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Results from different patient populations using combined therapy with alprostadil and sildenafil: predictors of satisfaction

J.H. MYDLO, M.A. VOLPE and R.J. MACCHIA
Department of Urology, State University of New York, Downstate Medical School, Brooklyn, New York, USA

Objective To evaluate the outcome of combined therapy (using intraurethral alprostadil and oral sildenafil) in private and clinic patients with erectile dysfunction, and thus assess predictors of satisfaction.

Patients and methods In all, 360 men were treated for erectile dysfunction using single and/or combined therapy, comprising 214 private-practice and 166 clinic patients. Responses were evaluated using the International Index for Erectile Function (IIEF) questionnaire before and after treatment. Serum testosterone levels, education and socio-economic status were also assessed. Group 1a consisted of 33 private patients and Group 1b of 24 clinic patients who tried the maximum dose of intraurethral alprostadil monotherapy initially, followed by the maximum dose of sildenafil monotherapy, and remained dissatisfied. Group 2a consisted of 32 private patients and group 2b of 31 clinic patients who tried the maximum dose of sildenafil monotherapy initially, followed by the maximum dose of alprostadil monotherapy, and were also dissatisfied. These two groups of 65 private and 55 clinic patients then underwent combined therapy.

Results The mean (SD) score for erectile function was 24.1 (2) for combined therapy (a 123% improvement), and 19.8 (1.8) (83% improvement) and 15.2 (1.6) (41% improvement) for sildenafil and alprostadil monotherapies ($P < 0.05$ for both patient groups). The men also reported an improvement in their satisfaction with intercourse. However, at 18 months, 60 of the 65 private patients but only 40 of the 55 clinic patients continued with combined therapy; thus, the discontinuation rate was three times greater among clinic than among private patients. Furthermore, the private patients had an overall improvement in the satisfaction score of 128%, compared with 51% for the clinic patients.

Conclusion Although there were no significant differences in erectile function improvement within the two satisfied combined therapy groups, the differences in overall satisfaction and long-term withdrawal rates suggests that other factors beside motivation must be involved for success, e.g. education, persistence, realistic expectations, and certain psychological factors. Combined therapy should be considered for those patients who have a suboptimal response to monotherapy and refuse or are not candidates for surgical options. Generally, those patients with a higher education, greater persistence and more realistic expectations were more satisfied with combined therapy.

Keywords Erectile dysfunction, alprostadil, sildenafil, questionnaire

Introduction

Intraurethral suppositories of alprostadil (MUSE™) and oral sildenafil (Viagra™) are two new pharmacotherapies for erectile dysfunction (ED) [1–8]. The results using alprostadil have varied; Padma-Nathan *et al.* [9] reported that 66% of men achieved erections sufficient for intercourse after intraurethral injections administered in a clinic setting. In contrast, Fulgham *et al.* [10] reported only a 30% response rate to the intraurethral administration of alprostadil, suggesting that perhaps the method of administration of MUSE is one of the factors determining the success or failure of this treatment. Goldstein *et al.* [11] reported a 69% success rate with oral sildenafil, evaluated in both private and clinic patients, both at home and in the hospital. We recently reported initial results of improved erectile function using a combined therapy of sildenafil and alprostadil for those patients who failed monotherapy [12]. We now present our long-term results on a larger sample and assess patient predictors for the success of and satisfaction with combined therapy.

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Patients and methods

The study comprised two samples of patients being treated for ED; the larger sample was from private practice and the smaller from a clinic where the patients were generally of a lower educational and socio-economic status, as assessed by hospital statistics. Before sildenafil became available, 192 patients (120 private and 72 clinic) were initially treated for ED with intraurethral alprostadil. Of this sample, 64 patients were satisfied; the remaining 128 patients were willing to undergo further treatment to improve the suboptimal response. Once sildenafil became available, they stopped alprostadil and tried the former; of this group, 71 were satisfied. The remaining 57 patients were dissatisfied and willing to undergo combined therapy (33 private patients, group 1a, and 24 clinic patients, group 1b). These patients had been titrated to the maximum dose of alprostadil (1 mg) monotherapy over a 3-month period as initial therapy, followed by sildenafil monotherapy, which was titrated to the maximum dose (100 mg) over 3 months (Fig. 1a). The second group of patients was evaluated after sildenafil became available. Of 188 patients (94 private and 94 clinic) who were being treated with sildenafil initially, 124 were satisfied. The remaining 64 patients were then tried on alprostadil monotherapy, titrated as in group 1. Only one patient was satisfied to continue on alprostadil monotherapy. The remaining 63 patients were willing to undergo combined therapy (32 private, group 2a, and 31 clinic, group 2b, Fig. 1b). Combined therapy consisted of 100 mg of sildenafil 45–60 min before intercourse and the self-administration of 1 mg alprostadil intraurethrally 10–15 min before intercourse. The mean (range) age of the 120 patients was 64 (46–79) years; 63% of the men were married and the remaining 37% were in a stable relationship. Thirty-one had impotence after radical prostatectomy, 40 had diabetes, 24 had peripheral vascular disease and 25 were on hypertensive therapy (Table 1). ED was assessed using the International Index for Erectile Function (IIEF) assessment questionnaire [13]. This instrument comprises 15 questions to assess five variables of sexual dysfunction; erectile function (score 1–30), orgasmic function (score 0–10), sexual desire (score 2–10), intercourse satisfaction (score 0–15), and overall satisfaction (score 2–10). Both groups were evaluated using the IIEF questionnaire at baseline, and after monotherapy and combined therapy. The results were analysed using the repeat-measurement design method and chi-square tests, with significance indicated at $P < 0.05$.

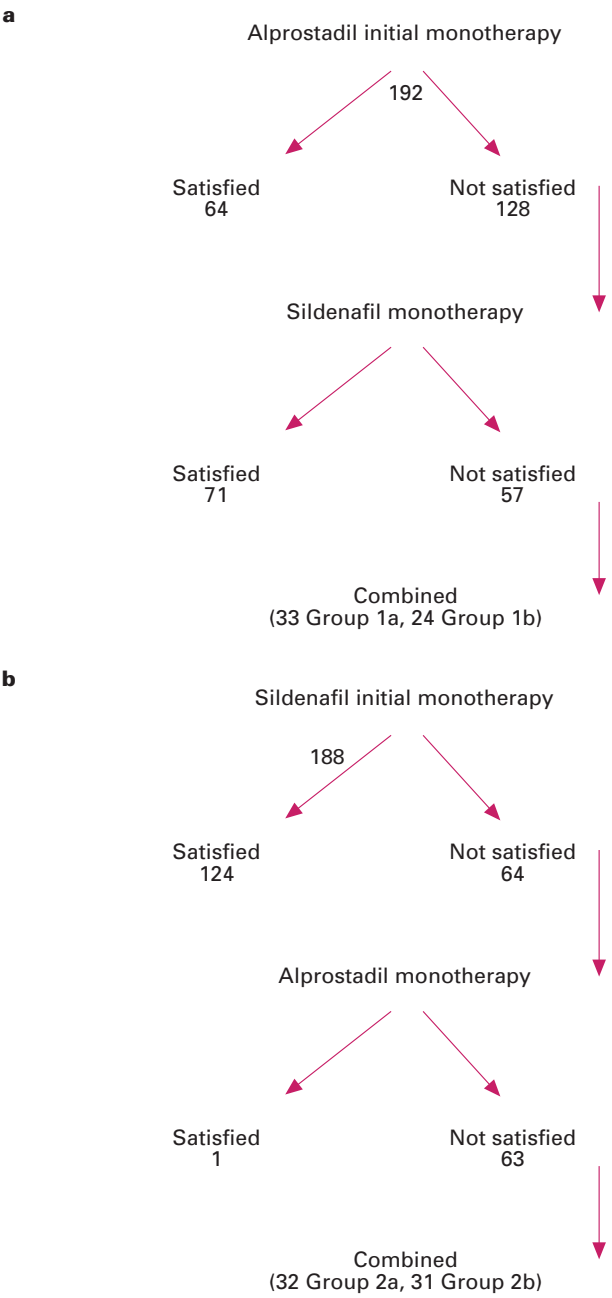

Fig. 1. Flow charts of patients who used **a,** alprostadil monotherapy initially before combination therapy or **b,** sildenafil monotherapy initially before combination therapy (group 1a private, 1b clinic).

Results

Of the 65 private patients (31 of 33 in group 1a and 29 of 32 in group 2a) and 40 of 55 clinic patients (17 of 24 in group 1b and 23 of 31 in group 2b) continued to use combined therapy for 18 months. Five private patients on combined therapy stopped after one year because they found it either too cumbersome or costly. Fifteen clinic patients stopped for similar reasons, or because they reported it to be no longer effective. The remaining patients using combined therapy continued with no

Table 1 The aetiology of erectile dysfunction

Cause	*Group 1*	*Group 2*	*Mean testosterone level (μg/L)*
After radical prostatectomy	15	16	7.20
Diabetes	21	19	7.04
Hypertensive therapy	12	12	6.78
Peripheral vascular disease	14	11	8.10
Total	62	58	7.28

complaints. Discomfort with monotherapy ranged from urethral burning, throbbing, headache, nausea, increased sensation of the glans, dizziness, dyspepsia, and blue vision. These symptoms were slightly increased with combined therapy but were still relatively mild, according to the patients, and caused none to stop treatment. No patient had priapism (Table 2).

There was an improvement in the erectile function score by 123% for combined therapy, 83% for sildenafil monotherapy and 41% for alprostadil monotherapy (Table 3; $P<0.05$) for all patients. Furthermore, the improvement in intercourse satisfaction for all patients was 125%, compared with sildenafil monotherapy (82%) and alprostadil monotherapy (39%; $P<0.05$; Table 3). However, the private patients improved by 128% and the clinic patients by 51% for overall satisfaction using combined therapy. The serum testosterone levels were within the normal range in all groups (Table 1) and there were no significant differences with the therapeutic response (data not shown).

As there were no differences in response between groups 1 and 2 for ED, the response to combined therapy did not differ depending on which monotherapy was started first (Table 2), or with the aetiology of ED. There were no significant effects on orgasmic function or sexual desire using either monotherapy or combined therapy. In addition to the significant difference between the private practice and clinic settings in the overall satisfaction response to combined therapy, the discontinuation rate was greater in the clinic than in the private patients (27% vs 7.6%). The follow-up continued for 18 months; although most patients who used combined therapy still favoured it, the intervals between usage increased because patients reported they had improved erections between treatments. Then they used the therapy as an intermittent 'booster'.

Table 2 The number of patients reporting symptoms/discomfort from using the therapies

*Symptom**	*Alprostadil*	*Sildenafil*	*Combined*
Urethral burning	17		19
Throbbing	9		13
Headache		9	11
Nausea		3	8
Increased glans sensation	3	5	9
Dizziness	1	5	6
Dyspepsia	2	4	7
Blue vision		3	4

*All symptoms were reported as mild and therefore no patient stopped treatment.

Discussion

This retrospective study evaluated five variables of sexual function based on a self-administered questionnaire in men using combined therapy for ED. Although retrospective and on a selected sample of patients, these initial results are encouraging. We hope to corroborate the findings in a randomized, double-blinded study.

Alprostadil and sildenafil promote erections by stimulating different pathways within the corporal smooth muscle. Alprostadil is a synthetic compound identical to PGE1 that directly stimulates cAMP synthesis by the cavernosal smooth muscle cells. This increase in cAMP leads to smooth muscle relaxation, which then initiates an erection [9]. Sildenafil is a selective inhibitor of type 5 cGMP phosphodiesterase, an enzyme found primarily in corporal tissue [11]. Inhibition of this enzyme causes an increased level of cGMP, which leads to smooth muscle relaxation and then erection [11]. Both drugs produce the same biological effect, i.e. erection, but through different pharmacological pathways. Therefore, combining these medications may produce drug synergy, as suggested by the present study [14,15].

There were several important observations during the present study. Even after demonstrating in the office and the clinic how intraurethral alprostadil should be administered, many patients were not administering it correctly, especially the clinic patients, and required numerous 'refresher' courses. This may have led to the greater discontent and withdrawal rate among the clinic patients. Because of the complex and cumbersome technique required, we suggest that education, motivation, persistence and realistic expectations all have an effect on the success and satisfaction of combined therapy.

Adverse publicity in the media also had a role for some clinic patients in their decision to discontinue combined therapy. Some of these patients abruptly stopped using combined therapy when reports in the press suggested that several deaths were attributed to sildenafil. Interestingly, none of the private practice patients stopped using sildenafil because of these reports once they sought medical consultation and reassurance. They understood that these deaths may have been secondary

Table 3 The IIEF scores for the different domains at baseline and when using the three therapies

IIEF domain (possible score)	*Mean (SD) scores [% above baseline]*			
	Baseline	*Alprostadil*	*Sildenafil*	*Combined*
Erectile function (1–30)	10.8 (1.1	15.2 (1.6) [41]	19.8 (1.8) [83]	24.1 (2.0) [123]
Orgasmic function (0–10)	4.5 (0.4)	4.4 (0.4)	4.6 (0.5)	5.0 (0.6)
Sexual desire (2–10)	6.1 (0.7)	6.2 (0.7)	6.5 (0.8)	6.3 (0.8)
Intercourse satisfaction (0–15)	5.1 (0.6)	7.1 (0.8) [39]	9.3 (1.0) [82]	11.5 (1.2) [125]
Overall satisfaction (2–10)	4.7 (0.4)	5.8 (0.6) [40]	7.8 (0.8) [86]	10.7 (0.9) [128]/7.1 (0.8) [51]†

†Private/clinic.

to other medical problems or ill-health of the patient. However, the clinic patients resisted further medical treatment even after being reassured about the reported deaths.

There were no significant differences in response to combined therapy whether patients started on alprostadil or sildenafil initially. The combined therapy was effective regardless of age or the aetiology of impotence. Sexual desire and orgasmic function did not significantly improve with pharmacotherapy. The main difference was in the satisfaction with combined therapy and the withdrawal rate between private and clinic patients. The proportion of patients in both samples wishing to use combined therapy was similar (65 of 214, 30%, vs 55 of 166, 33%) but there was greater frustration and less persistence in the otherwise motivated clinic patients to continue combined therapy. Furthermore, when questioned about the timing of combination therapy (sildenafil 45–60 min before, followed by alprostadil 10–15 min before intercourse) there was a greater discrepancy among the clinic patients than among the private patients. Most of the private patients had high-school, college and even postgraduate training when compared with most of the clinic population who (according to the hospital records) did not even graduate from high-school and were of a relatively lower socio-economic status. It is possible that education and socio-economic status may influence the correct usage, timing, persistence with and realistic expectations of combined therapy.

ED has many psychological implications; perhaps the private patient had more success rate because he felt that the physician had provided more time and/or attention. The clinic patient may have perceived more haste or less attention, as is sometimes the case in many busy medical institutional clinics, and therefore did not attain a similar rate of satisfaction. These possible 'intangible' factors may have affected the present results; these psychological factors may be addressed in future studies using a randomized, double-blinded study.

We cannot explain why some patients did not respond to alprostadil but did to sildenafil, and vice versa, even if they had the same primary aetiology. There was no correlation between the degree of initial ED, and surgical/medical aetiology and response. There were men in whom the severity of ED was similar whether it was caused by prostatectomy or medical conditions. As impotence is usually a multifactorial process, it is difficult to ascribe the severity of ED to one specific cause.

There were several weaknesses in the present study; the two groups of initial patients were compared at different times. It was easy to titrate patients on intraurethral alprostadil as sildenafil was not then available. Once sildenafil was marketed, it was difficult to convince patients who had a suboptimal response to this medication to try intraurethral alprostadil for a long period, as the response was usually worse. As seen in group 2, only one patient had satisfactory results from alprostadil after failing sildenafil and stayed on this medication long-term.

The lack of objective penile rigidity measurements (Rigiscan™) before and after tumescence when using combined therapy might also be criticized. However, Rigiscan results are sometimes unreliable [16] and thus comparing Rigiscan data among patients may not be accurate [16,17]. However, the end result is how the patient performs and his subjective response to the therapy, regardless of what Rigiscan or Doppler flow studies may show. Thus, the IIEF questionnaire is an appropriate instrument for assessing the response to pharmacotherapy.

Many other factors can also affect sexual activity, e.g. increased comorbidity with age, relationships with sexual partners, and physical and other psychological issues. Interestingly, the serum testosterone levels were normal and there were no differences with the response to therapy. Cost may also be an issue, especially when insurance companies may restrict the amount of reimbursement for such treatments; this may affect the long-term use of this therapy. Although intracavernosal alprostadil was offered to the patients who failed either monotherapy, they refused to undergo any treatment that involved using a needle-based injection into the penis, even if it was more effective and cheaper; nor did

they wish to risk possible scar formation, as can happen with injections.

Although this study comprised fewer patients than included in large, multi-institutional studies, it has the advantage of having a heterogeneous population, consistency of treatment and rapport between the patients and one urologist. However, these selected patients were motivated to try further treatment [18,19].

In conclusion, combined therapy appears to be a relatively safe and effective treatment for patients with ED. The patients were a highly motivated group who were willing to undergo treatment using an oral medication and a urethral suppository simultaneously. However, we caution that the success and satisfaction with combined therapy depends not only on the motivation of the patient, but possibly on other factors, e.g. education, persistence, realistic expectations and possible intangible psychological factors. These factors may affect the administration, timing sequence, and perhaps the frustrating emotional aspects and withdrawal rate of pharmacological treatments for ED. Although the present results are preliminary and from a retrospective study they are encouraging and serve as an impetus to analyse a larger sample in a randomized, double-blind study. Combined therapy should be considered in patients who fail or have a suboptimal response to monotherapy and refuse invasive treatment.

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Authors

J.H. Mydlo, MD, Associate Professor.

M.A. Volpe, MD, Chief Resident.

R.J. Macchia, MD, Professor and Chairman.

Correspondence: J.H. Mydlo, Department of Urology, Temple University Hospital, Suite 350, Parkinson Pavilion, Broad and Ontario Streets, Philadelphia, PA 19140 USA.