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## TREATMENT OF MEN WITH ERECTILE DYSFUNCTION WITH TRANSURETHRAL ALPROSTADIL

HARIN PADMA-NATHAN, M.D., WAYNE J.G. HELLSTROM, M.D., FRAN E. KAISER, M.D., RICHARD F. LABASKY, M.D.,  
TOM F. LUE, M.D., WOLFRAM E. NOLTEN, M.D., PAUL C. NORWOOD, M.D., CRAIG A. PETERSON, M.S.,  
RIDWAN SHABSIGH, M.D., PETER Y. TAM, B.S., VIRGIL A. PLACE, M.D., AND NEIL GESUNDHEIT, M.D., M.P.H.,  
FOR THE MEDICATED URETHRAL SYSTEM FOR ERECTION (MUSE) STUDY GROUP\*

### ABSTRACT

**Background** Erectile dysfunction in men is common. We evaluated a system by which alprostadil (prostaglandin E<sub>1</sub>) is delivered transurethraly to treat this disorder.

**Methods** Alprostadil was delivered transurethraly in a double-blind, placebo-controlled study of 1511 men, 27 to 88 years of age, who had chronic erectile dysfunction from various organic causes. The men were first tested in the clinic with up to four doses of the drug (125, 250, 500, and 1000 µg); those who had sufficient responses were randomly assigned to treatment with either the effective dose of alprostadil or placebo for three months at home.

**Results** During in-clinic testing, 996 men (65.9 percent) had erections sufficient for intercourse. Of these men, 961 reported the results of at least one home treatment; 299 of the 461 treated with alprostadil (64.9 percent) had intercourse successfully at least once, as compared with 93 of the 500 who received placebo (18.6 percent,  $P < 0.001$ ). On average, 7 of 10 alprostadil administrations were followed by intercourse in men responsive to treatment. The efficacy of alprostadil was similar regardless of age or the cause of erectile dysfunction, including vascular disease, diabetes, surgery, and trauma ( $P < 0.001$  for all comparisons with placebo). The most common side effect was mild penile pain, which occurred after 10.8 percent of alprostadil treatments, but the pain rarely resulted in refusal to continue in the study. Hypotension occurred in the clinic in 3.3 percent of men receiving alprostadil. Hypotension-related symptoms were uncommon at home. No men had priapism or penile fibrosis.

**Conclusions** In men with erectile dysfunction, transurethral alprostadil therapy resulted in erections in the clinic and in intercourse at home. (*N Engl J Med* 1997;336:1-7.)

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**E**RECTILE dysfunction (impotence) affects approximately 10 million to 20 million men in the United States.<sup>1,2</sup> It becomes more frequent with age,<sup>3</sup> but is not an inevitable consequence of normal aging.<sup>4</sup> It is usually due to organic factors or diseases, such as pelvic vascular disease, diabetes mellitus, neurodegenerative disorders, side effects of medication, pelvic surgery, and trauma.<sup>3,4</sup> Erectile dysfunction impairs sexual performance, diminishes self-esteem,<sup>2,3</sup> and disrupts personal relationships.<sup>1</sup>

Current treatments for erectile dysfunction include oral medications, vacuum pumps, vascular surgery, penile prostheses, and intracavernosal injections. Oral medications, such as yohimbine, have limited efficacy.<sup>5,6</sup> Vacuum pumps may be difficult for some men to use<sup>1</sup> and may cause penile trauma if used improperly.<sup>6-8</sup> The success rate of vascular surgery ranges from 31 to 80 percent; revascularization is more effective in younger men with discrete lesions of the pudendal or common penile artery.<sup>2,9</sup> The implantation of a penile prosthesis is invasive,

From the Department of Urology, University of Southern California, Los Angeles, and the Male Clinic, Santa Monica, Calif. (H.P.-N.); the Department of Urology, Tulane University Medical Center, New Orleans (W.J.G.H.); the Division of Geriatric Medicine, St. Louis University School of Medicine, St. Louis (F.E.K.); the Division of Urology, University of Utah, Salt Lake City (R.F.L.); the Department of Urology, University of California, San Francisco (T.F.L.); the Section of Endocrinology, University of Wisconsin, Madison (W.E.N.); the Peachwood Medical Group, Clovis, Calif. (P.C.N.); the Department of Clinical Research, Vivus, Inc., Menlo Park, Calif. (C.A.P., P.Y.T., V.A.P., N.G.); and the Department of Urology, Columbia-Presbyterian Hospital, New York (R.S.). Address reprint requests to Dr. Gesundheit at Vivus, 545 Middlefield Rd., Suite 200, Menlo Park, CA 94025.

Other authors were Christy Cowley, B.S., Kerry J. Nemo, Alfred P. Spivack, M.D., Darby E. Stephens, B.S., and Leslie K. Todd, B.A. — all from Vivus, Inc., Menlo Park, Calif.

\*The members of the MUSE Study Group are listed in the Appendix.

expensive, and irreversible and can cause penile deformity.<sup>10-12</sup> Intracavernosal injections of vasoactive drugs are satisfactory or effective in 30 to 90 percent of men,<sup>13-19</sup> but they can be associated with pain, priapism, penile hematomas, and fibrosis.<sup>14-20</sup> There is clearly a need for additional treatments.

We report the results of a randomized, prospective, double-blind, placebo-controlled trial of a novel delivery system designed to administer alprostadil (prostaglandin E<sub>1</sub>) to the urethral mucosa for absorption and transfer to the erectile bodies (the corpora cavernosa and the corpus spongiosum). We evaluated responses to alprostadil in the clinic among men with chronic erectile dysfunction from various organic causes and the subsequent occurrence of sexual intercourse at home.

## METHODS

### Study Subjects

We evaluated 1511 men with chronic erectile dysfunction and their partners at 58 investigational sites in the United States. To be included in the study, each man had to be in a stable, monogamous, heterosexual relationship and to have been unable to achieve a spontaneous erection sufficient for intercourse at any time within the preceding three months. All the men were found to have erectile dysfunction with a primarily organic cause on the basis of medical history, physical examination, laboratory evaluation, penile biometry, determination of the penile brachial index, penile duplex ultrasonography, or pharmacocavernosometry and pharmacocavernosography (not all tests were conducted in each man).

Men were excluded from the study if they had a history of urethral stricture or obstruction; an indwelling urethral catheter; anu-

ria; a penile implant or prior penile surgery; sickle cell disease; paraplegia or quadriplegia; congestive heart failure, unstable angina, or recent acute myocardial infarction; poorly controlled diabetes mellitus; hypogonadism with inadequate testosterone-replacement therapy; or markedly abnormal blood chemistry or results of hematologic tests; or if they had received any investigational treatment within the preceding 30 days.

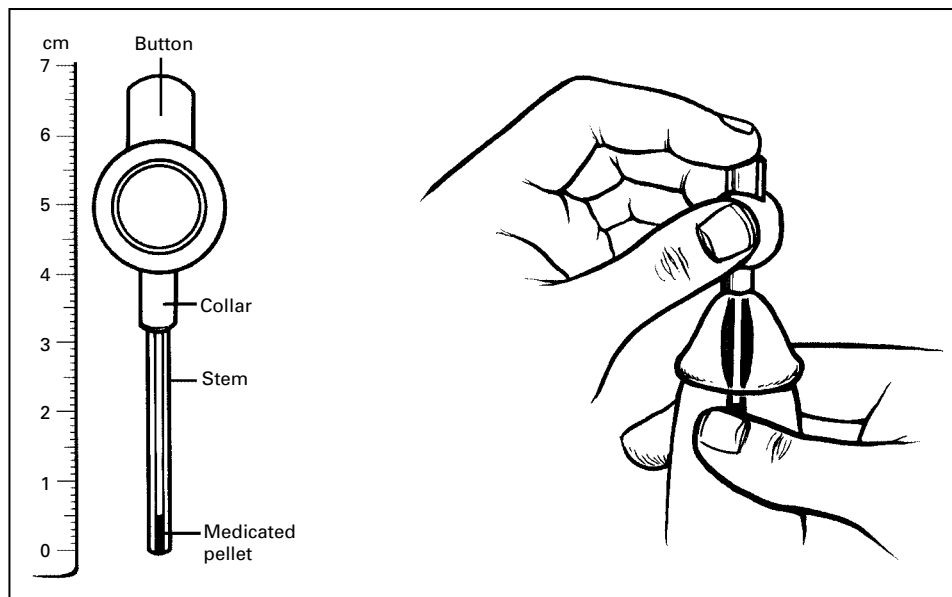
The men were required to discontinue any other treatment for erectile dysfunction at least 30 days before entering the study. The protocol was approved by the institutional review board at each study site, and all the men and their partners gave informed consent.

### Study Design

Men who met the criteria for entry were tested in the clinic to determine the appropriate doses of transurethral alprostadil. Each man administered one dose of either 125 or 250  $\mu$ g of alprostadil to himself, with the dose selected at random in a double-blind manner. On a subsequent visit, they administered the other dose of the drug.

Alprostadil was administered to the distal urethra by a proprietary drug-delivery system (MUSE, Vivus, Menlo Park, Calif.) that consisted of a polypropylene applicator with a hollow stem 3.2 cm in length and 3.5 mm in diameter; the tip contained a semisolid pellet of medication (Fig. 1). The stem of the applicator was inserted fully into the urethra, a button was depressed to deposit the pellet, and the applicator was removed. The men were instructed to urinate immediately before application; residual urine facilitated the insertion of the applicator and the dispersion of the drug.

The penile responses were evaluated with an Erection Assessment Scale<sup>13,19</sup> on which a score of 1 denoted no response; 2, some enlargement; 3, full enlargement (but insufficient rigidity); 4, erection sufficient for intercourse; and 5, full rigidity. Scores were assigned by the men and confirmed by the investigators. The duration of the penile response was also recorded, and



**Figure 1.** The Applicator Used for the Transurethral Administration of Alprostadil.

To use the applicator, each man was asked to urinate, insert the 3.2-cm stem gently into the urethra, and then depress the button, releasing the medicated pellet.

each man rated his overall level of comfort from "very comfortable" to "very uncomfortable." These evaluations were made immediately before the administration of each dose of alprostadil and 15, 30, 45, and 60 minutes thereafter.

The 287 men who had maximal penile responses of 4 or 5 at any time with either the 125- $\mu$ g dose, the 250- $\mu$ g dose, or both were not given higher doses. In the second step of testing, men whose maximal penile response was less than 4 returned for two additional visits, at which time each man administered 500  $\mu$ g or 1000  $\mu$ g of alprostadil to himself (one dose per visit) in a random, double-blind manner, as before; 709 men had responses of 4 or 5 with one or both of these doses. The remaining 515 men, who did not have a response of 4 or 5 with any dose of alprostadil or who did not tolerate the treatment, were discharged from the study. For their home treatment, the men selected the dose they found most comfortable that had produced a maximal penile response of 4 or 5. No retesting of a dose in the clinic was allowed, and the dose could not be changed at home.

In the three-month, double-blind study conducted at home, the 996 men in whom alprostadil testing in the clinic was effective were randomly assigned in approximately equal numbers to alprostadil at the selected dose or placebo. After each administration of the study treatment, both the man and his sexual partner made entries in a diary that documented the penile response, the occurrence of sexual intercourse (vaginal penetration), whether the man reached orgasm, the overall level of comfort associated with the use of the medication, and any adverse effects noted by the man or his partner. The men were evaluated monthly in the clinic by an investigator who was unaware of the study-group assignments. On these visits the diaries were reviewed, and information about compliance with the study protocol was obtained.

### Statistical Analysis

The base-line demographic characteristics of the men in the alprostadil group and the placebo group were assessed by Fisher's exact test in the case of categorical data or by analysis of variance with F tests in the case of continuous data. In the study of efficacy, the groups were compared by the Cochran-Mantel-Haenszel chi-square test (for categorical data) and by the van Elteren test (for continuous data). The van Elteren test is based on the optimal linear combination of the within-strata Wilcoxon statistics.<sup>21</sup> In comparing percentages of successful treatments, we used the bootstrap method in such a manner that each man's entire history was resampled as a unit.<sup>22</sup> The effect of the cause of erectile dysfunction, the subject's age, the dose of alprostadil selected for use in the study, and other characteristics on rates of sexual intercourse was evaluated by chi-square tests of the homogeneity of the odds ratio among subgroups.<sup>23</sup>

SAS software (version 6.10, SAS Institute, Cary, N.C.) was used in all the statistical analyses. The analysis of the efficacy of in-clinic testing included all men who received at least one dose in the clinic; the analysis of efficacy at home included all men who reported at least one home administration of alprostadil or placebo; and the analysis of safety included all men enrolled in the study.

## RESULTS

The demographic characteristics of the men studied are shown in Table 1. The characteristics of the 1511 men who underwent testing in the clinic were similar to those of the 996 men who began home treatment, and the characteristics of the men in the two study groups using home treatment were also similar.

### Responses in the Clinic

In the clinic, 996 of the 1511 men (65.9 percent) had maximal penile responses of 4 or 5 on the Erec-

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE MEN WITH ERECTILE DYSFUNCTION.**

CHARACTERISTIC	MEN STUDIED IN THE CLINIC (N = 1511)	MEN USING TREATMENT AT HOME		P VALUE, ALPROSTADIL VS. PLACEBO
		ALPROSTADIL (N = 485)	PLACEBO (N = 511)	
Age (yr)				
Mean	61	62	61	0.71
Range	27-88	38-84	30-83	
Partner's age (yr)				
Mean	56	56	57	0.64
Range	22-84	22-79	26-81	
Cause of dysfunction (% of men)*				
Vascular disease	28.7	28.9	28.4	0.86
Diabetes	20.6	18.8	19.2	0.87
Surgery or trauma	29.6	31.8	31.1	0.83
Other	21.0	20.6	21.3	0.78
Duration of dysfunction (mo)				
Mean	51	48	49	0.55
Range	3-528	3-528	3-360	
Capable of partial erection (% of men)†	61.1	63.3	60.9	0.43
Previous therapy (% of men)‡	55.3	52.4	56.9	0.15

\*Because of rounding, percentages shown do not all total 100 percent. "Other causes" of dysfunction included abuse of alcohol or tobacco, neurologic disease, and side effects of drugs.

†Partial erections refer to erections occurring naturally that are not sufficient for intercourse.

‡Previous therapies included constriction-band therapy, counseling, hormones, intracavernosal injections, and vacuum pumps.

tion Assessment Scale, without substantial adverse effects, with at least one of the doses of alprostadil. The 125- $\mu$ g dose was selected for home use by 116 men (12 percent), the 250- $\mu$ g dose by 171 men (17 percent), the 500- $\mu$ g dose by 302 men (30 percent), and the 1000- $\mu$ g dose by 407 men (41 percent).

The proportion of men who had maximal responses of 4 or 5 increased as the dose of alprostadil increased (Table 2). The mean duration of the response also correlated positively with the dose. The mean times from the administration of alprostadil to the onset of erection and to the maximal response were similar with each of the various doses. At least 88 percent of the men receiving each dose rated the transurethral application of alprostadil at that dose as "neutral," "comfortable," or "very comfortable."

### Responses at Home

Of the 996 men who had treatment at home, 961 reported the results of at least one administration (and were therefore included in the analysis of efficacy), and 873 (87.7 percent) completed the entire three-month treatment period. Among the men who did not complete the study, 27 did not comply with

**TABLE 2.** RESPONSES TO ALPROSTADIL DURING IN-CLINIC TESTING.

VARIABLE	DOSE OF ALPROSTADIL			
	125 µg	250 µg	500 µg	1000 µg
No. of men*	1490	1492	1117	1140
Percentage with a maximal response of 4 or 5†	12.3	16.6	39.6	48.8
Mean time to onset of response (min)	7	7	7	7
Mean time to maximal response (min)	21	22	23	24
Mean time to return to nonerect state (min)	67	70	74	79
Rating of comfort level (% of men)‡				
Very comfortable	15.7	13.0	14.2	12.5
Comfortable	48.5	48.6	51.8	50.1
Neutral	26.8	26.8	24.5	26.1
Uncomfortable	8.7	10.7	8.9	9.0
Very uncomfortable	0.4	0.9	0.7	2.4

\*Numbers shown are the total numbers of men in whom the indicated doses of alprostadil were tested; for each variable studied, data were collected on at least 95 percent of doses administered. None of the men received a given dose more than once during the testing period.

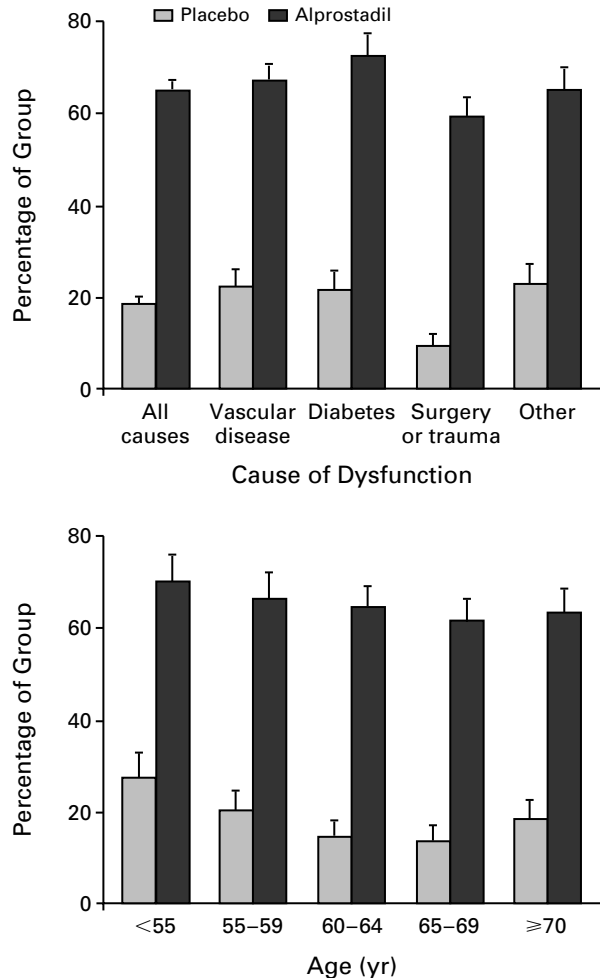
†Maximal penile responses were scored on the Erection Assessment Scale as described in the Methods section. Men who had maximal responses scored as 4 or 5 with more than one of the doses of alprostadil may be counted in more than one column.

‡Because of rounding, percentages shown do not all total 100 percent.

the study protocol, 26 withdrew for personal reasons, 23 were lost to follow-up, 15 withdrew because of adverse effects, 13 withdrew because the treatment was not efficacious, 3 had unrelated illnesses, and 16 withdrew for other reasons.

During the three-month period of home treatment, sexual intercourse was reported as having occurred at least once by 299 of the 461 men in the alprostadil group (64.9 percent), as compared with 93 of the 500 men in the placebo group (18.6 percent,  $P < 0.001$ ) (Fig. 2). Similarly, 293 men in the alprostadil group (63.6 percent) reported having an orgasm at least once, as compared with 118 men in the placebo group (23.6 percent,  $P < 0.001$ ).

Although the primary objective of the study was to restore the capacity for sexual intercourse, the men were permitted to use the study medication to facilitate other sexual activity. Table 3 shows that 10.4 percent of administrations of placebo resulted in intercourse and 15.4 percent in intercourse, orgasm, or an erection sufficient for intercourse of at least 10 minutes. By contrast, 50.4 percent of administrations of alprostadil resulted in intercourse and 57.0 percent in intercourse, orgasm, or an erection sufficient for intercourse of at least 10 minutes ( $P < 0.001$  for the comparison between groups). These findings suggest that alprostadil may have been used



**Figure 2.** Mean (±SE) Percentages of Men Who Reported Having Intercourse after Home Treatment with Alprostadil or Placebo, According to the Primary Cause of Erectile Dysfunction and Age.

Each subgroup included at least 74 men.  $P < 0.001$  for each comparison between alprostadil and placebo.

for self-stimulation after approximately 7 percent of administrations.

Among the men in the alprostadil group who reported having sexual intercourse at least once, 7 of 10 administrations were followed by intercourse. In these men, the frequency with which the administration of alprostadil led to intercourse was similar during each of the three months of home treatment (66.4 percent of administrations in the first month, 69.0 percent in the second, and 73.5 percent in the third).

Transurethral alprostadil was effective regardless of the organic cause of erectile dysfunction or the age of the subject ( $P < 0.001$  for each comparison with placebo) (Fig. 2). Alprostadil was more effective than placebo at each dose studied, and the dif-

**TABLE 3.** EFFICACY OF HOME TREATMENT WITH ALPROSTADIL OR PLACEBO IN FACILITATING SEXUAL ACTIVITY.

TYPE OF SEXUAL ACTIVITY	PLACEBO GROUP (N=500)	ALPROSTADIL GROUP	
		ALL MEN USING HOME TREATMENT (N=461)*	MEN WHO HAD INTERCOURSE AT LEAST ONCE (N=299)
		no. of successful treatments/no. of treatments (%)†	
Intercourse	454/4346 (10.4)	2485/4933 (50.4)	2485/3593 (69.2)
Intercourse or orgasm	668/4331 (15.4)	2770/4921 (56.3)	2612/3586 (72.8)
Intercourse, orgasm, or a 10-min erection sufficient for intercourse	669/4331 (15.4)	2797/4906 (57.0)	2634/3572 (73.7)

\*P<0.001 for each comparison with the placebo group.

†A successful treatment was one that was followed by sexual activity of the type indicated. The denominators used in each group vary slightly because not all men answered all questions.

ference in responsiveness between alprostadil and placebo was similar with each dose of alprostadil ( $P<0.001$ ). In addition, the responses were consistent among the men regardless of whether a partial erection was possible without treatment, regardless of how long the erectile dysfunction had lasted, and regardless of whether prior therapy for the condition had been attempted.

#### Adverse Effects

Penile pain was reported by 35.7 percent of the men during the clinic testing. This pain was usually mild, and only 36 men (2.4 percent) discontinued the study because of it. The transurethral administration of alprostadil was generally rated as comfortable (Table 2). In the clinic, hypotension occurred in 3.3 percent of men and syncope in 0.4 percent. The frequency of hypotension increased with the dose (it was 0.5 percent in the group receiving 125  $\mu\text{g}$ , 0.7 percent in those receiving 250  $\mu\text{g}$ , 0.7 percent in those receiving 500  $\mu\text{g}$ , and 2.4 percent in those receiving 1000  $\mu\text{g}$ ).

During home treatment, penile pain was reported after 10.8 percent of alprostadil administrations and by 32.7 percent of men. At least one episode of minor urethral trauma was reported by 5.1 percent (Table 4); typically, the trauma consisted of a superficial urethral abrasion resulting in a drop of blood at the meatus. Dizziness was reported by 1.9 percent, but there were no episodes of syncope. Urinary tract infections were rare. No man had urethral stricture, penile fibrosis, or priapism (a rigid erection lasting six or more hours) either in the clinic or at home.

#### DISCUSSION

Penile erection is a neurovascular event that depends on the relaxation of smooth muscle in the erectile bodies. The relaxation of smooth muscle in-

**TABLE 4.** ADVERSE EFFECTS IN THE 996 MEN WITH ERECTILE DYSFUNCTION WHO BEGAN HOME TREATMENT WITH ALPROSTADIL OR PLACEBO.\*

ADVERSE EFFECT	ALPROSTADIL GROUP (N=486)	PLACEBO GROUP (N=511)
	no. (%)	
Local urogenital		
Penile pain†	159 (32.7)	17 (3.3)
Minor urethral trauma	25 (5.1)	5 (1.0)
Urinary tract infection	1 (0.2)	3 (0.6)
Priapism-prolonged erection	0	0
Penile fibrosis	0	0
Systemic		
Dizziness	9 (1.9)	1 (0.2)
Hypotension	0	1 (0.2)

\*Numbers of men shown here include all men who received alprostadil or placebo at home. One man received both active and placebo doses at home. His adverse effects, if any, are reported according to the corresponding treatment.

†Penile pain occurred after 10.8 percent of administrations of alprostadil.

volves the release of nitric oxide and other mediators, which stimulate the production of intracellular cyclic nucleotides that cause relaxation.<sup>24-27</sup> With the relaxation of corporal smooth muscle, rapid arterial filling begins, resulting in engorgement of the sinusoids in the cavernosa and veno-occlusion due to the compression of the subtunical venules against the tunica albuginea.<sup>28,29</sup>

The use of locally applied drugs is an appealing way to treat erectile dysfunction, because it initiates the hemodynamic events of a natural erection. Alprostadil (a synthetic compound identical to prostaglandin  $E_1$ ) was chosen for local delivery because it increases intracellular concentrations of cyclic AMP<sup>30-33</sup> and has a short half-life.<sup>34-36</sup> Previously, therapy for

erectile dysfunction with alprostadil and other drugs has involved injections into the corpus cavernosum. Alternative methods of delivering drugs to the erectile bodies have been evaluated. The application of a cream containing prostaglandin E<sub>2</sub> to the urethral meatus in 20 men with erectile dysfunction resulted in full penile tumescence in 30 percent of subjects.<sup>37</sup> In pilot studies, transdermal nitroglycerin, minoxidil, and prostaglandin E<sub>1</sub> failed to induce rigid erections,<sup>38,39</sup> apparently because of insufficient transfer of the drug through the skin.

Although the urethral mucosa is not commonly recognized as a route of drug transfer, it is a more suitable surface for absorption than the skin, because it is lined by complex columnar cells rather than stratified squamous epithelium. There are submucosal veins that communicate between the corpus spongiosum (surrounding the urethra) and the corpora cavernosa, providing a potential route of drug transfer. In this study, the intraurethral administration of alprostadil proved effective in men with erectile dysfunction. Among 1511 men in whom up to four different doses of alprostadil were tested in the clinic, 996 (65.9 percent) had erections sufficient for intercourse. The purpose of the clinic testing was to identify patient-specific doses. The men who did not have responses may have had strong inhibitions in the clinic or more severe disease, such as corporal fibrosis, and thus may have needed more potent (multidrug) therapy. There were no base-line characteristics that predicted responsiveness to transurethral alprostadil.

After the clinic testing, 64.9 percent of men reported having sexual intercourse at home at least once after the administration of alprostadil, as compared with 18.6 percent of men in the placebo group ( $P < 0.001$ ). Among the men in the alprostadil group who reported sexual intercourse, 7 of 10 administrations of the drug were followed by intercourse. The efficacy of treatment with regard to the primary end point, intercourse, was confirmed in each subgroup of men and at each dose of alprostadil ( $P < 0.001$  for each comparison between alprostadil and placebo).

The 64.9 percent rate of intercourse among the men in the alprostadil group indicates that erections in the clinic were not perfectly predictive of intercourse at home. The discordance may be due to several factors possibly present in the home, including inhibitory influences, failure to administer the medication properly, use of the medication for self-stimulation rather than intercourse, and changes in motivation. In addition, the men were not allowed to change their doses during the study, and the clinic testing allowed at most only one exposure to each dose. A more flexible testing program might have produced a better response rate.

The study group was composed of men with chron-

ic erectile dysfunction from diverse organic causes. The average duration of erectile dysfunction among the men treated at home was 48 months (range, 3 months to 44 years). Despite the diverse causes of erectile dysfunction and its persistence for long periods, the efficacy of transurethral alprostadil was confirmed in all the subgroups of men studied and was not affected by their base-line characteristics. This broad efficacy may be attributable to the site of drug administration. By relying on local rather than systemic delivery, we may have lessened the influence of factors such as age and underlying disease.

Penile pain was the most common adverse effect associated with transurethral alprostadil, but it rarely resulted in withdrawal from the study. The delivery system was well accepted, as indicated by the favorable comfort ratings (Table 2) and the 88 percent rate of study completion. Priapism, hematoma, and fibrosis, known to be complications of injection therapy,<sup>14-17,40</sup> were not observed. In future studies, the risk of hypotension may be minimized by administering the lowest effective dose.

The range of doses of alprostadil used in this study (125 to 1000  $\mu\text{g}$ ) was higher than that used in intracavernosal injections (2 to 80  $\mu\text{g}$ ), because of differences in local metabolism or patterns of absorption and distribution. Despite the higher dose, transurethral alprostadil therapy appears to cause less priapism and penile fibrosis than does intracavernosal injection,<sup>14-19</sup> and systemic effects were uncommon. Both therapies take effect within a similar number of minutes and have high response rates. The degree to which men accept one method as compared with the other has not been studied.

In summary, transurethral administration of alprostadil was well tolerated and effectively restored the capacity for erections and sexual intercourse in a substantial proportion of men with chronic erectile dysfunction.

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## APPENDIX

The following investigators and study coordinators participated in the MUSE Study Group: Dallas — J.M. Adelglass, J. Rosenstock, P. Davis, T. Cook, S.G. Dorfman, K.A. Goldberg, and K. Walker; Tacoma, Wash. — R.G. Anderson and M. Ellis; Newport Beach, Calif. — S.M. Auerbach and S. King; Albany, N.Y. — J.H. Barada and J. Lin; Minneapolis — C.J. Billington and

M. Backes; Phoenix, Ariz. — M.B. Block and K. Tysiac; Portland, Oreg. — S. Bookin and L. Tinkham; Chicago — C.B. Brendler, B. Contreras, K.T. McVary, and M. Niewegowski; Santa Monica, Calif. — S.A. Brosman and A. Aleony; Baltimore — A.L. Burnett, M.J. Duckett, C. Lawrence, and I. Truehart; Los Angeles — K. Chiu, S.G. Korenman, A. Melendrez, H. Padma-Nathan, A.L. Teresi, and S. Viosca; Gainesville, Fla. — M.S. Cohen, K. Yeckring, and D. Moody; Washington, D.C. — R.A. Costabile, J. Keyes, D.G. McLeod, J.B. Regan, and M. Spevak; Houston — G.R. Cunningham, E. Cordero, I.J. Fishman, and R. Hughes; Newark, Del. — G.S. DeCherney and L. Sanderson; Durham, N.C. — C.F. Donatucci and D. Hanson; Iowa City, Iowa — B. Fallon and B. Schaeffer; Scottsdale, Ariz. — R.G. Ferrigni and C. Komurke; Albuquerque, N.M. — N.M. Friedman and M. Chaney; Charlottesville, Va. — J.Y. Gillenwater and G. Carter; North Miami, Fla. — M.C. Gittelman and S. Acosta; Seattle — F.E. Govier and D. Kramer-Levien; Spokane, Wash. — W.L. Gray and D. McCoy; Redwood City, Calif. — S.A. Heatley and A. Madayag; New Orleans — W.J.G. Hellstrom and M. Vincent; New Hyde Park, N.Y. — K.S. Hershon and L. Lazerson; Norfolk, Va. — G.H. Jordan and D. Pendergrass; St. Louis — F.E. Kaiser, J.E. Morley, and K. Houston; Nashville — L.D. Knoll, J.R. McRae, K. Wolff, and E. Daniel; Salt Lake City — R.F. Labasky, E. Lingell, and K. Rafferty; San Francisco — I.D. Sharlip, C. Eltchinoff, T.F. Lue, E.A. Tanagho, and L. Nunes; Greenbelt, Md. — M.I. Murdock and E. D'Antonio; Charleston, S.C. — R.P. Nelson and R. Fischer; Madison, Wis. — W.E. Nollen, D.S. Schalch, and H. Schalch; Fresno, Calif. — P. Norwood and M. Norwood; Boston — M.P. O'Leary and J. Spolarich; Rochester, Minn. — D.E. Patterson and K. Hanson; Springfield, Ill. — M.A. Pfeifer and D. Drew; Longmont, Colo. — D.A. Podlecki and J. Cormier; New York — N.A. Romas, R. Shabsigh, A. Sawczuk, and G. Holmes; Irvine, Calif. — S. Rosenblatt and B. Czaja; Oklahoma City — J.B. Roy and M. Malik; San Antonio, Tex. — S.L. Schwartz and J. Roman; Everett, Wash. — G.M. Stack and R. Henry; Lexington, Ky. — J.P. Tuttle and P.S. Leach; Laguna Hills, Calif. — J.M. Young, S. Glasgow, and E. Clee; Jacksonville, Fla. — P.R. Young and P. Cope; and Fort Myers, Fla. — I.A. Zucker and S. Kochheiser.

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