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Prostate Cancer

Acceptance of and Discontinuation Rate from Erectile Dysfunction Oral Treatment in Patients following Bilateral Nerve-Sparing Radical Prostatectomy

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Abstract

Objectives: Assess acceptance of and discontinuation rate from erectile dysfunction (ED) treatment in patients after bilateral nerve-sparing radical retropubic prostatectomy (BNSRRP).

Methods: We analyzed acceptance and discontinuation data of 100 consecutive, age-comparable, preoperatively self-reported potent BNSRRP patients who at the discharge from the hospital received a phosphodiesterase type 5 inhibitor (PDE5-I) prescription. Patients were informed of the pharmacokinetic properties of the available compounds and the option of on-demand versus rehabilitative therapy. Thereafter, patients did not receive any specific counseling throughout the entire follow-up period and freely decided to use or not use any ED therapy. Complete preoperative data were obtained on hospital admission and included a medical and sexual history and the International Index of Erectile Function (IIEF). The IIEF was completed every 6 mo postoperatively, and patients participated in a semi-structured interview about the treatment adherence at the 18-mo follow-up.

Results: Forty-nine (49%) patients freely decided not to start any ED therapy (group 1). Of the remaining patients, 36 (36%) opted for an as-needed PDE5-I (group 2), whereas 15 (15%) decided to use a daily PDE5-I (group 3). At the 18-mo follow-up, the overall discontinuation rate from both treatment modalities was 72.6% (eg, 72.2% vs. 73.3% in group 2 vs. group 3; $p = 0.79$). Treatment effect below expectations was the main reason for treatment discontinuation, followed by loss of interest in sex due to partner's causes.

Conclusions: Almost 50% of BNSRRP patients freely decided not to start any ED treatment postoperatively. Roughly 73% of patients who started therapy eventually discontinued it.

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1. Introduction

Radical prostatectomy (RP) is a widely performed procedure for patients with clinically localized prostate cancer (PCa) and a life expectancy of at least 10 yr [1]. This procedure may be associated with treatment-specific sequelae affecting health-related quality of life with urinary incontinence and erectile dysfunction (ED) being the most prevalent. However, the postoperative ED rate is extremely variable among the published series, ranging between 16% and 86% [2].

Phosphodiesterase type 5 inhibitor (PDE5-I) therapy is the most frequently used first-line treatment for ED following a nerve-sparing radical prostatectomy (NSRP) [2–6]. Results of this therapeutic approach remain unsatisfactory in a significant proportion of patients [2–4]. Indeed, the best modality to optimize postoperative ED treatment has not yet been discovered. In this context, early intracavernous injection therapy following RP was demonstrated to facilitate sexual intercourse, patient satisfaction, and potentially earlier return of natural erections [2]. Similarly, in a randomized, double-blind, placebo-controlled trial of early postoperative nightly sildenafil after bilateral nerve-sparing radical retropubic prostatectomy (BNSRRP), the daily administration of the drug promoted a greater rate of return to normal, spontaneous (drug-free) erectile function (EF), as compared with placebo [7].

Previous research indicated that the vast majority of men who initially respond to sildenafil after RP continue to do so at the 3-yr follow-up and are compliant with the treatment regimen [8]. In contrast, sildenafil treatment failure in previously untreated patients results in a high discontinuation rate from further ED drug treatment in the broad-spectrum ED population [9]. Common reasons for sildenafil discontinuation include effect below expectations, high cost, loss of interest in sex, and inconvenience in obtaining the drug [10]. Several studies have shown that how ED subjects used medication and the adequacy of education in the initial therapy period may also have a significant impact on the compliance with sildenafil treatment [9–11].

Few objective data are available regarding the acceptance of PDE5-Is and discontinuation rate in patients after RP in a real-life setting. This prospective study assessed both the acceptance of and discontinuation rate from ED treatment throughout a follow-up period of at least 18 mo after BNSRRP.

2. Patients and methods

On admission to our institution the day prior to surgery, all candidates for BNSRRP are comprehensively assessed with a detailed medical and sexual history. In particular, subjectively self-reported EF and the use of any erectogenic drug are carefully investigated during the patient interviews. To provide a frame of reference for objectively interpreting surgical outcomes, we also asked all patients to participate in a preoperative semi-structured interview (Appendix 1) and to complete a set of validated questionnaires including the International Index of Erectile Function (IIEF) [12].

For the patients in this series, surgeries were performed by five experienced surgeons within our department. Anatomic BNSRRP was performed according to the technique described by Walsh [13], with several modifications [1,14,15].

For the specific aim of this study, we prospectively analyzed data regarding 100 consecutive, age-comparable, preoperatively self-reported sexually active, sexually satisfied, potent BNSRRP patients undergoing surgery between November 2002 and September 2005, who had never used an erectogenic drug and were not already included in any trial for postoperative ED treatment. All patients included in the study were informed of the option of using a PDE5-I to facilitate the recovery of postoperative EF at discharge from the hospital. Patients were also informed of the pharmacokinetic properties reported in the summary of product characteristics of the available compounds and the option of on-demand versus rehabilitative therapy. All treatments were suggested to be initiated at the usual starting dose, for at least eight consecutive pills, and to be eventually up-titrated when needed. When the rehabilitative treatment was chosen, dosing regimens were 50 mg sildenafil, 10 mg vardenafil, or 10 mg tadalafil daily, starting 15 d postoperatively.

On discharge, patients were assigned to one of three treatment groups, depending exclusively on their own choice, as follows: group 1, patients who decided not to use any compound to recover postoperative EF; group 2, patients who preferred an on-demand PDE5-I; and group 3, patients who decided to use a PDE5-I with a rehabilitative protocol.

Patients included in this study were comprehensively followed-up at the uro-oncology office, but they did not receive formal sexual counseling regarding the postoperative EF at the Center for Sexual Medicine at our institute throughout the period analyzed for the specific purpose of this analysis. In addition, they did not receive any subsequent specific counseling about the PDE5-I treatment throughout the 18-mo follow-up period. During the follow-up, patients were invited to complete the IIEF every 6 mo. At the 18-mo follow-up, patients were also asked to complete a multiple-choice GAQ regarding specific reasons for eventual therapy discontinuation.

The primary end point of the present study was to assess the acceptance of and discontinuation rate from ED treatment in patients undergoing BNSRRP. The secondary end point was to detail the reasons for PDE5-I discontinuation.

Data are presented as mean ± standard deviation (SD). Data for the three groups were tested statistically using analysis of variance and χ^2 tests. For all statistical comparisons, significance was defined as $p < 0.05$.

3. Results

Table 1 lists the preoperative characteristics for the three groups of patients. Most of the patients subjectively reported both preoperative satisfactory sexual activity and EF. In addition, the baseline IIEF-EF targeting the 4 wk prior to the BNSRRP showed an average normal EF, according to the Cappelleri criteria [16]. These criteria allowed us to segregate patients' EF according to their IIEF-EF domain scores, thus subdividing those with a normal EF, from those with mild ED, those with either mild to moderate or moderate ED, and severe ED, as well.

Forty-nine (49%) of the 100 men verbally self-reporting to be preoperatively potent and strongly motivated to maintain postoperative EF freely decided not to use any postoperative ED therapy at the time of hospital discharge (group 1). During the first postoperative 18 mo, an increasing percentage of men in this group actually did not attempt any intercourse, according to the IIEF evaluations.

Table 2 reports patient characteristics throughout the 18-mo follow-up for each group. Thirty-seven of the 51 patients who were prescribed treatment, and actually initiated the therapy, discontinued it, with an overall discontinuation rate of 72.6%. Interestingly enough, four (4.6%) patients from group 1 and one (20%) patient from group 3 freely decided to start on-demand PDE5-I at the 12-mo follow-up date. However, three (75%) of the patients who previously moved from group 1 to group 2 subsequently decided to discontinue the therapy due to effect below expectations. According to their own reports, these patients did not adequately up-titrate the oral compounds after the starting dose.

Table 1 – Baseline patient characteristics for each treatment group

	Group 1	Group 2	Group 3	p^*
No. of patients (%)	49/100 (49)	36/100 (36)	15/100 (15)	0.0003 ($\chi^2 = 13.28$)
Age, yr, mean ± SD	62.3 ± 7.3	61.1 ± 5.3	60.0 ± 3.5	0.40 ($F = 2.13$)
Preoperative sexual activity, prior 4 wk				
No. patients sexually active (%)	49/49 (100)	36/36 (100)	15/15 (100)	
No. patients very satisfied (%)	41/49 (83.7)	34/36 (94.4)	14/15 (93.3)	0.73 ($\chi^2 = 0.12$)
No. patients moderately satisfied (%)	8/49 (16.3)	2/36 (5.6)	1/15 (6.7)	0.20 ($\chi^2 = 1.67$)
Preoperative erectile function, last 4 wk				
No. patients very satisfied (%)	47/49 (95.9)	35/36 (97.2)	15/15 (100)	0.92 ($\chi^2 = 0.01$)
No. patients moderately satisfied (%)	2/49 (4.1)	1/36 (2.3)	0/15 (0)	0.44 ($\chi^2 = 0.60$)
Preoperative IIEF-EF	26.6 ± 3.5	27.3 ± 3.2	27.5 ± 2.7	0.60 ($F = 0.512$)

IIEF-EF = International Index of Erectile Function-Erectile Function.
* The p value was determined according to χ^2 test or analysis of variance, as indicated.

Table 2 – Treatment group characteristics throughout the 18-mo follow-up

	Baseline	6 mo	12 mo	18 mo	p^*
Group 1					
No. patients (%)	49/100 (49)	87/100 (87)	83/100 (83)	86/100 (86)	0.04 ($\chi^2 = 4.46$)
IIEF-EF		8.9 ± 5.2	17.5 ± 9.9	19.4 ± 9.6	< 0.001 ($F = 23.63$)‡
No attempts (%)†		10/87 (11.5)	12/83 (14.5)	14/86 (16.3)	0.08 ($\chi^2 = 3.08$)
Group 2					
No. patients (%)	36/100 (36)	8/100 (8)	13/100 (13)	10/100 (10)	0.0003 ($\chi^2 = 13.13$)
IIEF-EF		17.3 ± 9.8	22.5 ± 8.4	22.5 ± 7.8	0.29 ($F = 1.27$)
No attempts (%)		0/8 (0)	0/13 (0)	0/10 (0)	
Group 3					
No. patients (%)	15/100 (15)	5/100 (5)	4/100 (4)	4/100 (4)	0.006 ($\chi^2 = 7.59$)
IIEF-EF		19.0 ± 8.6	21.5 ± 6.1	23.5 ± 2.1	0.9 ($F = 0.19$)
No attempts (%)		0/5 (0)	0/4 (0)	0/4 (0)	

IIEF-EF = International Index of Erectile Function-Erectile Function.
* The p value was determined according to χ^2 test or analysis of variance, as indicated.
† No attempts: patient did not attempt intercourse during the 4 wk prior to psychometric evaluation.
‡ $p < 0.001$: baseline vs. 6-mo and 12-mo follow-up; 6-mo vs. baseline vs. 12-mo, and vs. 18-mo follow-up; 12-mo vs. baseline and vs. 6-mo follow-up.

Table 3 – Reasons for discontinuation in treatment groups 2 and 3 (*n* = 37 of 51 patients)

Reason	No. patients (%)
Effect below expectations, without any treatment titration	28/37 (75.7)
Effect below expectations, with inadequate drug absorption	3/37 (8.1)
Loss of interest in sex (patient's reasons)	1/37 (2.7)
Loss of interest in sex (partner's reasons)	5/37 (13.5)
High cost	0/37 (0)
Side effects	0/37 (0)

Of note, the mean IIEF-EF domain scores in group 1 patients were significantly lower than those of groups 2 and 3 only at the 6-mo follow-up (*F* ratio = 13.33; $p < 0.001$). In contrast, EF was comparable among groups both preoperatively (*F* ratio = 0.51; $p = 0.60$) and at the 12-mo (*F* ratio: 2.18; $p = 0.12$) and 18-mo follow-up (*F* ratio = 0.89; $p = 0.42$).

The reasons for treatment discontinuation are listed in Table 3. Treatment effect below expectations was the main reason for treatment dropout, followed by loss of interest in sex due to partner's causes (ie, women's hypoactive sexual desire disorders in all cases). Of the patients who discontinued treatment due to effect below expectations, 75.7% did not request any treatment titration. Interestingly, three patients who discontinued the treatment due to effect below expectations also reported an inadequate drug absorption immediately after a high-fat dinner. In addition, none of those patients requested trying a different compound throughout the 18-mo follow-up period, although they had been counseled at their discharge from the hospital regarding other PDE5-Is.

4. Discussion

RP is performed to treat a substantial number of men with PCa every year worldwide. Anatomic RP was pioneered by Walsh [13], and the procedure was aimed at preserving continence and potency in appropriate candidates [1,13,14]. Unfortunately, the postoperative ED rate in this population is still an issue [2]. Patient compliance to ED treatment after RP has been either scarcely or not investigated in non-sponsored trials. In addition, to the best of our knowledge, no studies have addressed the rate of acceptance for ED treatment following BNSRRP.

In the series reported here, 49% of BNSRRP patients preoperatively self-reporting to be fully potent and strongly motivated to maintain postoperative EF decided not to begin treatment with an ED compound on discharge from the hospital. In addition, over the course of the 18-mo follow-up, an increasing number of these men did not even attempt sexual intercourse. Finally, 72.5% of those patients who after surgery freely decided to start PDE5-I therapy (either an on-demand or rehabilitative regimen), but who were not formally counseled in the Center for Sexual Medicine throughout the follow-up period, discontinued the treatment during the 18-mo follow-up.

Discontinuation from PDE5-I therapy has been investigated in the general ED population [17–22]. Harrold et al [18] found that 61% of all patients refilled sildenafil prescriptions within 3 mo of the first one and that patients having a history of previous treatment (ie, intracavernous injection) were more likely to fill a second prescription. In contrast, another study reported that only 52% of sildenafil users who had been followed up for 2 yr were still using sildenafil, although the data could be biased due to a 46% rate of loss to follow-up [19]. Likewise, Souverein et al [9] found that only 53% of their original cohort with a previous history of prescription for ED treatment (nearly all on intracavernous injection therapy) continued sildenafil. Therefore, these studies concluded that the proportion of patients continuing treatment in a real-life setting is lower than that reported in extensions of controlled trial populations.

More recently, the discontinuation rates of sildenafil responders were reported to range from 29% to 35%, with a follow-up of 6–12 mo [20,21]. In a cohort of >2100 men with ED who received sildenafil prescriptions at a single institution from 1999 to 2002, the 3-yr follow-up results demonstrated that the discontinuation rate in the sildenafil responders was 57% [10]. Common reasons for discontinuation were effects below expectations (42.3%), high cost (37.8%), and loss of interest in sex (30.5%). Significantly, partner reluctance was claimed as the main reason for discontinuation in 14.6% of the patients who discontinued treatment. Only 11.8% reported drug-related adverse events as a cause of discontinuation.

In the current series, effect below expectations was the main reason for discontinuation, with partner's loss of interest in sex being the second leading cause. However, neither treatment-related adverse events nor costs were reported by our small cohort of patients. Likewise, Gruenwald et al [22] reported that treatment-related side effects are mild to moderate in intensity and relatively well tolerated; the discontinuation rate related to adverse events ranged from 0.4% to 10%.

Lack of adequate education on PDE5-I use at the beginning of treatment and lack of continuous follow-up, with careful counseling, is probably an important factor in treatment failure and discontinuation [8,22]. In a multicenter study on patients who had discontinued sildenafil treatment due to insufficient response or dissatisfaction, patients reported that discontinuation was mostly due to the fact that they had received limited or no instructions on drug use when sildenafil was first prescribed [22]. Moreover, the study elegantly demonstrated that counseling and patient re-education were both mandatory and effective in achieving an excellent response to a second trial of sildenafil. Hatzimouratidis et al [23] confirmed in a real-life setting that ED patients who received insufficient information on the appropriate use of PDE5-Is had a significant rate of treatment failure. In their opinion, formal counseling aimed at addressing mistreatment factors must therefore become the first step in rechallenging previously misused ED treatments.

Our study is not devoid of limitations. The small number of selected patients enrolled, for instance, did not allow us to either segregate results according to each PDE5-I or to compare characteristics of those who continued versus those who discontinued treatment. In addition, this study did not use a tool dedicated to the assessment of psychological distress, which is a parameter that may have directly caused the dramatic discontinuation rate. Indeed, despite the significant increases in treatment effectiveness, the diagnosis and treatment of cancer remain some of the most emotionally distressing events in medical care.

The rate of preoperative ED also must be considered. Several studies have suggested that a significant proportion of patients with clinically localized prostate cancer and self-reported full potency in fact had suffered from ED preoperatively [24,25]. Because this study used rigorous inclusion criteria, this should not be a confounding factor here. However, preoperative ED could be one of the main reasons for effects below expectations—thus causing discontinuation of PDE5-I treatment after RP—in everyday clinical practice.

To our knowledge, no other study has examined the discontinuation rate of PDE5-Is in patients who have undergone radical prostatectomy. Our data reveal a significant discontinuation rate throughout an 18-mo follow-up in inadequately counseled patients who underwent BNSRRP. Therefore, our findings suggest that more intensive counseling regarding postoperative treatment for ED (or psychosexual counseling) is mandatory in these patients.

Educating patients and providing them with full information on the pros and cons of various treatment options should help patients feel that they are being treated with a therapy that fits their needs, thus increasing the likelihood of continuation of treatment for optimal efficacy. In support of these suggestions, Titta et al [26] reported that sexual counseling oriented toward intracavernous injection in ED patients increased the efficacy of the treatment itself, promoted patient compliance and adherence to the medication, and decreased the treatment dropout rate.

5. Conclusions

Results from the current study indicate that roughly half of BNSRRP patients preoperatively self-reporting to be fully potent and strongly motivated to maintain postoperative EF actually decided not to start any ED treatment compound on hospital discharge. Moreover, a significant proportion of inadequately counseled patients discontinued PDE5-I treatment after BNSRRP. The main reasons for this significant discontinuation rate were effects below expectations and loss of interest in sexual activities for both the patients and their partners. Specific counseling on ED treatment modalities, coupled with re-education of the patients, may represent key points in promoting a reduction of the discontinuation rate. A prospective study aimed at comparing differences in terms of both acceptance of and discontinuation rate from post-BNSRRP ED treatment in formally counseled versus non-counseled patients has been already started at our institute. In addition, the influences of preoperative EF, psychological distress, and the patient's partner's sexual health on postoperative ED treatment discontinuation also need further research.

Conflicts of interest

All authors have made a substantial contribution to the information or material submitted for publication; all have read and approved the final manuscript; authors have no direct or indirect commercial financial incentive associated with publishing the article; no commercial funding is associated with this manuscript; the manuscript or portions thereof are not under consideration by another journal or electronic publication and have not been previously published.

Moreover, there is no ethical problem or conflict of interest in relation to this manuscript.

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Appendix 1. Preoperative semi-structured interview for entering the current prospective trial

a) Have you been sexually active during the during the last 4 wk?
   1) Yes
   2) No

b) How would you rate your overall sexual function during the last 4 wk?
   1) Very satisfactory
   2) Moderately satisfactory
   3) Almost equally satisfactory and dissatisfactory
   4) Moderately dissatisfactory
   5) Very dissatisfactory

c) How would you rate your potency during the last 4 wk?
   1) Very satisfactory
   2) Moderately satisfactory
   3) Almost equally satisfactory and dissatisfactory
   4) Moderately dissatisfactory
   5) Very dissatisfactory

d) Have you ever taken any medication for improving your potency?
   1) Never
   2) Seldom (1 or 2 times)
   3) Occasionally ($\geq$ 3 times)
   4) Always

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