

Treatment of Erectile Dysfunction: Update

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Erectile dysfunction (ED) is the inability to achieve and maintain an erection. Erectile function is dependent upon complex interactions of neural and vascular pathways. A major neurotransmitter that facilitates erectile function is nitric oxide. Treatment of ED has expanded to include effective oral agents. Previous ED treatments have consisted of intracavernosal injection,

transurethral dilators, and vascular constriction devices. Clinical management of ED will be presented with some discussion on the prostatectomy client.

Keywords: erectile dysfunction; nitric oxide; intracavernosal injection; transurethral dilators; vascular constriction devices

Erectile dysfunction (ED) is the inability to achieve and maintain an erection sufficient for satisfactory sexual activity (National Institutes of Health Consensus Conference: Impotence [NIH], 1993). 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 function 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 patient (Padma-Nathan, 1997).

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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 presenting for evaluation and treatment. Sildenafil is effective in most men with ED in the general population including men with spinal cord injury, diabetes mellitus, and patients who have had nerve-sparing radical prostatectomy (RP).

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

Molecular Physiology of Erection

Both the peripheral and central nervous systems 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—produces lacunar smooth muscle relaxation (Anderson & Wagner, 1995). Once the smooth muscles have relaxed, blood flows rapidly into the lacunar spaces, increasing the volume in the corpora cavernosa. 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 (Raijfer, Aronson, Bush, Dorey, & Ignarry, 1992). 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 (Holmquist, Anderson, Fovaeus, & Hedlund, 1990). 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) (Iwanga, Hanyu, & Tamaki, 1992; Kim, Kim, Hagan, & Carson, 1995).

Smooth muscle relaxation is counterbalanced by neurotransmitters and substances that cause the smooth muscles to contract (Kerfoot, Schwartz, Hagen, & Carson, 1991). 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 (Kim & Ooh, 1992). Other similar molecules may also play a role on smooth muscle contraction, including endothelin-1, prostaglandin F₂, and epinephrine (NIH, 1993). 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.

Evaluation of ED

Recently, a better understanding of the physiology of ED has led to the development of better diagnostic tests. However, clinical evaluation that includes a detailed history and physical examination is still the cornerstone in the evaluation of ED (Dimitrios et al., 2002). The appropriate evaluation of all men with ED should include a medical and detailed sexual history (including practices and techniques), a physical examination, a psychosocial evaluation, and basic laboratory studies. A written patient questionnaire may be helpful but should not be a substitute for the interview. The International Index of Erectile Function (IIEF) is the commonly used validated questionnaire (Rosen et al., 1997). These 15 questions have been condensed to form an abridged 5-item version IIEF-5 or sexual health inventory for men (SHIM). The sensitivity and specificity of the SHIM score are similar to IIEF-15 (Rosen et al., 1997). Each question has responses from 0 to 5 (0 = no sexual activity, 1 = almost never, 2 = less than half the time, 3 = half of the time, 4 = more than half of the time, 5 = almost always). Numerous diagnostic tests are available for the evaluation of ED. The yield of these sophisticated tests is limited. Moreover, the knowledge about the causes and specific therapy for ED is limited. Based on these facts, the "goal-directed" approach is commonly followed nowadays. Some of these tests may be helpful in patients having organic causes of ED. IC injection testing may form the initial procedure for diagnostic evaluation. Inadequate response suggests underlying organic vascular disease. These patients and patients with prior pelvic trauma are suitable candidates for further vascular investigation with pharmaco-penile duplex ultrasonography, cavernosography. Primary care physicians and other medical specialists have gradually replaced urologists and andrologists in first-line treatment of ED.

Standard Treatments for Erectile Dysfunction—Pre-Sildenafil Era

Vacuum Constriction Device

Vacuum constriction devices 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 band(s) 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 radical prostatectomy or radiation therapy (Dutta & Eid, 1999). 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 a 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% to 40%. The primary reasons for discontinuation were bruising and petechiae (5%), pivoting at the base of the penis (6%), coldness and numbness around the penis (5%), pain related to VCD or the constriction band (10%), and decreased ability to achieve orgasm with the device (10%) (Cookson & Nadig, 1993).

Turner and his associates did a prospective comparison of intracorporeal injection of papaverine/phentolamine and external vacuum devices in terms of usage rates, effectiveness, side effects, dropout rates, and impact on patient's 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 (Turner et al., 1992).

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

(Soderdahl, Thrasher, & Hansberry, 1997). For these patients, VCD may be a reasonable alternative. Gould and colleagues reported that 71% of patients who failed to achieve satisfactory erections by IC subsequently received adequate rigidity and satisfactory erection with VCD (Gould, Switters, Broberick, & deVere White, 1992). In men with preoperative ED, where recovery of function and the nonphysiological erection is not a major issue, there is no disadvantage to this form of therapy (Blackard, Borkon, Lima, & Nelson, 1996). 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% (Sidi, Becher, Zhang, & Lewis, 1990). Noncompliant 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 prevention of postsurgery veno-occlusive dysfunction by increasing the frequency of tissue oxygenation. Early sexual rehabilitation after pelvic surgery may enhance earlier recovery of nocturnal erections, as treatments enhance oxygenation of the corpora cavernosa and prevent formation of collagen and fibrosis, a cofactor in smooth relaxation and erectile function (Fraiman et al., 2000).

According to our experience, daily use of VCD after RP (with/without the constriction ring) to either maintain corporeal engorgement or to achieve vaginal intercourse during a 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 a 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%

Table 1. Comparison Between Patients With Nerve-Sparing and Non-Nerve-Sparing RP in Response to Early Use of VCD

Variable	Bilateral NS (<i>n</i> = 25)	Unilateral NS (<i>n</i> = 19)	Non-NS (<i>n</i> = 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) presurgery→ postsurgery→after VCD use	4.76→.91→3.61	4.33→.86→3.24	4.1→.85→3.14
IIEF Q4 (erection, maintenance) presurgery→ postsurgery→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

Note: 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 is calculated by totaling the response to all five domains of the IIEF questionnaire. NS = nerve-sparing; RP = radical prostatectomy; VCD = vacuum constriction device; IIEF = International Index for Erectile Function.

at 9 months is not significantly different from our contemporary series (without early VCD), which had a 15% potency rate at 9 months. The authors' study was consistent with the study conducted 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 (Wiles, 1988). Longer follow-up is needed 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 these authors' study (Table 1) (Raina, Klepacz, Agarwal, & Zippe, 2002).

VCDs are an important option in the armamentarium for clinicians who treat ED. 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

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

(Cavalini, 1994). 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 (Heaton et al., 1990; Nunez & Anderson, 1993). A randomized, placebo-controlled, double-blind trial reported that inpatients 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 (Cavalini, 1991). 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, Polepalle, Riggi, and Pelham (1999) reported that 67% to 75% of patients had an erection (compared with 17% of the controls) within 60 min 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 approval for use in ED. This therapy currently represents an 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 analog of prostaglandin E1) is delivered into the male urethra, which is absorbed by the cavernosal tissue through vascular communications from the corpus spongiosum. Intraurethral

Table 2. Responses to the IIEF Questionnaire of 19 Postprostatectomy Patients Before and After MUSE Treatment

Questions	Mean Score Before Surgery \pm SD)	Mean Score After Surgery \pm SD)	Mean Score After MUSE (\pm SD)	<i>p</i> (Before vs. After IC Therapy)
3. Frequency of penetration	4.47 \pm 1.07	1.36 \pm 1.42	1.94 \pm 1.47	<.001
4. Frequency of maintained erection	4.63 \pm 0.59	1.31 \pm 1.29	2 \pm 1	<.001
7. Frequency of satisfactory intercourse	4.94 \pm 0.22	1.78 \pm 1.65	2.29 \pm 1.57	<.001
Efficacy score	14.05 \pm 1.68	4.2 \pm 3.45	5.94 \pm 4.37	<.001

Note: 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. IIEF = International Index for Erectile Function; MUSE = medicated urethral system for erection; SD = standard deviation; IC = intracavernosal injection.

alprostadil, when introduced by Padma-Nathan et al. in 1997, was reported to have an overall efficacy rate of 44%, but subsequent investigations could not confirm these initially favorable results and reported significant urethral pain and burning. Studies suggest that medicated urethral system for erection (MUSE) is much less successful in patients with ED caused by pelvic surgery or RP. Costabile and associates (1998) examined the effect of transurethral alprostadil in 384 men with ED after RP and reported overall success rate of 40%. However, Paolone and associates (1998) at the Cleveland Clinic reported that MUSE was effective in only 15% of men who had pelvic surgery.

More recently, the efficacy and compliance of MUSE was studied in a contemporary RP series at the Cleveland Clinic, using the International Index of Erectile Function questionnaire to validate responses. The results identified 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 the study, there were no statistically significant differences in the responses among different etiologic subgroups (Thukral et al., 2000).

When intraurethral therapy is compared with IC injections, most patients who have tried intraurethral therapy (MUSE) and IC injection therapy favor injections and find that it produces a firmer erection. Porst (1997) compared intraurethral (MUSE) and IC-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. Since the introduction of oral therapy, the use of MUSE has decreased because comparative studies reported that sildenafil has better efficacy and 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 (2000) demonstrated that a combination of sildenafil (100 mg) and intraurethral prostaglandin E1 (1000 mcg) salvaged a selected population of men with ED. The use of combination therapy will create a new area of interest in the treatment for ED. Further studies are required to confirm this interesting result.

The most common complication related to intraurethral therapy (MUSE) 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 ED. 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 ED.

Intracavernosal Injection Therapy

Intracavernosal injection became a standard treatment for ED when it was introduced in the United States at the 1983 Meeting of the American Urological Association (Brindley, 1986). 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 (Stakl, Hasun, & Marberger, 1990). Whereas phentolamine is a direct adrenoceptor blocker, alprostadil and papaverine modulate levels of cyclic 3',5'-adenosine monophosphate

Table 3. Responses to the IIEF Questionnaire (Qs 3, 4, and 7) and Efficacy Score of 98 Postprostatectomy Patients Before and After IC Injection Treatment

Questions	Mean Score Before Surgery (\pm SD)	Mean Score After Surgery (\pm SD)	Mean Score After IC Injection Therapy (\pm SD)	<i>p</i> (Before vs. After IC Therapy)
3. Frequency of penetration	4.78 \pm 0.62	1.45 \pm 1.53	3.91 \pm 1.52	<.001
4. Frequency of maintained erection	4.84 \pm 0.63	1.30 \pm 1.18	3.81 \pm 1.67	<.001
7. Frequency of satisfactory intercourse	4.79 \pm 0.77	1.44 \pm 1.38	3.61 \pm 1.67	<.001
Efficacy score	14.41 \pm 1.85	4.2 \pm 3.45	11.13 \pm 1.67	<.001

Note: 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. IIEF = International Index for Erectile Function; IC = intracavernosal injection; SD = standard deviation.

in the cells, eventually increasing the penile blood flow by relaxing the arterial and trabecular smooth muscles (Khan et al., 1999). 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 (McMahon, 1996).

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% (Lakin, Montague, VanderBrug Medendorp, Tesar, & Schover, 1990). 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 (Evans, 1999). 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. (1999) reported that 75% of 720 men in their study, which included patients with ED of all etiologies, had a good response to IC injection. These authors 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 one of seven (14.2%) patients. In a similar study, Purvis, Egdetveit, and Christiansen (1999) also reported that 87% of their patient sample (which included all etiologies) were fully or partially satisfied with IC 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.

Postprostatectomy patients were treated with IC injections at the Cleveland Clinic and were followed

to analyze the efficacy and satisfaction rates and to document the reasons for its discontinuation using the IIEF questionnaire (Zippe et al., 2001). 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 3), nearly 50% of the patients discontinued therapy. 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 (Raina et al., 2004). During the period of neuropraxia that follows nerve-sparing RP (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 (Fraiman, Lopor, & McCullough, 1999; Moreland et al., 1995). This concept is supported by a recent report by Montorsi et al. (1996), 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* < .01). These subjective results were also confirmed by hemodynamic and nocturnal testing.

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 those 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.

Table 4. Comparison of IIEF-5 Scores and Partner Satisfaction in Long-Term Intracavernous Injection Users Who Successfully Switch to Sildenafil Citrate

IIEF-5 Scores	On IC Therapy (<i>n</i> = 36)	Switch From IC to Sildenafil (<i>n</i> = 22)	
		Successful Switch to Sildenafil (<i>n</i> = 15)	Combination Therapy (<i>n</i> = 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	4.80
Total IIEF-5 score	20.21	12.17	22.58
Partner satisfaction	71.8%	60.7%	72.8%

Note: IIEF = International Index for Erectile Function; IC = intracavernosal injection.

The Viagra Era—1998 and Beyond

The treatment algorithm for patients with ED improved dramatically with the availability of sildenafil citrate (Viagra, Pfizer Pharmaceutical, New York, NY), the first effective oral medication. Following the landmark publication by Goldstein et al. in 1998, 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.

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 the drug, its clinical efficacy and safety, 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 been reported for patients treated with prostate cancer and 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 report the drug is effective in patients with a broad spectrum of ED etiologies and that its overall tolerability is good (Sadovsky, Miller, Moskowitz, & Hackett, 2001).

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 nonadrenergic, noncholenergic nerves are damaged or destroyed, transmission of NO diminishes or does not occur at all (Raijfer et al., 1992). Without NO, guanylate cyclase is not activated and therefore cannot convert guanosine triphosphate into cyclic guanosine monophosphate (cGMP). cGMP relaxes the electrogenic smooth muscles by activating the intracellular sodium pump system, opening potassium channels, and causing a decrease in intracellular potassium with resultant smooth muscle relaxation (Ballard et al., 1998; Moreland, Goldstein, & Traish, 1998). 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 RP and study the impact of the presence or absence of the neurovascular bundles (Zippe et al., 2000; Zippe, Kedia, Kedia, Nelson, & Agarwal, 1998). The study by Zippe et al. (2000) consisted of patients who were not able to have an erection or who had unsatisfactory erections following RP. All eligible men had a complete history and physical to exclude any contraindications to the drug. Those patients 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.

Table 5. Characteristics of 91 Postprostatectomy Patients With Erectile Dysfunction Before Sildenafil Citrate (Viagra) Therapy

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	22.0	14.0	14.5
Presurgery 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

Note: NS = nerve-sparing; Tx = treatment.

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 RP 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%) 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 nonneurogenic mechanism.

The author (Zippe, Kedia, Kedia, Nelson, & Agarwal, 1998) individually interviewed all of the patients' spouses or partners and identified that the quality of erection was excellent in all 48 responders and that the mean duration of intercourse ranged from 4.5 to 12 min. 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 were also reported by Zagaja, Mhoon, Aikens, and Brendler (2000) from the University of Chicago, who reported 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- to 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 hr before intercourse. The drug requires sexual stimulation to be effective (Jarow, Burnett, & Geringer, 1999). Morales, Gingell, Collins, Wicker, and Osterloh (1998) summarized the side effects of sildenafil that occurred in 18 randomized, double-blind placebo-controlled studies and reported that 16% of patients experienced headache, 10% experienced flushing, and 7% experienced dyspepsia. The side effects 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 RP in the Cleveland Clinic. Montorsi and associates (2000) 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 under way 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 (Fraiman, Lepor, & McCullough, 1999).

The authors' study identified that sildenafil citrate could 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. The results

Table 6. Comparison Between Patients With Nerve-Sparing and Non-Nerve-Sparing Prostatectomies in Response to Sildenafil Citrate (Viagra)

Variable	Bilateral NS (<i>n</i> = 53)	Unilateral NS (<i>n</i> = 12)	Non-NS (<i>n</i> = 26)	<i>p</i> value
Number of doses	8.0	8.5	6.5	NS
Able to penetrate (% , <i>n</i>)	71.7 (38/53)	50 (6/12)	15.4 (4/26)	.001
Mean duration of intercourse (min)	10	4.5	12	NSF
Spouse satisfaction (% , <i>n</i>)	66 (35/53)	41.6 (5/12)	15.4 (4/26)	.001
IIEF (responders)	<i>n</i> = 38	<i>n</i> = 6	<i>n</i> = 4	
Q3 (freq. of penetration)	1.2-4.8	1.0-2.8	1.5-3.3	<i>p</i> = .04*
Q4 (freq. of maintenance)	1.2-4.8	-2.6	1.5-3.3	<i>p</i> = .02*
Q7 (sexual satisfaction)	1.3-4.2	1.2-2.5	1.3-3.0	<i>p</i> = .02*

Note: NS = nerve sparing; NSF = not significant.

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

suggest that urologists can initiate treatment with sildenafil at any time 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 (Zippe, Kedia, Kedia, & Pasqualotto, 1999).

Recently, there have been clinical research efforts to use combination therapy (sildenafil with MUSE) to improve efficacy. A study conducted by Nehra and colleagues (2000) reported that a combination of sildenafil (100 mg) and intraurethral prostaglandin E1 (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.

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 RP 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 mg if needed. The responses to the abridged five-item IIEF questionnaire, the number of patients' attempts at successful intercourse, partner satisfaction, and side effects were assessed.

At 3 years, 71% (29/41) of patients were still responding to sildenafil. Thirty-one percent (9/29) of these respondents had augmented their dose from 50

mg to 100 mg. The dropout 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 who respond to sildenafil continue to report excellent long-term efficacy and compliance (Raina, Lakin, Agarwal, Ausmundson, Montague, & Zippe, 2004).

New Oral Therapies

Myriad new therapeutic agents are emerging for the treatment of sexual dysfunction. Apomorphine sublingual has a central mechanism of action; it is administered sublingually 20 min prior to expected sexual activity. At the approved doses of 2 and 3 mg, apomorphine sublingual has been reported 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 with increased potency and selectivity. Tadalafil (Cialis), a PDE5 inhibitor, significantly increased International Index scores of ED and was safe and well tolerated. The drug significantly improved erectile function and was well tolerated by the 10- and 20-mg dose groups in the patients. Carson et al. (2004) studied the efficacy of tadalafil in different doses in a placebo-controlled trial; they reported a

Table 7. Three-Year Update of Sildenafil Citrate Use

Variable	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	<i>n</i> = 5	<i>n</i> = 1	<i>n</i> = 0
Lack of efficacy	<i>n</i> = 2	<i>n</i> = 1	<i>n</i> = 2
Able to penetrate	18/25 (72%)	1/2 (50%)	0/2 (0%)
Total IIEF-5 score after surgery-after 1 yr-after 3 yrs	4.81-18.09-20.49	4.21-12.34-15.79	3.02-10.01-11.39
Q3 (Penetration, frequency) after surgery-after 1 yr-after 3 yrs	1.3-4.6-4.96	1.5-3.3-3.3	1-2.8-2.6
Q4 (Erection, maintenance) after surgery-after 1 yr-after 3 yrs	1.2-4.6-4.86	1.3-3.3-3.34	1-2.8-2.34

Note: 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. BNS = bilateral nerve sparing; UNS = unilateral nerve sparing; NNS = non-nerve-sparing; IIEF = International Index for Erectile Function.

significant improvement ($p < .001$) in the doses compared to the placebo. Montorsi et al. (2004) conducted a randomized, double-blind, placebo-controlled multicenter study including 303 men (mean age 60 years) with preoperative normal erectile function who had undergone a bilateral nerve-sparing RP 12 to 48 months before the study and were randomized (2:1) to tadalafil (201) or placebo (102). Patients receiving tadalafil reported greater improvement on all primary and secondary end points ($p < .001$) compared to placebo, with mean percentage of successful penetration attempts being 54% and mean percentage of successful intercourse attempts being 41%.

Another PDE5 inhibitor, vardenafil, is a new potent and selective PDE5 inhibitor. The results reported that vardenafil is a selective and potent PDE5 inhibitor (Fraiman, Lepor, & McCullough, 2000). Vardenafil has been tested in patients with ED after RP in a multicenter, placebo-controlled randomized study. The results of the study identified that with administration of vardenafil, 71% reported improvement in erectile function, with 47% able to maintain the erection sufficient for vaginal penetration. 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 after RP (Montorsi et al., 2004).

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-Viagra 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 RP.

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 (Blackard et al., 1996). For these patients, VCD may be a reasonable alternative. Gould and colleagues (1992) reported that 71% of patients who were not able to achieve satisfactory erections by IC injection subsequently received adequate rigidity and satisfactory erection with a VCD. In men with preoperative ED, where recovery of function and the nonphysiological erection is not a major issue, there is no disadvantage to this form of therapy (Fraiman et al., 2000). 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 associates (1992) prospectively compared IC injection (papaverine and phentolamine) with external VCDs in terms 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 two treatments in sexual or psychological impact.

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 (1997) compared intraurethral therapy (MUSE) 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 they produce firmer erections. Motivated men who fail to respond to these second-line treatments (VCD, IC injections, MUSE) or reject them as unappealing usually consider penile prosthesis implantation.

Conclusion

Today, physicians can offer men with ED a variety of solutions consistent with 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 clinicians 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 procedure. Nonoral 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. This century will witness many additional agents designed for patients with specific conditions causing ED. Clinicians can expect these oral agents, assisted by topical and injectable agents, to successfully restore erectile function in the majority of men suffering from ED.

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