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Vardenafil (Levitra, Bayer Healthcare/GlaxoSmithKline, USA) is a phosphodiesterase 5 inhibitor developed specifically for use as an oral therapy for erectile dysfunction (ED). This review provides an overview of recent clinical trial results that support the use of this compound as first-line therapy in patients with ED. Specifically, data from clinical trials performed in multiple countries have shown strong efficacy and good safety in the general population as well as in difficult-to-treat subpopulations, such as patients post bilateral nerve sparing radical prostatectomy and patients with diabetes mellitus. Furthermore, the features of a rapid onset of action, good reliability and increased patient satisfaction, while elements such as erection hardness and overall sexual experience may provide additional benefits to this particular patient group. Together with a good safety profile and minimal interactions with food and alcohol, it is clear that vardenafil offers a viable first-line treatment choice for men with ED.

**Key Words:** Cardiovascular safety; Clinical studies; Diabetes; Erectile dysfunction; Onset of action; Phosphodiesterase inhibitor; Prostatectomy; Reliability; Vardenafil

It is well known that erectile dysfunction (ED) has a substantial impact on patient quality of life; in particular, it impacts on men's self-esteem and their intimate relationships. With this in mind, it becomes even more important that the ED treatments developed are effective the first few times they are used, and continue to be effective over time. Local therapies, while effective, suffered due to the lack of spontaneity, or were invasive, painful or unappealing. The appearance of sildenafil revolutionized ED therapy. Oral phosphodiesterase 5 (PDE5) inhibitors have become the first treatment of choice for the management of ED. Sildenafil has been available since 1998, and has been shown to be efficacious and safe for the treatment of ED (1,2). However, a high rate of dissatisfaction and discontinuation of treatment has been reported; only approximately 39% of patients receiving sildenafil renewed their prescription after one year (3). In fact, discontinuation rates range from 14% to as high as 47%. The most frequent reason cited for the discontinuation of sildenafil therapy is lack of efficacy. These results have been confirmed in an independent global survey evaluating men's attitudes towards life events and sexuality (MALES), conducted from February to April 2001 in 27,838 men aged 20 to 75 years (4). These findings demonstrate that there is an unmet need for new oral medications that will meet patient expectations of a reliable treatment.

**THERAPEUTIC EFFICACY**

The results of a number of large scale clinical trials have shown that vardenafil has strong efficacy and a favourable safety profile in the general population, as well as in harder-to-treat subpopulations such as patients post nerve-sparing radical prostatectomy (NSRP) and patients with diabetes mellitus (5-9). Most studies were of randomized, double-blind, multicentre, fixed-dose design, and of 12 or 26 weeks in duration, with one long term study extended to 104 weeks (10). There were no restrictions regarding food or alcohol consumption. Primary endpoints included the Erectile Function (EF) domain score of the International Index of Erectile Function (IIEF) questionnaire (11), two Sexual Encounter Profile (SEP) diary questions: "Were you able to insert your penis into your partner's vagina?" (SEP2) and "Did your erection last long enough for you to have successful intercourse?" (SEP3). Additional endpoints included IIEF domain scores that focused on intercourse satisfaction, orgasmic function, sexual desire and overall satisfaction, additional diary questions (eg, satisfaction with erection hardness and overall satisfaction with sexual experience), and the Global Assessment Question (GAQ), “Has the treatment you have been taking over the past 4 weeks improved your erections?”
Vardenafil – A new and effective treatment for ED

Table 1 summarizes the efficacy results (IIEF-EF domain score, SEP3 and GAQ) with oral vardenafil in the broad ED patient population, as well as in patients with ED and diabetes and patients with ED post-NSRP. In these studies, the adverse event profiles were characteristic of PDE5 inhibitors, with the most frequent adverse events being transient headache, flushing, and rhinitis of mild-to-moderate intensity.

It is important to note that, in each of these studies, patients in the vardenafil-treated groups consistently reported improved intercourse satisfaction and orgasmic function, based on responses in the IIEF questionnaire. These patients also reported improved satisfaction with erection hardness and with the overall sexual experience (13-15).

Data from the North American and European pivotal trials conducted in the broad ED population were pooled and then examined to determine the therapeutic efficacy of vardenafil in various subpopulations with ED. These subgroups were defined based on a number of factors including etiology (organic/psychogenic/mixed), severity of ED at baseline and age (16,17). Other categories included those who had specific comorbidities such as hypertension, hyperlipidemia and diabetes mellitus, and patients who were taking antihypertensive medications (18,19). In each of these subpopulations, vardenafil significantly improved indices of erectile function compared with placebo, thereby providing evidence of efficacy in a broad range of men with ED.

In clinical practice, it is most likely that patients will be prescribed one dose of medication and then titrated up or down on an as-needed basis, according to tolerability and efficacy. This flexible-dose regimen was assessed in a 12-week, double-blind, placebo-controlled study in which patients were initially randomized to vardenafil 10 mg or placebo, to be taken on demand (20). After four weeks and eight weeks, the vardenafil dose could be adjusted up to 20 mg or down to 5 mg. The baseline average EF domain scores in this patient population (n=309) indicated ED of moderate severity (12.6 for vardenafil and 13.1 for placebo).

TABLE 1
Efficacy of vardenafil in men with erectile dysfunction (broad population and harder-to-treat populations). Results of randomized, double-blind, fixed-dose, multicentre trials

| Efficacy variables | Duration/Parameter | Placebo | Vardenafil 5 mg | Vardenafil 10 mg | Vardenafil 20 mg |
|-------------------|--------------------|---------|----------------|----------------|----------------|
| Broad population study (6) |                   |         |                |                |                |
| EF domain score | LOCF, n=170-195 | 12/26 weeks | 15.0/14.8 | 18.4*/17.8* | 20.6*/21.2* | 21.4*/21.8* |
| BL 12.5-13.6 | SEP3 – Overall mean success | rate per patient (%) | 12/26 weeks | 32/33 | 51*/52* | 65*/65* | 65*/67* |
| n=171-194 BL 14%–15% | GAQ – %, completers | n=91-169 | 12/26 weeks | 39/28 | 65*/65* | 73*/80* | 81*/85* |
| % of patients returning | BL – mild | 21 | 64 | 89 | 79 |         |
| to normal erectile function (LOCF at 12 weeks), n=9-84 | BL – mild-mod | 17 | 44 | 55 | 47 |         |
| Diabetes population study (9,12) | EF domain score, mean | LOCF, n=138-145 | 12 weeks | 12.6 | NA | 17.1* | 19.0* |
| BL 10.9-12.0 | SEP3 – Overall mean success | rate per patient (%) | 12 weeks | 23 | NA | 49* | 54* |
| n=137-147 BL 9%-14% | GAQ – %, completers | n=131-137 | 12 weeks | 13 | NA | 57* | 72* |
| Post-NSRP population study (8) | EF domain score, mean | LOCF, n=140-147 | 12 weeks | 9.2 | NA | 15.3* | 15.3* |
| BL 9.1-9.3 | SEP3 – Overall mean success | rate per patient (%) | 12 weeks | 10 | NA | 37* | 34* |
| n=140-147 BL 6%-7% | GAQ – %, completers | n=131-137 (bilateral NSRP) | 12 weeks | 13 (11) | NA | 59 (60)* | 65 (71)* |

*P≤0.001 versus placebo; †P<0.03 versus vardenafil 10 mg. BL Baseline; EF Erectile function; GAQ Global Assessment Question; LOCF Last observation carried forward; NA Not applicable; NSRP Nerve-sparing radical prostatectomy; SEP-3 Sexual Encounter Profile question 3

In the above table, the efficacy results are summarized for different populations, including broad ED, diabetes, and post-NSRP populations. The table provides a detailed comparison of the efficacy of vardenafil at different doses (5 mg, 10 mg, 20 mg) against placebo. Significant improvements were observed in all domains measured, including EF domain score, SEP3, and GAQ, with a robust placebo effect as a control. The table also highlights the consistency of vardenafil’s effects across various subgroups, demonstrating its broad efficacy profile in ED management.

In conclusion, vardenafil has been shown to be a safe and effective treatment for ED, with consistent improvements across different populations and subgroups. Its flexible-dose regimen further enhances its utility in clinical practice. However, further research is needed to explore its long-term safety and efficacy, as well as its impact on quality of life and patient satisfaction.
VARDENAFIL WORKS RAPIDLY

The pharmacokinetic properties of a compound, i.e., the time to reach sufficient concentrations in the blood that will lead to a therapeutic effect and the time to metabolize the active species, play a crucial role in the proper medical management of patients. With medications used to treat ED, one must also consider the time element as it relates to the sexual encounter itself. An oral medication that is rapidly absorbed and has an associated fast onset of action could allow a couple to enjoy the element of spontaneity in their sexual activity. Vardenafil has a time to maximum plasma concentration of less than an hour and a half-life of 4 to 5 h. To determine how this translates to the clinical level, the time elapsed after swallowing the pill until achieving an erection sufficient for sexual intercourse was measured in an at-home setting (21). In this large-scale, randomized, double-blind study, men with varying severities of ED were randomized to receive either vardenafil 20 mg or placebo over a four week period. The earliest time among the first four doses that men perceived an erection adequate for penetration and intercourse was determined using a stopwatch. The outcome of the sexual encounter that followed was recorded in diaries. The primary variable was the earliest time that men perceived an erection adequate for penetration and intercourse. Secondary outcomes were time points for onset for SEP-2 and SEP-3 rates in men who had objective measures of success. No differences were observed between placebo and vardenafil for the primary efficacy variable. In addition, significant differences between placebo and vardenafil in SEP2 rates were not observed, although vardenafil rates were numerically higher than that of placebo. In those patients who perceived an erection that was confirmed by subsequent success in completing intercourse, a statistically significant greater proportion responding on vardenafil.

IS RELIABILITY IMPORTANT?

The importance of having a medication that is effective the first few times it is used, and continues to be effective over time, cannot be overstated as it relates to intimate relationships. Vardenafil has been shown to provide good reliability in terms of first time success and subsequent success rates for vaginal penetration (SEP2), successful completion of intercourse (SEP3) and overall patient satisfaction with the sexual experience. Retrospective analyses were conducted on data from the North American pivotal trial, and the North American and European pivotal trials, combined (22). In the analyses, evaluation was done for the first attempt and for subsequent per-patient attempts at intercourse up to week 12. In the pooled data, the SEP-2 first-attempt → subsequent success rates were 76%–91% for vardenafil 20 mg, compared with 44%–74% for placebo. For SEP-3, first-attempt → subsequent success rates were 59%–84% for vardenafil 20 mg, compared with 25%–56% for placebo. Finally, for overall satisfaction with the sexual experience, first-attempt → subsequent success rates were 56%–79% for vardenafil 20 mg compared with 19%–48% for placebo. These results, which are similar to those from the single study, show that vardenafil provides high reliability in key efficacy parameters important to patients in choosing and continuing oral treatment for ED.

A separate study spanning two years provides information on the long-term efficacy and tolerability of vardenafil (10). Following a four-week baseline period, 1020 men with ED of broad etiology and severity were randomized to 10 mg or 20 mg of vardenafil (fixed dose, double-blind) to be taken as needed for up to one year. Of 755 patients (74%) completing the one year treatment period, 556 men continued to receive double-blind medication for an additional year. The mean EF domain of the 479 patients (85%) completing the study was 13.4 to 13.8 (moderate ED). Mean IIEF-EF domain scores reached levels considered as normal erectile function (at least 26) by week 8 and were sustained through week 104. Table 3 shows the results of the key efficacy parameters at baseline and at 104 weeks (LOCF). Both the 10 mg and 20 mg doses of vardenafil were well tolerated, the majority of adverse events reported were mild to moderate and included rhinitis (17%/21% for 10 mg and 20 mg, respectively), flushing (14%/21%), and headache (18%/20%). Adverse events led to premature discontinuation of a small percentage (1%/2% for 10 mg and 20 mg, respectively) of patients.

As part of the overall apprehensions about reliability, lack of response to sildenafil is a major concern in the treatment of ED. To address this, a multinational, randomized, double-blind study was recently conducted to determine whether vardenafil was effective in patients who had a documented history of lack
of response to sildenafil (23). The study was not designed to be a head-to-head comparison with sildenafil, but rather an investigation of the efficacy of vardenafil in this patient population, and therefore a sildenafil comparator arm was not included. There were six criteria used to define sildenafil nonresponders, and all six had to be met to include patients in this study. In this study, the flexible-dose regimen was again used to reflect the real-world experience. Patients were randomized to receive placebo or vardenafil 10 mg for four weeks, with the option to stay on 10 mg, or titrate to 5 mg or 20 mg after each of two consecutive, four-week intervals (total of 12 weeks). Three primary endpoints were the IIEF-EF domain score, SEP2 and SEP3, and the GAQ was a secondary endpoint. As would be expected, mean baseline EF domain scores indicated a population with severe ED (9.3 to 9.7). With vardenafil, statistically significant and clinically meaningful improvements were seen in all the primary endpoints. There was a four-fold increase in successful intercourse completion rates over baseline, and EF domain scores were brought into the mild to moderate range.

In addition, the GAQ scores where 62% for patients treated with vardenafil versus 15% on placebo (P<0.001). One of the major shortcomings of this study was the lack of a sildenafil comparator arm. There is significant evidence to suggest that sildenafil failures, when rechallenged, can often be converted to successes. The results of this study support the practice of rechallenge treatment failures with another PDE5 inhibitor.

SAFETY

Vardenafil has been shown to be generally well-tolerated in the 12- and 26-week trials, and also in the trials that last up to two years. The most frequently reported adverse events, such as headache and flushing, are typical of those in the PDE5 inhibitor class. Discontinuation rates due to adverse events are relatively small in the vardenafil-treated groups (3.4%), compared with placebo (1.1%). The cardiovascular safety profile of vardenafil has been analysed in the total patient population participating in five large-scale, placebo-controlled randomized trials (n=2605) and in smaller special population studies (24), such as in patients with coronary artery disease. Overall, the results from the pooled analysis indicate that vardenafil has a favourable cardiovascular safety profile. As expected from the mechanism of action of PDE5 inhibitors, small, transient decreases in blood pressure and increases in heart rate are observed with vardenafil relative to placebo, but the overall incidence of clinically significant changes in vital signs is very small. In addition, concomitant use of antihypertensive medications, overall or within the different classes, resulted in no or small incremental decreases in blood pressure that were generally similar in magnitude across the different classes. Cardiovascular adverse events were very few in the studies, and the incidence of these events were similar for patients receiving placebo or vardenafil.

In two double-blind, randomized studies, the effects of vardenafil 10 mg and 20 mg were assessed in men with stable coronary artery disease, undergoing an exercise stress test. In both studies, vardenafil did not impair the ability of men with stable coronary artery disease to exercise to a level similar to or greater than that associated with sexual intercourse (25,26).

CONCLUSION

Vardenafil is a selective and potent PDE5 inhibitor that is highly effective in the treatment of ED in the majority of patients with mild to severe ED of varying etiology, including the more challenging patients with diabetes, post NSRP, or those patients who were considered to be sildenafil nonresponders by history. Vardenafil exhibits a rapid onset of action, an optimal window of responsiveness, and minimal interactions with food or alcohol, providing added benefits in terms of ease of use. Patients using vardenafil experienced high levels of first time success, which continued for the duration of the study periods. These features, together with proven reliability over time and a generally well-tolerated side effect profile of mostly mild and transient side effects, indicate that vardenafil should be considered as a first-line treatment option in men with ED who are suitable candidates for oral PDE5 inhibitor therapy.

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