

## NEW MEDICINES ON THE MARKET

Evaluated Information for NHS Managers, Budget Holders and Prescribers

# SILDENAFIL CITRATE

## Summary

### *Clinical Impact*

- Sildenafil offers an opportunity to treat male erectile dysfunction with an effective, licensed oral preparation.
- It is taken on a “when required” basis and only works in the presence of sexual stimulation.
- 70-80% of men in trials show a statistically significant improvement in erectile or sexual function compared with about 25% of men who receive placebo. In the dose-escalation study in 329 men, around 2 men would need to be treated with sildenafil for 12 weeks for one man to report improved erections (NNT). There is no clear figure of how this relates to successful sexual intercourse, although 69% of all attempts were successful compared to 22% with placebo.
- Open label follow up studies indicate that most men who initially respond to the drug continue to take it. A fully-published randomised controlled trial has also demonstrated the efficacy of sildenafil in men with diabetes mellitus and erectile dysfunction.
- Sildenafil appears to be well tolerated. 2.5% of patients withdrew from studies because of adverse effects, compared to 2.3% with placebo. The US Food and Drug Administration has reported 69 deaths in people taking sildenafil which led to an update of the US label. Forty-six deaths were known to be due to cardiovascular events. Since sexual activity is itself a risk factor in cardiovascular death the role of sildenafil is difficult to determine.
- As yet there are no direct comparisons of sildenafil with alternative treatments.
- The long-term safety profile of sildenafil is yet to be established.

### *NHS Impact*

- From 1st July 1999, NHS prescription of impotence treatments by GPs will be restricted to a select group of patients, although other patients may receive a private prescription.

Date Published: August 1999

Monograph Number: 4/99/11

Marketed: September 1998

Region of Origin to whom queries should be directed: South Thames

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<b>APPROVED NAME</b>	Sildenafil citrate
<b>BRAND NAME</b>	Viagra (Pfizer Ltd.)
<b>PRESENTATION</b>	Tablets containing 25mg, 50mg, or 100mg sildenafil citrate available in packs of 4 or 8 tablets.
<b>THERAPEUTIC CLASS</b>	Drugs for impotence [BNF 7.4.5]
<b>LICENSED INDICATION</b>	Treatment of erectile dysfunction in men
<b>DOSE</b>	Sildenafil should be taken approximately 1 hour before sexual activity. The recommended starting dose for most patients is 50mg. However, based on efficacy and adverse effects the dose may be increased to a maximum of 100mg or decreased to 25mg. The maximum recommended dosing frequency is once daily.
<b>THERAPEUTIC COMMENT</b>	<p>From July 1st 1999, impotence treatments will be available for GPs to prescribe on the NHS for men who have had radical pelvic surgery; men who have had their prostate removed and / or have been treated for prostate cancer (surgery and other treatment); treated for renal failure (transplant and dialysis); spinal cord and severe pelvic injury; diabetes; multiple sclerosis; single gene neurological disease, poliomyelitis, spina bifida and Parkinson's disease. In addition, men who were receiving treatment for impotence on September 14th 1998 will also be eligible. Guidance will be issued asking doctors to aim to prescribe no more than one treatment / patient / week. Guidance on identification and management, within specialist services, of men suffering from severe distress due to impotence will be prepared by the Department of Health [1].</p> <p>Men who do not fall into these categories may receive private prescriptions from their GP, although GPs must not charge for writing them [1].</p>
<b>SECTOR OF USE</b>	Hospital [Y]                      Community [Y]
<b>NEW CLASS OF DRUG</b>	[Y]
<b>COST/COURSE</b>	£4.15, £4.84 and £5.88 per tablet for the 25mg, 50mg, and 100mg tablets respectively.
<b>TREATMENT ALTERNATIVES</b>	Cost of a single dose for a selection of products (NHS prescription of these products is also subject to the same restrictions as sildenafil).

## *Prices taken from MIMS July 1999*

Alprostadil intracavernosal injection; (Caverject™)	5 mcg	£6.74
	10mcg	£7.70
	20mcg	£9.95
	40mcg	£18.83
(Viridal™)	5mcg	£6.74
	10mcg	£7.70
	20mcg	£9.95
(Viridal Duo™) without applicator	10mcg	£8.47
	20mcg	£10.95
	40mcg	£13.93
Alprostadil direct urethral application; (MUSE™)	125mcg	£9.14
	250mcg	£9.95
	500mcg	£9.95
	1000mcg	£10.18

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## PHARMACOLOGY

Penile erection is dependent on the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO increases the levels of cyclic guanosine monophosphate (cGMP) which results in smooth muscle relaxation and inflow of blood. Sildenafil enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP in the corpus cavernosum. In the absence of sexual stimulation, sildenafil should have no effect on erectile function [2, 3].

Sildenafil may also inhibit PDE6 and, to a lesser extent, other phosphodiesterases. PDE6 is found in the retina and its inhibition may be the cause of the abnormalities in colour vision seen with higher sildenafil doses and plasma concentrations [2, 3].

## PHARMACOKINETICS

Sildenafil is rapidly absorbed after oral administration reaching maximum plasma concentration within 30-120 minutes of dosing in fasted subjects. It has a bioavailability of about 40% and fatty food has been shown to reduce the rate of absorption and the peak concentrations achieved, without affecting the extent of absorption. It is therefore advised that sildenafil is taken 30-60 minutes before planned sexual activity. One small study, which is only available as an abstract, has shown that sildenafil still has an effect on erectile function for 4-5 hours after dosing [4].

Sildenafil is mainly eliminated by hepatic metabolism (principally cytochrome P450 3A4) and converted to the active N-desmethyl metabolite, which accounts for about 20% of its overall pharmacological effect. Both sildenafil and the metabolite have terminal half-lives of about 4 hours and are excreted predominately in the faeces. No significant accumulation is expected to occur on single daily dosing. Studies have shown that renal insufficiency (creatinine clearance (CL<sub>cr</sub>) <30ml/min), hepatic insufficiency and age (over 65 years) are all associated with increased plasma concentrations when compared with matched controls. Sildenafil and its major metabolite are highly bound to plasma proteins [5, 6, 7].

## EFFICACY

Sildenafil offers an opportunity to treat male erectile dysfunction with an effective, licensed oral preparation. When this monograph was initially written, there were only two fully published, large trials of sildenafil in men with erectile dysfunction [8,9], although details of additional studies can be found in the addendum to this monograph. In the first trial, consisting of two separate studies, 532 men took part in a 24-week dose-response study, and 329 different men were enrolled in a 12-week, dose-escalation study of which 225 were then entered in a 32-week, open-label extension study. Patients were eligible if they had a clinical

diagnosis of erectile dysfunction for at least six months and were involved in a stable relationship with a female partner. As well as the usual clinical trial exclusions, men were excluded from participation if they had a penile anatomical defect, spinal cord injury, poorly controlled diabetes mellitus, active peptic ulcer disease, a recent stroke or myocardial infarction (MI), or were receiving nitrate therapy. Other erectile dysfunction therapies were discontinued four weeks before study medication was administered. Overall 70% of trial participants were judged to have organic ED, 11% psychogenic ED and 18% mixed ED at trial entry.

Outcomes were assessed using the responses to some of the questions in the validated assessment tool: the International Index of Erectile Function (IIEF). The IIEF was developed by Pfizer and validated using sildenafil. It is a self-administered questionnaire in which patients are asked to assess the status of erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction [10]. Patients were also asked to keep an event log in which they recorded details such as date and dose of medication taken, presence of sexual stimulation, hardness of erection achieved, whether sexual intercourse was successful and whether they felt the treatment improved their erection. Hardness of erection was graded on a four point scale; grade 3 and 4 considered hard enough for intercourse.

In the dose-response study, men were randomised to take 25, 50 or 100mg of sildenafil or placebo (no more than once daily) one hour before planned sexual activity for 24 weeks. Using the IIEF it was shown that increasing doses of sildenafil were associated with both increased frequency of penetration and maintenance of erection after penetration ( $p < 0.001$ ). The patients' event log showed that in the last four weeks of the study 72%, 80%, 85% and 50% of men receiving sildenafil 25mg, 50mg, 100mg and placebo respectively achieved erections hard enough for intercourse (i.e. grade 3 or 4;  $p < 0.001$  for all strengths of sildenafil vs. placebo). Successful sexual intercourse resulted after 80% of the grade 3 erections and 94% of the grade 4 erections. At the end of the 24-week study period, 56%, 77%, 84% and 25% of men receiving 25mg, 50mg, 100mg and placebo respectively reported having improved erections ( $p < 0.001$  for treatment effect).

In the dose-escalation study, men were initially randomised to take placebo or sildenafil 50mg, approximately one hour before sexual activity, for a 12-week period. At each follow up visit, doses were doubled or halved on the basis of therapeutic response and adverse effects. Men who completed the study without experiencing any serious adverse effects were eligible to receive open-label sildenafil for an additional 32 weeks. Again, using the IIEF, sildenafil was associated with statistically significant increases in frequency of penetration and maintenance of erection after penetration ( $p < 0.001$ ). The mean scores for the domains of erectile function, orgasmic function, intercourse satisfaction and overall satisfaction, assessed within IIEF, were also significantly higher in patients receiving sildenafil ( $p < 0.001$ ). Sexual desire was not significantly different between the

two groups ( $p=0.13$ ). The patients' event log showed that during the last four weeks of the study, 69% of all attempts at sexual intercourse were successful for men receiving sildenafil compared with 22% for men receiving placebo. This corresponds to a mean of 5.9 and 1.5 successful attempts respectively. Of the men who completed the global efficacy question, 74% of those receiving sildenafil and 19% of those receiving placebo reported improved erections ( $p<0.001$ ). This means that around 2 patients would need to be treated with sildenafil for 12 weeks for one patient to report improved erections (number needed to treat, NNT). It is not possible to determine the NNT for successful intercourse as the data is reported for episode rather than for individuals.

The second fully-published RCT was a multicentre, double-blind placebo-controlled study in 268 men with diabetes mellitus [9]. Patients were eligible if they had a clinical diagnosis of ED for at least 6 months and Type I diabetes for at least 5 years or type II diabetes for at least 2 years. Involvement in a stable relationship with a female partner and stability of medical management of diabetes were also necessary, with an  $HbA_{1c} < 0.12$  and fasting plasma glucose  $\leq 16.6$  mmol/l. The exclusion criteria were similar to the first study but also covered hypotension, hypertension, active proliferative diabetic retinopathy, severe autonomic neuropathy, ketoacidosis in the past 3 years and androgen treatment. Other erectile dysfunction therapies were discontinued at screening. After a four week run-in phase, patients were randomised to placebo or sildenafil 50mg no more than once daily, one hour before sexual activity, for 12 weeks. Based on the investigator's judgement of efficacy and tolerability, the dose could be increased to 100mg or decreased to 25mg. The primary endpoints were the responses to the IIEF questions assessing the ability to penetrate (question 3) and maintain an erection after penetration (question 4).

At 12 weeks, significant improvements were demonstrated in the ability to penetrate (question 3) and maintain an erection after penetration (question 4) with sildenafil compared to placebo ( $p<0.001$ ). These differences occurred regardless of age, duration of ED and duration of diabetes. Scores to the remaining questions of the IIEF also improved significantly with sildenafil. 56% of patients taking sildenafil reported improved erections compared with 10% taking placebo, and 61% had at least one successful attempt at intercourse with sildenafil compared to 22% with placebo ( $p<0.001$ ). Sexual desire did not differ between the two groups. The majority of patients (about 80%) in this study had type II diabetes; there were too few men with type I diabetes to allow adequate comparisons between these groups [9].

A much smaller two-phase study of sildenafil has also been published. This was undertaken in 12 patients with ED of at least 6 months duration [11]. Patients with known organic causes e.g. diabetes mellitus, hypertension or alcohol abuse were excluded. The first phase was a double-blind, placebo-controlled, hospital-based, four-way crossover trial in which patients received a single dose of sildenafil (10, 25 or 50mg) or placebo before undergoing visual sexual stimulation (VSS),

lasting two hours and starting 30 minutes after dosing. None of the patients had received other treatments for erectile dysfunction for at least two weeks before the start or throughout the study. Drug efficacy was evaluated by measuring penile rigidity (at base and tip) during periods of tumescence. In the 10 evaluable patients, it was shown that tumescence started within a few minutes of commencing VSS i.e. 30-40 minutes post-dosing. The mean duration of rigidity of greater than 80% at the base of the penis (in min.) was 1.3 (95% CI: 0.4-3.1), 3.5 (1.6-7.3;  $p=0.009$ ), 8.0 (3.7-16.7;  $p=0.003$ ) and 11.2 (5.6-22.3;  $p<0.001$ ) on placebo, 10mg, 25mg and 50mg sildenafil respectively. Significant changes from placebo were also seen for duration of rigidity at the tip of the penis for 10mg and 50mg ( $p=0.001$ ) and 25mg ( $p=0.002$ ) of sildenafil. Published evidence has suggested that a penile rigidity  $\geq 70\%$  is adequate for sexual intercourse [12, 13].

The second phase was a double-blind, randomised, placebo-controlled, home-based, two-way crossover study of single daily doses of sildenafil (25mg) or placebo for 7 days [11]. Patients recorded a significantly greater number of erections when taking sildenafil than with placebo. The mean (95% CI) total number of erections was 6.1 (3.2-11.4) vs. 1.3 (0.5-2.7) respectively ( $p=0.005$ ). Sildenafil was shown only to have a significant effect on the number of erections that occurred within 2 hours of dosing. The practical significance of the effect attributed to sildenafil i.e. the 6.2-9.9 minute prolongation of erection shown in this trial has been questioned [14]. In response, Boolell states that rigidity  $>80\%$  lasting over 20 minutes occurred in 6/12 patients receiving sildenafil and 0/12 receiving placebo [15]. The value of Rigiscan measures of radial rigidity to determine if an erection is sufficiently hard for vaginal intercourse was also disputed, as axial rigidity is a better indicator [14]. In defence, the authors state that radial rigidity is linearly related to axial rigidity, and there is presently no technique available to provide continuous measurement of the axial buckling force of the penis [15].

Other trials comparing sildenafil with placebo have been completed in various patient groups including patients with spinal injury. So far the results have only been presented in abstract form, so only brief details of methodology and results are available, and peer review is lacking. Brief details of most of these trials are outlined in Appendix 1. Trials are also underway in patients with multiple sclerosis, treated depression, diabetes and post-radical prostatectomy [16].

A meta-analysis of the double-blind, placebo-controlled studies, which used the IIEF to assess efficacy, indicate that sildenafil is effective in patients with ED who are diabetic, depressed or taking antihypertensives [17]. Another analysis indicates that the drug is as effective in patients aged 65 years or over as it is in younger patients [18]. Both these analyses are only available in abstract form.

From the trial data available, it would appear that around 70-80% of patients with ED respond to sildenafil by demonstrating a clinically significant improvement in sexual or erectile function, compared with about 25% on placebo.

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Most patients continue to take sildenafil on an ongoing basis. It should be noted that comparative studies with established treatments like intracavernosal injection of alprostadil have not been undertaken. Also, although sildenafil has been proven to be effective at increasing male patients' overall satisfaction with their sex lives, it has not yet been shown how this impacts on the patients, or their partners', overall quality of life. One abstract has indicated a statistically significant improvement in seven of eleven quality of life endpoints with up to 12 weeks of sildenafil treatment. However, the physical health summary showed a significant effect in favour of placebo, and details of the overall study are limited [19].

## PROMOTIONAL MATERIAL

Most safety and efficacy claims in the promotional material are well supported by the main published studies discussed in this document. However, occasionally statements are unclear. For example, the educational pack states "*an overall response rate of approximately 80% has been reported when using sildenafil to treat men with ED of various causes*". This may be ambiguous as no attempt is made to define what is meant by "response" and the study discussed [8] used various measures of response and efficacy. After discussion with the company we understand that this figure refers to the percentage of men who reported improved erections with 50 to 100mg sildenafil.

The hospital detail piece states that "*in patients for whom it works, Viagra is successful in four out of every five attempts*". This refers to data on file, which is not readily accessible but was supplied promptly to us on request from Pfizer.

The hospital and GP detail pieces and "Oral treatment for erectile dysfunction" document claim "*The discontinuation rate for Viagra was as low as 2.5% compared with 2.3% for placebo*". This refers to the discontinuation rate due to adverse effects in a study by Morales *et al* [20]. Although this statement is placed under 'safety profile', it may have been clearer to state "*discontinuation rate due to adverse effects*" as some readers may assume this was the total discontinuation rate for the drug. This study is also used to support claims that sildenafil has a "*good safety profile*" and that "*it's well tolerated*". However, it must be noted, as discussed in the editorial comment to this paper, that the long-term safety and efficacy profile of sildenafil, in terms of years, is still largely unknown.

The promotional material attempts to discourage recreational misuse and misconceptions of sildenafil, commonly presented by the media, by stating that the drug is not an aphrodisiac or fertility treatment and there is no data on its effects on erectile function in those without ED.

The education pack gives a non-biased and balanced view of all available treatments of erectile dysfunction and suggests alternative management strategies to consider before a pharmacological approach.

## ADVERSE EFFECTS

Morales *et al* have combined the data from 18 randomised controlled trials (involving a total of 2722 patients exposed to sildenafil and 1552 to placebo for up to six months) and 10 long-term open label studies (2199 patients for up to one year) [20]. The safety database for these 28 studies totalled 1631 patient years of sildenafil exposure. This calculation uses shorter duration of usage and does not enable determination of safety for repetitive use in an individual over longer periods of time. The flexible dose, placebo-controlled studies, where the drug is taken when required, may best reflect how the drug might be used in practice. In these studies, the most common adverse events reported by patients receiving sildenafil were headache (16% cf. 4% in placebo groups), flushing (10% cf. 1%), dyspepsia (7% cf. 2%), nasal congestion (4% cf. 2%), abnormal vision (3% cf. 0%), diarrhoea (3% cf. 1%), dizziness and rash (both 2% cf. 1%). The overall rate of discontinuation from treatment due to adverse events of all causes was 2.5% in sildenafil groups compared with 2.3% with placebo. In the fixed dose studies, the incidences of dyspepsia (17%) and abnormal vision (11%) were higher at 100mg than with lower doses of sildenafil. In the open label long term studies a similar toxicity profile is described with headache (10%), flushing (9%), dyspepsia (6%) and respiratory tract infection (6%) being most common. In this review, the incidence of serious cardiovascular events (MI, angina, and other coronary artery disorders) was comparable in patients who took sildenafil within placebo-controlled studies (4.1 events per 100 years of treatment), sildenafil in open-label studies (3.5) and in patients who took placebo (5.7). The abnormal vision described seems to mainly involve a colour tinge to vision, but may also include increased sensitivity to light or blurred vision. Within the flexible dose studies, only one patient has discontinued treatment because of visual effects. It must be borne in mind that because of the exclusion criteria of clinical trials, these data may not be a true reflection of safety in clinical practice.

The United States Food and Drug Administration (FDA) issued details of 69 deaths that occurred after taking sildenafil between March and July 1998, during which time 3.6 million prescriptions were dispensed [21]. Of these deaths, 46 were known to be due to cardiovascular events (MI, cardiac arrest, cardiac symptoms, coronary artery disease and severe hypotension). Fifty one patients had one or more risk factors for cardiovascular or cerebrovascular disease and 12 had been exposed to a nitrate or nitro-glycerine, during or after taking sildenafil. Consequently, details of these events and others (such as hypertension, anxiety, seizures, haematuria and ocular effects) reported post-marketing have been added to the US prescribing information [22]. It is not possible to determine 'expected' deaths from coronary heart disease over this period of time for the same population. There has been a recent report of acute MI in a patient taking sildenafil, without a history of previous chest pain or risk factors for cardiovascular disease [23]. Although consideration of a causal relationship was suggested, this is an isolated case and trials with large patient numbers are necessary to

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evaluate this. The updated US labelling states that it is not possible at present to determine whether the cardiovascular events are directly related to Viagra, sexual activity, the patients' underlying disease or a combination of these factors [22].

Although there were no reports of priapism in clinical trials [20], it has been reported in postmarketing surveillance [7].

As with any new drug, the long-term safety profile of sildenafil needs to be established.

## CONTRAINDICATIONS

Sildenafil is contraindicated in patients who are hypersensitive to the active substance or any of the excipients contained in Viagra™ and in patients concurrently using nitric oxide donors (e.g. amyl nitrite) or nitrates in any form, as the drug has been shown to potentiate their hypotensive effects. It is not recommended for use in combination with other treatments for erectile dysfunction as there are no safety and efficacy data available. Also patients should not be prescribed sildenafil if they have recently had a stroke or a heart attack, have low blood pressure, severe heart disorders or liver impairment, or certain rare inherited eye diseases (e.g. retinitis pigmentosa). The drug is contraindicated under 18 years of age [7].

## PRECAUTIONS

Sexual activity is associated with a degree of cardiac risk and prescribers may wish to consider the cardiovascular status of the patient before initiating any treatment for ED. It should not be used in men for whom sexual activity is inadvisable e.g. those with severe cardiovascular disorders such as unstable angina or severe heart failure. In addition, the hypotensive effect (although usually mild and transient) should be considered. Similarly, such agents should be used with caution in patients with anatomical deformation of the penis and in patients predisposed to priapism (e.g. sickle cell anaemia, multiple myeloma, or leukaemia) [7].

Caution should be taken in patients taking drugs or other substances that inhibit the cytochrome P450 isoform 3A4, which is the major route of sildenafil metabolism. It has been shown that drugs such as cimetidine, ketoconazole and erythromycin will reduce sildenafil clearance and could predispose to the dose-related adverse effects described above [7]. A starting dose of 25mg should be considered in patients where clearance may be reduced due to renal failure (CL<sub>cr</sub><30ml/min), hepatic impairment, concomitant drug therapy or in elderly patients [7]. The European Agency for the Evaluation of Medicinal Products (EMA) has recently approved amendments to the Summary of Product Characteristics (SPC) after findings of increased sildenafil plasma concentrations with ritonavir, a protease inhibitor. The changes are to include advice to avoid co-administration

of sildenafil with ritonavir. If sildenafil must be prescribed for a patient on ritonavir, the maximum dosage of sildenafil must not exceed 25mg in 48 hours. As with other cytochrome P450 3A4 inhibitors, a starting dose of 25mg of sildenafil should be considered for patients taking other HIV protease inhibitors, including saquinavir [24].

As sildenafil has been reported to cause dizziness and altered vision, patients should be advised to be aware of how they might react to the drug before driving or operating machinery. They should also be cautioned to seek medical attention should they have an erection which lasts continuously for more than four hours. For more information please consult the SPC [7].

## ADDENDUM

Additional data, received immediately prior to completion of this bulletin, relate to the effects of sildenafil in special categories of patients. In subjects with spinal injury, 50mg sildenafil significantly enhanced erectile response to vibratory stimuli in 17 of 26 subjects compared with only two of 26 given placebo (p<0.01). In a domestic setting, nine of 12 such subjects given sildenafil and one of 14 given placebo, reported an improvement in erection (p<0.005). No significant difference emerged between the active and placebo groups with respect to the mean number of erections hard enough for penetration, or the mean proportion of successful attempts at intercourse. (The authors attributed this apparent lack of efficacy of sildenafil to a statistical artefact i.e. closure of sequential analysis of the primary response variable) [37]. Further work, reported in abstract form, has endorsed the potential value of sildenafil in spinal injury subjects [38]. More study is needed.

An open and uncontrolled study examined response to sildenafil in 50 men aged 54 to 78, following radiotherapy for prostatic cancer. Improvement in erectile function was seen in 37, partial improvement in two and no improvement in 11. The most important predictor of response to sildenafil was the extent of impaired sexual response before its use. Of 29 subjects with pre-existing partial erections, 26 had a significant response to sildenafil treatment compared with 11 of 21 of those with flaccid erections (p=0.02) [39].

An abstract of a two year study of sildenafil use reported that among 365 men (many of whom had a past or present history of cardiovascular disease) who completed the study, 93% were satisfied with their erectile responses. Only four patients withdrew because of side-effects. The abstract also provides a summary of 43 studies showing an overall incidence of MI of 0.84/100 patient years (95% CI 0.63-1.11) from a total of 6053 patient years exposure to sildenafil. For placebo subjects, the incidence was 1.05/100 patient years (95% CI 0.34-2.46) [40].

This suggestion of a lack of significant adverse cardiological effect has been endorsed by a recently published literature overview [41] and by a study which included 357 men with a

past or present history of ischaemic heart disease not taking nitrates [42]. The warning that underlying cardiovascular disease might be adversely affected by the vasodilator effects of sildenafil, especially in combination with sexual activity, is reiterated by the authors of this study.

Use of sildenafil in depressed subjects, led to improved erections in 91% (n=74) compared with 11% of those given placebo (n=78) [43].

Use of the International Index of Erectile Function (IIEF) to assess response to flexible dosing with sildenafil in broad-spectrum erectile dysfunction (n=57, revealed values significantly greater than in placebo subjects (n=54) ( $p < 0.01$ ) and approaching those of normal controls (n=109). The IIEF is a categorical five point assessment; calculation of average scores to two places of decimals might give a false illusion of assessment precision [44].

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Author and Ref	Protocol	Outcome Measures	Main Results
Christiansen E. <i>et al</i> [25] Viraj R. <i>et al</i> [26]	A 16 week open-label dose finding study of sildenafil in 233 patients with predominately no known organic cause for their ED [25]. In an 8 week follow up study 205 patients were randomised to take their optimum dose or placebo when required [26].	Patients were asked if sildenafil improved their erections and % patients taking each strength of sildenafil tested at the end of the study was recorded. Patients were asked to compare the erections they achieved on their allocated drug with those they achieved previously on open label sildenafil.	At the end of the study 2%, 11%, 29% and 58% of patients were taking 10mg, 25mg, 50mg and 100mg sildenafil respectively. 93% of evaluable patients thought that sildenafil improved their erections. 23% and 86% of those who received sildenafil and placebo respectively thought their erections were slightly or much worse than when they received open label drug.
Gingell <i>et al</i> [27] Buvat <i>et al</i> [28]	A double-blind, placebo-controlled study in which 351 patients with no known organic cause for their ED were randomised to receive placebo, 10mg, 25mg, or 50mg of sildenafil once daily for 28 consecutive days [27]. 317 patients elected to receive open-label therapy for a further 12 months, although only 311 were eligible to receive treatment [28].	Patients were asked to rate frequency, hardness and duration of erection, quality of sex life and record number of satisfactory intercourse attempts. In the follow up study, the number of patients who elected to remain on therapy was recorded.	Dose response relationships were shown for all measures of efficacy. A described improvement in erections was reported in 38%, 65%, 79% and 89% of patients taking placebo, 10mg, 25mg and 50mg sildenafil respectively ( $p < 0.001$ ). After 12 months 87.1% of patients recruited were still taking sildenafil. Similar dose-response relationships were discovered for number of satisfactory intercourses.
Cuzin B <i>et al</i> [29]	A double-blind study in which 315 patients with ED of mixed aetiology were randomised to flexible dose sildenafil (25-100mg) or placebo for six months.	Efficacy was assessed by IIEF questionnaire and a global efficacy question.	At end of study period: 79% of sildenafil and 23% of placebo recipients reported improved erections ( $p < 0.0001$ ). IIEF questions on the ability to penetrate and maintain erections indicated that sildenafil was significantly better than placebo ( $p < 0.0001$ ).
Young JM <i>et al</i> [30]	329 patients with ED of mixed aetiology were randomised to flexible dose sildenafil (25 -100mg) or placebo for 12 weeks.	Efficacy was assessed using the IIEF, a global efficacy question and a partner survey.	Statistically significant improvements in response to questions assessing frequency of penetration and frequency of maintained erection were seen in patients receiving sildenafil compared with placebo and these results were corroborated by the partner questionnaire results. 74% of sildenafil patients felt that the drug improved their erections compared with 16% of placebo patients ( $p < 0.0001$ ).
Abel P <i>et al</i> [31]	A double-blind, placebo-controlled study in which 111 patients with ED were randomised to flexible dose sildenafil (25-100mg) or placebo for 12 weeks.	Response assessed using IIEF at baseline and at week 12. 109 age-matched healthy controls also completed IIEF.	81% of sildenafil recipients and 18% placebo recipients reported improved erections ( $p < 0.0001$ ). The various aspects of sexual intercourse showed greater mean IIEF scores with sildenafil than placebo ( $p < 0.0001$ ). A "near normalisation" in these domains was noted for patients receiving sildenafil compared with age-matched controls.
Lue TF [32]	A double-blind, placebo-controlled study in which 416 patients with ED of mixed aetiology were randomised to receive sildenafil (5, 25, 50, or 100mg) or placebo for 8 weeks.	Efficacy assessed using IIEF and a global assessment question at week 8.	The results suggested a trend between the perceived ability to achieve and maintain an erection and the dosage of sildenafil administered. It is stated that the other aspects of erectile and sexual function assessed by IIEF also demonstrated a dose-response relationship.
Giuliano F <i>et al</i> [33] Hultling C <i>et al</i> [34] Hultling C <i>et al</i> [35]	A double-blind, placebo-controlled study in which 178 patients with ED caused by traumatic spinal cord injury were randomised to receive flexible dose sildenafil (25-100mg) or placebo in a two-way crossover study. Each treatment period lasted six weeks and was followed by a 2 week wash out period.	Efficacy was assessed using the IIEF and event log data to record % successful attempts at intercourse. The patients' partners were also asked to assess the trial participants' ability to achieve and maintain erections. Quality of life (QOL) of trial participants was assessed using a battery of QOL assessment tools.	83% of sildenafil recipients reported improved erections and preferred sildenafil to placebo ( $p < 0.001$ ) and 80% thought it improved their ability to have sexual intercourse compared with 10% for placebo ( $p < 0.0001$ ). The median % of successful attempts at intercourse was 55% for sildenafil and 0% for placebo ( $p < 0.0001$ ). Partners' perceptions of the efficacy of sildenafil corroborated the results described above. Statistically significant improvements in some aspects of QOL were seen using some tests of QOL but no statistically significant improvement was seen using other measures.
Boolell M <i>et al</i> [36]	21 diabetic patients took part in a two-phase study (with a similar methodology to study [11] see main text).	Duration of penile rigidity > 60% was measured using a RigiScan (during VSS following a single dose) and in the 10 day follow up study patients were asked to assess improvement in erection.	The mean duration of rigidity at the base of the penis >60% was 1.5, 2.4, and 7.2 minutes in patients receiving placebo, 25mg and 50mg sildenafil respectively. In the follow up study the mean number of erections sufficiently rigid for sexual intercourse were 0.7, 1.7 and 1.9 and the % patients reporting improvement in the quality of erections were 10%, 48% ( $p = 0.001$ ) and 52% ( $p = 0.002$ ) respectively.