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Efficacy and safety of flexible-dose oral sildenafil citrate (Viagra®) in the treatment of erectile dysfunction in Brazilian and Mexican men

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A 12-week, double-blind, placebo-controlled, multicenter study evaluated the efficacy and safety of flexible-dose sildenafil citrate (Viagra®) treatment (25, 50 or 100 mg) in Brazilian and Mexican men with erectile dysfunction (ED) of broad-spectrum etiology. Efficacy was assessed on the basis of responses to the 15-item International Index of Erectile Function (IIEF) questionnaire, completed at baseline and after 12 weeks of treatment. At end point, mean scores for all IIEF domains of sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction) were significantly ($P < 0.0001$) higher in the sildenafil group ($n = 109$) than in the placebo group ($n = 105$). These findings confirm the significant increases in frequency of penetration and frequency of maintained erections reported previously. Sildenafil treatment was well tolerated. The most common adverse events were headache and flushing. In conclusion, sildenafil is a well-tolerated and effective treatment for ED of broad-spectrum etiology in Latin American men.
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Introduction

Sildenafil citrate (Viagra®) was approved for the oral treatment of erectile dysfunction (ED) in Brazil and Mexico in 1998. In men with ED, sildenafil facilitates penile erection during sexual stimulation by selectively inhibiting cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), the enzyme responsible for the catabolism of cGMP in the corpus cavernosum, thereby enhancing the nitric oxide/cGMP mechanism of penile erection.[1] The safety and efficacy of sildenafil as an oral treatment for ED was established by numerous double-blind, placebo-controlled clinical trials conducted initially in the USA, UK and Europe[2,3] and subsequently in other countries worldwide.[4] Epidemiological data suggesting a prevalence of ED of approximately 30% to 40% among Latin American men indicate the need for an effective treatment for ED in this population.[5,6]

The present clinical trial was conducted to evaluate the safety and efficacy of oral flexible-dose sildenafil treatment over a 12-week period in Latin American men with ED of broad-spectrum etiology. As in the initial controlled clinical evaluations of sildenafil for the treatment of ED,[2,3] efficacy was assessed primarily on the basis of responses to the 15-item International Index of Erectile Function (IIEF) questionnaire,[7] with the primary efficacy variables being responses to question 3 (Q3, frequency of penetration) and question 4 (Q4, frequency of maintained erection after penetration). The efficacy of sildenafil treatment was also assessed on the basis of responses to other questions of the IIEF, responses to a global efficacy question (GEQ) and responses to questions on an event log (secondary efficacy variables). Glina *et al* have previously reported the primary efficacy outcomes of this study as well as global efficacy outcomes derived from analysis of responses to GEQ and event

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log data.[8] We now report additional efficacy outcomes of the study, specifically, the effects of sildenafil treatment on IIEF domains of male sexual function. These findings extend and further support the efficacy results reported previously.

Patients and methods

Study design and patients

This was a double-blind, randomized, placebo-controlled, multicenter, parallel-group, flexible-dose study of oral sildenafil taken as required (but not more than once daily) approximately 1 h before anticipated sexual activity. The study was conducted at six clinics in Mexico and nine clinics in Brazil. The study protocol was approved by local ethics committees. All study participants gave written informed consent.

Male outpatients aged 18 y or older with a primary clinical diagnosis of ED of ≥ 6 months' duration and who were in a stable, heterosexual relationship for a duration of ≥ 6 months were eligible for enrolment in the study. Excluded were subjects with genital anatomical deformities; ED secondary to spinal cord injury; primary diagnosis of other sexual disorders, including hypoactive sexual desire; prolactin level > 3 times the upper limit of the normal range or free testosterone level $> 20\%$ below the lower limit of the normal range; uncontrolled major psychiatric disorder; diabetes mellitus that was poorly controlled or associated with untreated proliferative retinopathy; history of stroke, myocardial infarction or significant cardiovascular disease within the previous 6 months; hypotension or hypertension (blood pressure $> 170/100$ mmHg); history of major hematological, renal, or hepatic abnormalities, alcoholism or substance abuse; or retinitis pigmentosa. Patients receiving nitrates or nitric oxide donors were excluded.

During a screening period (week-4), all study participants underwent physical examination, medical history taking, 12-lead electrocardiogram (ECG), measurement of vital signs (sitting blood pressure and heart rate) and laboratory safety tests (hematology and biochemistry). Sitting blood pressure and heart rate were also measured at weeks 0, 2, 4, 8 and 12, and physical examination, 12-lead ECG and laboratory safety tests were repeated after the 12-week treatment period.

After a 4-week, treatment-free, run-in period, patients were randomized to receive 12 weeks of double-blind treatment with either sildenafil or placebo. All patients were started on a 50-mg dose of sildenafil or matching placebo for a period of two weeks, after which (at weeks 2, 4, 8 or 12), the dose could be increased to 100 mg because of lack of efficacy or decreased to 25 mg if the patient did not tolerate the current higher dose. Concurrent use of vacuum devices, intracavernosal injection, testosterone or any other medications or therapies to treat ED was not permitted.

Efficacy assessments

Efficacy was assessed on the basis of self-reported responses to the 15-item IIEF, a validated questionnaire that addresses five domains of male sexual function.[7] Patients completed the IIEF at baseline (week 0) and at the end of 12 weeks of double-blind treatment. The primary efficacy variables were Q3 and Q4, as described previously.[8] Other efficacy measures were a GEQ asking if treatment improved participants' erections and an event log in which men recorded the date and dose of study medication and/or engagement in sexual activity, presence/absence of sexual stimulation and whether sexual intercourse was successful/unsuccessful.

Table 1 International Index of Erectile Function (IIEF) domains of male sexual function

Domain	*Total score range*	*Item in each domain*
Erectile function	1–30	Q1: ability to achieve an erection Q2: frequency of erections hard enough for penetration Q3: frequency of penetration Q4: ability to maintain an erection after penetration Q5: ability to maintain erection to sexual intercourse completion Q15: confidence in getting and maintaining erection
Orgasmic function	0–10	Q9: frequency of ejaculation Q10: frequency of orgasm
Sexual desire	2–10	Q11: frequency of sexual desire Q12: level of sexual desire
Intercourse satisfaction	0–15	Q6: frequency of attempted sexual intercourse Q7: satisfaction of sexual intercourse Q8: enjoyment of sexual intercourse
Overall satisfaction	2–10	Q13: satisfaction with sex life Q14: satisfaction with sexual relationship with partner

Responses to the 15 questions of the IIEF were grouped into domains addressing five major aspects of male sexual function (Table 1): (i) erectile function; (ii) orgasmic function; (iii) sexual desire; (iv) intercourse satisfaction; and (v) overall satisfaction with sex life. All of the responses to the IIEF questions were rated on a 5-point scale, with a score of 1 representing the worst response and 5 the best response. For example, in response to questions related to erectile function (Q1–4), orgasmic function (Q9 and Q10), sexual desire (Q11) or intercourse satisfaction (Q7), a score of 1 corresponded to a response of 'almost never/never' and a score of 5 to a response of 'almost always/always'. For overall satisfaction (Q13 and Q14), a score of 1 corresponded to a response of 'very dissatisfied' and a score of 5 to 'very satisfied.' A score of 0 (for Q1–10) corresponded to 'no sexual activity', 'no sexual stimulation' or 'did not attempt intercourse.' The domain scores were computed by adding the scores for the individual questions in each domain. A subject's scores were eliminated from the calculation of a particular domain score if any item of that domain was missing.

Safety assessments

Safety was assessed primarily by adverse events occurring during treatment or within seven days of the end of treatment. The investigator assessed the severity of each adverse event and its relationship to study medication. Abnormal changes from screening in laboratory safety tests, physical examination, 12-lead ECG, heart rate or blood pressure were additional safety parameters. All patients who took at least one dose of study medication were included in the safety analysis.

Statistical analysis

All subjects who were randomized, took at least one dose of study medication and had at least one post-randomization efficacy evaluation were included in the analysis (intent-to-treat population). The five IIEF domains were analyzed using analysis of covariance (ANCOVA), including terms for treatment, baseline, center, treatment by baseline interaction and treatment by center interaction. As described previously, the primary efficacy variables (IIEF Q3 and Q4) were analyzed using ANCOVA, the GEQ was analyzed using logistic regression and the proportion of successful attempts at intercourse derived from event log data were estimated using an ANCOVA model.[8] All statistical analyses were performed using SAS® version 6.12 (Cary, NC).[9] Statistical tests were two-sided and tested at the 5% significance level.

Results

Across the 15 centers, a total of 245 patients, 124 from Mexico and 121 from Brazil, were randomized to treatment with sildenafil ($n=124$) and placebo ($n=121$). The two treatment groups had similar demographics at baseline (Table 2). The most common concomitant medical conditions were

Table 2 Patient demographics at baseline

	Sildenafil (n = *124*)	*Placebo* (n = *121*)
Mean age, y (range)	58 (28–85)	55 (27–84)
Mean time since diagnosis, y (range)	3.7 (0.5–25.6)	3.4 (0.5–21.7)
Race, *n* (%)		
Hispanic	60 (48.4)	57 (47.1)
White	60 (48.4)	58 (47.9)
Other	4 (3.2)	6 (5)
Etiology of ED, *n* (%)		
Organic	51 (41.2)	50 (41.3)
Psychogenic	25 (20.2)	18 (14.9)
Mixed	48 (38.7)	53 (43.8)
Concomitant medical disorders, *n* (%)		
Hypertension, unspecified essential	36 (29)	29 (24)
Diabetes mellitus	30 (24)	22 (18)
Prostatic hyperplasia	6 (5)	8 (7)
Visual disturbance, unspecified	5 (4.0)	7 (5.8)
Concomitant medications, *n* (%)		
Antihypertensive agents	29 (23.4)	30 (24.8)
Antidiabetic agents	27 (21.8)	27 (22.3)
Beta-adrenoceptor blockers	11 (8.9)	9 (7.4)
Sedatives, hypnotics, anxiolytics	7 (5.6)	4 (3.3)
Anti-inflammatory analgesics	6 (4.8)	13 (10.7)
Antihyperlipidemic agents	6 (4.8)	4 (3.3)
Diuretics	6 (4.8)	6 (5)

hypertension and diabetes mellitus and subsequently, the most common concomitant medications were antihypertensives and antidiabetic agents.

The sildenafil treatment group took a median of 36 doses over a median of 84.5 days and the placebo group took a median of 32 doses over a median of 84 days. The majority of study patients preferred the highest dose of study drug. Of the 124 patients in the sildenafil group, four (3%) were taking 25 mg, 48 (39%) were taking 50 mg and 71 (57%) were taking 100 mg at study end or last dose dispensed.

Overall, 15 of 124 (12%) patients in the sildenafil group and 16 of 121 (13%) patients in the placebo group prematurely discontinued the study. Discontinuations were treatment related in four (3%) patients receiving sildenafil and three (3%) patients receiving placebo. These discontinuations were due to adverse events (severe transient headache in one patient receiving sildenafil) or lack of efficacy (sildenafil, $n=3$; placebo, $n=3$).

Efficacy

A significant treatment effect in favor of sildenafil ($P<0.0001$ *vs* placebo) was seen for Q3 and Q4 and for the GEQ and the percentage of successful attempts at sexual intercourse as reported in patients' event logs).[8]

Sildenafil treatment significantly improved all five IIEF domains of male sexual function, compared with placebo (Figure 1; $P<0.0001$). Also, a significant effect in favor of sildenafil treatment was seen in each of the responses to the 15 questions of the IIEF, at the week 12 end point.

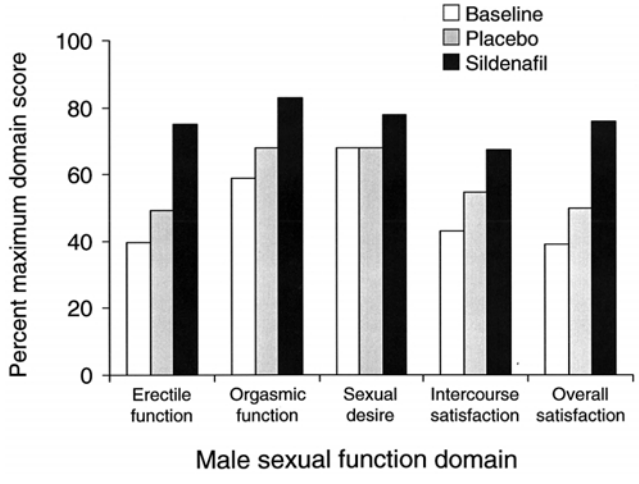

Figure 1 Percent maximal domain scores (±standard error) of the International Index of Erectile Function at baseline ($n=214$) and for men receiving sildenafil ($n=109$) or placebo ($n=105$) at the end of 12 weeks of double-blind treatment by intent-to-treat analysis.

Erectile function. In addition to significant increases in both the frequency of penetration (Q3; $P<0.0001$) and the frequency of maintained erection after penetration (Q4; $P<0.0001$), patients receiving sildenafil reported significant improvements in the ability to get an erection (Q1; $P<0.0001$), the frequency of erections hard enough for penetration (Q2; $P<0.0001$) and the ability to maintain an erection until completion of sexual intercourse (Q5; $P<0.0001$), relative to patients receiving placebo. Patients receiving sildenafil also reported significantly greater self-confidence in achieving and maintaining an erection (Q15), compared with patients receiving placebo ($P<0.0001$) and compared with their level of self-confidence at baseline ($P<0.05$).

Orgasmic function. The sildenafil group experienced significantly greater frequencies of both ejaculation (Q9; $P=0.0004$) and orgasm (Q10; $P<0.0001$), compared with the responses in the placebo group, and for Q10, also compared with baseline ($P<0.05$).

Sexual desire. The sildenafil group had significantly more frequent feelings of sexual desire (Q11; $P<0.0001$) and a significantly higher rating of sexual desire (Q12; $P=0.0003$), compared with the placebo group, and compared with baseline ($P<0.05$ for both questions).

Intercourse satisfaction. Both the satisfaction (Q7; $P<0.001$) and enjoyment (Q8; $P<0.001$) of sexual intercourse were significantly increased in the sildenafil group, compared with the placebo group. Enjoyment of sexual intercourse was also significantly increased from baseline ($P<0.05$). Sildenafil-treated patients also attempted sexual intercourse more frequently than placebo-treated patients (Q6; $P=0.05$).

Overall satisfaction. The sildenafil-treated patients were significantly more satisfied with their sex life (Q13; $P<0.0001$) and with their sexual relationships with their partners (Q14; $P<0.0001$) than patients receiving placebo.

Safety

The safety data have been previously reported.[8] Briefly, sildenafil was well tolerated; adverse events led to treatment discontinuation in only one patient who experienced severe transient headache while receiving a 100-mg dose of sildenafil. The most common adverse events considered related to sildenafil treatment by the investigator were flushing

(8.9% *vs* 0% with placebo), headache (8.9% *vs* 3.3% with placebo), dyspepsia (6.5% *vs* 0% with placebo), rash (3.2% *vs* 0% with placebo), dizziness (3.2% *vs* 0.8% with placebo), abnormal vision (3.2% *vs* 0.8% with placebo) and rhinitis (1.6% *vs* 0% with placebo). The majority of the adverse events were mild in intensity. No serious treatment-related adverse events occurred.

Discussion

The present double-blind, placebo-controlled clinical trial demonstrated that in Latin American men with ED of a broad range of etiologies, treatment with sildenafil at flexible doses on an as-needed basis for 12 weeks significantly improved numerous aspects of male sexual dysfunction. Consistent with and in support of the significant improvements in the primary efficacy variables reported previously (Table 3),[8] after 12 weeks of treatment, patients receiving sildenafil showed significant improvements in broad domains of male sexual function, including erectile function, intercourse satisfaction, orgasmic function, sexual desire and overall sexual satisfaction, compared with patients receiving placebo. The greatest increases from baseline in mean scores were observed in the erectile function (+89%), intercourse satisfaction (+55%) and overall satisfaction (+93%) domains. Furthermore, mean scores for each of the 15 items of the IIEF were significantly higher for patients receiving sildenafil than for those receiving placebo.

On the basis of assessment of erectile function using the 15-item IIEF scale, Rosen *et al* determined that the mean IIEF scores for these domains for healthy men with no history of ED were approximately 25.8 for erectile function, 8.8 for orgasmic function, 7.0 for sexual desire, 10.6 for intercourse satisfaction and 8.6 for overall satisfaction.[7] Rosen *et al* also demonstrated that, compared with these healthy controls, men with ED had significantly lower mean scores for all of these domains. Consistent with these comparisons, in the present study, the mean baseline scores for the study patients were approximately 11.9 for erectile function, 5.9 for orgasmic function, 6.8 for sexual desire, 6.5 for intercourse satisfaction and 3.9 for overall satisfaction. After 12 weeks of flexible-dose sildenafil treatment, a highly significant improvement was observed in each domain. At end point, the corresponding mean scores for these five domains (22.5, 8.3, 7.8, 10.1 and 7.6, respectively) approached or exceeded the corresponding mean scores reported for healthy men without ED.

These improvements in domain scores mirror those reported by Dinsmore *et al* in a study of 111 men with ED of broad-spectrum etiology.[3] In their placebo-controlled, double-blind study, mean IIEF scores after 12 weeks of treatment for patients receiving flexible-dose sildenafil (25, 50 or 100 mg) were significantly higher than for patients receiving placebo for all 15 questions of the IIEF. Mean IIEF scores for patients receiving sildenafil approached those observed in age-matched healthy control subjects, representing a 'near normalization' of erectile function after 12 weeks of sildenafil treatment. These findings provide evidence of the long-term effectiveness of sildenafil.

The improvements in the IIEF domains observed in the present study generally confirm the findings of other double-blind, placebo-controlled, clinical evaluations of flexible-dose sildenafil treatment in men with ED of broad-spectrum etiology.[2,10] Sexual desire, however, appears to be variably affected by sildenafil treatment. Similar to the present study, the flexible-dose, placebo-controlled study reported recently by Meuleman *et al* found sildenafil treatment to be associated with a mean domain score for sexual desire of 7.2 after 12 weeks ($P=0.04$ *vs* baseline) and 7.0 ($P=$ not significant *vs* baseline) after 26 weeks of treatment, compared with a baseline score of 6.3.[10] As in the present study, sildenafil treatment increased the mean sexual desire domain score to within the normal range (7.0),[7] both at 12 and 26 weeks. However, a previous flexible-dose study found no significant difference in the mean sexual desire domain scores for sildenafil and placebo groups after the same duration of treatment.[2] This suggests that the increase in sexual desire may occur secondary to improvements in erectile function rather than as the result of a direct effect of sildenafil on sexual desire or libido. There is no current evidence to indicate that orally administered sildenafil has effects in the brain. Indeed, previous studies have found much less of an increase in the sexual desire domain, compared with other domains.[2,11]

Sildenafil treatment was well tolerated, despite the use of the maximum dose of 100-mg by over half

Table 3 Mean scores (±standard error) for the frequency of penetration (IIEF Q3) and frequency of maintained erections after penetration (IIEF Q4) at baseline and after 12 weeks of double-blind treatment with sildenafil or placebo, by intent-to-treat analysis

IIEF question	*Baseline* (n = *214*)	*Placebo* (n = *105*)	*Sildenafil* (n = *109*)	P-*value*
Question 3	2.07 ± 0.09	2.56 ± 0.16	3.93 ± 0.15	< 0.0001
Question 4	1.75 ± 0.08	2.33 ± 0.15	3.83 ± 0.15	< 0.0001

IIEF = International Index of Erectile Function.
Adapted from Glina *et al,* 2001.[8]

(57%) of the study patients at end point. Headache and flushing were the most common adverse events of sildenafil treatment, consistent with reports from other flexible-dose, placebo-controlled studies,[2,3,10] and during general clinical use of sildenafil.[4,12] Adverse events rarely led to treatment discontinuation; only one patient discontinued sildenafil treatment at the maximum recommended dose (100 mg) after experiencing a transient, severe headache.

In conclusion, the results of this flexible-dose study demonstrate that sildenafil is an effective and well-tolerated oral treatment for ED of broad-spectrum etiology in Latin American men. The results of this study also suggest that in this patient population, sildenafil treatment can enhance male sexual function to levels approaching those reported in healthy controls with no history of ED.

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