The American Urological Association
Erectile Dysfunction Clinical Guidelines Panel

Report on

The Treatment of Organic Erectile Dysfunction

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Clinical Practice Guidelines

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The Erectile Dysfunction Clinical Guidelines Panel consists of board-certified urologists who are experts in erectile dysfunction treatment. Portions of this *Report on the Treatment of Organic Erectile Dysfunction* were developed in parallel with the text for *Impotence: Diagnosis and Management of Erectile Dysfunction*, published by W.B. Saunders Company in 1994, and appear in different forms in both publications.

This report was extensively reviewed by nearly 50 urologists throughout the country in 1995. The panel finalized its recommendations for the American Urological Association (AUA) Practice Parameters, Guidelines and Standards Committee, chaired by Joseph W. Segura, M.D., in June 1996, and the AUA Board of Directors approved these practice guidelines in July 1996.

The Summary Report also underwent independent scrutiny by the Editorial Board of the *Journal of Urology*, and was accepted for publication and appeared in the December 1996 issue. *A Patient's Guide* and *Evidence Working Papers* have also been developed and are available from the AUA.

The AUA expresses its gratitude for the dedication and leadership demonstrated by the members of the Erectile Dysfunction Clinical Guidelines Panel in producing this guideline.

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Introduction

The treatment of impotence, more precisely termed erectile dysfunction, has received increasing attention in recent years. There are, however, considerable gaps in the knowledge base. Little is yet known about prevalence and how it varies relative to such factors as patient age, race, ethnicity and concomitant disease. There is much to be learned as well about the pathophysiology of erectile dysfunction. Although research in this area continues to burgeon, often the pathophysiology cannot be accurately classified in an individual patient.

Nevertheless, the greater attention being given erectile dysfunction has begun to bear fruit in the form of improved diagnostic methodologies and new and improved nonsurgical treatment methods. Many patients and health care providers may not yet be fully aware of today's treatment options, but awareness is spreading rapidly; and treatment of erectile dysfunction now constitutes a sizable portion of the average urologist's practice.

To provide guidance regarding therapies for erectile dysfunction, the American Urological Association (AUA) convened the Erectile Dysfunction Clinical Guidelines Panel and charged it with the task of producing practice recommendations based primarily on outcomes evidence from the treatment literature. The result of the panel's efforts is this *Report on the Treatment of Organic Erectile Dysfunction.*

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The panel was charged with producing recommendations to assist physicians specifically in the treatment of acquired organic erectile dysfunction. The panel took diagnostic factors into consideration when necessary, but the focus of this report is the treatment of erectile dysfunction. The report also deals only peripherally with psychological factors and with other forms of sexual dysfunction such as libido and ejaculatory disorders. The definition of the standard patient is a man who develops erectile dysfunction after a well-established period of normal erectile function and whose erectile dysfunction is primarily organic rather than psychological and who has no evidence of hypogonadism or hyperprolactinemia.

The panel recognizes, however, that it is important for urologists to diagnose and treat sexual problems due to primary endocrine disorders. The panel also recognizes that there is frequently a psychogenic overlay in the etiology of organic erectile dysfunction and there may be a need with particular patients to combine different types of treatment, including sexual counseling and in some cases psychotherapy.

In general, treatment of erectile dysfunction is a rapidly evolving therapeutic area, but with various treatment choices and no clearly dominant therapy to date, making it an especially appropriate area for the kind of evidence-based practice recommendations offered in this report. A summary of this report has been published in the *Journal of Urology* (December 1996), and *A Patient's Guide* with illustrations of recommended treatments is available for purchase through the AUA.

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Table of Contents

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Executive Summary –
Report on the treatment of organic erectile dysfunction

Definition and methodology

Erectile dysfunction, the more precise and now preferred term for impotence, is defined as "the inability to achieve or maintain an erection sufficient for satisfactory sexual performance" (*NIH Consensus Statement*, 1992).

To develop the recommendations in this *Report on the Treatment of Organic Erectile Dysfunction*, the Erectile Dysfunction Clinical Guidelines Panel reviewed the literature available on treatment of erectile dysfunction, covering the period from January 1979 to December 1994, and extracted all relevant data to estimate as accurately as possible the outcomes of the different treatment modalities. The panel followed an explicit approach to the development of practice recommendations, which emphasizes the use of scientific evidence in estimating outcomes (Eddy, 1992). When the evidence has limitations, they are clearly stated. When panel opinion is necessary, the explicit approach calls for an explanation of why it is necessary and/or discussion of the factors considered. For a full description of the methodology, see Chapter 1.

Background

Research on etiology, diagnosis and treatment of erectile dysfunction is relatively recent, and etiologic factors and their interplay remain poorly understood. Until the 1970s, erectile dysfunction was commonly attributed to psychogenic causes or, physiologically, to abnormalities in testosterone metabolism. Studies since then indicate that, although testosterone deficiency may affect the libido, it does not necessarily affect the ability to have erections. Psychological factors, such as depression, anxiety and the quality of relationships with sexual partners, obviously affect erectile function, but other factors may be involved as well. Erectile dysfunction may be associated with psychogenic, neurogenic or vasculogenic factors or penile structural factors such as Peyronie's disease.

In the majority of patients, erectile dysfunction appears to stem from multiple factors acting in concert, although one set of factors may predominate. This report focuses on patients with acquired erectile dysfunction that is primarily organic in nature, excluding Peyronie's disease and hypogonadism and other endocrine disorders.

Physiology and prevalence

Physiologically, erectile response is a vascular event initiated, in its most common form, by neuronal action which integrates psychological stimuli, such as sexual perception and desire, and controls sympathetic and parasympathetic innervation of the penis. Once initiated, a sexually stimulated erection is maintained by a complex interplay between vascular and neurologic events, in which sensory stimuli from the penis are especially important. Smooth muscle relaxation, arterial dilation and venous compression must occur simultaneously to create an erection. A defect in any of these three elements—problems with smooth muscle relaxation, arterial insufficiency or corporovenous occlusive dysfunction—may cause or contribute to erectile dysfunction.

Estimates of erectile dysfunction prevalence vary, but 10 to 20 million men in the United States are thought to be affected. If men with partial erectile dysfunction were included, the total would approach 30 million (*NIH Consensus Statement*, 1992). The majority of these men are older than age 65. Age is a statistically significant predictor of erectile dysfunction (Goldstein and Hatzichristou, 1994). The association between erectile dysfunction and age has been attributed mostly to the increased likelihood with aging of developing illnesses such as diabetes and vascular disease that are risk factors for erectile dysfunction, and to the greater use of medications that may impair erectile function. Erectile dysfunction does not invariably

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occur with aging. In many men, erectile function remains adequate well beyond age 80.

Treatment methods and treatment outcomes

Five basic types of therapy reported in the literature are potential options for treating organic erectile dysfunction:

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

Probability estimates for outcomes of these therapies are shown in the outcomes balance sheet tables on pages 24 to 25. The estimates, presented in decimal form, can be converted to percentages by moving the decimal point two places to the right.

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Oral drug therapy

Yohimbine, frequently prescribed as an oral treatment for organic and psychogenic erectile dysfunction, is an indole alkaloid with a chemical similarity to reserpine. Until recently, published studies of the effects of yohimbine on penile physiology and human male sexual function described its use only in combination with other agents. The drug was grandfathered by the Food and Drug Administration (FDA) in 1976, bypassing controlled trials to demonstrate efficacy and safety in treating erectile dysfunction. Controlled efficacy studies using yohimbine alone have been few and have only been published since 1982.

Based on the results to date, the efficacy of yohimbine remains to be proven. For both return to intercourse and patient satisfaction following yohimbine therapy, the outcomes balance sheet shows a probability estimate of only 24.7 percent. This is based on combined data for four patient groups, 445 patients total. Three of the four patient groups were placebo controlled, with a median placebo probability of 11.2 percent for patient satisfaction. The difference between yohimbine and placebo, given the number of patients involved, does not exclude a pure placebo effect. Adverse events from treatment are minimal and consist mainly of sympathetic stimulation.

The status of other oral drugs for treatment of erectile dysfunction is still investigational. These drugs include oral phentolamine (not available in the United States), trazodone and pentoxifylline. The efficacy of topical applications, such as minoxidil and nitroglycerin pastes, has also been studied. Reported results of recent studies of oral and topical drugs are discussed on pages 23 and 26 of Chapter 3.

Vacuum constriction devices

The vacuum constriction device (VCD) causes penile rigidity by means of a vacuum, and then traps the blood in the penis with an elastic band, disk or O-ring placed around the base of the penis. The equipment includes a transparent plastic chamber, a hand-operated or electric (battery-powered) vacuum pump and the elastic band or other constriction device.

Vacuum pressure must be at least 100 mm Hg, but need not exceed 225 mm Hg. A vacuum regulator to limit the maximum vacuum is essential because excessive negative pressure increases the chances of ecchymosis and hematoma formation. To maintain rigidity when the vacuum is released, the elastic disk, ring or band is applied to constrict the base of the penis. It must be tight enough to maintain penile rigidity, but not so tight as to injure the penis. Constriction sufficient to maintain rigidity may safely be maintained for 30 minutes.

Differences from a normal erection include decreased penile skin temperature, cyanosis, distention of the penile veins and increased penile circumference. The penis also pivots at the point of constriction, which may require the patient to stabilize the penis during vaginal penetration. When vacuum-induced erection is not overly prolonged, injury to the penis is unlikely.

The panel emphasizes that only prescription VCD equipment should be used. Rings made of metal or other inelastic materials should not be used as constriction bands.

The outcomes balance sheet shows relatively high probability estimates for return to intercourse and for patient and partner satisfaction with use of vacuum constriction devices. For occurrence of pain, the balance sheet shows a probability estimate of 18.8 percent based on number of men reporting

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any degree of discomfort, however minor. Reports specifying the degree of discomfort indicate that severe pain occurs infrequently. Patient dropout because of pain is also infrequent. For local adverse events, there is a probability of 9.5 percent. However, as noted in the discussion on page 27, most complications of vacuum device therapy are minor and require no treatment.

Intracavernous vasoactive drug injection therapy

Various vasoactive drugs are available for intracavernous injection therapy to treat erectile dysfunction. Currently papaverine, phentolamine and prostaglandin E1 (PGE_1) are the most widely used, singly or in combination.

Papaverine is an effective smooth muscle relaxant, but patients should be monitored for prolonged erections, corporal nodules and plaques or fibrosis. Phentolamine, also a smooth muscle relaxant, seldom produces a satisfactory erection when used as a single agent. It has often been used in combination with papaverine and more recently with PGE_1 to treat erectile dysfunction.

PGE_1 is one of a group of compounds, the prostaglandins, that occur naturally in the body and mediate a number of diverse physiologic processes. PGE_1 is also referred to by the generic name of its synthetic form, alprostadil, the form in which it is administered. Under the trade name Caverject™, alprostadil was approved by the FDA in 1995 for injection therapy to treat erectile dysfunction. Patient and partner satisfaction rates of 70 percent and higher have been reported for alprostadil. Prolonged erection may occur, but the most frequent side effect is pain. The outcomes balance sheet shows the estimated probability of pain at 23.3 percent. The estimated probability of prolonged erection is 3.1 percent.

The goal of intracavernous injection therapy is to achieve an erection that lasts sufficiently long for patient and partner to engage in satisfactory foreplay and sexual intercourse, but the erection generally should not exceed one hour. The patient must be cautioned about the possibility of a prolonged pharmacologic erection, defined as an erection lasting more than four hours or a painful erection of shorter duration. (Prolonged pharmacologic erection is discussed in detail on pages 17 to 18.)

The outcomes balance sheet shows fairly high probability estimates for return to intercourse and patient and partner satisfaction for the various vasoactive agents, but some estimates are based on meager data. Studies of papaverine and phentolamine used in combination provided the panel with the largest amounts of extractable data. Studies reporting extractable outcomes data for PGE_1 monotherapy (alprostadil) and the now widely used papaverine/phentolamine/ PGE_1 triple therapy were fewer. No data were available for PGE_1/phentolamine combination therapy, which is consequently absent from the balance sheet.

For papaverine/phentolamine/PGE_1 triple therapy, the few available studies did not provide sufficient extractable information to generate probability estimates for patient and partner satisfaction or systemic and local adverse events. The estimated probability for return to intercourse following triple therapy is based on data from one study.

Partner satisfaction data has been reported in few studies for any type of vasoactive drug injection therapy. The partner satisfaction estimates in the balance sheet for papaverine/phentolamine and PGE_1 therapies are each based on data from a single study. For triple therapy no data were available.

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Penile prosthesis implantation

Penile prostheses can be divided into two general types: nonhydraulic and hydraulic. Nonhydraulic devices are also commonly referred to as semirigid rod prostheses, and hydraulic devices are often referred to as inflatable prostheses. Nonhydraulic prostheses include the American Medical Systems (AMS) Malleable 600/650, the DuraPhase/Dura-II (Dacomed), the Mentor Malleable and the Mentor Acu-Form. Hydraulic devices include the AMS Dynaflex (one-piece), the Mentor Mark II and AMS Ambicor (two-piece) and the AMS 700CX, AMS Ultrex and Mentor Alpha I (three-piece). These devices are described in detail on pages 18 to 19.

The outcomes balance sheet table for prostheses shows a range of estimated probabilities for patient satisfaction with various types of devices. The patient satisfaction rate is 83.3 percent for malleable semirigid rod devices and 88.9 percent for multicomponent hydraulic devices. The 95.7 percent rate for mechanical (nonhydraulic) prostheses was derived from combined data reported for DuraPhase/Dura-II (Dacomed) devices.

The balance sheet table shows probability estimates for three undesirable outcomes: infection, mechanical failure and erosion. These device problems usually require reoperation.

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Venous and arterial surgery

Venous surgery to correct corporovenous occlusive dysfunction generally involves resection and/or ligation of penile veins. Surgical techniques to correct arterial insufficiency of the corpora cavernosa are based on neoarterialization of the dorsal penile artery, cavernous artery and/or deep dorsal vein. The inferior epigastric artery is generally used as the donor vessel.

For venous surgery, the outcomes balance sheet shows an estimated probability for return to intercourse of 43.3 percent, based on data from 43 patient groups (1,801 patients). The estimated probability for patient satisfaction following venous surgery is 43.8 percent. For arterial surgery, the balance sheet shows an estimated probability of 60.3 percent for return to intercourse (19 patient groups, 713 patients). Also, it has been reported that approximately 25 percent of men who have had vascular surgery (venous or arterial) can be salvaged with the aid of vasoactive drug injection therapy.

In general, surgical treatments for erectile dysfunction of venogenic and/or arteriogenic origin are in an immature state of evolution. Almost all published studies are based on nonstandardized diagnostic techniques, and on nonobjective and uncontrolled followup methods. In addition, there are a number of well-known potential postoperative complications, such as infection, pain, postoperative priapism, persistent edema, penile shortening and glans hypervascularization (Jarow and DeFranzo, 1992; Wolf and Lue, 1992).

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Treatment recommendations

The panel's practice recommendations for treatment of erectile dysfunction apply to the standard patient. This patient is defined as a man who develops erectile dysfunction after a well-established period of normal erectile function and whose erectile dysfunction is primarily organic rather than psychological and who has no evidence of hypogonadism or hyperprolactinemia.

As previously stated, the panel generated its treatment recommendations based both on outcomes evidence from the literature and on panel opinion. The recommendations were graded according to three levels of flexibility, based on the strength of the evidence and on the panel's assessment of patient preferences. These three levels—standards, guidelines and options—are defined on page 10. Standards have the least flexibility, guidelines have significantly more flexibility and options are the most flexible. In this report, the terms are used to indicate the strength of the recommendations. A recommendation was labeled a standard, for example, if the panel concluded that it should be followed by virtually all health care providers for virtually all patients. Regardless of level of flexibility, the panel considered it important to consider likely preferences of individual patients when selecting from among the different treatments for erectile dysfunction.

Recommended treatment modalities and patient information

Following are considerations for discussion when informing the patient about the three recommended treatment options: vacuum constriction device (VCD) therapy, intracavernous vasoactive drug injection therapy and penile prosthesis implantation. (See first two recommendations on page 6.) These considerations include selection factors and contraindications resulting from the diagnostic assessment. In the panel's opinion, it is important to involve the partner in discussion of therapeutic alternatives and treatment goals when possible. Interviewing and educating the partner can alleviate much of the stress that erectile dysfunction brings to a relationship, with the goal being honest appraisal of the benefits and potential difficulties of therapy.

Informing the patient about vacuum constriction devices

The VCD should be discussed as a treatment option based on the results of the diagnostic assessment. The discussion should be unbiased, and advantages and shortcomings should be stated. The use of VCDs in conjunction with vasoactive drug injection therapy can also be discussed.

The VCD will cause penile rigidity in most men that is sufficient for vaginal penetration regardless of the reason for erectile dysfunction. Men with decreased penile sensation because of spinal cord injury or other neurologic problems should use the VCD with caution. Only prescription vacuum constriction devices should be used, and constriction should not exceed 30 minutes.

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Informing the patient about vasoactive drug injection therapy

As with VCD therapy, intracavernous vasoactive drug injection therapy should be presented as a treatment option in an unbiased manner, preferably using patient handouts or video presentations that examine the benefits and risks of each treatment modality available. Complications, including prolonged erection, painful erection and fibrosis, should be discussed. Also as with VCD therapy, the presentation should be based on the diagnostic assessment.

A good response to test doses of vasoactive agents during the diagnostic assessment in a patient with organic erectile dysfunction or refractory psychogenic erectile dysfunction, indicates a suitable candidate for treatment by vasoactive pharmacotherapy. However, a poor response may be situational and does not necessarily preclude treatment of the patient with vasoactive agents.

Relative contraindications to vasoactive injection include penile fibrosis, coagulopathy, uncontrolled psychiatric disorders, regular use of monoamine oxidase (MAO) inhibitors and severe cardiovascular disease that could be exacerbated by a complication of the injection (Padma-Nathan, Goldstein, Payton, et al., 1987). Patients taking MAO inhibitors are at risk for hypertensive crisis if adrenergic agents are used to treat prolonged erection. Patients with chronic systemic illnesses should be followed in conjunction with their primary physician. Poor manual dexterity or morbid obesity, which could preclude self-injection, may be overcome by teaching the injection technique to an able and willing partner.

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Informing the patient about penile prosthesis implantation

Prosthesis implantation is a highly reliable but invasive form of therapy. Candidates considering this treatment option should be aware that postoperative pain after implantation could be significant and typically lasts four to eight weeks, although this is quite variable. Patients will need to restrict strenuous physical activity for at least four weeks, and coitus should not be resumed for at least four weeks.

Complications, especially infection and erosion, need to be discussed. The patient should know that infection and erosion usually require device removal. The patient also needs to know that any type of penile prosthesis can fail mechanically, and the probability of device failure tends to be proportional to device complexity. The potential implant recipient should be told that correction of device failure requires reoperation.

The patient should be aware that implantation of a penile prosthesis does not ordinarily affect libido, orgasm, ejaculation, urination or genital sensation. A few implant recipients experience unexplainable persistent pain or decreased penile sensation. Fortunately, these complications are rare.

It is important that potential implant recipients understand that an erection produced by a prosthesis always differs from a normal erection. Many recipients feel that the erection a prosthesis produces is shorter than a normal erection. Moreover, the appearance of the flaccid penis will be different to some degree. These departures from the normal state are variable. The variability depends on the type of prosthesis chosen, differences in the anatomy of individual patients and factors related to the healing process.

If the option of being implanted with a prosthesis is selected, the different prostheses offered by the implanting surgeon should be comparatively discussed with the patient and, whenever possible, with the partner. No single prosthesis is best for every patient. The patient's or couple's wishes are important factors in device selection.

If the patient wants a simple device that has the lowest possibility of subsequent mechanical failure and he is willing to accept the limitations inherent in a nonhydraulic prosthesis, a malleable or positionable prosthesis can be considered. However, if the patient wants the most natural flaccidity and erection possible with today's devices, a three-piece hydraulic prosthesis is the best choice.

Other devices, such as one- and two-piece hydraulic devices, provide a compromise between nonhydraulic and three-piece hydraulic devices. When considering hydraulic penile prostheses, factors such as patient motivation, intelligence, manual dexterity and strengths need to be considered in order to avoid implantation of a device that the patient will be unable to cycle.

Although some penile implantations are done using local anesthesia (Dos Reis, Glina, Da Silva, et al., 1993; Kaufman, 1982), most continue to be done using general, spinal or epidural anesthesia. The need for and the type of anesthesia should, therefore, be discussed.

(continues on page 8)

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Recommendations

Recommended treatment modalities and patient information

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

Guideline: Based on review of the literature and analysis of the data, the panel recommends three treatment options for organic erectile dysfunction in the standard patient, as this patient is defined on page 4. The three recommended treatments are: vacuum constriction device therapy, intracavernous vasoactive drug injection therapy and penile prosthesis implantation.

Oral drug therapy (yohimbine)

Guideline: Based on the data to date, yohimbine does not appear to be effective for organic erectile dysfunction, and thus should not be recommended as treatment for the standard patient.

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Vacuum constriction device (VCD) therapy

Guideline: In order to optimize efficacy and safety, men interested in trying the VCD should be given individual instruction in its use. Only VCDs available by prescription should be used.

Vasoactive drug injection therapy

Standard: The physician should inform the patient using vasoactive drug injection therapy that a prolonged erection can occur and that the patient should present for treatment after a prolonged erection of four hours. The physician should be familiar with the methods used to reverse a prolonged erection and should inform the patient of how to contact the treating physician or a knowledgeable substitute at any time.

Guideline: For patients beginning initial therapy, PGE_1 (alprostadil) monotherapy is preferred. For patients who fail PGE_1 therapy because of pain or inadequate erection, other drugs should be considered.

Guideline: For combination therapy, papaverine/phentolamine and papaverine/phentolamine/PGE_1 appear equally efficacious and safe. For PGE_1/phentolamine combination therapy, insufficient data have as yet been reported in the literature; but panel opinion is that this combination appears to be an effective therapy.

(continues on page 7)

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Recommendations *(continued)*

Option: Papaverine monotherapy may be considered in some patients because of lower risk of pain and lower cost in comparison with PGE_1 monotherapy. Physicians using papaverine monotherapy should be aware of the higher risk of prolonged erection and fibrosis as compared with PGE_1 monotherapy.

Penile prosthesis implantation

Standard: Penile prosthesis implantation should not be performed in men with psychogenic erectile dysfunction unless a psychiatrist or psychologist participates in the preoperative evaluation and concurs with the need for prosthesis implantation.

Standard: The patient considering prosthesis implantation and, when possible, his partner should be informed of the following factors: types of prostheses; duration of postoperative pain and restriction of activity; possibility of infection and erosion, mechanical failure and consequent reoperation; and differences from the normal flaccid and erect penis.

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Standard: The implant recipient and, when possible, his partner should be informed that penile prosthesis implantation may preclude subsequent successful use of a vacuum constriction device or vasoactive injection therapy.

Standard: Surgery should not be done in the presence of systemic infection or cutaneous infection in the operative field. Prior to operation the absence of bacteriuria should be confirmed.

Venous and arterial surgery

Guideline: Based on the evidence to date, penile venous surgery is considered investigational and should only be performed in a research setting with long-term followup available.

Guideline: Arterial reconstructive and dorsal vein arterialization procedures in men with arteriolosclerotic disease are investigational and should only be performed in a research setting with long-term followup available.

Option: Arterial revascularization may be effective for treating young men with normal corporovenous function who have arteriogenic erectile dysfunction secondary to pelvic and perineal trauma.

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Costs can be an important factor in decision making, depending on the patient's insurance coverage and/or financial resources. In general, the cost of a prosthesis is proportional to its design complexity. The surgical implantation fee usually depends on device complexity as well.

Modality-specific recommendations

The following discussion augments the modality-specific panel recommendations on pages 6 to 7. Recommendations and discussions are presented by modality in the order in which the five modalities appear in the outcomes balance sheet.

Oral drug therapy (yohimbine)

In various populations of men with organic erectile dysfunction, yohimbine has shown only a modest beneficial effect, and there is a significant placebo effect that may account for half of its beneficial effect. Furthermore, based on present studies, the subpopulation of men with erectile dysfunction who are most likely to benefit from yohimbine therapy cannot be accurately identified (see pages 14 and 23).

The status of other oral drugs for treatment of erectile dysfunction is investigational (see pages 23 and 26).

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VCD therapy

Successful use of a VCD requires careful instruction. Patients who rely only on the manufacturer's printed or videotaped instructions are less likely to master the use of the VCD than those given a demonstration by a physician or experienced medical assistant (Lewis, Sidi and Reddy, 1991).

Vasoactive drug injection therapy

The choice of vasoactive pharmacotherapy to treat erectile dysfunction places the patient in the situation of performing a minimally invasive drug injection on an intermittent basis. With any vasoactive agent or combination, physicians should be prepared to aggressively treat all potential complications. (Treatment of prolonged pharmacologic erection is discussed on pages 17 to 18.) Complications can be minimized and patient acceptance and satisfaction facilitated by careful attention to diagnosis, teaching and followup. Education of the patient is particularly important to minimize frustration and decrease the probability of untoward side effects. Good teaching of technical details and a willingness to elucidate difficulties in technique or to observe injection technique periodically may decrease the incidence of improper injection and failed responses. When appropriate, the patient should be able to adjust within specific bounds the total dose of medication injected to match the specific situation for which it is used. It is recommended that vasoactive drug injection therapy not be used more than once in a 24-hour period.

Penile prosthesis implantation

The ideal candidate for prosthesis implantation is the man with organic erectile dysfunction who failed treatment by other means or finds other treatment unacceptable and is a suitable surgical risk. Prosthesis implantation is not recommended for patients in whom erectile dysfunction is situational or reversible. Men with psychogenic erectile dysfunction should only be considered for penile prosthesis implantation when sex therapy has failed and a prosthesis has been recommended by the therapist or the therapist believes that sex therapy is not feasible for that individual or couple.

Abnormalities of the tunica albuginea or fibrosis of the cavernosal tissue may complicate prosthesis implantation. The penile prosthesis recipient should be free of urinary tract infection and should have no infections elsewhere in the body that might result in bacterial seeding during the healing phase. In addition, there should be no active dermatitis, wounds or other cutaneous lesions in the operative area. Antibiotics to provide broad-spectrum coverage should be administered, such that tissue levels are adequate at the start of the operation. In diabetic implant recipients, good control of diabetes mellitus may reduce the risk of infection (Bishop, Moul, Sihelnik, et al., 1992).

Prosthesis recipients with spinal cord injury are at increased risk for both infection and erosion (Golji, 1979; Rossier and Fam, 1984). Erosion in these patients may occur in part because of infection, but lack of sensation also contributes to erosion. Inflatable prostheses in spinal cord injured patients offer a reduced risk of erosion. Inflatable prostheses are also considered advantageous in patients, such as those with a history of bladder tumor or urethral stricture, who may require periodic lower tract endoscopic procedures.

Uncircumcised men should be examined for abnormalities of the prepuce or glans penis. Mild phimosis or balanitis may be an indication for circumcision either before or at the time of prosthesis

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implantation. Postimplant problems with phimosis in uncircumcised men are unusual if foreskin and glans are normal.

Venous and arterial surgery

As discussed in Chapter 2 (page 20) and Chapter 3 (pages 38 to 39), objective criteria to select patients for penile vascular surgery still do not exist. In addition, the measures of success are nonstandardized and unpredictable. Postoperative success in most surgical series has been based predominantly on subjective patient reporting. Because patients are reluctant to have invasive studies postoperatively, few studies report objective postoperative data such as from angiography or cavernosometry. Moreover, reported success rates have been relatively low.

Research recommendations

New and better methods for evaluation of erectile dysfunction are clearly needed—beginning with a standardized diagnostic approach and establishment of normal criteria for diagnostic tests. Among tests needing standardization are vascular analysis with duplex ultrasound, cavernosometry, cavernosography and arteriography. Needed as well are expanded research on evaluating nocturnal penile tumescence and rigidity and the development of methods for evaluating specific neurologic factors in erectile dysfunction.

For treatment, the ultimate goal is a therapy that is not only reliable with minimal side effects, but simple to employ. Such a therapy will most likely be some form of oral or topical medication. Areas for exploration include medications to activate vasodilation through actuation of nitric oxide synthesis and release, smooth muscle relaxants that may have specific receptors in the penile vasculature and medications that may work on a central level to inhibit the adrenergic response, particularly in patients who have mild organic disease with a psychogenic overlay.

Needed too are better-designed studies, including where possible prospective, randomized, controlled trials. Uniform methods of reporting outcomes are needed to produce more reliable data that can be used for analysis. Especially needed are well-designed prospective patient and partner satisfaction studies for all treatment modalities.

Meeting the need for better study design will require the development of standard criteria for reporting outcomes, including adverse events and specific treatment complications, as well as the development of uniform inclusion/exclusion criteria for enrolling patients in prospective trials. Better study designs will also require the development of outcome assessment instruments, from sexual function and sexual satisfaction questionnaires to physiologic assessment tools, that can be applied uniformly to patients treated with different modalities.

There are, in addition, research needs specific to particular treatment modalities. For vacuum constriction devices, which were developed empirically, scientific studies are now needed to address physiologic concerns, such as defining safe limits for negative pressure and constriction. For vasoactive drug injection therapy, the ideal agent has yet to be developed. This would be an inexpensive agent that is stable over time and provides a consistent, dose-dependent erection result with low risk of pain, prolonged erection or other complications. For penile prostheses, in addition to needed improvements such as devices less subject to mechanical failure, more research is needed on causes and prevention of infection—the single most important problem associated with penile prosthesis implantation.

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Chapter 1 – Methodology

Methods and definitions

The recommendations in this *Report on the Treatment of Organic Erectile Dysfunction* were developed following an explicit approach to the development of practice policies (Eddy, 1992), as opposed to an approach that relies solely on panel consensus without explicit description of evidence considered.

The explicit approach attempts to arrive at recommendations that consider the relevant factors for making selections between alternative interventions. Such factors include estimated outcomes from the interventions, patient preferences and (when possible to assess) the relative priority of the interventions for a share of limited health care resources. Emphasis is placed on scientific evidence in estimating the outcomes of the interventions. If the evidence has limitations, the limitations are clearly stated. When panel opinion is necessary, the explicit approach calls for an explanation of why it is necessary and/or discussion of the factors considered.

In developing the recommendations in this report, the Erectile Dysfunction Clinical Guidelines Panel made an extensive effort to review all the relevant literature available on erectile dysfunction and to estimate the outcomes of the different treatment modalities as accurately as possible. The review of the evidence began with a literature search and extraction of outcomes data. The panel used the FAST*PRO meta-analysis package (Eddy and Hasselblad, 1992) to combine the outcomes evidence from the various studies, as described on pages 11 to 12.

Estimates of outcomes for treatment modalities are arrayed in the outcomes balance sheet tables in Chapter 3 (pages 24 to 25). A balance sheet, as the term implies, displays the probability estimates for desirable and undesirable outcomes to allow physicians and patients to compare and evaluate the outcomes of various treatments. The balance sheet tables in Chapter 3 show probability estimates of outcomes for five treatment modalities:

- Oral drug therapy (yohimbine);
- Vacuum constriction devices;
- Intracavernous vasoactive drug injection therapy;
- Penile prosthesis implantation; and
- Venous and arterial surgery.

Also discussed in Chapter 3 is evidence from studies that may not have provided outcomes data suitable for meta-analysis, but provided useful information considered by the panel in making treatment recommendations.

The panel's treatment recommendations and statements in Chapter 4 are based on outcomes evidence from the literature and on panel opinion. Because existing studies of treatment modalities for erectile dysfunction report health outcomes variably, interpretation was often required to assess treatment success or failure.

Recommendations were graded according to three levels of flexibility based on the strength of the evidence and the panel's assessment of patient preferences. The three levels (Eddy, 1992; American Academy of Family Physicians, 1995) are defined as follows:

- Standard: A treatment policy is considered a standard if the outcomes of the alternative interventions are sufficiently well-known to permit meaningful decisions and there is virtual unanimity about which intervention is preferred.
- Guideline: A policy is considered a guideline if the outcomes of the interventions are sufficiently well-known to permit meaningful decisions and an appreciable but not unanimous majority agree on which intervention is preferred.
- Option: A policy is considered an option if (1) the outcomes of the interventions are not sufficiently well-known to permit meaningful decisions; (2) preferences among the outcomes are not known; (3) patients' preferences are divided among the alternative interventions; and/or (4) patients are indifferent about the alternative interventions.

Standards obviously have the least flexibility, guidelines have significantly more flexibility and

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options are the most flexible. In this report, the terms are used to indicate the strength of the recommendations. A recommendation was labeled a standard, for example, if the panel concluded that it should be followed by virtually all health care providers who treat men with erectile dysfunction. Regardless of level of flexibility, the panel considered it important to take into account likely preferences of individual patients when selecting from among the different treatments for erectile dysfunction.

Literature searches and article review

From January 1993 to January 1995, multiple literature searches were performed, utilizing the MEDLINE data base and hand searching bibliographies from published articles. The searches covered studies published in the period from January 1979 to December 1994. There were four basic review criteria for panel acceptance of a study for data extraction:

- The study must have a defined population and defined outcome(s);
- The study must be published in a peer-reviewed publication in the English language;
- The data must be presented in raw form, not in percentages or ratios; and
- Treatment arms must be identifiable.

A total of 1,888 articles was retrieved on the basis of abstract review by panel members. Of these articles, 619 were selected by panel members for closer review. The final review stage yielded 209 studies for entry into the data base for data extraction. Figures A-3 and A-4 in Appendix A depict the stages of review. Also see Table A-1 in Appendix A for titles, authors and sources of the 209 articles from which outcomes data were extracted. The data extraction form devised by the panel to capture as much pertinent information as possible from each of the 209 studies is provided in Appendix B.

Articles cited in the text of this report, for referencing particular points, were not necessarily among the articles that the panel reviewed to extract outcomes data. These text citations also include articles published since the January 1995 cutoff date for data extraction literature searches.

Most studies rejected by the panel in selecting articles for data extraction did not meet one or more of the four basic review criteria. Studies were also rejected for other reasons, such as information duplicated in another article by the same author(s); device reported on (prosthesis or vacuum device) no longer available; no patients with organic erectile dysfunction (psychogenic only); diagnostic study without treatment outcomes data; review article (not a study and in some instances reviewing unpublished data); case report of treatment complication; and anecdotal information.

Evidence combination

In order to generate a balance sheet, estimates of the probabilities and/or magnitudes of the outcomes are required for each alternative intervention. Ideally, these come from a synthesis of the evidence. This synthesis can be performed in a variety of ways depending on the nature and quality of the evidence. For example, when there is one good randomized controlled trial, the results of that one trial alone may be used in the balance sheet. Other studies of significantly lesser quality may be ignored.

When there are no studies of satisfactory quality for certain balance sheet cells or the studies found are not commensurable, the panel's expert opinion can be used to fill in those cells or they can remain blank with an indication of "No data."

When there are a number of studies that have some degree of relevance to a particular cell or cells, then meta-analytic mathematical methods may be used. Different specific methods are available depending on the nature of the evidence. For the *Report on the Treatment of Organic Erectile Dysfunction,* the panel elected to use the Confidence Profile Method (Eddy, 1989; Eddy, Hasselblad and Shachter, 1990). This method allows analysis of data from studies that are not necessarily randomized controlled trials. The FAST*PRO computer package (Eddy and Hasselblad, 1992) was used in the analysis.

The package was used to combine treatment arms from various clinical studies to estimate outcomes for a particular treatment. The studies that were combined frequently showed very different results, implying site-to-site variations. Because of the differences, a random effects or hierarchical model was used to combine the studies.

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A random effects model assumes that for each site there is an underlying true rate for the outcome being assessed. It further assumes that this underlying rate varies from site to site. This site-to-site variation in the true rate is assumed to be normally distributed. The method of meta-analysis used in analyzing the erectile dysfunction treatment data attempts to determine this underlying distribution.

The results of the Confidence Profile Method are probability distributions. They can be described using a median probability estimate with a confidence interval. In this case, the 95 percent confidence interval is such that the probability (Bayesian) of the true value being outside the interval is 5 percent.

Following is a simple example to illustrate use of the FAST*PRO software: Two studies looked at a certain outcome after a treatment for a given disease. In each study, 75 percent of the patients had the outcome. The first study had a total of 20 patients, and the second had a total of 1,000. If the software is used to update the probabilities for each site, the resultant (posterior) probability distributions of the true probability of the outcome are as shown in Table 1 on this page (95% confidence interval column for studies 1 and 2). Note that there is a much wider confidence interval (CI), indicating much more uncertainty about the true value, for study 1 with 20 patients (95% CI: 0.536 - 0.898) than for study 2 with a sample of 1,000 (95% CI: 0.722 - 0.776).

A third study involved 600 patients with 400 (66.7 percent) having the outcome. The range of uncertainty for this study is intermediate between that of the first two studies. When all three studies are combined using the Confidence Profile Method as previously described, the result is the combined profile shown in the bottom row of the table. The 95 percent confidence interval is narrow, indicating little difference among studies. Since two studies have the same result and the other is close, it is not surprising that there would be minimal site-to-site variation suggested by these studies.

The method of computation is Bayesian in nature, which implies the assumption of a prior distribution that reflects knowledge about the probability of the outcome before the results of any experiments are known. The prior distributions selected for this analysis are among a class of noninformative prior distributions, which means that they correspond to little or no preknowledge. The existence of such a prior distribution can cause small changes in results, particularly for small studies. In the foregoing example, for instance, the mean of the distribution for the sample size 20 is 0.746 rather than 0.75. The effect of the prior distribution is to slightly discount the value of the experiment. This effect will not be pronounced except in very small studies, and the combination of multiple studies will reduce this tendency further.

Table 1: Meta-analysis example

Study	Median	95% CI
1	0.746	0.536 - 0.898
2	0.750	0.722 - 0.776
3	0.667	0.628 - 0.703
Combination	0.716	0.687 - 0.743

For the statistically sophisticated reader, the prior distribution for all probability parameters is Jefferey's prior (beta distribution with both parameters set to 0.5). The prior for the variance for the underlying normal distribution is gamma distributed with both parameters set to 0.5.

Outcomes considered important to patients receiving treatment for erectile dysfunction were analyzed in the manner indicated previously. Evidence from all studies meeting inclusion criteria that reported a certain outcome were combined within each treatment modality.

As stated previously, the existing studies of erectile dysfunction treatments report their data variably. The probabilities for certain outcomes can vary widely from study to study within a treatment modality. Such variability may result in wide confidence intervals, reflecting either considerable uncertainty about the outcome or considerable differences among sites and practitioners. The outcome probabilities in this report represent the best estimates possible at the present time, pending new studies reporting more reliable data from prospective clinical trials.

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Chapter 2 – Erectile dysfunction and its treatments

Background

The National Institutes of Health Consensus Development Conference on Impotence (December 7-9, 1992) defined impotence as "male erectile dysfunction, that is, the inability to achieve or maintain an erection sufficient for satisfactory sexual performance" (*NIH Consensus Statement*, 1992). Erectile dysfunction is the more precise term, especially given the fact that sexual desire and the ability to have an orgasm and ejaculate may well be intact despite the inability to achieve or maintain an erection.

Research on etiologies, diagnoses and treatments of erectile dysfunction began to escalate in the 1970s and has continued to escalate since. Possible social factors stimulating this research include an aging population, a new awareness of sexuality and the refusal by many older men to accept erectile dysfunction as an inevitable part of the aging process.

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Most research is relatively recent, and etiologic factors and their interplay are still poorly understood. Until the 1970s, erectile dysfunction was commonly attributed to psychogenic causes or, physiologically, to abnormalities in testosterone metabolism. Studies since then indicate that although testosterone deficiency may affect the libido, it does not necessarily affect the ability to have erections (Bancroft and Wu, 1983; Kaiser, Viosca, Morley, et al., 1988; Lue, 1991). Psychological factors, such as depression, anxiety and the quality of relationships with sexual partners, obviously affect erectile function, but other factors may be involved as well. Erectile dysfunction may be associated with psychogenic, neurogenic or vasculogenic factors or with penile structural factors, such as Peyronie's disease.

In the majority of patients, erectile dysfunction appears to stem from multiple factors acting in concert, although one set of factors may predominate. This *Report on the Treatment of Organic Erectile Dysfunction* focuses on patients with acquired erectile dysfunction that is primarily organic in nature, excluding Peyronie's disease and hypogonadism and other endocrine disorders.

Physiology

In its most common form, erectile response is a vascular event initiated by neuronal action that integrates psychological stimuli, such as sexual perception and desire, and controls sympathetic and parasympathetic innervation of the penis. A sexually stimulated erection, once initiated, is maintained by a complex interplay between vascular and neurologic events, in which sensory stimuli from the penis are especially important (*NIH Consensus Statement*, 1992).

A key element in the physiology of erections is relaxation of corporal smooth muscle. During periods of penile flaccidity, the corporal smooth muscle is in a state of tonic contraction maintained by an underlying sympathetic tone (adrenergic tone). As the smooth muscle relaxes, the sinusoidal spaces engorge with blood, coinciding with an increase in penile arterial inflow in response to the simultaneous relaxation of arterial smooth muscle. The emissary veins between the sinusoids and the tunica albuginea are compressed, retarding venous outflow from the corporal bodies. As inflow exceeds outflow, tumescence ensues. Continued stimulation further increases smooth muscle relaxation, and the increased turgor of the corporal tissue against the unyielding tunica albuginea increases intracavernosal pressure, resulting in a rigid erection. Thus, an erection is a mechanical manifestation of a hemodynamic event (Barada and McKimmy, 1994).

Smooth muscle relaxation, arterial dilation and venous compression must occur simultaneously to create an erection. A defect in any one of these three elements could cause or contribute to erectile dysfunction. Various combinations of partially reduced arterial inflow and/or venous compression and/or smooth muscle relaxation may also account for erectile dysfunction in many men (Sharlip, 1994).

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Prevalence of erectile dysfunction and relation to age

Estimates of the prevalence of erectile dysfunction vary, but 10 to 20 million men in the United States are thought to be affected. When men with partial erectile dysfunction are included, the total approaches 30 million (*NIH Consensus Statement*, 1992).

The majority of these men are older than age 65. The *NIH Consensus Statement* reported an estimated prevalence among U.S. men of about 5 percent at age 40, increasing to 15 to 25 percent at age 65 and older. Other reports have also pointed out a clear association between erectile dysfunction and age. For example, the Massachusetts Male Aging Study (MMAS) surveyed 1,290 men between the ages of 40 and 70, in 11 randomly selected cities and towns near Boston (Feldman, Goldstein, Hatzichristou, et al., 1994). The overall probability of erectile dysfunction (minimal, moderate and complete) was found to be 38.9 percent at age 40 and 67.1 percent by age 70. Moreover, age was found to be a statistically significant predictor of erectile dysfunction (Goldstein and Hatzichristou, 1994).

This association between erectile dysfunction and age has been attributed mostly to the increased likelihood with aging of developing illnesses, such as diabetes and vascular disease, that are risk factors for erectile dysfunction, and to the greater use of medications that may impair erectile functioning (Feldman, Goldstein, Hatzichristou, et al., 1994; Gundle, Reeves, Tate, et al., 1980; Jünemann, Persson-Jünemann and Alken, 1990; Morley, 1988; Morley, Korenman, Mooradian, et al., 1987; Mulligan, Retchin, Chinchilli, et al., 1988; Oaks and Moyer, 1972; Slag, Morley, Elson, et al., 1983; Virag, Bouilly and Frydman, 1985; Wabrek and Burchell, 1980; Whitehead and Klyde, 1990). Other factors may be involved, such as the possibility that greater risks for peripheral neuropathy and loss of smooth muscle elasticity may be associated with aging; but there is no conclusive evidence for such an association.

By no means, of course, does erectile dysfunction invariably occur with aging. In many men, erectile functioning remains adequate well past the age of 80.

Treatment methods

Five basic types of therapy reported in the literature are potential options for treating organic erectile dysfunction:

- Oral drug therapy;
- Vacuum constriction device (VCD) therapy;
- Intracavernous vasoactive drug injection therapy;
- Penile prosthesis therapy; and
- Venous and arterial surgery.

Oral drug therapy

Yohimbine is a drug frequently prescribed as an oral treatment for organic and psychogenic erectile dysfunction. It is an indole alkaloid with a chemical similarity to reserpine. Among its properties is a selective inhibition of alpha$_2$-adrenergic receptors. In humans, yohimbine can cause elevations of blood pressure and heart rate, increased motor activity, irritability and tremor (Weiner, 1985).

Yohimbine has long been considered an aphrodisiac. Until recently, however, published studies of its effects on penile physiology and male sexual function reported its use only in combination with other agents (Margolis, Prieto, Stein, et al., 1971). Yohimbine increases sexual motivation in rats (Clark, Smith and Davidson, 1984), but this aphrodisiac effect has not been confirmed in humans. The drug was grandfathered by the FDA in 1976, bypassing controlled trials to demonstrate efficacy and safety for its use in treating erectile dysfunction. Controlled studies of its efficacy, when used alone for that purpose, have been few and have appeared only since 1982 (Morales, Condra, Owen, et al., 1987; Morales, Surridge, Marshall, et al., 1982; Reid, Surridge, Morales, et al., 1987; Susset, Tessier, Wincze, et al., 1989). Based on the results to date, the efficacy of yohimbine clearly remains to be proven. (See the outcomes balance sheet on page 24 and the analysis on page 23 of Chapter 3.)

Other oral drugs being tested for treatment of erectile dysfunction include oral phentolamine (not available in the U.S.), trazodone and pentoxifylline. In addition, the efficacy of topical applications such as minoxidil and nitroglycerin pastes has been studied. The status of all these drugs is considered

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investigational. Reported results of recent studies are discussed on pages 23 and 26 of Chapter 3.

Vacuum constriction device (VCD) therapy

The prototype of the present VCD was developed early in this century, but inexplicably it remained obscure for almost seven decades. The first scientific report of the safety and efficacy of the VCD was published in 1986 (Nadig, Ware and Blumoff, 1986). Since that time, the VCD has gained acceptance and popularity among physicians and patients. It is now widely prescribed for erectile dysfunction and is recognized as the safest and least expensive treatment available (Aloui, Iwaz, Kokkidis, et al., 1992; Blackard, Borkon, Lima, et al., 1993; Cookson and Nadig, 1993; van Thillo and Delaere, 1992; Vrijhof and Delaere, 1994).

The VCD causes penile rigidity by means of a vacuum, then traps the blood in the penis with an elastic band, disk or O-ring placed around the base of the penis. The equipment consists of a transparent plastic chamber, a hand-operated or electric (battery-powered) vacuum pump and the elastic band or other constriction device. The vacuum chamber must be of a length and diameter to accommodate the patient's penis. One end of the vacuum chamber is open. If the opening is of optimum size, the expanded penis fills the proximal part of the cylinder helping to seal the vacuum. If the opening is not large enough, the penis cannot expand completely and will not become rigid. If the opening is too large, the vacuum will be difficult to maintain and loose scrotal skin can be pulled into the cylinder.

Before using the VCD, a water-soluble lubricant is applied generously to the penis, particularly at its base, where an airtight seal must form. The penis is then placed in the chamber, pressing the base of the chamber tightly against the pubic bone, and a vacuum is applied for approximately six minutes. Improved penile rigidity results from the technique of double pumping, that is, applying the vacuum for one to two minutes, relieving it momentarily and reapplying it for an additional three to four minutes. Vacuum pressure must be at least 100 mm Hg, but need not exceed 225 mm Hg (Nadig, 1989). A vacuum regulator to limit the maximum vacuum is essential because excessive negative pressure increases the chances of ecchymosis and hematoma formation. Men taking aspirin or other anticoagulants are more likely to have this complication.

To maintain rigidity when the vacuum is released, the elastic disk, ring or band is applied to constrict the base of the penis. It must be tight enough to maintain penile rigidity, but not so tight as to injure the penis. Constriction sufficient to maintain rigidity may safely be maintained for 30 minutes. Severe penile cellulitis was reported in one case study of a spinal cord injured man who fell asleep for four hours with three constriction bands on his penis (LeRoy and Pryor, 1994).

The erection-like state caused by the VCD differs in a number of ways from a normal erection. Differences include decreased penile skin temperature, cyanosis and distention of veins of the penis, and increased penile circumference. These changes result from a decrease in penile arterial flow and partial obstruction of all the veins of the penis (superficial and cavernosal). The penis also pivots at the point of constriction, which may require the patient to stabilize the penis during intercourse. The corporal distention that occurs is passive, and the corporal cross-sectional area does not increase to the extent of a natural or pharmacologically induced erection. Penile blood stasis occurs during a vacuum-induced erection, and a state of relative ischemia exists while the constricting band is in place (Broderick, McGahan, Stone, et al., 1992). To reduce the risk of injury to the penis, the vacuum-induced erection should not be overly prolonged.

Constriction bands alone can be used to maintain but not initiate an erection. No reports of the indications for this use or of its efficacy have yet appeared in the peer-reviewed literature, but because constriction bands maintain the rigidity of a vacuum-induced erection, they should be expected to maintain a physiologically normal erection and can be recommended for trial by selected patients.

The panel emphasizes that only prescription VCD equipment should be used. Rings made of metal or other inelastic materials should not be used as constriction bands.

Intracavernous vasoactive drug injection therapy

Clinical use of intracavernous vasoactive drug injection therapy to treat erectile dysfunction was developed independently by Virag (1982) and Brindley (1983), and has since become one of the

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most common and effective methods of treatment. In addition, some men report an increase in frequency of spontaneous erections with regular self-injection therapy (Marshall, Breza and Lue, 1994). Various agents are now available for this therapy and more are being developed. Currently the most widely used drugs, either singly or in combination, are papaverine, phentolamine and PGE_1.

Papaverine is an effective smooth muscle relaxant. Its plasma half-life is one to two hours (Hakenberg, Wetterauer, Koppermann, et al., 1990; Tanaka, 1990), but it remains active within the penis much longer. Patients should be monitored for the development of prolonged erections, corporal nodules and plaques or fibrosis (Needleman, Corr and Johnson, 1985; Seidmon and Samaha, 1989). Currently, papaverine treatment for erectile dysfunction is an off-label use. In addition, its distribution outside of hospital pharmacies has been restricted recently.

Phentolamine is a competitive, nonspecific, alpha-adrenergic receptor antagonist. It is also a smooth muscle relaxant. Phentolamine seldom produces a satisfactory erection when used as a single agent. It has often been used in combination with papaverine, and more recently with PGE_1, to treat erectile dysfunction. The addition of phentolamine speeds the onset of tumescence and rigidity and allows for lower doses of the primary agent. It has a plasma half-life of 30 minutes. Intravenously administered phentolamine (used for treating hypertension) may cause tachycardia, orthostatic hypotension, cardiac arrhythmias, angina pectoris and abdominal pain because of intestinal hyperperistalsis (Needleman, Corr and Johnson, 1985). Fortunately, these effects are rarely, if ever, seen with intracavernous injection of phentolamine (Jünemann and Alken, 1989).

PGE_1, administered with increasing frequency to treat erectile dysfunction, is one of a group of compounds, the prostaglandins, that also occur naturally in the body and mediate a number of diverse physiologic processes (Linet and Neff, 1994). With only slight variations in structure, prostaglandins can produce markedly different effects. For example, whereas PGE_1 is a potent smooth muscle relaxant, another prostaglandin ($PGF_{2\alpha}$) is a potent agent for causing smooth muscle to contract (Hedlund and Andersson, 1985).

Throughout the remainder of this report, PGE_1 is also referred to by the generic name of its synthetic form, alprostadil, the form in which it is administered. Under the trade name Caverject™, alprostadil was approved by the FDA in 1995 for injection therapy to treat erectile dysfunction. Patient and partner satisfaction rates of 70 percent and higher have been reported (Godschalk, Chen, Katz, et al., 1994; Linet and Neff, 1994; Livi, Faggian, Sorbara, et al., 1993; von Heyden, Donatucci, Kaula, et al., 1993).

Prolonged erection may occur, but the most frequent side effect of intracorporeal alprostadil is pain (Jünemann and Alken, 1989; Linet and Neff, 1994; von Heyden, Donatucci, Kaula, et al., 1993). The outcomes balance sheet shows the estimated probability of pain at 23.3 percent. The estimated probability of prolonged erection is 3.1 percent. One case has also been reported of penile curvature and development of a Peyronie's-like plaque after nine months of alprostadil self-injection by the patient (Chen, Godschalk, Katz, et al., 1994).

Use of vasoactive agents

For using intracavernous vasoactive agents, singly or in combination, the first step is an office test injection. Visual sexual stimulation or manual genital stimulation following injection of a test dose may be used to achieve a better result. Following dose titration, it is important to instruct the patient in self-injection, emphasizing clean technique with a sterile solution and needle (Parfitt, Wong, Dobbie, et al., 1992). Patient education in penile anatomy appropriate to intracavernous injection is also important.

The goal of intracavernous vasoactive injection therapy is to achieve an erection that lasts sufficiently long for patient and partner to engage in satisfactory foreplay and sexual intercourse, but the erection generally should not exceed one hour. The patient must be cautioned about the possibility of a prolonged pharmacologic erection, defined as an erection lasting more than four hours or a painful erection of shorter duration. (Prolonged pharmacologic erection is discussed in detail in this section on pages 17 to 18.)

If a prolonged erection occurs, the patient should know how to contact the treating physician or a knowledgeable physician substitute at any time for instructions. If the physician is unavailable, the patient should know to report to the appropriate emergency facility. A physician who prescribes intracavernous vasoactive injection therapy should be familiar with the use of alpha-sympathetic agonists and injection/irrigation protocols for such agents in order to reverse prolonged pharmacologic erections that may occur.

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Long-term followup includes examination regarding corporal fibrosis, review of injection technique and patient adjustment as necessary for satisfaction with this technique.

Intracavernous vasoactive injection therapy has been successfully used in special populations, such as patients with psychogenic erectile dysfunction (Dhabuwala, Kerkar, Bhutwala, et al., 1990; Turner, Althof, Levine, et al., 1989; Weiss, Ravalli and Badlani, 1991); with spinal cord injuries (Bodner, Leffler and Frost, 1992; Earle, Keogh, Ker, et al., 1992); and elderly patients (Kerfoot and Carson, 1991; Richter, Gross and Nissenkorn, 1990). Patients who have psychogenic or neurogenic erectile dysfunction generally require reduced doses of vasoactive agents to achieve satisfactory erections, compared to patients who have diabetic or vascular causes for erectile dysfunction. Elderly patients may require special instruction for injection techniques because of poor hand-to-eye coordination. In some cases, the partner may need to be instructed in injection techniques.

Prolonged pharmacologic erection

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With the use of various intracavernous vasoactive drugs, the iatrogenic prolonged pharmacologic erection has become a concern for physicians. Because the definitive diagnosis of erectile dysfunction etiology is as much a function of diagnostic experience as of reliance on objective testing, prolonged erection following intracavernous vasoactive drug injection is most commonly seen during office diagnostic testing and dose titration and in the early stages of home use.

Patients with a psychogenic or neurogenic etiology are more likely to be sensitive to vasoactive drugs, with a smaller margin of safety between an erection of sufficient rigidity and duration and a prolonged pharmacologic erection that requires treatment. Also, men who fail to achieve an adequate erection following injection of the prescribed dose may proceed to "double-inject" with a variable second dose. The cumulative dose results in an unpredictable response and may increase the risk of prolonged erection.

Definitions of prolonged pharmacologic erection vary in the literature, but the urgency for treatment is uniformly accepted. Prolonged pharmacologic erection is on the priapism continuum and, if left untreated, the subsequent smooth muscle fibrosis and lack of response to vasoactive agents are indistinguishable from classic priapism. As yet, the incidence of significant changes, histologic or clinical, following a prolonged pharmacologic erection is unknown.

The optimal time between onset of erection and the reversal treatment to induce detumescence is also not known. The interval may vary depending on the agents used, with longer intervals for alprostadil compared to papaverine/phentolamine combinations. In the panel's opinion, patients should be instructed to contact their treating physicians when a rigid erection does not subside within four hours. Treatment should occur as soon as feasible. (By the time patients present for treatment, the interim since injection has usually been six to eight hours.) Prolonged pharmacologic erection can eventually result in ischemic priapism with damage to cavernosal smooth muscle tissue because of hypoxia.

In treating prolonged pharmacologic erection, the goal is to restore the flaccid penile hemodynamics; that is, to lower arterial inflow, contract sinusoidal spaces and enhance venous outflow. The patient who presents relatively early may only require aspiration of blood or a single injection of phenylephrine followed by a period of observation. More commonly, it is necessary to reverse the pharmacologic erection using corporal injection or irrigation with alpha-adrenergic agents.

Aspiration and irrigation permit removal of the residual inciting pharmacologic agent as well as the addition of a reversing agent. The most widely used agents are dilute solutions of phenylephrine or epinephrine. One effective method is to aspirate 10 ml of blood followed by injection of 0.5-1 ml of a solution using 10 mg/ml phenylephrine mixed with 19 ml saline (Lue, 1995: personal communication). The choice of phenylephrine is due to its $alpha_1$ selective action and lack of $beta_1$ activity. Metaraminol as a vasoactive agent for the treatment of prolonged pharmacologic erection is to be avoided because of potential hypertensive crisis and death (Lue and McAninch, 1988; Stanners and Colin-Jones, 1984).

Precautions to prevent systemic toxicity include aspiration prior to injection, using low volumes of the reversal agents and the avoidance of injection/aspiration after detumescence is achieved. Because of the potential for hypertension, tachycardia and arrhythmias from systemic absorption, the patient should have blood pressure and heart rate monitoring. Failure to respond to corporal aspiration/irrigation with alpha-adrenergic agents or persistence of hyperviscous ischemic

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blood is an indication for formal corporal shunting by percutaneous or open methods (Grayhack, McCullough, O'Conor, et al., 1964; Quackels, 1964; Sacher, Sayegh, Frensilli, et al., 1972; Wendel and Grayhack, 1981; Winter, 1976).

Penile prosthesis therapy

Penile prostheses can be divided into two general types: nonhydraulic and hydraulic. Nonhydraulic devices are also commonly referred to as semirigid rod prostheses, and hydraulic devices are often referred to as inflatable prostheses. Unless otherwise stated, exposed surfaces of prostheses are made of medical grade silicone.

Nonhydraulic implant types

The American Medical Systems (AMS) Malleable 600 prosthesis is a paired, malleable, silicone, semirigid rod device. Adjustment between sizes is made by adding rear tip extenders. Experience with the AMS Malleable 600 device has been favorable (Dorflinger and Bruskewitz, 1986; Moul and McLeod, 1986). To date no mechanical failures have been reported with this device. A modification, the AMS Malleable 650, has been recently introduced.

The DuraPhase penile prosthesis consists of paired cylinders containing 12 polysulfone segments that articulate with adjacent segments and are movable through an angle of approximately 17 degrees. A stainless steel cable runs through the center of each segment, and a spring on each end maintains constant tension between the segments. Each prosthetic cylinder is covered with polytetrafluoroethylene, and varying sized proximal and distal tips are attached to produce the proper length. This prosthesis design produces better device positionability than other implants. Early experience with the prosthesis has been encouraging (Hrebinko, Bahnson, Schwentker, et al., 1990; Thompson, Rodriquez and Zeidman, 1990). However, in a multicenter study, four cable breaks occurred in 63 implant recipients (Mulcahy, Krane, Lloyd, et al., 1990). The Dura-II prosthesis is a recently introduced, newly designed version replacing the DuraPhase device.

The Mentor Malleable penile prosthesis is a paired, semirigid rod device containing a coiled wire for malleability and enhanced column strength. Length adjustment is made by trimming the prosthesis at the desired cm mark and then applying a standard ±0.5 or ±1 cm tail cap.

The Mentor Acu-Form penile prosthesis is a semirigid rod prosthesis that contains no coiled wires.

Hydraulic implant types

One-piece: The AMS Dynaflex penile prosthesis is currently the only one of this design available. The prosthesis is a paired, hydraulic device totally confined within the corpora cavernosa. The pump for this prosthesis is the distal portion of the device, and the reservoir is the proximal portion. Adjustment between lengths is made by the addition of one or more snap-on rear tip extenders.

Two-piece: Mentor introduced a two-piece prosthesis in 1988. The cylinders of this device are constructed from Bioflex™, a polyurethane polymer. They are connected to a scrotal component, which is both a pump and a fluid reservoir. Rear tip extenders are supplied to make length adjustments. This device was later named the Mentor G.F.S. inflatable prosthesis. After connectors were eliminated from the device, it was renamed the Mark II Inflatable Penile Prosthesis. One patient satisfaction study (Fein, 1994) reported only one mechanical failure with the Mark II in a group of 138 patients followed for 12 to 50 months (mean followup 31.7 months).

American Medical Systems introduced a two-piece prosthesis in 1994. This device, the Ambicor prosthesis, consists of paired corporal cylinders connected to a small scrotal pump. The fluid reservoirs are in the rear tips of the penile cylinders. The cylinders have a nondistensible design. When deflated, the cylinders are partially collapsed and lack significant rigidity. When the scrotal pump is used to transfer fluid into the cylinders, they become full without stretching. Further cycling of the pump then results in high cylinder pressures and penile rigidity. Adjustment between lengths is made by the addition of one or more 0.5 cm rear tip extenders.

Three-piece: The Scott inflatable penile prosthesis manufactured by American Medical Systems is a three-piece device consisting of paired cylinders, a scrotal pump and an abdominal fluid reservoir. The first report by Scott, Bradley and Timm (1973) was followed by numerous reports of clinical experience with this device (Fallon, Rosenberg and Culp, 1984; Fishman, Scott and Light, 1984; Furlow, 1978; Furlow and Barrett, 1984; Furlow, Goldwasser and Gundian, 1988; Furlow and Motley, 1988; Gregory and Purcell, 1987; Kabalin

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and Kessler, 1988a, 1989; Kessler, 1980, 1981; Light and Scott, 1981; Malloy, Wein and Carpiniello, 1979, 1982, 1983, 1988; Merrill, 1983a; Montague, 1983; Montague, Hewitt and Stewart, 1979; Scarzella, 1988; Scott, Byrd, Karacan, et al., 1979; Wilson, Wahman and Lange, 1988; Woodworth, Carson and Webster, 1991).

These reports revealed initially high mechanical complication rates that decreased progressively as improvements occurred in prosthesis design and in implantation techniques. A satisfaction rate of 83 percent was reported for 272 patients who had the prostheses implanted between April 1983 and December 1986 (mean followup 23 months), with a partner satisfaction rate of 70 percent for 265 partners (McLaren and Barrett, 1992).

The AMS 700CX, a three-piece inflatable prosthesis with a redesigned cylinder, was introduced in 1987. The cylinder has three layers: a silicone outer layer that prevents tissue ingrowth into the device, an inner layer consisting of a silicone tube into which fluid is pumped and, between them, a woven-fabric middle layer that controls girth expansion. Reliability in terms of cylinder aneurysms and leaks has improved (Furlow and Motley, 1988; Knoll, Furlow and Motley, 1990; Montague, 1990; Mulcahy, 1988; Nickas, Kessler and Kabalin, 1994; Quesada and Light, 1993; Scarzella, 1993). A smaller version, the AMS 700CXM, is also available.

The AMS Ultrex, a three-piece inflatable prosthesis with a modification of the CX cylinder design, was introduced in 1990. The middle layer of the three-layer cylinder is a fabric that provides both controlled girth and controlled length expansion. In a report concerning length expansion characteristics of this device, the intraoperative pubis to midglans length increase from deflation to inflation varied between 1 and 4 cm with a mean increase of 1.9 cm (Montague and Lakin, 1992).

The Mentor three-piece inflatable penile prosthesis was introduced in 1983 (Brooks, 1988; Engel, Smolev and Hackler, 1986, 1987; Fein and Needell, 1985; Fuerst and Bendo, 1986; Hackler, 1986; Merrill, 1983b, 1986, 1988, 1989). This prosthesis consists of an abdominal fluid reservoir, a scrotal pump and paired cylinders made of the polyurethane polymer Bioflex™, which is stronger than silicone and does not require a controlled expansion fabric.

The current version of the Mentor three-piece prosthesis is the Alpha I Inflatable penile prosthesis, which has a pump preattached to the cylinders (Goldstein, Bertero, Kaufman, et al., 1993; Randrup, Wilson, Mobley, et al., 1993). Length adjustment between sizes is made by the addition of 1, 2 or 3 cm rear tip extenders. A satisfaction study of the Alpha I (Garber, 1994) reported a 98 percent rate of satisfaction for 50 men followed from two to 41 months (average 15 months). Decreased penile length was the most common complaint.

Preoperative preparation for implantation

Preoperative preparation of the implant recipient is directed primarily at reducing the risk of infection. The recipient should be free of urinary tract infection, and he should have no infections elsewhere in the body that might result in bacterial seeding during the healing phase. There should be no dermatitis, wounds or other cutaneous lesions in the operative area. In diabetic implant recipients, good control of diabetes mellitus may reduce the risk of infection (Bishop, Moul, Sihelnik, et al., 1992).

Broad-spectrum antibiotics providing gram-negative and gram-positive coverage are administered prophylactically. Frequently used agents are an aminoglycoside and vancomycin or an aminoglycoside and a cephalosporin. These antibiotics should be administered before the incision is made; they are usually continued for 24 to 48 hours postoperatively.

The operative area is shaved immediately prior to the operation. If shaving is done earlier, small cuts in the skin may become infected. After the patient is shaved, a thorough skin preparation is performed. Penile prosthesis implantation is usually performed under general, spinal or epidural anesthesia, but has been performed under local anesthesia (Dos Reis, Glina, Da Silva, et al., 1993; Kaufman, 1982).

Surgical approaches

Implantation of a penile prosthesis can be performed through a variety of surgical approaches. Those commonly used today include only three: the infrapubic, subcoronal and penoscrotal.

The primary advantage of the infrapubic approach is that it permits reservoir implantation under direct vision. Its disadvantages include possible injury to the dorsal nerves of the penis,

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problems in limitation of corporal exposure and difficulty in scrotal pump fixation.

The subcoronal approach can only be used for nonhydraulic or one-piece hydraulic devices. The primary advantage of this approach is that it allows implantation of a prosthesis with minimal bending of the device. This is important with an implant such as the DuraPhase, where excessive bending during implantation might weaken the cable. Disadvantages include prolonged sensitivity of the incision and possible difficulty in proximal crural dilation from the distal corporotomy.

Advantages of the penoscrotal approach, which was first used for semirigid rod implantation (Barry and Seifert, 1979) and is now used for implantation of all types of penile prostheses, include optimal corporal exposure, avoidance of the dorsal neurovascular bundle and easy pump fixation in the scrotum. The disadvantage of this approach is that it requires blind reservoir placement for three-piece hydraulic devices.

Penile prosthesis implant technique

After corporal exposure through one of the foregoing surgical approaches, longitudinal corporotomies of 2 to 3 cm are made. The corpora are dilated proximally and distally in preparation for device implantation. Proximal and distal measurements are obtained and a device of appropriate length is chosen. Many hydraulic prostheses are now supplied prefilled with normal saline. If the surgeon fills the device, normal saline or an isotonic contrast solution must be used because silicone is semipermeable. After the cylinders are implanted into the corpora, the corporotomies are closed. In the case of a one-piece device, the implantation is now complete. For a two-piece device, a Dartos pouch is made for the pump or pump reservoir. For a three-piece device, after the pump is implanted into a Dartos pouch, entry into the retropubic space is made for reservoir implantation. The empty reservoir is placed into the retropubic space and then filled with isotonic fluid. To avoid autoinflation of the prosthesis postoperatively, the reservoir should only be filled to zero pressure and the cylinders should not be maintained in a state of constant inflation. The components of the prosthesis are then connected using the sutureless connectors supplied by the device manufacturer.

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Venous and arterial surgery

The consensus among research and clinical authorities is that vasculogenic dysfunction constitutes the most common pathogenesis of erectile dysfunction in older men. The possibility of restoring natural function by surgically correcting vascular pathology is appealing, and various techniques have been proposed by different surgeons. However, no definite conclusions can be drawn from the current literature about the efficacy of penile vascular surgery because almost all published studies are based on nonstandardized diagnostic techniques, and nonobjective and uncontrolled followup methods. (See the outcomes analysis on pages 38 to 39 of Chapter 3.)

Venous surgery

Surgery to correct corporovenous occlusive dysfunction generally involves resection and/or ligation of penile veins. Because tests to establish the diagnosis of corporovenous occlusive dysfunction have been incompletely validated, it is likely that the diagnostic criteria for this type of surgery have led to inappropriate selection of some, if not many, patients as candidates for the surgery. Failure rates have been high, especially when long-term followup is reported (Freedman, Costa Neto, Mehringer, et al., 1993; Lue and Donatucci, 1994; *NIH Consensus Statement*, 1992; Rossman, Mieza and Melman, 1990). However, it has been reported that some patients who did not respond positively to intracavernous injection of vasoactive drugs before venous surgery have been able to achieve adequate erections with pharmacologic assistance after venous surgery.

Arterial surgery

Surgical techniques to correct arterial insufficiency of the corpora cavernosa are based on neoarterialization of the dorsal penile artery, cavernous artery and/or deep dorsal vein. The inferior epigastric artery is generally used as the donor vessel. Again, the use of nonstandardized diagnostic techniques and nonobjective, uncontrolled postoperative followup has raised serious doubt about the reliability and reproducibility of these operations (Sharlip, 1991, 1994). In general, arterial revascularization procedures have a limited role in treatment of erectile dysfunction. They may be effective in patients with pure arteriogenic erectile dysfunction caused by pelvic, and possibly perineal, trauma (Sharlip, 1994).

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Chapter 3 – Outcomes of treatments for erectile dysfunction

General categories of outcomes

For purposes of comparative analysis, outcomes of a therapeutic medical intervention can be categorized as either beneficial or harmful (Eddy, 1990, 1992). The benefits and harms of alternative therapies for erectile dysfunction were reviewed and analyzed in detail by the Erectile Dysfunction Clinical Guidelines Panel in developing the practice recommendations in Chapter 4 of this report. Both benefits, such as return to intercourse, and possible harms, such as prolonged erection, are listed with their estimated probabilities in the outcomes balance sheet tables on pages 24 to 25.

Treatment outcomes, desirable and undesirable, are also frequently categorized as direct or indirect outcomes. Direct health outcomes are felt directly by the patient and have a direct impact on the quantity or quality of life. Indirect biologic outcomes are physiologic end points. Used as measures of treatment success or as criteria for choice of treatment modality, indirect outcomes are often of great importance to physicians and clinical researchers although the patients may not view them as important end points per se.

Distinctions between direct and indirect outcomes are evident, for example, in the treatment of benign prostatic hyperplasia (BPH). Improvement of peak urinary flowrate (Q_{max}) and decrease in postvoid residual urine are indirect biologic outcomes from successful active treatment of BPH. These values are important parameters for many physicians. Patients, however, are likely to be more interested in direct health outcomes when choosing a treatment option. Examples of direct outcomes following treatment of BPH are the degree of symptom improvement and the possible occurrence of posttreatment complications, such as urinary tract infection. These outcomes can be felt directly and have an immediate impact on patient quality of life.

Similar distinctions can be made between direct and indirect (biologic) outcomes following treatment of erectile dysfunction. However, in the case of erectile dysfunction, the distinctions are less relevant for the purpose of choosing among treatment options. For this purpose, direct treatment outcomes, such as return to intercourse and patient/partner satisfaction, are usually considered most important by physicians and clinical researchers as well as by patients. Thus, the tables in the outcomes balance sheet show estimates only for direct outcomes.

Treatment of erectile dysfunction is different in a number of ways from treatment of most other diseases. Sexual activity by its nature is intermittent and generally involves a partner whose support is vital to therapeutic success. Moreover, although erectile dysfunction is commonly physical in origin, it can have significant psychological overlays for both the patient and partner. These can affect direct treatment outcomes, such as patient satisfaction and partner satisfaction in individual cases.

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Combined outcomes data

Outcomes balance sheet

The term balance sheet, as applied to display of outcomes information, refers to a table or tables that list "beneficial and harmful health outcomes and their magnitudes, including a range of uncertainty for each" (Eddy, 1992). This form of summary display allows "simultaneous consideration of all the important outcomes."

In the outcomes balance sheet, the tables summarize results following confidence profile (FAST* PRO) meta-analyses of combined outcomes data from the erectile dysfunction treatment literature. The meta-analytic process used is described in Chapter 1. Results are displayed in the tables as outcome probability estimates in decimal form. Estimates can be converted to percentages by moving the decimal point two places to the right. It

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should also be noted that median in these tables is the median of the probability distribution resulting from FAST*PRO meta-analysis. It is not the median of an array of individual study results.

Each treatment modality in the outcomes balance sheet has its own set of outcomes, which may apply only to that modality. For example, prosthesis erosion obviously applies only to prosthesis therapy. Most outcomes listed apply to more than one modality, but not to all modalities. For example, discomfort/pain as a potential outcome of therapy applies to all modalities except oral drug therapy. If an outcome is not relevant to a particular modality, the pertinent cells are shaded. For return to intercourse under prostheses, there is also an explanatory note as to why probability estimates for the outcome are irrelevant for this modality. In the G/P column for each modality, the top number in a cell is the number of patient groups/treatment arms (G) and the bottom number is the total number of patients (P).

The first listing in the outcomes column is return to intercourse. The desired result is an erection or artificial erection sufficient for intercourse. The data for this outcome, as for patient satisfaction and partner satisfaction, were patient/partner reported.

Possible systemic adverse events include hypotension, tachycardia, vasovagal response, liver dysfunction, flushing and dizziness. They apply only to oral drug therapy and vasoactive drug injection therapy. Local adverse events include hematoma, ecchymosis and petechia, which apply only to vacuum device and vasoactive drug injection therapies. Surgical complications include hyperemia, edema, anastomotic failure, surgical morbidity and death.

In the absence of current data in the literature on the amount of patient time necessary for each treatment modality, the panel developed the estimates in Table 2 by consensus.

Limitations in combining outcomes evidence

Those outcome estimates in the balance sheet tables with wide confidence intervals suggest considerable uncertainty in the medical knowledge base. One reason may be data limitations because of the relatively few studies of a given therapy that met panel inclusion criteria (such as having identifiable treatment arms) or because of few studies reporting a given health outcome directly. In some instances, data were insufficient for meaningful estimates even with wide confidence intervals. The balance sheet tables indicate these instances with the notation “No data” in the pertinent cells.

Two major reasons for outcome estimates with wide confidence intervals are:

(1) the wide variability in how studies have reported treatment data, and

(2) wide variations from study to study in the reported incidence of certain outcomes for particular treatment modalities. For example, the reported incidence of complications associated with vacuum devices varies considerably across studies.

The combined analysis may also be weakened by the quality of individual studies. Most data analyzed by the panel came from clinical series. The limitations of including these types of studies are obvious. Yet, if clinical series were not included, little could be said about the benefits and harms of various types of therapy for erectile dysfunction.

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Table 2: Estimated patient time commitments

Treatment modality	Visits to physicians (cumulative time)*	Days lost from usual activities because of surgery
Injection therapy	2.5 to 3.5 days	N/A
Vacuum devices	1 to 1.5 days	N/A
Yohimbine therapy	1 to 1.5 days	N/A
Prostheses	2.5 days	10 to 30 days
Venous surgery	2.5 days	5 to 7 days
Arterial surgery	2.5 days	14 to 28 days

* One visit equals a half day.

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Greater certainty about treatment outcomes can be obtained through well-controlled, randomized studies that test the effectiveness of different therapies in well-defined patient populations. Ideal outcomes data for treatments of erectile dysfunction should include durability of effect, discomforts associated with the treatments and information on partner as well as patient satisfaction.

New outcomes studies, in addition to the development of new therapies in this rapidly changing field, are under way and will make updating of this report necessary. Meanwhile, on the basis of what is known about current therapies, guidance can still be given to physicians and patients dealing with the problem of erectile dysfunction at the present time.

Analysis of treatments and treatment outcomes

The outcomes data used to generate median probabilities in the outcomes balance sheet tables, the sources of these data and the results of data analysis are discussed for each treatment modality in the following sections. Also discussed, in a general analysis of each treatment modality and its outcomes are clinical studies that may not have provided data suitable or sufficient for statistical analysis, but which provided useful information that the panel may have considered in developing treatment recommendations. (For oral drug therapy on this page and venous and arterial surgery on pages 38 to 39, the balance sheet analysis and general analysis are combined.) The overall format of the following sections is structured by treatment modalities, rather than by outcomes, because of the number of outcomes that are treatment specific.

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Analysis of oral drug therapy

Yohimbine treatment

For return to intercourse and patient satisfaction following yohimbine therapy, the outcomes balance sheet shows a probability estimate of only 24.7 percent. This is based on combined data for four patient groups (445 patients). Unfortunately, because of study design and vagaries of diagnosis, the 445 patients treated included a significant number with psychogenic erectile dysfunction. Overall, the adverse events from treatment were minimal and consisted mainly of sympathetic stimulation.

Three of the four patient groups were placebo controlled, with a probability estimate of 11.2 percent for patient satisfaction in the placebo column on the balance sheet. The difference between yohimbine and placebo, given the number of patients involved, does not exclude a pure placebo effect.

Yohimbine does not appear to have a significant role in the treatment of organic erectile dysfunction. Efficacy has yet to be proven, and demonstrations of efficacy will require larger trials of better design.

Other drug treatments

A number of alternative delivery systems, including oral and topical administration, have been investigated for use of drugs to treat erectile dysfunction. In one trial, oral phentolamine (not available in the U.S.) was administered to 85 men with erectile dysfunction, 36 (42.3 percent) of whom achieved full erections sufficient for intercourse (Zorgniotti, 1994). The trial included diabetic patients and patients with nonspecific as well as vascular causes for erectile dysfunction. In a subsequent trial, as part of the same study, using buccal phentolamine, 69 patients each placed a 20 mg tablet of phentolamine mesylate between gum and cheek 20 to 30 minutes before intercourse. Of these 69 men, 22 (31.8 percent) achieved full erections.

In another study, oral trazodone (50 mg three times a day) was administered over a 30-day period to 23 patients with erectile dysfunction believed to be of nonorganic etiology (Kurt, Özkardes, Altug, et al., 1994). A positive response rate of 65.2 percent was reported. However, prolonged erections associated with trazodone have been reported to occur in men with normal erectile function (Saenz de Tejada, Ware, Blanco, et al., 1991).

Oral pentoxifylline was used with 18 couples over a period of 12 weeks (Korenman and Viosca, 1993). Subjects were randomized to pentoxifylline or placebo (double-blind random assignment by hospital pharmacy). Nine of the 18 couples achieved successful intercourse defined as vaginal penetration, orgasm and ejaculation. Three couples had no improvement, and six did not attempt intercourse because of health or family problems.

Topical application of vasoactive drugs has been used to induce pharmacologic erections. Agents

(continues on page 26)

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OUTCOMES
BALANCE SHEET

OUTCOMES OF TREATMENTS		ORAL DRUG THERAPY				VACUUM DEVICES		VASOACTIVE DRUG INJECTION THERAPY							
		G/P[1]	YOHIMBINE	G/P[1]	PLACEBO	G/P[1]	VCD	G/P[1]	Pap Mono	G/P[1]	Pap/Phent	G/P[1]	PGE_1	G/P[1]	
RETURN TO INTERCOURSE	Median:	4	.247	0	no	18	.757	1	.999	10	.714	3	.771	1	.781
	95% CI:	445	.188 - .317	0	data	1,943	.668 - .828	20	.883 - 1.000	672	.588 - .821	77	.642 - .872	146	.706 - .841
PATIENT SATISFACTION[2]	Median:	4	.247	3	.112	20	.763	1	.674	12	.776	2	.706	0	no
	95% CI:	445	.188 - .317	110	.051 - .202	859	.686 - .826	144	.593 - .745	1,112	.666 - .864	19	.442 - .898	0	data
PARTNER SATISFACTION	Median:	0	no	0	no	7	.742	0	no	1	.976	1	.886	0	no
	95% CI:	0	data	0	data	218	.582 - .867	0	data	172	.946 - .992	10	.619 - .989	0	data
DROPOUT	Median:	0	no	0	no	22	.253	2	.640	17	.309	4	.346	2	.158
	95% CI:	0	data	0	data	1,072	.218 - .291	195	.533 - .734	2,074	.227 - .407	253	.098 - .677	262	.067 - .295
SYSTEMIC ADVERSE EVENTS[3]	Median:	2	.067	0	not			4	.070	8	.029	6	.019	0	no
	95% CI:	297	.044 - .102	0	reported			452	.046 - .104	635	.017 - .043	639	.008 - .036	0	data
LOCAL ADVERSE EVENTS[4]	Median:					18	.095	1	.040	9	.147	4	.098	0	no
	95% CI:					884	.054 - .150	136	.013 - .089	1,045	.077 - .242	287	.057 - .151	0	data
DISCOMFORT/PAIN	Median:					20	.188	3	.189	9	.171	9	.233	2	.035
	95% CI:					2,481	.135 - .254	377	.101 - .303	1,059	.076 - .306	856	.175 - .304	262	.011 - .081
PROLONGED ERECTION/PRIAPISM	Median:							10	.093	19	.061	14	.031	3	.035
	95% CI:							997	.049 - .156	2,084	.043 - .085	1,191	.017 - .053	490	.011 - .080
FIBROSIS/NODULES/ PLAQUES	Median:							2	.093	14	.062	4	.001	2	.027
	95% CI:							117	.002 - .452	1,371	.035 - .099	332	.000 - .008	262	.002 - .110
DEVICE PROBLEMS:															
INFECTION	Median:														
	95% CI:														
MECHANICAL DEVICE FAILURE	Median:														
	95% CI:														
PROSTHESIS EROSION	Median:														
	95% CI:														
SURGICAL COMPLICATIONS	Median:														
	95% CI:														

Shaded cells indicate that outcomes are not pertinent to particular modalities.

1 G = Number of groups/treatment arms P = Number of patients

2 Patient satisfaction groups for venous and arterial surgery include only those patients able to return to intercourse

3 Systemic adverse events include hypotension, tachycardia, vasovagal response, liver dysfunction, flushing and dizziness

4 Local adverse events include petechiae, ecchymoses, hematomas, abrasions and discomfort on ejaculation

5 Nonmalleable semirigid prostheses are no longer available

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OUTCOMES
BALANCE SHEET

OUTCOMES OF TREATMENTS		PROSTHESES										VENOUS/ARTERIAL SURGERY			
		G/P[1]	Semirigid[5]	G/P[1]	Malleable	G/P[1]	Mechanical (Nonhydraulic)	G/P[1]	Hydraulic	G/P[1]	Multicomponent Hydraulic	G/P[1]	VENOUS	G/I	
RETURN TO INTERCOURSE	Median: 95% CI:	Intercourse is possible with any functional prosthesis										43 1,801	.433 .378 - .488	19 713	.603 .538 - .664
PATIENT SATISFACTION[2]	Median: 95% CI:	3 80	.533 .302 - .754	8 254	.833 .773 - .880	2 73	.957 .877 - .992	5 177	.644 .539 - .737	12 1,953	.889 .838 - .925	11 515	.438 .357 - .522	11 245	.738 .660 - .803
PARTNER SATISFACTION	Median: 95% CI:	2 43	.540 .270 - .795	2 37	.789 .567 - .932	1 16	.986 .857 - .999	1 12	.581 .312 - .820	4 478	.879 .746 - .959	1 72	.319 .222 - .435	0 0	no data
DROPOUT	Median: 95% CI:														
SYSTEMIC ADVERSE EVENTS[3]	Median: 95% CI:														
LOCAL ADVERSE EVENTS[4]	Median: 95% CI:														
DISCOMFORT/PAIN	Median: 95% CI:	2 212	.144 .044 - .315	4 145	.102 .030 - .233	1 63	.019 .002 - .072	2 118	.087 .012 - .269	5 983	.025 .001 - .050	6 156	.216 .116 - .346	1 11	.192 .040 - .467
PROLONGED ERECTION/PRIAPISM	Median: 95% CI:											8 218	.028 .001 - .059	1 15	.077 .007 - .272
FIBROSIS/NODULES/ PLAQUES	Median: 95% CI:														
DEVICE PROBLEMS:															
INFECTION	Median: 95% CI:	6 695	.025 .015 - .038	9 465	.033 .019 - .051	2 89	.024 .005 - .070	12 1,051	.038 .028 - .051	36 5,133	.025 .021 - .029				
MECHANICAL DEVICE FAILURE	Median: 95% CI:	2 181	.062 .033 - .103	7 476	.046 .031 - .069	2 89	.069 .029 - .134	6 355	.183 .146 - .227	26 2,225	.096 .084 - .109				
PROSTHESIS EROSION	Median: 95% CI:	2 262	.012 .003 - .030	6 242	.039 .019 - .067	1 26	.009 .000 - .091	2 125	.025 .007 - .063	21 2,396	.011 .008 - .016				
SURGICAL COMPLICATIONS	Median: 95% CI:	0 0	no data	0 0	no data	0 0	no data	1 107	.299 .220 - .392	3 531	.055 .038 - .077	27 1,250	.172 .152 - .194	15 377	.215 .176 - .259

Shaded cells indicate that outcomes are not pertinent to particular modalities.

1 G = Number of groups/treatment arms P = Number of patients

2 Patient satisfaction groups for venous and arterial surgery include only those patients able to return to intercourse

3 Systemic adverse events include hypotension, tachycardia, vasovagal response, liver dysfunction, flushing and dizziness

4 Local adverse events include petechiae, ecchymoses, hematomas, abrasions and discomfort on ejaculation

5 Nonmalleable semirigid prostheses are no longer available

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include minoxidil and nitroglycerin pastes. One study (Beretta, Saltarelli, Marzotto, et al., 1993) reported some success with minoxidil, but others have reported poor results (Chancellor, Rivas, Panzer, et al., 1994; Radomski, Herschorn and Rangaswamy, 1994). In a study of transcutaneous nitroglycerin therapy (Meyhoff, Rosenkilde and Bødker, 1992), restored potency was reported in four of 10 patients. Another study reported erections sufficient for vaginal penetration in five of 17 patients (Sønksen and Biering-Sørensen, 1992).

Treatment by vacuum constriction devices: Balance sheet analysis

The outcomes balance sheet shows relatively high probability estimates for return to intercourse, patient satisfaction and partner satisfaction with use of vacuum constriction devices. Included in the combined data from which probability estimates were generated are data from a manufacturer-sponsored study of 1,517 patients (Witherington, 1989). The panel decided to include this study after finding that excluding it did not significantly change any of the probability estimates.

For occurrence of pain, the balance sheet shows an estimated probability of 18.8 percent based on the number of men reporting any degree of discomfort, however minor. Reports specifying the degree of discomfort indicate that severe pain occurs infrequently and that patient dropout because of pain is also infrequent (Papyrus numbers 271, 627, 1091 and 8425 in Table A-1, Appendix A). For local adverse events, there is a probability of 9.5 percent. However, as noted, most complications from use of vacuum device therapy are minor and require no treatment.

General analysis of vacuum constriction device (VCD) therapy

Patient acceptance and satisfaction

The VCD causes penile rigidity sufficient for vaginal penetration in most men regardless of the cause of erectile dysfunction (Aloni, Heller, Keren, et al., 1992; Arauz-Pacheco, Basco, Ramirez, et al., 1992; Bodansky, 1994; Heller, Keren, Aloni, et al., 1992). Only men with extensive scarring and deformity of the penis, such as that caused by an infected penile prosthesis, can be predicted to fail to obtain rigidity with the VCD (Meinhardt, Lycklama, Nijeholt, et al., 1993). Successful use does require careful instruction (Gilbert and Gingell, 1992). Patients are more likely to master use of the VCD when given individual training by a physician or an experienced nurse or medical assistant.

The outcomes balance sheet shows that about 75 percent of those men who obtain a VCD continue to use it regularly. Men who discontinue regular use usually do so within the first three months (Cookson and Nadig, 1993; Meinhardt, Lycklama, Nijeholt, et al., 1993; Sidi, Becher, Zhang, et al., 1990; Turner, Althof, Levine, et al., 1990). The majority of men using the VCD report satisfaction with penile rigidity, length and circumference; frequency of intercourse; and partner satisfaction (Sidi and Lewis, 1992; van Thillo and Delaere, 1992). They also report improvement in self-esteem and sense of well-being. In one study (Cookson and Nadig, 1993), patient and partner satisfaction were 84 percent and 89 percent, respectively, in a group of 115 men followed from 11 to 63 months (mean followup 29 months).

With particular regard to penile rigidity, in response to a questionnaire returned by 161 of 216 users (72 percent) after a median followup of three months, 94 percent of the respondents reported they were satisfied with the hardness of the erection produced by the VCD. A second questionnaire was sent to another group of VCD users after a median followup of 29 months. The questionnaire was returned by 115 of 202 users (57 percent) in this second group, and 92 percent reported satisfaction with the hardness of the erection (Cookson and Nadig, 1993).

The most frequent complaint by men using a VCD is the unnatural interruption of the act of lovemaking to use the device. Some men complain of discomfort on ejaculation, but most do not describe this discomfort as objectionable. Other complaints include numbness of the penis, coldness of the penis, penile pain and difficulty in achieving orgasm.

VCD therapy compared with vasoactive pharmacotherapy

Few studies have been published comparing the VCD with vasoactive injection therapy or comparing the impact of these therapies on the psychological and sexual functioning of the user's sexual partner. In one comparative study focusing on the partner (Althof, Turner, Levine, et al., 1992), women responded equally well to both treatments,

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experiencing significant increases in their levels of sexual arousal and satisfaction, and in frequency of intercourse and coital orgasm. They felt more at ease in their marital relationships, and they spontaneously commented on how relaxed, unhurried, assured and enjoyable sex had become. Negative responses concerned the lack of spontaneity with both therapies, worry about side effects by the self-injection group, and annoyance at the coldness of the penis and need for lubricant by the VCD group.

In studies focusing on the man (Turner and Althof, 1992; Turner, Althof, Levine, et al., 1992), VCD therapy was compared directly with self-injection therapy using papaverine and phentolamine. Both treatment modalities caused a comparable improvement in the quality of erections and frequency of intercourse, and sexual satisfaction was comparably increased over pretreatment levels. The group using self-injection therapy had a 59 percent dropout rate, and plaque-like nodules appeared in 57 percent of the patients. In contrast, the VCD group had only a 16 percent dropout rate, and the most common side effect was blocked ejaculation.

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VCD use in conjunction with vasoactive injections or prostheses

The VCD can enhance the effect of intracavernous vasoactive injections in patients for whom injections alone fail to induce penile rigidity adequate for vaginal penetration (Lue, 1989; Marmar, DeBenedictis and Praiss, 1988; Sidi, Becher, Zhang, et al., 1990). Smooth muscle relaxation caused by pharmacologic agents apparently augments the vacuum-induced tumescence. Ten or 15 minutes should be allowed to pass from the time of injection before the vacuum is applied so as not to induce ecchymosis or hematoma as a result of blood leaking from the injection site.

It is possible that the VCD may be used successfully after removal of a penile prosthesis. It is also possible, when a malfunctioning prosthesis is still in place, that the VCD may be used to obtain rigidity or increase the girth of the penis (Korenman and Viosca, 1992; Sidi, Becher, Zhang, et al., 1990).

VCD complications

The majority of complications from using the VCD are minor and require no treatment. Petechiae often develop on the skin of the penis after use of the VCD, presumably as a result of capillary rupture. These are painless and disappear within 48 hours. Vacuum pressure above 225 mm Hg should be avoided. It is unnecessary and can lead to subcutaneous bleeding. All VCDs should have a vacuum regulator to prevent excessive pressures. Ecchymoses can occur, particularly in men taking aspirin or other anticoagulant drugs, but have caused no problems. In one case study, a single patient developed Peyronie's disease after four years of complication-free use. Approximately five months before presentation, he experienced a severe burning sensation in the left side of the penis at midshaft during creation of the vacuum before placement of the constriction band (Kim and Carson, 1993).

Men whose foreskin is phimotic are at risk for paraphimosis when the penis becomes tumescent and should be circumcised before trying the VCD. Men with spinal cord injuries and other neurologic problems that impair penile sensation should use the VCD with caution (LeRoy and Pryor, 1994; Meinhardt, Kropman and Lycklama, 1990).

Treatment by injection of vasoactive agents: Balance sheet analysis

There is now a considerable body of literature on vasoactive drug injection therapy, although many reports were rejected for data extraction because they did not meet the review criteria outlined on page 11. Studies of papaverine and phentolamine used in combination provided the largest amounts of extractable data. Articles reporting extractable outcomes data for PGE_1 monotherapy (alprostadil) and the now widely used papaverine/-phentolamine/PGE_1 triple therapy were fewer in number. No data were available for PGE_1/phentolamine combination therapy, which consequently is absent from the balance sheet.

For papaverine/phentolamine/PGE_1 triple therapy, the few studies available did not provide sufficient extractable information to generate probability estimates for patient and partner satisfaction or for systemic and local adverse events. The estimated probability for return to intercourse following the triple therapy is based on data from one study (Number 8243 in Table A-1 in Appendix A).

Partner satisfaction data has been reported in few studies for any type of vasoactive drug injection therapy. The partner satisfaction estimates in the balance sheet for papaverine/phentolamine therapy and for PGE_1 therapy are each based on data

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reported in a single study (Number 8524 and Number 8112 in Table A-1), and for the triple therapy no data were available.

General analysis of vasoactive injection therapy

Papaverine monotherapy

Papaverine hydrochloride was the first intracavernous vasoactive agent used to treat erectile dysfunction. Virag (1982) described a bimonthly injection of 80 mg papaverine followed by corporal infusion with heparin solution to maintain a rigid erection for 15 minutes. This in-office therapy proved beneficial after two or more treatments and was subsequently repeated by Virag and other investigators, using larger groups of patients and varying doses of papaverine (Virag, Bouilly, Daniel, et al., 1986; Virag, Frydman, Legman, et al., 1984).

In-office vasoactive therapy did not prove to be as successful as initially hoped; intermittent stimulation therapy did not return the majority of patients to normal sexual function. Thus, attention turned to the development of home pharmacologic erection programs (Brindley, 1986; Gilbert and Gingell, 1991). Home programs are now routine for most patients using vasoactive injection therapy.

It soon became clear that papaverine used as a single agent has a significant risk of prolonged erection and fibrosis as well as systemic reactions. The incidence of prolonged erection following diagnostic and therapeutic use of papaverine as vasoactive pharmacotherapy is shown in Table 3. (Also see pages 17 to 18 for a detailed discussion of prolonged erection.)

Notwithstanding variability in study populations, papaverine doses and definitions of a prolonged erection, prolonged erection is an evident complication of papaverine monotherapy. Statistically significant risk factors for prolonged erection that have been reported are younger age, better quality of spontaneous erection and neurogenic or psychogenic etiology (Lomas and Jarow, 1992).

Data for papaverine-induced corporal fibrosis are also subject to variability in how the data are reported. Moreover, the pathophysiology of corporal fibrosis development is not clearly understood. Proposed mechanisms include microtrauma from needle injection, low pH of the injection solution or microprecipitation of papaverine at physiologic pH (Aboseid, Jüenemann, Luo, et al., 1987; Seidmon and Samaha, 1989). The presentation of fibrosis can be subtle and localized, with changes apparent only on ultrasound examination of the tunica albuginea or corporal tissue. At the other extreme are diffuse changes with complete corporal fibrosis (Brindley, 1986; Buvat, Lemaire, Marcolin, et al., 1986; Desai and Gingell, 1988; Tullii, Degni and Pinto, 1989).

The incidence of fibrosis ranges from one to 33 percent (Brindley, 1986; Buvat, Lemaire, Marcolin, et al., 1987; Ruutu, Lindström, Virtanen, et al., 1988; Tullii, Degni and Pinto, 1989). Fibrotic changes appear to be mostly dose dependent and cumulative, but significant changes following limited injections coupled with prolonged erection have been reported (Corriere, Fishman, Benson, et al., 1988). The appearance of fibrosis may result in a recommendation to discontinue therapy. The natural history of fibrosis after withdrawal of injection therapy is unknown. Another study reported minimal histologic changes of corporal tissue at the

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Table 3: Reported incidence of papaverine-induced prolonged erection

Reference	Papaverine dose (mg)	Number of patients	Incidence
Brindley, 1986	16-120	34	35.3%
Lue, Hricak, Marich, et al., 1985	60	90	18.8%
Virag, 1985	80	227	18.5%
Lomas and Jarow, 1992	60 or 15	400	17%
Bodner, Lindan, Leffler, et al., 1987	7.5-60	20	15%
Cooper, 1991	30-128	20	10%
Pettirossi and Serenelli, 1988	20-110	144	8.3%
Postma, Steffens and Steffens, 1988	25-50	48	6.3%
Gilbert and Gingell, 1991	30-120	194	2.6%

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Table 4: Complications of papaverine/phentolamine combination therapy

Author	Number of patients	Prolonged erections (%)	Fibrosis (%)
Zorgniotti, 1986	97	1.0%	4.1%
Stief, Gall, Scherb, et al., 1988	156	1.9%	1.9%
Goldstein, Payton and Padma-Nathan, 1988	300	2.3%	–
Girdley, Bruskewitz, Feyzi, et al., 1988	78	23%	16%
Robinette and Moffat, 1986	101	6.9%	–
Nellans, Ellis and Kramer-Levien, 1987	69	8.7%	1.4% *
Levine, Althof, Turner, et al., 1989	111	1.8%	57%

*Painless nodules at 12 months

time of prosthesis implantation after failure of papaverine vasoactive pharmacotherapy (Sidi, Cherwitz and Becher, 1989).

Systemic reactions of pallor, dizziness, facial flushing and sweating have been reported following the use of papaverine (Lue, Hricak, Marich, et al., 1985; Sidi and Chen, 1987; Wespes and Schulman, 1988). Tanaka (1990) measured systemic papaverine levels following corporal injection and noted that patients who had a poor erectile response had statistically higher peripheral blood levels, suggestive of corporovenous occlusive dysfunction.

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Papaverine/phentolamine combination therapy

In an effort to increase the safety profile of vasoactive pharmacotherapy, Zorgniotti and Lefleur (1985) combined papaverine with phentolamine. In 250 patients evaluated with a solution of 30 mg papaverine and 1 mg phentolamine, 72 percent of the patients achieved an erection satisfactory for intercourse and 97 percent of these patients went on to self-injection with excellent response and a low dropout rate (Zorgniotti, 1986). A prolonged erection occurred in four of the diagnostic injections (1.6 percent), but in only one on home therapy. Four of the 97 patients on home therapy (4.1 percent) developed fibrotic changes confined to the tunica albuginea, prompting discontinuation of therapy.

As indicated previously, papaverine/phentolamine therapy has been widely studied. Efficacy studies of this therapy, compared to placebo or with papaverine and phentolamine alone, demonstrate superior efficacy of the combination in men with organic erectile dysfunction (Gasser, Roach, Larsen, et al., 1987; Stief and Wetterauer, 1988). Reported rates for patient satisfaction typically exceed 75 percent (Gall, Sparwasser, Bähren, et al., 1992; Goldstein, Payton and Padma-Nathan, 1988; Robinette and Moffat, 1986; Sidi, Reddy and Chen, 1988; Stief, Gall, Scherb, et al., 1988). Reported complication rates vary (Table 4), but in general they compare favorably with reported complication rates for papaverine monotherapy.

Girdley, Bruskewitz, Feyzi, et al. (1988) reported on 78 patients, of whom 93.5 percent had at least one complication (primarily transient pain with injection). Prolonged erection (more than six hours) occurred in 23 percent. In spite of the complications, 69 percent of the patients rated the therapy acceptable.

A study of 33 diabetic men using papaverine/phentolamine injection therapy reported a higher failure rate, with 12 satisfactory responses and 21 unsatisfactory responses (Bell, Cutter, Hayne, et al., 1992). The only significant difference between the two groups was age. Only one of 14 patients over age 60 had a satisfactory response, whereas 11 of 19 patients under age 60 had satisfactory responses.

Armstrong, Convery and Dinsmore (1993) reported papaverine/phentolamine treatment results for 160 patients with diverse etiologies, including diabetes. Positive response rates were reported by etiology as follows: vasculogenic (50 patients), 48 percent; psychogenic (41 patients), 93 percent; neurogenic (25 patients), 92 percent; diabetic (22 patients), 68 percent; idiopathic (8 patients), 63 percent; traumatic (5 patients), 60 percent; alcohol related (5 patients), 80 percent; drug related (4 patients), 75 percent.

Table 4 summarizes the incidence of prolonged erection and corporal fibrosis associated with papaverine/phentolamine combination therapy.

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PGE1 monotherapy (alprostadil)

The clinical use of PGE1 began with the observation of Ishii, Watanabe, Irisawa, et al. (1989) that patients receiving intravenous PGE1 for peripheral vascular disease also experienced less erectile dysfunction. This prompted the authors to use intracavernous PGE1 at the same dose (20 µg) as that used in intravenous therapy. The onset of action was rapid, within two to three minutes after injection. Full or partial erections were observed in 86 percent of 135 patients with various erectile dysfunction etiologies. Patients with previous pelvic fracture or diabetes mellitus were less likely to respond favorably. The duration of erection was one to three hours, and no patient had a prolonged erection requiring reversal. Dull penile pain following injection was present in "a limited number" of patients.

In direct comparisons of PGE1 with papaverine monotherapy, more favorable responses and fewer prolonged erections were noted with PGE1 (Buvat, Buvat-Herbaut, Dehaene, et al., 1986; Buvat, Lemaire, Marcolin, et al., 1986; Chen, Hwang and Yang, 1992; Earle, Keogh, Wisniewski, et al., 1990; Kattan, Collins and Mohr, 1991; Mahmoud, el Dakhli, Fahmi, et al., 1992; Sarosdy, Hudnall, Erickson, et al., 1989). PGE1 was also compared favorably with papaverine/phentolamine combination therapy (Lee, Stevenson and Szasz, 1989; Lui and Lin, 1990).

The most notable adverse outcomes reported for PGE1 therapy were painful injections and/or diffuse penile pain during erection (Buvat, Lemaire, Marcolin, et al., 1986; Chen, Hwang and Yang, 1992). The lack of systemic side effects was attributed to the local metabolism of PGE1 and the rapid first pass clearance in liver and lung tissue (Hamberg and Samuelsson, 1971; Hedlund and Andersson, 1985).

PGE1 therapy has been used for patients who failed to respond to office testing with papaverine or who had limited success with home injection. Reiss (1989) reported on 12 patients, two of whom had a gradual loss of papaverine response over several months. A dose range of 5 to 20 µg PGE1 was used. All 12 patients reported erections sufficient for intercourse, and seven began a home injection program with good results.

Ravnik-Oblak, Oblak, Vodusek, et al. (1990) used PGE1 in 41 patients with erectile dysfunction due to diabetes mellitus and noted a response sufficient for intercourse in 29 of the 41 (71 percent).

Schramek, Dorninger, Waldhauser, et al. (1990) used PGE1 for diagnosis and therapy in 149 men with erectile dysfunction. A vasculogenic etiology was present in 72 percent of the men, psychogenic in 17 percent, neurogenic in 10 percent and diabetic in 1.0 percent. Seventy-nine percent responded to 5 to 40 µg PGE1, injected in the office, with an erection sufficient for intercourse. Three patients (2.0 percent) had prolonged erections of more than seven hours that required treatment. All three had a nonvasculogenic etiology. Overall, 40 percent of the patients reported pain with injection and/or erection. Sixteen percent had severe penile discomfort following injection. Again this side effect was significantly greater in patients with a nonvasculogenic etiology. Of 11 patients who went on to home injection therapy, with a mean followup of seven months, nine had good responses with no side effects, except for one patient who had tolerable pain during injection.

Gerber and Levine (1991) reported on 72 patients in a PGE1 home pharmacologic erection program. Thirty-seven patients (51 percent) failed to continue beyond the in-office dose titration/teaching period. Another 15 patients discontinued therapy later, for a total dropout rate of 72 percent. The most common reason for dropout was penile pain following injection (17 percent). Failure to achieve adequate erection with PGE1 was a reason for dropout in an additional 12.5 percent of patients. There were no instances of prolonged erection, significant hematoma, systemic reaction or cavernous fibrosis in the patients continuing with the pharmacologic erection program.

The problem of pain following PGE1 injection was addressed in a study of 24 patients with a history of PGE1-induced pain (Schramek, Plas, Hübner, et al., 1994). The authors reported a significant decrease in incidence of local pain using a combination of 20 µg PGE1 and 20 mg procaine.

In summary, PGE1 is an effective vasoactive agent for the diagnosis and treatment of erectile dysfunction. Specific advantages of PGE1, in comparison with papaverine or papaverine/phentolamine combination therapy, are its reliable dose response and rapid metabolism in the corpora, which results in a lower incidence of prolonged pharmacologic erection. In addition, the incidences of systemic side effects and delayed cavernous fibrosis are significantly lower, perhaps due to the rapid local metabolism of PGE1 or its potential for membrane stabilization.

On the negative side, PGE1 is more likely than other agents to result in pain with injection and/or erection to a degree that may prevent the patient

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from continuing therapy. Other disadvantages that may limit widespread acceptance of PGE_1 are relatively high cost per dose, limited shelf life and need for refrigeration.

As noted on page 16, PGE_1 (alprostadil) was approved by the FDA in 1995 for intracorporeal injection under the trade name Caverject™. It is available in single-dose vials with 10 or 20 µg of lyophylized powder.

Papaverine/phentolamine/PGE_1 (P/P/P) combination therapy

Each of the individual vasoactive agents described in the preceding sections has associated limitations at physiologically active dose concentrations. These shortcomings prompted the combining of papaverine, phentolamine and PGE_1 for therapy (Bennett, Carpenter and Barada, 1991). As each agent acts on a specific site in the erection process, resulting in smooth muscle relaxation and arterial inflow, it is possible to take advantage of synergism at very low doses of each individual agent. The widely used original formulation is shown in Table 5. Other investigators have subsequently reported successful results with different formulations (Allen, Engel, Smolev, et al., 1992; Govier, McClure, Weissman, et al., 1993; Montorsi, Guazzoni, Bergamaschi, et al., 1993a; Montorsi, Guazzoni, Bergamaschi, et al., 1994).

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Table 5: Formulation of papaverine/phentolamine/PGE1 solution

Vasoactive agent	Dose (ml)
Papaverine HCL (30 mg/ml)	2.50
Phentolamine (5 mg/ml)	0.50
Alprostadil (500 µg/ml)	0.05
0.9% Saline for injection	1.20
Total volume	4.25

Bennett et al. performed a diagnostic evaluation of 116 patients with the P/P/P combination using a starting volume of 0.25 ml containing a total of 4.4 mg papaverine, 0.15 mg phentolamine and 1.5 µg PGE_1. A lower dose was used in patients with suspected psychogenic and neurogenic etiology. Eighty-nine percent of the patients had a positive response and went on to home injection therapy. Overall, 78 patients (74 percent) were maintained at a volume of 0.25 ml per injection with a frequency of use averaging 3.1 times per month. Two patients (1.9 percent) had prolonged erections (greater than six hours) requiring treatment; both had a psychogenic etiology. Two patients (1.9 percent) complained of pain at the injection site or with intercourse, prompting one to discontinue therapy. With an average followup of 12.7 months, no patient had corporal fibrosis.

In a later study (Barada and Bennett, 1991), 110 patients with 12 to 28 months of followup were contacted. Sixty-five percent continued injection therapy. Of these, 89 percent were satisfied with the drug combination as a treatment option. Seven prolonged erections (5.6 percent) greater than three hours occurred, but only one patient required intervention. No patient treated exclusively with P/P/P therapy developed fibrosis or nodules.

Goldstein, Borges, Fitch, et al. (1990) used a similar combination of P/P/P in 32 patients who had failed previous pharmacotherapy with papaverine/phentolamine or PGE_1 alone. Twenty patients (62 percent) had erections sufficient for satisfactory intercourse. Eight patients (25 percent), six of whom were diabetic, reported pain with injection. No systemic side effects or prolonged erections were seen.

Hamid, Dhabuwala and Pontes (1992) used Bennett's formulation (Table 4) in 100 consecutive patients with erectile dysfunction at a dose range of 0.05 to 0.35 ml. A positive response was seen in 88 patients, and only five complained of pain at the injection site. One patient required corporal aspiration for a prolonged (four hours) erection.

McMahon (1991), in a randomized crossover study of 228 patients, compared the P/P/P combination with papaverine/phentolamine and PGE_1 alone. In men with severe arteriogenic or mild corporovenous occlusive disease, P/P/P was significantly better, with a lower incidence of prolonged erection when compared to papaverine/phentolamine (0.9 versus 7.9 percent).

In summary, a combination of papaverine, phentolamine and PGE_1 has been used for the treatment of erectile dysfunction. The available data indicate that this vasoactive agent combination has a success rate equivalent to that of PGE_1 alone, with a lower cost and lower incidence of painful erections than PGE_1 alone (see the outcomes balance sheet). Further clinical evaluation is required to determine the long-term effects of this combination therapy.

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Investigational injection therapies

Other injection therapies currently being investigated include a combination of PGE_1 and calcitonin gene-related peptide (CGRP). In one study, the combination (10 µg PGE_1 + 5 µg CGRP) was tested: (1) in 28 patients who had venous leakage and failed penile venous surgery; (2) in another 28 patients with venous leakage who declined surgery; and (3) in 12 patients without venous leakage who had a poor response to maximum doses of papaverine/phentolamine injection therapy (Truss, Becker, Thon, et al., 1994). The first group of 28 patients responded with 19 erections sufficient for intercourse (67.9 percent), and the second group of 28 with 20 full erections (71.4 percent). Of the 12 patients who had failed papaverine/phentolamine therapy, 11 (91.7 percent) responded with erections sufficient for intercourse. No significant side effects were reported in any group.

In another experimental study, the same PGE_1/-CGRP combination and dosage were used in 59 nonresponders to papaverine/phentolamine therapy (Djamilian, Stief, Kuczyk, et al., 1993). Thirty-three patients (56 percent) achieved full erections. The combination was used also in six patients who had cavernous fibrosis from papaverine/phentolamine therapy. Five of the six (83 percent) had full erections. Two patients in the group of 59 experienced penile pain. There were no other side effects in either group.

In a study of the nitric oxide donor linsidomine chlorhydrate (SIN-1) as treatment for erectile dysfunction, 63 patients were injected with 1 mg SIN-1 (Stief, Holmquist, Djamilian, et al., 1992). Twenty-nine patients (46 percent) had full erections. There were no side effects. However, Wegner and Knispel (1993) reported that in 30 patients with venous leakage, responses to 1 mg SIN-1 were no more successful, and in 22 patients less successful, than the responses to 20 µg PGE_1.

In summary, injection therapy with new drugs or combinations appears possible, but as yet no new drugs or combinations superior to those already established have emerged.

Pharmacotherapy dropout

The couple who selects intracavernous pharmacotherapy for treatment must be sufficiently motivated to begin a therapy that may involve a period of frustration as the technique is mastered and dosing is adjusted. The patient has multiple opportunities to reject or discontinue therapy during the diagnostic/teaching phase, the early home injection phase or later. This may result in a relatively high rate of patient dropout compared with other therapies, although it does not necessarily mean that these patients will select penile prostheses or vacuum devices as an alternative therapy.

Unfortunately, although dropout rates are reported in the literature for vasoactive pharmacotherapy, the reasons for discontinuing and the identification of subsequent alternative therapies are not well described. Also, some reasons for discontinuing, such as loss of partner or deteriorating health, may be unrelated to treatment-associated problems (Armstrong, Convery and Dinsmore, 1993; Irwin and Kata, 1994).

Reported dropout rates have ranged from zero to 72 percent (Hollander, Gonzalez and Norman, 1992; Gerber and Levine, 1991; Stackl, Hasun and Marberger, 1988). Most studies report approximately 30 percent dropout with at least a six-month followup. For papaverine/phentolamine combination therapy, the outcomes balance sheet shows an estimated probability for dropout of 30.9 percent (95% CI: 0.227-0.407), based on a FAST*PRO meta-analysis of combined data from 17 studies (2,074 patients).

Althof, Turner, Levine, et al. (1989) evaluated 131 patients for a vasoactive pharmacotherapy program. A cumulative dropout rate of 46 percent was observed. The highest dropout risk occurred in the diagnostic/teaching phase, with patients who declined therapy accounting for approximately three-quarters of the total dropouts. Once the patient was entered into home therapy, the dropout rate decreased dramatically. The primary reasons for late dropout were loss of treatment effectiveness and the cost of treatment (medication, supplies and followup). Listed in the box below are potential reasons for dropout, some of which may occur in

Potential reasons for discontinuing vasoactive pharmacotherapy

- Inadequate response to medication
- Return of spontaneous erections
- Fear of needles/injection
- Concern over side effects
- Dissatisfaction with artificial erection
- Lack of spontaneity
- Lack of partner support/ satisfaction
- Financial
- Complications of therapy:
  - Pain following injection
  - Prolonged erection
  - Systemic reaction to injection
- Significant life event:
  - Loss or death of partner
  - Major illness/operation
  - Social stressors, such as job loss or marital discord

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patients who can achieve a satisfactory erectile response to intracavernous pharmacotherapy.

Cooper (1991) examined the reasons for dropout in a small group of patients and found that patients who discontinued therapy were more likely to have a poor relationship with a sexual partner or have a partner who was not regularly available. All patients who discontinued pharmacotherapy had a relative decline in libido during its use.

Van Driel, Mooibroek, Van de Wiel, et al. (1991) followed 152 patients who were considered candidates for intracavernous pharmacotherapy with papaverine or papaverine/phentolamine. Fifty-three patients (34.9 percent) declined injection therapy. The remaining 99 patients (65.1 percent) entered into therapy. Seventy-six of the 99 (77 percent) were able to attain a functional erection during the dose titration phase. Of these, 18 (24 percent) discontinued therapy early in the program, generally for reasons of fear of injection, episodes of prolonged erection or inconsistency of erectile rigidity. At two-year followup, 32 additional patients (44 percent) had discontinued therapy, many for the same reasons, but others because they had a return of normal erections or a loss of sexual interest. Cumulatively, 82 percent (126/152) were considered dropouts or treatment failures. This study indicates that despite the utility of vasoactive pharmacotherapy for treatment of erectile dysfunction, many men will not accept this treatment option or will terminate therapy early.

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Treatment with penile prostheses: Balance sheet analysis

The outcomes balance sheet table for prostheses displays a range of probability estimates for patient satisfaction with various types of devices. Nonmalleable semirigid rods, which have the lowest patient satisfaction probability, are no longer available. Nevertheless, for historical purposes, the panel decided to extract and combine the data reported in the literature for semirigid prostheses. The estimated outcome probabilities for mechanical (nonhydraulic) prostheses were derived from combined data reported for DuraPhase/Dura-II (Dacomed) devices. (For a description, see page 18.)

The balance sheet table shows estimated probabilities for three undesirable outcomes: infection, mechanical failure and erosion. These device problems usually require reoperation.

One of the clearest differences in the balance sheet table between types of devices with regard to device problems is the difference between hydraulic and nonhydraulic devices for probability of mechanical failure. The table shows, for example, a 9.6 percent estimated probability of mechanical failure for a multicomponent prosthesis compared with a 4.6 percent probability estimate for a malleable prosthesis. Although the multicomponent device offers more natural flaccidity and more natural erections, as pointed out on page 43, the risk of reoperation because of mechanical failure is greater.

General analysis of penile prosthesis implantation

Satisfaction

Most satisfaction studies after penile prosthesis implantation have been retrospective. Some involved only the recipient (Berg, Mindus, Berg, et al., 1984; Beutler, Scott, Rogers, et al., 1986; Hollander and Diokno, 1984; Telang and Farah, 1992). Others involved the recipient and his partner (Beutler, Scott, Karacan, et al., 1984; Schlamowitz, Beutler, Scott, et al., 1983). These studies indicate generally reasonable levels of satisfaction postoperatively although satisfaction rates are not as high as surgical success rates. Presumably the patients or couples who were dissatisfied postoperatively despite good surgical results did not have their expectations met.

Generally satisfactory results have been reported for penile prosthesis implantation in patients whose erectile dysfunction was caused by spinal cord injury or diabetes (Dietzen and Lloyd, 1992; Jaworski, Richards and Lloyd, 1992; Perkash, Kabalin, Lennon, et al., 1992). In a report of men with Peyronie's disease treated with semirigid rod implants, 48 patients and 29 partners were followed for a minimum of five years. Only 23 patients (48 percent) and 12 partners (40 percent) were satisfied with the long-term result (Montorsi, Guazzoni, Bergamaschi, et al., 1993b). However, in another report (Wilson and Delk, 1994), 118 of 138 patients with Peyronie's disease (86 percent) were successfully treated using an inflatable three-piece prosthesis together with a new technique of manual penile modeling over the prosthesis.

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Complications

The frequency of many complications occurring during and after penile prosthesis implantation can be minimized by careful attention to detail and proper technique before, during and after the operation. Nevertheless, even the most careful surgeon will have some patients who experience various complications, and the ability to properly recognize and manage these problems is essential.

Patients familiar with the publicity about silicone breast implants may be concerned about possible complications from silicone in penile prostheses. No evidence has been reported in the medical literature demonstrating a health risk from silicone prostheses, and it is the firm opinion of this panel that no such health risk exists.

Infection

Infection is the most significant complication of penile implant surgery (Carson and Robertson, 1988; Thomalla, Thompson, Rowland, et al., 1987). It usually requires reoperation and frequently requires device removal. After an infected penile prosthesis is removed, cavernosal fibrosis occurs, making the penis smaller. Implantation of another prosthesis at a later date is not a significant problem with regard to pump or reservoir placement. However, implantation of new cylinders is often very difficult. Also, in the panel's opinion, the risk of infection is greater for revisions than for primary implantations (Quesada and Light, 1993).

The overall incidence of infection associated with penile prostheses has been estimated to be about two percent with infection rates of 0.6 to 16.7 percent for nonhydraulic devices, 3.0 to 8.1 percent for one-piece hydraulic devices and 0.8 to 8.0 percent for three-piece hydraulic devices (Moul and Carson, 1989). Most periprosthetic infections are the direct result of the implant procedure, but late hematogenous spread of infection from distant sources has been shown to occur (Carson and Robertson, 1988).

Staphylococcal organisms are found in more than 50 percent of infections, with the remainder of infections usually caused by gram-negative bacteria (Kabalin and Kessler, 1988b; Licht, Montague, Angermeier, et al., 1995; Montague, 1987; Persky, Luria, Porter, et al., 1986). From 5 to 7 percent of prostheses may become infected with *Staphylococcus epidermidis* at time of implantation, developing into a subclinical state of infection manifested by chronic pain (Parsons, Stein, Dobke, et al., 1993). In a study of 269 patients who underwent penile prosthesis implantation between 1979 and 1989 (Radomski and Herschorn, 1992), the authors reported that perioperative antibiotics, intraoperative shave and scrub and strict surgical technique resulted in a low prosthesis infection rate (1.9 percent). The authors also concluded that despite the precautions, a group of patients exists who are at risk for urinary tract infection because of predisposing conditions, such as neurogenic bladder, diabetes or ileal conduit.

Unusual infectious complications reported in the literature are fungal infections (Peppas, Moul and McLeod, 1988); gonococcal infections (Nelson and Gregory, 1988); and Fournier's gangrene (Walther, Andriani, Maggio, et al., 1987). Penile necrosis occurs rarely (Bejany, Perito, Lustgarten, et al., 1993; Bour and Steinhardt, 1984; Shelling and Maxted, 1980). It is sometimes caused by infection, but can also be caused by ischemia related to other factors. To help avoid penile necrosis after prosthesis implantation, pressure dressings on the penis are either not used or are applied with minimal compression of the penile tissues.

An early sign of infection is adherence of the skin and subcutaneous tissue to an underlying prosthesis component. This condition is most frequently seen in the scrotum where the scrotal tissues become adherent to the pump. The tissue adherent to the pump gradually becomes thinner, and eventually pump erosion occurs. Other signs of infection include persistent pain, swelling and erythema of tissue, fever and purulent drainage.

The cause of bacterial adherence to the prosthesis has been shown to be the ability of bacteria to produce an extracellular matrix or glycocalyx composed of polysaccharides. This glycocalyx acts as a physical barrier and impedes antibiotic and host defense mechanisms (Thomalla, Thompson, Rowland, et al., 1987). Superficial wound infections will usually respond to standard treatment, but deep infections in the periprosthetic space will usually not clear even with intensive antibiotic therapy. Because of adherence of bacteria to the prosthesis, removing all the prosthetic material is important when prosthesis explantation is required. Standard treatment in the past has been to reimplant a new prosthesis at a later date. However, because of the difficulty with prosthesis implantation into fibrotic corpora, alternative methods of dealing with infection have been sought.

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Furlow and Goldwasser (1987) introduced the concept of a salvage procedure for dealing with penile prosthesis erosion. They were able to successfully salvage 16 of 22 cases of scrotal pump erosion, eight of eight cases of reservoir erosion and zero of two cases of cylinder erosion. Because erosion is often associated with infection, salvage procedures are now considered reasonable alternatives for dealing with infection. In a salvage procedure for infection, all prosthetic material is explanted and cultures are taken. The operative field is irrigated with copious amounts of saline and antibiotic solution; all new prosthetic material is then implanted.

Infection in diabetic, spinal cord injured and renal transplant patients

The literature provides no clear preponderance of evidence that diabetic men either are or are not at greater risk than nondiabetics for incurring infection following prosthesis implantation. Some studies suggest increased risk (Kaufman, Linder and Raz, 1982; Small, 1978; Wilson, Wahman and Lange, 1988). Other studies find no evidence of increased risk (Kabalin and Kessler, 1988b; Montague, 1987; Thomalla, Thompson, Rowland, et al., 1987). Investigators agree, however, that infectious complications which occur in diabetic patients are potentially more severe than in nondiabetic men. The data in one study (Bishop, Moul, Sihelnik, et al., 1992) indicate that preoperative elevated glycosylated hemoglobin values (11.5 percent or higher) may correlate with an increased incidence of prosthesis infection in diabetic men.

Patients with spinal cord injury (SCI), in the panel's opinion, are at greater risk than non-SCI patients for infection and erosion following prosthesis implantation. Rates of prosthesis-associated infection reported in the literature for SCI patients tend to be high (Dietzen and Lloyd, 1992).

Renal transplant patients who undergo placement of a prosthesis are not per se at greater risk for prosthesis-associated infection and erosion, in the panel's opinion and as indicated by recent reports (Hill, Jordon and Bahnson, 1993; Rowe, Montague, Steinmuller, et al., 1993). However, as with diabetic men, there is agreement that infectious complications, when they occur, are potentially more severe in renal transplant patients.

Fibrosis

The most common cause of significant fibrosis is infection following previous penile prosthesis implantation. Fibrosis can be severe following priapism and can lead to significant difficulties with prosthesis implantation (Bertram, Carson and Webster, 1985). Fortunately, priapism resulting in fibrosis is rather uncommon. Fibrosis associated with intracavernous pharmacotherapy has been reported and consists of intracorporeal nodules and plaques, as in Peyronie's disease (Lakin, Montague, Mendendorp, et al., 1990). The degree of fibrosis in men who have been on intracavernous pharmacotherapy is rarely severe, and prosthesis implantation is usually accomplished with only minimal difficulty in such patients.

Peyronie's disease causes fibrotic plaques which occur within the tunica albuginea of the corporal bodies. Cavernosal smooth muscle is not usually affected, and the corpora are usually easy to dilate. If a malleable semirigid rod prosthesis is implanted, the penis can often be straightened by bending the prosthesis (Montague, 1984). With an inflatable penile prosthesis and sometimes with nonmalleable semirigid rod devices, plaque excision or incision or a Nesbit procedure may be necessary to correct penile curvature (Eigner, Kabalin and Kessler, 1991; Knoll, Furlow and Benson, 1990; Subrini, 1984).

Penile fibrosis may occur in implant recipients as a result of one or more of the previously described conditions (infection, priapism, Peyronie's disease, intracavernous pharmacotherapy) and following radiation therapy. Idiopathic penile fibrosis may also be encountered unexpectedly during prosthesis implantation, and the surgeon should be prepared to deal with this problem.

Erosion

A common cause of erosion is tissue injury during the implant procedure. If the urethra is entered, the implant procedure, at least on that side, should be abandoned. Lateral perforation of the tunica albuginea can still permit prosthesis implantation if another more medial plane for dilation is established and the perforation is closed. If the crus is perforated during proximal corporal dilation, usually the crus can still be adequately dilated down to its bone attachment. A rod prosthesis or hydraulic cylinder can then be inserted, making certain that the proximal end of the prosthesis does not extend through the perforation. Alternatively, a Dacron™ or polytetrafluoroethylene sock can be constructed to prevent prosthesis migration out into the perineum (Fritzler, Flores-Sandoval and Light, 1986; Mulcahy, 1987).

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Infection is also a common cause of erosion, and it is not always possible to tell whether erosion occurred because of infection or other factors. This makes the true incidence of periprosthetic infection difficult to judge. Erosion with or without infection requires device removal either with a salvage procedure or reimplantation at a later date.

Erosion can occur because of ischemia, which may be associated with many contributing factors. This is particularly true if the prosthesis is too long to fit in the corpora without pressure. Lack of sensation, usually associated with spinal cord injury, contributes to erosion. Radiation therapy, diabetes mellitus and atherosclerosis may also contribute to erosion. Finally, ischemic erosion and gangrene may result from a pressure dressing or urethral catheter (Steidle and Mulcahy, 1989).

After cystectomy, the retropubic space is part of the abdominal cavity. Placement of a reservoir in a standard fashion results in intraperitoneal reservoir placement, which has been associated with various complications. These include small bowel obstruction (Nelson, 1988); erosion into an ileal conduit (Godiwalla, Beres and Jacobs, 1987); and erosion into small and large bowel (Singh and Godec, 1992). If a three-piece hydraulic prosthesis is implanted in a patient who has had a cystectomy, extraperitoneal reservoir implantation through a separate incision can be performed.

Erosion of reservoirs into the bladder has been reported (Dupont and Hochman, 1988; Fitch and Roddy, 1986; Furlow and Goldwasser, 1987). A salvage procedure is usually advisable in these cases. Scrotal pump erosion is most often a manifestation of infection, and prosthesis removal with reimplantation at a later date or a salvage procedure should be done. Furlow and Goldwasser (1987) reported 22 salvage procedures for eroded pumps with success in 16 cases.

Sizing errors

Inadequate distal dilation of the corpora and placement of a prosthesis that is too short will result in poor support of the glans penis. This is commonly referred to as an SST deformity because of its resemblance to the nose of the supersonic transport aircraft. This is not only a cosmetic but a functional deformity because poor glanular support usually causes pain during coitus. Treatment involves removal of the prosthesis. Long Metzenbaum scissors are then inserted distally, and the fibrous capsule is perforated with the scissors. Hegar dilators are used to dilate the distal portion of the corpora. New measurements are taken and a longer prosthesis is implanted. Alternatively, a dorsal subcoronal incision can be made, and subcutaneous horizontal mattress sutures can be placed to pull the dorsal aspect of the glans back onto the distal penile shaft (Ball, 1980; De Stefani, Simonato, Capone, et al., 1994). Care should be taken so that these sutures do not injure the dorsal neurovascular structures or damage an underlying hydraulic device.

Placement of a hydraulic cylinder that is too long will result in buckling or folding of the cylinder, which may result in early cylinder wear and fluid loss. With the AMS Ultrex cylinder, in which elongation takes place, a cylinder that is too long can result in an S-shaped deformity of the penis when the cylinders are inflated. For this reason, it is advisable to implant AMS Ultrex cylinders that are 1 cm shorter than usual. An SST deformity is unlikely since these cylinders lengthen with inflation.

Implantation of a nonhydraulic or semirigid rod prosthesis, as already mentioned, may result in erosion. An earlier sign is persistent pain. Penile pain following prosthesis implantation generally persists for one to two months. Pain that lasts beyond this time may be due to infection or a prosthesis that is too long. Treatment of pain due to an oversized prosthesis involves removal of the prosthesis, resizing of the corporal bodies and implantation of a shorter device.

Insufficient length and/or rigidity

Penile prosthesis recipients frequently complain that their new erection is shorter than their former natural erection. This complaint is inherent in prosthetic treatment of erectile dysfunction, only partially corrected by the length-elongating AMS Ultrex cylinders. Patients should be counseled preoperatively regarding this difference between natural and prosthetic erections.

When an implant recipient complains of insufficient rigidity, the complaints may or may not be realistic and the urologist should determine this by careful examination. Pressure on the glans penis toward the body is a good test of long axial rigidity. A one- or two-piece hydraulic prosthesis will provide sufficient rigidity for many men, but often not for those with longer penises. When rigidity is insufficient, conversion to a three-piece inflatable prosthesis may be necessary. Men with semirigid rod prostheses may also have insufficient rigidity, which is more likely if the penis is long or a small

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diameter or nonmalleable rod prosthesis has been implanted. Again, conversion to another prosthesis may be necessary.

Component displacement

The most common component displacement problem is upward pump migration. When the pump is low in the scrotum, the cosmetic appearance is better and the pump is easier to cycle. Upward pump migration not only affects the cosmetic appearance and makes pumping more difficult, but the pump may impinge on the base of the penis and interfere with complete vaginal intromission. Treatment requires reoperation to move the pump to a lower location.

Distal cylinder crossover results in both distal cylinders being in the same corpus cavernosum. The cylinder that has crossed over pushes the other cylinder tip laterally, which frequently results in pain. Treatment requires removal of the cylinder which has crossed over, distal dilation of that corpus cavernosum and reimplantation of the same cylinder. The problem may also occur with nonhydraulic devices.

A reservoir may pop out through the transversalis fascia and present as a bulge in the inguinal canal. The bulge can be distinguished from a hernia by inflation of the prosthesis, which causes the bulge to disappear or become smaller. Treatment is replacement of the reservoir and repair of the fascial defect through a separate inguinal incision.

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Mechanical failures

Mechanical failures of penile prostheses, more common with hydraulic devices, also occur with nonhydraulic or semirigid rod prostheses (Parulkar, Hamid and Dhabuwala, 1994). Breakage of strands in the silver wire core of the Jonas penile prosthesis, fractures of the Small-Carrion and Finney Flexi-Rod devices and cable breakage of the OmniPhase and DuraPhase prostheses have been reported (Agatstein, Farrer and Raz, 1986; Hrebinko, Bahnson, Schwentker, et al., 1990; Huisman and Macintyre, 1988; Levinson and Whitehead, 1989; Mulcahy, Krane, Lloyd, et al., 1990; Pearman, 1967; Tawil and Gregory, 1986; Tawil, Hawatmeh, Apte, et al., 1984; Walther and Foster, 1985).

Early experience with the Scott-Bradley-Timm AMS inflatable penile prosthesis revealed mechanical failure rates ranging from 21 to 45 percent (Furlow, 1979; Kabalin and Kessler, 1988a; Malloy, Wein and Carpiniello, 1982; Merrill, 1983a; Montague, 1983). Four reports indicate significant improvement in mechanical reliability of the AMS 700 prosthesis compared to the pre-700 AMS models (Fallon, Rosenberg and Culp, 1984; Scarzella, 1988; Wilson, Wahman and Lange, 1988; Woodworth, Carson and Webster, 1991).

The current models of the AMS three-piece hydraulic prostheses (AMS 700CX, AMS Ultrex and AMS Ultrex Plus) utilize triple-ply cylinders with input tubing protection, a sutureless connector system, kink-resistant tubing and seamless reservoirs. Long-term experience with these new devices is not yet available, but preliminary reports indicate that their mechanical reliability will be considerably better than the reliability of earlier models (Furlow and Motley, 1988; Knoll, Furlow and Motley, 1990; Mulcahy, 1988; Parulkar, Hamid and Dhabuwala, 1993). (See Chapter 2, page 19.)

The Mentor three-piece hydraulic prosthesis was introduced in 1983 (see page 19). Initial reports indicated a 7.3 percent mechanical failure rate (Brooks, 1988; Merrill, 1986). A later report indicated a mechanical failure rate of 3.0 percent (Merrill, 1988). Mentor cylinders have a single layer constructed from Bioflex™, a polyurethane polymer. The reservoir and pump are silicone.

Autoinflation

Autoinflation can occur in three-piece hydraulic devices when resting pressure in the reservoir is greater than zero, because physical activity will result in fluid being transferred from the reservoir through the pump into the cylinders until cylinder and reservoir pressures are equal. Autoinflation can be prevented or minimized by ensuring that fluid pressure in the reservoir after implantation is zero and by maintaining the prosthesis in the deflated state during the healing process while a fibrous pseudocapsule is forming around the device. Finally, a reservoir in the prevesical space is less subject to increases in pressure due to physical stress than a reservoir that is implanted between the rectus muscle and peritoneum. Treatment for autoinflation requires reoperation, at which time the above principles are followed (see page 20).

Sensory disturbances

With the infrapubic or subcoronal surgical approaches for penile prosthesis implantation, injury to the dorsal nerves of the penis is possible. However, even when these approaches are used, dorsal nerve injury is rare. With ventral (penoscrotal) approaches, dorsal nerve injury is avoided.

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Complaints of decreased sensation following penile prosthesis implantation with any of these approaches are rare.

A somewhat more frequent but still rare problem is persistent pain following penile prosthesis implantation. Pain after prosthesis implantation generally persists for one to two months, although the duration varies from patient to patient. Pain lasting more than two months may be the result of a nonhydraulic device that is too long or periprosthetic infection. Patients with sensory neuropathy associated with their primary disease (for example, diabetes mellitus) often experience more severe and prolonged pain than other implant recipients. They often describe this pain as a burning sensation, which is different from the kind of pain described by other patients. When persistent pain is the result of infection, clinical signs of infection will eventually develop. Treatment is then directed toward the infection. Usually, pain due to a sensory neuropathy will gradually resolve. A prosthesis seldom needs to be explanted because of pain that does not result from infection.

Ejaculatory incompetence

If the ability to have an orgasm (with or without ejaculation) is present before penile prosthesis implantation, it should still be present postoperatively. However, ejaculatory incompetence, a term used to describe the inability to reach orgasm, occasionally occurs after penile prosthesis implantation. In the early postoperative period when some discomfort is still present, this complaint is more common and the problem usually resolves with further healing. It may, however, persist as a long-term problem.

This problem is due, at least in part, to a difference between natural and prosthetic erections. A man without a prosthesis does not attempt coitus unless sexually aroused because arousal is needed to obtain an erection. The implant recipient, on the other hand, can use his prosthesis for coitus without being sexually aroused. This results in less pleasure during coitus, and the threshold for orgasm might not be reached. When a couple is given permission to have coitus after prosthesis implantation, they are encouraged to use a water-soluble lubricant and ample foreplay before vaginal intromission. Partner anxiety during initial coital attempts may impair vaginal lubrication. The lubricant can later be discarded if natural lubrication appears adequate. If a couple continues to have problems with coitus despite the absence of surgical or prosthetic problems, referral to a sex therapist is indicated (Schover, 1989).

Venous and arterial surgery analysis

As noted in Chapter 2 (page 20), various surgical techniques have been developed for potentially correcting vasculogenic erectile dysfunction caused by corporovenous occlusive dysfunction or by insufficient arterial flow. However, based on results reported in the literature, chances of success do not appear high enough to justify routine use of such surgery.

Venous surgery

For venous surgery, the outcomes balance sheet shows an estimated probability for return to intercourse of 43.3 percent, based on data from 43 patient groups with a total of 1,801 patients. The estimated probability for patient satisfaction is 43.8 percent. It has also been reported that approximately 25 percent of men who have had venous surgery can return to intercourse using intracavernous injections of vasoactive drugs.

Reported outcomes suggest that although erectile function can improve in the short term for some men following venous surgery, the probability of success after 12 months is low (Afsar, Metin, Sozduyar, et al., 1992; Anafarta, Bedük, Aydos, et al., 1992; Austoni, Colombo, Mantovani, et al., 1992; Bar-Moshe and Vandendris, 1992; Claro, de Lima and Netto, 1992; Gilbert, Sparwasser, Beckert, et al., 1992; Hauri, Alund, Spycher, et al., 1992; Katzenwadel, Popken and Wetterauer, 1993; Knoll, Furlow and Benson, 1992; McLoughlin, Asopa and Williams, 1993; Montague, Angermeier, Lakin, et al., 1993; Motiwala, Patel, Joshi, et al., 1993; Puech-Leão, 1992; Schild and Muller, 1993; Sparwasser, Drescher, Pust, et al., 1994; Stief, Djamilian, Truss, et al., 1994; Weidner, Weiske, Rudnick, et al., 1992; Wespes, Delcour, Preserowitz, et al, 1992; Wespes and Schulman, 1993; Yu, Schwab, Melograna, et al., 1992).

In one study, for example, 46 men with venous leakage who underwent penile vein ligation were available for followup for more than 12 months (Freedman, Costa Neto, Mehringer, et al., 1993). Erections allowing normal intercourse were observed in 34 men (74 percent) within the first six months, but after 12 months only 11 men (24 percent) were able to achieve erections sufficient for intercourse. Associated complications included

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penile shortening in 20 men (43 percent) and penile hypoesthesia in nine men (20 percent).

Arterial surgery

For arterial surgery, the outcomes balance sheet shows a probability estimate of 60.3 percent for return to intercourse. In addition, it has been reported that about 25 percent of men who have had arterial surgery can return to intercourse aided by vasoactive drug injection therapy. To generate outcome estimates displayed in the balance sheet for arterial surgery, data were combined for more than one type of procedure. Most techniques described in the literature are variations of microsurgical penile revascularization by anastomosis of the inferior epigastric artery to the dorsal penile artery, cavernous penile artery and/or deep dorsal vein (Cookson, Phillips, Huff, et al., 1993; Grasso, Lania, Castelli, et al., 1992; Janssen, Sarramon, Rischmann, et al., 1994; Löbelenz, Jünemann, Köhrmann, et al., 1992; Melman and Riccardi, 1993; Sarramon, Janssen, Rischmann, et al., 1994; Schramek, Engelmann and Kaufmann, 1992). Although not confirmed or refuted statistically, panel expert opinion is that the best results of penile revascularization surgery are achieved in young, nonsmoking men with normal serum cholesterol whose erectile dysfunction is due to pelvic, and possibly perineal, trauma.

In general, surgical treatments for erectile dysfunction of venogenic and/or arteriogenic origin are still in an immature state of evolution. Initially, newly developed operations suffered from crude and inaccurate diagnostic tests, so that some patients were operated on who actually did not have vasculogenic erectile dysfunction. With more sophisticated diagnostic techniques, it is now possible to identify more accurately the patients who have vasculogenic erectile dysfunction. Also, investigators have recently begun to use more objective selection criteria and postoperative followup methods (Melman and Riccardi, 1993). Yet current tests are still not standardized, and methods of postoperative followup are often inaccurate and subjective. The literature reflects this immature state.

In addition, there are a number of well-known potential postoperative complications, such as infection, pain, postoperative priapism, persistent edema, penile shortening and glans hypervascularization (Jarow and DeFranzo, 1992; Wolf and Lue, 1992). The outcomes balance sheet shows estimated probabilities for surgical complications of 17.2 percent for venous surgery and 21.5 percent for arterial surgery.

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Chapter 4 – Recommendations for treatment of erectile dysfunction

Overview

The AUA Erectile Dysfunction Clinical Guidelines Panel analyzed outcomes data for the following methods of treating organic erectile dysfunction: (1) oral drug therapy (yohimbine); (2) vacuum constriction devices; (3) intracavernous vasoactive drug injection therapy; (4) penile prosthesis implantation; and (5) venous and arterial surgery.

Panel recommendations regarding these treatment options are based primarily on evidence from the literature, both as summarized in the outcomes balance sheet (pages 24 to 25) and as discussed in the analysis sections of Chapter 3, and secondarily on panel expert opinion.

The choice of treatment modality or combination of modalities depends in part on the desires of the patient. The panel believes, as recommended in the 1992 *NIH Consensus Statement* on erectile dysfunction, that "treatment should be individualized to the patient's desires and expectations." The panel also recognizes that some patients will choose the option of no treatment.

Treatment choices depend as well on results of the diagnostic assessment, which will govern patient options. The panel, therefore, included in this chapter an initial overview section on diagnostic evaluation of men with erectile dysfunction. The recommendations in this diagnostic section are based solely on panel opinion and not on a rigorous systematic review of the literature like that described in Chapter 1, which was used for the treatment recommendations. Moreover, they are general recommendations only and are not intended to be all-inclusive or limiting with regard to assessment of individual patients.

Diagnostic assessment

An appropriate assessment of men with erectile dysfunction includes these key elements: (1) general medical history; (2) detailed sexual history; (3) psychological evaluation; (4) physical examination; and (5) basic laboratory studies (*NIH Consensus Statement*, 1992).

Medical and sexual history and psychological evaluation

The medical history may identify specific risk factors that account for or contribute to erectile dysfunction. A detailed history of medications should be included. Vascular risk factors include hypertension, diabetes, smoking, coronary artery disease, peripheral vascular disorders and blood lipid abnormalities. Neurologic risk factors include diabetes mellitus or alcoholism with associated peripheral neuropathy. Certain neurologic disorders, such as multiple sclerosis, spinal injury and cerebrovascular accidents, are often well defined prior to presentation. A history of significant pelvic or perineal trauma may indicate either vascular or neurologic risk factors. The general medical history may also reveal that a patient has had a psychiatric illness, such as depression.

For the sexual history, ideally the patient and the patient's sexual partner should be interviewed, although not necessarily at the same time if the partner's presence inhibits the patient. A detailed history is required to define the patient's complaint accurately and to distinguish erectile dysfunction from problems, such as orgasmic or ejaculatory disturbances or decreased sexual desire, which may indicate a hypogonadal state or depression.

Specific questions should include queries such as whether the patient has painful erections or a penile deformity (possible Peyronie's disease). Other questions should be aimed at eliciting the patient's (and the partner's) perception of erectile dysfunction, details of sexual techniques used, patient and partner expectations, situational circumstances, occurrence of performance anxiety, the nature of the patient-partner relationship (including possible discord) and specific motivation for treatment.

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The physician who takes a good history is also performing a screening psychosocial evaluation. Various psychological tests and sexual questionnaires are available for use as part of the evaluation. Formal psychological consultation should be obtained as necessary. If the initial evaluation reveals that the dysfunction is primarily psychogenic or a major relationship problem exists, referral to a specialist is indicated. The evaluation also may reveal evidence of psychiatric disorders.

Physical examination

The physical examination includes an assessment of neurologic and secondary sex characteristics, femoral and lower extremity pulses and the patient's general state of health. It includes palpation of the shaft of the penis to detect Peyronie's plaques; evaluation of testis size and consistency; a digital rectal examination of the prostate; and assessment of anal sphincter tone, perianal sensation and the bulbocavernosus reflex.

Laboratory tests

Among the tests to exclude unrecognized diabetes or other systemic diseases are a complete blood count, urinalysis, creatinine, lipid profile and fasting blood sugar or glycosylated hemoglobin testing (*NIH Consensus Statement*, 1992). Endocrine evaluation begins with a serum testosterone determination. Low testosterone indicates obtaining a repeat total testosterone measurement and assessment of free testosterone, prolactin and luteinizing hormone.

Other tests

Intracavernous injection of test doses of vasoactive drugs has become a popular office diagnostic test. A rigid or nearly rigid response indicates adequate corporovenous occlusive function and a threshold arterial response. However, a rigid or nearly rigid erection does not exclude the possibility of arterial disease. In patients with no history or physical evidence of neurologic or vascular disease, an excellent response to vasoactive drug injection testing suggests a psychological basis for the problem. Although these generalizations can be made about the man who has a good or excellent response to diagnostic injection, little can be said about the man who has a poor or absent response to the injection. A man with a poor response may have arterial insufficiency and/or corporovenous occlusive dysfunction, or he may have psychogenic erectile dysfunction and fail to respond to the test injection presumably because of high sympathetic tone mediated by anxiety.

Vascular testing is often done by duplex ultrasonography of the cavernosal arteries after intracavernous vasoactive drug injection. Measurement of peak systolic velocities in the cavernosal arteries is reproducible, and values have been obtained in normal subjects. This test is generally regarded as the most useful and accurate assessment of the status of the cavernosal arteries. Penile arteriography is usually reserved for patients who are candidates for arterial bypass surgery.

Measurement of corporovenous occlusive status is generally done by performing infusion cavernosometry and cavernosography after vasoactive drug injection. Complete cavernosal smooth muscle relaxation must be obtained by vasoactive drug injection. Often this does not occur, presumably because of patient anxiety. If complete smooth muscle relaxation does not occur, the false diagnosis of corporovenous occlusive dysfunction may be made. This test limitation, together with the absence of test values in control subjects, limits the usefulness of these tests for corporovenous occlusive dysfunction. Techniques such as visual sexual stimulation have been used in an effort to create the best possible erectile response during diagnostic evaluation and reduce patient anxiety that may cause falsely abnormal test results.

For measurement of neurologic function, few useful tests exist. There is no clinically validated test for measurement of neurologic function of the corpus cavernosum. Biothesiometry measures vibratory sensory thresholds and is of some use clinically. Tests, such as bulbocavernosus reflex latency and somatosensory evoked potentials, have generally been performed only in a research setting and at this time are not regarded as being clinically useful.

One test for erectile dysfunction is the measurement of nocturnal penile tumescence and rigidity (NPTR). As demonstrated by studies in control subjects, normal males of all ages have nocturnal erections which mostly occur during rapid eye movement stages of sleep. Men with erectile dysfunction who have normal NPTR are likely to have a psychogenic etiology, whereas men with impaired or absent NPTR may have an organic etiology. Exceptions to this generalization include men with sleep disorders, depression and neurologic disease.

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Treatment recommendations

The panel's practice recommendations for treatment of erectile dysfunction apply to the standard patient. This patient is defined as a man who develops erectile dysfunction after a well-established period of normal erectile function and whose erectile dysfunction is primarily organic rather than psychological and who has no evidence of hypogonadism or hyperprolactinemia.

The panel generated its treatment recommendations, as previously stated, based on outcomes evidence from the literature and on panel opinion. As explained in Chapter 1, the recommendations were graded according to three levels of flexibility, based on the strength of the evidence and on the panel's assessment of patient preferences. The definitions of these three levels are repeated as follows from Chapter 1:

- Standard: A treatment policy is considered a standard if the outcomes of the alternative interventions are sufficiently well-known to permit meaningful decisions and there is virtual unanimity about which intervention is preferred.
- Guideline: A policy is considered a guideline if the outcomes of the interventions are sufficiently well-known to permit meaningful decisions and an appreciable but not unanimous majority agree on which intervention is preferred.
- Option: A policy is considered an option if: (1) the outcomes of the interventions are not sufficiently well-known to permit meaningful decisions; (2) preferences among the outcomes are not known; (3) patients' preferences are divided among the alternative interventions; and/or (4) patients are indifferent about the alternative interventions.

Standards obviously have the least flexibility. Guidelines have significantly more flexibility, and options are the most flexible. In this report, the terms are used to indicate the strength of the recommendations. A recommendation was labeled a standard, for example, if the panel concluded that it should be followed by virtually all health care providers for virtually all patients. Regardless of level of flexibility, the panel considered it important to take into account likely preferences of individual patients when selecting from among the different treatments for erectile dysfunction.

Recommended treatment modalities and patient information

Recommendations

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

Guideline: Based on review of the literature and analysis of the data, the panel recommends three treatment options for organic erectile dysfunction in the standard patient, as this patient is defined above. The three recommended treatments are: vacuum constriction device therapy, intracavernous vasoactive drug injection therapy and penile prosthesis implantation.

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Following are considerations for discussion in informing the patient about the three recommended treatment options: vacuum constriction device (VCD) therapy, intracavernous vasoactive drug injection therapy and penile prosthesis implantation. These considerations include selection factors and contraindications resulting from the diagnostic assessment. In the panel's opinion, it is important to involve the partner, when possible, in discussion of the therapeutic alternatives and treatment goals. Interviewing and educating the partner can alleviate much of the stress that erectile dysfunction brings to a relationship, with the goal being an honest appraisal of the benefits and potential difficulties of therapy.

Informing the patient about VCDs

The VCD should be discussed as a treatment option based on the results of the diagnostic assessment. The discussion should be unbiased, and advantages and disadvantages should be stated. The use of VCDs in conjunction with vasoactive drug injection therapy can also be discussed.

The VCD, as noted in Chapter 3 (page 26), will cause penile rigidity in most men sufficient for vaginal penetration regardless of the reason for erectile dysfunction. As also noted in Chapter 3, men with decreased penile sensation because of spinal cord injury or other neurologic problems should use the

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VCD with caution. Only prescription VCD equipment should be used, and constriction should not exceed 30 minutes.

Informing the patient about vasoactive drug injection therapy

As with VCD therapy, intracavernous vasoactive drug injection therapy should be presented as a treatment option in an unbiased manner, preferably using patient handouts or video presentations that examine benefits and risks of each treatment modality available. Complications, including prolonged erection, painful erection and fibrosis, should be discussed. Also as with VCD therapy, the presentation should be based on the diagnostic assessment.

A good response to test doses of vasoactive agents during the diagnostic assessment, in a patient with organic erectile dysfunction or refractory psychogenic erectile dysfunction, indicates a suitable candidate for treatment by vasoactive pharmacotherapy. However, a poor response may be situational and does not necessarily preclude treatment of the patient with vasoactive agents.

Relative contraindications to vasoactive injection include penile fibrosis, coagulopathy, uncontrolled psychiatric disorders, regular use of monoamine oxidase (MAO) inhibitors and severe cardiovascular disease that could be exacerbated by a complication of the injection. Patients taking MAO inhibitors are at risk for hypertensive crisis when adrenergic agents are used to treat prolonged erection (Padma-Nathan, Goldstein, Payton, et al., 1987). Patients with chronic systemic illnesses should be followed in conjunction with their primary physician. Poor manual dexterity or morbid obesity, which could preclude self-injection, may be overcome by teaching the injection technique to an able and willing partner.

Informing the patient about penile prosthesis implantation

Prosthesis implantation is a highly reliable, but invasive form of therapy. Candidates considering this treatment option should be aware that postoperative pain after implantation may be significant and typically lasts four to eight weeks, although this is quite variable. Patients will need to restrict strenuous physical activity for at least four weeks, and coitus should not be resumed for at least four weeks.

Complications, especially infection and erosion, need to be discussed. The patient should know that infection and erosion usually require device removal. The patient also needs to know that any type of penile prosthesis can fail mechanically, and that the probability of device failure tends to be proportional to device complexity. The potential implant recipient should be told that correction of device failure requires reoperation.

The patient should be aware that implantation of a penile prosthesis does not ordinarily affect libido, orgasm, ejaculation, urination or genital sensation. However, a few implant recipients do experience either persistent pain or decreased penile sensation which are unexplainable. Fortunately, these complications are rare.

It is very important that potential implant recipients understand that an erection produced by a prosthesis always differs from a normal erection. Many recipients feel that the erection a prosthesis produces is shorter than a normal erection. Moreover, the appearance of the flaccid penis will be different to some degree. These departures from the normal state are variable. The variability depends on the type of prosthesis chosen, differences in anatomy of individual patients and factors related to the healing process.

If the option of being implanted with a prosthesis is selected, the different prostheses offered by the implanting surgeon should be comparatively discussed with the patient and, whenever possible, with the partner. No single prosthesis is best for every patient. The patient's or couple's wishes are important factors in device selection.

If the patient wants a simple device that has the lowest possibility of subsequent mechanical failure, and he is willing to accept the limitations inherent in a nonhydraulic prosthesis, a malleable or positionable prosthesis can be considered. If, however, the patient wants the most natural flaccidity and the most natural erection possible with current devices, a three-piece hydraulic prosthesis is the best choice.

Other devices, such as one- and two-piece hydraulic devices, provide a compromise between nonhydraulic and three-piece hydraulic devices. When considering hydraulic penile prostheses, factors such as patient motivation, intelligence, manual dexterity and strength need to be considered in order to avoid implantation of a device that the patient will be unable to cycle.

Although some penile implantations are done under local anesthesia (Dos Reis, Glina, Da Silva,

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et al., 1993; Kaufman, 1982), most continue to be done under general, spinal or epidural anesthesia. The need for and type of anesthesia to be used should therefore be discussed.

Costs can be an important factor in decision making, depending on the patient's insurance coverage and/or financial resources. In general, the cost of a prosthesis is proportional to its design complexity. The surgical implantation fee usually depends on device complexity as well.

Modality-specific recommendations

Following are practice recommendations specific to the five treatment modalities for which estimated benefits and harms are shown in the outcomes balance sheet tables. The recommendations and their accompanying discussion are presented by modality in the order in which the five modalities appear in the outcomes balance sheet.

Oral drug therapy (yohimbine)

Recommendations

Guideline: Based on the data to date, yohimbine does not appear to be effective for organic erectile dysfunction, and thus should not be recommended as treatment for the standard patient.

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In varying populations of men with organic erectile dysfunction, yohimbine has shown only a modest beneficial effect, and there is a significant placebo effect that may account for half of yohimbine's beneficial effect. Furthermore, based on present studies, the subpopulation of men with erectile dysfunction who are most likely to benefit from yohimbine therapy cannot be accurately identified.

The status of other oral drugs for treatment of erectile dysfunction is investigational (see pages 23 and 26).

VCD therapy

Recommendations

Guideline: In order to optimize efficacy and safety, men interested in trying the vacuum constriction device should be given individual instruction in its use. Only VCDs available by prescription should be used.

Successful use of a VCD requires careful instruction. Patients who rely only on the manufacturer's printed or videotaped instructions are less likely to master the use of the VCD than those given a demonstration by a physician or experienced medical assistant (Lewis, Sidi and Reddy, 1991).

Vasoactive drug injection therapy

Recommendations

Standard: The physician should inform the patient using vasoactive drug injection therapy that a prolonged erection can occur and that the patient should present for treatment after a prolonged erection of four hours. The physician should be familiar with the methods used to reverse a prolonged erection and should inform the patient of how to contact the treating physician or a knowledgeable substitute at any time.

Guideline: For patients beginning initial therapy, PGE_1 (alprostadil) monotherapy is preferred. For patients who fail PGE_1 therapy because of pain or inadequate erection, other drugs should be considered.

Guideline: For combination therapy, papaverine/phentolamine and papaverine/phentolamine/PGE_1 appear equally efficacious and safe. For PGE_1/phentolamine combination therapy, insufficient data have as yet been reported in the literature; but panel opinion is that this combination appears to be an effective therapy.

Option: Papaverine monotherapy may be considered in some patients because of lower risk of pain and lower cost in comparison with PGE_1 monotherapy. Physicians using papaverine monotherapy should be aware of the higher risk of prolonged erection and fibrosis as compared with PGE_1 monotherapy.

The choice of vasoactive pharmacotherapy to treat erectile dysfunction places the patient in the situation of performing a minimally invasive drug injection on an intermittent basis. With any vasoactive agent or combination, physicians should be prepared to aggressively treat all potential complications. Complications can be minimized and

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patient acceptance and satisfaction facilitated by careful attention to diagnosis, teaching and followup. Education of the patient is particularly important to minimize frustration and to decrease the probability of untoward side effects. Good teaching of technical details and a willingness to elucidate difficulties in technique or to observe injection technique periodically may decrease the incidence of improper injection and failed responses. When appropriate, the patient should be able to adjust within specific bounds the total dose of medication injected to match the specific situation for which it is used. It is recommended that vasoactive drug injection therapy not be used more than once in a 24-hour period.

Penile prosthesis implantation

Recommendations

Standard: Penile prosthesis implantation should not be performed in men with psychogenic erectile dysfunction unless a psychiatrist or psychologist participates in the preoperative evaluation and concurs with the need for prosthesis implantation.

Standard: The patient considering prosthesis implantation and, when possible, his partner should be informed of the following factors: types of prostheses; duration of postoperative pain and restriction of activity; possibility of infection and erosion, mechanical failure and consequent reoperation; and differences from the normal flaccid and erect penis.

Standard: The implant recipient and, when possible, his partner should be informed that penile prosthesis implantation may preclude subsequent successful use of a vacuum constriction device or vasoactive injection therapy.

Standard: Surgery should not be done in the presence of systemic infection or cutaneous infection in the operative field. Prior to operation the absence of bacteriuria should be confirmed.

The ideal candidate for prosthesis implantation is the man with organic erectile dysfunction who failed treatment by other means or finds other treatments unacceptable and is a suitable surgical risk. Prosthesis implantation is not recommended for patients whose erectile dysfunction is situational or reversible. Men with psychogenic erectile dysfunction should only be considered for penile prosthesis implantation if they have failed sex therapy and are recommended for a prosthesis by the therapist, or if the therapist feels that sex therapy is not feasible for these individuals or couples.

Abnormalities of the tunica albuginea or fibrosis of the cavernosal tissue may complicate prosthesis implantation. The penile prosthesis recipient should be free of urinary tract infection and should have no infections elsewhere in the body that might result in bacterial seeding during the healing phase. In addition, there should be no active dermatitis, wounds or other cutaneous lesions in the operative area. Antibiotics to provide broad spectrum coverage should be administered such that tissue levels are adequate at the start of the operation. In diabetic implant recipients, good control of the diabetes mellitus may reduce the risk of infection (Bishop, Moul, Sihelnik, et al., 1992).

Prosthesis recipients with spinal cord injury are at increased risk for both infection and erosion (Golji, 1979; Rossier and Fam, 1984). Erosion in these patients may occur in part because of infection; however, lack of sensation also contributes to the erosion problem. Inflatable prostheses in spinal cord injured patients offer a reduced risk of erosion. Inflatable prostheses are also considered advantageous in patients, such as those with a history of bladder tumor or urethral stricture, who may require periodic lower tract endoscopic procedures.

Uncircumcised men should be examined for abnormalities of the prepuce or glans penis. Mild phimosis or balanitis may be an indication for circumcision either before or at the time of prosthesis implantation. Postimplant problems with phimosis in uncircumcised men are unusual when the foreskin and glans are normal.

Venous and arterial surgery

Recommendations

Guideline: Based on the evidence to date, penile venous surgery is considered investigational and should only be performed in a research setting with long-term followup available.

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Recommendations *(continued)*

Guideline: Arterial reconstructive and dorsal vein arterialization procedures in men with arteriolosclerotic disease are investigational and should only be performed in a research setting with long-term followup available.

Option: Arterial revascularization may be effective for treating young men with normal corporovenous function who have arteriogenic erectile dysfunction secondary to pelvic and perineal trauma.

As discussed in Chapter 2 (page 20) and Chapter 3 (page 39), objective criteria to select patients for penile vascular surgery still do not exist. In addition, the measures of success are nonstandardized and unpredictable. Postoperative success in most surgical series has been based predominantly on subjective patient reporting. Because patients are reluctant to have invasive studies postoperatively, few studies report objective postoperative data such as from angiography or cavernosometry. Moreover, reported success rates have been relatively low. (See Chapter 3, pages 38 to 39.)

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Research recommendations

Focused research is needed in a number of areas to address deficiencies in the erectile dysfunction knowledge base. New and better methods for evaluation of erectile dysfunction are clearly needed, beginning with a standardized diagnostic approach and establishment of normal criteria for diagnostic tests. Among tests needing standardization are vascular analysis with duplex ultrasound, cavernosometry and cavernosography studies and arteriography. Needed as well is expanded research on evaluating nocturnal penile tumescence and rigidity, and methods need to be developed for evaluating specific neurologic factors in erectile dysfunction.

For treatment, the ultimate goal is a therapy that is not only reliable with minimal side effects, but simple to use. Such a therapy will most likely be some form of oral or topical medication. Areas for exploration include medications to activate vasodilation through actuation of nitric oxide synthesis and release and smooth muscle relaxants that may have specific receptors in the penile vasculature. Also needed are medications that may work on a central level to inhibit the adrenergic response, particularly in patients who have mild organic disease with a psychogenic overlay.

Needed too are better designed studies, including prospective, randomized, controlled trials when possible. Uniform methods of reporting outcomes are needed to produce more reliable data that can be used for analysis. Especially needed are well-designed prospective patient and partner satisfaction studies for all treatment modalities.

Meeting the need for better study design will require development of standard criteria for reporting outcomes, including adverse events and specific treatment complications. (See the box on the next page for suggested particulars to be reported.)

Also required will be appropriate inclusion/exclusion criteria for enrolling patients in prospective clinical trials and the development of outcome assessment instruments, from sexual function and sexual satisfaction questionnaires to physiologic assessment tools, which can be applied uniformly to patients treated with different modalities.

Many research needs are specific to particular treatment modalities. For vacuum constriction devices, which were developed empirically, scientific studies are needed to address physiologic issues and concerns, such as defining safe limits for negative pressure and constriction. Questions to be answered with regard to VCDs include:

- Why does the use of the VCD increase maximum arterial flow into the penis (Donatucci and Lue, 1992)?
- Why does “double pumping” accelerate development of penile rigidity?
- Why, if no venous backflow occurs under negative pressure, does standing or sitting facilitate development of penile tumescence and rigidity during the negative pressure phase?
- For those men who fail to achieve adequate rigidity at 225 mm Hg negative pressure, would increasing negative pressure result in a higher success rate and how much can negative pressure be safely increased (Nadig, 1989)?

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Techniques and outcomes to be reported

Diagnostic modalities

Patient diagnosis:
- Vasculogenic
  - Arteriogenic
  - Corporovenous occlusive dysfunction
- Neurogenic
- Diabetic
- Psychogenic
- Postoperative
- Mixed
- Unclassified

Vacuum constriction device type

Vasoactive pharmacotherapy:
- Preparation
- Dosage range
- Route/technique

Prosthesis type

Prosthesis implantation:
- Anesthetic
- Prophylactic antibiotic(s)
- Surgical approach

Complications rates:
- Prolonged erection (definition)
- Corporal nodules/plaques
- Corporal fibrosis
- Hematoma
- Pain: localized and diffuse
- Pain scale
- Systemic reactions
- Infection (prosthesis)
- Erosion (prosthesis)
- Mechanical failure (prosthesis)
- Device malposition/migration (prosthesis)

Intervention for prolonged erection:
- Vasoactive drug aspiration/irrigation
- Surgical shunt procedures

Outcomes data:
- Followup (mean, minimum, maximum)
- Rate of return to intercourse
- Patient satisfaction with therapy
- Partner satisfaction with therapy
- Return of spontaneous erections
- Rates of adequate rigidity/duration
- Quality of rigidity/duration (definition)
- Injection frequency
- Dropout rates and reasons

- How much longer than 30 minutes can constriction devices be left in place before ischemic changes occur?

For vasoactive drug injection therapy, the ideal agent has yet to be developed. This agent would be inexpensive, stable over time, and provide a consistent, dose-dependent erection result with low risk of pain, prolonged erection or other complications. Among questions to be answered with regard to vasoactive drug injection therapy are:

- Why do some patients experience pain from alprostadil? How can the pain response be predicted? How can the pain response be blocked without compromising the erectile response?
- What are the limitations on frequency of use in injection of vasoactive drugs?
- What are the mechanisms by which injection-associated penile plaques and fibrosis occur? How can such plaques and fibrosis be treated? How can they be prevented?
- What are possible home therapies that can be used successfully for prolonged pharmacologic erection?

For penile prostheses, in addition to needed improvements such as devices less subject to mechanical failure, more research is needed on causes and prevention of infection, the single most important problem associated with penile prosthesis implantation. Questions to be answered include:

- Why do infections occur in some patients but not others, even with the same preventive measures? What are the sources of the infecting organisms? What additional preventive measures can be taken?
- What are the optimal conditions and techniques for penile prosthesis salvage (infected prosthesis removal with immediate new device implantation)? Would the development of antibiotic impregnated prosthetic devices lower the infection rate?
- For patients to master inflation and deflation more easily in hydraulic prostheses, can the mechanisms be simplified for going from flaccid to erect and back to flaccid?
- How can penile prosthetic devices be improved for greater mechanical reliability?

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Appendix A – Data presentation

Figure A-1. Articles Retrieved, Rejected and Extracted by Year of Publication

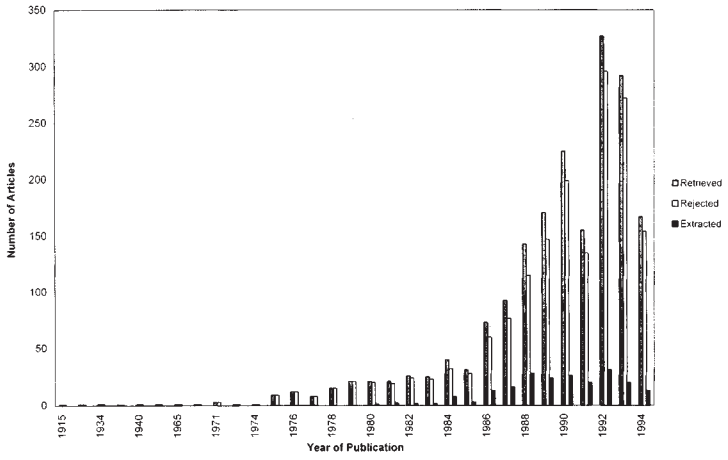

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Figure A-2. Articles Retrieved, Rejected and Extracted by Top 10 Journals

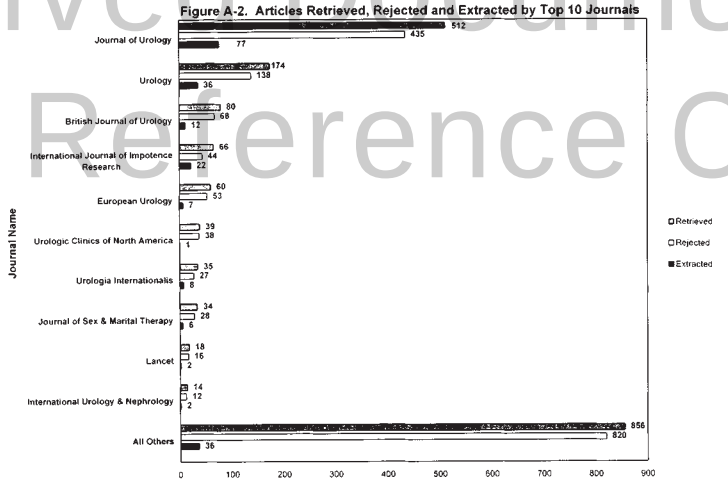

Figure A-3. Articles Retrieved from MEDLINE (N = 1,888)

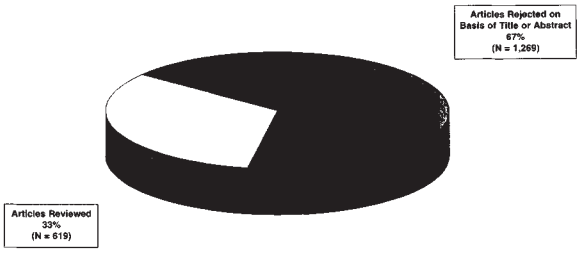

Figure A-4. Status of Reviewed Articles (N = 619)

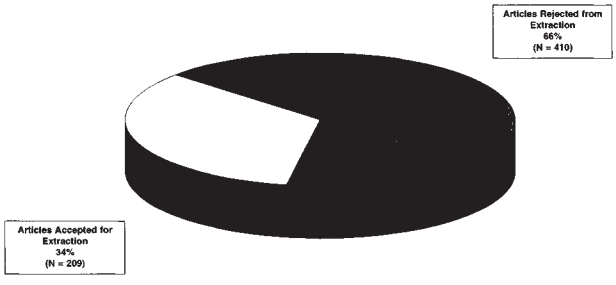

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Table A-1 Articles extracted by Papyrus reference number

Papyrus Ref.	Journal	Year	Volume	Pages	Title	Authors
2	Acta Urologica Belgica	1988	56	220-225	Experiences with a standardized diagnostic procedure on out-patient basis in 150 impotent males	Postma, H.J.P.M., Steffens, J., and Steffens, L.
5	Acta Urologica Belgica	1988	56	211-219	Intracavernous injection of papaverine, phentolamine and phenoxybenzamine	Pettirossi, O., Serenelli, G.
21	Angiology	1984	35	79-87	Intracavernous injection of papaverine as a diagnostic and therapeutic method in erectile failure	Virag, R., Frydman, D., Legman, M., and Virag, H.
29	Archives of Physical Medicine & Rehabilitation	1989	70	712-716	Synergist erection system in the management of impotence secondary to spinal cord injury	Zasler, N.D., Katz, P.G.
34	Archives of Surgery	1986	121	774-777	Deep-penile-vein arterialization for arterial and venous impotence	Balko, A., Malhotra, C.M., Wincze, J.P., Susset, J.G., Bansal, S., Carney, W.I., and Hopkins, R.W.
45	Australian & New Zealand Journal of Surgery	1989	59	959-962	Complications associated with penile implants used to treat impotence	Earle, C.M., Watters, G.R., Tulloch, A.G.S., Wisniewski, Z.S., Lord, D.J., and Keogh, E.J.
52	British Journal of Psychiatry	1986	149	210-215	Maintenance treatment of erectile impotence by cavernosal unstriated muscle relaxant injection	Brindley, G.S.
56	British Journal of Urology	1986	58	692-695	Intracorporal injection of papaverine and phentolamine in the management of impotence	Robinette, M.A., Moffat, M.J.
61	British Journal of Urology	1988	61	151-155	Diagnosis and treatment of venous leakage: a curable cause of impotence	Williams, G., Mulcahy, M.J., Hartnell, G., and Kiely, E.A.
63	British Journal of Urology	1987	59	164-169	Assessment of the immediate and long-term effects of pharmacologically induced penile erections in the treatment of psychogenic and organic impotence	Kiely, E.A., Williams, G., and Goldie, L.
66	British Journal of Urology	1989	63	546-547	Use of the "Correctaid" device in the management of impotence	Asopa, R., Williams, G.
67	British Journal of Urology	1990	65	68-71	Prostaglandin E1 in erectile dysfunction. Efficiency and incidence of priapism	Schramek, P., Dorninger, R., Waldhauser, M., Konecny, P., and Porpaczy, P.
68	British Journal of Urology	1989	64	535-540	Deep dorsal vein arterialisation in vascular impotence	Wespes, E., Corbusier, A., Delcour, C., Vandenbosch, G., Struyven, J., and Schulman, C.C.
73	British Medical Journal - Clinical Research	1988	296	161-162	Successful non-invasive management of erectile impotence in diabetic men	Wiles, P.G.
77	British Medical Journal - Clinical Research	1987	295	595-596	Impotence: treatment by autoinjection of vasoactive drugs	Williams, G., Mulcahy, M.J., and Kiely, E.A.
82	Cardiovascular & Interventional Radiology	1988	11	237-239	Therapeutic roles of intracavernosal papaverine	Goldstein, I., Payton, T., and Padma-Nathan, H.
110	European Urology	1989	16	175-180	Effects of intracavernosal pharmacotherapy on self-esteem, performance anxiety and partnership in patients with chronic erectile dysfunction	Bähren, W., Scherb, W., Gall, H., Beckert, R., and Holzki, G.
114	European Urology	1988	15	209-212	Long-term results of deep dorsal penile vein transsection in venous impotence	Lunglmayr, G., Nachtigall, M., and Gindl, K.

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124	International Urology & Nephrology	1989	21	485-490	Surgical treatment of impotence due to venous outflow	Török, A., Székely, J., Márk, B., and Götz, F.
144	Journal of Psychosomatic Research	1987	31	413-418	Preliminary experience with a vacuum constriction device (VCD) as a treatment for impotence	Cooper, A.J.
150	Journal of Sex & Marital Therapy	1989	15	163-176	Self-injection of papaverine and phentolamine in the treatment of psychogenic impotence	Turner, L.A., Althof, S.E., Levine, S.B., Risen, C.B., Bodner, D.R., Kursh, E.D., and Resnick, M.I.
152	Journal of Sex & Marital Therapy	1988	14	184-201	Psychosocial follow-up of penile prosthesis implant patients and partners	Tiefer, L., Pedersen, B., and Melman, A.
155	The Journal of Trauma	1984	24	579-585	Erectile failure following pelvic trauma: a review of pathophysiology, evaluation, and management, with particular reference to the penile prosthesis	VanArsdalen, K.N., Wein, A.J., Hanno, P.M., and Malloy, T.R.
156	Journal of Urology	1986	136	1210-1212	Another surgical approach for vasculogenic impotence	Lewis, R.W., Puyau, F.A., and Bell, D.P.
157	Journal of Urology	1990	143	60-61	Early experience with the DuraPhase penile prosthesis	Hrebinko, R., Bahnson, R.R., Schwentker, F.N., and O'Donnell, W.F.
159	Journal of Urology	1987	137	1168-1172	Is yohimbine effective in the treatment of organic impotence? Results of a controlled trial	Morales, A., Condra, M., Owen, J.A., Surridge, D.H., Fenemore, J., and Harris, C.
160	Journal of Urology	1987	138	52-54	Pharmacological erection: diagnosis and treatment applications in 69 patients	Nellans, R.E., Ellis, L.R., and Kramer-Levien, D.
163	Journal of Urology	1987	138	65-67	Infectious complications of penile prosthetic implants	Thomalla, J.V., Thompson, S.T., Rowland, R.G., and Mulcahy, J.J.
166	Journal of Urology	1987	138	310-311	The application of intracavernous injection of vasoactive medications for erection in men with spinal cord injury	Bodner, D.R., Lindan, R., Leffler, E., Kursh, E.D., and Resnick, M.I.
169	Journal of Urology	1987	137	676-677	Scott's inflatable penile prosthesis: evaluation of mechanical survival in the series 700 model	Gregory, J.G., Purcell, M.H.
172	Journal of Urology	1987	137	678-680	Intracavernous self-injection with phentolamine and papaverine for the treatment of impotence	Gasser, T.C., Roach, R.M., Larsen, E.H., Madsen, P.O., and Bruskewitz, R.C.
177	Journal of Urology	1986	136	599-601	Reconstructive surgery for vasculogenic impotence	Bennett, A.H., Rivard, D.J., Blanc, R.P., and Moran, M.
182	Journal of Urology	1990	143	518-519	Duraphase penile prosthesis--results of clinical trials in 63 patients	Mulcahy, J.J., Krane, R.J., Lloyd, L.K., Edson, M., and Siroky, M.B.
191	Journal of Urology	1984	132	270-271	Long-term followup in patients with an inflatable penile prosthesis	Fallon, B., Rosenberg, S., and Culp, D.A.
192	Journal of Urology	1984	131	894-895	The inflatable penile prosthesis, reoperation and patient satisfaction: a comparison of statistics obtained from patient record review with statistics obtained from intensive followup search	Apte, S.M., Gregory, J.G., and Purcell, M.H.
197	Journal of Urology	1985	133	796-798	Venous leakage: surgical treatment of a curable cause of impotence	Wespes, E., Schulman, C.C.
199	Journal of Urology	1985	133	39-41	Auto-injection of the corpus cavernosum with a vasoactive drug combination for vasculogenic impotence	Zorgniotti, A.W., Lefleur, R.S.
204	Journal of Urology	1980	124	205-207	Finney hinged penile implant: experience with 100 cases	Finney, R.P., Sharpe, J.R., and Sadlowski, R.W.
207	Journal of Urology	1986	135	929-931	Experience with the AMS 600 malleable penile prosthesis	Moul, J.W., McLeod, D.G.
209	Journal of Urology	1986	135	704-706	Intracavernous drug-induced erections in the management of male erectile dysfunction: experience with 100 patients	Sidi, A.A., Cameron, J.S., Duffy, L.M., and Lange, P.H.
211	Journal of Urology	1990	143	1138-1141	Intracavernous injection therapy: analysis of results and complications	Lakin, M.M., Montague, D.K., VanderBrug Medendorp, S., Tesar, L., and Schover, L.R.

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Papyrus Ref.	Journal	Year	Volume	Pages	Title	Authors
212	Journal of Urology	1983	129	517-521	Microscopic penile revascularization	McDougal, W.S., Jeffery, R.F.
217	Journal of Urology	1983	129	295-298	Reactions to the implantation of an inflatable penile prosthesis among psychogenically and organically impotent men	Schlamowitz, K.E., Beutler, L.E., Scott, F.B., Karacan, I., and Ware, C.
226	Journal of Urology	1988	140	972-974	Intracavernous self-injection for impotence: a long-term therapeutic option? Experience in 78 patients	Girdley, F.M., Bruskewitz, R.C., Feyzi, J., Graversen, P.H., and Gasser, T.C.
227	Journal of Urology	1989	142	729-731	Negative pressure devices in the explanted penile prosthesis population	Moul, J.W., McLeod, D.G.
233	Journal of Urology	1989	141	58-59	Experience with the Hydroflex penile prosthesis	Kabalin, J.N., Kessler, R.
234	Journal of Urology	1989	141	54-57	Side effects of self-administration of intracavernous papaverine and phentolamine for the treatment of impotence	Levine, S.B., Althof, S.E., Turner, L.A., Risen, C.B., Bodner, D.R., Kursh, E.D., and Resnick, M.I.
235	Journal of Urology	1988	140	1420-1421	Use of CX cylinders in association with AMS700 inflatable penile prosthesis	Mulcahy, J.J.
237	Journal of Urology	1988	140	1424-1427	Clinical experience with the Mentor inflatable penile prosthesis in 301 patients	Merrill, D.C.
238	Journal of Urology	1988	140	1422-1423	The Hydroflex self-contained inflatable prosthesis: experience with 100 patients	Mulcahy, J.J.
239	Journal of Urology	1988	139	956-958	Evaluation of patients and partners 1 to 4 years after penile prosthesis surgery	Pedersen, B., Tiefer, L., Ruiz, M., and Melman, A.
241	Journal of Urology	1988	139	947-950	Clinical experience with a self-contained inflatable penile implant: the Flexi-Flate	Stanisic, T.H., Dean, J.C., Donovan, J.M., and Beutler, L.E.
242	Journal of Urology	1988	139	951-952	Eleven years of experience with the inflatable penile prosthesis	Wilson, S.K., Wahman, G.E., and Lange, J.L.
245	Journal of Urology	1981	126	475-476	Jonas silicone-silver penile prosthesis: initial experience in America	Krane, R.J., Freedberg, P.S., and Siroky, M.B.
246	Journal of Urology	1988	139	1217-1219	Treatment of impotence due to perineal venous leakage by ligation of crura penis	Bar-Moshé, O., Vandendris, M.
247	Journal of Urology	1988	140	66-68	Intracavernous injection of prostaglandin E1 in impotent men	Stackl, W., Hasun, R., and Marberger, M.
252	Journal of Urology	1988	139	945-946	The inflatable penile prosthesis: clinical experience with a new controlled expansion cylinder	Furlow, W.L., Motley, R.C.
265	Journal of Urology	1989	141	551-553	A prospective double-blind trial of intracorporeal papaverine versus prostaglandin E1 in the treatment of impotence	Sarosdy, M.F., Hudnall, C.H., Erickson, D.R., Hardin, T.C., and Novicki, D.E.
267	Journal of Urology	1989	141	1360-1363	Effect of yohimbine hydrochloride on erectile impotence: a double-blind study	Susset, J.G., Tessier, C.D., Wincze, J., Bansal, S., Malhotra, C., and Schwacha, M.G.
271	Journal of Urology	1989	141	320-322	Vacuum constriction device for management of erectile impotence	Witherington, R.
273	Journal of Urology	1989	141	323-325	Intracavernous injection of prostaglandin E1 for the treatment of erectile impotence	Ishii, N., Watanabe, H., Irisawa, C., Kikuchi, Y., Kubota, Y., Kawamura, S., Suzuki, K., Chiba, R., Tokiwa, M., and Shirai, M.
275	Journal of Urology	1988	139	48-49	42 months of experience with the Mentor inflatable penile prosthesis	Brooks, M.B.

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279	Journal of Vascular Surgery	1989	10	117-121	Experience in diagnosis and treatment of impotence caused by cavernosal leak syndrome	DePalma, R.G., Schwab, F., Druy, E.M., Miller, H.C., Emsellem, H.A., Edwards, C.M., and Bergsrud, D.
280	Journal of the American Geriatrics Society	1990	38	217-220	Use of a vacuum tumescence device in the management of impotence	Korenman, S.G., Viosca, S.P., Kaiser, F.E., Mooradian, A.D., and Morley, J.E.
296	The Lancet	1987	2	421-423	Double-blind trial of yohimbine in treatment of psychogenic impotence	Reid, K., Surridge, D.H.C., Morales, A., Condra, M., Harris, C., Owen, J., and Fenemore, J.
308	Microsurgery	1988	9	258-261	Microsurgical arterialization for vascular impotence	Wagenknecht, L.V.
321	Plastic & Reconstructive Surgery	1987	80	284-288	Penile revascularization in the treatment of vasculogenic impotence	Pearl, R.M., McGhee, R.D.
337	Radiology	1986	161	807-809	Erectile dysfunction caused by venous leakage: treatment with detachable balloons and coils	Courtheoux, P., Maiza, D., Henriet, J.P., Vaislic, C.D., Evrard, C., and Theron, J.
385	Urologic Clinics of North America	1988	15	115-121	Venous surgery for impotence	Lewis, R.W.
401	Urology	1990	35	304-306	Synergist Erection System: clinical experience	al-Juburi, A.Z., O'Donnell, P.D.
404	Urology	1990	35	405-406	Mentor GFS inflatable prosthesis	Engel, R.M.E., Fein, R.L.
406	Urology	1984	23	141-143	Success with penile prosthesis from patient's viewpoint	Hollander, J.B., Diokno, A.C.
408	Urology	1982	20	271-275	Treatment of vasculogenic sexual impotence by revascularizing cavernous and/or dorsal arteries using microvascular techniques	Crespo, E., Soltanik, E., Bove, D., and Farrell, G.
411	Urology	1987	30	23-26	Cavernous artery revascularization in vasculogenic impotence: new simplified technique	Carmignani, G., Pirozzi, F., Spano, G., Corbu, C., and De Stefani, S.
415	Urology	1988	31	114-115	Systemic complication of intracavernous papaverine injection in patients with venous leakage	Wespes, E., Schulman, C.C.
418	Urology	1990	35	35-37	Cavernosometry: corroboratory method to surgical treatment of impotence due to venous leakage	Rodrigues Netto, N. Jr., Reinato, J.A.S., Cara, A., and Claro, J.F.A.
420	Urology	1986	28	480-485	AMS malleable penile prosthesis	Dorflinger, T., Bruskewitz, R.
421	Urology	1987	29	498-500	Mentor inflatable penile prosthesis	Engel, R.M.E., Smolev, J.K., and Hackler, R.
423	Urology	1986	28	489-491	Mentor inflatable penile prosthesis: a reliable mechanical device	Hackler, R.H.
424	Urology	1988	32	311-314	Clinical evaluation of inflatable penile prosthesis with combined pump-reservoir	Fein, R.L.
429	Urology	1989	34	22-27	Venous surgery in erectile dysfunction: a critical report on 116 patients	Treiber, U., Gilbert, P.
430	Urology	1989	33	17-19	Penile prosthesis surgery: review of ten-year experience and examination of reoperations	Kabalin, J.N., Kessler, R.
431	Urology	1988	31	483-485	Mid-term results of autoinjection therapy for erectile dysfunction	Stief, C.G., Gall, H., Scherb, W., and Bähren, W.
434	Urology	1988	31	486-489	Cylinder reliability of inflatable penile prosthesis. Experience with distensible and nondistensible cylinders in 325 patients	Scarzella, G.I.
443	Urology	1984	23 Suppl	86-92	Experience with inflatable penile prosthesis	Fishman, I.J., Scott, F.B., and Light, J.K.
444	Urology	1984	23 Suppl	83-85	Experience with Jonas malleable penile prosthesis	Montague, D.K.
451	Urology	1986	27	126-131	Noninvasive device to produce and maintain an erection-like state	Nadig, P.W., Ware, J.C., and Blumoff, R.

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Papyrus Ref.	Journal	Year	Volume	Pages	Title	Authors
485	Acta Europaea Fertilitatis	1989	20	305-308	Prostaglandin E1 in the therapy of erectile deficiency	Beretta, G., Zanollo, A., Ascani, L., and Re, B.
621	Journal of Sex & Marital Therapy	1989	15	121-129	Why do so many people drop out from auto-injection therapy for impotence	Althof, S.E., Turner, L.A., Levine, S.B., Risen, C., Kursh, E., Bodner, D., and Resnick, M.
626	International Journal of Impotence Research	1989	1	49-54	Fibrosis of the cavernous bodies following intracavernous auto-injection of vasoactive drugs	Tullii, R.E., Degni, M., and Pinto, A.F.C.
627	International Journal of Impotence Research	1989	1	55-58	Six years experience with the vacuum constriction device	Nadig, P.W.
629	International Journal of Impotence Research	1989	1	175-180	Infected penile prostheses: incidence and outcome	Fallon, B., Ghanem, H.
630	International Journal of Impotence Research	1990	2	21-27	Penile venous surgery for the management of cavernosal venous leakage	Knoll, L.D, Furlow, W.L., and Benson, R.C. Jr.
631	International Journal of Impotence Research	1990	2	29-34	Results of deep penile vein resection in impotence caused by venous leakage	Kropman, R.F., Lycklama à Nijeholt, A.A.B., Giesbers, A.G.M., and Zwartendijk, J.
632	International Journal of Impotence Research	1990	2	35-42	Sexual performance and satisfaction with penile prostheses in impotence of varoius etiologies	Fallon, B., Ghanem, H.
641	Journal of Urology	1990	144	79-82	Treating erectile dysfunction with external vacuum devices: Impact upon sexual, psychological and marital functioning	Turner, L.A., Althof, S.E., Levine, S.B., Tobias, T.R., Kursh, E.D., Bodner, D., and Resnick, M.I.
642	Journal of Urology	1990	144	679-682	Penile vein ligation for corporeal incompetence: an evaluation of short-term and long-term results	Rossman, B., Mieza, M., and Melman, A.
644	International Journal of Impotence Research	1990	2 Suppl	229-234	Experience with deep dorsal vein arterialization: Furlow-Fisher modification in 11 patients	Oh, C.H., Moon, Y.T., and Kim, S.C.
645	International Journal of Impotence Research	1990	2 Suppl	199-204	Penile prostheses for Chinese patients	Chiang, H-S., Wen, T-C., Wu, C-C., and Chiang, W-H.
647	International Journal of Impotence Research	1990	2 Suppl	181-186	Clinical experience of vacuum tumescence enhancement therapy for impotence	Park, N.C., Min, K.S., Cha, Y.I., and Yoon, J.B.
648	International Journal of Impotence Research	1990	2 Suppl	155-156	Treatment of venous impotence by ligation of the crura penis	Hashine, K., Kimura, K., Tamura, M., Kawanishi, Y., and Imagawa, A.
649	International Journal of Impotence Research	1990	2 Suppl	153-154	Ligation of the deep dorsal vein of the penis in 57 cases	Hashine, K., Kimura, K., Tamura, M., Kawanishi, Y., and Imagawa, A.
650	International Journal of Impotence Research	1990	2 Suppl	147-151	Treatment of impotence: comparison between the efficacy and safety of intracavernous injection of papaverine plus phentolamine (regitine) and prostaglandin E1	Lui, S.M-C., Lin, J.S-N.
653	Journal of Urology	1988	140	1428-1430	Five-year follow-up of the Scott inflatable penile prosthesis and comparison with semirigid penile prosthesis	Kabalin, J.N., Kessler, R.
655	Urology	1986	28	385-387	Reliability of AMS M700 inflatable penile prosthesis	Malloy, T.R., Wein, A.J., and Carpiniello, V.L.
657	International Journal of Impotence Research	1989	1	127-130	Intracavernosal self-injection with injection pen	Kromann-Andersen, B., Nielsen, K.K.
659	Journal of Urology	1988	140	293-294	Patient acceptance of and satisfaction with vasoactive intracavernous pharmacotherapy for impotence	Sidi, A.A., Reddy, P.K., and Chen, K.K.
662	Journal of Urology	1987	138	68-69	Periprosthetic infections	Montague, D.K.
918	Journal of Sex & Marital Therapy	1990	16	15-21	The role of yohimbine for the treatment of erectile impotence	Sonda, L.P., Mazo, R., and Chancellor, M.B.

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935	Journal of Urology	1991	146	1022-1024	Pharmacologically induced erections among geriatric men	Kerfoot, W.W., Carson, C.C.
954	Journal of Urology	1991	146	786-789	Pharmacological erection program using prostaglandin E1	Gerber, G.S., Levine, L.A.
965	Arch Ital Urol Nefrol Androl	1991	63	95-100	Arterial and venous surgery for vasculogenic impotence: a combined French and American experience	Virag, R., Bennett, A.H.
976	British Journal of Urology	1991	67	640-643	Treatment of organic impotence	Cumming, J., Pryor, J.P.
995	Urology	1991	37	531-539	Patient satisfaction with Mentor inflatable penile prosthesis	Whalen, R.K., Merrill, D.C.
1002	Journal of Urology	1991	145	1176-1177	Outpatient 3-piece inflatable penile prosthesis	Lubensky, J.D.
1061	Journal of Urology	1991	145	284-286	Vacuum tumescence devices: the role of papaverine in the selection of patients	Broderick, G.A., Allen, G., and McClure, R.D.
1077	Urology	1990	36	502-504	Clinical experience implanting an inflatable penile prosthesis with controlled-expansion cylinder	Knoll, L.D., Furlow, W.L., and Motley, R.C.
1084	Urology	1990	36	406-409	Management of Peyronie disease by implantation of inflatable penile prosthesis	Knoll, L.D., Furlow, W.L., and Benson, R.C., Jr.
1091	Journal of Urology	1990	144	1154-1156	Patient acceptance of and satisfaction with an external negative pressure device for impotence	Sidi, A.A., Becher, E.F., Zhang, G., and Lewis, J.H.
1155	European Urology	1990	18	42-44	Surgical exclusion of the crural ending of the corpora cavernosa: late results	Glina, S., Puech-Leão, P., dos-Reis, J.M.M., Reichelt, A.C., and Chao, S.
1266	Journal of Urology	1988	139	741-742	Implantation of model AMS 700 penile prosthesis: long-term results	Furlow, W.L., Goldwasser, B., and Gundian, J.C.
1267	International Journal of Impotence Research	1990	2 Suppl	457-458	Experience with AMS 700CX penile prosthesis	Montague, D.K.
1269	Journal of Urology	1989	142	988-991	Use of the malleable penile prosthesis in the treatment of erectile dysfunction: a prospective study of postoperative adjustment	Krauss, D.J., Lantinga, L.J., Carey, M.P., Meisler, A.W. and Kelly, C.M.
1271	World Journal of Urology	1987	5	156-159	Clinical experience with vasoactive intracavernous pharmacotherapy for treatment of impotence	Sidi, A.A., Chen, K-K.
1272	World Journal of Urology	1987	5	160-165	Intracavernosal pharmacotherapy: the pharmacologic erection program	Padma-Nathan, H., Goldstein, I., Payton, T., and Krane, R.J.
1274	Urology	1981	18	470-472	Complications of inflatable penile prostheses	Kessler, R.
1275	Journal of Urology	1984	131	670-673	Long-term evaluation of the inflatable penile prosthesis	Joseph, D.B., Bruskewitz, R.C., and Benson, R.C., Jr.
1297	International Journal of Impotence Research	1991	3	95-104	Intracavernous pharmacotherapy: psychological, sexological and medical aspects	Van Driel, M.F., Mooibroek, J.J., Van de Wiel, H.B.M., and Mensink, H.J.A.
1299	International Journal of Impotence Research	1991	3	113-121	A comparison of the response to the intracavernosal injection of a combination of papaverine and phentolamine, prostaglandin PGE1 and a combination of all three agents in the management of impotence	McMahon, C.G.
1300	International Journal of Impotence Research	1991	3	129-137	Cavernosometry and penile vein resection in corporeal incompetence: an evaluation of short-term and long-term results	Claes, H., Baert, L.
1301	Journal of Urology	1991	146	1564-1565	Improved vasoactive drug combination for pharmacological erection program	Bennett, A.H., Carpenter, A.J., and Barada, J.H.
1306	International Journal of Impotence Research	1990	2	143-149	Intracavernous injection of prostaglandin E1 in impotent diabetic men	Ravnik-Oblak, M., Oblak, C., Vodusek, D.B., Kristl, V., and Ziherl, S.

For Peer Review Only

Papyrus Ref.	Journal	Year	Volume	Pages	Title	Authors
1307	International Journal of Impotence Research	1991	3	105-111	Diagnostic value of intracavernous injections of 20 ug of prostaglandin E1 in impotence	Buvat, J., Buvat-Herbaut, M., Lemaire, A., Marcolin, G., and Dehaene, J.L.
1309	Journal of Urology	1985	134	899-901	Long-term results with the Jonas malleable penile prosthesis	Benson, R.C., Jr., Patterson, D.E., and Barrett, D.M.
1310	Journal of Urology	1988	139	953-955	Infectious complications of penile prosthesis surgery	Kabalin, J.N., Kessler, R.
1314	Journal of Sex & Marital Therapy	1991	17	81-93	External vacuum devices in the treatment of erectile dysfunction: a one-year study of sexual and psychosocial impact	Turner, L.A., Althof, S.E., Levine, S.B., Bodner, D.R., Kursh, E.D. and Resnick, M.I.
1315	Journal of Sex & Marital Therapy	1991	17	94-100	Assisted erection follow-up with couples	Villeneuve, R., Corcos, J., and Carmel, M.
1320	Urology	1991	38	533-536	Inflatable penile prosthesis: effect of device modification on functional longevity	Woodworth, B.E., Carson, C.C., and Webster, G.D.
1322	International Journal of Impotence Research	1991	3	33-36	Experience with the Synergist erection system in the management of impotence	Earle, C.M., Keogh, E.J.
1325	Journal of the American Geriatrics Society	1992	40	61-64	Use of a vacuum tumescence device in the management of impotence in men with a history of penile implant or severe pelvic disease	Korenman, S.G., Viosca, S.P.
1327	Urology	1992	39	139-144	Twelve-month comparison of two treatments for erectile dysfunction: self-injection versus external vacuum devices	Turner, L.A., Althof, S.E., Levine, S.B., Bodner, D.R., Kursh, E.D., and Resnick, M.I.
1329	Urologia Internationalis	1992	48	332-335	Treatment of impotence due to venous leakage by resection of the deep dorsal vein of the penis	Anafarta, K., Beduk, Y., Aydos, K., Baltaci, S., and Safak, M.
1337	Probl Urol	1991	5	577-593	Arteriogenic Impotence. Diagnosis and management (deep dorsal vein arterialization)	Furlow, W.L., Knoll, L.D.
1348	World Journal of Urology	1990	8	104-110	Selective microsurgery in arteriogenic erectile failure	Sohn, M., Sikora, R., Bohndorf, K., and Deutz, F-J.
1350	Urology	1991	38	32-34	Mechanical complications associated with Mentor inflatable penile prosthesis	Steinkohl, W.B., Leach, G.E.
1362	Canadian Journal of Psychiatry - Revue Canadienne De Psychiatrie	1991	36	574-578	Evaluation of I-C papaverine in patients with psychogenic and organic impotence	Cooper, A.J.
1368	Sex Marital Ther	1991	6	49-56	The results of an intracorporeal papaverine clinic	Gilbert, H.W., Gingell, J.C.
1370	Urology	1992	39	439-441	Patient satisfaction with pharmacologic erection program	Hollander, J.B., Gonzalez, J., and Norman, T.
1375	Journal of Urology	1992	147	1280-1281	Risk factors for papaverine-induced priapism	Lomas, G.M., Jarow, J.P.
1465	International Journal of Impotence Research	1992	4	11-18	Venous leakage and the role of the suspensory ligament of the penis: surgical-haemodynamic observations and new therapies	Austoni, E., Colombo, F.
1486	Journal of Urology	1992	147	66-68	The G.F.S. Mark II inflatable penile prosthesis	Fein, R.L.
1495	International Journal of Impotence Research	1992	4	149-155	The effect of chronic external vacuum device usage on cavernous artery function.	Donatucci, C.F., Lue, T.F.
2001	Lancet	1982	2	938	Intracavernous injection of papaverine for erectile failure	Virag, R.
8006	Scandinavian Journal of Urology & Nephrology - Supplementum	1994	157	107-112	Long-term results of therapy with intracavernosal injections and penile venous surgery in chronic erectile dysfunction	Sparwasser, C., Drescher, P., Pust, R.A., and Madsen, P.O.

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8025	Diabetic Medicine	1994	11	410-412	Treatment of male erectile dysfunction using the active vacuum assist device	Bodansky, H.J.
8030	Urology	1994	44	400-403	Long-term experience with controlled expansion cylinders in the AMS 700CX inflatable penile prosthesis and comparison with earlier versions of the Scott inflatable penile prosthesis	Nickas, M.E., Kessler, R., and Kabalin, J.N.
8052	Journal of Urology	1994	152	888-890	Objective criteria in the long-term evaluation of penile venous surgery	Wespes, E., Moreira de Goes, P., Sattar, A.A., and Schulman, C.
8053	Journal of Urology	1994	152	884-887	Investigation of vascular changes following penile vein ligation	Kerfoot, W.W., Carson, C.C., Donaldson, J.T., and Kliewer, M.A.
8058	British Journal of Urology	1994	74	102-105	Vacuum constriction devices in erectile dysfunction: acceptance and effectiveness in patients with impotence of organic or mixed aetiology	Vrijhof, H.J.E.J., Delaere, K.P.J.
8090	British Journal of Urology	1994	73	561-565	Microsurgical arterio-arterial and arterio-venous penile revascularization in patients with pure arteriogenic impotence	Janssen, T., Sarramon, J.P., Rischmann, P., Bennis, S., and Malavaud, B.
8112	Journal of Urology	1994	151	1530-1532	Treatment of erectile failure with prostaglandin E1: a double-blind, placebo-controlled, dose-response study	Godschalk, M.F., Chen, J., Katz, P.G., and Mulligan, T.
8153	Journal of Urology	1994	151	880-883	Prognostic factors for the postoperative outcome of penile venous surgery for venogenic erectile dysfunction	Stief, C.G., Djamilian, M., Truss, M.C., Tan, H., Thon, W.F., and Jonas, U.
8160	Urology	1994	43	214-217	Mentor Alpha 1 inflatable penile prosthesis: patient satisfaction and device reliability	Garber, B.B.
8161	Urology	1994	43	209-213	GFS Mark II inflatable penile prosthesis: four-year clinical study	Fein, R.L.
8171	European Urology	1994	25	29-33	Deep dorsal vein arterialization in vascular impotence	Sarramon, J.P., Janssen, T., Rischmann, P., Bennis, S., and Malavaud, B.
8191	Urology	1994	43	84-87	High attrition rate with intracavernous injection of prostaglandin E1 for impotency	Irwin, M.B., Kata, E.J.
8210	Annals of the Academy of Medicine, Singapore	1993	22	675-678	Retrograde penile venoablation	Schild, H.H., Muller, S.C.
8235	Urology	1993	42	554-558	Effectiveness and safety of multidrug intracavernous therapy for vasculogenic impotence	Montorsi, F., Guazzoni, G., Bergamaschi, F., Dodesini, A., Rigatti, P., Pizzini, G., and Miani, A.
8243	Journal of Urology	1993	150	1822-1824	Experience with triple-drug therapy in a pharmacological erection program	Govier, F.E., McClure, R.D., Weissman, R.M., Gibbons, R.P., Pritchett, T.R., and Kramer-Levien, D.
8244	Journal of Urology	1993	150	1819-1821	Patient-partner satisfaction with semirigid penile prostheses for Peyronie's disease: a 5-year followup study	Montorsi, F., Guazzoni, G., Bergamaschi, F., and Rigatti, P.
8245	Journal of Urology	1993	150	1814-1818	Early experience with the first pre-connected 3-piece inflatable penile prosthesis: the Mentor Alpha-1	Goldstein, I., Bertero, E.B., Kaufman, J.M., Witten, F.R., Hubbard, J.G., Fitch, W.P., Geller, R.A., McKay, D.L., Krane, R.J., Borges, F.D., Babayan, R.K., Tuttle, J.P., Gruber, M.B., Harik, V., and Levenson, S.
8265	International Journal of STD & AIDS	1993	4	214-216	Intracavernosal papaverine and phentolamine for the medical management of erectile dysfunction in a genitourinary clinic	Armstrong, D.K.B., Convery, A., and Dinsmore, W.W.
8282	Urology	1993	42	305-308	Clinical experience with Mentor Alpha I inflatable penile prosthesis. Report on 333 cases	Randrup, E., Wilson, S., Mobley, D., Suarez, G., Mekras, G., and Baum, N.

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Papyrus Ref.	Journal	Year	Volume	Pages	Title	Authors
8312	International Journal of Impotence Research	1993	5	47-52	The success of microsurgical penile revascularization in treating arteriogenic impotence	Melman, A., Riccardi, R., Jr.
8326	Urologia Internationalis	1993	51	9-14	Experience with penile venous surgery	Motiwala, H.G., Patel, D.D., Joshi, S.P., Baxi, H.M., Desai, K.D., and Shah, K.N.
8330	Journal of Heart & Lung Transplantation	1993	12	484-486	Use of prostaglandin E1 in the treatment of sexual impotence after heart transplantation: initial clinical experience	Livi, U., Faggian, G., Sorbara, C., Gambino, A., Calabro', A., Artibani, W., Bortolotti, U., and Pagano, F.
8352	European Urology	1993	23	352-356	Surgical treatment of venous leakage: medium-term follow-up	McLoughlin, J., Asopa, R., and Williams, G.
8370	Journal of Urology	1993	149	1308-1312	Analysis of microsurgical penile revascularization results by etiology of impotence	Cookson, M.S., Phillips, D.L., Huff, M.E., and Fitch, W.P., III
8372	Journal of Urology	1993	149	1301-1303	Long-term results of penile vein ligation for impotence from venous leakage	Freedman, A.L., Costa Neto, F., Mehringer, C.M., and Rajfer, J.
8375	Journal of Urology	1993	149	1288-1290	Intracavernous pharmacotherapy for impotence: selection of appropriate agent and dose	von Heyden, B., Donatucci, C.F., Kaula, N., and Lue, T.F.
8396	Urologia Internationalis	1993	50	71-76	Penile venous surgery for cavernosal venous leakage: long-term results and retrospective studies	Katzenwadel, A., Popken, G., and Wetterauer, U.
8407	Urology	1993	41	225-230	Use of vacuum tumescence device for impotence secondary to venous leakage	Blackard, C.E., Borkon, W.D., Lima, J.S., and Nelson, J.
8414	British Journal of Urology	1993	71	52-57	Pelvic floor exercise versus surgery in the treatment of impotence	Claes, H., Baert, L.
8422	Journal of Urology	1993	149	306-307	Penile venous ligation in 18 patients with 1 to 3 years of followup	Montague, D.K., Angermeier, K.W., Lakin, M.M., and Ignaut, C.A.
8425	Journal of Urology	1993	149	290-294	Long-term results with vacuum constriction device	Cookson, M.S., Nadig, P.W.
8430	Journal of Urology	1993	149	46-48	The AMS 700 inflatable penile prosthesis: long-term experience with the controlled expansion cylinders	Quesada, E.T., Light, J.K.
8470	Archivio Italiano di Urologia, Nefrologia, Andrologia	1992	64	309-312	Deep dorsal vein arterialization in vasculogenic impotence: our experience	Grasso, M., Lania, C., Castelli, M., Deiana, G., Francesca, F., and Rigatti, P.
8492	Acta Urologica Belgica	1992	60	9-13	The vacuum erection device. A noninvasive treatment for impotence	van Thillo, E.L., Delaere, K.P.J.
8499	Urologia Internationalis	1992	49	40-47	Venous surgery in erectile dysfunction. The role of dorsal-penile-vein ligation and spongiosolysis for impotence	Gilbert, P., Sparwasser, C., Beckert, R., Treiber, U., and Pust, R.
8500	Urologia Internationalis	1992	49	33-39	Penile venous ligation surgery for the management of cavernosal venous leakage	Knoll, L.D., Furlow, W.L., and Benson, R.C.
8501	Urologia Internationalis	1992	49	29-32	Venous surgery in erectile dysfunction.	Puech-Leão, P.
8502	Urologia Internationalis	1992	49	24-28	Venous surgery in veno-occlusive dysfunction: long-time results after deep dorsal vein resection	Weidner, W., Weiske, W.H., Rudnick, J., Becker, H.C., Schroeder-Printzen, J., and Brähler, E.
8503	Urologia Internationalis	1992	49	19-23	Surgical approach of venous leakage	Bar-Moshe, O., Vandendris, M.
8522	Journal of Urology	1992	147	1028-1031	Microsurgical arteriovenous revascularization in the treatment of vasculogenic impotence	Schramek, P., Engelmann, U., and Kaufmann, F.

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8524	Andrologia	1992	24	285-292	Long-term results of corpus cavernosum autoinjection therapy for chronic erectile dysfunction	Gall, H., Sparwasser, C., Bähren, W., Scherb, W., and Irion, R.
8534	Journal of Urology	1992	148	815-820	Preliminary report: penile vein occlusion therapy: selection criteria and methods used for the transcatheter treatment of impotence caused by venous-sinusoidal incompetence	Schwartz, A.N., Lowe, M., Harley, J.D., and Berger, R.E.
8548	European Urology	1992	21	120-125	Penile revascularization in nonresponders to intracavernous injections using a modified microsurgical technique	Löbelenz, M., Jünemann, K.P., Köhrmann, K.U., Seemann, O., Rassweiler, J., Tschada, R., and Alken, P.
8549	European Urology	1992	21	115-119	Impotence due to corporeal veno-occlusive dysfunction: long-term follow-up of venous surgery	Wespes, E., Delcour, C., Preserowitz, L., Herbaut, A.-G., Struyven, J., and Schulman, C.
8554	British Journal of Urology	1992	70	81-83	Vacuum constriction devices: second-line conservative treatment for impotence	Gilbert, H.W., Gingell, J.C.
8571	International Urology & Nephrology	1992	24	65-68	Erectile dysfunction due to venous incompetence treated by dorsal vein ligation	Afsar, H., Metin, A., Sozduyar, N., Salih, M., and Gulsoy, U.
8575	Urology	1992	40	36-40	Factors predicting efficacy of phentolamine-papaverine intracorporeal injection for treatment of erectile dysfunction in diabetic male	Bell, D.S.H., Cutter, G.R., Hayne, V.B., and Lloyd, L.K.
8580	Urology	1992	39	526-528	Clinical trial of a simplified vacuum erection device for impotence treatment	Sidi, A.A., Lewis, J.H.
8582	Psychiatric Medicine	1992	10	283-293	The clinical effectiveness of self-injection and external vacuum devices in the treatment of erectile dysfunction: a six-month comparison	Turner, L.A., Althof, S.E.
8612	British Journal of Urology	1992	69	404-407	Comparison of effects following the intracorporeal injection of papaverine and prostaglandin E1	Chen, J.-K., Hwang, T.I.S., and Yang, C.-R.
8654	Journal of Urology	1992	147	623-626	Comparative value of prostaglandin E1 and papaverine in treatment of erectile failure: double-blind crossover study among Egyptian patients	Mahmoud, K.Z., el Dakhli, M.R., Fahmi, I.M., and Abdel-Aziz, A.B.A.
8655	Journal of Urology	1992	147	618-622	Preoperative and postoperative dynamic cavernosography and cavernosometry: objective assessment of venous ligation for impotence	Yu, G.W., Schwab, F.J., Melograna, F.S., DePalma, R.G., Miller, H.C., and Rickholt, A.L.
8665	Journal of Urology	1992	147	383-385	Risk factors associated with penile prosthesis infection	Radomski, S.B., Herschorn, S.
8670	Journal of Urology	1992	147	62-65	Patient and partner satisfaction with the AMS 700 penile prosthesis	McLaren, R.H., Barrett, D.M.
8691	Revista Paulista de Medicina	1992	110	280-282	Surgical treatment of veno-occlusive dysfunction: evaluation of short-term and long-term results	Claro, J.A., de Lima, M.L., and Rodrigues Netto, N., Jr.

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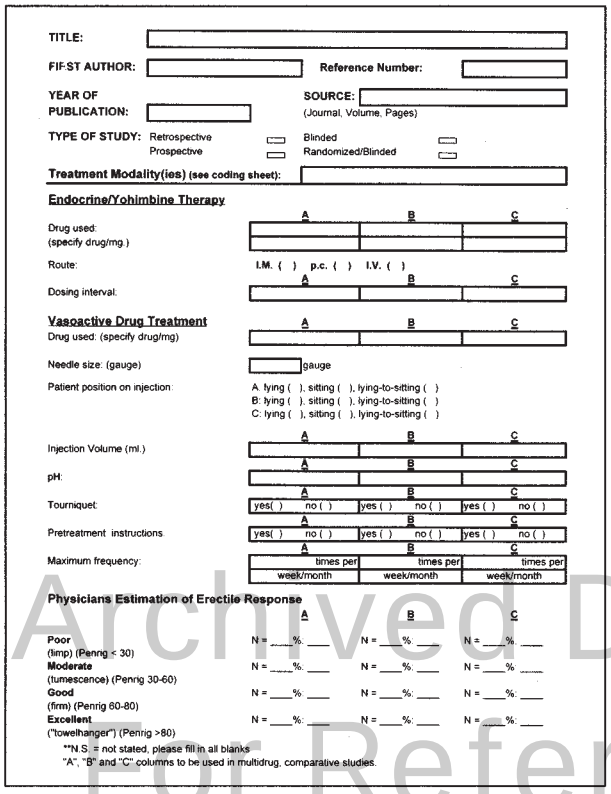
Appendix B – Data extraction form



TITLE:

FIRST AUTHOR: Reference Number:

YEAR OF PUBLICATION: SOURCE: (Journal, Volume, Pages)

TYPE OF STUDY: Retrospective Prospective Blinded Randomized/Blinded

Treatment Modality(ies) (see coding sheet):

Endocrine/Yohimbine Therapy

	A	B	C
Drug used: (specify drug/mg.)			
Route:	I.M. ( ) p.c. ( ) I.V. ( )		
Dosing interval:			

Vasoactive Drug Treatment

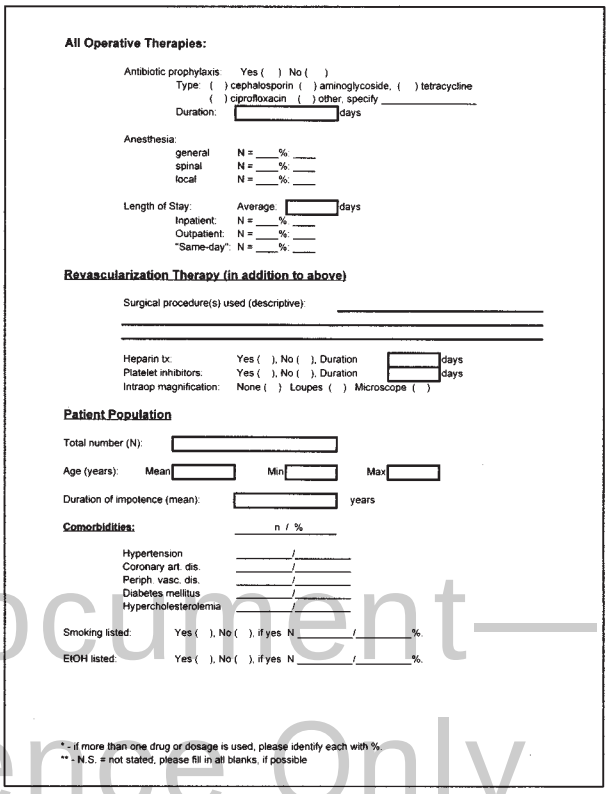
	A	B	C
Drug used: (specify drug/mg)			
Needle size: (gauge)	gauge		
Patient position on injection:	A: lying ( ), sitting ( ), lying-to-sitting ( ) B: lying ( ), sitting ( ), lying-to-sitting ( ) C: lying ( ), sitting ( ), lying-to-sitting ( )		
Injection Volume (ml.)			
pH:			
Tourniquet:	yes( ) no ( )	yes ( ) no ( )	yes ( ) no ( )
Pretreatment instructions:	yes( ) no ( )	yes ( ) no ( )	yes ( ) no ( )
Maximum frequency:	times per week/month	times per week/month	times per week/month

Physicians Estimation of Erectile Response

	A	B	C
Poor (limp) (Penrig < 30)	N = ___%: ___	N = ___%: ___	N = ___%: ___
Moderate (tumescence) (Penrig 30-60)	N = ___%: ___	N = ___%: ___	N = ___%: ___
Good (firm) (Penrig 60-80)	N = ___%: ___	N = ___%: ___	N = ___%: ___
Excellent ("towelhanger") (Penrig >80)	N = ___%: ___	N = ___%: ___	N = ___%: ___

**N.S. = not stated, please fill in all blanks

"A", "B" and "C" columns to be used in multidrug, comparative studies.



All Operative Therapies:

Antibiotic prophylaxis: Yes ( ) No ( )
Type: ( ) cephalosporin ( ) aminoglycoside, ( ) tetracycline
( ) ciprofloxacin ( ) other, specify _____
Duration: ____ days

Anesthesia:
general N = ___%: ___
spinal N = ___%: ___
local N = ___%: ___

Length of Stay: Average: ____ days
Inpatient: N = ___%: ___
Outpatient: N = ___%: ___
"Same-day": N = ___%: ___

Revascularization Therapy (in addition to above)

Surgical procedure(s) used (descriptive): _____

Heparin tx: Yes ( ), No ( ), Duration ____ days
Platelet inhibitors: Yes ( ), No ( ), Duration ____ days
Intraop magnification: None ( ) Loupes ( ) Microscope ( )

Patient Population

Total number (N): ____

Age (years): Mean ____ Min ____ Max ____

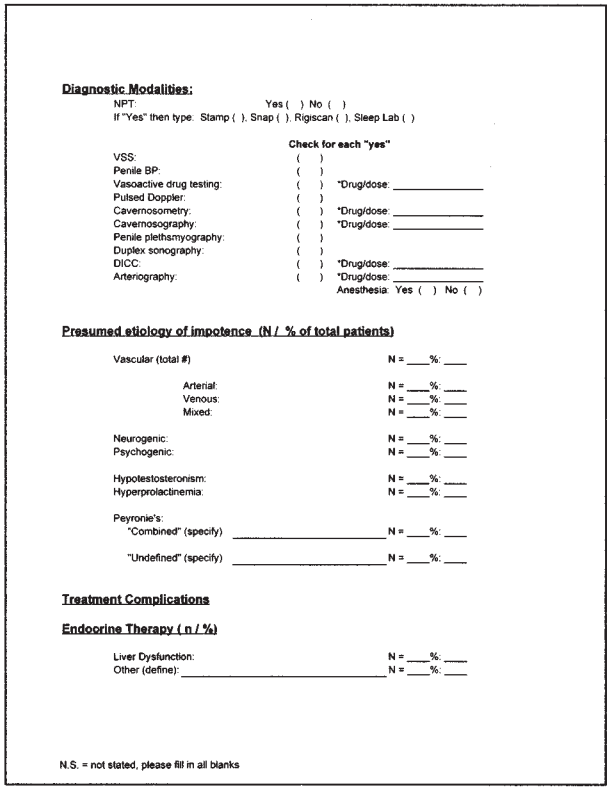
Duration of impotence (mean): ____ years

Comorbidities: n / %

Hypertension ____/____
Coronary art. dis. ____/____
Periph. vasc. dis. ____/____
Diabetes mellitus ____/____
Hypercholesterolemia ____/____

Smoking listed: Yes ( ), No ( ), if yes N ____/____%.
ETOH listed: Yes ( ), No ( ), if yes N ____/____%.

* - if more than one drug or dosage is used, please identify each with %.
** - N.S. = not stated, please fill in all blanks, if possible



Diagnostic Modalities:

NPT: Yes ( ) No ( )
If "Yes" then type: Stamp ( ), Snap ( ), Rigiscan ( ), Sleep Lab ( )

	Check for each "yes"	
VSS:	( )	
Penile BP:	( )	
Vasoactive drug testing:	( )	*Drug/dose: ____
Pulsed Doppler:	( )	
Cavernosometry:	( )	*Drug/dose: ____
Cavernosography:	( )	*Drug/dose: ____
Penile plethsmyography:	( )	
Duplex sonography:	( )	
DICC:	( )	*Drug/dose: ____
Arteriography:	( )	*Drug/dose: ____
		Anesthesia: Yes ( ) No ( )

Presumed etiology of impotence (N / % of total patients)

Vascular (total #) N = ___%: ___
Arterial: N = ___%: ___
Venous: N = ___%: ___
Mixed: N = ___%: ___

Neurogenic: N = ___%: ___
Psychogenic: N = ___%: ___

Hypotestosteronism: N = ___%: ___
Hyperprolactinemia: N = ___%: ___

Peyronie's:
"Combined" (specify) _____ N = ___%: ___
"Undefined" (specify) _____ N = ___%: ___

Treatment Complications

Endocrine Therapy (n / %)

Liver Dysfunction: N = ___%: ___
Other (define): _____ N = ___%: ___

N.S. = not stated, please fill in all blanks

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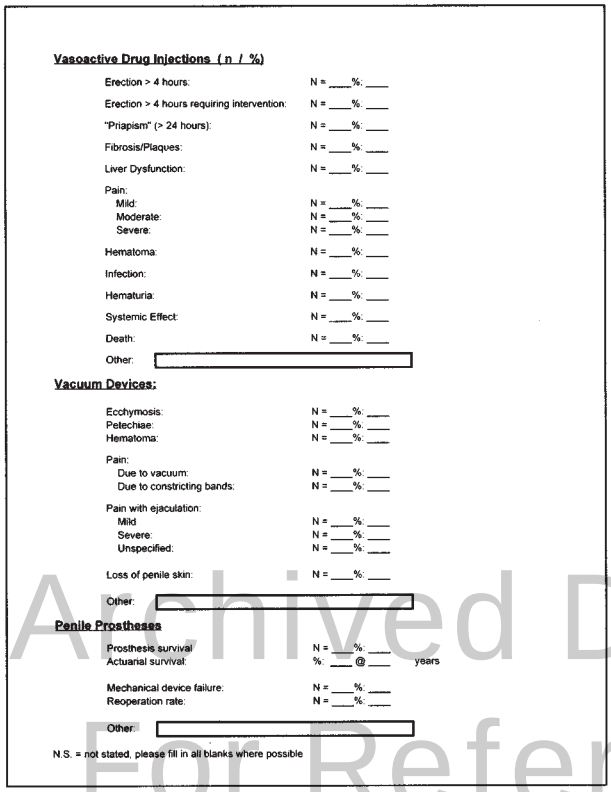
Appendix B con't.



Vasoactive Drug Injections (n / %)

Erection > 4 hours: N = ___%: ___
Erection > 4 hours requiring intervention: N = ___%: ___
"Priapism" (> 24 hours): N = ___%: ___
Fibrosis/Plaques: N = ___%: ___
Liver Dysfunction: N = ___%: ___
Pain:
Mild: N = ___%: ___
Moderate: N = ___%: ___
Severe: N = ___%: ___
Hematoma: N = ___%: ___
Infection: N = ___%: ___
Hematuria: N = ___%: ___
Systemic Effect: N = ___%: ___
Death: N = ___%: ___
Other: _____

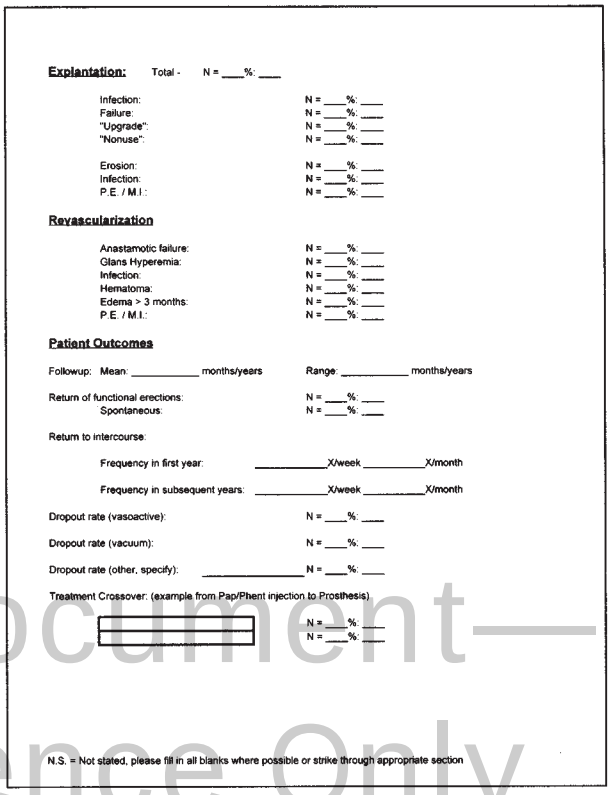
Vacuum Devices:

Ecchymosis: N = ___%: ___
Petechiae: N = ___%: ___
Hematoma: N = ___%: ___
Pain:
Due to vacuum: N = ___%: ___
Due to constricting bands: N = ___%: ___
Pain with ejaculation:
Mild N = ___%: ___
Severe: N = ___%: ___
Unspecified: N = ___%: ___
Loss of penile skin: N = ___%: ___
Other: _____

Penile Prostheses

Prosthesis survival: N = ___%: ___
Actuarial survival: %: ___ @ ___ years
Mechanical device failure: N = ___%: ___
Reoperation rate: N = ___%: ___
Other: _____

N.S. = not stated, please fill in all blanks where possible



Explantation: Total - N = ___%: ___
Infection: N = ___%: ___
Failure: N = ___%: ___
"Upgrade": N = ___%: ___
"Nonuse": N = ___%: ___
Erosion: N = ___%: ___
Infection: N = ___%: ___
P.E. / M.I.: N = ___%: ___

Revascularization

Anastamotic failure: N = ___%: ___
Glans Hyperemia: N = ___%: ___
Infection: N = ___%: ___
Hematoma: N = ___%: ___
Edema > 3 months: N = ___%: ___
P.E. / M.I.: N = ___%: ___

Patient Outcomes

Followup: Mean: _____ months/years Range: _____ months/years
Return of functional erections: N = ___%: ___
Spontaneous: N = ___%: ___
Return to intercourse:
Frequency in first year: _____X/week _____X/month
Frequency in subsequent years: _____X/week _____X/month
Dropout rate (vasoactive): N = ___%: ___
Dropout rate (vacuum): N = ___%: ___
Dropout rate (other, specify): _____ N = ___%: ___
Treatment Crossover: (example from Pap/Phent injection to Prosthesis)
_____ N = ___%: ___
_____ N = ___%: ___

N.S. = Not stated, please fill in all blanks where possible or strike through appropriate section

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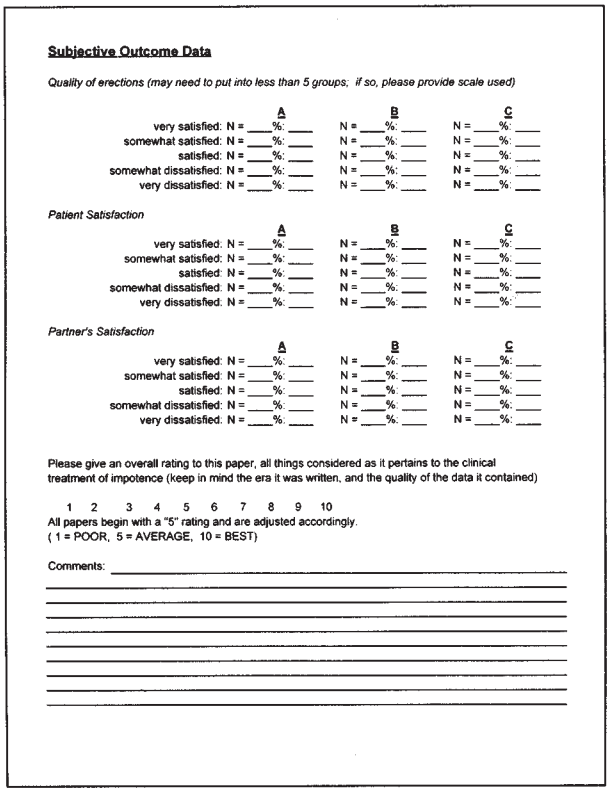

Subjective Outcome Data

Quality of erections (may need to put into less than 5 groups; if so, please provide scale used)

	A	B	C
very satisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
somewhat satisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
satisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
somewhat dissatisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
very dissatisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___

Patient Satisfaction

	A	B	C
very satisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
somewhat satisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
satisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
somewhat dissatisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
very dissatisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___

Partner's Satisfaction

	A	B	C
very satisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
somewhat satisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
satisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
somewhat dissatisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___
very dissatisfied:	N = ___%: ___	N = ___%: ___	N = ___%: ___

Please give an overall rating to this paper, all things considered as it pertains to the clinical treatment of impotence (keep in mind the era it was written, and the quality of the data it contained)

1 2 3 4 5 6 7 8 9 10
All papers begin with a "5" rating and are adjusted accordingly.
(1 = POOR, 5 = AVERAGE, 10 = BEST)

Comments: _____

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This *Report on the Treatment of Organic Erectile Dysfunction* was developed by the Erectile Dysfunction Clinical Guidelines Panel of the American Urological Association, Inc.

This Report is intended to furnish to the skilled practitioner a consensus of clear principles and strategies for quality patient care, based on current professional literature, clinical experience and expert opinion. It does not establish a fixed set of rules or define the legal standard of care, pre-empting physician judgment in individual cases.

An attempt has been made to recommend a range of generally acceptable modalities of treatment, taking into account variations in resources and in patient needs and preferences. It is recommended that the practitioner articulate and document the basis for any significant deviation from these parameters.

Finally, it is recognized that conformance with these guidelines cannot ensure a successful result. The parameters should not stifle innovation, but will, themselves, be updated and will change with both scientific knowledge and technological advances.

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Report on the Treatment of Organic Erectile Dysfunction

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