Finasteride 5 mg and Sexual Side Effects: How Many of these are Related to a Nocebo Phenomenon?

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ABSTRACT

Introduction. Sexual adverse experiences such as erectile dysfunction (ED), loss of libido, and ejaculation disorders have been consistent side effects of finasteride in a maximum percentage of 15% after 1 year of therapy. Such data could be seen as far from reality, if compared to a higher percentage that may be found in any common clinical practice.

Aim. This study aims to explain the dichotomy between literature's data and clinical practice data.

Methods. One hundred twenty patients with a clinical diagnosis of benign prostatic hyperplasia (BPH), sexually active and with an International Index of Erectile Function-erectile function (IIEF-EF) domain ≥25 were randomized to receive finasteride 5 mg concealed as an "X compound of proven efficacy for the treatment of BPH" for 1 year with (group 2) or without (group 1) counseling on the drug sexual side effect. The phrase used to inform group 2 patients was ". . . it may cause erectile dysfunction, decreased libido, problems of ejaculation but these are uncommon".

Main Outcome Measures. The estimation of side effect was conducted at 6 and 12 months using the male sexual function-4 (MSF-4 item) questionnaire and a self-administered questionnaire.

Results. One hundred seven patients completed the study. Group 2 patients (N = 55) reported a significant higher proportion of one or more sexual side effects as compared to group 1 (N = 52) (43.6% vs. 15.3%) ($P = 0.03$). The incidence of ED, decreased libido, and ejaculation disorders were 9.6, 7.7, and 5.7% for group 1, and 30.9, 23.6, and 16.3% for group 2, respectively ($P = 0.02$, $P = 0.04$, and $P = 0.06$).

Conclusion. In the current study, blinded administration of finasteride was associated with a significantly higher proportion of sexual dysfunction in patients informed on sexual side effects (group 2) as compared to those in which the same information was omitted (group 1) ($P = 0.03$). A scenario similar to group 2 of the current study is likely to occur in clinical practice, where the patient is counseled by the physician and has access to the drug information sheet. The burden of this nocebo effect (an adverse side effect that is not a direct result of the specific pharmacological action of the drug) has to be taken into account when managing finasteride sexual side effects. **Mondaini N, Gontero P, Giubilei G, Lombardi G, Cai T, Gavazzi A, and Bartoletti R. Finasteride 5 mg and sexual side effects: How many of these are related to a nocebo phenomenon? J Sex Med 2007;4:1708–1712.**

Key Words. Finasteride; BPH; LUTS; Erectile Dysfunction; Decreased Libido; Sildenafil

Introduction

Sexuality is an essential aspect of a couple's relationship and has a significant impact on life satisfaction. Benign prostatic hyperplasia (BPH) is a condition that commonly affects older men and is often associated with lower urinary tract symptoms (LUTS) and sexual dysfunction [1]. Men with moderate-to-severe LUTS are at increased risk for sexual dysfunction, including moderate-to-severe erectile dysfunction (ED), ejaculatory dysfunction (EjD), and hypoactive desire [1]. The results of several recent large-scale studies have shown a consistent and strong relationship

between LUTS and both ED and EjD [2]. It appears that the patophysiological mechanisms of LUTS and the related prostatic enlargement of BPH, as well as certain treatments for this condition, may have an impact on both the erection and ejaculation components of the sexual response [3,4]. Finasteride is the first 5alpha-reductase inhibitor that received clinical approval for the treatment of human BPH and androgenetic alopecia (male pattern hair loss) [5]. A large randomized trial has also shown that finasteride can decrease the incidence of prostate cancer [6]. These clinical applications are based on the ability of finasteride to inhibit the type II isoform of the 5alpha-reductase enzyme, which is the predominant form in human prostate and hair follicles, and the concomitant reduction of testosterone to dihydrotestosterone [5]. Sexual adverse experiences such as ED, loss of libido, and ejaculation disorders have been consistent side effects of finasteride in a maximum percentage of 15% after 1 year of therapy as reported in the PLESS study [7]. Following a low dose (1 mg) administration of finasteride for androgenic alopecia, none of 186 young patients (age range between 19–43 years; mean age, 28.3 years) scored abnormal values for the sexual health inventory for men questionnaire [8]. Such data could be seen as far from reality, if compared to a higher percentage that seems perceived in clinical practice. A.R. Zlotta et al. reported 38.6% of patients treated with finasteride considered their sexual function as deteriorated after 6 months of therapy for BPH [9]. The current study aims to assess whether counseling on sexual side effects may generate a higher rate of sexual dysfunction than no counseling, thus relating the dichotomy between literature's data and clinical practice data to a nocebo effect (an adverse side effect that is not a direct result of the specific pharmacological action of the drug) as reported by A. Silvestri et al. for beta-blockers [10].

Materials and Methods

A consecutive series of men with an age range between 45 and 65 complaining of LUTS underwent prostate-specific antigen (PSA) and total testosterone testing, digital rectal examination (DRE), transrectal ultrasound sonography, medical history, international prostate symptoms score (IPSS), and uroflowmetry. The patients were requested to complete the International Index of Erectile Function (IIEF) [11] and the male sexual function-4 (MSF-4 Item) [12,13] questionnaires. The MSF-4 is a psychometrically validated questionnaire with good reproducibility and clinical validity, which allows easy and appropriate assessment of male sexual function in the clinical setting ([i] interest in sex; [ii] quality of erection; [iii] achievement of orgasm; and [iv] achievement of ejaculation.) MSF-4 scoring comprises a global score (from 0 to 20 with higher scores indicating more sexual disorders) and subscores from zero (normality for the relative item) to five (maximal dysfunction for the relative item) for each of the item. The patients were eligible for the study for a total score of <8 and/or for individual item scores not exceeding two.

The patients were enrolled if they met the following inclusion criteria: (i) a clinical diagnosis of BPH (defined as follows: IPSS >7; uroflowmetry maximal urinary flow rate (Qmax) between >4 and >15 mL/s; PSA between >1.5 < 4 ng/mL; DRE nonsuspicious for prostate cancer, ultrasound prostate volume >40 cc); (ii) age ranging between 45 and 65; (iii) being sexually active with no sexual dysfunction (defined as an erectile function (EF) domain score of the IIEF >25 and a score of <2 for each question of the MSF-4) and in a stable relationship for at least 6 months; (iv) testosterone level within the normal range; (v) never on previous BPH medications; (vi) anamnesis and objective check up negative for genital pathologies; and (vii) having signed the study informed consent. The exclusion criteria included any medical therapy for pathologies considered at risk for sexual disorders.

One hundred twenty patients out of a total number of 265 that were screened in the period June–December 2005 were eligible and randomized to receive finasteride 5 mg concealed as an "X compound of proven efficacy for the treatment of BPH" with two different modes of counseling on sexual side effects: Group 1: In this group, the patients knew the "X molecule" had proven efficacy for the treatment of BPH, but were kept blinded to its potential sexual side effect. Group 2: In this group, the patients received counseling on the "X molecule" efficacy for the treatment of BPH as well as on its potential risk of sexual side effects. The phrase used to inform the patients regarding the possible occurrence of sexual problems was ". . . it may cause erectile dysfunction, decrease libido, problems of ejaculation but it is uncommon".

At 6 and 12 months follow-up, the patients were asked to complete the MFS-4 as well as a self-administered nonvalidated questionnaire that

Table 1 Demographics of the study

Characteristic	Group 1	Group 2
Mean age (year)	60 (range 52–65)	61 (range 51–65)
Main PSA (ng/mL)	2.9	2.7
Mean IPSS	14.3	15.4
Mean Qmax (mL/s)	10.7	11.2
Median prostate volume (g)	45	45.7
Mean IIEF	27	26.8
Mean testosterone (ng/DL)	425	434

PSA = prostate-specific antigen; IPSS = international prostate symptoms score; Qmax = maximal urinary flow rate; IIEF = International Index of Erectile Function.

investigated changes in sexual function by answering yes or no to the following four items:

1. Was your overall sexual function affected in the last few months?
2. Did you notice any impairment in your erectile function?
3. Did you notice any change in your ejaculatory function?
4. Has your sexual drive been affected in the last few months?

Sexual dysfunction was defined as a total MSF-4 score ≥ 8 together or as a score >2 in any individual item and at least one positive answer to the self-administered questionnaire.

In patients who discontinued prematurely for sexual side effects, a follow-up information was obtained 6 months after discontinuation to determine whether their sexual side effect had been resolved.

The patients who reported to have still ED used sildenafil 50 mg tablet on demand. We used sildenafil because it has a positive impact on men with mild to moderate LUTS [14].

This randomized observational study was approved by the ethics committee of our institution.

Statistical Analysis

The difference in distribution among the groups of patients was calculated at 1 year by using the Mann–Whitney U-test. Statistical significance was achieved if P was <0.05. All reported P values are two sides.

Results

Data are referred to 107 patients who completed the study. Thirteen were lost during a follow-up. Baseline clinical features of study patients are reported in Table 1, and did not significantly differ among the two groups.

At 6 months follow-up, the overall incidence of sexual dysfunction in patients from both groups was 24.3%, ED 15.8%, decreased libido 11.2%, and ejaculation disorders 8.4%. In group 1, 52 patients: 11.5% (six patients) reported sexual dysfunction. The incidence of ED was 5.7% (three patients), decreased libido 3.8% (two patients), and ejaculation disorders 5.7% (three patients). In group 2, 55 patients: 36.3% (20 patients) reported sexual dysfunction. The incidence of ED was 25.4% (14 patients), decreased libido 18.1% (10 patients), and ejaculation disorders 10.9% (six patients).

At 1 year, the incidence of sexual dysfunction in all patients was 29.9%, ED was 20.5%, decreased libido 15.8%, and ejaculation disorders 11.2%. In group 1, 52 patients: 15.3% (eight patients) reported sexual dysfunction. The incidence of ED was 9.6% (five patients), decreased libido 7.7% (four patients), and ejaculation disorders 5.7% (three patients). In group 2, 55 patients: 43.6% (24 patients) reported sexual dysfunction. The incidence of ED was 30.9% (17 patients), decreased libido 23.6% (13 patients), and ejaculation disorders 16.3% (nine patients) (Table 2).

Table 3 shows the evolution in the subscoring for each of the four-item MSF-4 questionnaire at 6

Table 2 Side effects at 1 year reported by patients + MSF-4

	Side effects			
	Any sexual adverse experience (%)	ED (%)	Decreased libido (%)	Ejaculation disorders (%)
All patients	29.90	20.50	15.80	11.20
Group 1	15.30	9.60	7.70	5.70
Group 2	43.60	30.90	23.60	16.30

MSF-4 = male sexual function-4; ED = erectile dysfunction.

Table 3 Changes in MSF-4 global score at 6–12 months of therapy

	Interest (SLQ1)	Erection (SLQ2)	Orgasm (SLQ3)	Ejaculation (SLQ4)
6 months	1.2	2	1	0.8
12 months	1.7	2.2	1.2	1

SLQ1 asked respondents about their interest in sex; SLQ2, the quality of their erection; SLQ3, achieving orgasm; and SLQ4, achieving ejaculation.

and 12 months in the patients who reported sexual side effects (8 in group 1 and 24 in group 2).

The patients were revaluated 6 months later for sexual side effects. Only three patients were reported to have still ED, which was resolved with sildenafil 50 mg cpr on demand.

Discussion and Conclusion

LUTS and male sexual dysfunction are highly prevalent and strongly linked in aging men. ED risk factors are very prevalent among patients with LUTS [15]. Various treatment strategies for BPH/LUTS may affect sexuality, with differences between drug classes and between drugs within the same class. The 5alpha-reductase inhibitors finasteride and dutasteride are associated with a greater risk of ED, EjD, and decreased libido than placebo. The main objective of our study was to assess whether a discrepancy exists in finasteride-related sexual side effects between double blind trials and clinical practice, and if the difference might be partially related to a nocebo effect.

To address these questions, a selected series of BPH patients with no sexual dysfunction was randomized to receive an "X compound" corresponding to the molecule finasteride in two groups that differed in the mode of counseling on treatment side effects. While group 1 patients were kept blinded on the potential side effects of the X compound in a similar way to a "single blind" trial design, information regarding the drug sexual side effects were disclosed to group 2 patients in a manner closer to a clinical scenario. The significantly higher rate of sexual disturbances among the patients aware of the drug side effects compared to those blinded to the drug side effects is consistent with a nocebo effect [16].

Notably, the incidence of sexual side effects detected by the MSF-4 in our "blinded" arm was similar to the incidence reported at 1 year in the treatment arm of randomized double blind studies such as the PLESS study [7]. A cumulative 1 year sexual side effect rate as high as 29.9% in all patients (group 1 + group 2) is likely to represent a more reliable estimation of the burden of sexual complaints encountered in clinical practice than that suggested by clinical trials. As previously reported, the maximum incidence of side effects is present after 1 year of therapy [7]. This observation is further supported by our results because a considerable proportion of patients from both arms developed side effects in the treatment period between 6 and 12 months.

Patients who are taking active medications frequently experience adverse side effects, which are not a direct result of the specific pharmacological action of the drug. Although this phenomenon is common, distressing, and costly, it is rarely studied and poorly understood. Our data confirm that the nocebo effect occurs frequently in clinical practice. These have a high prevalence in erectile disease where placebo has good results in 30–35% patients [17]. In managing adverse drug reactions through oral assumption, the nocebo effect is mandatory to recognize false positive responses. Some mechanisms have been postulated, which might be associated with the development of nocebo effects: the patient's expectations of adverse effects at the outset of treatment; a process of conditioning in which the patient learns from prior experiences to associate medication-taking with somatic symptoms; certain psychological characteristics such as anxiety, depression, and the tendency to somatize; and situational and contextual factors [18].

Recent experimental evidence indicates that negative verbal suggestions induce anticipatory anxiety about the impending pain increase, and this verbally induced anxiety triggers the activation of cholecystokinin (CCK), which, in turn, facilitates pain transmission. CCK-antagonists have been found to block this anxiety-induced hyperalgesia, thus opening up the possibility of new therapeutic strategies whenever pain has an important anxiety component [19]. Physicians and other health care personnel can attempt to ameliorate nonspecific side effects to active medications by identifying in advance those patients most at risk for developing them, and by using a collaborative relationship with the patient to explain and help the patient to understand and tolerate these bothersome but nonharmful symptoms.

In conclusion, because finasteride has different effects on sexuality, the sexual dimension should be

considered when assessing patients' expectations. The physician relationship with his/her patients is fundamental for an excellent result in terms of a low incidence of sexual side effects.

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