Erectile dysfunction (ED) is a common complication of diabetes mellitus. In four independent, 12-week, randomised, placebo-controlled clinical trials that evaluated the pro-erectile properties of the selective phosphodiesterase type 5 (PDE-5) inhibitors, sildenafil (Viagra) (25–100 mg), tadalafil (10 and 20 mg) and vardenafil (10 and 20 mg) in men with ED secondary to diabetes mellitus, all the active drugs were significantly superior to placebo. In this difficult-to-treat population, the greatest difference from placebo for the overall responder rate of diabetic men reporting improved erections occurred with vardenafil 20 mg (72% vs. 13% for placebo).

All the PDE-5 inhibitors were generally well tolerated. There were fewer reports of visual disturbance with vardenafil or tadalafil than with sildenafil, which may be due to their greater selectivity for PDE-5 inhibition and less cross-reactivity with retinal PDE-6 inhibition.

The studies suggest there may be significant differences between the three drugs. However, only head-to-head studies will determine true differences in both efficacy and side effect profile.

Key words: diabetes, erectile dysfunction, PDE-5 inhibitors, sildenafil, tadalafil, vardenafil.

Introduction
The association between diabetes mellitus and erectile dysfunction (ED) is well established and diabetes mellitus has been shown to be an important risk factor for ED in several studies. ED can also be the first symptom of as yet undiagnosed diabetes. ED in men with diabetes can have profound additional effects on their quality of life (QoL) over and above those experienced by non-diabetic men with ED. This is possibly because normal sexual desire, thwarted by an inability to physically engage in sexual intercourse, can lead to increased levels of frustration and discouragement, a lower acceptance of diabetes and a higher risk of depressive illness. The link between ED and impaired QoL justifies treatment of ED in diabetic and non-diabetic men as an important public health issue.

This review will provide a brief overview of the pathophysiology of ED and its prevalence in diabetic patients and will summarise the current knowledge about the benefits of treatment with selective phosphodiesterase type 5 (PDE-5) inhibitors for patients suffering from diabetes-associated ED. In this context, the results of the placebo-controlled trials with sildenafil (Viagra), tadalafil and vardenafil in men with diabetes mellitus and co-morbid ED will be discussed and issues requiring further research will be defined.

The mechanisms behind erectile dysfunction
Erectile dysfunction is the inability to achieve and maintain a penile erection that is sufficiently rigid to enable penetration during sexual intercourse and occurs when a component of the normal penile erection mechanism becomes dysfunctional.

Penile erection occurs as a result of relaxation of smooth muscle in the corpora cavernosa. Within penile smooth muscle cells, relaxation is mediated via cyclic nucleotide second messengers such as cyclic guanosine monophosphate (cGMP) that operate in response to specific extracellular first messengers. Nitric oxide (NO) is the first messenger in the cGMP pathway and is probably the principal neurotransmitter mediating tumescence. It is released by non-adrenergic, non-cholinergic nerves in response
to sexual stimulation and by the endothelium of the corpus cavernosum in response to the sheer stress of blood flow in the presence of acetyl choline. When cGMP causes relaxation of cavernosal smooth muscle, the inflow of blood into the penis is faster than its venous outflow and the result is penile rigidity. The metabolic breakdown of pro-erectile cGMP by phosphodiesterase enzymes eventually leads to detumescence.

The aetiology of ED can be neurogenic or vascular (see Eardley pp 272–6). Any disruption of the primary haemodynamic events mediated through the central or peripheral neural networks that promote an erectile response will impair erectile function. Diabetic men with ED show impairment in both the endothelium-dependent and neural mechanisms that mediate relaxation of the smooth muscle of the corpus cavernosa. ED in diabetic patients is, therefore, mainly related to organic causes, involving possible microvascular, neurological and endocrinological components.

The prevalence of erectile dysfunction in diabetes mellitus

Estimates of the prevalence of ED in the general adult male population are influenced by a number of variables that include age, severity, illness-related factors and, importantly, the historical social and cultural reluctance of patients and physicians to discuss sexual problems. The possibility that formal measurements of the prevalence of ED in the general population are probably underestimated is illustrated by the number of people seeking treatment following extensive media coverage of the availability of the first effective oral PDE-5 inhibitor, sildenafil. Overall, ED affects about three to four times more diabetic than non-diabetic men and between one third and three quarters of men with diagnosed diabetes suffer from ED. The onset of ED usually occurred within the first 10 years of diagnosis of type 1 and type 2 diabetes in > 50% of men affected by ED. ED is often related to the duration and severity of diabetes and correlates with glycaemic control.

Measurement of erectile dysfunction

The intensely personal nature of ED and its treatment raises some unique factors about techniques for its measurement. Objective measurement of penile rigidity in experimental situations (e.g. using an ambulatory RigiScan device that monitors tumescence in response to visual sexual stimulation) has been used to evaluate the effect of pharmacological interventions in patients with ED. The limitations of such methods have given rise to the use of self-administered questionnaires for the assessment of erectile function in a more natural home setting. Some questionnaires also enable involvement of a sexual partner in the evaluation of intervention efficacy. While some questionnaires may be limited by scope and bias in reporting, the International Index of Erectile Function (IIEF) designed and developed for assessment of sexual function in clinical trials, has been extensively validated and is widely accepted. Other commonly used questions in clinical trials in ED are elements of the Sexual Encounter Profile (SEP) and global ratings of clinical improvement, such as Global Assessment Questions (GAQ) (table 1). It is these questionnaires that have formed the basis of the evaluation of the effect of PDE-5 inhibitors in patients with ED.

PDE-5 inhibitors in diabetic patients with erectile dysfunction

Most men with ED can benefit from treatment. Treatment options include psychosexual counselling, pharmacological treatment and mechanical or surgical intervention (see Ali et al. pp 255–61). Among the pharmacological options, oral treatment with on-demand PDE-5-inhibitors is now considered first-line therapy because they are convenient, effective and generally well tolerated. PDE-5 inhibitors block the action of PDE-5 causing cGMP to accumulate. This amplifies the neural NO/cGMP pathway that is essential for the relaxation of smooth muscle and subsequent penile tumescence. As such, these drugs restore a satisfactory erectile response to sexual stimulation.

Trials with PDE-5 inhibitors

This review of clinical trial data from four 12-week, randomised, placebo-controlled trials in diabetic patients with ED will focus on

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**Table 1. Erectile function assessment instruments**

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Score range*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a) IIEF erectile function domain score</strong></td>
<td>Score range*</td>
</tr>
<tr>
<td>1. Over the past four weeks, how often were you able to get an erection during sexual activity?</td>
<td>0–5</td>
</tr>
<tr>
<td>2. Over the past four weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?</td>
<td>0–5</td>
</tr>
<tr>
<td>3. Over the past four weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?</td>
<td>0–5</td>
</tr>
<tr>
<td>4. Over the past four weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?</td>
<td>0–5</td>
</tr>
<tr>
<td>5. Over the past four weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?</td>
<td>0–5</td>
</tr>
<tr>
<td>15. Over the past four weeks, how do you rate your confidence that you can keep your erection?</td>
<td>1–5</td>
</tr>
<tr>
<td><strong>Total range</strong></td>
<td>1–30*</td>
</tr>
<tr>
<td><strong>b) Sexual Encounter Profile (SEP)</strong></td>
<td>Yes/No</td>
</tr>
<tr>
<td>2. Were you able to insert your penis into your partner's vagina?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>3. Did your erection last long enough to have successful intercourse?</td>
<td>Yes/No</td>
</tr>
<tr>
<td><strong>c) Global Assessment Questionnaire (GAQ)</strong></td>
<td>Yes/No</td>
</tr>
<tr>
<td>1. Has the treatment you have been taking improved your erections?</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

*The higher the score, the better is the erectile function
three PDE-5 inhibitors. Sildenafil is the first PDE-5 inhibitor to be introduced into clinical practice. Two further PDE-5 inhibitors, tadalafil and vardenafil, that have shown improved potency and selectivity for PDE-5 inhibition in experimental studies are currently in late-stage clinical development. The largest trial in diabetic patients involved vardenafil (n=439 patients). Three smaller trials have been reported in diabetic populations with ED, two with sildenafil (n=268 and n=219) and one with tadalafil (n=216).

Demographic and patient characteristics in the trials
The four trials included men, with a mean age between 55 and 59 years, who were in a stable heterosexual relationship and had been diagnosed with ED in conjunction with diabetes with a baseline HbA1C < 11% (sildenafil), < 12% (sildenafil and vardenafil) or < 13% (tadalafil). The duration of diabetes was long-standing across the trials, with the mean duration of diabetes ranging between 9.7 and 12.1 years. The majority of patients in each trial had type 2 diabetes (range 84–100% patients) (table 2).

The duration of ED was, however, slightly different in the trials. The mean duration of ED in the sildenafil trials ranged between 3.7 and 5.8 years and in the vardenafil trial, 3.3 to 3.7 years. For tadalafil, 93% of patients had a diagnosis of ED for more than one year at entry, although data on the mean duration of ED are not available. The longer overall duration of ED in the earlier sildenafil trial is probably a reflection of the fact that sildenafil was the first PDE-5 inhibitor to be investigated in this population and, at the time of this study, there was a lack of other attractive therapeutic options.

The majority of patients (range 64–96%) in all the trials had an organic aetiology of ED. Most of the remaining patients had ED of mixed organic and psychogenic aetiology and only a small proportion of patients (≤ 8%) were considered to have an exclusively psychogenic aetiology. The mean baseline severity of ED, measured by the IIEF erectile function (EF) domain score, ranged between 9.4 and 12.9 across the trials and this is suggestive of slight differences in the severity of ED in the different trial populations. The baseline mean EF domain score was lowest in the sildenafil trials and highest in the tadalafil trial (table 2) indicating that patients who were treated with tadalafil included a less severe group of ED patients.

Patients were excluded from the trials if they had a history of radical prostatectomy or spinal cord injury, or if they had a penile anatomical deformity. Other standard exclusion criteria common to trials of a regulatory nature were observed, notably significant recent haematological, hepatic, renal and cardiovascular conditions or major psychiatric illness. The concomitant use of nitrates was an absolute exclusion criterion in all the studies because of the interaction that has been observed with sildenafil.

Trial procedures
After a four-week run-in period, patients were permitted to take their PDE-5 inhibitor (or placebo) in their home environment, as needed, but no more frequently than once-daily for up to 12 weeks. In the sildenafil and vardenafil trials, patients were advised to take their drug about an hour prior to sexual activity. Patients in the tadalafil and vardenafil trials were randomised to receive a fixed dose (placebo or either 10 mg or 20 mg of active drug) throughout the trial. Flexible dosing was allowed in both of the sildenafil trials within the dose range 25 mg to 100 mg. By the end of the trial period, however, the vast majority of patients in these trials (77% and 93%) had increased their dose from the starting level of 50 mg to the higher dose (100 mg) of sildenafil.

Efficacy outcomes in diabetic patients
All three PDE-5 inhibitors were significantly superior to placebo in improving erectile response to sexual stimulation in diabetic patients. Measurements of effect on the IIEF EF domain score demonstrate this.

In the vardenafil trial, baseline EF domain scores for patients subsequently receiving placebo, 10 mg and 20 mg of vardenafil were 11.2, 11.0 and 12.4, respectively (table 2). After
12 weeks of treatment, the EF domain score in placebo-treated patients had increased minimally to 12.6 but the final scores for 10 mg vardenafil were significantly higher at 17.1 (p<0.0001 versus placebo) and 19.0 for 20 mg vardenafil (p<0.0001 versus placebo).

For sildenafil, both trials showed a significant improvement in erectile function compared with placebo. At endpoint, the EF domain score with placebo treatment was 10.424* and 11.5, while for sildenafil-treated patients, the majority of whom were taking 100 mg, the scores rose to 17.5* (p<0.001 versus placebo) and 20.4 (p<0.0001 versus placebo) in each trial, respectively. Similarly, EF domain scores in the tadalafil trial showed changes from baseline of 0.1 with placebo, but 6.4 with 10 mg tadalafil (p<0.001 versus placebo) and 7.3 for 20 mg tadalafil (p<0.001 versus placebo).

Significant improvements were reported with all the active drugs in the specific questions relating to the success rates for vaginal penetration (EF domain Question 3 / SEP Question 2) and for the maintenance of erection to completion of intercourse (EF domain Question 4 / SEP Question 3). All three medications were superior to placebo at endpoint for these specific parameters (p<0.0001 for sildenafil and vardenafil, p<0.001 for sildenafil and tadalafil).

Quality of life data were reported for only two of the trials, with all the active drugs in the specific questions relating to the success rates for vaginal penetration (EF domain Question 3 / SEP Question 2) and for the maintenance of erection to completion of intercourse (EF domain Question 4 / SEP Question 3). All three medications were superior to placebo at endpoint for these specific parameters (p<0.0001 for sildenafil and vardenafil, p<0.001 for sildenafil and tadalafil).

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Figure 1. Affirmative responses to a global assessment question on improved erections in four placebo-controlled, 12-week trials of vardenafil, sildenafil and tadalafil in diabetic patients with ED

12 weeks of treatment, the EF domain score in placebo-treated patients had increased minimally to 12.6 but the final scores for 10 mg vardenafil were significantly higher at 17.1 (p<0.0001 versus placebo) and 19.0 for 20 mg vardenafil (p<0.0001 versus placebo).

At the end of the trials, the proportion of patients who gave an affirmative response to a global rating of improvement (“Has the treatment you have been taking improved your erections?”) was always statistically superior with the active drugs compared with placebo (p<0.001–p<0.0001). Responder rates ranged from 56% (tadalafil 10 mg and sildenafil variable dose; p<0.001 vs. placebo for both studies) to 72% (vardenafil 20 mg; p<0.0001 vs. placebo) reporting improved erections (figure 1).

Comparison of response in diabetic and non-diabetic patients

While sub-group analyses in each study indicated that specified trial parameters were improved by the PDE-5-inhibitors, irrespective of the level of glycaemic control, there is some emerging evidence that vardenafil, but not sildenafil nor tadalafil, is equally effective in treating ED in diabetic and non-diabetic patients.

For non-diabetic patients treated with vardenafil, the proportion who responded ‘Yes’ to GAQ1 at endpoint (“Has the treatment you have been taking improved your erections?”) was 30% for placebo and 76% and 80% for vardenafil 10 mg and 20 mg respectively in a Phase IIb at-home trial. The difference in response between placebo and vardenafil was, therefore, 46% and 50% for each dose, respectively. In diabetic patients, the corresponding difference between placebo and vardenafil was 44% for 10 mg and 59% for 20 mg. Thus, in these two groups of patients, the pro-erectile properties of vardenafil appear to be equivalent, indicating no loss of efficacy in diabetic patients compared with non-diabetic men treated with vardenafil.
By contrast, an analysis of combined data from 11 double-blind, placebo-controlled trials has shown that the response to sildenafil in diabetic patients with ED was lower than that in patients without diabetes. Similarly, the difference between placebo and tadalafil in the GAQ1 ‘Yes’ response was almost 25% lower in diabetic patients treated with 20 mg tadalafil than non-diabetic patients treated with 25 mg tadalafil.

While this may suggest that vardenafil has a broader spectrum of activity across all patient types with ED, dedicated comparative trials will be required to confirm these observations.

Safety and tolerability of PDE-5 inhibitors in diabetic patients

In each of the trials of the PDE-5 inhibitors in diabetic patients with ED, the drugs were generally well tolerated. Treatment-related side effects were mostly headache, flushing, dyspepsia and rhinitis/nasal congestion – effects that might be expected from this pharmacological class of drug. However, there may be some discreet differences in the incidence of these side effects with each drug. Headache and flushing were most commonly reported for sildenafil in 18.2% and 14.5% of patients for each effect, respectively, when controlled for placebo effects. Dyspepsia was more common with tadalafil (11.0%) than with other PDE-5-inhibitors. Rhinitis was more common with vardenafil (6.0%).

Of particular note is the more frequent occurrence of visual disturbances with sildenafil which occurred in 4.5% of patients. This higher incidence of blue colour vision, related to the inhibition of retinal PDE-6, is to be expected for sildenafil because of its lower selectivity for PDE-5 in comparison with vardenafil and tadalafil.

Discussion

There is no doubt that ED is a frequent complication of diabetes that, if untreated, has a negative impact on patients. While recent advances in treatment for patients with ED in general, and diabetes in particular, have helped to improve erectile function in these patients, it was the introduction of the first oral, on-demand PDE-5 inhibitor, sildenafil, that offered an attractive new option for ED patients. Sildenafil has been shown to be effective but remains associated with some limitations that newer PDE-5 inhibitors, vardenafil and tadalafil, show promise in overcoming.

Comparisons between independent studies in a review of this nature are, of course, fraught with limitations, including not only those arising from selected diabetic patient populations that may have some important baseline differences but also because they use different dosage regimens (fixed versus flexible doses). Nevertheless, in the absence of direct head-to-head comparisons, this review draws on available data to make a preliminary comparative appraisal of potential differences and similarities between these three PDE-5 inhibitors in a difficult-to-treat population.

In the studies reviewed here, all three PDE-5-inhibitors significantly improve erectile function in diabetic men as measured by validated assessment questionnaires. This improvement appears to occur in diabetic patients irrespective of potential confounding variables such as age, glycaemic control (within the confines of the inclusion criteria of these trials) and duration of diabetes. Adverse events in the selected trial populations evaluated in these studies were generally rare, mild to moderate in severity, transient in nature and typical of this class of drug.

Although there are broad similarities in clinical efficacy between sildenafil and the new PDE-5-inhibitors, vardenafil and tadalafil, a number of pharmacodynamic and pharmacokinetic properties differentiate between them. The time to onset of effect is a feature that has an influence on how much forward planning is necessary to enable the couple to engage in successful sexual intercourse. Pharmacokinetic data suggest an advantage for vardenafil in this respect. Vardenafil has a shorter mean time to maximum plasma concentration (t\text{max}) (0.66 hours) than both sildenafil (1.16 hours) and tadalafil (2.0 hours) and the variability seems to be less, with a range of 0.25–3.0 hours for vardenafil compared to 0.5–12.0 hours for tadalafil (table 3). Whether this translates into a real advantage remains to be established through dedicated onset-of-effect studies for all substances.

Further, compared with vardenafil and sildenafil, tadalafil exhibits a considerably longer plasma clearance half-life (t\text{1/2}) after oral dosing (table 3). Although the half-life required for an optimal ‘window of opportunity’ remains a matter of discussion, a very long half-life may offer both advantages and disadvantages. While a longer duration of action, mediated through a longer half-life, may translate into enhanced spontaneity of sexual activity by virtue of extending the window of effectiveness for over one day, the slower clearance may have safety implications. The longer half-life of tadalafil of 17.5 hours, compared with around four hours for sildenafil and vardenafil, has raised some concerns about possible consequences and the impact of these pharmacokinetic properties of tadalafil requires further investigation.

From a pharmacodynamic viewpoint, tadalafil and vardenafil exhibit a higher PDE-5:PDE-6 selectivity ratio than that of sildenafil. This greater selectivity manifests as an absence of colour vision changes. Sildenafil, on the other hand, exhibits potential cross-reactivity with PGE-6 in the retina, the consequences of which have still to be elucidated in men with diabetic retinopathy.

### Table 3. Pharmacokinetics of vardenafil, sildenafil and tadalafil (given for the maximum doses that were used in the trials)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sildenafil (100 mg)</th>
<th>Tadalafil (20 mg)</th>
<th>Vardenafil (20 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t\text{max} (median) (h)</td>
<td>1.16 ± 0.99*</td>
<td>2.0 (0.5-12.0)</td>
<td>0.66 (0.25-3.00)</td>
</tr>
<tr>
<td>(range)</td>
<td>(range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t\text{1/2} (geometric mean) (h)</td>
<td>3.82 ± 0.84*</td>
<td>17.5 (11.5-29.6)*</td>
<td>3.94 (2.57-6.23)</td>
</tr>
<tr>
<td>(range)</td>
<td>(range)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± s.d.; 5th and 95th percentile
ED is a frequent complication of diabetes that impairs a patient’s quality of life, self-esteem and relationship with his partner.

Treatment options for men with ED have advanced considerably over the past decade and the oral cGMP-specific PDE-5 inhibitors represent the closest achievement so far to optimal first-line therapy in the majority of ED patients.

There may be important differences between the three drugs discussed. These will need to be resolved by head-to-head studies.

All three drugs are very effective in the diabetic population – direct comparisons with head-to-head studies will determine whether or not there are true differences in efficacy and side effect profile.

References