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Original Article

Efficacy, safety and predictive factors of therapeutic success with sildenafil for erectile dysfunction in patients with different spinal cord injuries

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Study design: Multicenter, open, prospective, before-after study.
Objective: To assess the efficacy and safety of sildenafil therapy for erectile dysfunction in patients with spinal cord injury, and the association between the response to sildenafil and factors such as causes and levels of spinal cord injury, grade of ASIA deficit, time since injury, orgasmic perception, and degree of baseline erection.
Setting: Homes of outpatients of 16 spinal cord injury units in Spain.
Method: One hundred and seventy patients with erectile dysfunction secondary to spinal cord injury, from whom baseline data were collected on their sexual function, and who started treatment with sildenafil 50 mg. An efficacy assessment was made by the patient and his partner, and the score of the International Index of Erectile Function (IIEF) was recorded.
Results: It was reported by 88.2% of the patients and 85.3% of their partners that treatment with sildenafil had improved their erections, regardless of the baseline characteristics of the spinal cord injury and erectile function. In responders, this improvement was confirmed by an increase from 12.5 to 24.8 points ($P<0.001$) of the Erectile Function Domain of IIEF. A significant improvement was also seen in patients' satisfaction with sexual activity and general satisfaction derived from sexual life. Preservation of orgasmic perception and a baseline degree of erection of 3 or 4 ($P=0.006$) were predictors of therapeutic success. No serious adverse events occurred.
Conclusion: Sildenafil is an effective, well-tolerated treatment for erectile dysfunction caused by spinal cord injury, regardless of the cause, neurological level, ASIA grade, and time since injury.
Sponsorship: Spanish Society of Paraplegia.
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Keywords: erectile dysfunction; spinal cord injury; sildenafil

Introduction

Erectile dysfunction (ED) was defined as the inability to achieve and/or maintain an erection adequate for satisfactory sexual intercourse by the National Institutes of Health Consensus Panel.[1] In spinal cord injuries, organic disorders occur in both sexuality and fertility; however, sexual desire is usually well preserved and is not affected by the injury. Once the injury has occurred, the complex mechanism controlling normal sexual activity will be severely impaired. In men, this will cause a serious impairment in the physical events controlling sexual activity, such as erection, ejaculation and orgasmic perception, leading to a change in the sexual behavior of the patient with spinal cord injury. Eighty per cent of patients with spinal cord injury achieve some type of erection, either reflex, psychogenic or mixed.[2,3] However,

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the majority of these erections are inadequate for satisfactory sexual intercourse, and some form of treatment is usually required. The relaxation of the corpora cavernosa of the penis through non-adrenergic, non-cholinergic receptors is mediated by nitric oxide (NO) and cGMP. Type 5 phosphodiesterase 5 (PDE5), an enzyme found in the corpora cavernosa of the penis, the smooth muscle of vessels and the platelets, degrades cGMP.[4,5] Sildenafil is a competitive and selective inhibitor of PDE5 which enhances NO-cGMP-dependent relaxation of the smooth muscle of the corpora cavernosa of the penis, thus improving physiological erection in response to sexual stimula.[6]

Objectives

The objectives of this study were: (1) to assess the effect of sildenafil (Viagra®) on erectile function using the International Index of Erectile Function (IIEF) questionnaire,[7] and assessment by the patient and his partner by the overall efficacy question (OEQ); (2) to establish the safety and tolerability of treatment; and (3) to compare the efficacy between patients with different causes and levels of spinal cord injury, degree of ASIA deficit,[8] time since the start of erectile dysfunction, degree of baseline erection and ejaculation capacity, amongst others.

Methods

Study design
Multicenter, prospective, open, before-after study to assess the effect of sildenafil (Viagra®) on erectile function and its tolerance in 170 patients with spinal cord injury. Since this was a prospective, open study with no control group, each patient acted as his own control in the primary analysis. The following clinical data on the spinal cord injury were obtained at baseline: date, time since occurrence, cause, injury level, degree of ASIA deficiency, and presence or absence of bulbocavernous reflex. The following baseline sexual data were also recorded: orgasmic perception, ejaculatory capacity and characteristics of the erection (for this, we have used a classification of erection adapted to patients with spinal cord injury, regardless of whether erection was reflex, voluntary or mixed: Grade 0, absolute impotence; grade 1, tumescence; grade 2, erection inadequate for penetration; grade 3, can penetrate, but erection is not sufficiently rigid, and grade 4, adequate rigidity, but short-lasting).

Baseline laboratory measurements including complete blood count, biochemistry, electrocardiogram and sitting blood pressure measurement were also made.

Patients
The patients selected were men aged above 18 years with spinal cord injury who had overcome the period of medullary shock, with a stable partner and ED. Reasons for study exclusion were as follows: patients with anatomic deformities of the penis; patients in whom sexual activity was not advised, ie, patients with severe cardiovascular dysfunction such as unstable angina or severe heart failure not controlled with drugs; hypotension (BP $\leqslant$ 90/50 mmHg); recent history (less than 3 months) of stroke or acute myocardial infarction; patients treated with drugs containing nitrates; patients treated with any drug or therapy for ED they were not willing to discontinue during the study; history of retinitis pigmentosa; severe liver or kidney failure, and patients already treated with sildenafil.

Study drug
The patients received sildenafil (Viagra®) at flexible doses, starting with a 50 mg dose taken as required, approximately 30–45 min before the start of sexual activity; the recommended maximum frequency of administration was once daily. The first two doses were of 50 mg. If the patient considered the response inadequate after the second administration of 50 mg, the dose could be increased to 100 mg.

Administration of concomitant medication to treat the underlying disease of the patients and any other type of drug considered necessary at the investigator's criterion was accepted.

Variables analyzed
During the study, the overall efficacy of treatment perceived by the patient and his partner was assessed using the overall efficacy question (OEQ): Do you think that treatment has improved your erections?, ejaculatory function, the final dose of sildenafil and the response to the International Index of Erectile Function (IIEF) questionnaire. In all patients, treatment tolerability was assessed by recording potential adverse events, and by noting if they caused treatment discontinuation. The IIEF questionnaire was assessed as an overall score before and after treatment, and separated in the different dimensions of sexual function: Erectile Function (EF): questions 1 to 5 and 15; Orgasmic Function (OF): questions 9 and 10; Sexual Desire (SD): questions 11 and 12; Satisfaction with Sexual Activity (SS): questions 6 to 8; and Overall Satisfaction derived from Sexual Activity (OS): questions 13 and 14.

Statistical analysis
The statistical methods included a baseline descriptive analysis, overall and of the resulting subpopulations. A Gaussian adjustment was performed in all cases using the Kolmogorov-Smirnov test. The measurement of statistically significant differences before and after treatment in the score of IIEF questionnaire was tested by the Wilcoxon paired rank test. The Fisher exact test and the chi-squared test were used to assess the

association between qualitative variables, and the McNemar test when dichotomic variables were analyzed before and after treatment. The Mann-Whitney test was used to check baseline homogeneity of the subpopulations. A bivariant logistic regression analysis was used to analyze the potential interaction between baseline qualitative and quantitative variables with the response to treatment. An analysis of covariance (ANCOVA) was used to compare the baseline-final changes between subpopulations. All tests used for data analysis were performed assuming a maximum α error of 5% ($P<0.05$) and a two-sided contrast. The study was protected against type II errors with a power above 90%. The study was assessed by intention-to-treat.

Results

Study population

The age of the patients ranged from 19 to 65 years, with an overall mean age of 37.3 ± 9.4 years (mean $\pm$ standard deviation (SD)). Mean duration of ED (time after the spinal injury) was 7.7 ± 6.6 years (range, 0.2–32.7 years). Among the patients, 43.5% were smokers, 32.9% did not drink alcohol, and 18 patients were being treated with intracavernous prostaglandin E1 (10.6%).

The spinal cord injury had been caused by a traffic accident in 84 cases (49.4%), by an occupational accident in 23 patients (13.5%), by a casual accident in 41 patients (24.1%), and by another cause: medical/surgical complications (vascular, tumoral and iatrogenic) in the remaining 22 patients (12.9%). The spinal cord or cauda equina injury was in the cervical spine in 35 patients (20.6%), in the thoracic spine in 99 (58.2%), in the lumbar spine in 30 (17.6%) and at the sacrococcygeal level in the remaining six patients (3.6%).

The injury was located above T10 in 100 subjects (58.8%), and below that level in 70 patients (41.2%). The ASIA classification provided the following results: 94 patients in category A (57.3%), 14 in B (8.5%), 27 in C (16.5%) and 29 in D (17.7%).

At the time of study inclusion, patients had the following grades of erection: nine patients (5.3%) grade 0; 28 (16.5%) grade 1; 50 (29.4%) grade 2; 54 (31.8%) grade 3, and 29 (17.1%) grade 4.

The bulbocavernous reflex was present in 132 patients (77.6%). Orgasmic perception was reported by 57 subjects (34.1%), and ejaculation was present in 51 patients (30.5%) before study inclusion.

Efficacy assessment by the patient and partner

Among the 170 patients evaluated, 150 (88.2%) reported improved erections with the study treatment (positive response to OEQ or responders). This improvement was confirmed by 85.3% (99/116) of the partners of the patients (kappa index of agreement of 0.89).

An efficacy analysis was performed of all qualitative and quantitative variables that could be associated with a positive response to treatment, including the response to the IIEF questionnaire. For this analysis, the patients were separated based on the response to OEQ in responders (positive response, $n=150$, 88.2%) and non-responders (negative response, $n=20$, 11.8%).

Both groups were statistically homogeneous at baseline in all variables tested, except for the proportion of patients with preserved orgasmic perception, which was significantly higher in responders than in non-responders, and the degree of erection, showing a higher association of grade 3–4 with the effective response to treatment than grade 0–2. The bulbocavernous reflex is also present in a greater proportion of responders as compared to non-responders, but these differences are not statistically significant.

The distribution of responding and non-responding patients based on the ASIA classification was homogeneous. Category A is the most common classification in both subgroups. The degree of medullary deficit, either complete (ASIA A) or incomplete (non-A ASIA), showed no significant differences in the proportion of positive responses to treatment.

Table 1 Analysis of variables not associated with a positive response to sildenafil

Variable	*Responders (n=150)*	*Non-responders (n=20)*	*Odds ratio* (IC 95%)*	P**
Age (years)	37.5 (9.3)	35.6 (9.7)	–	0.380
ED duration (years)	7.9 (6.7)	6.4 (6.5)	–	0.357
Smoker	65/148 (43.9%)	8/20 (40.0%)	1.2 (0.5–3.0)	0.927
Alcohol consumption	48/147 (32.7%)	7/20 (35.0%)	0.9 (0.1–1.8)	0.965
Prior treatment with Caverject	14/150 (9.3%)	4/20 (20.0%)	0.4 (0.1–1.4)	0.285
Preserved ejaculation	46/148 (31.1%)	5/19 (26.3%)	1.3 (0.4–3.7)	0.873
Spinal cord injury <T10	59/150 (39.3%)	11/20 (55.0%)	0.5 (0.2–1.4)	0.273
Spinal cord injury >T10	91/150 (60.7%)	9/20 (45.0%)	1.9 (0.1–3.7)	0.273
Bulbocavernous reflex (+)	120/150 (80.0%)	12/20 (60.0%)	2.7 (1.0–7.1)	0.081
ASIA A	80/144 (55.6%)	14/20 (70.0%)	1.9 (0.7–4.3)	0.326
Non-A ASIA	64/144 (44.4%)	6/20 (30.0%)		

Mean (Standard deviation), *Calculated for dichotomic variables (95% confidence interval). **Student's *t*-test Chi^2 or Fisher's exact tests, depending on the variable

Table 1 shows the values of these variables, with the corresponding odds ratio and significance *P* level.

No significant differences were found in the cause of the spinal cord injury between the two subgroups, which can therefore be considered homogeneous for this variable. The distribution of the causes of spinal cord injury is shown in Table 2.

No significant differences were found either between responders and non-responders in the level of spinal cord injury. The thoracic medullary level is the most frequent site of spinal cord injury in both subgroups.

As shown in Table 3, orgasmic perception was present in a significantly higher proportion of responding than non-responding patients. On average, the presence of orgasmic perception was five times more frequent (with a minimum of 1.1 and a maximum of 22.6 times) in patients with a positive response to sildenafil (Viagra®) than in non-responders. Thus, the probability of a positive response is multiplied by 5 (with a minimum of 1.1 and a maximum of 22.6) when the patient has orgasmic perception.

On the other hand, it has been seen that the degree of erection of patients at the start of the study shows a significant linear association with a positive response to treatment with sildenafil (Viagra®).

In order to establish the degree of association and to assess its intensity by the calculation of the corresponding odds ratio, the patients have been grouped by grade of erection into two subgroups: grades 0 to 2, and grades 3 and 4. Table 4 shows that when patients are grouped in this way, no differences are seen between the two groups in the proportion of patients responding to sildenafil (Viagra®). However, the percentage of non-responders is significantly higher ($P=0.006$) in the group with erection grades 0 to 2 than in patients with erection grades 3 and 4.

On average, it can be said that moving from erection grade 0–2 to erection grade 3 and 4 multiplies the probability for a positive response by 4.5 (with a minimum of 1.4 and a maximum of 13.9).

The following efficacy variables were also analyzed:

- response to treatment as measured by the IIEF questionnaire, individually and grouped by dimensions ($n=150$)
- sexual activity assessed as the number of attempts at sexual intercourse and the percentage of successful attempts ($n=169$)
- effective dose of sildenafil (Viagra®) and proportion of patients achieving successful sexual intercourse at the first attempt ($n=169$)
- ejaculatory function ($n=158$).

IIEF questionnaire according to the patient's response to OEQ Tables 5 and 6 show the response to the IIEF questionnaire, separated by total score, by dimensions, and individually by questions. Both subgroups are homogeneous at the baseline. In the group of non-responders, none of the variables in the IIEF questionnaire is significantly changed by treatment with sildenafil (Viagra®), while in responders, all dimensions and questions of the IIEF significantly improve, causing this change to be also significantly higher in responders than in non-responders in all IIEF variables, except for the sexual desire field (Q11, Q12) and also for Q6 (frequency of attempted sexual intercourse) (Figures 1 and 2).

Table 2 Analysis of variables not associated with a positive response to sildenafil: Cause of the spinal cord injury

Cause of SCI		*Responders (n=150)*	*Non-responders (n=20)*
Traffic accident	Frequency	72	12
	%	48.0	60.0
Occupational accident	Frequency	20	3
	%	13.3	15.0
Casual accident	Frequency	28	3
	%	25.3	15.0
Medical/surgical complications	Frequency	20	2
	%	13.3	10.0

$Chi^2=1.57$, $P=0.666$

Table 3 Analysis of variables associated with a positive response to sildenafil

Variable	*Responders (n=150)*	*Non-responders (n=20)*	*Odds ratio* (IC 95%)*	P**
Preserved orgasmic perception (%)	55/148 (37.2%)	2/19 (10.5%)	5.0 (1.1–22.6)	0.021

*Calculated for dichotomic variables (95% confidence interval). **Fisher's exact test

Table 4 Baseline erection grades 0–2 *vs* baseline erection grades 3–4

Variable	*Responders (n=150)*	*Non-responders (n=20)*	*Odds ratio* (IC 95%)*	P**
Erection grade 0 to 2 ($n=87$)	71/87 (81.6%)	16/87 (18.4%)	4.5 (1.4–13.9)	0.006
Erection grade 3 and 4 ($n=83$)	79/83 (95.2%)	4/83 (4.8%)		

*Calculated for dichotomic variables (95% confidence interval). **Chi^2 test

Attempts at sexual intercourse Information is available for 169 patients. Of these, 147 (87%) reported at least one successful attempt at sexual intercourse. Of the total attempts (603) at sexual intercourse made during the study, 431 (71.5%) were successful.

Assessment of the effective dose of sildenafil (Viagra®) Of the 150 patients with a positive response, 69.8% were taking 50 mg and 30.2%, 100 mg.

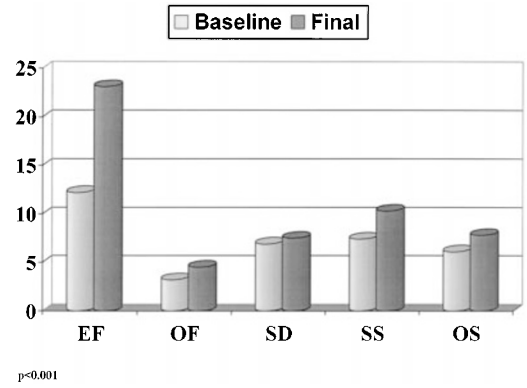

Figure 1 Baseline/final response according to IIIEF domains. Erectile function (EF); orgasmic function (OF); sexual desire (SD); satisfaction with sexual activity (SS); overall satisfaction (OS)

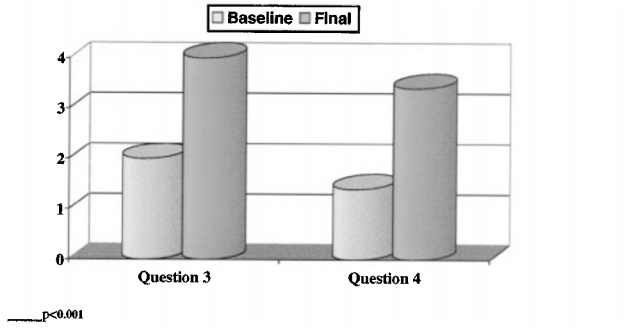

Figure 2 Questions 3 and 4 of IIEF. Question 3: Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate your partner? Question 4: Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?

Table 5 Score of the dimensions of the IIEF questionnaire

Subgroup	*Baseline*[c]	*Final*	*Change*[d] *Pts*[a]	*%*[b]	P[e]
Erectile function					
Responders ($n=133$)	12.5 (7.9)	24.8 (6.3)	12.3***	100.0	***
Non-responders ($n=17$)	10.1 (7.8)	10.4 (6.8)	0.4	16.7	ns
Orgasmic function					
Responders ($n=133$)	3.3 (3.0)	4.7 (3.0)	1.4**	0.0	***
Non-responders ($n=17$)	2.5 (2.0)	2.4 (2.1)	–0.1	0.0	ns
Sexual desire					
Responders ($n=133$)	7.0 (2.1)	7.6 (1.7)	0.6	0.0	***
Non-responders ($n=17$)	6.1 (1.6)	6.6 (1.7)	0.5	0.0	ns
Sexual satisfaction					
Responders ($n=133$)	7.3 (4.2)	10.7 (2.5)	3.4***	25.0	***
Non-responders ($n=17$)	7.5 (4.4)	6.9 (3.2)	–0.6	0.0	ns
Overall satisfaction					
Responders ($n=133$)	6.1 (2.2)	8.0 (1.5)	1.9***	28.6	***
Non-responders ($n=17$)	6.1 (2.2)	6.0 (2.1)	–0.1	0.0	ns

Values expressed as mean (standard deviation). [a]Mean change in points, [b]Median % change. Comparisons between means have been performed using [c]the Mann–Whitney test for between-group baseline comparisons, [d]Analysis of covariance (ANCOVA) for between-group comparisons of baseline-final change, and [e]Wilcoxon test for within-group baseline-final paired comparisons. $*P<0.05$, $**P<0.01$, $***P<0.001$ when significant differences exist, ns = not significant

Table 6 Questions 3 and 4 of the IIEF questionnaire

Subgroup	*Baseline*[c]	*Final*	*Change*[d] *Pts*[a]	*%*[b]	P[e]
Question 3: Capacity to achieve an erection					
Responders ($n=133$)	2.1 (1.7)	4.3 (1.2)	2.2***	100.0	***
Non-responders ($n=17$)	1.5 (1.5)	1.7 (1.5)	0.2	0.0	ns
Question 4: Capacity to maintain erection after penetration					
Responders ($n=133$)	1.4 (1.4)	3.7 (1.6)	2.3***	200.0	***
Non-responders ($n=17$)	1.2 (1.4)	1.2 (0.9)	–0.1	0.0	ns

Values expressed as mean (standard deviation), [a]Mean change in points, [b]Median % change. Comparisons between means have been performed using [c] the Mann–Whitney test for between-group baseline comparisons, [d]Analysis of covariance (ANCOVA) for between-group comparisons of baseline-final change, and [e]Wilcoxon test for within-group baseline-final paired comparisons. $*P<0.05$, $**P<0.01$, $***P<0.001$ when significant differences exist, ns = not significant

Ejaculatory function No significant changes were seen in ejaculatory function after treatment (McNemar, $P=1.0$). Three patients who had their ejaculatory function preserved before treatment were unable to ejaculate in none of the sidenafil dose administration during the study period. The reason for this was not studied, although it could be due to the low amount of sexual intercourse during study. However, four patients with no ejaculation before treatment with sildenafil (Viagra®) had ejaculation after treatment. These four patients, who responded to treatment, had ages ranging from 34 to 50 years, and the injury level was below T10 in three cases (L3, ASIA A; T11 ASIA C; T11 ASIA B). Time since SCI was more than 12 years in the first three patients and 3 years in the fourth patient. The bulbocavernous reflex was present in three cases, and the grade of erection was 3 in three cases and 2 in the remaining one. Finally, two patients had orgasmic perception with ejaculation.

Analysis of safety and tolerance

The safety of treatment was assessed by a simple descriptive analysis of the incidence of adverse events during treatment and their percentages. The safety analysis included all 170 patients receiving at least one tablet of sildenafil (Viagra®).

Adverse events were found in 41 of the 170 (24.1%) patients evaluated, of whom 10 had headache, 15 flushing, seven gastrointestinal discomfort, eight nasal congestion, and seven visual disturbances, whereas nine patients reported restlessness, palpitations, hiccup, and dry mouth. These adverse events did not persist with continued treatment.

Adverse events only required treatment discontinuation in one patient (0.59%). The reason was unbearable abdominal pain.

Discussion

The results of this study are consistent with those reported in the scientific literature for this type of patient.

Unlike other studies,[9–12] this study has been able to establish factors which allow, with a high statistical significance, to predict a positive response, such as: preserved orgasmic function and erection grades 3 and 4 at baseline.

The patients who assessed their response made it based on the criterion of the achievement of an erection hard enough for penetration and lasting long enough for maintaining satisfactory sexual intercourse. Of these, 88.2% reported an improvement in ED after treatment with sildenafil (Viagra®). To support this, the OEQ for the partner was included. An improvement was also perceived by 85.3% of partners, with a very high kappa index of agreement in responses: 0.89.

Significant differences in the response were not observed when different groups were made by level of SCI, by segments (cervical, thoracic, lumbar and sacrococcygeal and neither cervical, T1-T5, T6-T12, lumbar and sacrococcygeal). Finally we decided to make two groups: injuries above T10 (leaving intact below the injury the sympathetic and parasympathetic centers that control erection) and injuries below T10, because these two groups are better adjusted to the reflect response. No significant differences were found in all groups and the proportion of responders and non-responders was the same. Same results were found when the groups were made by grade of ASIA deficit, therefore the final groups are ASIA A and Non-A ASIA.

Response to treatment was not modified (as expected) by the cause of injury, or the time since SCI. A high percentage of patients have perceived sildenafil (Viagra®) to be an effective drug for the treatment of ED, regardless of the cause, level and time since the spinal cord injury, and of the ASIA deficit.

The fact that a patient with L3 level and ASIA A had ejaculated after taking sildenafil (Viagra®) may be explained by the sympathetic center not being affected by the injury. The case of the two patients with T11 injuries are explained because both patients had incomplete SCI that allowed them a bigger stimulation when achieving a maintained erection and therefore ejaculation. In the case of the patient with T4 ASIA A injury, the ejaculation was reflex.

Conclusions

The general conclusions that can be drawn after the statistical assessment of this study are as follows: 88.2% of men with ED due to spinal cord injury treated with sildenafil (Viagra®) reported an improvement in ED. This improvement was also perceived by their partners (85.3%), with a very high kappa index of response agreement: 0.89.

A dose of 50 mg of sildenafil (Viagra®) was required by 69.8% of patients to achieve efficacy, whereas the remaining 30.2% required a dose of 100 mg. A little over half of the patients achieved successful sexual intercourse on the first attempt (57.4%).

Significance differences in the response to treatment were not found in the analysis of the next groups: cause of SCI, level of SCI, time since SCI or ASIA deficit.

The efficacy of treatment is confirmed by the response to the IIEF questionnaire. All dimensions and individual questions significantly improved particularly erectile function and, to a lower extent, orgasmic function and sexual desire. Sildenafil (Viagra®) significantly improves the patient's satisfaction with sexual activity and overall satisfaction from sexual life ($P<0.001$).

Of all baseline variables analyzed, the presence of orgasmic perception before treatment ($P=0.021$) and erection grades 3 and 4 ($P=0.006$) are significantly associated with a positive response to treatment and, therefore, are factors predicting response.

A preserved bulbocavernous reflex is also associated with a positive response to sildenafil (Viagra®), though less strongly than the above variables.

Treatment with sildenafil (Viagra®) is safe and well-tolerated. Only one patient discontinued treatment for adverse events.

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