

Improvement in erection hardness and intercourse success with first dose of sildenafil citrate 100 mg

John P Mulhall¹
Dana L Creanga²
Vera J Stecher³

¹Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²Consultant to Pfizer Inc., New York, NY, USA; ³Medical Affairs, Primary Care Business Unit, Pfizer Inc., New York, NY, USA

Purpose: To determine, in men with erectile dysfunction (ED), the extent of improvement in erection hardness and in the rate of successful sexual intercourse (SSI) during the final intercourse attempt using sildenafil 50 mg compared with the subsequent initial attempt after a dose increase to 100 mg.

Patients and methods: This post hoc analysis used data from two randomized, double-blind, placebo-controlled studies of flexible-dose sildenafil for the treatment of men with ED, who were given sildenafil 50 mg or matching placebo, to be taken as needed before sexual intercourse. After 2 weeks, those with no tolerability concerns were titrated up to 100 mg, forming the subgroup of this analysis. The main outcome measures were event log data, including an Erection Hardness Score (EHS) and a question on SSI (“Did your erection last long enough for you to have successful sexual intercourse?”), for each attempt at sexual intercourse, analyzed by study and treatment group (sildenafil or placebo). Statistical comparisons were conducted by using the Fisher’s exact test.

Results: In both studies, the sildenafil group had a larger proportion of EHS4 (completely hard and fully rigid) erections ($P < 0.001$) and SSI ($P < 0.005$) compared with the placebo group, both before and after the dose increase. Between the final 50 mg sildenafil dose and the initial 100 mg sildenafil dose, the outcomes improved and significantly so in the larger study.

Conclusion: The improved efficacy with sildenafil 100 mg versus 50 mg, which occurs rapidly, suggests that patients should be encouraged to use 100 mg if they are unable to achieve completely hard and fully rigid erections or SSI with the 50 mg dose.

Keywords: erectile function, successful sexual intercourse, erection hardness score, dose response

Introduction

The recommended starting dose of sildenafil citrate (Viagra[®], Pfizer Inc., New York, NY, USA) for most men with erectile dysfunction (ED) is 50 mg. For many men, 50 mg is effective and provides a clinically meaningful benefit.¹ Consequently, 100 mg may not be offered because the incremental improvement in erectile function is not appreciated. However, evidence of a dose response between sildenafil 50 mg and 100 mg was seen as early as the initial controlled clinical trials supporting regulatory approval.¹ More recently, results of a double-blind, placebo-controlled, flexible-dose study showed that 88% of men who initiated sildenafil at a dose of 50 mg increased their dose to 100 mg to improve efficacy, and 98% of those who increased their dose to 100 mg remained on the higher dose.² For men who do not initially respond to sildenafil, increasing their dose to 100 mg and reeducating them

Correspondence: John P Mulhall
Memorial Sloan Kettering Cancer Center,
Urology Service, Department of Surgery,
353 E 68th Street, New York,
NY 10021, USA
Tel +1 646 422 4388
Fax +1 212 988 0768
Email mulhallj1@mskcc.org

on proper use may improve treatment response, including erectile function and rate of successful sexual intercourse (SSI), treatment satisfaction, and adherence to treatment.³⁻⁷ The central role of dose optimization in improving treatment response, regardless of reeducation, is suggested by the failure to demonstrate a statistically significant difference in scores on the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) among 1,272 men who were randomized to education to optimize ED treatment outcomes and 1,301 who received only normal clinical care (EDITS index = 77.3 versus (vs) 76.6) ($P = 0.1722$), in a prospective study conducted in treatment-naïve men prescribed sildenafil by their medical practitioner; standardized educational materials included a physician tear-off sheet, for use during consultation, and a brochure and video for the patient to take home.⁸

Quality of life is decreased by ED, which is associated with low self-esteem, depression, and anxiety.⁹⁻¹² The increased frequency of “erections hard enough for intercourse” and SSI associated with sildenafil treatment has been correlated with improvement in self-esteem and confidence, as assessed with the Self-Esteem And Relationship (SEAR) questionnaire.^{13,14} Even a shift in erection hardness from “hard enough for penetration but not completely hard” (Erection Hardness Score [EHS]3) to “completely hard” (EHS4) was associated with a significant improvement in SEAR scores.¹⁵ Furthermore, improvement in the overall SEAR score was found to be greater in men treated with sildenafil 100 mg compared with those taking sildenafil 50 mg.²

Thus, it is reasonable to assume that following a sildenafil dose increase prompted by previous suboptimal dosing, an increase in erection hardness and SSI would be achieved, bringing an improvement in self-esteem, confidence, and continued treatment adherence. However, to prevent further erosion of self-esteem and confidence, and to minimize patient discouragement and treatment discontinuation, the increase in erection hardness and ability to achieve SSI would ideally occur during the first few attempts following the dose increase.

The objective of this study was to determine the extent of improvement in erection hardness and in the rate of SSI during the final attempt at sexual intercourse when using a dose of 50 mg compared with the results for the subsequent initial attempt at sexual intercourse after a dose increase to 100 mg. Tolerability and safety were not specifically addressed in this analysis because the safety profiles of sildenafil 50 and 100 mg were previously shown to be comparable in a large

review of the double-blind, placebo-controlled trials database of sildenafil.¹⁶

Patients and methods

This analysis uses data from two previously published, randomized, double-blind, placebo-controlled, multicenter, flexible-dose studies of sildenafil for the treatment of men with ED. Both studies complied with all appropriate regulations and obtained written informed consent from all participants. The studies were conducted in the US,¹⁷ Brazil, Turkey, and the European Union.¹⁴ Men with ED at screening (score $\leq 25/30$ on the Erectile Function domain of the International Index of Erectile Function) were randomly assigned to receive a double-blinded, flexible-dose of sildenafil or matching placebo for either 6 weeks, in the larger study (clinicaltrials.gov identifier NCT00159900)¹⁴ ($n = 307$), or 10 weeks, in the smaller study (clinicaltrials.gov identifier, NCT00147628)¹⁷ ($n = 209$). These studies were selected from the overall sildenafil clinical trials database of 74 double-blind, placebo-controlled trials because both administered a flexible-dose regimen of sildenafil and assessed EHS and SSI. The men were given sildenafil 50 mg or matching placebo at the beginning of the double-blind placebo-controlled phase, to be taken as needed, approximately 1 hour before anticipated sexual intercourse. After 2 weeks, the dosage could be adjusted based on tolerability and efficacy; patients who had no tolerability concerns and insufficient efficacy were titrated up to 100 mg. Those who were unable to tolerate 50 mg were titrated down to 25 mg (larger study) or had their sildenafil therapy discontinued (smaller study).

The details of the inclusion and exclusion criteria and of the efficacy assessments have been reported previously.^{14,17} The population included in this post hoc analysis is the subgroup of men whose dose was increased from 50 mg to 100 mg after 2 weeks of treatment.

After each sexual encounter, study participants recorded the following in an event log: study medication use and whether sexual stimulation occurred, an erection was achieved, sexual intercourse was attempted, and whether the intercourse was successful (“Did your erection last long enough for you to have successful sexual intercourse?”). This event log also included the validated EHS, which asked the man to rate the hardness of his erection as follows: increase in size but not hard (EHS1); hard but not hard enough for penetration (EHS2); hard enough for penetration but not completely hard (EHS3); and completely hard and fully rigid (EHS4).¹⁸

Event log data (EHS and the outcome [success or failure] of sexual intercourse) for each attempt at sexual intercourse with sexual stimulation and medication use from the patients

whose treatment dose was increased from 50 mg to 100 mg were analyzed by study and by treatment group (sildenafil or placebo). Statistical comparisons between the reported results on the last dose before titration and the results reported on the first dose after titration were conducted by using Fisher's exact test.

Results

For the subgroups included in the current study, the population from the smaller, 10-week study was older, heavier, had a longer duration of ED, and had more frequent comorbidities than the population from the larger, 6-week study; in both studies, the distribution of ED severity was similar between the placebo and sildenafil groups, except for slight differences for severe ED and mild ED in the larger study (Table 1).

Erection hardness and the rate of SSI were calculated for attempts at sexual intercourse with medication use and sexual stimulation, before and after the dose increase (Table 2). In both studies, the sildenafil group had a larger proportion of EHS4 (completely hard and fully rigid) erections ($P < 0.001$) and SSI ($P < 0.005$) compared with the placebo group, both before and after dose increase. In both studies, the proportion of EHS4 erections increased with the initial 100 mg dose, more so in the sildenafil group

than in the placebo group. The increase in the proportion of EHS4 erections between the final 50 mg dose and the initial 100 mg dose was statistically significant in the larger study (8% vs 18% for the placebo group [$P = 0.0466$] and 34% vs 58% for the sildenafil group [$P = 0.0003$]) and showed clinical significance and borderline statistical significance in the sildenafil group of the smaller study (32% vs 49%) ($P = 0.0578$). In both studies, the rate of SSI increased with the initial 100 mg dose. The increase in rate of SSI between the final 50 mg dose and the initial 100 mg dose was statistically significant in the placebo group of the smaller study (45% vs 63%) ($P < 0.05$) and in the sildenafil group of the larger study (67% vs 80%) ($P < 0.05$). When assessed at each of the three subsequent intercourse attempts after dose increase, the increase in proportion of EHS4 erections and in the rate of SSI were sustained in the sildenafil and placebo groups, in both trials, with no more than a three percentage point decrease in proportion of EHS4 erections and a five percentage point decrease in the rate of SSI, in any group at any of the three additional assessments.

Discussion

This post hoc analysis directly compared erection hardness and the rate of SSI (with medication use and sexual

Table 1 Baseline characteristics in the subgroups of men who increased dosage from 50 mg to 100 mg

	Subset from smaller study ¹⁷		Subset from larger study ¹⁴	
	Placebo (n = 92)	Sildenafil (n = 87)	Placebo (n = 139)	Sildenafil (n = 125)
Age, mean ± SD, yrs	50.2 ± 11.7	53.0 ± 12.1	45.2 ± 8.7	44.9 ± 7.5
Race, n (%)				
White	69 (75.0)	71 (81.6)	127 (91.4)	116 (92.8)
Black	11 (12.0)	8 (9.2)	3 (2.2)	2 (1.6)
Asian	0	1 (1.1)	0	0
Other	12 (13.0)	7 (8.0)	9 (6.5)	7 (5.6)
Weight, mean ± SD (range), kg	96.2 ± 23.3	93.3 ± 17.6	82.6 ± 14.4	78.9 ± 12.8
Comorbidities, n (%)				
Hypertension	38 (41.3)	36 (41.4)	23 (16.5)	18 (14.1)
Diabetes	17 (18.5)	13 (14.9)	14 (10.1)	15 (12.0)
Hyperlipidemia and/or hypercholesterolemia	28 (30.4)	30 (34.5)	11 (7.9)	6 (4.8)
Benign prostatic hyperplasia	15 (16.3)	14 (16.1)	4 (2.9)	5 (4.0)
Depression	9 (9.8)	8 (9.2)	1 (0.7)	0
Coronary artery disease	3 (3.3)	5 (5.7)	0	2 (1.6)
Erectile dysfunction				
Duration, mean (range), yrs	3.9 (0–13)	4.6 (0–41)	2.1 (0–21)	2.5 (0–18)
IIEF-EF mean (range) score	14.8 (3–26)	14.7 (3–25)	15.9 (2–29) ^a	15.0 (1–28)
Mild/mild-moderate/moderate/severe, %	13/32/26/28 ^b	14/33/24/29 ^b	15/32/34/17 ^b	9/31/35/23 ^b
Etiology (mixed/organic/psychogenic), %	25/59/16	23/59/18	45/15/40	40/13/47

Notes: The IIEF-EF score is classified into five categories: no erectile dysfunction (26 to 30), mild (22 to 25), mild to moderate (17 to 21), moderate (11 to 16), and severe (≤ 10). ^aBaseline IIEF-EF results are missing for one patient; ^bscore was "no erectile dysfunction" for one placebo patient in the smaller study and for three placebo patients and two sildenafil patients in the larger study.

Abbreviations: IIEF-EF, Erectile Function domain of the International Index of Erectile Function; SD, standard deviation; yrs, years; n, number.

Table 2 Erection hardness and sexual intercourse success before and after dose increase during the double-blind phase

	Subset from smaller study ¹⁷						Subset from larger study ¹⁴					
	Placebo			Sildenafil			Placebo			Sildenafil		
	Final 50 mg dose	Initial 100 mg dose	P-value ^a	Final 50 mg dose	Initial 100 mg dose	P-value ^a	Final 50 mg dose	Initial 100 mg dose	P-value ^a	Final 50 mg dose	Initial 100 mg dose	P-value ^a
Attempting sexual intercourse, n ^b	64	71		72	68		107	112		115	112	
EHS3, n (%)	38 (59)	37 (52)	0.4881	37 (51)	26 (38)	0.1293	52 (49)	60 (54)	0.5003	59 (51)	35 (31)	0.0030
EHS4, n (%)	4 (6)	11 (15)	0.1054	23 (32)	33 (49)	0.0578	9 (8)	20 (18)	0.0466	39 (34)	65 (58)	0.0003
Intercourse success, n (%)	29 (45)	45 (63)	0.0393	55 (76)	59 (87)	0.1320	44 (42) ^c	60 (54)	0.0785	77 (67)	89 (80)	0.0369

Notes: ^aComparisons between first and last doses were done using Fisher's exact test; ^bwith medication use and sexual stimulation; ^cbased on n = 104 patients with data.

Abbreviation: EHS, Erection Hardness Score; n, number.

stimulation) between the final attempt at sexual intercourse before and the initial attempt after a sildenafil dose increase from 50 mg to 100 mg. An increase in sildenafil dose from 50 mg to 100 mg was associated with a higher proportion of completely hard and fully rigid erections and a higher rate of SSI during the initial attempt using the higher dose, improvements that were statistically significant in the larger study. Although the proportion of EHS4 erections and the rate of SSI increased in the sildenafil group of both studies, the absence of statistical significance in the sildenafil group of the smaller study may be attributed to a lack of power due to small sample size (beta error).

The results of the current analysis add to previously reported results that suggested a dose-response relationship, between sildenafil 50 mg and 100 mg, in the ability to achieve completely hard and fully rigid erections. For example, results of a double-blind, placebo-controlled study of fixed-dose sildenafil showed that completely hard erections (EHS4) were achieved by 25% (95% CI 19%–33%) of men in the 50 mg group (n = 94) and 35% (95% CI 27%–43%) in the 100 mg group (n = 99).¹⁹ In an international survey of more than 3,500 men with ED, the quality of erections and, specifically, the capacity to enable hard erections, was the primary attribute sought in a treatment for ED.^{14,20}

The EHS is psychometrically validated in men with ED,^{18,21} and SSI is a subjective clinical outcome that has a demonstrable relationship with erection hardness.²⁰ The odds of achieving SSI with an EHS4 were previously shown to be 24 times (95% CI, 20–29) ($P < 0.0001$) that for EHS3, with an approximately curvilinear increase in the percentage of SSI with the increase in mean EHS, from almost 60% at EHS3 to 93% at EHS4.²⁰ However, the fact that SSI might be achieved with an erection that is merely hard enough for penetration but not completely hard (EHS3) means that an increase in hardness from EHS3 to EHS4 might not be reflected in a change in SSI status. In the current study, between the final attempt at sexual intercourse before and the initial attempt at sexual intercourse after a sildenafil dose increase from 50 mg to 100 mg, the proportion of SSIs increased by 1.2-fold (from 67% to 80%) in the patients from the larger study and by 1.1-fold (from 76% to 87%) in the patients from the smaller study, despite an increase in the proportion of EHS4 erections by 1.7-fold (from 34% to 58%) and 1.5-fold (from 32% to 49%), respectively. The increase in the proportion of erections hard enough for penetration (EHS3 or EHS4) was only four percentage points in each study (from 85% to 89% in the patients from the larger study and from 83% to 87% in the patients from the smaller study). Regardless,

the higher proportion of SSI during the initial attempt using the higher sildenafil dose was statistically significant in the larger study. This result supports previously published results from controlled clinical trials of fixed-dose sildenafil that showed statistically significant dose-related (100 mg vs 50 mg) improvements in outcomes (with no dose-related increase in adverse events), on questions about the quality of the sexual experience, including the ability to have better sex ($P = 0.0103$),¹⁹ and on the odds that the patient would be able to have sexual intercourse (odds ratio, 1.96; 95% CI 1.12–3.41) ($P = 0.018$), that sexual intercourse would be attempted (odds ratio 1.29; 95% CI 1.02–1.63) ($P = 0.035$), that an erection would be maintained long enough to have successful intercourse (odds ratio 1.29; 95% CI 1.00–1.67) ($P = 0.046$), and that orgasm would be achieved (odds ratio 1.30; 95% CI 1.03–1.64) ($P = 0.025$).²²

The EHS has a demonstrable and quantifiable relationship with several health-related quality-of-life patient-reported outcomes.^{18,21,23} As reviewed by Mulhall et al,²³ EHS4 erections correlated positively (r value > 0.50) with several ED-specific and psychometrically validated patient-reported outcomes of satisfaction concepts, including individual sexual satisfaction (the Individual Satisfaction domain of the Sexual Experience Questionnaire),²⁴ satisfaction in the context of the couple or relationship (SEAR Overall Relationship Satisfaction subscale²⁵ and the Sexual Experience Questionnaire Couples Satisfaction domain), and satisfaction with erection (Quality of Erection Questionnaire).^{24,26} Also, previously reported results showed that the increased frequency of erections hard enough for intercourse and of SSI associated with sildenafil treatment correlated with improvement in self-esteem and confidence, as assessed with the SEAR questionnaire,^{13,14} that a shift in erection hardness from EHS3 to EHS4 was associated with a significant improvement in SEAR scores,¹⁵ and that improvement in the overall SEAR score was greater in men treated with sildenafil 100 mg compared with sildenafil 50 mg.² Thus, the rapid improvements in erection hardness and SSI with the 100 mg dose of sildenafil in the current analysis suggest that it should increase satisfaction and help prevent further erosion of self-esteem and confidence.

In building on previously reported results, the current analysis shows that the increase in the ability to achieve completely hard and fully rigid erections and to have SSI after sildenafil treatment is related to dose, occurs as rapidly as the initial attempt after increasing to a dose of 100 mg, and is sustained during subsequent attempts. The results from these analyses are applicable to men with ED who tolerate sildenafil 50 mg. Limitations of this research are that the

analyses were post hoc and the sample size was relatively small; however, the data are informative.

Conclusion

Men with ED who received sildenafil 50 mg for 2 weeks and then received a dose increase to sildenafil 100 mg had a higher proportion of completely hard and fully rigid erections and a higher rate of SSI at the initial sexual intercourse attempt with sexual stimulation and using the higher dose than they did with the final sexual intercourse attempt with sexual stimulation and using the lower dose. These rapid improvements in efficacy with the higher dose (100 mg) of sildenafil suggest that it should help prevent further erosion of self-esteem and confidence and minimize patient discouragement and treatment discontinuation. From a clinical care perspective, these data support a recommendation that in the absence of contraindications, men failing to achieve completely rigid erections or who have less than satisfactory SSI rates when using sildenafil 50 mg should be prescribed the 100 mg dose. Such men should be informed that they are likely to experience greater efficacy in the initial sexual attempts when using the higher dose of sildenafil.

Disclosure

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