

Sexual dysfunction

Is there a role for continuous dosing of PDE5 inhibitors for erectile dysfunction in men with diabetes?



Mike Cummings, Consultant Physician and Honorary Reader, Queen Alexandra Hospital, Portsmouth

Although originally investigated as a treatment for angina, oral phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil and vardenafil) were first granted a license for 'as-required' dosing to treat erectile dysfunction (ED).

Moreover, this class of drugs has continued to be used on an as-required basis, with little attention given to the potential benefits of continuous dosing upon erectile performance and factors outside of the corpus cavernosum.

Hatzichristou and colleagues (summarised alongside) have examined the effects of daily, continuous dosing with tadalafil in men with diabetes and ED. They conclude that the use of a lower daily dose of tadalafil (2.5 or 5 mg) than is traditionally used on an as-required basis (10–20 mg) is efficacious and well tolerated compared with placebo. This eliminates the need to forward-plan sexual activity within a limited time frame, which is often a source of additional anxiety for men with ED.

Apart from the convenience and psychological advantages for the management of ED, are there any other proven benefits of continuous treatment with PDE5 inhibitors for men with diabetes? In the last issue of *Diabetes Digest*, I commented upon the regression of microalbuminuria with the use of PDE5 inhibitors. In addition, Aversa et al (summarised below) have examined the effect of 7 days' treatment with oral sildenafil upon endothelial function (a predictor of vascular disease) in men with type 2 diabetes; endothelial function significantly improved, and so did circulating markers of vascular inflammation and endothelial function. Moreover, these findings are consistent with another recent study of men with type 2 diabetes treated with sildenafil (Morano et al; summarised on page 104), in which these improvements in endothelial function were enhanced further by the addition of an anti-oxidant, propionyl L-carnitine. Collectively, these data challenge the concept that PDE5 inhibitors should be prescribed on an as-required basis.

DIABETIC MEDICINE

Tadalafil once-daily is effective for ED

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 Although men with diabetes have a higher risk for erectile dysfunction (ED), phosphodiesterase 5 (PDE5) inhibitors, such as tadalafil 10 or 20 mg, taken before sexual activity are effective and well tolerated.

2 Furthermore, as tadalafil has a mean elimination half-life of 17.5 hours, once-daily administration of tadalafil 2.5 or 5 mg has been shown to be efficacious for ED in the general population.

3 This randomised, double-blind, placebo-controlled study examined whether once-daily treatment with tadalafil 2.5 or 5 mg is safe and effective for ED in men with diabetes.

4 In total, 298 men with diabetes and ED were randomised to once-daily treatment with placebo, tadalafil 2.5 mg or tadalafil 5 mg, and were assessed in terms of International Index of Erectile Function—Erectile Function Domain (IIEF—EF) score, safety and overall treatment satisfaction over 12 weeks.

5 Both doses of once-daily tadalafil significantly improved ED, as measured by changes in IIEF—EF score, and significantly improved achievement of sexual activity and overall satisfaction with the treatment.

6 Patients were concordant with the daily administration of tadalafil, and treatment was well tolerated with few side effects; headache, back pain and dyspepsia were adverse events that occurred in the treatment groups.

7 Results showed that tadalafil taken once a day, instead of on demand, significantly improved erectile function and was well tolerated in men with ED and diabetes.

DIABETIC MEDICINE

Sildenafil improves endothelial function

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 As treatments known to improve endothelial function are less effective in people with diabetes, the study determined the effects of chronic therapy with sildenafil (a phosphodiesterase 5 inhibitor) on vascular reactivity and endothelial function in 20 men with type 2 diabetes but without erectile dysfunction.

2 Participants were given a loading dose of sildenafil 100 mg for three days, then were randomised to receive

either sildenafil 25 mg three times a day for 4 weeks or sildenafil 25 mg three times a day for 4 days followed by placebo three times a day for 3 weeks.

3 After 1 week, a significant increase (>50%) in flow-mediated dilatation was seen in both groups (62% and 64%).

4 This increase continued in people receiving chronic sildenafil therapy (78%, 86% and 94% at 2, 3 and 4 weeks), whereas a decrease was seen in the placebo group (45%, 18% and 6% at 2, 3 and 4 weeks).

5 Prolonged, daily sildenafil therapy improved endothelial function in men with type 2 diabetes.

Aversa A, Vitale C, Volterrani M et al (2008) Chronic administration of sildenafil improves markers of endothelial function in men with type 2 diabetes. *Diabetic Medicine* 25: 37–44

Hatzichristou D, Gambla M, Rubio-Aurioles E et al (2008) Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. *Diabetic Medicine* 25: 138–46

‘Results showed a clear link between ED and ACE genotype, and support the finding that the D allele is a risk factor for the micro- and macrovascular diseases in the metabolic syndrome.’

INTERNATIONAL JOURNAL OF ANDROLOGY

ED linked with lower androgen levels

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 This study looked at the relationship between erectile dysfunction (ED) and total, bioavailable and free testosterone levels as well as cardiovascular risk factors in 198 men

with type 2 diabetes.

2 In all, 129 men had ED; these men had significantly lower bioavailable and free testosterone levels than men without ED, with no significant difference in total testosterone levels between groups.

3 ED was also found to have an association with current smoking, age, a higher waist circumference and hypertension in men with type 2 diabetes.

Kapoor D, Clarke S, Channer KS, Jones TH (2007) Erectile dysfunction is associated with low bioactive testosterone levels and visceral adiposity in men with type 2 diabetes. *International Journal of Andrology* **30**: 500–7

INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH

Link between ACE DD genotype and ED

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 This study determined whether angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism is associated with erectile dysfunction (ED) in 331 men with the metabolic syndrome.

2 All men underwent complex evaluation including erectile function score. ACE I/D polymorphism was determined by polymerase chain reaction.

3 The prevalence of ED was 55% (182 men); in these men the prevalence of the DD genotype was significantly higher than in men without ED ($P<0.001$).

4 In men with ED, the DD genotype was associated with disease onset at a younger age ($P<0.001$), and the higher the prevalence of the DD genotype, the more severe the disease.

5 Results showed a clear link between ED and ACE genotype, and support the finding that the D allele is a risk factor for the micro- and macrovascular diseases in the metabolic syndrome.

Mazo EB, Gamidov SI, Mamedov MN, Iremashvili VV (2008) Association between the insertion/deletion polymorphism of the angiotensin-converting enzyme gene and erectile dysfunction in patients with metabolic syndrome. *International Journal of Impotence Research* **20**: 68–72

ANDROLOGIA

ED link with CAN increases with age

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The study looked at any association between erectile dysfunction (ED) and cardiovascular autonomic neuropathy (CAN) in 22 men with type 2 diabetes.

2 No participants had evidence of cardiovascular disease, hypertension, or neurological, renal or thyroid disease, and were assessed for ED and CAN.

3 Ten men had ED and six men had CAN, three had both.

4 There was no significant relationship between ED and CAN ($P=1.00$); however, the association between CAN and ED significantly increased with age ($P=0.036$).

5 Thus the presence of ED may be an indication of future CAN. Debono M, Cachia E, Cassar A et al (2008) Is erectile dysfunction a sentinel symptom for cardiovascular autonomic neuropathy in patients with type 2 diabetes? *Andrologia* **40**: 1–6

EUROPEAN UROLOGY

Sildenafil plus antioxidant therapy improves erectile function

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 This study determined whether antioxidant treatment with propionyl L-carnitine and sildenafil would reduce reactive oxygen species production by circulating monocytes and endothelial dysfunction markers in 32 men with type 2 diabetes and erectile dysfunction.

2 In a double-blind, placebo-controlled study, eight men received propionyl L-carnitine alone (2g/day), eight men received propionyl L-carnitine (2g/day) plus sildenafil (50mg/day twice-weekly), eight men received sildenafil alone (50mg/day twice-weekly) and eight men received placebo.

3 Measures of monocyte oxidative activity (stimulation index and intercellular adhesion molecule-1 [ICAM-1]), P-selectin, Doppler sonography and International Index of Erectile Function-5 (IIEF-5) score were taken at baseline and after 12 weeks' treatment; IIEF-5 was also measured 4 weeks after treatment.

4 IIEF-5 score significantly improved in all men treated with propionyl L-carnitine and sildenafil ($P<0.03$) or with sildenafil alone ($P<0.05$); IIEF-5 score 4 weeks post-treatment was higher in men treated with PLC plus sildenafil ($P=0.05$).

5 Stimulation index was significantly reduced in the propionyl L-carnitine plus sildenafil group ($P<0.05$); ICAM-1, P-selectin and end diastolic velocity values were also reduced.

6 Propionyl L-carnitine in combination with sildenafil was efficacious in reducing circulating monocyte oxidative activity and markers of endothelial dysfunction in men with type 2 diabetes and ED.

Morano S, Mandosi E, Fallarino M et al (2007) Antioxidant treatment associated with sildenafil reduces monocyte activation and markers of endothelial damage in patients with diabetic erectile dysfunction. *European Urology* **52**: 1768–76