

Evidence Tables

EREC 1: Are PDE5 inhibitors effective for the treatment of erectile dysfunction in people with type 2 diabetes?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Goldstein I, Young JM, Fischer J, Bangerter K, Segerson T, Taylor T. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: A multicenter double-blind placebo-controlled fixed-dose study. <i>Diabetes Care</i> 2003; 26(3):777-783. Ref ID: 3254	RCT, double-blind 1++	N=452 (ITT analysis done on 430, 47 centres USA and Canada (88% T2D with poor glycaemic control)	Inclusion criteria: men 18yrs+, type 1 or 2 diabetes, HbA1c ≤12%, Exclusion criteria: erectile dysfunction with any other known cause, cardiac history in the last 6 months, liver disease, haematological disease, resting hypotension or hypertension, neuropathy, hypo/hyper thyroidism, severe uncontrolled migraines. Previous exposure to sildenafil was allowed unless patients had discontinued use because of significant side effects or because of dissatisfaction with its efficacy Demographic and baseline characteristics were distributed similarly among patient groups.	Vardenafil 10mg N=153 Vardenafil 20mg N=149 To be taken as needed but no more than once a day and approximately 1h before intercourse Mean no. of doses per patient per week: 10mg – 2.1 20mg – 2.0 Placebo – 1.8	Placebo N=150	12 week 4 week unmedicated phase	EF domain on the IIEF, SEP diary questions (Q2 successful insertion, Q3 successful intercourse), GAQ (global assessment question) 'Has the treatment you have been taking over the past 4 weeks improved your erections?'	*EF domain score There were significant increases in the EF domain of the IIEF with the treatment groups with increases of 5.9 (10mg) and 7.8 (20mg) compared with placebo (1.4), p<0.0001. a dose related response was also noted for the EF domain (p=0.03). * SEP Diary questions The diary entry recordings showed significant improvement with treatment compared with placebo (p.0001). No dose response was noted. *GAQ The responder rate (the proportion of men reporting improved erections on the GAQ at 12 weeks was 72% for the 20mg vardenafil group, 54% for the 10mg vardenafil group and these rates were significantly higher than the 13% of men in the placebo group, p<0.0001. the response rate at 20mg was also significantly higher than at 10mg in both LOCF and completer analysis (p≤0.02). *Severity of ED The average success rate for those with	Bayer

								<p>severe ED in the 20mg vardenafil group reached 40% compared with 11% in the placebo group (p<0.0001).</p> <p>*Glycaemic control Findings indicated no clear relationship between response to vardenafil and glycaemic control.</p> <p>*Naïve to sildenafil From the subset of men who were naïve to sildenafil the responses were similar to those from patients who had taken sildenafil previously.</p> <p>*Adverse events The most frequent adverse events were headache, cutaneous flush and rhinitis.</p> <p>* Discontinuation 73 participants discontinued the study (distribution between treatment groups not identified). 11 discontinued due to adverse events (n=2 in the placebo group, n=4 in the 10mg vardenafil group and n=5 in the 20mg vardenafil group</p>	
Rendell MS RJ. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil	RCT multicentre, double blind, flexible-dose	N = 268	Inclusion criteria: Medically documented ED which was documented in the prior medical record to be of at least 6 month's duration, and a clinical diagnosis of at least 5	Sildenafil 50mg ¹ N= 136	Placebo N= 132	12 week ²	1. IIEF Q3 (achieving an erection) and Q4 (maintaining an erection)	IIEF * The least squares mean scores to the IIEF questions assessing the ability to achieve (Q3) and maintain (Q4) erections demonstrated significant improvements among patients receiving	Pfizer

¹ Based on the investigator's judgment of efficacy and tolerability, the dose could be increased to 100mg or decreased to 25mg of sildenafil or placebo. At the end of the study, 126 patients (93%) were receiving 100mg of sildenafil, 10 patients (7%) were receiving 50mg of sildenafil, and no patient was 25 mg of sildenafil. For patients receiving placebo, 127 patients (96%), 5 patients (4%), and no patients were taking the high, medium, and low doses respectively.

² Preceded by a 4-week run-in phase

<p>Diabetes Study Group. JAMA : the journal of the American Medical Association 1999; 281(5):421-426. Ref ID: 75</p>	<p>1++</p>		<p>years duration for type 1 and at least 2 years duration for type 2 diabetes. Medical management of diabetes had to be stable for at least 3 months prior to screening, with HbA1c < 12% and FPG ≤ 16.6 mmol/l.</p> <p>The patients also had to be in a stable relationship with a female partner for at least the previous 6 months.</p> <p>The baseline characteristics of the patients in the 2 treatment groups were similar.</p>				<p>2. Global efficacy question "did the treatment improve your erections"</p> <p>3. an event log in which patients recorded the number of attempts at sexual intercourse and the number of attempts that were successful.</p> <p>Adverse events</p>	<p>sildenafil compared with those receiving placebo (P< 0.001)</p> <p>For Q3, the mean score was 3.2 for patients in the sildenafil group compared with 2.0 for those in the placebo group, which represents increases from baseline of 78% (mean score at baseline 1.8) and 25% (mean score at baseline 1.6) respectively.</p> <p>For Q4, the mean score was 2.9 (93% increase from baseline mean score of 1.5) for the sildenafil group compared with 1.6 (14% increase from baseline mean score of 1.4) for the placebo group.</p> <p>* Of the remaining 13 questions of the IIEF, mean scores to 11 questions assessing other aspects of male sexual function, showed significant improvements for the sildenafil group compared with the placebo group (p<0.001).</p> <p>The mean scores for IIEF question 11 and 12, which assessed frequency of sexual desire and the level of sexual desire, respectively, indicated no statistically significant differences between the 2 groups (p=0.71 and P= 0.17, respectively)</p> <p>Global Efficacy Question 74 (56%) of 131 patients taking sildenafil reported improved erections compared with 13 (10%) of 127 patients taking placebo (p<0.001)</p>	
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								<p>Event Log in</p> <p>The proportion of men reporting successful attempts at sexual intercourse during the last 4 weeks of treatment was 48% (56/117) in the sildenafil group compared with 12% (14/114) in the placebo group (p<0.001).</p> <p>The proportion of men with at least 1 successful attempt at intercourse was 61% (71/117) for the sildenafil group vs 22% (25/114) for the placebo group (p< 0.001)</p> <p>Subanalysis</p> <p>Treatment with sildenafil significantly improved erectile function across all 3 efficacy variables regardless of patient age, the duration of ED, and the duration of diabetes.</p> <p>* Adverse Events</p> <p>AEs related to treatment were reported for 16% (22/136) of patients taking sildenafil and 1% (1/132) of patients taking placebo.</p> <p>- Headache Sildenafil : 11% Placebo: 2%</p> <p>- Dyspepsia Sildenafil 9% Placebo: 0%</p> <p>- Respiratory track disorder Sildenafil 6% Placebo: 2%</p> <p>- Cardiovascular AEs (others than flushing) Sildenafil 3% Placebo: 5%</p>	
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								* Discontinuation The rate of discontinuation from treatment was 4% (5/136) for sildenafil and 8% (11/132) for placebo.	
Safarinejad MR. Oral sildenafil in the treatment of erectile dysfunction in diabetic men: A randomized double-blind and placebo-controlled study. Journal of Diabetes & its Complications 2004; 18(4):205-210. Ref ID: 3260	RCT double blind, fixed dose study 1++	N= 282	Inclusion criteria: aged 18 or older. Documented ED for at least 6 months. Stable relationship with a female partner for at least the previous 6 months. HbA1c <12%. FBG <200mg/dl for at least 3 months prior to screening. Normal serum testosterone and prolactin levels. Patient characteristics: mean age 46 years (range 2.5 – 12). None of the patients has received other treatment for ED for at least 4 weeks before the start of the study. The majority of patients (83%) had type 2 diabetes. At baseline, the study and placebo groups were similar in demographic and clinical characteristics	Sildenafil 100mg N= 144	Placebo N= 138	16 weeks	1. IIEF Q3 (achieving an erection) and Q4 (maintaining an erection) 2. Global Efficacy Question (Did the treatment improve your erections?) 3. Event log-in 4. Adverse events	Sildenafil significantly improved erectile function across all three efficacy variables regardless of patient age, the duration of ED, and the duration of diabetes (p <0.002 vs placebo for all three variables) 1. IIEF * Question 3 The mean score was 2.8 for patients in the Sildenafil group compared with 2.2 for those in placebo group. * Question 4 The mean score was 2.9 for the Sildenafil group compared with 2 for the placebo group 2. GEQ 68 (51%) of 134 patients taking Sildenafil reported positive clinical results compared with 14 (11%) of 128 patients in the placebo group (p<0.003) 3. Event log-in 59% of the patients reported at least one successful attempt at sexual intercourse in the sildenafil group as compared with 21% successful attempts during placebo treatment (p<0.002) * Other questions The mean score for IIEF Q11 and Q12,	Not reported

							<p>which assessed frequency of sexual desire and rating of sexual desire, respectively, indicated no statistically significant differences between the two groups (p=0.75 and P=0.2 respectively)</p> <p>The remaining 11 questions assessing other aspect of male sexual function showed significant improvements for the sildenafil group compared with the placebo group (p<0.05)</p> <p>Subanalysis Sildenafil significantly improved erectile function across all three efficacy variables regardless of patient age, the duration of ED, and the duration of diabetes (p <0.002 vs placebo for all three variables)</p> <p>HbA1c, BP, etiology of ED, and age of subjects who responded to sildenafil were similar to those found in patients who did not respond to sildenafil</p> <p>Adverse Events AEs related to treatment were noted in 22% (32/144) of patients taking sildenafil and 1.4% (2/138) of patients taking placebo (p<0.001)</p> <table border="1"> <thead> <tr> <th>AE</th> <th>S</th> <th>P</th> </tr> </thead> <tbody> <tr> <td>Headache</td> <td>20%</td> <td>2%</td> </tr> <tr> <td>Flushing</td> <td>19%</td> <td>0%</td> </tr> <tr> <td>Dyspnoea</td> <td>9%</td> <td>2%</td> </tr> <tr> <td>Rhinitis</td> <td>6%</td> <td>0%</td> </tr> <tr> <td>Cardiovasc*</td> <td>7%</td> <td>0%</td> </tr> </tbody> </table> <p>* the incidence of CV events were</p>	AE	S	P	Headache	20%	2%	Flushing	19%	0%	Dyspnoea	9%	2%	Rhinitis	6%	0%	Cardiovasc*	7%	0%
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								<p>significantly much higher ($p < 0.001$) in the patients taking sildenafil compared with patients taking placebo.</p> <p>in the sildenafil group, 4 patients had new chest pain of whom 2 manifested an ST elevation $> 3\text{mm}$ with documented myocardial infarction.</p> <p>Other CV events in the sildenafil group were two congestive heart failures and 4 hypertensions.</p> <p>Reasons for discontinuation</p> <p><u>Sildenafil</u></p> <table> <tr> <td>AEs</td> <td>8</td> </tr> <tr> <td>Lack of efficacy</td> <td>1</td> </tr> <tr> <td>Lost to follow-up</td> <td>1</td> </tr> <tr> <td>Total:</td> <td>10</td> </tr> </table> <p><u>Placebo</u></p> <table> <tr> <td>Lack of efficacy</td> <td>3</td> </tr> <tr> <td>Lost to follow-up</td> <td>2</td> </tr> <tr> <td>Others</td> <td>5</td> </tr> <tr> <td>Total:</td> <td>10</td> </tr> </table>	AEs	8	Lack of efficacy	1	Lost to follow-up	1	Total:	10	Lack of efficacy	3	Lost to follow-up	2	Others	5	Total:	10	
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Stuckey BGA, Jadzinsky MN, Murphy LJ, Montorsi F, Kadioglu A, Fraige F et al. Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: Results of a	RCT Multicentre double blind, placebo controlled 1++	N=191 N=188 took study drug Patients from Argentin	Inclusion criteria: Male patients age 18 or over with a clinical diagnosis of ED of more than 6 months duration in a stable relationship with a female partner of more than 6 months duration. Patients had a clinical diagnosis of type 1	Sildenafil 50mg N=95 ³ To be taken one hour before anticipated	Placebo N=93	12 weeks ⁴	Primary efficacy assessment: IIEF Q3 (achieving an erection) and Q4 (maintaining an erection)	<p>* Q3 Achieving an erection. Mean score were significantly higher (33%) in the sildenafil group 3.61 ± 0.48; $p \leq 0.001$ compared with the placebo group (2.71 ± 0.47).</p> <p>* Q4 maintaining an erection. Mean score were significantly higher</p>	Pfizer																

³ All patients started at a 50-mg dose of sildenafil or matching placebo with the option of adjusting the dose to 25 or 100mg based on efficacy and tolerability.

⁴ Following a 4-week run-in period patients entered the 12-week double-blind treatment period with follow-up visits after 2,4,8 and 12 weeks of treatment.

<p>randomized controlled trial. Diabetes Care 2003; 26(2):279-284. Ref ID: 3262</p>		<p>a, Australia, Brazil, Canada, Hong Kong, Italy, Spain, Thailand and Turkey</p>	<p>diabetes of at least 1 years duration. HbA1c levels had to be <11%. Exclusions: Anatomical deformities and psychiatric disorders, alcoholism or substance abuse, ED due to spinal cord injuries, a history of MI, stroke, heart failure, or unstable angina or a history of hypotension and those taking nitrates. Also recurrent hypoglycaemic episodes, severe and autonomic neuropathy.</p> <p>Mean age was 47 years, mean weight 78kg, 94% were white, mean time since ED diagnosis 5 years, baseline mean HbA1c, 8.6%, 30% were hypertensive.</p>	<p>sexual activity. No more than 2 units of alcohol were to be consumed.</p>			<p>Secondary efficacy assessment: Global efficacy question (GEQ) "Has the treatment you have been taking over the past 4 weeks improved your erections?". IIEF domains Event log of Erectile Function: Intercourse success rates were derived from these logs.</p>	<p>(48% in the sildenafil group 3.25 ± 0.52; $p \leq 0.001$ compared with the placebo group (2.19 ± 0.5).</p> <p>NOTE: Patients with mild/moderate ED achieved higher final scores for Q3 and Q4 (4.48 and 4.05) than patients with severe ED (2.39 and 2.41) but also started with approximately three times higher baseline scores.</p> <p>* % of successful intercourse attempts was significantly higher in the sildenafil group ($p < 0.051$) with twice as many patients answering in the affirmative compared with the placebo group</p> <p>* GEQ Positive responses to the GE ("Has treatment improved your erections?") were higher in the sildenafil group, with 66% of patients with mild/moderated ED responding in the affirmative compared with 29% of patients taking placebo.</p> <p>Patients with severe ED (sildenafil, $n=33$; placebo, $n=41$) reported a lower percent of improved erections (sildenafil, 30%; placebo, 10%)</p> <p>* Erectile Function The EF domain showed on average a 6-point increase in the mean score over placebo, irrespective of the ED severity ($p = 0.001$)</p> <p>As observed for the other efficacy parameters, men with mild/moderate</p>	
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								<p>ED achieved a higher overall score compared with men with severe ED.</p> <p>Note: When efficacy was analyzed for patients with baseline HbA1c levels <8% (n=54-57) or ≥ 8% (108-117), no significant differences were found in end-of-treatment scores for any of the efficacy parameters.</p> <p>Similarly, sildenafil efficacy was maintained in patients who had never smoked (n=55-62) as well as in those currently smoking (n=53-54) with no statistical differences in end-of-treatment scores between groups.</p> <p>Finally, patients with cardiovascular complications (n=56-61) did equally well with sildenafil when compared with the overall patient group (n=162-174) for all efficacy parameters</p> <p>*Adverse Events The most common treatment-related adverse events included headache, flushing, and dyspepsia; all other AEs occurred in <5% of patients. All events were transient and mild to moderate in nature, and the rate of discontinuations because of these events was low (2.2% and 1.1.% for sildenafil and placebo respectively).</p> <p>Reasons for discontinuation: Placebo Patients who took study drug n= 93 Withdrawn n= 16 - lack of efficacy 3</p>	
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								<ul style="list-style-type: none"> - AEs 3 - lost to follow-up 1 - Did not meet IC 1 - Withdrew consent 3 <p>Sildenafil Patients who took study drug n= 97 Withdrawn n= 10</p> <ul style="list-style-type: none"> - lack of efficacy 2 - AEs 2 - lost to follow-up 1 - Withdrew consent 5 	
Boulton AJM, Selam JL, Sweeney M, Ziegler D. Sildenafil citrate for the treatment of erectile dysfunction in men with Type II diabetes mellitus. Diabetologia 2001; 44(10):1296-1301. Ref ID: 3250	RCT multicentre double blind, flexible-dose escalation study 1+	N= 219	Inclusion criteria: Participants had to be 37 years of age or older with a clinical diagnosis of ED and be in a stable relationship of more than 6 months duration with a female partner. Patients had to have a clinical diagnosis of T2D of at least 2 years' duration. Diabetes had to be generally stable with HbA1c. The baseline characteristics of patients in both groups were largely similar.	Sildenafil ⁵ (50mg) N= 110	Placebo N= 109	12 weeks ⁶	Primary efficacy assessment IIEF Q3 (achieving an erection) and Q4 (maintaining an erection) Secondary efficacy assessment - Global Efficacy Question - Patient event log	<p>IIEF</p> <p>* Question 3 The mean score for Q3 improved significantly in patients receiving sildenafil compared with placebo (3.42 ± 0.23 vs 1.86 ± 0.22) p< 0.0001</p> <p>* Question 4 The mean score for Q4 improved significantly in patients receiving sildenafil compared with placebo (3.35 ± 0.24 vs 1.84 ± 0.23) p< 0.0001</p> <p>GEQ The GEQ-score was significantly higher in the sildenafil group with 64.6% answering in the affirmative compared with only 11.1% in the placebo group p< 0.0001</p> <p>Patient event log</p>	Pfizer

⁵ All patients started at a 50-mg dose of sildenafil or matching placebo with the option of adjusting the dose to 25 or 100mg based on efficacy and tolerability.

⁶ Preceded by a 4-week run-in period

							<p>- life satisfaction checklist</p> <p>- Remaining IIEF questions</p>	<p>The estimated number of successful intercourse attempts was improved in patients receiving sildenafil compared with those receiving placebo. (58.8% and 14.4% respectively) p<0.0001</p> <p>Life Satisfaction Checklist Sildenafil was shown to improve scores for sexual life 1.5 fold over placebo treatment. P<0.0001</p> <p>Subanalysis Efficacy was independent of HbA1c (≤ 8.3% or > 8.3%). However, men with fewer diabetic complications seemed to respond marginally better to IIEF questions 3 and 4 and the GEQ and reported slightly more successful attempts at intercourse than the men who had more conditions typically associated with diabetes.</p> <p>Adverse Events</p> <table border="1"> <thead> <tr> <th>AE</th> <th>S</th> <th>P</th> </tr> </thead> <tbody> <tr> <td>Headache</td> <td>18.2%</td> <td>3.7%</td> </tr> <tr> <td>Flushing</td> <td>14.5%</td> <td>0%</td> </tr> <tr> <td>Dyspepsia</td> <td>1.8%</td> <td>0.9%</td> </tr> <tr> <td>Abnormal vision</td> <td>4.5%</td> <td>0%</td> </tr> </tbody> </table>	AE	S	P	Headache	18.2%	3.7%	Flushing	14.5%	0%	Dyspepsia	1.8%	0.9%	Abnormal vision	4.5%	0%	
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Buvat J, van AH, Schmitt H, Chan M, Kuepfer C, Varanese L. Efficacy and safety	RCT, double-blind, multi-	N= 762 diabetic patients with ED	Inclusion criteria: for this analysis, patients with T1 diabetes were defined as <40 years of age at diagnosis and	Tadalafil ⁷ 20mg 3-times per week	Tadalafil 20mg On-demand	10-12 weeks	IIEF Sexual Encounter	Efficacy (IIEF/SEP) General vs Diabetic population The efficacy of tadalafil in patients with	Eli-Lilly															

⁷ The patients followed protocol instructions, which included no restrictions on food or alcohol intake

<p>of two dosing regimens of tadalafil and patterns of sexual activity in men with diabetes mellitus and erectile dysfunction: Scheduled use vs. on-demand regimen evaluation (SURE) study in 14 European countries. Journal of Sexual Medicine 2006; 3(3):512-520. Ref ID: 3251</p> <p>Post-hoc analysis of SURE study</p>	<p>centre, cross-over. 1+</p>	<p>from the 4,262 patients randomized in the SURE study.</p>	<p>on insulin treatment only. All other patients were classified as having T2 diabetes. T2 N= 636 (83.5%) T1 N=126 (16.5%)</p> <p>Patients were to have the same female partner during the study for recording responses to efficacy questionnaires and have at least four sexual attempts with that partner during the run-in period. The patients agreed not to use any other ED treatment during the study. Patient who previously used another commercially available PDE5 inhibitor were not excluded.</p> <p>Exclusion criteria: The key exclusion criteria included patients who were receiving treatment with nitrates, cancer chemotherapy, or antiandrogens, or treatment for symptomatic congestive heart failure.</p> <p>Patient characteristics: The mean age of all patients with diabetes was 57 years. Nearly 90% of these patients had an ED history of 1 year or longer, and in more than 70%, the baseline ED severity was moderate or severe.</p>	<p>5- 6 weeks</p> <p>Then 1-week washout period</p> <p>Schedule A (Monday, Wednesday, and Friday)</p> <p>Schedule B (Tuesday, Thursday, and Saturday)</p>	<p>5- 6 weeks</p> <p>Then 1-week washout period</p> <p>(prior to potential sexual activity at a maximum frequency of 1 dose/day)</p>		<p>Profile (SEP) questions 1-5</p> <p>Treatment Preference Question "Which treatment regimen did you prefer?"</p> <p>Adverse events</p>	<p>diabetes was slightly lower than in the overall SURE study population. (no statistical analysis was performed).</p> <p>IIEF The mean IIEF erectile function (EF) score for patients with diabetes on either regimen improved by about nine points, with an end point of approx 22 (P=0.188). A normal EF domain score (≥ 26) at end point was reached by more than 40% of patients.</p> <p>The IIEF score in patients with diabetes was slightly higher in patients on the 3-times per week regimen than in those taking tadalafil on demand. (no statistical analysis was performed).</p> <p>SEP The success rate (mean per patient) after baseline for SEP 1-5 was slightly but significantly higher for the 3-times-per-week regimen (p<0.05 for SEP 1-5)</p> <p>The mean per-patient rate after baseline after baseline was greater than 85% for SEP1, 73.0% for SEP2, and 58.0% for SEP3 on both treatment regimens. In the assessment of satisfaction, the rate for both regimens was greater than 45% for SEP4 and SEP5.</p> <p>There was no statistically significant difference in all efficacy measure between patient with T1 or T2 diabetes or between patients who were obese or</p>	
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								<p>non-obese when on either treatment.</p> <p>Sexual attempts & Time after dosing (0 to <4h - >4to ≤12h - >12 to ≤ 24 - >24 to ≤ 36h - > 36h)</p> <p>Approx 50% of the sexual attempts on the on-demand regimen and 73% on the 3-times-per-week regimen occurred >4hours post-dosing.</p> <p>The % of successful intercourse attempts (SEP£) was approx 60% for both treatment regimens across all the time intervals, up to 36 hours post-dosing.</p> <p>Attempts took place each day of the week with the highest number occurring on Sunday on the on-demand regimen and on Saturday on the 3-times-per-week regimen.</p> <p>Treatment preference The treatment preference for patients with diabetes was 57.2% for the on-demand regimen and 42.8% for the 3-times-per-week treatment (p<0.001), similar to the overall treatment preference in the SURE study.</p> <p>Adverse events Tadalafil 20mg was well tolerated by patients with diabetes and ED in both treatment regimes. The most common adverse events (≥2% incidence) were: Dyspepsia, headache, back pain and flushing.</p>	
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<p>Ishii N, Nagao K, Fujikawa K, Tachibana T, Iwamoto Y, Kamidono S. Vardenafil 20-mg demonstrated superior efficacy to 10-mg in Japanese men with diabetes mellitus suffering from erectile dysfunction. International Journal of Urology 2006; 13(8):1066-1072. Ref ID: 3255</p>	<p>RCT, double-blind, multi-centre</p> <p>1+</p>	<p>N=790 (ITT analysis on 778), Japan</p> <p>Type of diabetes unspecified</p>	<p>Inclusion criteria: ED >3yrs, diabetes >3yrs and taking hypoglycaemic drug treatment or HbA1c >6.5% at visit 1, aged 20-45 yrs, heterosexual relationship, have made at least 4 attempts at sexual intercourse on 4 separate days in the baseline period with at least 50% unsuccessful</p> <p>Exclusion criteria: any unstable medical or psychiatric disorder, spinal cord injury, history of surgical prostatectomy, hepatitis B or C, penile abnormalities, cardiac history, resting hypotension or hypertension, haematological disorders, liver disease, peptic ulceration, taking any of the prohibited medications,</p> <p>Previous unsuccessful use of a PDE5 inhibitor</p> <p>Groups were similar at baseline</p>	<p>Vardenafil 10mg N=339</p> <p>Vardenafil 20mg N=340</p> <p>(3:3:1 – treatment to placebo ratio)</p> <p>Single dose taken 1 hr prior to sexual intercourse, not more than one dose per day and at least 24hrs between doses.</p>	<p>Placebo N=111</p>	<p>12 week study</p> <p>4 week unmedicated run in</p>	<p>Erectile function (EF) domain score in the International Index of Erectile Function (IIEF), SEP (Sexual Encounter Profile) (patient diaries)</p>	<p>*EF domain score Vardenafil 10mg and 20mg significantly improved the EF domain score from 13.6 and 13.9 to 21.8 and 22.9 at LOCF (last observation carried forward score) respectively, compared with placebo (13.7 at baseline to 16.3 at LOCF), p<0.0001.</p> <p>For those with severe ED (N=275) the improvement in EF domain score was significant for 20mg compared with 10mg, p<0.05</p> <p>*Patient diary questions For the 20mg compared with the 10mg groups there was a significantly higher percentage of patients who answered yes to the question 'success in penetration', p<0.05. This was also identified in the 'success in maintaining erection during intercourse', p<0.05</p> <p>*Adverse events The most common adverse events were hot flush (placebo 3%, 10mg group 9%, 20mg group 13%) and headache (2%, 4% and 6% respectively)</p> <p>*Discontinuation</p> <table border="1" data-bbox="1624 1077 2049 1268"> <thead> <tr> <th></th> <th>n</th> <th>(%)</th> </tr> </thead> <tbody> <tr> <td>10mg</td> <td>11</td> <td>3%</td> </tr> <tr> <td>- due to adverse events</td> <td>2</td> <td>1%</td> </tr> <tr> <td>20mg</td> <td>28</td> <td>8%</td> </tr> <tr> <td>- due to adverse events</td> <td>9</td> <td>3%</td> </tr> <tr> <td>Placebo</td> <td>14</td> <td>13%</td> </tr> <tr> <td>- due to adverse events</td> <td>2</td> <td>2%</td> </tr> </tbody> </table>		n	(%)	10mg	11	3%	- due to adverse events	2	1%	20mg	28	8%	- due to adverse events	9	3%	Placebo	14	13%	- due to adverse events	2	2%	<p>Bayer</p>
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<p>Saenz dT, I, Anglin G, Knight JR, Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes.[see comment]. Diabetes Care 2002; 25(12):2159-2164. Ref ID: 438</p>	<p>RCT multicentre, double blind 1+</p>	<p>N= 216 from 18 centres in Spain</p>	<p>Inclusion criteria: mean aged ≥ 18 years with a clinical diagnosis of T1 or T2 diabetes (mean duration 11.7 years), a minimum 3-month story of mild to severe ED, and a stable monogamous relationship with a female partner. (men with a history of hypertension (N=80; 37%) and hypercholesterolemia (N=38; 18%) were included. Patients were eligible for study inclusion, irrespective of previous responses to ED treatments, including sildenafil.</p> <p>Exclusion criteria included: patients with angina during intercourse, unstable angina, or any other evidence of recently diagnosed coronary artery disease.</p> <p>Patient characteristics: the vast majority of patients (> 72%) had moderate to severe ED, an ED history of >1 years (93%) and a diagnosis of T2D (>90%) at study onset.</p> <p>At baseline, the study and placebo groups were similar in demographic and clinical characteristics.</p>	<p>Tadalafil⁸ 10mg N= 73</p> <p>Tadalafil 20mg N=72</p>	<p>Placebo N=71</p>	<p>12 weeks</p>	<p><u>Primary outcomes</u></p> <p>IIEF (EF domain)</p> <p>Sexual Encounter Profile (SEP) Q2 “Were you able to penetrate” and Q3 “were you able to complete intercourse”</p> <p><u>Secondary outcomes</u></p> <p>IIEF (other questions)</p> <p>Global assessment question.</p>	<p>Primary outcomes Therapy with Tadalafil (particularly at 20mg) significantly enhanced erectile function across all three co-primary efficacy outcomes variables: IIEF erectile function domain, erection vaginal penetration rates (SEP-Q2) , and successful intercourse rates (SEP-Q3) All $p < 0.001$</p> <p>Secondary outcomes Tadalafil therapy at each dose significantly increased scores on IIEF-Q3 and IIEF-Q4 versus placebo ($p < 0.001$)</p> <p>Tadalafil therapy improved scores on: intercourse satisfaction (10mg vs. placebo $p = 0.001$; 20mg vs placebo $p = 0.012$). Orgasmic function (10mg vs placebo $p = 0.001$, 20mg vs placebo $p = 0.014$) Overall satisfaction ($p < 0.001$)</p> <p>Each dose of Tadalafil also significantly enhanced patients’ erections according to responses to the GAQ. The proportions of positive responses to the GAQ in the Tadalafil 10 and 20 mg groups were 56 and 64% respectively, compared with 25% in the control group (both $P < 0.001$)</p> <p><i>Treatment with tadalafil at 10 and 20mg improved these outcomes regardless of</i></p>	<p>Eli Lilly</p>
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⁸ All taken up to once daily when groups anticipated sexual activity .There were no restrictions on food or alcohol intake.

								<p><i>baseline HbA1c, type of diabetes or type of diabetes treatment</i></p> <p>Adverse events The most common treatment-emergent events in the Tadalafil groups were dyspepsia and headache. Only the incidence of dyspepsia was significantly different across treatment groups: ~11% in either the 10 or 20mg group, compared with 0% in the control arm (p=0.005). No treatment-related visual disturbances were reported. ECGs, clinical laboratory values, and vital signs exhibited no clinically significant changes.</p> <p>Drop-out Of the 216 men enrolled 191 (88%) completed treatment. A total of six (3%) patients discontinued because of treatment-emergent AEs. Of these six, four were randomized to Tadalafil treatment: one man in the Tadalafil 10-mg group experienced mild pain and the three patients in the 20-mg group experienced either moderate myalgia, moderate headache, or severe flushing. The other 2 patients discontinuation were due to MI: one in the placebo group and one who was randomized to the 20-mg group but never took the study drug.</p>	
Ziegler D, Merfort F, van AH, Yassin A,	RCT, double-	N=318 (302)	Inclusion criteria: men 18 yrs or older, heterosexual	Vardenafil 10mg ⁹	Placebo N=155	12 weeks ¹⁰	SEP diary questions,	*Diary questions - SEP2 The rate of successful insertion with	GSK

⁹ Efficacy and tolerance assessed at 4 and 8 weeks and dose either maintained, increased or decreased by one step according to the three applicable dosing strengths (5,10 and 20mg), to a maximum of 20mg (10mg in patients ≥65yrs)

<p>Reblin T, Neureither M. Efficacy and safety of flexible-dose vardenafil in men with type 1 diabetes and erectile dysfunction. Journal of Sexual Medicine 2006; 3(5):883-891. Ref ID: 3265</p>	<p>blind, multi-centre 1+</p>	<p>used for ITT analysis), type 1 diabetes, 82 sites in Germany</p>	<p>relationship, ED, established type 1 diabetes, HbA1c<12% Exclusion criteria: anatomical abnormalities of the penis, spinal cord injury, radical prostatectomy, retinitis pigmentosa, hepatitis B or C, cardiac history, liver impairment, haematological conditions, peptic ulcer, resting or postural hypotension, resting hypertension, history of malignancy within the past 5 yrs, prohibited medications</p> <p>Participants must not have had previous use of a PDE5 inhibitor.</p> <p>Groups were similar at baseline</p>	<p>N=163</p> <p>At the end of week 12 87.7% were receiving 20mg, 10.8% 10mg and 1.5% 5mg</p> <p>Not more than a single dose of a study drug was permitted per calendar day</p>			<p>EF domain of the IIEF, non-EF domains of the IIEF</p>	<p>vardenafil was significantly increased at all time points compared with placebo (4,8 and 12 weeks), p<0.0001. (weeks 0-4, 61%vs50%; weeks 4-8, 71%vs52%; weeks 8-12, 73%vs53%).</p> <p>*Diary questions - SEP3 The mean rate of maintained erections allowing successful intercourse was also significantly increased compared with placebo for all time intervals, p<0.0001.</p> <p>*EF domain score The EF domain score increased significantly from mean at baseline by 7.79 for vardenafil compared with 2.05 for placebo, p<0.0001.</p> <p>* Other domains of IIEF All other domains of the IIEF, including intercourse satisfaction (mean change with vardenafil 3.43, with placebo 0.72, p<0.001), orgasmic function (mean changes 1.99 and 0.30, p<0.001), sexual desire (mean changes 0.67 and 0.09, p<0.007) and overall satisfaction (mean changes 2.32 and 0.52, p<0.001) also showed significant improvements in the vardenafil group compared with placebo.</p> <p>*Glycaemic control The improvement in EF with vardenafil was not affected by the level of</p>	
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¹⁰ Preceded by a 4-week run-in period

								glycaemic control. *Adverse events Similar proportions of patients in both groups reported no adverse events (70.6% with vardenafil and 79.4% with placebo), the most common drug-related adverse events were mild-to-moderate headache and flushing. *Discontinuation Overall rates not given, discontinuation due to adverse events were n=2 in the placebo group and n=3 in the vardenafil group	
Price DE, Gingell JC, Gepi AS, Wareham K, Yates P, Boolell M. Sildenafil: study of a novel oral treatment for erectile dysfunction in diabetic men. Diabetic Medicine 1998; 15(10):821-825. Ref ID: 20	RCT double blind, three-way crossover (pilot study) 1-	N= 21 T1 n=7; T2 n=14	Inclusion criteria: mean aged 18-70 years with a history of diabetes type 1 or 2 of 5 years or more and with ED (defined as the inability to achieve and/or maintain erection for satisfactory sexual activity) of at least 6 months' duration. Exclusion criteria: clinically significant ischemic heart disease or peripheral vascular disease; treatment with antidepressants/tranquillizers, nitrates, anticoagulants, or salicylates in the 2 weeks prior to the study; history of a bleeding disorder; severe untreated proliferative diabetic retinopathy.	Sildenafil 50mg Sildenafil 25mg	Placebo	10 days for each intervention (there was a washout period of 3-10 days at each crossover stage) Each of the three treatment periods consisted of two parts.	* daily diary of erectile activity, evaluating the quality of erection ¹¹ * Global efficacy question (did the quality of your erections improve during the 10 days you took the treatment?)	Part I was not included: single dose + clinical setting Part II * Quality of erections Both 25mg and 50mg doses of sildenafil significantly increased the total number of erections hard enough for sexual intercourse (i.e. grade 3 or 4) compared with placebo The mean numbers of erections (95% CI) grade 3 or 4 per week were: 1.3 (0.9-1.8, p=0.0025) for patients taking 25mg of sildenafil and 1.6 (1.1 – 2.1, p=0.0002) for patients taking 50mg of sildenafil compared with 0.6 (0.4 – 0.9) for placebo-treated patients	Pfizer

¹¹ Classification system for self-grading erections: Grade 1: increase in size but not hard. Grade 2: hard but not hard enough for vaginal penetration. Grade 3: Hard enough for vaginal penetration (but not completely hard) Grade 4: completely hard

			<p>The mean age of the men was 51 (range 42 – 665) years. The mean duration of diabetes was 11 (range 3-32) years, and the median duration of ED was 3 (range 1-14) years.</p>			<p>Part I The effect of single dose of sildenafil or placebo on penile rigidity during visual sexual stimulation was assessed in the clinic using penile plethysmography.</p> <p>Part II Started the day after completion of part I, daily diary records and a patient global efficacy question were used to evaluate the effect of once-</p>	<p>Seven men had no discernible erectile activity with daily administration of 25mg or 50mg of sildenafil. Four patients had erections in response to one dose but not the other dose of sildenafil.</p> <p>* GEQ At the end of 10 days of treatment, a significantly greater percentage of patients reported improvement in their erections with daily administration of sildenafil. Of the 20 patients who completed treatment with both placebo and 25 mg of sildenafil, 10 patients (50%) reported that their erections were improved on 25mg of sildenafil compared with two patients (10%) on placebo (p=0.028). Of these 21 patients, nine reported improvement on sildenafil but not placebo and two on both sildenafil and placebo.</p> <p>*Adverse Events Treatment with sildenafil was well tolerated. The most frequent adverse events were headache, diarrhoea, nausea, and myalgia, with the majority of these considered to be related to the study drug. AEs were mostly mild or moderate in nature; nine AEs of a severe nature were reported 25mg of sildenafil: 3 events (diarrhoea, myalgia, and chest pain); 50mg of sildenafil: five events (back pain, myalgia, diarrhoea, headache, and dyspepsia); and placebo: one event (diarrhoea) with six of these events considered treatment-related.</p>	
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						daily dosing with 25mg or 50mg of sildenafil or placebo			
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