.
33. Khan MA et al: The role of prostaglandins in the etiology and treatment of erectile dysfunction. *Prostaglandin Leukot Essent Fatty Acids* 1999; 60: 169-174.
34. McMahan R: A pilot study for the role of intracavernosal injection of vasoactive intestinal polypeptide (VIP) and phentolamine mesylate in the treatment of erectile dysfunction. *Int J Impot Res* 1996; 8: 233-236.

35. Lakin MM, Chen RN, Llorens SA et al: Prostaglandin E1 injection therapy for post-prostatectomy impotence: an outcome analysis. *J Urol* 1996; 155: 639.
36. Evans C: Complications of intracavernosal therapy for impotence. In: Carson C, Kirby R, Goldstein I (eds.). *Textbook of Erectile Dysfunction*. Oxford: Isis Medical Media, 1999; 365-370.
37. Mulhall JP, Jahoda A, Cairney M et al: The causes of patient dropout from penile self-injection therapy for impotence. *J Urol* 1999; 162: 1291-1294.
38. Purvis K, Egdetveit I, Christiansen E: Intracavernosal therapy for erectile failure-Impact of treatment and reasons for dropout and dissatisfaction. *Int J Impot Res* 1999; 11: 287-299.
39. Raina R, Agarwal A, Craig D, Zippe et al: Management of erectile dysfunction following radical Prostatectomy. Review article *Current Urology Report* Vol. 2 issue 6 Dec. 2001.
40. Raina R, Agarwal A, Craig D, Zippe et al: Long term Intracavernous (IC) Therapy responders can potentially switch to sildenafil citrate after radical prostatectomy. Abstract submitted AUA 97th Annual meeting for May 2002.
41. Moreland RB, Abdulmageed T, McMillin MA et al: PGE1 suppresses the induction of collagen synthesis by transforming growth factor beta 1 in human corpus cavernosum smooth muscle. *J Urol* 1998; 153: 811-815.
42. Fraiman MC, Lepor H, McCullough AR: Changes in penile morphometrics in men with erectile dysfunction after nerve-sparing radical prostatectomy. *Mol Urol* 1999; 3: 109-115.
43. Montorsi F, Guazzoni G, Strambi LF et al: Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: Results of a prospective, randomized trial. *J Urol* 1996; 155: 639.
44. Goldstein I, Lue TF, Padma-Nathan H, et al: for the Sildenafil Study Group: Oral sildenafil in the treatment of erectile dysfunction. *N Eng J Med* 1998; 338: 1397-1404.
45. R Saovsky, T Miller and M Moskowitz et al: three year update of sildenafil citrate (Viagra) efficacy and safety. *International journal of clinical practices* March 2001 Vol 55 no. 2.
46. Rajjfer J, Aronson W1, Bush PA et al: Nitric oxide as a mediator of the corpus cavernosum in response to non-cholinergic non-adrenergic neurotransmission. *N Engl J Med* 1992; 326: 90-94.
47. Moreland RB, Goldstein I, Traish A: Sildenafil: a novel inhibitor of phosphodiesterase type 5 in human corpus cavernosum smooth muscle cells. *Life Sciences* 1998; 62: 309-318.
48. Ballard SA, Gingell CJ, Tang K et al: Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isoenzymes. *J Urol* 1998; 159: 2164-2171.
49. Zippe CD, Jhaveri FM, Klein EA, Kedia S et al: Role of Viagra after radical prostatectomy. *Urology* 2000; 55(2): 241.
50. Zippe CD, Kedia AW; Kedia K et al: Treatment of erectile dysfunction after radical prostatectomy with sildenafil citrate (Viagra). *Urology* 1998; 52(6): 963-966.
51. Zagaja GP, Mhoon DA, Aikens JE, Brendler CB: Sildenafil in the treatment of erectile dysfunction after radical prostatectomy. *Urology* 2000; 56(4): 631-634.
52. Jarow JP, Burnett AL, Geringer AM: Clinical efficacy of sildenafil citrate based on etiology and response to prior treatment. *J Urol* 1999; 162: 722-725.
53. Morales A, Gingell C, Collins C et al: Clinical safety of oral sildenafil citrate (Viagra) in the treatment of erectile dysfunction. *Int J Impot Res* 1998; 10: 69-74.
54. Montorsi R, Maga T, Salonia A et al: Sildenafil taken at bedtime significantly increases nocturnal erectile activity: results of a prospective Rigiscan study. *J Urol* 2000; 164: 148.
55. Fraiman MC, Lepor H, McCullough AR: Nocturnal penile tumescence activity in 81 patients presenting with erectile dysfunction after nerve sparing radical prostatectomy. *J Urol* 1999; 161: 179.
56. Fraiman MC, Lepor H, McCullough AR: Predictive value of nocturnal penile tumescence (NPT) on long term return of erectile function in men with erectile dysfunction (ED) after nerve sparing radical prostatectomy (NSRRP). *J Urol* 2000; 163: 242.
57. Zippe CD, Kedia S, Kedia AW, Pasqualotto F: Sildenafil citrate (Viagra) after radical retropubic prostatectomy: pro. *Urology* 1999; 54: 583586.
58. S Rogers, Ching-Shwun, Lin, Angie Lau et al: Expression of three isoforms of cGMP binding cGMP specific phosphodiesterase (PDE-5) in penile cavernosum. Abstract no.862 AUA 95th annual meeting April 29 - 4 May 2000 Georgia World Congress Center Atlanta, Georgia.
59. Francois Giuliano, Hartmut Porst, Harin Padma-Nathan, Jay Saoud, Kenneth Ferguson, Steven. Whitaker, William Pullman, Raymond Rosen: Daily and on-demand IC351 treatment of erectile dysfunction. . Abstract no. 894 AUA 95th annual meeting April 29-4 May 2000 Georgia World Congress Center Atlanta, Georgia.
60. Richard Sachse, Gabriele Rohde, Stefan Stark, Theodor Klotz: Safety, tolerability and pharmacokinetics of bay 38-9456 in patients with erectile dysfunction. Abstract no.904 AUA 95th annual meeting April 29-4 May 2000 Georgia World Congress Center Atlanta, Georgia.
61. Raina R, Ashok Agarwal, Craig D. Zippe: Long term efficacy and compliance of sildenafil citrate for ED following radical prostatectomy: 3 year update. Abstract submitted AUA 97th Annual meeting for May 2002.