

The efficacy and safety of PDE5 inhibitors

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Inhibition of phosphodiesterase-5 (PDE5) reduces the degradation of cyclic guanosine monophosphate, which allows erectile function to occur by relaxation of penile smooth muscle. Three PDE5 inhibitors (sildenafil, tadalafil, and vardenafil) in a range of doses are available. PDE5 therapy, compared with placebo, significantly improves scores on the International Index of Erectile Function and has been found to be effective in special clinical populations, such as those with prostate cancer, diabetes, and cardiovascular disease. Sildenafil and vardenafil show some interaction with food intake. Time to onset of action is usually 30-120 minutes, but there are reports of shorter times to onset of action. The duration of action of sildenafil and vardenafil is about 4 hours, whereas that of tadalafil is about 36 hours. The overall safety of the treatments is good, even in patients with a history of cardiovascular disease. However, there is a risk of hypotension if nitrates are given concurrently. Increased QTc intervals have been reported, the longest with vardenafil, shortest with tadalafil, and intermediate with sildenafil. Priapism and prolonged erection are rare adverse events. Common side-effects include headache, facial flushing, nasal congestion, and dyspepsia. There may be interactions with other medications metabolized in a similar way, such as erythromycin and HIV protease inhibitors. (*Clinical Cornerstone*. 2005;7[1]:47-55) Copyright © 2005 Elsevier BV.

The ideal drug therapy for erectile dysfunction (ED) would be effective, easily administered, and free from toxicity and side-effects. Of all treatments currently on offer (see the article by W. Dinsmore, p. 37-44), the phosphodiesterase-5 (PDE5) inhibitors (the licensed members of the class are sildenafil, vardenafil, and tadalafil) most closely approach this theoretical ideal. In practice, their characteristics have made them a popular choice for doctors and patients, and for many they have become the preferred treatment option.^{1,2}

MECHANISM OF ACTION

For a normal penis to become erect, the penile smooth muscle must relax. When smooth muscle relaxes, more blood flows into the penis, accumulating within the vascular trabecula and resulting in an erection. The main mediator of smooth-muscle relaxation is nitric oxide (NO), which is released from parasympathetic nerve terminals and from the vascular endothelium. Within the smooth-muscle cell, NO stimulates the enzyme guanylate cyclase to convert guanosine triphosphate to the active second messenger, cyclic guanosine monophosphate (cGMP). High levels of cGMP prompt phosphorylation of the myosin

light chains of the smooth muscle, causing it to relax.³ cGMP's action is stopped by the enzyme PDE5; drugs that inhibit this enzyme potentiate the smooth-muscle relaxation induced by a sexual stimulus.

PDE5 inhibitors, unlike some other treatments for ED, do not directly affect the penis and do not cause spontaneous erections. They work only when NO is released; a sexual stimulus is thus always required for these drugs to have an effect.

COMPARISON OF THE THREE PDE5 INHIBITORS

Dose

Sildenafil. Most patients start with a dose of 50 mg of sildenafil. This can be titrated, depending on efficacy and tolerability, up to 100 mg or down to 25 mg. Only 1 dose of sildenafil should be taken in a day.⁴

Tadalafil. In most countries, the recommended starting dose of tadalafil is 10 mg, with titration up to 20 mg or (unusually) down to 5 mg. Geriatric patients use the same dosage.⁵ The recommended maximum dosing frequency is usually once a day.

Vardenafil. Most patients begin with 10 mg of vardenafil; again, it can be titrated up to 20 mg or down to 5 mg. A maximum of 1 dose of vardenafil per day is recommended.^{6,7}

General efficacy

Nobody has yet directly compared the 3 PDE5 inhibitors. Comparing them across clinical trials is difficult, especially because the pivotal trials have used different study designs and patient populations. They have, however, used similar end-points, including the preferred end-point: change in erectile function as measured by the International Index of Erectile Function (IIEF) questionnaire.

Sildenafil. Data, pooled from 11 double-blind trials of 1,329 patients who received placebo and 1,338 who received sildenafil, show an association between sildenafil treatment and significantly higher mean scores for individual IIEF questions on achieving and maintaining an erection satisfactory for sexual performance.⁸ Sildenafil was also associated with improved scores for the 6 IIEF questions that cover erectile function/performance.⁸ Treatment was effective across all subgroups, including race and ethnicity, age, body mass index, severity and type of ED, and other medical conditions.⁸ With long-term therapy in open-label extension studies lasting 1–3 years, 95% of the patients were satisfied with their treatment.⁸

In a dose-response study of 532 men, increasing doses of sildenafil were associated with improved erectile function, as measured by questions about achieving and maintaining erections.⁹ In a 12-week study of 329 men in which the dose was escalated to 100 mg of sildenafil, the mean score (out of a possible 5) for achieving an erection increased from 2 at baseline to 4.⁹ In the last 4 weeks of the 12-week study, 69% of all attempts at sexual intercourse were successful in men taking sildenafil compared with 22% in those receiving placebo ($p < 0.001$). The mean number of successful attempts at sex per month was 5.9 for men receiving sildenafil and 1.5 for those receiving placebo.⁹

In 14 parallel-group, flexible, as-needed trials, 83% of the 2,205 men taking sildenafil experienced at least 1 successful attempt at intercourse compared with 45% of the men receiving placebo (relative benefit increase, 1.15; 95% confidence interval [CI], 1.7–1.9; for 2,205 men).¹⁰ Similarly, there was a significantly higher proportion of successful attempts at intercourse in 2,283 men taking

sildenafil compared with those on placebo (57% versus 21%, weighted mean difference 33.7; 95% CI, 29.2–38.2).¹⁰

Tadalafil. In 11 clinical trials, a total of 2,102 men with mild-to-moderate ED were randomized to fixed “on-demand” doses of 10 mg or 20 mg tadalafil for 12 weeks.¹¹ Those on the 10-mg dose of tadalafil improved their IIEF score by 6.5, whereas those on the 20-mg dose improved their score by 8.6; both improvements were significantly better than placebo ($p < 0.001$). The mean success rate for attempts at sexual intercourse was 58% and 68% for the 2 doses of tadalafil, respectively, compared with 31% in the placebo group ($p < 0.001$).¹¹

KEY MESSAGE PDE5 INHIBITORS ARE SAFE AND EFFECTIVE IN MOST PATIENT POPULATIONS, INCLUDING THOSE WITH ISCHAEMIC CARDIOVASCULAR DISEASE, THOSE TAKING ANTIHYPERTENSIVE DRUGS, THOSE WITH DIABETES, AND THOSE WITH PREVIOUS NERVE-SPARING RETROPUBIC RADICAL PROSTATECTOMY

In a 12-week trial of 1,112 men with mild-to-severe ED (mean age 59 years), those receiving 20 mg tadalafil improved their score relative to baseline on the IIEF by a mean of 7.9 ($p < 0.001$ compared with placebo).¹² In that study, 75% of attempts at sexual intercourse in the men receiving tadalafil were successful, as measured by question 3 of the Sexual Encounter Profile (SEP), significantly better than with placebo ($p < 0.001$).¹² A multicentre, randomized, double-blind, placebo-controlled, parallel-group study of 348 men found that, 36 hours after dosing, 59.2% of intercourse attempts in men taking 20 mg tadalafil were successful compared with 28.3% in the placebo group ($p < 0.001$).¹³ There was a similar significant difference 24 hours after dosing (52.9% versus 29.1%; $p < 0.001$).

In a trial of 235 men (59% of whom had moderate-to-severe ED), tadalafil, compared with placebo, improved erectile function at doses

ranging from 2.5 mg to 20 mg.³ Treated men had significantly greater improvements from baseline in the erectile function domain of the IIEF ($p < 0.001$). The end-point IIEF score with 10 mg tadalafil was 21.1, and 23.9 with 20 mg, compared with 15.1 in controls receiving placebo.³ Those in the 20-mg group approached the IIEF erectile function score for “no ED”. Response to each dose of tadalafil was better than that with placebo, and response to the 20-mg dose was consistently greater than the response to the 10-mg dose.³

Vardenafil. A multicentre study in which 805 men with moderate-to-severe ED were randomized to different doses of vardenafil or placebo showed that 5-, 10- and 20-mg doses of vardenafil were significantly more effective than placebo at every measurement of efficacy over 26 weeks.¹⁴ At baseline, the mean score on the erectile function domain was 13–14, consistent with moderate ED. In a Last Observation Carried Forward (LOCF) analysis, the IIEF domain score after 26 weeks of treatment was 17.79 with a 5-mg dose of vardenafil, 21.2 with 10 mg, and 21.8 with 20 mg (compared with 14.84 with placebo; $p < 0.0005$). At the end of the study, 89.4% of the patients on 20 mg vardenafil, 81.0% of those on 10 mg, and 74.0% on 5 mg responded to treatment (compared with 64.6% on placebo). There was a similar statistical difference in the intention-to-treat population, using a LOCF analysis. Improvements in the IIEF score meant that those taking the 10- and 20-mg doses had achieved a mean score that indicated mild disease.¹⁴

A study of 601 men using vardenafil at home found that the percentage of successful intercourse attempts with 3 doses of vardenafil (5, 10, and 20 mg) was between 71% and 75%, as measured by the erectile function domain of the IIEF.¹⁵ Vardenafil has also produced significant improvements in men with severe ED who were unresponsive to sildenafil.¹⁵

THE EFFECTS OF HIGH-FAT FOOD AND ALCOHOL

Sildenafil. Food reduces and delays the absorption of sildenafil from the gut; sildenafil taken after a high-fat meal has a slower onset of action.⁶ The mean delay in the time to maximum concentration (T_{max}) is 60 minutes, and a mean reduction in the maximum concentration of the drug (C_{max}) is 29%.⁴ Some perceived, lack of efficacy of sildenafil may be attributable to men attempting intercourse after a high-fat meal.¹³ It has also been

suggested that inadequate patient instruction on food and alcohol intake with sildenafil may be one reason for a loss of efficacy over time and a low compliance rate after 1 year.¹⁴

Vardenafil. A high-fat meal has been found to delay the absorption of vardenafil up to 1 hour and to slightly reduce the C_{max} , but a medium-fat meal had no clinically relevant effect. However, the researchers behind this study concluded that no changes to dose were necessary because of the wide therapeutic index of vardenafil and its efficacy in trials where food was not restricted.¹⁶

Tadalafil. A review of tadalafil concluded that its prolonged period of effectiveness was independent of food and alcohol.¹⁷

THE TIME TO ONSET OF ACTION

The time to onset of action of the 3 drugs appears to be similar. For sildenafil, it is 30 minutes to 2 hours after taking a dose, although it may be as early as 11 minutes post-dose. For tadalafil, a time of 16 minutes has been recorded, and adequate efficacy has been reported for most men after 30–120 minutes.⁶ The time to onset of action for vardenafil is usually 30 minutes to 2 hours (median 0.7 hour), but a time of 16 minutes after dosing has been reported.^{15,18}

DURATION OF ACTION

Both sildenafil and vardenafil are effective for about 4 hours after dosing, whereas the long half-life of tadalafil (17.5 hours) means that most patients can complete intercourse up to 36 hours after dosing.^{2,13,15,19}

SPECIAL PATIENT POPULATIONS

After prostate cancer

After radical prostatectomy, more than one-third of men experience ED, even if attempts are made to spare nerve tissue. Radiotherapy for prostate cancer also increases the risk of ED because of an acceleration of microvascular angiopathy, leading to cavernosal fibrosis, and so to loss of erectile function. All 3 treatments improve ED in men who have had prostate cancer.

Sildenafil. Data pooled from 11 double-blind, placebo-controlled, flexible-dose trials of men on sildenafil treatment after radical prostatectomy revealed that the men on sildenafil achieved a significantly better (higher) score on the erectile

function domain questions of the IIEF compared with those on placebo (2.3 versus 1.1 for question 3; $p < 0.001$; and 2.4 versus 1.3 for question 4; $p < 0.005$).⁸ The overall erectile function domain score was 15.7 in prostate surgery patients who were receiving sildenafil compared with 8.6 for those receiving placebo ($p < 0.001$).⁸

However, the pooled data showed that men with ED after radical prostate removal had lower response rates to sildenafil than did men with other comorbidities. Sildenafil, as do all PDE5 inhibitors, requires intact innervation of the penis to be most effective; the effectiveness of sildenafil is related to the number of neurovascular bundles spared during surgery: 33–80% (of nerve bundles spared) for bilateral nerve-sparing, 0–80% for unilateral nerve-sparing, and 0–20% for non-nerve-sparing surgery.⁸

KEY MESSAGE THE PDE5 INHIBITORS HAVE DIFFERENT PHARMACOKINETIC PROPERTIES, ESPECIALLY REGARDING THE DURATION OF ACTION AND THE INFLUENCE OF MEALS AND ALCOHOL ON ABSORPTION, DICTATING SPECIFIC CLINICAL BENEFITS

Findings on the timings of sildenafil treatment are more variable: 1 study suggests it is equally effective whether given during the 6 months immediately after surgery, from 6–12 months, or even later.⁸ Another study concluded that response was poor 6–9 months after surgery.⁸

Tadalafil. Compared with placebo, tadalafil significantly improved IIEF scores after radical prostatectomy (13.3 versus 17.7; $p < 0.001$) and improved the ability to insert the penis (54% versus 32%; $p < 0.001$) and to maintain an erection (41% versus 19%; $p < 0.001$).⁵

Vardenafil. Treatment with vardenafil significantly improved key indices of erectile function in 440 men with severe ED after radical retropubic prostatectomy.²⁰ At baseline, 70% of the men had severe ED (IIEF score < 11). The men were randomized to placebo, or to 10 or 20 mg of vardenafil. Nearly two-thirds (65.2%) of those on

the higher dose of treatment, and 59.4% of those on the 10-mg dose, reported improved erections. Only 12.5% of the men on placebo reported improved erectile function. The difference was significant ($p < 0.0001$). For men receiving 20 mg vardenafil, the average intercourse success rate was 74% in those with mild-to-moderate ED and 28% in those with severe ED. This compares with an intercourse success rates of 49% in men with mild-to-moderate ED and 4% in those with severe ED who were on placebo.²⁰

Diabetic patients

ED is a common complication of diabetes; more than 50% of men with diabetes develop ED within 10 years of diagnosis, and the overall prevalence of ED in men with diabetes is estimated between 35% and 70%. The prevalence of ED in men with diabetes increases from 9% in diabetic men aged 20–29 years to 95% in men with diabetes over 70 years.²¹ Response to treatment for ED is generally poorer than for the general population because of the multifactorial pathogenesis of diabetes. However, the convenience of oral PDE5 inhibitors has made them popular among men with diabetes who have developed ED. More selective PDE5 inhibitors may be more effective in difficult-to-treat ED patients with diabetes.^{8,21,22}

Sildenafil. In 2 12-week double-blind, placebo-controlled studies, with 259 and 261 men with diabetes, respectively, researchers found that treatment with sildenafil resulted in improvement of erection in 51–56% of the men on active treatment and in 10–12% of those on placebo.⁸ In those trials, 80% of the men had type 2 diabetes, and 20% had type 1 diabetes.⁸ There was improvement in the ability to achieve and maintain an erection sufficient for intercourse, although the mean IIEF scores for questions 3 and 4 (the erectile function domain of the IIEF) were lower than those seen in the general clinical population.⁸

Similar results were found in a study of 268 men with diabetes, 252 of whom completed the study.²³ Over the 12 weeks of the study, 61% of the sildenafil-treated men reported a successful attempt at sexual intercourse compared with 22% of the placebo group.²³

A randomized, placebo-controlled study of sildenafil was carried out in 219 men with type 2 diabetes.²⁴ After 12 weeks, the mean scores on IIEF

questions 3 and 4 improved significantly for men receiving sildenafil compared with those receiving placebo ($p < 0.0001$). The percentage of attempts at sexual intercourse that were successful was also significantly higher in the sildenafil-treated group than in the placebo group ($p < 0.0001$). Sildenafil was effective in treating ED in men in whom glycaemic control was poor, and who had multiple chronic complications.²⁴

A pooled analysis of 4 trials that evaluated the efficacy of sildenafil by subgroups found that the overall score for the erectile function domain of the IIEF, as well as separate scores for question 3 and question 4, the global efficacy question (GEQ), and the percentage of successful intercourse attempts, tended to be lower in older patients, in men with more severe ED, or in those with a longer duration of ED.⁸ Treatment also tended to be less successful in men who had had diabetes for longer times or in those with more diabetic complications. However, the differences between these subgroups did not reach statistical significance ($p > 0.05$).⁸

Tadalafil. A randomized, double-blind, placebo-controlled, parallel-arm, prospective trial found improvements in erectile function in a group of 215 patients with type 1 or type 2 diabetes treated with 10 mg or 20 mg tadalafil compared with patients treated with placebo.⁵ Scores on the erectile function domain of the IIEF were 19.3 for those on 10 mg and 18.7 for those on 20 mg (compared with 12.2 for those on placebo; $p < 0.001$). Questions on the SEP revealed that significantly more men managed to insert their penis during sex (54–57% on tadalafil compared with 30% on placebo), and significantly more managed to maintain an erection (42–48% on tadalafil compared with 20% on placebo).⁵

Vardenafil. Treatment with vardenafil, compared with placebo, improved erectile function in patients with diabetes and with ED. In a prospective multicentre, double-blind, placebo-controlled, fixed-dose, parallel-group trial, 452 patients with diabetes were randomized to receive placebo, or 10 mg or 20 mg of vardenafil.²² After 12 weeks, the changes from baseline in scores on the erectile function domain of the IIEF reached significance for men on the 10- and 20-mg doses of vardenafil, with changes in score of 5.9 and 7.8, respectively, both significantly greater than the change of 1.4 with placebo ($p < 0.0001$). Final IIEF scores reached 19 with the highest dose of vardenafil compared with 12.6 with placebo. Both doses of

vardenafil were associated with significantly more successful penetration and successful intercourse.²² Treatment was effective for men with all degrees of severity of ED, for each level of plasma hemoglobinA_{1c}, and for both type 1 and type 2 diabetes.²²

Cardiovascular disease

ED and cardiovascular disease are common comorbidities, as they share a number of risk factors, such as hypertension, diabetes, hyperlipidaemia, smoking, and age.

Sildenafil. In men with ED and cardiovascular disease receiving β -blockers and/or angiotensin-converting enzyme inhibitors and/or calcium-channel antagonists, sildenafil produced a significant improvement in erectile function (IIEF questions 3 and 4, GEQ) in a double-blind, placebo-controlled trial ($p = 0.0001$). None of the men were on nitrates, because nitrate use is a contraindication for sildenafil.⁸

A subanalysis of data from 9 randomized trials on men with ischaemic heart disease given a range of doses of sildenafil (from 5 to 200 mg) or placebo for periods from 4 weeks to 6 months found that there were significant improvements ($p < 0.0001$) in all efficacy measures (GEQ, question 3 and question 4 of the IIEF, overall score for the erectile function domain of the IIEF).⁸

In an analysis of pooled data, erectile function, as measured by IIEF scores (question 3, question 4, and overall erectile function domain), improved from baseline in men with ED and peripheral vascular disease when they were treated with sildenafil.⁸ The mean scores increased twofold. No statistical analysis was provided.⁸

Sildenafil was found to be effective in men with a history of hypertension, as well as those currently taking antihypertensives. In a double-blind, placebo-controlled study in which 83% of the men had hypertension, sildenafil treatment was significantly more effective at achieving and maintaining erections compared with placebo ($p < 0.0001$).⁸

Tadalafil. Tadalafil has no effect on blood pressure or heart rate in healthy men. In men with ED and diabetes mellitus, a group at high risk of cardiovascular disease, tadalafil increased erectile function domain scores of the IIEF from the baseline by 6.4 points (with 10 mg) and 7.3 points (with 20 mg). In comparison, placebo improved those scores by 0.1 points ($p < 0.001$).⁵

Vardenafil. In a study on the effect of vardenafil in men with diabetes and ED, the participants were at high cardiovascular risk.⁷ About one-half had current hypertension, and about the same proportion were being treated with renin-angiotensin-system-acting agents. About one-third of the patients in the trial were being treated with lipid-lowering agents. Those with a previous myocardial infarction (MI), stroke, ischaemia, or life-threatening arrhythmia were allowed to take part in the trial as long as the event had not occurred in the previous 6 months. In this group of patients at high cardiovascular risk, 57% responded with improved erections to the 10-mg dose of vardenafil, and 72% responded to the 20-mg dose.⁷

COMPARISON OF SAFETY OF PDE5 INHIBITORS

Cardiovascular events

The many shared risk factors such as age, hypertension, diabetes, and hyperlipidaemia mean that men with cardiovascular disease are more likely to have ED than are men in general. In patients with coronary artery disease, PDE5 inhibitors dilate epicardial coronary arteries, improve endothelial function, and inhibit platelet activation, although the effect is less than with an isosorbide dinitrate. Flow-mediated dilation of the brachial artery may also be of benefit, particularly in men with diabetes. These are potentially beneficial effects.¹⁵

Overall, PDE5 inhibitors have been shown to have a good safety profile in most men, including those with cardiovascular disease and those taking antihypertensives (other than nitrates). Data from controlled clinical trials and — for sildenafil — prescription event monitoring (reflecting use by doctors in general practice without formal inclusion and exclusion criteria) indicate no more MIs or cardiovascular deaths than would have been expected from similar age-standardized populations not taking PDE5 inhibitors.¹⁵

In any patient with cardiovascular disease, sexual activity may increase cardiac risk.^{4,5,7} The absolute risk is slight, with a relative risk of about 2.5 for an MI within 2 hours of sex for patients with coronary artery disease compared with other times.²⁵

A study of vardenafil in men with symptomatic stable coronary artery disease (although not necessarily with ED) was somewhat reassuring. It found that vardenafil treatment did not affect exercise-tolerance results, neither the total exercise time nor the time to awareness of angina. There was actually a 15% increase in the ischaemic

threshold, measured by ST segment depression, in the vardenafil-treated group compared with the placebo group. There were no untoward haemodynamic events in either the placebo group or vardenafil-treated group. The results support the conclusion that administration of vardenafil does not exacerbate ischaemic response to exercise any more than placebo at levels of energy expenditure similar to or greater than those required for sexual intercourse. The same study also found similar results with sildenafil.²⁵

Risk of hypotension (with or without nitrates)

All PDE5 inhibitors have a hypotensive effect, but the size of this effect varies by drug. The effect of PDE5 inhibitors on NO/cGMP may be potentiated by nitrate therapy. Although trials in which PDE5 inhibitors and nitrates were co-administered have identified no excess risk of MI or death, the risk of hypotension and cardiac complications means that PDE5 inhibitors are contraindicated in patients taking nitrates.¹⁵

Sildenafil at a 100-mg dose has been found to reduce blood pressure by about 10 mmHg in healthy volunteers.¹⁵ Vardenafil also reduces both systolic and diastolic blood pressure by 7/8 mmHg (although it also produces a small increase in heart rate).¹⁵ Tadalafil is associated with smaller reductions of 4.5/2 mmHg.¹⁵

Co-administration of sildenafil and α -adreno-receptor antagonists may cause additive but not necessarily potentiating reductions in blood pressure, and their administration within 4 hours of one another is contraindicated.¹⁵ There is a similar contraindication against concomitant use of α -adrenoreceptor antagonists with vardenafil (although there do not seem to be any significant haemodynamic effects when vardenafil is given with the calcium-channel antagonist nifedipine).¹⁵ Tadalafil has a similar contraindication to α -adrenoreceptor antagonists, except tamsulosin. A study of 20 mg tadalafil given with 0.4 mg tamsulosin daily resulted in no significant decrease in blood pressure.¹⁵

The moderate vasodilatory and hypotensive effects of sildenafil and vardenafil mean they should not be given to patients who are already hypotensive. The reduced hypotensive effect of tadalafil may be attributable to its long half-life and part of an overall reduced effect on the circulatory system.⁶

Risk of increased QTc interval

An 8-ms increase in the QTc interval was reported in a study of 59 healthy middle-aged men taking

10-mg and 80-mg doses of vardenafil. Patients with congenital QT prolongation and those taking some antiarrhythmic drugs, such as quinidine, procainamide, amiodarone, and sotalol, should therefore avoid using vardenafil.^{7,25}

A 6-ms increase in the QTc interval has been reported with 50 mg sildenafil, and a smaller, 3.5-ms increase with tadalafil.^{5,26}

Risk of prolonged erections/priapism

There are rare reports of prolonged erections of more than 4 hours and priapism (erections lasting more than 6 hours) with all PDE5 inhibitors. Priapism is a medical emergency that can cause irreversible tissue damage and needs to be treated urgently.⁴⁻⁷

Sperm characteristics

Analysis of the semen of 20 healthy volunteers found that taking sildenafil had no effect on seminal parameters.²⁷ There are no clinically relevant effects on sperm concentration, sperm count, motility, or morphology in placebo-controlled trials of tadalafil lasting up to 6 months.⁵ There was no effect on sperm motility or morphology after single 20-mg oral doses of vardenafil in healthy volunteers.⁷

Renal insufficiency, hepatic impairment, and diabetes mellitus

In patients with severe renal impairment, exposure to sildenafil was doubled. There was no pharmacokinetic impact of moderate renal impairment. In volunteers with hepatic cirrhosis, sildenafil clearance was reduced (exposure as measured by area under the concentration-time curve [AUC] increased by 84%). Because hepatic impairment and severe renal impairment are associated with increased plasma sildenafil levels, especially in men over 65 years, a starting dose of 25 mg should be considered.⁴

In men with diabetes, after a 10-mg dose of tadalafil, exposure (AUC) was reduced by 19% below that seen in healthy men. Maximum serum concentration was 5% lower. No change to dosing is needed for patients with diabetes who are prescribed tadalafil.⁵

Exposure to tadalafil (AUC) doubled in patients with mild-to-moderate renal insufficiency. A dose of 5 mg, no more than once a day, is recommended for men with severe renal insufficiency, and a starting dose of 5 mg increased to no more than 10 mg for men with moderate renal insufficiency. Exposure to tadalafil in patients with mild-to-

moderate hepatic impairment who took a 10-mg dose of tadalafil was similar to that in healthy patients. The maximum dose for men with mild-to-moderate hepatic impairment is 10 mg, and treatment is not currently recommended for those with severe hepatic impairment.⁵

Exposure to vardenafil is increased by 20–30% in those with moderate-to-severe renal impairment, and by 17% in those with mild hepatic impairment. With moderate hepatic impairment, exposure is increased by 160%, so a starting dose of 5 mg is recommended in patients with moderate hepatic impairment.⁷

Side-effects of PDE5 inhibitors

Treatment of ED with PDE5 inhibitors is generally well tolerated. Typical side-effects are headache, facial flushing, nasal congestion, and dyspepsia.⁵ Many of the common side-effects (headache, flushing, upset stomach, and nausea) are probably related to the vasodilator action of PDE5 inhibitors.^{4-7,10,17}

Key differences between the different members of the class are the visual disturbances, most common with sildenafil and least common with tadalafil. Because of these disturbances, patients with retinitis pigmentosa are excluded from treatment with sildenafil. The difference in effect may be because sildenafil has an effect on PDE6, which is involved in visual functioning, although evidence for this is sparse.⁴ Back pain/myalgia is more common with tadalafil, possibly due to effects on PDE11, found, among other places, in skeletal muscle tissue.⁵

Sildenafil. The most common side-effects are headache (16%), flushing (10%), dyspepsia (7%), nasal congestion (4%), urinary tract infection (3%), abnormal vision (3%), diarrhoea (3%), dizziness (2%), and rash (2%).⁴ In placebo-controlled trials, 2.5% of the patients taking sildenafil discontinued due to side-effects compared with 2.3% of those on placebo.

Tadalafil. The most common side-effects were headache (11–15% depending on dose), dyspepsia (4–10%), back pain (3–6%), myalgia (1–4%), nasal congestion (2–3%), flushing (2–3%), and limb pain (1–3%).⁵ In 8 placebo-controlled trials, 3.1% of the patients discontinued treatment because of side-effects compared with 1.4% of those on placebo.⁵ In a trial of 378 men, there were no visual-perceptual changes, cardiovascular events, or clinically significant findings with tadalafil on ECG findings, heart rate, or blood pressure.¹³

Vardenafil. The most common side-effects are headache (15%), flushing (11%), rhinitis (9%), dyspepsia (4%), sinusitis (3%), flu syndrome (3%), dizziness (2%), increased creatine kinase (2%), and nausea (2%).⁷ In controlled and uncontrolled trials, 3.4% of the patients discontinued vardenafil treatment because of side-effects compared with 1.1% of those on placebo.⁷

Drug interactions with PDE5 inhibitors

The PDE5 inhibitors are all metabolized largely by the CYP3A4 isoform of cytochrome P450, so dose adjustment may be needed for drugs that inhibit the enzyme. These drugs include erythromycin, ketoconazole, and itraconazole, and HIV protease inhibitors. Grapefruit juice also interacts with this pathway, and may also increase exposure to PDE5 inhibitors. These interactions may warrant dose adjustment and caution about dosing frequency. Cimetidine interacts with sildenafil, but there is no evidence of interaction of the other PDE5 inhibitors with cimetidine or other histamine H₂ antagonists.

Some drugs such as rifampin induce CYP3A4, but the effect is modest, and there is no need for dose adjustment. Erythromycin and the HIV protease inhibitor saquinavir increase exposure to sildenafil when co-administered. Stronger inhibitors of CYP3A4, which include ketoconazole and itraconazole, would be expected to have an even stronger interaction with sildenafil.⁴

The HIV protease inhibitor ritonavir increases exposure to sildenafil (AUC) fourfold. Other protease inhibitors probably have similar effects. It is likely that other protease inhibitors interact with sildenafil in a similar way. Cimetidine, a non-specific CYP inhibitor, also increases plasma concentrations of sildenafil. Erythromycin, ketoconazole, and the HIV protease inhibitors indinavir and ritonavir all increase the AUC and C_{max} of vardenafil when co-administered. Cimetidine and vardenafil do not appear to interact.⁶ Both ketoconazole and the HIV protease inhibitor ritonavir increase exposure to tadalafil. Other HIV protease inhibitors, erythromycin, itraconazole, and grapefruit juice are also likely to increase tadalafil exposure because of their inhibition of CYP3A4.⁵

Another key drug interaction of PDE5 inhibitors is with nitrates and NO donors. PDE5 inhibitors also interact with α -adrenoreceptor antagonists.

PDE5 inhibitors and sexually transmitted diseases (including HIV)

Older men who have suffered a period of ED who are then successfully treated with PDE5 inhibitors may return to sexual activity without factual knowledge of HIV transmission, and they may believe that they (and their potential new sexual partners) are not susceptible to the disease. Prescribers of PDE5 inhibitors may want to include such patients in appropriate HIV/AIDS prevention programmes.²⁸

One study has found that sildenafil use is an independent risk factor predictive of potentially transmitting sexual risk behaviour (PTSRB), and subsequent HIV infection in a group of 413 men.²⁹ The abuse of sildenafil (and other PDE5 inhibitors) taken recreationally to reverse the effects of illicit “club drugs” such as MDMA (“ecstasy”), and ketamine, which increase libido but reduce erectile function, may facilitate high-risk sexual practices and increase risk of HIV transmission. Several surveys have identified such abuse.³⁰ There are also risks of dangerous interactions between sildenafil and amyl and butyl nitrites (“poppers”), which were ingested by 15% of homosexual and bisexual men in 1 survey. Such co-ingestion may result in cardiac complications including life-threatening hypotension. In addition, there may be interactions between sildenafil, whether legally prescribed or not, and HIV protease drugs in sexually active HIV-positive gay men who may use sildenafil as a recreational drug. Combining PDE5 inhibitors and HIV protease drugs can increase adverse effects. In a small trial of 6 HIV-positive patients taking sildenafil and a protease inhibitor, there were reductions in blood pressure of up to 14/10 mmHg, which is far more than blood pressure reductions reported for the highest dose of sildenafil (100 mg). Physicians should discuss risk behaviour and HIV prevention before prescribing PDE5 inhibitors. In particular, they should discuss the risks of using them with “club drugs” containing nitrates and with antiviral drugs used in the treatment of HIV-positive patients.²⁹

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Dialogue Box

EDITORIAL BOARD

On the whole, PDE5 inhibitors seem to be a fairly safe group of drugs. Should they be made available as “over-the-counter” medications without the need for prescription?

RASHID

I would not support these drugs as “over-the-counter” medications. Sexual dysfunction is more complex to correct than simply taking a pill, and, in my view, a full medical assessment is necessary in all men with erectile dysfunction. Over-the-counter availability would inevitably lead some men to miss out the medical assessment.

EDITORIAL BOARD

If a patient taking nitrates and a PDE5 inhibitor develops chest pain during intercourse, what is the best course of action?

RASHID

Concurrent use of nitrates and a PDE5 inhibitor is contraindicated, so this situation should never arise. However, patients often need to discuss their individual situation with a specialist in ED.

EDITORIAL BOARD

Should GPs routinely perform an electrocardiogram (ECG) before and after prescribing a PDE5 inhibitor?

RASHID

There is no need for an ECG in most circumstances. For some patients with unstable cardiac disease, a comprehensive cardiac assessment is needed, but for most with no cardiac disease or with stable cardiac disease, a full cardiological assessment is not necessary.¹

EDITORIAL BOARD

I am encountering more women with sexual dysfunction requesting PDE5 inhibitors. Is there any evidence that they have any positive or negative actions in this group of patients?

RASHID

These drugs are not licensed for use in women. There is limited evidence that, in some women, there may be benefit, but trials in women have ceased.

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