

Review

Vardenafil for the Treatment of Erectile Dysfunction: A Critical Review of the Literature Based on Personal Clinical Experience

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Abstract

Objective: To critically review the literature on vardenafil in the treatment of erectile dysfunction while integrating the clinical findings with the personal experience of the authors.

Methods: Analysis of published full-length papers that were identified through Medline search from January 2000 through May 2004. Abstracts published in peer-reviewed journals from the same period were also considered.

Results: Efficacy, tolerability and safety, as reported in the peer-reviewed literature compares well with the authors' personal experience. Authors' personal observations include discussions on potency, selectivity, selection of initial dose, counselling for patients characteristically considered difficult-to-treat (diabetes, prostatectomy, depression), including the determination of the maximal efficacious dose and the possible role of daily dosing, optimisation of the use of vardenafil according to its pharmacokinetic and pharmacodynamic profiles (onset and reliability), and management of ED patients with or at risk for cardiovascular disease.

Conclusions: Extensive experience with vardenafil as reported in peer reviewed literature confirms the important role of vardenafil in the management of patients with ED. The development of each physician's own experience with vardenafil is key to optimise overall satisfaction of this therapy by the patient and his partner.

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Keywords: Erectile dysfunction; Vardenafil; Phosphodiesterase type 5 inhibitors; Review

1. Introduction

At present, the first-line oral pharmacotherapy for the treatment of the majority of patients with erectile dysfunction (ED) is represented by phosphodiesterase type 5 (PDE-5) inhibitors, of which three are currently available worldwide. Sildenafil, the first PDE-5 inhibitor, was approved in 1998. More recently, tadalafil and vardenafil were introduced to EU and US in 2003/2004, respectively. This review provides a critical analysis of clinical features of vardenafil emanating from published literature. In addition to this, the

authors included comments and suggestions to readers which derive from their personal experience based on 280 patients treated with vardenafil and which may not necessarily adhere to the product labelling for vardenafil or the other PDE-5 inhibitors.

Methods of data acquisition: In this regard, 101 published full-length papers were identified through Medline search from January 2000 through May 2004. In additions, 212 abstracts published in peer-reviewed journals from the same period were also considered.

1.1. Vardenafil chemistry

Vardenafil is a potent and selective inhibitor of PDE5 [1,2]. Its chemical structure differs from that

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of sildenafil and tadalafil (Fig. 1), reflecting differing pharmacological properties. In vitro studies have shown that the potency of vardenafil in inhibiting PDE5 purified from human corpus cavernosum tissue was approximately 25-fold greater than that of sildenafil and 48-times greater than that of tadalafil (IC_{50} values 0.14, 3.5, and 6.74 nmol/L, respectively) (Table 1) [2]. Furthermore, vardenafil showed highly

selective inhibition of PDE5 compared with other PDE isozymes, except for PDE 6. (Table 1) [2]. The greater potency of vardenafil relative to sildenafil has also been demonstrated in human corpus cavernosum smooth muscle cells in vitro [3]. In vivo preclinical studies have revealed that the potency and selectivity of sildenafil, tadalafil, and vardenafil, are preserved relative to the in vitro studies with isolated, purified, or recombinant enzymes.

In clinical practice, greater potency may not necessarily translate to greater therapeutic efficacy (as measured by validated instruments). Other pharmacokinetic characteristics, such as bioavailability and metabolism (see below) may also contribute to the net pharmacodynamic effects of each of these drugs. Clinical experience with PDE-5 inhibitors suggests that potency mainly dictates the dose of the drug capable of eliciting therapeutic effects.

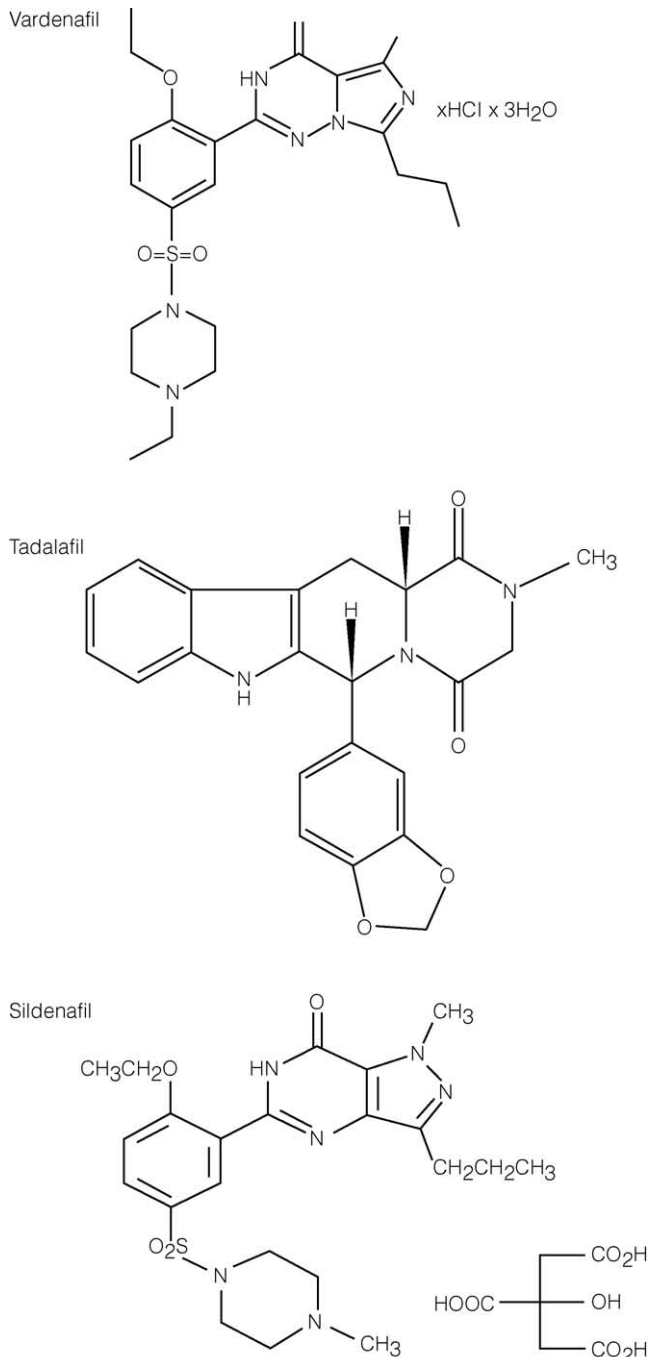


Fig. 1. Chemical structures of vardenafil, tadalafil, and sildenafil.

2. Pharmacokinetics

2.1. Absorption and distribution

Studies in men with ED have shown that single doses of vardenafil 10–40 mg were rapidly absorbed following oral administration, with maximum plasma concentrations (C_{max}) reached in some men within 15 minutes (median 0.6–0.9 hours) (Table 2) [4,5]. The mean C_{max} and area under the plasma concentration time curves (AUC) increased in an almost dose-proportional manner. Vardenafil has a mean absolute bioavailability of 15%. The rate and extent of absorption did not alter when vardenafil 20 mg was administered immediately after a typical meal (approximately 30% of calories as fat) compared with in the fasting state. A high-fat meal (57% of calories as fat), however, reduced the rate of absorption with an increase in time to maximum plasma concentration (T_{max}) of 1 hour and reduced the C_{max} by 18% [6]. According to the authors' personal experience in the use of all three available PDE5 inhibitors, it is wise to suggest to patients to initially use them with an empty stomach (at least two hours after completion of a meal) to maximise the therapeutic effect and optimise onset time. Responders are then routinely allowed to ingest these drugs irrespective of food or alcohol intake, with the possibility that the overall therapeutic effect may be reduced.

Based on pharmacokinetic data, a starting dose of 5 mg is recommended for elderly men with ED [5]. However, according to the authors' everyday clinical practice, vardenafil can be safely administered at the first dose of either 10 mg or 20 mg in these elderly

Table 1Potency (IC₅₀ values) and selectivity ratios of vardenafil, sildenafil, and tadalafil for PDE isozymes

PDE isozyme	IC ₅₀ (nmol/L)			Selectivity ratio of IC ₅₀ values (vs. PDE5)		
	Vardenafil	Sildenafil	Tadalafil	Vardenafil	Sildenafil	Tadalafil
PDE1 ^a	70	281	>30,000	500	80	>4450
PDE2 ^a	6200	>30,000	>100,000	44290	>8570	>14,800
PDE3 ^a	>1000	16,200	>100,000	>7140	4630	>14,800
PDE4 ^a	6100	7680	>100,000	43570	2190	>14,800
PDE5^a	0.14	3.5	6.74	1	1	1
PDE6 (rod) ^a	3.5	37	1260	25	11	187
PDE6 (cone) ^a	0.6	34	1300	4	10	193
PDE7A ^b	>30,000	21,300	>100,000	>214,000	6090	>14,800
PDE8A ^b	>30,000	29,800	>100,000	>214,000	8510	>14,800
PDE9A ^b	581	2610	>100,000	4150	750	>14,800
PDE10A ^b	3000	9800	>100,000	21,200	2800	>14,800
PDE11A ^b	162	2730	37	1160	780	5

IC₅₀: concentration required to inhibit 50% of PDE activity; PDE: phosphodiesterase Adapted from (Keating and Scott 2003), data from [2] and (Ballard et al., 1998).

^a Native human enzymes.

^b Recombinant human enzymes.

patients because no serious adverse events have ever been encountered in this clinical setting. In addition, the 5 mg dose of vardenafil should be used in men with severe renal impairment [7] and in men with mild or moderate hepatic dysfunction because of the potential for significant increase in the AUC and C_{max} of the drug [5]. Since vardenafil is predominantly metabolised by the hepatic enzyme cytochrome P450 (CYP) 3A4, and to a lesser extent by CYP3A5 and CYP2C, inhibitors of these enzymes may reduce vardenafil clearance. Consequently, concomitant use of vardenafil with potent CYP 3A4 inhibitors, such as ritonavir, indinavir, erythromycin, itraconazole, and ketoconazole is not recommended according to the product labelling. However, according to our personal experience, we feel that vardenafil may produce a positive therapeutic effects in this patient population, provided that their first dose of 5 mg is always used to optimise safety. Our current strategy is to monitor serum ALT, AST, and γ -glutamyl transferase levels in these patients every three months.

3. Pharmacodynamics

3.1. Haemodynamic effects

PDE5 inhibitors are peripheral vasodilators. In phase I studies involving healthy volunteers, vardenafil elicited mild and transient decreases in blood pressure that did not translate into any clinical effects [5]. These slight hypotensive actions of vardenafil may be exaggerated, however, by concomitant administration of vardenafil with nitrates. Therefore, concomitant use is currently contraindicated [5]. However, according to the authors' personal experience, patients presenting with ED and on concomitant nitrate therapy, and who could potentially be responders to, and benefit from PDE-5 inhibitory therapy, should be referred to their cardiologist. It has been our experience that PDE-5 inhibitors can be used safely and successfully in many patients in whom other forms of cardiological pharmacotherapy replace the use of nitrates.

We personally believe that the issue of concomitant use of vardenafil and alpha-blockers remains contro-

Table 2Pharmacokinetic parameters of single-dose oral vardenafil 10, 20, and 40 mg in men aged 22–59 years with ED (*n* = 21)

	Vardenafil 10 mg	Vardenafil 20 mg	Vardenafil 40 mg
T _{max} (hours), median (range)	0.917 (0.25–2.5)	0.660 (0.25–3.00)	0.677 (0.25–3.03)
T _{1/2} (hours), mean (S.D.)	4.18 (1.27)	3.94 (1.31)	4.79 (1.24)
C _{max} (μg/L), mean (S.D.)	9.05 (1.63)	20.9 (1.83)	50.8 (1.68)
AUC (μg/L), mean (S.D.)	32.6 (1.59)	74.5 (1.82)	164 (1.49)

Data from Klotz et al. [4] for 10 mg and 20 mg and Stark et al. [5] for 40 mg doses.

versial. According to the revised labelling of vardenafil, concomitant treatment of vardenafil should only be initiated if the patient has been stabilised on alpha blocker therapy [8]. The maximum dose of vardenafil must not exceed 5 mg in such patients. In addition, vardenafil should not be taken within 6 hours of an alpha blocker with the exception of tamsulosin for which this precaution should not be necessary. However, the results of a placebo-controlled cross-over study in 22 men with benign prostatic hypertrophy demonstrated that coadministration of vardenafil 10 mg and 20 mg with tamsulosin (0.4 and 0.8 mg daily) did not produce clinically significant hypotension [9].

3.2. *Erectile response*

The pharmacodynamic properties of single doses of vardenafil 10, 20, and 40 mg were demonstrated in two randomised, double-blind, cross-over, placebo-controlled studies involving otherwise healthy men with ED [3,4]. In these studies, penile rigidity and tumescence were measured using the RigiScanTM device, from 30 minutes prior to 2.5 hours after dosing with vardenafil or placebo. The study participants watched three 20-minute erotic videos, starting 20 minutes after dosing, and with 20 minutes of no stimulation between viewings. With vardenafil 10 mg, 20 mg, and 40 mg, both penile rigidity and the duration of rigid erections were statistically greater than placebo. Although there were no statistically significant differences in these parameters between the 20 and 40 mg dose, it has to be noted that only patients with mild to moderate ED, or patients who were able to obtain a spontaneous erection after viewing an erotic video were included in these studies. In other words, we hypothesize that if patients with severe ED had been included in these trials, a significantly better rigidity might have been observed with the 40 mg dose, as compared to the 20 mg dose.

4. **Vardenafil clinical efficacy**

4.1. *Efficacy of vardenafil in the general population of men with ED*

In for registration clinical trials, vardenafil has been taken by more than 3750 men with ED aged 18–89 years, many of whom had multiple comorbid conditions [5]. Most studies were randomised and double-blind, with either fixed dose [10–14], or flexible-dose design [15–17]. During the studies, patients took vardenafil 5, 10, or 20 mg on an ‘as needed’ basis, but not more than once daily, and were instructed to take study medication approximately 1 hour before attempting

intercourse. Efficacy of treatment was assessed by means of validated questionnaires and patient diaries.

Two at-home clinical trial conducted in European and North American centres demonstrated the efficacy of vardenafil 5–20 mg in men with ED [10,12] (Fig. 2a). Overall, more than 1400 patients, were randomized to receive fixed doses of vardenafil 5 mg, 10 mg, or 20 mg or placebo for 12 or 26 weeks. At the end of the treatment period, mean scores for IIEF questions 3 and 4 were significantly improved for vardenafil 5 mg (48% and 66.6% increase of Q3 and Q4, respectively), vardenafil 10 mg (50% and 71.4% increase of Q3 and Q4, respectively), vardenafil 20 mg (60% and 81% increase of Q3 and Q4, respectively) as compared to placebo (8% and 25% increase of Q3 and Q4, respectively; $p < 0.001$). Vardenafil produced a 54% increase of the EF domain of the IIEF which was statistically greater than the 11% increase seen after placebo ($p < 0.001$). The net increase of the EF domain seen after administration of vardenafil 20 mg (9.0 points) was not only statistically significant, but also of significant clinical impact, according to the recent interpretation of the IIEF [18]. Similarly, treatment with vardenafil resulted in significant improvements compared with placebo in others domain of the IIEF, intercourse satisfaction (placebo 13.7% increase; vardenafil 5 mg 41% increase; vardenafil 10 mg 49% increase, vardenafil 20 mg 50.7% increase), orgasmic function (placebo 0% increase; vardenafil 5 mg 32.7% increase; vardenafil 10 mg 25.8% increase; vardenafil 20 mg 30% increase), sexual desire (placebo 0% increase; vardenafil 5 mg 7.5% increase; vardenafil 10 mg 5.7% increase; vardenafil 20 mg 8.4% increase) and overall satisfaction (placebo 17.4% increase; vardenafil 5 mg 44.7% increase; vardenafil 10 mg 56.5% increase; vardenafil 20 mg 60.8% increase) ($p < 0.001$ for all doses versus placebo) [12].

Information from the patient diaries indicated that vardenafil increased the rate of successful intercourse (defined as attempting, penetrating, and completing intercourse with ejaculation) compared with placebo. Most patients receiving vardenafil indicated that their erections had improved after 12 weeks of treatment.

In the Hellstrom et al. study [10], many patients were returned to normal erectile function (EF domain score ≥ 26) after treatment with vardenafil; for example, of those patients with mild ED at baseline, 89% returned to normal function after vardenafil 10 mg, compared with 21.4% receiving placebo and of those with severe ED at baseline, 40% were returned to normal function after vardenafil 20 mg compared with only 4% receiving placebo. It should be noted that this does not mean a return to a normal spontaneous erectile

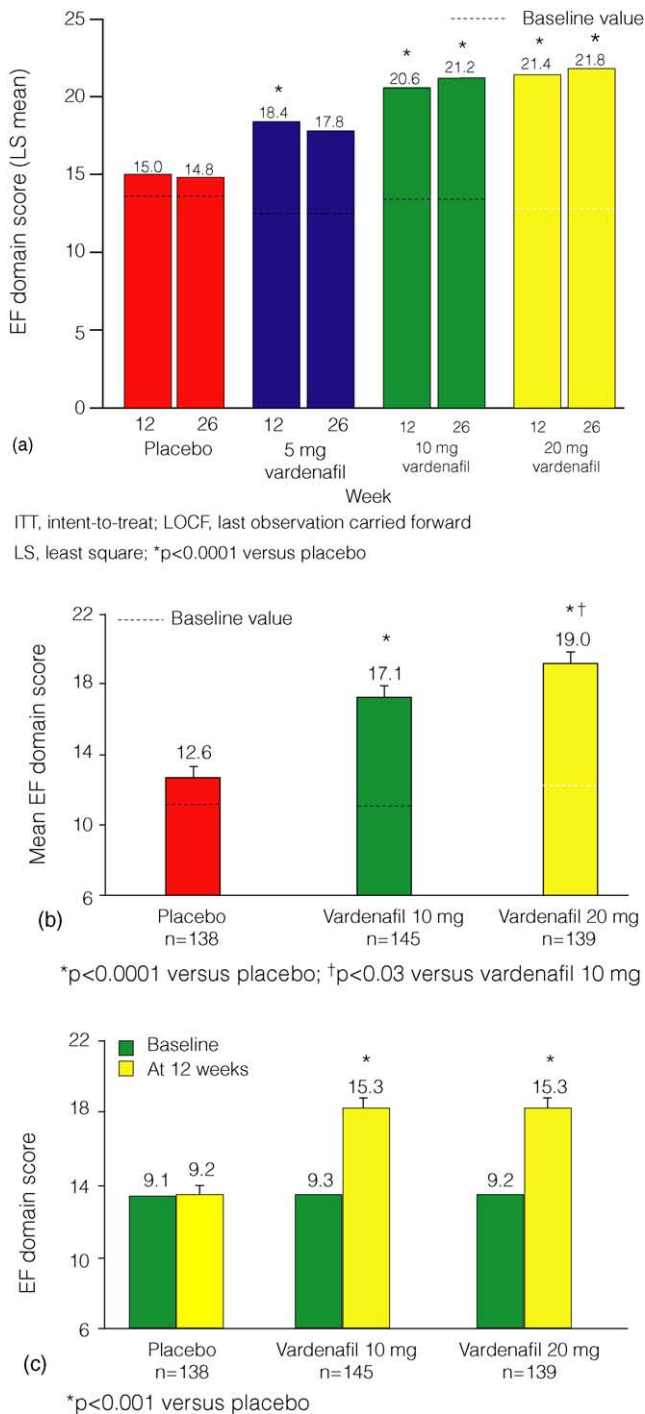


Fig. 2. Improvements in erectile function (EF) domain score with vardenafil in randomised, double-blind, fixed-dose, placebo-controlled clinical trials, (a) 26-week North American Pivotal Study involving 508 men with erectile dysfunction [10], (b) 12-week study involving 452 men with diabetes and erectile dysfunction [11], (c) 12-week study involving 440 men with erectile dysfunction after radical retropubic prostatectomy [14]. Reproduced with permission.

function; it means that a significant proportion of patients when using vardenafil did obtain IIEF erectile function domain scores within the normal range. We believe that patients with a baseline severe ED accord-

ing to IIEF should be advised that their successful response to the use of PDE5 inhibitor does not necessarily mean to achieve the same performance status they were used to have before the development of ED. We feel that avoiding unrealistic patient's expectations is a key factor to obtain a satisfied patient.

4.2. Efficacy of vardenafil in special populations

4.2.1. Diabetes

The efficacy of vardenafil 10 mg and 20 mg were evaluated in a 12-week, multicentre, randomised, double-blind, placebo-controlled, fixed-dose study, involving 452 men with ED and diabetes (type 1 or type 2) [11] (Fig. 2b). Fifty-three percent had moderate or severe ED at study baseline and 58% had previously used sildenafil (all were sildenafil-responders). Patients who did not respond to previous therapy with sildenafil were excluded. After 12 weeks, the IIEF-EF domain score, SEP-2, SEP-3, and GAQ were significantly improved following vardenafil treatment relative to placebo. Success rates were independent of baseline ED severity, level of glycaemic control, and irrespective of whether patients had type 1 or type 2 diabetes. The efficacy of vardenafil was sustained after an additional three months of therapy [19]. In patients with diabetes and ED the proportion of patients reporting the improvement of erection following treatment with any PDE5 inhibitor is less than the improvement seen in the general ED patient population [11,20,21]. It should be stated that patients with systemic complications of diabetes, including progressive diabetic retinopathy, or severe autonomic neuropathy were not included in this, or any other phase III clinical trials examining the efficacy and tolerability of sildenafil, tadalafil, and vardenafil. Thus, these trials do not fully represent the diabetic patient population predisposed to or manifest ED that is typically seen in clinical practice. In other words, in the experience of the authors of this review, the overall success rates obtained with PDE5 inhibitors as observed in clinical practice are somewhat less than those reported in clinical trials. In addition, we believe that the largest available PDE-5 inhibitor dose should be used in patients with diabetes from the time of initiation of therapy to permit a potentially higher rate of response with the obvious positive psychological implications. Patients who respond well to the highest maximum dose may be then given the opportunity to reduce the dose of the drug if they wish. In addition we have initial and anecdotal experience on salvaging patients with severe diabetic ED non responding to 20 mg of vardenafil by using the 40 mg dose.

4.2.2. Radical prostatectomy

The efficacy of fixed doses of vardenafil 10 mg and 20 mg were evaluated in 440 men with ED six months to five years after nerve-sparing radical retropubic prostatectomy in a 12-week, multicentre, randomised, double-blind, placebo-controlled study [14] (Fig. 2c). Most patients (73%) had undergone bilateral nerve-sparing prostatectomy. All enrolled patients had normal erectile function 6 months before surgery, but at study baseline mean EF domain score was 9.0–9.1 and 70% of men had severe ED.

After 12 weeks, the IIEF-EF domain score, SEP-2, SEP-3, and GAQ were significantly improved following vardenafil treatment relative to placebo. Namely the net results seen with placebo, vardenafil 10 and 20 mg, were as follows: IIEF-EF Domain score: 9.2, 15.3, 15.3; SEP 2: 22%, 47%, 48%; SEP 3: 10%, 37%, 34%; GAQ: 12.5%, 59.4%, 65.2%. In men who had undergone bilateral nerve-sparing prostatectomy, 71.1% experienced improved erections with vardenafil 20 mg, 59.7% with vardenafil 10 mg, and only 11.5% with placebo ($p < 0.0001$). Patients with residual spontaneous erectile function after surgery (positive response to SEP-1 at baseline) experienced greater improvements in each of these efficacy parameters [22].

In the opinion of the authors of this review, results of a PDE-5 inhibitor after bilateral nerve-sparing radical prostatectomy for intracapsular disease are mainly dependent upon a number of pre-operative parameters, including patient age, presence of vascular comorbidities, the status of erectile function, and the admitted sporadic or constant use of a PDE-5 inhibitor. In addition, we believe that surgical technique maintains a role of paramount importance. In a well-selected patient who undergoes a well-done bilateral nerve sparing procedure, vardenafil, as well as the other PDE5 inhibitors should be expected to produce extremely positive results.

Presently, a “hot” topic relates to the prophylactic use of PDE-5 inhibitors in patients treated with bilateral nerve-sparing procedures. Initial data suggests that daily dosing at bedtime of sildenafil (50 mg and 100 mg) for 9 months postoperatively was able to produce a significantly better rate of recovery of spontaneous erections as compared to placebo [23]. According to our clinical experience, we feel that appropriately designed studies employing vardenafil and tadalafil will yield similar results and we are aware that specifically devoted studies are close to be initiated.

4.2.3. Depressive symptomatology

ED is strongly associated with depression. The efficacy of vardenafil 5–10 mg in 280 men with ED

and depression was assessed in a 12-week, multicentre, randomised, placebo-controlled, flexible-dose study [24]. Enrolled men had mild major depressive disorder, with a Hamilton Depression Scale (HAM-D) score of 11–17, and were not receiving psychotherapy or antidepressants. Treatment with vardenafil significantly improved all parameters relating to erectile function. Notably, treatment with vardenafil resulted in improvement in depressive symptoms, as evidenced by a two specifically designed and validated instruments. Further analysis of the time course of improvements in EF domain and HAM-D scores indicated that improved erectile function appeared to precede improvement in depressive symptoms [25].

The authors of this review believe that the routine use of specific validated questionnaires in the initial assessment of ED may allow for the identification of the general population of patients with depression or similar mood disorders, as in our practice the number of ED patients showing this comorbidity has been progressively increasing. In our practice, a patient who presents with erectile dysfunction and concomitant untreated minor depression is provided with a prescription for a PDE-5 inhibitor, and is strongly advised to be concomitantly assessed and treated by neurologist/psychologist/psychiatrist.

4.3. Vardenafil period of responsiveness

The prescribing information for vardenafil recommends that a dose be taken approximately 1 hour before sexual intercourse [8]. In real life, however, couples may desire more flexibility in their sexual activities.

In a randomised, double-blind, at-home study, 471 men with ED were given 4 weeks supply of vardenafil 20 mg or placebo and were asked to start sexual activity immediately after dosing [26]. For the first four doses, men recorded with a stopwatch the earliest time at which they experienced an erection they perceived adequate for penetration and intercourse. Subsequent intercourse completion was recorded in diaries. A significantly greater proportion of men successfully completed intercourse with vardenafil compared with placebo at all time points from 25 minutes down to 16 minutes ($p < 0.05$). At 16 minutes success rates were 34% and 24%, respectively ($p = 0.013$), while at 25 minutes, 48% of men on vardenafil completed intercourse compared with 30% on placebo ($p < 0.0001$). Even earlier success was observed in another similarly designed at-home study involving 665 men with ED [27] (Fig. 3a and b). Compared with placebo, men receiving vardenafil 10 mg or 20 mg experienced a significantly higher rate

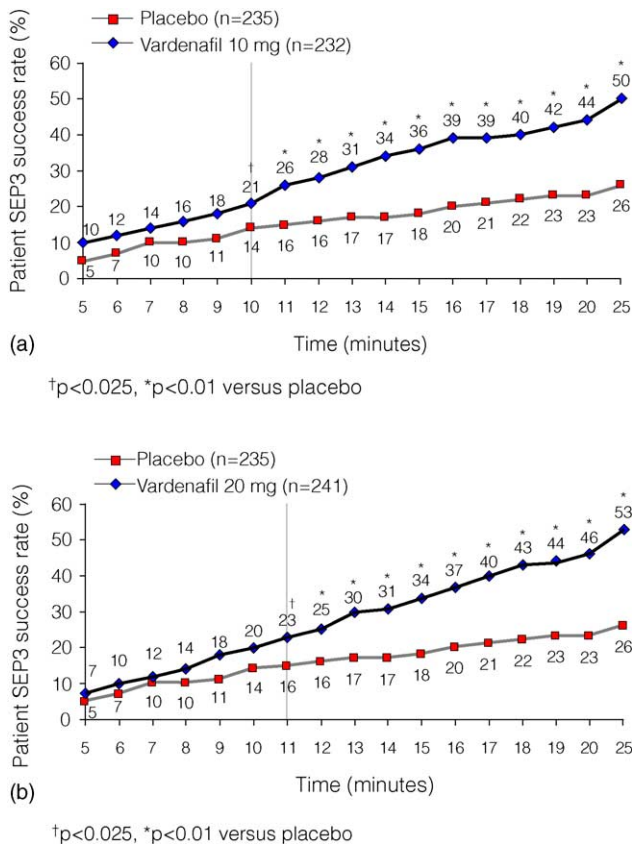


Fig. 3. Per-patient success rates for Sexual Encounter Profile question 3 (SEP3) “did your erection last long enough for you to have successful intercourse?” by time after dosing with (a) vardenafil 10 mg or (b) vardenafil 20 mg in a randomised, double-blind, placebo-controlled study of 665 men with erectile dysfunction. Men were instructed to start sexual activity immediately after dosing and record the time at which they attained an erection that was sufficient to subsequently complete intercourse [27].

of intercourse completion as early as 10 minutes after dosing ($p < 0.025$). Within 25 minutes of dosing, 53% and 50% of men taking vardenafil 10 mg and 20 mg, respectively, had erections sufficient for penetration and completion of intercourse, compared with 26% on placebo ($p < 0.0001$).

The authors of this review feel that patients using vardenafil for the first time should be advised to engage in sexual activity approximately one hour after ingestion of the pill (i.e. the time necessary to reach C_{max}). Responders may then be counselled to shorten the time of initiation of sexual activity after dosing if they have the desire to do so.

Couples may also wish to initiate sexual activity some hours after dosing with ED therapy. In the rabbit model, vardenafil was effective in enhancing NO-induced erections 7 hours after dosing, which is four times the plasma $t_{1/2}$ of vardenafil in the rabbit [28]. As vardenafil $t_{1/2}$ in humans is approximately 4–5 hours, these preclinical findings suggest that the efficacy of

vardenafil in humans could extend for considerably longer than predicted from its pharmacokinetic properties. Reasons for this unexpected finding may relate to a particularly strong binding between vardenafil and its receptor on the PDE-5 enzyme [29]. In a pooled analysis of two randomised, double-blind studies, a small number of patients elected to engage in sexual activity from 8–12 hours after dosing (5–20 mg vardenafil) and reported significantly improved SEP3 success rates as compared to placebo [30]. According to the experience of the authors of this review, patients may be advised to take their usual vardenafil dose approximately one hour prior to their evening meal, thus allowing the drug to reach its C_{max} at the time the meal starts, and then to enjoy sexual activity at any time during the evening.

4.4. Reliability of vardenafil efficacy

In a retrospective analysis of two 12-week, randomised, double-blind, placebo-controlled studies involving 1650 men with ED, vardenafil improved the reliability of penetration (SEP2), maintenance of erection (SEP3), and overall satisfaction with sexual experience compared with placebo [27]. This means that the majority of patients who successfully responded to the first dose of vardenafil maintained a positive response 12 weeks later. In another double-blind study, Stief et al. demonstrated that vardenafil was able to yield successful responses in the majority of patients for up to two years of treatment [13]. However, we feel that the long-term reliability a PDE-5 inhibitor is dependent upon many factors including the general health condition of the partner, the desire to maintain an active sexual life, and the availability of his partner. Overall, it is possible that these latter factors may play a greater role than the pure pharmacological efficacy and tolerability of the drug.

4.4.1. Dose optimisation with vardenafil

The authors of this review feel that it is of major importance to provide the patient with the initial dose of initiator to yield a satisfactory response. Thus, although the labelling of vardenafil suggests to initiate treatment in the general ED population with the 10 mg dose, we believe that in patients with severe ED at baseline and an organic etiology, the 20 mg dose of vardenafil as the initial dose is more appropriate.

5. Vardenafil safety and tolerability

Vardenafil has been administered to more than 3750 patients in premarketing clinical trials worldwide.

Table 3

Incidence (%) of treatment-related adverse events reported by $\geq 2\%$ of patients treated with vardenafil and more frequent on drug than placebo in fixed-dose studies

	Vardenafil (n = 1812)	Placebo (n = 793)
Headache	16	6
Flushing	12	1
Rhinitis	10	4
Dyspepsia	4	1
Accidental injury	3	2
Sinusitis	3	1
Flu syndrome	3	2
Dizziness	2	1
Increased creatine kinase	2	1
Nausea	2	1
Arthralgia	2	1

Adapted from Young [31].

More than 1630 patients were treated for ≥ 6 months and more than 730 patients received vardenafil for at least one year [5,31].

5.1. Adverse events

Across the fixed-dose placebo-controlled studies, the most frequent adverse events reported by patients on vardenafil were headache, flushing, and rhinitis, consistent with the vasodilatory properties of PDE5 inhibitors (Table 3). Treatment-emergent adverse events were generally mild-to-moderate intensity and transient in nature. During the 104-week study, the incidence of treatment-emergent adverse events was greater during the first few weeks of the study, and rapidly decreased during long-term treatment.

Serious adverse events were infrequent, reported by 1–5% of patients receiving vardenafil 5–20 mg and 3–5% of placebo recipients in short-term studies [10–12] and in 11% and 13% of patients receiving vardenafil 10 mg and 20 mg, respectively, in the 104-week study, but only one event (reduced visual acuity) was judged as possibly related to vardenafil treatment [13].

The authors of this review feel that, in general terms, the methods used to assess adverse events in randomized, placebo-controlled clinical trials for all pharmaceuticals, although universally meeting the

regulatory authority requirements, have been substandard. We currently lack information about the duration of adverse events and about their actual intensity as measured by scientifically validated instruments (i.e., the use of a visual analog scale for headache).

5.2. Cardiovascular effects

In a pooled analysis of data from seven clinical studies, which included 1812 men receiving vardenafil and 793 receiving placebo, vardenafil was associated with a small reduction in systolic (-4.6 mmHg) and diastolic (-3.1 mmHg) change in blood pressure and small increase in heart rate (2 bpm) change in patients receiving concomitant antihypertensive medications [32]. The incidence of electrocardiographic (ECG) abnormalities, oedema, syncope, angina, hypotension, or myocardial ischaemia was between 0% and $<0.6\%$ and was not related to the dose of vardenafil. One patient using vardenafil experienced a myocardial infarction, while three individual patients in the placebo group experienced myocardial infarction, cerebrovascular accident, and cardiovascular surgery, respectively [33]. There was no evidence of long-term cardiovascular safety concerns according to vital sign and ECG recordings, during 2 years of treatment with vardenafil [13].

A placebo-controlled, cross-over study assessed the effect of vardenafil 10 mg or 20 mg on ischemic events during exercise in 41 men with stable coronary artery disease [34,35]. The exercise test was designed to simulate a level of exertion similar to or greater than sexual intercourse. Compared with placebo, vardenafil had no significant effect on mean total exercise time or time to first awareness of angina (Table 4). Vardenafil 10 mg (but not 20 mg) significantly prolonged the time to ischemic threshold (ie ST-segment depression ≥ 1 mm compared with baseline) ($p = 0.002$). These findings indicate that vardenafil does not exacerbate ischemic response to exercise in men with stable coronary artery disease.

The effect of vardenafil on QT interval have also been shown to be not clinically significant

Table 4

Effects of vardenafil 10, 20 mg, and placebo on exercise testing in men with stable coronary artery disease [32]

	Vardenafil 10 mg (n = 27)	Placebo	Vardenafil 20 mg (n = 36)	Placebo
Treadmill exercise time	433 (110)	428 (101)	414 (114)	411 (124)
Time to angina awareness	292 (125)	290 (103)	354 (137)	347 (143)
Time to ST-segment depression (≥ 1 mm vs. baseline)	377 (109)*	331 (104)	364 (101)**	366 (105)

All values are mean seconds (S.D.).

* $p = 0.002$ vs. placebo.

** $n = 33$.

[36]. The author of this review feel that the initial assessment of patients with ED in the urologist office may represent a unique opportunity to identify undiagnosed cardiovascular disease. It has been suggested [37,38] that erectile dysfunction may be a sentinel for ischemic heart disease. Unfortunately, we currently lack guidelines to identify patients with ED who are asymptomatic from a cardiovascular point of view, and still might need to be assessed by a cardiologist. In our clinical practice, if we observe a patient who has a negative cardiac history, ED, but has ≥ 2 vascular risk factors, we suggest him to undergo a cardiological consultation, which includes a stress ECG. Finally, patients with known history of cardiovascular disease should be managed according to the algorithm proposed by the Princeton panel, which stratifies patients into three different levels of cardiac risk. [39].

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