# New treatments for erectile dysfunction

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## Abstract

**Erectile dysfunction (ED) is common in men with diabetes and is associated with microvascular disease, maladaptation to chronic illness, poor quality of life, and increased levels of diabetes-specific health distress. Traditionally, most diabetologists were poor at asking about ED and patients themselves are not always forthcoming with information, given the embarrassing nature of the disease. However, times are changing and the inclusion of screening for ED in Quality and Outcomes Framework and current general practice templates emphasises its current importance. Licensed treatments have been limited in their application towards the provision of symptomatic relief and are offset by adverse effects, intolerance, limited effectiveness and contraindications in the presence of co-existent cardiovascular disease. This review critically considers the utility of novel treatments for ED in diabetes that have been developed to overcome these barriers.**


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**Key words:** erectile dysfunction, diabetes, autonomic neuropathy, vascular insufficiency, alprostadil

**Abbreviations and acronyms**

| | |
|---|---|
| AKT | protein kinase B |
| AT1 | angiotensin 1 |
| cGMP | cyclic guanosine monophosphate |
| COX-2 | cyclo-oxygenase-2 |
| ED | erectile dysfunction |
| ERK | extracellular signal-regulated kinase |
| FOXO1 | Forkhead box O1 |
| GAQ | Global Assessment Questionnaire |
| IIEF | International Index of Erectile Function |
| NO | nitric oxide |
| PSAE | Patient Self-Assessment of Erection |
| PDE-5 | phosphodiesterase-5 |
| PGE-0 | prostaglandin $E_0$ |
| PGE-1 | prostaglandin $E_1$ |
| PI3K | phosphoinositide 3-kinase |
| QOF | Quality and Outcomes Framework |
| SEP | Sexual Encounter Profile |
| SHIM | Sexual Health Inventory for Men |

## Introduction

ED is defined as an inability to generate and sustain a penile erection sufficient to achieve a satisfactory sexual performance. Evidence from the 1980s suggests that ED affected about 30–35% of men with diabetes, with up to 50% developing ED after 10 years of diabetes. A survey of 541 diabetic male patients (60% with type 1 diabetes and 40% with type 2 diabetes) revealed the presence of ED in 35% of men aged 20–59 years, and in 25% of men aged <50 years.[1] More recent evidence suggests that ED remains a significant problem in diabetes, despite improvements in antidiabetic therapy in the last three decades, as ED has been found to affect 54% of patients with type 1 diabetes[2] and 34% of patients with type 2 diabetes.[3] An increased risk of developing ED is associated with age, duration of diabetes, suboptimal glycaemic control, obesity, hypertension, microalbuminuria, retinopathy and a higher cardiovascular risk score.

Further evidence suggests that ED is associated with an inferior psychological adaptation to chronic disease, a poor quality of life, and increased levels of diabetes-specific health distress. Erectile problems are associated with an increased prevalence of severe depressive symptoms, lower scores in the mental components of the Short Form-36 Health Survey Scoring Demonstration, and an unsatisfactory sexual life. Diabetologists are traditionally poor at asking about ED and patients themselves are not always forthcoming with information, due to embarrassment about the condition. A study from Italy in 2002 found that 63% of patients reported that their physicians had never investigated their sexual problems.[3] However, times are changing and the importance of screening for ED is highlighted by its previous inclusion in QOF and current general practice templates.[4]

Current therapies for ED are effective, but subject to some limitations against the background of an increasing prevalence of diabetes and its associated burden of microvascular disease. Novel therapies aim to surmount these barriers. This review will critically consider the limitations of current therapy and the potential role of new treatments for ED in people with diabetes (Table 1 provides an overview of current and potential future therapeutic opportunities in this area).

## Erectile physiology

### Physiological mechanisms

Penile erection is a complex psycho-neurovascular phenomenon,

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**Table 1** Overview of current and future pharmacologic therapies for the management of erectile dysfunction in people with diabetes

| Drug class | Drugs available for prescription[a] | Comments |
|---|---|---|
| **PDE-5 inhibitors** | | |
| First-generation | Sildenafil (Viagra®, Pfizer; Nipatra®, AMCo) | |
| | Tadalafil (Cialis®, Lilly) | |
| | Vardenafil (Levitra®, Bayer) | |
| Highly selective | Avanafil (Spedra®, Menarini) | |
| | Lodenafil | Not yet approved (UK)[a] |
| | Mirodenafil | Not yet approved (UK)[a] |
| | Udenafil | Not yet approved (UK)[a] |
| **Alprostadil** | Caverject® (Pharmacia) | For intracavernosal injection |
| | Viridal® Duo (UCB Pharma) | For intracavernosal injection |
| | Muse® (Meda) | Intra-urethral suppository |
| | Vitaros® (Takeda) | Topical cream applied to the tip of the glans penis |
| **Papaverine** | Papverine | Unlicensed, but sometimes used for this purpose |
| **Testosterone replacement** | Various oral, buccal, transdermal, injectable formulations | For ED secondary to hypogonadism/testosterone deficiency |
| **Mas receptor antagonists** | Angiotensin(1–7)[b] | Investigational |
| **Regenerative therapies** | New treatment approaches based on restoring and repairing damaged tissue, e.g. through use of stem cells. | Investigational |

Compiled from information in Prescribing Information for individual agents (see www.medicines.co.uk/emc) and the British National Formulary (BNF, January 2015).

[a] All agents are approved for prescription for use in erectile dysfunction (ED) in people with diabetes in the UK, unless stated otherwise – drugs for the management of ED are prescribed according to limitations in Drug Tarriffs for England and Wales, Northern Ireland or Scotland; see BNF for further details.

[b] Endogenous peptide being studied as a template for future drug discovery.

resulting from interplay between autonomic innervation, hormonal signalling and psychogenic arousal. Initially, parasympathetic fibres from the sacral plexus release acetylcholine, which triggers the release of NO from endothelial cells in the trabecular arteries. NO diffuses to the smooth muscle of the arterial wall: there, activation of guanyl cyclase increases the concentration of cGMP, which causes vasodilatation. Indeed, the mechanisms of action of pharmacologic treatments for ED involve induction of vasodilatation within the corpora cavernosa, as described below. As the arteries dilate, the corpora cavernosa and corpora spongiosum fill with blood; simultaneous compression of the subtunical venules and contraction of the bulbospongiosus and ischiocavernosus muscles compress the veins of the corpora cavernosa against the tunica albuginea, reducing the rate of venous egress of blood and thus maintaining the erection. Detumescence occurs following hydrolysis of cGMP by the enzyme PDE-5, resulting in smooth muscle contraction and vasoconstriction.[5]

### Clinical measures of erectile function

Clinical measures of erectile function are based on self-report questionnaires. The IIEF is a multi-dimensional survey used for the assessment of erectile function that has been recommended as a primary endpoint for clinical trials of ED and for diagnostic evaluation of ED severity. It has since been adopted as the 'gold standard' measure for assessing the efficacy of treatments in clinical trials.[6]

Another clinical tool used for assessing erectile function is the SEP questions 2 and 3, which asks the following questions: "*Were you able to insert your penis into your partner's vagina*" and "*Did your erection last long enough for you to have successful intercourse?*". The GAQ has also been used in clinical trials to assess male sexual function. It asks the following two questions respectively: "*Has the treatment you have been taking improved your erectile function and if yes, has the treatment improved your ability to engage in sexual activity?*"

Finally the SHIM questionnaire has been widely used for screening and diagnosing ED and the severity of ED in clinical practice and research. A 5-year review of research and clinical experience found that the SHIM was employed as a primary measure in 23 studies on the efficacy of ED interventions, 21 studies on the prevalence of ED, and eight observational studies.[7] Limitations of the IIEF, SEP, GAQ and SHIM include: a lack of validity, subjective and retrospective recall bias with the possibility to over-report success rates, and research imposition.

## Limitations of current treatments for erectile dysfunction

Current licensed treatments have revolutionised the management of ED in diabetes, but they are not universally accepted and may produce side-effects. For example, PDE-5 inhibitors such as sildenafil, tadalafil and vardenafil are administered orally, with success rates of about 50–80%, but are hindered by side-effects that include: headache (7–30%), facial flushing (up to 25%), dyspepsia (up to 15%), nasal congestion (up to 10%) and visual disturbance (up to 10%).[8] In addition, most men with diabetes who have ED also have underlying cardiovascular disease, and recent myocardial

infarction or stroke, unstable angina, hypotension, co-prescription of nitrates, or severe heart failure are contraindications for the use of PDE-5 inhibitors. These drugs are also contraindicated in patients with severe hepatic impairment or retinitis pigmentosa, and in those receiving treatment with ketoconazole or protease inhibitors. The utility of PDE-5 inhibitors is limited further by the need to use them with caution or at a reduced dose for elderly patients, or those with hypertension, heart disease, Peyronie's disease, renal or hepatic impairment, active peptic ulcer disease, and haematological conditions associated with priapism such as leukaemia, multiple myeloma, and sickle cell disease. Finally, PDE-5 inhibitors are not as effective in patients who have severe vascular disease or who have undergone radical prostatectomy.

A substantial unmet medical need exists among patients who have ED as a result of these conditions. Furthermore, most clinical experience has been reported with on-demand usage of PDE-5 inhibitors that have short half-lives. More recently, the role of chronic PDE-5 inhibition has been studied using tadalafil, a PDE-5 inhibitor with a half-life of 17.5 hours that results in erectile responsiveness for up to 36 hours after a single dose. Several studies demonstrated that tadalafil, given once-daily in low-doses, was highly effective and well tolerated and allowed patients and their partners to disconnect the administration of medication from sexual activity with an improvement in preference factors such as spontaneity and 'naturalness'.[9]

Other licensed treatments for ED in diabetes are not without problems. For example, intracavernosal injection of vasodilator drugs (alprostadil, a prostaglandin analogue, or papaverine, an endothelium-independent vasodilator sometimes used off-label for managing ED) is associated with success rates of about 60%, but is limited by an undesirable invasive method of administration that may exacerbate the psychogenic component of ED, local pain, priapism, and fibrosis at the injection site in about 5% of patients. A formulation of alprostadil designed for intraurethral application (Muse®, Meda Pharmaceuticals) may be more straightforward to administer, but was associated with penile pain in about one in three patients, urethral burning in about one in eight and minor urethral bleeding in about one in 20, according to the US Prescribing Information for this product.[10] These treatments are also contraindicated in haematological conditions associated with priapism.

The value of vacuum devices is limited by pain, haematoma formation and an unaesthetic method of administration. Similarly, penile prostheses concur risks of infection and mechanical failure.

Consequently, regimens based on the use of PDE-5 inhibitors, intracavernosal injection, and vacuum device therapies are associated with a high rate of discontinuation. This, coupled with the detrimental effects that ED incurs upon psychosocial well-being, has fuelled the need to develop newer, safer and better tolerated therapies for ED.

## Emerging therapies for erectile dysfunction

### Topical alprostadil cream

#### *Overview of the product*

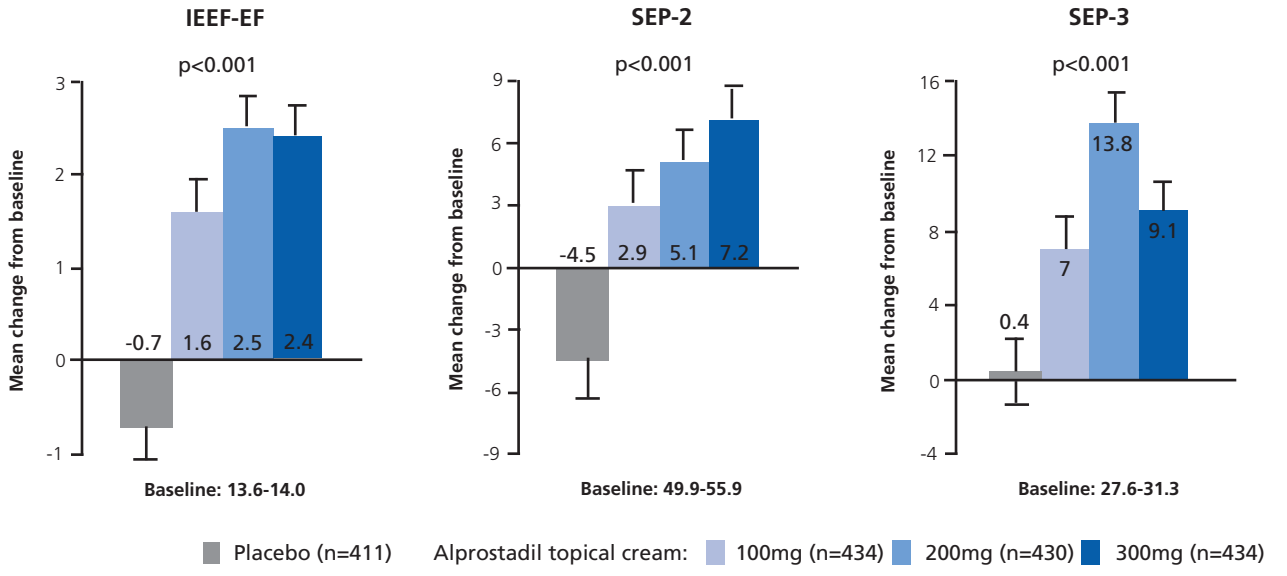
This new product (Vitaros®, Takeda) is designed to overcome the limitations of current therapies for ED in patients with diabetes. It contains a topical preparation of alprostadil combined with a novel dermal permeation enhancer that is self-administered to the tip of the glans penis. Two dosage strengths are available: 200 μg and 300 μg, in 100 mg of cream (only the higher strength is currently approved for use in the UK). The maximum frequency of usage is once per 24-hour period and no more than 2–3 times per week. It has an onset of action between 5–30 minutes with a short half-life resulting in penile erections that last approximately 1–2 hours. Systemic absorption, measured by plasma PGE-1 and PGE-0 levels, is very low or undetectable which enhances its cardiovascular safety profile. Preclinical safety data suggest that topical alprostadil has no effect on sperm count or morphology and is not genotoxic, although no carcinogenicity studies have been conducted. The safety and efficacy for topical alprostadil in combination with PDE-5 inhibitors has not been studied; accordingly, the prescribing information for topical alprostadil currently advises against combined use with PDE-5 inhibitors because an additive risk of cardiovascular effects cannot be excluded.

#### *Clinical experience*

A pooled analysis of two 12-week, multicentre, double-blind, randomised, parallel-group studies evaluated topical alprostadil cream in 1,732 patients with an ED score of 25 or less on the IIEF (430–434 in each group received placebo or aprostadil topical cream at dosage strengths of 100 mg, 200 mg or 300 mg).[11] Topical alprostadil cream was found to improve several secondary efficacy variables relating to ED, compared with placebo, including the other IIEF domain scores (orgasmic function, intercourse satisfaction, and overall satisfaction), PSAE, and GAQ. Adverse effects were mainly related to application site erythema and burning with associated meatal or glans pain but these were generally tolerated. Only 2.7% of patients withdrew from the study due to adverse events. Subgroup analyses revealed similar improvements in the IIEF erectile function domain scores for patients with diabetes, cardiac disease, prostatectomy, or hypertension; for patients who had not responded to previous therapy with sildenafil; and for patients aged above or below 65 years. The results of this study are summarised in Figure 1.

A large, multi-centre, open-label, long-term study in 1,161 patients with ED confirmed these findings.[12] For the first 28 days, patients could administer eight doses of 200 mg alprostadil cream; for the next nine months, patients then self-selected to continue to administer the 200 mg cream, or to switch to administering 300 mg or 100 mg cream, based on their perceived therapeutic response. About one patient in eight (12%) of patients discontinued due to hypo-/hyper-responsiveness and <5% discontinued because of adverse effects (application site erythema in 12%, meatal or glans pain in 4% and prolonged or painful erection in 1.3%), and only five patients reported priapism; 2.1% of partners reported vaginal burning or pruritus. Most patients (73%) selected 300 mg alprostadil cream as the final dose (the dosage strength available in the UK), and 74% demonstrated an overall improvement in erectile function (assessed using the IIEF, SEP, PSAE and GAQ indices).

**Figure 1.** Summary of results of a pooled analysis of two randomised evaluations of alprostadil topical cream in patients with erectile dysfunction




Values shown are least-squares differences from baseline (bars are SE). The p-values shown are from a comparison of treatment effects across groups. All individual mean changes in the alprostadil groups were significant relative to changes in the corresponding placebo groups ($p \leq 0.001$). Baseline values show the range of values across the four treatment groups. Drawn from data presented by Padma-Nathan and Yeager.[11]

Comparative studies between alprostadil and PDE-5 inhibitors are lacking. Nevertheless, current expert opinion recommends that alprostadil is used as second-line therapy in managing ED in patients with diabetes or as a potential first-line treatment in patients who are either non-responsive or intolerant to PDE-5 inhibitors.[13] However, topical alprostadil is unable to surmount the limitations of current therapies for ED in diabetes and remains contraindicated in patients with unstable angina, cerebrovascular disease and haematological conditions associated with priapism.

### Highly selective PDE-5 inhibitors

Newer PDE-5 inhibitors aim to conquer the limitations of current agents (see above) by means of improved selectivity for PDE-5, superior *in vivo* potency, enhanced oral bioavailability, and an extended duration of action. These drugs include avanafil, which has recently been licensed and is available for prescription, and lodenafil, mirodenafil and udenafil, which are currently in clinical development.

Clinical trial experience with novel highly-selective PDE-5 inhibitors is summarised below:

- **Avanafil** 100 mg and 200 mg was associated with significant improvements in the IEFF-EF domain score, SEP-2 and SEP-3 scores, potential shifts to normal erectile function domain scores, and responses to the GAQ relative to placebo, in a randomised, multicentre, double-blind, placebo-controlled phase III study of 200 patients.[14] There was no significant difference in effects between the 100 mg and 200 mg doses.
- **Lodenafil** was associated with significant improvements in the IEFF-EF domain score and SEP-2 and SEP-3 scores in a randomised, double-blind, placebo-controlled phase III clinical trial in 350 patients. However, more reports of headache, flushing, rhinitis, dizziness and visual disturbance occurred on lodenafil relative to placebo.[15]
- **Mirodenafil** is a potent and selective inhibitor of cGMP-specific PDE-5. A meta-analysis of three multi-centre, randomised, double-blind, placebo-controlled clinical trials involving 374 patients revealed that mirodenafil was found to be effective and well-tolerated over 12 weeks of treatment. There were significant improvements in both the IEFF-EF domain score and changes in this score from baseline compared with placebo. The most common adverse effects were flushing and headache.[16]
- Pooled results from a meta-analysis of five randomised controlled clinical trials involving 1,109 patients showed that **udenafil** was more effective than placebo in improving the IEFF-EF domain score from baseline. Most adverse events in all studies were mild or moderate in severity (mostly flushing and headache), with no serious adverse events. The concomitant use of antihypertensive drugs or $\alpha_1$-adrenoceptor antagonists did not significantly affect the efficacy and safety profile of udenafil.[17]

There are no comparative data on the clinical efficacy of the novel highly selective PDE-5 inhibitors versus sildenafil, vardenafil or tadalafil. Table 2 compares their half-lives.

### Angiotensin II antagonism and Mas receptor agonists

The renin angiotensin system plays a vital role in erectile function. Elevated angiotensin II levels have been detected in the corpus

**Table 2** Half-lives of PDE-5 inhibitors

| PDE-5 Inhibitor | Half-Life (hours) |
|---|---|
| First-generation agents: | |
| Sildenafil | 3–4 (2.6 for 25 mg; 3.7 for 100 mg) |
| Vardenafil | 3–4 |
| Tadalafil | 17 |
| Highly selective agents: | |
| Avanafil | 3 |
| Udenafil | 11–13 |
| Mirodenafil | 1.6 |
| Lodenafil | 3.3 |

cavernosum in patients with ED and increased activation of the AT1 receptor contributes to the development of ED. Conversely, pharmacological antagonism of the AT1 receptor improves erectile function. The heptapeptide, AT(1–7), opposes the biological actions of AT II and enhances penile erection via the activation of Mas receptor, via modulation of several different signalling pathways, such as the PI3K/AKT and ERK pathways, and downstream effectors such as NO, FOXO1, and COX-2.[18] Pre-clinical data from rodent studies showed that long-term treatment with an oral formulation of AT(1-7) reduced penile fibrosis, attenuated oxidative stress, and improved endothelial function in ED induced by hypercholesterolaemia.[19] This suggests that AT(1-7) and Mas receptor activation are candidate therapeutic targets for the treatment of ED associated with hypercholesterolaemia in men with diabetes.

A crossover study of sexual activity in 160 newly diagnosed hypertensive men treated with either carvedilol 50 mg or valsartan 80 mg provided further evidence on the utility of AT II antagonism in improving erectile function.[20] Carvedilol induced a chronic worsening of sexual activity, whereas long-term therapy with valsartan was significantly associated with improved sexual activity. Other β-blockers, diuretics, and cardiac glycosides are associated with ED. However, antihypertensive medications that do not compromise erectile function include α-antagonists and calcium channel blockers.

### Penile revascularisation

Patients with arteriogenic ED caused by traumatic vascular lesions, such as pelvic fracture, can be treated successfully by penile revascularisation surgery. A 10-year follow-up study on 52 patients who underwent penile revascularisation surgery reported a long-term success rate of 48%, defined as satisfactory intercourse without additional therapy. Positive predictors of success included age <28 years and a non-smoking history.[21] However, there is scant evidence on the utility of penile revascularisation surgery in the treatment of ED of arteriosclerotic or neurogenic-aetiology, which are more commonly seen in diabetes.

Ligation of dorsal veins has been conducted with the intention of restoring erectile function in diabetic patients with venous insufficiency. However, this is rarely indicated as outcomes are disappointing, with only a temporary improvement in erectile function.

**Key messages**

- ED is common affecting between 30-35% of men with diabetes
- Licensed treatments for ED are limited in their application towards the provision of symptomatic relief and are offset by adverse effects, intolerance, limited effectiveness and contraindications in the presence of co-existent cardiovascular disease
- Newer treatments for ED, such as topical Alprostadil cream and highly selective PDE-5 inhibitors, offer hope of surmounting the limitations of current licensed treatments.

### Testosterone replacement

Testosterone increases the expression of nitric oxide synthase and PDE-5, both key enzymes involved in erectile physiology, and deficiency of this hormone is associated with a decline in erectile function. A significant proportion of men who fail to respond to PDE-5 inhibitors are testosterone deficient, because a minimum plasma concentration of testosterone is required for the successful restoration of erectile function with these agents. Testosterone replacement therapy can convert more than half of these men into responders to PDE-5 inhibitors. Additionally, testosterone replacement can restore erectile function in about 35–40% of hypogonadal men. It is now recommended that testosterone levels should be assessed in all patients with ED.[22]

### Regenerative therapies

Current treatments for ED in patients with diabetes are limited in their application towards the attainment of symptomatic relief rather than reversing the underlying vasculogenic and neurogenic aetiologies. Accordingly, regenerative therapies are geared towards regenerating damaged erectile tissue and restoring erectile function using disease-modifying approaches based upon stem cells and tissue engineering, growth factor therapy, and gene transfer. A wealth of pre-clinical data using both embryonic or adult stem cells derived from bone marrow, adipose tissue, and muscle have been used to investigate their differentiation potential towards penile endothelial, vascular, neural, or smooth muscle lineages with promising results. The penis contains an inherent population of adult stem cells; therapies geared towards endogenously manipulating the reparative potential of these cells are an exciting area of research.[23] However, the role of regenerative therapies in the treatment of ED in diabetes remains confined to pre-clinical studies on rodent models and the potential clinical utility of regenerative therapies for ED in diabetes remains uncertain.

## Conclusions

ED in patients with diabetes is challenging to manage. Accordingly, the prevalence and burden of ED in diabetes remains largely unchanged, despite significant improvements in developing effective

treatments for diabetes and associated microvascular disease over the last 30 years. Current licensed treatments provide symptomatic relief, but are limited by adverse effects, intolerance, a lack of effectiveness and contraindications in the presence of co-existent cardiovascular disease, which is common in the diabetic population. Novel, highly selective PDE-5 inhibitors with negligible systemic absorption, and agents that target new candidate receptors implicated in erectogenesis, offer hope of surmounting these hurdles. The ultimate goal of therapeutics in the treatment of ED in diabetes remains the attainment of a curative disease-modifying approach that treats the vasculogenic, neurogenic and psychogenic components of ED.

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