Sildenafil Citrate Improves Self-Esteem, Confidence, and Relationships in Men with Erectile Dysfunction: Results from an International, Multi-Center, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Introduction. Erectile dysfunction (ED) can significantly impact a man's relationships and well-being.
Aim. We assessed changes in self-esteem, confidence, sexual relationship satisfaction, and overall relationship satisfaction in men with ED using the validated Self-Esteem And Relationship questionnaire (SEAR).
Methods. This was a 12-week, double-blind, placebo-controlled, flexible-dose (25, 50, 100 mg, as needed) international study of sildenafil in men ≥18 years of age in Mexico, Brazil, Australia, and Japan.
Main Outcome Measures. The primary study outcome was change in self-esteem from baseline to the end of treatment. Secondary study measures were changes in other SEAR components, International Index of Erectile Function (IIEF) domains, percentage of intercourse attempts that were successful, and the response to a global efficacy question at the end of treatment.
Results. Patients were well balanced for age and duration of ED (placebo = 149 and sildenafil = 151). Compared with placebo, sildenafil significantly improved self-esteem, confidence, sexual relationship satisfaction, and overall relationship satisfaction ($P < 0.0001$). The psychosocial measures of well-being assessed with the SEAR were positively correlated (range 0.60–0.86, $P < 0.0001$) with erectile function, the frequency of achieving erections that allowed satisfactory sexual intercourse, the percentage of successful sexual intercourse attempts, and global treatment efficacy.
Conclusions. Significant improvements in self-esteem, confidence, sexual relationship satisfaction, and overall relationship satisfaction after treatment of ED with sildenafil were consistent among countries. These data suggest a substantial cross-cultural improvement in well-being after successful treatment of ED with sildenafil. **Althof S, O'Leary M, Cappelleri J, Hvidsten K, Stecher V, Glina S, King R, and Siegel R. Sildenafil citrate improves self-esteem, confidence, and relationships in men with erectile dysfunction: Results from an international, multi-center, double-blind, placebo-controlled trial. J Sex Med 2006;3:521–529.**

Key Words. Psychological Assessment of Sexual Dysfunction; Male Erectile Disorder; Oral Vasoactive Agents

Introduction

The reported prevalence estimates for erectile dysfunction (ED) in men from different countries vary greatly, ranging from 10% to more than 80% [1–9]. However, it is difficult to determine how much of the variability results from cultural differences, the definition of ED used, or from study methodology (e.g., clinic vs. general population, differing age groups, and so on). A worldwide study of the prevalence of sexual dysfunction across seven global regions reveals that the prevalence of ED in men aged 40–80 ranged from 13% to 28% in the 29 countries surveyed [10]. These data indicate that, despite cultural, religious, socioeconomic, and geographic differences, ED is a common problem. Factors that are more predictive of ED include age and coexisting

medical conditions, particularly diabetes, depression, hypertension, and cardiovascular disease [1,2,4–9].

The impact of ED extends beyond a patient's sexual life; it can also diminish well-being and quality of life [11]. ED is associated with depression, anxiety, and loss of self-esteem [11,12]. Because of its association with low physical and emotional satisfaction in men and their partners, ED is considered a couple's issue [11]. Successful treatment of ED can improve a man's mental and social health, well-being, and self-esteem [11]. The Self-Esteem And Relationship questionnaire (SEAR) is a validated instrument to assess how treatment of ED can affect specific psychosocial factors including self-esteem, confidence, sexual relationship satisfaction, and overall relationship satisfaction [13].

The SEAR has undergone rigorous development and validation using established psychometric principles [13], and showed construct validity and responsiveness to effective treatment of ED with sildenafil [14,15]. Subsequently, the 14-item SEAR was linguistically translated and culturally adapted for use cross-culturally. The SEAR consists of two domains: the Sexual Relationship domain (eight items) and the Confidence domain (six items). The Confidence domain has two subscales: the Self-Esteem subscale (four items) and the Overall Relationship subscale (two items). Scores on the SEAR are summed and transformed onto a 100-point scale for individual items, domains, subscales, and an overall SEAR score. Higher scores are more favorable.

In studies using the SEAR to assess the impact of treatment of ED with sildenafil citrate, successful treatment of ED was associated with significant and large improvements in self-esteem, confidence, sexual relationship satisfaction, and overall relationship satisfaction [14,15]. In an open-label study of men in the United States with ED, treatment with sildenafil was associated with normalization of relationship, confidence, and self-esteem scores on the SEAR to values reported from men without ED [16]. The International Index of Erectile Function (IIEF), considered the gold standard for measuring erectile function, has been linguistically validated and translated and used in studies in North, South, and Central America, Europe, Africa, and Asia [17–26]. Using the IIEF, these studies demonstrated that sildenafil was effective in improving erectile function in men with ED across many cultures [27].

Using the SEAR, we sought in the current study to investigate the impact of sildenafil treatment on psychosocial functioning and well-being in men with ED from four countries. In this report, we present the findings of the first international, double-blind, placebo-controlled study that utilized the SEAR to measure changes in self-esteem, confidence, sexual relationship satisfaction, and overall relationship satisfaction in men with ED after treatment with sildenafil.

Methods

Patients

Study participants were men with ED from Australia, Brazil, Japan, and Mexico. Patients were ≥18 years of age in a stable sexual relationship, who were diagnosed with ED (documented by a score of ≤21 on the Sexual Health Inventory for Men) [28], and had low self-esteem (documented by a score of ≤75 on the Self-Esteem subscale of the SEAR). Because the primary study outcome was the impact of sildenafil on changes in self-esteem, only patients with ED whose self-esteem was diminished (indicated by a SEAR score ≤75) were enrolled. This cutoff point allowed investigators to observe expected improvements in self-esteem scores after treatment with sildenafil or placebo. All patients provided written informed consent before entering the study, and the protocol was approved by local institutional review boards.

Major exclusion criteria included hypotension or hypertension, significant cardiovascular disease, prescribed or taking nitrates or ritonavir, relevant clinically significant abnormal laboratory results, and prior use of more than six tablets of sildenafil.

Study Design

This randomized, parallel-group, double-blind, placebo-controlled, flexible-dose study was conducted between July 2002 and March 2003 at 29 centers (Australia = 5, Brazil = 13, Japan = 2, and Mexico = 9). The study included a 2-week no-treatment screening phase followed by a 12-week treatment phase during which patients received sildenafil 50 mg adjustable to 25 mg or 100 mg, or matching placebo, taken approximately 1 hour before anticipated sexual activity but not more than once daily.

Efficacy Variables

The SEAR and IIEF were administered at baseline and at week 12. Throughout the study, patients recorded medication dose and sexual activity in an

at-home event log that was used to determine the percentage of sexual intercourse attempts that were successful. At the end of treatment, a global efficacy question (GEQ), "When you took a dose of study drug and had sexual stimulation, how often did you get an erection that allowed you to engage in satisfactory sexual intercourse?" was asked and scored on an ordinal scale from 1 (almost never or never) to 5 (almost always or always); a response of "did not attempt intercourse" was scored as a zero.

Main Outcome Measures

The primary study outcome, prospectively defined, was change from baseline to end of treatment on the Self-Esteem subscale of the SEAR. Secondary measures were change from baseline score to end of treatment for the other SEAR components, IIEF domains, and percentage of intercourse attempts that were successful. An additional secondary measure was response on the GEQ at end of treatment.

Statistical Analyses

Scores were collected and descriptively analyzed from individual study sites, and the data from all sites were also pooled for inferential analysis. Observed baseline and week 12 (or end-of-treatment for subjects who withdrew before week 12) scores were summarized descriptively for each country. Based on the combined data across countries, change scores from baseline to week 12 (or end of treatment) on the SEAR, IIEF, and percentage of successful intercourse attempts were analyzed inferentially using an analysis of covariance (ANCOVA) model, controlling for corresponding baseline score and center, with the treatment group as the key explanatory variable. Ninety-five percent confidence intervals (CI) of mean scores were determined for within-group changes and between-group comparisons. In addition, change scores from baseline to week 12 on the SEAR were analyzed using a linear model with baseline score, country, treatment, and treatment-by-country interaction to examine whether differences in change SEAR scores between treatments differed by country.

Effect sizes on a particular SEAR component, measured in standard deviation (SD) units, were calculated as the difference in the mean change scores between treatment groups, divided by the SD of the baseline scores on the corresponding SEAR component [29–31]. Based on common benchmarks, effect sizes of 0.20 SD units are considered small, 0.50 medium, and 0.80 large [32].

Finally, partial Pearson's correlations (controlling for treatment) were determined on changes of SEAR component scores with changes in IIEF domain scores and changes in the percentage of intercourse attempts that were successful, and also between SEAR and GEQ responses at the end of treatment.

All statistical tests were performed at the two-sided 5% level of significance, using Statistical Analysis System software, version 8 [33]. The analysis of efficacy was conducted on the intent-to-treat (ITT) population, defined as all randomized patients who took at least one dose of study medication and who presented efficacy data that could contribute to at least one post-treatment efficacy analysis. The last observation carried forward value was used for patients who discontinued early. The analysis of safety was conducted on all randomized patients who took at least one dose of study medication.

Results

Patient Characteristics

A total of 300 patients were randomized, received study medication (sildenafil N = 151; placebo N = 149), and were included in the safety analysis. Patients were well balanced for age, etiology and duration of ED, and baseline SEAR scores (Table 1). At the end of treatment, 282 patients were included in the ITT group for analysis of efficacy: 42 patients from Australia, 129 from Brazil, 17 from Japan, and 94 from Mexico.

Self-Esteem and Other Components of the SEAR

Compared with observed (raw) mean changes in SEAR scores in the placebo group, observed mean changes in Self-Esteem subscale scores were substantially and noticeably improved after treatment of ED with sildenafil for each country (Figure 1a). Patients in the four countries who received sildenafil had improvements in Self-Esteem scores that ranged from 33.6 to 46.3 points, compared with a change of −7.6 to 25.7 points for patients randomized to placebo (Figure 1b).

An analysis of the data combined across countries using an ANCOVA model controlling for baseline SEAR score and center, with treatment group as the key explanatory variable, revealed that the main effect for treatment was significant and considerable (Figure 2). Compared with patients receiving placebo, patients receiving sildenafil had significantly greater improvement in self-esteem, confidence, sexual relationship satisfaction, and

Table 1 Patient characteristics

	Placebo N = 149	Sildenafil N = 151
Age (year), mean ± SD (range)	54 ± 12 (23–78)	56 ± 11 (25–81)
Race, %		
White	50	50
Black	6	8
Asian	9	7
Other	36	34
Weight (kg), mean ± SD (range)	78 ± 14 (53–125)	80 ± 14 (47–127)
ED duration (year), mean ± SD (range)	4.7 ± 4.7 (0.1–34.6)	4.3 ± 4.5 (0.2–36.6)
Primary ED etiology, n (%)		
Mixed	58 (39)	67 (44)
Organic	51 (34)	58 (38)
Psychogenic	40 (27)	26 (17)
Baseline SEAR scores, mean ± SD (range)		
Sexual Relationship domain	39 ± 19 (0–91)	38 ± 18 (0–81)
Confidence domain	39 ± 18 (0–83)	37 ± 18 (0–79)
Self-Esteem subscale	38 ± 18 (0–81)	35 ± 18 (0–75)
Overall Relationship subscale	41 ± 26 (0–100)	42 ± 26 (0–100)
Overall index	39 ± 17 (7–88)	38 ± 16 (0–80)

overall relationship satisfaction across countries. The mean change (95% CI) in the Self-Esteem subscale score from baseline to the end of treatment was 41.4 (36.4–46.5) for men who received sildenafil, compared with 17.4 (12.2–22.6) for men who received placebo ($P < 0.0001$). Similar noticeable improvements were found for the Confidence domain, Sexual Relationship subscale, and Overall Relationship subscale, as well as the overall SEAR score.

A linear model with baseline score, country, treatment, and treatment-by-country interaction revealed no such statistically significant interaction ($P > 0.05$) for the Self-Esteem subscale and other four measures on the SEAR. Thus, for each SEAR component, there was no evidence that the difference in mean changes in SEAR scores between treatments differed by country.

Corresponding effect sizes (95% CI) of change in SEAR components across countries were indicative of a large response to treatment [32]: Self-Esteem subscale, 1.3 (1.1–1.6); Sexual Relationship domain, 1.3 (1.0–1.5); Confidence domain, 1.3 (1.0–1.6); Overall Relationship subscale, 0.8 (0.6–1.0); and Overall score, 1.4 (1.2–1.7). Moreover, compared with patients randomized to placebo, patients randomized to sildenafil had significantly greater improvements on each of the 14 individual SEAR questions ($P < 0.0001$; data not shown).

Erectile Function, Other Components of the IIEF Questionnaire, and Other Measures of Sexual Function

Compared with patients receiving placebo, patients receiving sildenafil had significantly

greater improvement in erectile function. An analysis of the combined data across countries using an ANCOVA model controlling for baseline IIEF score and center, with treatment group as the key explanatory variable, revealed that the main effect for treatment was significant and considerable (Figure 3). Sildenafil demonstrated significantly ($P < 0.001$) greater mean improvements (95% CI) over placebo on the Erectile Function domain: 11.7 (10.4–13.0) vs. 5.2 (3.9–6.5). Additionally, sildenafil provided significantly greater improvements over placebo on all other domains of the IIEF.

Furthermore, patients receiving sildenafil had a significantly ($P < 0.0001$) greater mean improvement (95% CI) from baseline in the percentage of successful intercourse attempts: 64% (58–71%) with sildenafil vs. 31% (24–38%) with placebo, giving a between-group difference of 33% (24–43%). In addition, the mean score (95% CI) for the GEQ indicated significantly ($P < 0.0001$) more frequent erections that allowed satisfactory successful intercourse for patients receiving sildenafil: 4.1 (3.8–4.3), compared with those receiving placebo: 2.9 (2.6–3.1). Consistent with the improvements in psychosocial function and well-being, these data revealed marked and parallel improvements in sexual function for patients who were randomized to receive sildenafil.
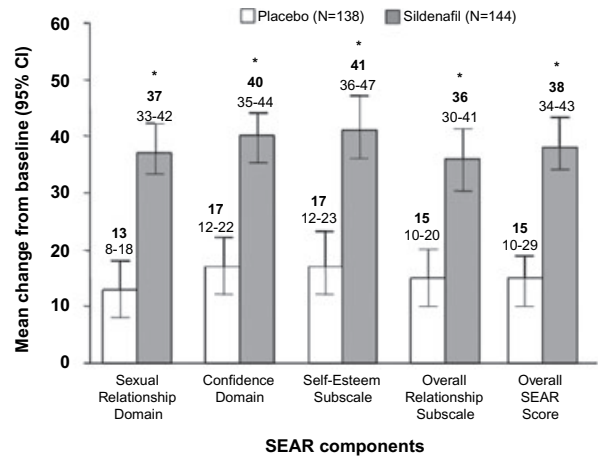
Correlations Between SEAR Components and Measures of Sexual Function

The correlation between improvements in Self-Esteem subscale scores with improvements in Erectile Function domain scores for all patients

(a)

(b)
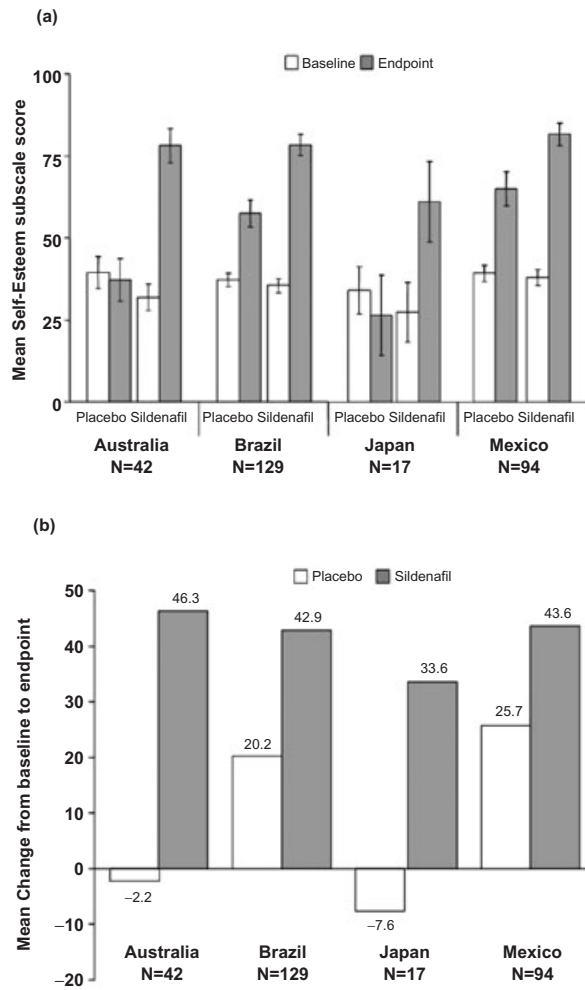
Figure 1 Mean observed scores and change from baseline to the end of treatment in Self-Esteem subscale scores for placebo- and sildenafil-treated patients subdivided by country: descriptive profiles. (a) Mean ± SE observed Self-Esteem subscale scores were determined at baseline and the end of treatment for patients with ED randomized to placebo or sildenafil in Australia, Brazil, Japan, and Mexico. (b) Corresponding mean change in observed scores from baseline to the end of treatment was determined.
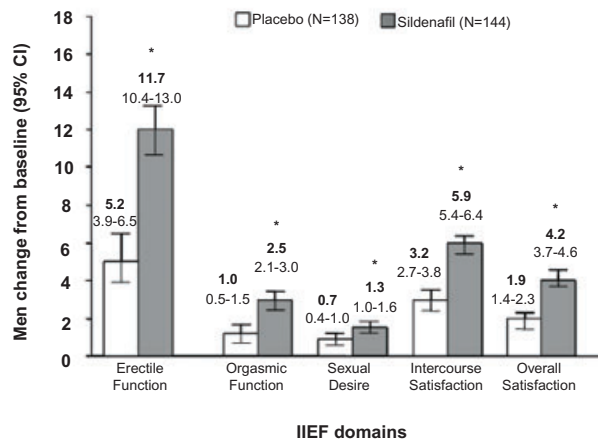

Figure 2 Adjusted mean change from baseline to the end of treatment in combined (pooled) SEAR component scores across countries within treatment group. Analysis of SEAR scores revealed greater change in mean scores from baseline for patients who received sildenafil, compared with those who received placebo. Values are the mean change in scores with 95% confidence interval (CI). *$P < 0.0001$ compared with placebo.

Safety

Sildenafil was well tolerated. Three patients who received sildenafil discontinued treatment due to worsening of existing depression, emergent mild coronary artery disease, and epigastric pain after dosing. Only the event of epigastric pain was con-

Figure 3 Adjusted mean change from baseline to the end of treatment in combined (pooled) IIEF domain scores across countries within treatment group. Analysis of IIEF scores revealed greater improvements in scores from baseline for patients who received sildenafil, compared with those who received placebo. Values are the mean change in scores with 95% confidence interval (CI). *$P < 0.001$ compared with placebo. IIEF domain scales ranged up to 30 (Erectile Function domain), 15 (Intercourse Satisfaction domain), and 10 (other domains).

was 0.71 ($P < 0.0001$; Table 2). Correlations between changes in all other SEAR component scores with changes in all other IIEF domain scores from baseline to week 12 were also significantly positive and perceptible ($P < 0.0001$; Table 2). In addition, changes in SEAR components scores correlated positively and significantly with changes in the percentage of successful sexual intercourse attempts. At week 12, SEAR component scores were positively and significantly correlated with the GEQ (frequency of erection allowing satisfactory intercourse).

Table 2 Correlations between measures of psychosocial function and well-being (SEAR components) and sexual function (IIEF domains, GEQ, event log) in men with ED

| SEAR components | Pearson's partial correlation coefficient, r* | | | | | | |
| | IIEF domains | | | | | | |
	Erectile Function	Orgasmic Function	Sexual Desire	Intercourse Satisfaction	Overall Satisfaction	GEQ[†]	% Successful intercourse[‡]
Sexual Relationship	0.73	0.51	0.27	0.62	0.69	0.85	0.60
Confidence	0.74	0.54	0.28	0.68	0.73	0.81	0.65
Self-Esteem	0.71	0.51	0.26	0.65	0.70	0.80	0.65
Overall Relationship	0.65	0.50	0.26	0.59	0.65	0.71	0.60
Overall score	0.78	0.55	0.29	0.68	0.75	0.86	0.66

*$P < 0.0001$ for all correlations, adjusted for treatment. All correlations are based on change scores except for the correlations between SEAR component scores and GEQ scores, which are based on end-of-study scores.
[†]GEQ was assessed at the end-of-treatment; "When you took a dose of study drug and had sexual stimulation, how often did you get an erection that allowed you to engage in satisfactory sexual intercourse?
[‡]Patients recorded sexual activity in an at-home event log that was used to determine the percentage of successful sexual intercourse attempts.
IIEF = International Index of Erectile Function; SEAR = Self-Esteem And Relationship questionnaire; GEQ = Global Efficacy Question.

sidered attributable to the study drug. One serious adverse event was reported for patients taking sildenafil; this patient developed severe coronary artery disease that was not considered related to the study medication. One patient who received placebo discontinued treatment because he developed a urinary tract infection. The most frequent adverse events (sildenafil vs. placebo) were headache (14% vs. 5%), flushing (10% vs. 2%), and dyspepsia (5% vs. 1%), which were generally mild and transient.

Discussion

The psychosocial impact of ED includes depression, anxiety, loss of self-esteem, and relationship distress [11,12]. Accordingly, there is a need for a psychometrically sound, self-administered, and disease-specific instrument to reliably assess the effect of ED and its treatment on these relevant psychosocial factors [11]. To meet this need, several instruments have been developed that include items that assess the psychological impact of ED [34–39]. While each of these instruments has merit in its own way, their usefulness has been limited to date because they include a single summary score rather than separate scores for subscales that measure the different types of psychological impact [34,35], lack robust psychometric properties [34], or lack proven sensitivity to effective treatment for ED in double-blind, placebo-controlled studies [34–39]. In addition, none of these instruments specifically measure self-esteem. The SEAR was developed, validated, and linguistically and culturally adapted to accurately assess the effect of ED and its treatment on self-esteem, confidence, sexual relationship satisfac-

tion, and overall relationship satisfaction. The SEAR recognizes the multidimensional nature of ED and, in doing so, extends our current knowledge of ED beyond sexual functioning to relational and emotional areas.

Attitudes regarding sex vary for people in Australia, Brazil, Japan, and Mexico, which may lead to differences in the expected outcome on the SEAR after sildenafil therapy. For example, in the Global Survey on Sexual Attitudes and Behaviors (GSSAB), men in East Asia, which included Japan, reported the second highest prevalence of at least one sexual problem, but were the least likely to seek medical help for their sexual problems [40]. Men from East Asia also had the highest odds ratio (4.66) of seeking medical help for believing that their sexual problems significantly affected their self-esteem, compared with an odds ratio of 0.85 for men from Central and South America, which included Brazil and Mexico, and an odds ratio of 2.3 for men from the non-European West, which included Australia [40].

The association between ED and poor relationship quality also appears to be stronger for men from East Asia. In an analysis of subjective sexual well-being from the GSSAB, men from Japan had among the lowest levels of emotional and physical satisfaction with their relationships compared with men from Australia, Brazil, and Mexico [41]. The high prevalence of sexual problems and low subjective sexual well-being may be why men from Japan had the lowest mean baseline and end-of-treatment Self-Esteem scores in the present study; however, low enrollment of patients in Japan limited definite comparative analyses between countries. Nevertheless, compared with placebo, sildenafil improved self-esteem, confidence, and

relationships for men with ED in all four countries. Improvements in self-esteem, confidence, and relationships, as measured by the SEAR, suggested that treatment of ED with sildenafil can improve these important psychosocial areas comparably in the four countries examined and independent of geographic location or cultural differences. The Overall Relationship subscale of the SEAR contains only two questions, neither of which is answered by the partner, and may be insufficient alone as a useful indicator of relationship satisfaction. A more detailed assessment may be required to assess a topic as intricate as overall relationship satisfaction. Nevertheless, the positive correlations observed between the SEAR and measures of erectile function suggest an interdependence between proper sexual function and enhanced psychological well-being and functioning. Sildenafil is only indicated for the treatment of ED. Thus, the effects on self-esteem and confidence are likely indirect and secondary to improvement in erectile and sexual function.

Improvements in erectile function offer tangible gains beyond sexual functioning and readiness; they are tied to improvements in self-esteem, confidence, and relationship satisfaction. Therefore, the SEAR contributes to a comprehensive and accurate profile of a patient's benefit from treatment. The positive correlations between the SEAR and the IIEF further validate the SEAR as an instrument that is responsive to successful treatment of ED. In general, a higher degree of recovery of erectile function corresponds to greater improvement in psychosocial well-being and functioning. Furthermore, the magnitude of the correlations between the IIEF and the SEAR suggest that they are measuring similar but different constructs: while the IIEF measures the effects of treatment on sexual function, the SEAR measures the effects of treatment on psychosocial indices—self-esteem, confidence, sexual relationship satisfaction, and overall relationship satisfaction—that the data indicate are associated with erectile function.

Conclusion

This investigation is the first international double-blind, placebo-controlled study that used the SEAR to determine the effect of sildenafil on self-esteem, confidence, sexual relationship satisfaction, and overall relationship satisfaction in men with ED. Improvement in psychological well-being and psychosocial function were consistent among men with ED from Australia, Brazil, Japan, and Mexico. Treatment of ED with sildenafil was associated with marked improvements in these psychosocial measures. Improvements in self-esteem, confidence, and relationship satisfaction correlated significantly, meaningfully, and consistently with improvements in measures of sexual and erectile function. These data suggest that, in addition to measures on sexual function, measures that gauge the psychosocial impact of ED should be included in a complete assessment of the treatment and management of ED.

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