Erectile dysfunction (ED) has become recognized as a frequently encountered medical condition with psychological and relationship consequences that often lead to impairments in patients’ quality of life.1–3 ED can be the result of organic factors (neurologic, vascular, hormonal, and cavernosal abnormalities), psychological factors, or a combination of these.4,5 Furthermore, ED is associated with aging.6 This may in part be related to the association of age-related conditions such as diabetes, hypertension, and ischemic heart disease with vascular and blood flow changes or to a negative impact on erectile function by some of the medications taken to treat these conditions.

The treatment of ED has been advanced by the introduction of oral treatments such as sildenafil citrate.7–11 Despite this option, many individuals have not yet successfully fulfilled their treatment needs. New phosphodiesterase (PDE) type 5 inhibitors, such as vardenafil hydrochloride (vardenafil), are also being developed. Compared with sildenafil, vardenafil has been shown to be, in vitro, approximately 10-fold more potent as an inhibitor of PDE-5, as well as more selective for PDE-5, with respect to PDE-6 and PDE-11.12 Initial study re-
sults have indicated that vardenafil improved erectile function and had a favorable adverse event profile consistent with its high PDE-5 selectivity.13–15

The first at-home study in 580 men with mild to severe ED indicated that vardenafil was efficacious and well-tolerated in a broad population.15 The present report examined, through additional analyses of that same study, the influence of the etiology and severity of ED and of patient age on vardenafil’s efficacy. In addition, the consistency of vardenafil’s activity was evaluated by examining both its efficacy and its tolerability monthly during the course of the 12-week trial.

MATERIAL AND METHODS

STUDY DESIGN AND PATIENT POPULATION

This report represents new subanalyses of the vardenafil study as described by Porst et al.15 In brief, after a 4-week unmedicated run-in period in which intercourse was attempted at least four times, patients were randomized into four, on-demand, oral treatment groups for 12 weeks: placebo and vardenafil 5, 10, and 20 mg. The study included men aged 21 to 70 years with mild to severe ED of organic, psychogenic, or mixed etiology, but excluded those with a history of diabetes mellitus, spinal cord injury, radical prostatectomy, hypogonadal testosterone (less than 300 ng/dL), or low thyroid-stimulating hormonal levels (less than 0.28 mU/L). All other therapies for ED were discontinued at least 7 days before the baseline period. Men with clinically significant coronary heart disease were excluded. All patients were specifically requested not to take nitrate or other nitric oxide-donor medication.

OUTCOME MEASURES

For these subgroup analyses, the International Index of Erectile Function (IIEF) erectile function domain (summation of questions 1 to 5, plus question 15) was used, with the last observation carried forward method used to account for missing data. For the time course determinations, the erectile function domain, as well as intercourse satisfaction (questions 6 to 8), orgasmic function (questions 9 and 10), sexual desire (questions 11 and 12), and overall satisfaction (questions 13 and 14) were calculated for those patients reporting data for each 4-week period.

ANALYSES ACCORDING TO PATIENT CATEGORIES

The etiologies of ED were categorized as organic, psychogenic, or mixed and were determined by the investigator on the basis of history, physical examination, and other suitable clinical tests. The baseline severity of ED was determined using a modified rating of Cappelleri et al.17 using the IIEF erectile function domain score (less than 11, severe; 11 to 17, moderate; 18 to 25, mild; greater than 25, none). Twenty-one men with a baseline erectile function domain considered in the normal range were not included in this analysis. The age categories were younger than 45, 45 to 55, 56 to 65, and older than 65 years.

ADVERSE EVENTS

Adverse events and vital signs were determined in all men receiving treatment, and patients were asked to report any adverse event throughout the course of the trial. Because of the limited number of adverse events in each age group, only the most common adverse event, headache, was analyzed according to age. In addition, the monthly rates of adverse events were determined for the three most common adverse events (headache, flushing, and dyspepsia).

STATISTICAL ANALYSIS

Analyses were based on the intent-to-treat population who had at least one measurement of IIEF. The analyses reported here were post-hoc secondary efficacy variables and no adjustment for multiple comparisons was made. Analyses were performed using analysis of covariance with terms for treatment center and baseline included. The P values reported are from the main effects model. Least square means IIEF domains were calculated for those patients valid for efficacy at baseline, at 0 to 4 weeks, at 4 to 8 weeks, and at 8 to 12 weeks.

RESULTS

DEMOGRAPHICS

The intent-to-treat study population consisted of 580 men: placebo, n = 147, vardenafil 5 mg, n = 146, vardenafil 10 mg, n = 140, and vardenafil 20 mg, n = 147. The mean age was approximately 52 years (range 51.9 to 53.3), and the mean duration of ED approached 3 years (range 2.6 to 3.0) for each treatment group. Of the 580 men, 134 were younger than 45 years old, 188 were 45 to 55 years old, 190 were 56 to 65 years old, and 64 were older than 65 years old. There was a similar distribution of etiologies of ED among the treatment groups: organic (26.5% to 33.6%), psychogenic (25.0% to 30.1%), or mixed (36.3% to 48.3%). The distribution of baseline severity was also similar, with approximately equal numbers of mild (25.7% to 28.3%), moderate (33.6% to 37.5%), and severe (31.9% to 35.7%) ED in each group. Approximately one half of the patients had taken sildenafil previously, and these were equally distributed among the treatment groups (range 47.9% to 50.7%).

EFFICACY ACCORDING TO ETIOLOGY OF ED

The final mean erectile function domain scores for all treatment groups were statistically significantly greater than placebo (P<0.01) whether the etiology of ED was classified according to organic, psychogenic, or mixed (Fig. 1). No difference in response was seen among the etiologic groups.

EFFICACY ACCORDING TO BASELINE SEVERITY OF ED

Vardenafil treatment resulted in significantly greater erectile function domain scores compared with placebo whether the baseline score was mild, moderate, or severe (P<0.01; Fig. 2). The mean scores for the vardenafil-treated patients in the severe group increased to the mild grade. For those in the moderate group, the placebo mean score after treatment remained in the moderate grade, and the mean score for all vardenafil doses moved well into the mild range. For those starting in the mild range, the mean scores for the 10-mg and 20-mg vardenafil groups reached the normal...
range. No statistically significant difference was seen among the dosage groups.

**Efficacy According to Patient Age**

For all age subgroups (Fig. 3), the final mean erectile function domain score was statistically significantly greater for all three vardenafil treatment groups than for the placebo treatment group (P <0.01). The oldest group had the apparent greatest difference in response among the three doses, but this was not statistically significant because of the few number of patients in each treatment arm in this age bracket.

**Efficacy According to Prior Use of Sildenafil**

Men who had tried sildenafil before this study had similar responses to those who were naive to sildenafil. For the prior-use group, the final erectile function domain score was 15.5, 20.5, 22.6, and 23.4 for placebo, and 5, 10, and 20 mg of vardenafil, respectively. The corresponding mean scores were 15.7, 21.2, 21.8, and 22.2 in the naive group.

**Consistency of Efficacy Over Time**

Of the study group, 576 patients had data valid at baseline for an analysis over time (4 individuals did not complete all questions). After 4 weeks of treatment, 544 had complete data, after 8 weeks 508 did so, and after 12 weeks 489 had complete data. The mean baseline values for the erectile function domain ranged from 13.8 to 14.2. By 4 weeks, the score for the placebo group had minimally increased to 14.5 compared with 20.3, 21.4, and 22.8 for the 5, 10, and 20-mg vardenafil groups (P <0.001 for all treatment groups). Statistically significant differences were seen between the 5 and 20-mg doses (P <0.001) but not between 10 mg and either 5 mg or 20 mg. Even after 12 weeks, the erectile function domains remained significantly elevated, with a mean score of 21.7, 23.0, and 23.4 for the 5, 10, and 20-mg group, respectively, compared with 15.9 for the placebo group (P <0.001), with the 5-mg score still significantly different from the 20-mg score (P <0.05). No differences were seen in the responses of placebo and vardenafil-treated patients for the sexual desire domain: baseline scores ranged from 6.7 to 7.1, with 12-week scores of 7.2 for the placebo group and 7.3 to 7.7 for the vardenafil groups.

For the other three domains, all had marked changes from baseline by 4 weeks. For the orgasmic function domain, baseline values ranged be-
between 5.8 and 6.2. By 12 weeks, placebo was essentially unchanged at 6.2. In contrast, the vardenafil groups had increased to 7.8 to 7.9. For the overall satisfaction domain, baseline values were low, ranging from 4.6 to 4.7. For placebo, those at 12 weeks reported a score of 5.3. In contrast, the mean score for the 5-mg, 10-mg, and 20-mg dose was 7.2, 7.4, and 7.6, respectively. For intercourse satisfaction, scored between 3 and 15, the baseline values ranged from 7.1 to 7.3. For the placebo group, the scores had increased to 8.5 by 12 weeks. For the vardenafil groups, the scores had improved from 10.4 to 10.9.

ADVERSE EVENTS

Because of the limited number of patients in each dosage group and age group (16 subgroups), only the most common treatment-emergent adverse event, headache, was examined to determine whether a relationship with age existed. The headache rates for all patients receiving vardenafil were averaged together for each age group. The proportion of patients who reported headache as an adverse event at least once during the study when taking the placebo was 5%, 0%, 7%, and 1% for the younger than 45, 45 to 55, 56 to 65, and older than 65-year age groups, respectively. For those taking vardenafil, the corresponding proportions were 14%, 7%, 9%, and 17%. Hence, no relationship was apparent of headache with age.

The incidence of headache, analyzed on a monthly basis, was similar throughout the study in groups receiving placebo (0% to 2%) or vardenafil of 5 and 10 mg (range 1% to 4%). In the vardenafil 20-mg group, however, the incidence of headache decreased from 11.5% during the first 4 weeks to 8% during the last 4 weeks of treatment. Similarly, dyspepsia was most apparent (5%) in the first 4 weeks of treatment in the vardenafil 20-mg group and decreased to 2% during the third month. The incidence of flushing was consistent throughout the study for all doses of vardenafil (6% to 10%). No serious drug-related adverse event occurred during the study. No color vision disturbances were seen, although 6 of 580 men reported some minor haziness and blurriness; however, this was noted in both vardenafil and placebo groups.

COMMENT

The present subgroup analyses of the data from the Phase IIb clinical study demonstrated that the efficacy of vardenafil was comparable among patients with different etiologies and severities of ED and among those of different ages. The previously reported study showed a statistically significant improvement in the responses to IIEF questions 3 and 4, a 75% rate of completion of sexual intercourse, and an improved erection responder rate of up to 80% by the 12-week study endpoint. The present results, which used the same data source, showed that the erectile function domain score was superior to placebo for all doses 4 weeks after the initiation of treatment with vardenafil and was maintained until the end of the 12-week treatment period.

Vardenafil appeared to be similarly effective at improving the erectile function domain scores of patients with organic, psychogenic, and mixed etiology ED. It should be noted that, in this study, men were excluded if they had conditions that made their ED more challenging to treat, such as ED resulting from diabetes mellitus, spinal cord injury, radical prostatectomy, or low testosterone or thyroid-stimulating hormonal levels. However, most of the men in this study were considered to have at least moderate or severe ED. When the treatment groups were subdivided according to the severity of ED, an improvement in score was evident in all subgroups and for each dose level of vardenafil. Vardenafil also improved erectile function in all age groups investigated in this study, including men older than 65 years of age, the age group in which ED is most prevalent. The lack of statistically significant differences between doses in these subanalyses may be the result of too few patients in each subgroup. If subgroups that were more challenging to treat were included, such a robust response for the 5-mg dose may not have been seen. It is of note that a major difference was not seen between the final erectile function domain scores for those who had been taking sildenafil previously compared with those who were naive, suggesting that the exclusion of sildenafil failures may not have particularly biased the data.

The potency and selectivity profile of vardenafil is consistent with the low frequency and generally mild to moderate severity of adverse events reported during treatment. Porst et al. reported that the greatest incidences of adverse events for the 12 weeks of the study were for headache (up to 15%), flushing (up to 11%), and dyspepsia or rhinitis (up to 7%). The present analysis showed that the monthly incidence rates of headache and dyspepsia were lower and tended to decrease during the 12-week treatment period. The incidences of headache and dyspepsia were lower at the 5-mg and 10-mg doses of vardenafil, with a maximal monthly rate of 5% and 3%, respectively. The greater rates of headache were not necessarily related to patient age.

CONCLUSIONS

This subanalysis of the Phase IIb trial of 580 men with mild to severe ED showed that vardenafil
compared with placebo had a significant and similar improvement in erectile function across etiology and baseline severity and irrespective of age or prior use of sildenafil. In addition, vardenafil improved all key IIEF domain scores after the first 4 weeks of treatment, and this treatment effect was consistently maintained during the 12-week treatment period.

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REFERENCES

EDITORIAL COMMENT
This reports a subanalysis of a group of men with ED treated with vardenafil. The initial evaluation of results was published previously and the information presented here, to many readers, is a bit repetitious, particularly in regard to the overall response during the short (12-week) period of treatment, as well as the adverse effects. This period of follow-up is too short to address the question of tachyphylaxis that has been raised but never proven with other PDE-5 inhibitors. The initial assessment of this group of men appeared in a specialized journal, and this one is aimed at a wider urologic audience. The addition of a safe and effective new alternative for the treatment of ED is a welcome development—a development carefully and methodically documented in this study. Although the similarities between vardenafil and sildenafil are evident, there are some differences that may be considered advantageous. Obviously, until the results of properly designed comparative trials become available, we will continue to wonder and speculate about the superiorities and drawbacks of this class of compounds.

Many readers would agree that the following points are worth expanding by the authors:

The statement that vardenafil had “a favorable adverse event profile...” is obscure, because the study did not compare vardenafil’s profile with other similar drugs. An adverse events profile is never favorable unless it is compared with a worse one. The reported adverse events, with the exception of the visual changes, appear to be quite similar to those reported with the use of sildenafil.

Nowhere in the manuscript is it unambiguously stated that failure to respond to sildenafil was an exclusion criterion. There are a number of references to the issue of naive and non-naive sildenafil subjects. This needs to be stated frankly. For instance the sentence, “one half of the patients had taken sildenafil previously” does not truly address this concern because it does not indicate whether they all responded to it.

Etiologic categorizations of ED are always problematic and more so in this study. It is fair to assume that these were the same patients reported in the initial analysis. They came from three continents. The point to ponder is that etiologic categorization (organic, psychogenic, mixed) is, under the best circumstances, very artificial and more so when no