A randomized, open-label, crossover trial evaluating sexual self-confidence and other therapeutic clinical results following the once-a-day administration of tadalafil vs. on-demand tadalafil or sildenafil in Mexican men with erectile dysfunction

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KEYWORDS
Tadalafil; Sildenafil; Erectile dysfunction; Mexican men; Psychosocial; Mexico.

Abstract

\textbf{Background:} Erectile dysfunction is an entity that has a high prevalence worldwide.
\textbf{Aims:} To compare the psychosocial clinical results of the analysis of a subgroup of Mexican men with erectile dysfunction that received tadalafil once a day (OaD), tadalafil on demand (PRN), or sildenafil PRN.
\textbf{Methods:} The present study was a post hoc analysis of a subgroup of Mexican men taken from an open, randomized, cross-sectional study of men presenting with erectile dysfunction that were previously treated with phosphodiesterase type 5 (PDE5) inhibitors PRN.
\textbf{Results:} Of the 378 patients included in the study, 84 were Mexican subjects. The change from the baseline to the endpoint was significantly greater in the Psychological and Interpersonal Relationship Scales (PAIRS) score of the Sexual Self-Confidence domain with tadalafil OaD vs. sildenafil PRN and also with tadalafil PRN vs. sildenafil PRN (differences of 0.25 ± 0.08 [0.10, 0.40]; \(p=0.001\) and 0.28 ± 0.08; [0.13, 0.43]; \(p<0.001\), respectively). No significant difference was observed with tadalafil OaD vs. tadalafil PRN (-0.03 ± 0.08 [-0.19, 0.12]; \(p=0.652\)). The changes in the PAIRS scores for the domains of Spontaneity and Time Concerns were significantly higher with tadalafil OaD vs. sildenafil PRN and with tadalafil PRN vs. sildenafil PRN. Three serious adverse events (SAEs) were reported.
\textbf{Conclusions:} Mexican men with ED showed a superior improvement in sexual self-confidence, spontaneity, and reduced time concerns related to sexual activity when treated with tadalafil OaD and tadalafil PRN, as opposed to sildenafil PRN.
Estudio aleatorizado, abierto con comparación cruzada de autoconfianza sexual y otros resultados clínicos terapéuticos tras la administración de tadalafil una vez al día vs. tadalafil o sildenafil a demanda, en hombres mexicanos con disfunción eréctil

Resumen

Objetivo: Comparar los resultados clínicos psicosociales del análisis de subgrupos de hombres mexicanos con disfunción eréctil que recibieron tadalafil una vez al día (OD), tadalafil a demanda (PRN) o sildenafil PRN.

Materiales y métodos: El presente constituyó un análisis post hoc de un subgrupo de hombres mexicanos extraído de un estudio con asignación aleatorizada, abierto y cruzado de hombres con disfunción eréctil previamente tratados con inhibidores de la fosfodiesterasa-5 (PDE-5) PRN.

Resultados: De 378 pacientes incluidos en el estudio, 84 fueron sujetos mexicanos. El cambio entre la basal y el punto final resultó significativamente superior en el puntaje del dominio de la “autoconfianza sexual” en Escalas Psicológicas y de Relaciones Interpersonales (PAIRS, por sus siglas en inglés, Psychological and Interpersonal Relationship Scales) con tadalafil OD vs. sildenafil PRN y también con tadalafil PRN vs. sildenafil PRN (diferencias de 0.25 ± 0.08 [0.10, 0.40], p=0.001; y 0.28 ± 0.08 [0.13, 0.43], p<0.001, respectivamente). No se observó ninguna diferencia significativa con tadalafil OD vs. tadalafil PRN (-0.03 ± 0.08 [-0.19, 0.12]; p=0.652). Los cambios en los puntajes de los dominios de “espontaneidad” y “preocupación por el tiempo” en PAIRS resultaron significativamente superiores con tadalafil OD vs. sildenafil PRN y con tadalafil PRN vs. sildenafil PRN. Se reportaron 3 eventos adversos serios (EAS).

Conclusiones: Hombres mexicanos con disfunción eréctil exhibieron una mejoría superior en la autoconfianza sexual, la espontaneidad y la reducción de la preocupación por el tiempo relacionadas con la actividad sexual, cuando fueron tratados con tadalafil OD y tadalafil PRN, que con sildenafil PRN.

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Introduction

Erectile dysfunction has a significantly negative impact on quality of life and relationships and is an important public health concern. In 1995, the estimated prevalence of erectile dysfunction worldwide was 152 million men and is calculated to grow to 322 million men by the year 2025.3

In Mexico, a study that analyzed 1,200 men 40 years of age or older found an erectile dysfunction prevalence of 55%. Risk factors for erectile dysfunction included prostate cancer, diabetes mellitus, and smoking. The sociodemographic factors associated with the increase of erectile dysfunction prevalence were aging, a low socioeconomic status, low educational level, unemployment, and bachelorhood; these findings were consistent with those reported for other populations.5-7

Phosphodiesterase type 5 (PDE5) inhibitors are the first-line therapy in the majority of patients with erectile dysfunction. The 3 authorized drugs in this therapeutic category are sildenafil citrate, tadalafil, and vardenafil hydrochloride (HCl). These drugs have pharmacokinetic differences; sildenafil and vardenafil have a shorter half-life (4-5 hours) and mean time for reaching the maximum plasmic concentration (1 hour); compared with tadalafil, which has a half-life of 17.5 hours and reaches maximum plasmic concentration in approximately 2 hours.12

The reestablishment of normal sexual life patterns in men with erectile dysfunction is an important therapeutic goal that goes beyond the reestablishment of erectile function; treatment should take into account the psychosocial and interpersonal problems related to this disorder.13,14 Tadalafil is capable of providing greater temporal flexibility for the patient and his partner because it has a longer half-life than the shorter acting PDE5 inhibitors, thus it can help the patient in the sense that he does not have to engage in sexual activity shortly after having taken the PDE5 inhibitor.9 This difference could represent a potential psychologic benefit over shorter acting inhibitors by reducing the anxiety related to performance before intercourse and improve the spontaneity of the sexual act.

The primary aim of the present post hoc analysis of subgroups of a study conducted in various countries was to compare the psychosocial clinical results of Mexican men with erectile dysfunction that were treated with tadalafil once a day (OaD) vs. those treated with sildenafil on demand (PRN), measuring the change in relation to the baseline in the Sexual Self-Confidence domain of the Psychological and Interpersonal Relationship Scales (PAIRS). Three treatment comparisons were carried out (tadalafil OaD, tadalafil PRN, and sildenafil PRN) in relation to the secondary aims that included additional evaluations of the psychosocial clinical results, efficacy, and safety. Informal comparisons were made between the clinical results of the Mexican subgroup and those of the total population of the previously published study.15
Methods

Study design

The main study was an open, randomized, crossover analysis, with an active 30-week drug comparison that included patients with erectile dysfunction previously treated with a PDE5 inhibitor PRN. A total of 378 patients from 34 different sites in the countries of Mexico, the United States, Europe, and Australia participated in the study. The present work is a post-hoc analysis of the data of the Mexican subgroup of the original study.

The study had an introductory period of 4 weeks after treatment was begun with sildenafil 100 mg PRN, tadalafil 5 mg OaD, or tadalafil 20 mg PRN, and the drugs were administered in a 3-period and 6-sequence design. Each 8-week treatment period was separated by a 7-day washout period (fig. 1).

The selected patients were evaluated at visit 1. During the 4-week introductory period, the patients were instructed not to take any treatment for erectile dysfunction and were asked to make at least 4 attempts at having intercourse. The baseline evaluations were made at visit 2 (PAIRS, Self-Esteem and Relationship [SEAR] questionnaire, the Erectile Function domain of the International Index of Erectile Function [IIEF-EF] questionnaire). The patients were stratified by country and PDE5 inhibitor use upon entering the study (tadalafil PRN, sildenafil PRN, vardenafil) and then were randomly assigned to one of 6 therapeutic sequences through an interactive and computerized voice response system. Each patient received each of the 3 treatments. The PAIRS, SEAR, IIEF, and Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) evaluations were carried out at the end of each 8-week treatment period (visits 3, 5, and 7).

Patients

The patients were enrolled in the main study within the time frame of September 2008 to March 2009. All the participants provided written statements of informed consent. The study was conducted in accordance with the principals of the Declaration of Helsinki and was approved by the ethics counsel.

Inclusion and exclusion criteria

The eligibility criteria were previously described in the main study. In short, the patients were men over the age of 18.

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OaD: once a day; PRN: on demand.

*Non-programmed visits for adjusting the dosage were only allowed during the first 4 weeks of each therapeutic stage.

Figure 1 Study design.
years with a history of erectile dysfunction and a satisfactory response to ongoing treatment with an oral PDE5 inhibitor PRN (tadalafil, sildenafil citrate, or vardenafil) for at least 6 months and for a minimum frequency of a single tablet per week. The patients that received prior treatment with a PDE5 inhibitor administered daily were excluded from the study. Other exclusion criteria were a surgical history of radical prostatectomy or other pelvic surgery with a subsequent failure to reach erection, patients with glycosylated hemoglobin >11%, and patients with a cardiovascular status for which sexual activity could be ill-advised.

Treatment
Each of the 3 treatments (sildenafil 100 mg PRN, tadalafil 5 mg OaD, and tadalafil 20 mg PRN) was administered by the patient according to the respective product information. The patients assigned to PRN treatment received 40 tablets and those assigned to OaD treatment received 60 tablets. Based on individual tolerability, doses could be reduced to sildenafil 50 mg PRN, tadalafil 2.5 mg OaD, or tadalafil 10 mg PRN within the first 4 weeks of each therapeutic period.

Main outcome measures of the clinical results
The clinical result of the main study was change with respect to the baseline in the PAIRS Self-Confidence domain. Secondary outcome measures included other PAIRS domains (Time Concerns and Spontaneity), the SEAR evaluation, efficacy measured by the IIEF Erectile Function domain, treatment satisfaction according to EDITS, and safety.

PAIRS is a self-applied questionnaire consisting of 3 domains (Sexual Self-Confidence, Time Concerns, and Spontaneity) related to the psychosocial clinical results associated with erectile dysfunction and its treatment. The Sexual Self-Confidence domain was the main outcome measure of the clinical result of the present study. The patients manifested their agreement or disagreement with the changes per least squares (LS), 95% bilateral confidence limits, standard errors (SE), and p values were produced for each analysis.

Safety
Safety was evaluated by the serious adverse events (SAEs) and the treatment-emergent adverse events (TEAEs). A SAE was defined as “any adverse event that causes death, requires hospitalization or prolongation of existing hospitalization, is life-threatening, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is considered significant by the researcher”. A TEAE was defined as “an event that happened for the first time or worsened after the baseline”.

Statistical analysis
The present retrospective statistical study reported the analyses of the primary and secondary clinical results of the main study (presented previously), limiting them to the subgroup of Mexican men. The primary aim was to compare the psychosocial clinical results between the therapeutic groups of tadalafil OaD and sildenafil PRN (according to the PAIRS Sexual Self-Confidence domain). The secondary aims included the therapeutic comparison between tadalafil PRN and sildenafil PRN, and tadalafil OaD vs. tadalafil PRN (the psychosocial clinical results evaluated through the scores of the PAIRS Time Concerns and Spontaneity domains and the SEAR evaluation; efficacy evaluated through the IIEF-EF; EDITS; and the safety profiles).

The changes between the treatment baseline and endpoint in each of the PAIRS and SEAR domains were analyzed as continuous variables. All the data of the primary and secondary clinical results were analyzed using the mixed effects model for the crossover design. The terms in the model were covariants for treatment, period of study, sequence, previous use of PDE5 inhibitors, country, country-per-treatment interaction, and baseline score in the PAIRS Sexual Self-Confidence domain. The model was created as part of the statistical analysis for the complete study that comprehended numerous countries. The inclusion of the term for country in the mixed model of reiterated measures (MMRM) made it possible to compare the questionnaire answers among countries, providing the scope for specific attention to the aspects that were pertinent for Mexican men. The subject within a sequence was included as a random effect, and the structure of covariance was established as non-structured. The means of the least squares for each therapeutic group were estimated based on the MMRM model per country and only Mexico was reported. The Kenward-Roger approximation was used to estimate the degrees of freedom in the denominator for the fixed effect tests. A washout period of 7 to 10 days was considered sufficient for eliminating any pharmacodynamic effect of tadalafil or sildenafil; consequently, no remnant effect was included. Means per treatment level, means of the differences per least squares (LS), 95% bilateral confidence limits, standard errors (SE), and p values were produced for each analysis.

In accordance with the protocol of the original study, the primary and secondary analyses were carried out with an intention-to-treat (ITT) focus on the complete analysis.
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group (CAG). The CAG population for the efficacy analyses included all the patients randomly assigned to treatment with baseline data measurement and at least one measurement after the baseline, whereas the safety analyses included all the randomly assigned patients that received at least one single drug dose in the study.

The total scores per SEAR questionnaire domain were determined adding the corresponding items and transforming them into a 0-100 scale calculating:

\[
\text{Transformed score} = 100 \times \frac{\text{Real score with no adjustment}}{\text{Possible score range without adjustment}} - \text{lowest possible score with no adjustment}
\]

All the therapeutic effect tests were performed at a bilateral alpha level of 0.05. The data were analyzed using the SAS™ version 9.2 program.

Results

Patient distribution

Of the 95 Mexican patients enrolled in the study, 11 were deemed screening failures; the 84 eligible patients were randomly assigned to one of the 6 therapeutic sequences. A total of 16 patients discontinued the study after the random assignation and 68 patients completed the study (fig. 2).

Baseline demographic data

Table 1 summarizes the baseline patient characteristics. The mean age of the patients was 56 years; all the patients were Hispanic, with the exception of one Caucasian. The majority of the patients (90.5%) had been diagnosed with erectile dysfunction ≥ 1 year before entering the study. Over half the patients (56.0%) had erectile dysfunction of mixed etiology. Approximately 69% of the patients had mild-to-moderate erectile dysfunction. Morning erections were slightly more frequent in the Mexican men (mean ± proportion of standard deviation, SD, 35.41 ± 30.2) than in the study in general (28.49 ± 26.6).

Psychosocial clinical results

The primary and secondary clinical results were reported as the mean difference by LS ± SE, 95% confidence interval (CI), and a \( p <0.05 \).

Primary clinical result: the difference in the improvement in the PAIRS Sexual Self-Confidence domain score was statistically significant with the administration of tadalafil OaD vs. sildenafil PRN (0.25 ± 0.08 [0.10, 0.40]; \( p=0.001 \)) (fig. 3). This observation contrasts with that of the original study, in which the difference in improvement between the 2 treatments was lower and was not statistically significant (0.06 ± 0.04 [-0.01, 0.14]; \( p=0.105 \)). This variation between the Mexican subpopulation and the total population was sustained by a significant treatment-per-country interaction (\( p=0.029 \)).

Secondary clinical results: the therapeutic comparisons between tadalafil OaD and sildenafil PRN were evaluated through the PAIRS Time Concerns and Spontaneity domains. The differences in the changes between the baseline and endpoint in the abovementioned scores were statistically significant in favor of tadalafil OaD (-0.39 ± 0.06 [-0.52, -0.27]; \( p<0.001 \) and 0.13 ± 0.06 [0.02, 0.24]; \( p=0.022 \), respectively) (fig. 3). These results were consistent with those of the original study.15

In addition to the comparisons between tadalafil OaD and sildenafil PRN (mentioned above), the changes in the scores of the PAIRS domains with tadalafil PRN vs. sildenafil PRN and tadalafil OaD vs. tadalafil PRN were also compared; the differences in Sexual Self-Confidence improvement among them were statistically significant with tadalafil PRN vs. sildenafil PRN (\( p<0.001 \), but not with tadalafil OaD vs. tadalafil PRN (\( p=0.652 \)). The differences in the reduction of Time Concerns were statistically significant with tadalafil PRN vs. sildenafil PRN (\( p < .001 \), but they were marginally
nonsignificant with tadalafil OaD vs. tadalafil PRN \( (p=0.059) \). The differences in Spontaneity were statistically significant with tadalafil PRN vs. sildenafil PRN \( (p=0.024) \), but not with tadalafil OaD vs. tadalafil PRN \( (p=0.953) \). In general terms, the results of the scores in the PAIRS domains in the Mexican subpopulation were similar to those observed in the original study population in numerous countries.\(^{15}\)

Table 2 shows the therapeutic comparisons among the 3 regimens using the SEAR scale domains and subscales. The differences in improvement in the total SEAR score, the Sexual Relationship score, and the Self-Esteem score were only statistically significant with tadalafil PRN vs. sildenafil PRN, but not with tadalafil OaD vs. tadalafil PRN or with tadalafil OaD vs. sildenafil PRN. Additionally, no statistically significant differences in the SEAR Overall Relationship scores were observed in any of the therapeutic regimens. In general terms, these results of the SEAR domains were consistent with those observed in the original study population.\(^{15}\)

**Clinical results on efficacy**

The differences in the clinical results in relation to efficacy between the therapeutic regimens were evaluated through the changes in the IIEF-EF scores. No clinically significant differences were observed in the change in the IIEF-EF score between the baseline and endpoint among the 3 therapeutic groups (Table 2). In the total study population small differences (< 1 point) were noticed that reached statistical significance in favor of one of the 2 PRN treatments. The differences in treatment satisfaction were evaluated based on the improvement in the EDITS scores; these differences were significant with tadalafil PRN vs. sildenafil PRN, but not with tadalafil OaD vs. sildenafil PRN or with tadalafil OaD vs. tadalafil PRN. No particular similarity tendency was observed upon comparing the results mentioned with those of the total study population.

**Safety**

SAEs were reported in 3 Mexican patients. An event of thyroid cancer occurred in one patient that received therapy with tadalafil PRN, preceded by therapy with...
sildenafil PRN. There was a myocardial infarction event in another patient that received therapy with tadalafil PRN, having previously received sildenafil PRN followed by tadalafil OaD, respectively. The third event was gastric cancer in one patient that received sildenafil PRN, preceded by therapy with tadalafil PRN. None of the SAEs were thought to be associated with the study drugs or any procedure related to the study. Headache, nasal congestion, and back pain were the most frequently reported TEAEs in any given treatment period (table 3). No deaths occurred during this study.

Discussion

The efficacy and safety of Tadalafil OaD and PRN in men with erectile dysfunction has been demonstrated on a worldwide level\(^{19,20}\) and the results of integrated analyses have corroborated that tadalafil is an effective, safe, and well tolerated therapy for Latin American men with erectile dysfunction of different etiologies, without taking the severity of the erectile dysfunction into account.\(^{21}\) In the present study that compared the psychosocial answers during different therapies with PDE5 inhibitors in men that had responded to a previous treatment, the improvement in Sexual Self-Confidence was statistically significant with tadalafil OaD and tadalafil PRN, compared with sildenafil PRN in this subpopulation of Mexican men. It was also found that the differences in the changes of the scores of the Time Concerns and Spontaneity domains were significant with tadalafil OaD and PRN, compared with sildenafil PRN. These results were consistent with previous reports that showed superior improvement in the scores of the PAiRS domains in patients that received tadalafil PRN, compared with those that received sildenafil PRN.\(^{22}\)

The comparisons of the score improvement in the Time Concerns and Spontaneity domains between the tadalafil OaD and tadalafil PRN therapeutic groups were not statistically significant in the present analysis, whereas those comparisons favored tadalafil OaD over tadalafil PRN in the total study population. This might be explained by the lower number of patients in the Mexican subgroup, which could have reduced the accuracy of the estimation, and not allowed a significant result. It is striking that the mean difference by LS in the therapeutic effect between the 2 groups was similar in both the total population and the Mexican subgroup (-0.11 y -0.12, respectively), even though the standard error value for the latter was twice that of the former.

The general results of the SEAR evaluation among the therapeutic groups were similar in the Mexican subgroup.
and the original study population, although the differences in improvement were statistically significant between tadalafil PRN vs. sildenafil PRN (p=0.021) in the Mexican subgroup, but not in the original study.

The comparisons of the differences between the therapeutic groups in the SEAR Confidence domain were not statistically significant, unlike the PAIRSexual Self-Confidence domain. The differences in the PAIRS and SEAR results could be explained by the manner in which confidence was evaluated by the two scales. The SEAR questionnaire includes a general Confidence domain with subscales related to general self-esteem and the overall relationship, whereas the PAIRS evaluates Sexual Self-Confidence; consequently, the 2 instruments evaluate different aspects of confidence.

Given that inadequate efficacy could affect the psychosocial clinical results, the maximum authorized dose was used in each treatment for the purpose of reducing the role of efficacy on the psychosocial clinical results to a minimum. The changes in the scores of the Erectile Function domain of the IIEF were consistent with previous findings, although no statistically significant differences in improvement in the Erectile Function domain scores of the IIEF were observed in any of the 3 therapeutic groups. In the total study population, the reduced numerical differences in the scores of the Erectile Function domain (< 1 point) among the 3 regimens were statistically significant, even though it is feasible that the differences did not have clinical significance.

The therapeutic differences in improvement in the EDITS score were significant with tadalafil PRN vs. sildenafil PRN (p=0.002), but not with tadalafil OaD vs. sildenafil PRN or with tadalafil OaD vs. tadalafil PRN in the Mexican subgroup. In general terms, these results were similar to those seen in the original study population, with the exception of tadalafil OaD vs. tadalafil PRN, which were marginally insignificant (p=0.053) in the Mexican subgroup, but significant (p=0.003) in the entire population. Once more, this could be explained by the reduced sample size of the present analysis, producing a higher standard error and preventing a significant result. An observational study that compared treatment satisfaction based on EDITS in patients that took tadalafil PRN vs. those that took sildenafil PRN reported that the scores were significantly higher from the statistical point of view in the patients that took their preferred treatment (tadalafil or sildenafil). The similarity of the EDITS scores in the therapeutic groups of this study perhaps indicates that EDITS is a more relevant indicator of erectile function than the psychosocial clinical results.25

In the total study population, the frequency of morning erections, measured by the proportion of days during the treatment period, was higher after OaD therapy, which was significantly superior to tadalafil PRN and sildenafil PRN. Even though the mentioned criterion of exploratory evaluation was not analyzed in the Mexican subgroup due to the limited number of subjects, a significant increase was observed in a previous study in the time lapse between drug administration and the first attempt at sexual intercourse among Latin American men that changed from sildenafil PRN to tadalafil.26 Even though Latin American men were analyzed as a single population group in that study, the finding suggests that it is also feasible that Mexican men (who made up about 30% of the Latin American population of said study) make use of the wide spectrum beyond 4 hours to carry out the first attempt at intercourse and thus could benefit from therapy with tadalafil OaD. The limited data available on Mexican men in particular also underlines the need for additional studies in order to better understand the specific preferences and behavior patterns of that population, which would contribute to better erectile dysfunction treatment in Mexican men.

The tolerability profile of tadalafil OaD was similar to that previously reported.19 The 3 treatments were well tolerated with few incidences of SAE and TEAE. The low incidence in the present study of TEAE that is frequently observed with PDE5 inhibitor therapy could be explained by the fact that the admitted patients were experienced PDE5 inhibitor users, thus excluding those that could have discontinued the therapy due to questions of tolerability. Close to half the patients that are prescribed a PDE5 inhibitor discontinue their therapy despite the effective reestablishment of erectile function;19 therefore it is feasible that the motives for discontinuation go beyond questions of lack of efficacy or tolerability, emphasizing the importance of understanding the psychosocial aspects of erectile dysfunction and PDE5 inhibitor treatment.
In summary, the primary clinical result and the majority of parameters of the secondary clinical results in the Mexican subgroup were similar to those observed in the main study population. The treatment-per-country interaction was significant in the PAIRS Sexual Self-Confidence and Time Concerns domains and in the SEAR Sexual Relationship domain and total score. Cultural differences and other unknown variations could more fully explain the differences observed in some of the parameters of the secondary clinical results in the Mexican patients, compared with the total patient population of this study conducted in several countries.

Strengths and limitations
A crossover design was chosen for the present study -vs. the more traditional random assignment and parallel group design- because there is much less intra-patient than inter-patient variation, making it possible to enroll fewer subjects. In addition, the patients were their own controls during the estimation of the therapeutic effect, improving the reliability of the therapeutic comparisons. In our opinion, the use of the most frequently prescribed oral PDE5 inhibitors as the compared drugs was appropriate. Likewise, we believe the study design was adequate for analyzing a chronic disease such as erectile dysfunction, commonly associated with the comorbidities of depression, high blood pressure, and diabetes.

Because this study was a retrospective post-hoc subgroup analysis, its limitations included a potential selection bias and a reduced sample size, and no adjustment was made in relation to analysis multiplicity. Furthermore, although characteristic of erectile dysfunction studies, all the evaluation criteria of the present study were clinical results reported by the patient. The patients treated with tadalafil or sildenafil PRN had a mean therapeutic dosage of 3 tablets per week (and 7 tablets per week in the case of tadalafil OaD), which could be a more frequent use of PDE5 inhibitors than that used by patients in real life. Taking into account that the present study only included Mexican patients with prior PDE5 inhibitor use, it is feasible that the results are only relevant for that specific population with erectile dysfunction. Other prospective studies on Mexican men with erectile dysfunction are needed in order to confirm the results of the present analysis.

Conclusions
Mexican men with erectile dysfunction exhibited statistically significant improvement in the PAIRS Sexual Self-Confidence domain when treated with tadalafil OaD, compared with sildenafil PRN; the differences in Sexual Self-Confidence improvement were not statistically significant with tadalafil OaD, when compared with tadalafil PRN. Score improvement in the Time Concerns and Spontaneity domains were also statistically significant with tadalafil OaD and tadalafil PRN, compared with sildenafil PRN.

The changes in the scores of the SEAR, IIEF-EF, and EDITS domains between the baseline and endpoint were similar in all the therapeutic groups among the Mexican men. The adverse effects reported in the present study were consistent with the events reported in previous studies on PDE5 inhibitors. These findings suggest that Mexican men may experience greater increases in sexual self-confidence and less time concerns related to sexual activity when they take tadalafil OaD or tadalafil PRN, compared with sildenafil PRN.

Conflict of interest
The authors declare that there is no conflict of interest.

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References