Systematic review of randomised controlled trials of sildenafil (Viagra®) in the treatment of male erectile dysfunction

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SUMMARY

Background: *Sildenafil (Viagra®), a new oral drug for the treatment of erectile dysfunction, was licensed for use across Europe in 1998.*

Aim: *To examine the effectiveness and safety of sildenafil as an oral treatment for erectile dysfunction.*

Design of study: *Systematic review and meta-analysis.*

Setting: *All published or unpublished randomised controlled trials comparing sildenafil with a placebo or alternative therapies.*

Method: *Published studies were sought by computerised searches of electronic databases using the keywords 'sildenafil' and 'Viagra'. A hand search was also done of the British Medical Journal, Lancet, Journal of the American Medical Association, New England Journal of Medicine, British Journal of General Practice, Drug, Inpharma and Scrip. An assessment of quality of all identified studies and data extraction was undertaken independently by two researchers. Results were combined in a meta-analysis where appropriate, using RevMan version 3.*

Results: *Twenty-one trials were identified. All trials showed a statistically significant improvement in erectile or sexual function in patients using sildenafil compared with a placebo. A meta-analysis of 16 trials reporting a global efficacy response showed that men were 3.57 (95% CI = 2.93–4.43) times as likely to have improved erections on sildenafil compared with those on a placebo. The number needed to treat to have one man with improved erections was two. The drug has a relatively safe side-effect profile.*

Conclusions: *Available research shows that sildenafil is an effective treatment for male erectile dysfunction. Many trial participants had some baseline erectile function and it is probable that in clinical practice, where the erectile function tends to be more impaired, the number needed to treat may be higher.*

Keywords: *erectile dysfunction; sildenafil; Viagra® impotence; randomised controlled trial; meta-analysis.*

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Submitted: 29 February 2000; Editor's response: 13 June 2000; final acceptance: 22 May 2001.

Introduction

ERECTILE dysfunction (ED) is the persistent or recurrent inability to attain an adequate erection or to maintain one until completion of sexual activity.[1,2] It may range from a partial decrease in penile rigidity or ability to sustain an erection, to complete erectile failure.[3] ED affects approximately 9% of adult males.[4] Sildenafil (Viagra®), a new oral drug specifically for the treatment of ED, was licensed for use across Europe in 1998. This review looks at the effectiveness and safety of sildenafil for the treatment of male ED.

The normal erection is a complex event resulting from the co-ordinated function of a number of psychological, neurological, hormonal, and vascular systems. Disturbance of any of these can lead to ED. It can be organic (where there is a clear physical cause), of no established organic cause, psychogenic (of established psychological origin), or of mixed aetiology.

Treatment options include psychological management, vacuum constriction devices, intracavernosal injections, transurethral drug delivery, penile prostheses, vascular surgery, and modification of medication contributing to the problem.[5] Many of these treatments have limited acceptability to users. The ideal goal in the treatment of ED is the restoration of erectile capacity using a minimally invasive and safe treatment. As a rule, the least invasive or dangerous procedures should be tried first.[2]

Sildenafil is the first oral drug to be marketed specifically for the treatment of ED. It is a selective inhibitor of Type 5 phosphodiesterase, which breaks down cyclic guanosine monophosphate (cGMP), a second messenger that amplifies the parasympathetic neural stimulation. By inhibiting the breakdown of cGMP, sildenafil augments the effect of nitric oxide, which is released in response to sexual stimulation to produce smooth muscle relaxation in the corpora cavernosa and then engorgement of the penis. It does not have a direct effect on libido or smooth muscle. Thus, sildenafil enables an erection rather than directly producing one, and it is ineffective in the absence of arousal.

Method

All published or unpublished randomised controlled trials comparing sildenafil with a placebo or alternative therapies were sought. Published studies were sought by computerised searches of electronic databases (MedLine, EMBASE, PsychLIT, Cochrane Library, National Research Register, Pharmline, PreMedline) in June 1999, using the keywords 'sildenafil' and 'Viagra'. There were no language restrictions. Internet search engines were used with the terms 'sildenafil' and 'Viagra'. In addition, a hand search was

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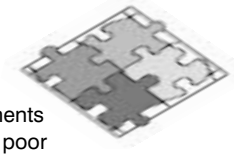

What do we know?

Prior to the launch of sildenafil, treatments formale erectile dysfunction (ED) had poor patient acceptability and low take-up, even when effective.

What does this paper add?

Sildenafil is a novel treatment for ED. This paper systematically reviews the available trial evidence and shows that sildenafil is an effective treatment for ED with a relatively safe side-effect profile. No head-to-head comparisons with other treatments were available at the time that this review was undertaken.

done of the *British Medical Journal, Lancet, Journal of the American Medical Association, New England Journal of Medicine, British Journal of General Practice, Drug, Inpharma* and *Scrip* up to January 1999. A key source of information was the Food and Drug Administration (FDA) Center for Drug Evaluation and Research Joint Clinical Review for NDA-20-895 Viagra® (Sildenafil).[6] Pfizer Ltd was contacted, as were experts in the field. References of all relevant studies were searched for further trial citations. The Science Citation Index was searched using all the studies identified.

An assessment of quality of all identified studies and data extraction was undertaken independently by two researchers, and they looked at concealment of allocation, blinding, losses to follow-up and intention-to-treat analysis. Discrepancies were resolved by discussion. Sildenafil is a new drug and all trials prior to its being licensed were sponsored by the drug company Pfizer. Where trials were only available in abstract form, further information was requested from Pfizer.

Q3: Over the past four weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?

Q4: Over the past four weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

Responses were scored on the following scale:
[0] Did not attempt intercourse
[1] Almost never or never
[2] A few times (much less than half the time)
[3] Sometimes (about half the time)
[4] Most times (much more than half the time)
[5] Almost always or always

Box 1. Questions from the International Index of Erectile Function (IIEF).

Primary outcome was defined as sexual function, as measured by questions 3 and 4 (Q3 and Q4) of the International Index of Erectile Function (IIEF). The IIEF is a questionnaire consisting of 15 items designed to measure sexual and erectile function (Box 1). It was specifically developed and validated to evaluate sildenafil.[7] Question 3 asks 'Over the past four weeks, when you have attempted sexual intercourse how often were you able to penetrate (enter) your partner?' Question 4 asks 'Over the past four weeks, during sexual intercourse, how often were you able to maintain your erection after you have penetrated (entered) your partner?' Responses are rated on a five-point ordinal scale. Zero is scored when responders did not attempt intercourse.

Secondary outcomes were composed of other questions on the IIEF, the global efficacy question 'Did treatment improve your erections?', measures of penile rigidity, an event log (of attempted and successful intercourse), and a partner questionnaire.

Results were combined in a meta-analysis where appro-

Comparison: 05 Sildenafil compared with placebo
Outcome: 01 Global Efficacy Question

Study	Experiment *n/N*	Control *n/N*	Risk difference (95% CI Random)	Weight %	Risk difference (95% CI Random)
101	202/310	22/74		6.6	0.354 (0.237 –– 0.471)
102	209/293	53/194		8.0	0.440 (0.359 –– 0.521)
103	101/136	23/141		7.5	0.580 (0.484 –– 0.675)
104	74/131	13/127		7.3	0.463 (0.363 –– 0.562)
106	262/338	27/108		7.5	0.525 (0.432 –– 0.618)
351	10/12	2/12		2.4	0.667 (0.368 –– 0.965)
353	186/242	35/91		6.8	0.384 (0.217 –– 0.497)
355	36/44	10/44		4.9	0.591 (0.423 –– 0.759)
356	81/99	28/106		6.8	0.554 (0.441 –– 0.667)
357	11/21	2/21		3.1	0.429 (0.181 –– 0.676)
358	18/27	2/27		4.0	0.593 (0.389 –– 0.796)
359	42/52	7/39		5.1	0.628 (0.467 –– 0.789)
361	128/167	6/47		6.7	0.639 (0.524 –– 0.754)
363	117/142	29/121		7.3	0.584 (0.486 –– 0.683)
364	276/359	27/114		7.7	0.532 (0.443 –– 0.621)
367	142/175	21/174		8.2	0.691 (0.615 –– 0.766)
Total (95% CI)	1895/2548	307/1440		100.0	0.537 (0.484 –– 0.589)

χ^2 = 49.17 (df = 15); Z = 19.88

-1 0 1
Favours control Favours treatment

Figure 1. Meta-analysis of results for global efficacy question.

Table 1. All Phase II and Phase III trials identified.

Study ID, location, and date	Source of information	Study design	Duration	*n*	Treatment	Outcomes measured	Cause of ED in trial participants	Patient characteristics
Phase II trials to evaluate penile rigidity								
105 USA Multi-centre 1996	FDA NDA-20-895[6]	4-period crossover 1-week washout	1 dose	54 54 53 53	Placebo Sildenafil 25 mg Sildenafil 50 mg Sildenafil 100 mg	Duration of ≥60% rigidity Duration of ≥80% rigidity	Broad aetiology (excluding spinal cord injury)	Mean age between 51–55 Mean duration of ED not reported
350 UK Single-centre 1993	FDA NDA-20-895[6]	2-period crossover 1-week washout	7 days	16 16	Placebo Sildenafil 25 mg	Duration of >60% rigidity Duration of >80% rigidity Event log	No established organic cause	Mean age not reported Mean duration of ED not reported
351 (Part I) UK Single-centre 1994	FDA NDA-20-895[6] Boolell *et al* 1996[9]	4-period crossover ≥3-day washout	1 dose	12 12 12 12	Placebo Sildenafil 10 mg Sildenafil 25 mg Sildenafil 50 mg	Duration of >60% rigidity Duration of >80% rigidity	No established organic cause	Mean age = 48 (range = 36–63) Mean duration of ED = 3.4 years
357 (Part I) UK Multi-centre 1994/95	FDA NDA-20-895[6] Price DE *et al* 1998[21]	3-period crossover 3–10 day washout	1 dose	21 21 21	Placebo Sildenafil 25 mg Sildenafil 50 mg	Duration of >60% rigidity Duration of >80% rigidity	Diabetes	Mean age = 50 (range = 29–66) Mean duration of ED = 3 years (range = 1–14) Diabetes >5 years
358 (Part I) UK Multi-centre 1995/96	FDA NDA-20-895[6] Maytom MC *et al* 1999[22]	2-period crossover 3–7 day washout	1 dose	27 27	Placebo Sildenafil 50 mg	Duration of >60% rigidity	Spinal cord injury (cord level range T6-L4/5)	Mean age = 33 (range = 21–49) Mean duration of ED = 6 years. Erectile response to vibrator
360 UK Single-centre 1995/96	Eardley *et al* 1997[27] (abstract) Boolell *et al* 1996[28] (abstract)	2-period crossover ≥1-week washout	1 dose	17 17	Placebo Sildenafil 50 mg	Duration of >60 % rigidity	No established organic cause	No established Mean age = 52 (range = 36–70) Median duration of ED = 1.5 years
369 UK Single-centre 1996	FDA NDA-20-895[7]	4-period crossover ≥1-week washout	1 dose	16 16 16 16	Placebo Sildenafil 100 mg Placebo Sildenafil 100 mg	Duration of >60% rigidity 4 hours after dose Duration of >60% rigidity 2 hours after dose	No established organic cause	Mean age = 55 years Mean duration of ED = 4.5 years
166-301 1995	Pfizer study report	3-period crossover ≥ 3-day washout	1 dose	10 10	Placebo Sildenafil 50 mg	Duration of >60% rigidity	No established organic cause	Age range = 32–69 ED for 3 months or more
Phase II and III trials with clinical outcomes								
101 USA Multi-centre 1995/96	FDA NDA-20-895[7] Leu *et al* 1997[15] (abstract)	Fixed dose Parallel group 2-4 week treatment-free run in	24 weeks	83 86 82 83 82	Placebo Sildenafil 5 mg Sildenafil 25 mg Sildenafil 50 mg Sildenafil 100 mg	Sexual function questionnaire Event log Partner questionnaire	Broad aetiology (excluding spinal cord injury)	Mean age = 57.6 years Mean duration of ED = 4.6 years
102 USA Multi-centre 1995/96	FDA NDA-20-895[7] Goldstein *et al* 1998[8] Pfizer study report	Fixed dose Parallel group 4-week treatment-free run in	24 weeks	216 102 107 107	Placebo Sildenafil 25 mg Sildenafil 50 mg Sildenafil 100 mg	IIEF Global efficacy question Quality of life questionnaire Partner questionnaire Pharmacokinetic data	Broad aetiology (excluding spinal cord injury)	Mean age = 57.6 years Mean duration of ED = 3.2 years

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Table 1 (continued). All Phase II and Phase III trials identified.

Study ID, location, and date	Source of information	Study design	Duration	*n*	Treatment	Outcomes measured	Cause of ED in trial participants	Patient characteristics
103 USA Multi-centre 1996	FDA NDA-20-895[7] Goldstein *et al* 1998[8] Pfizer study report	Variable dose Parallel group 4-week treatment-free run in	12 weeks	166 163	Placebo Sildenafil 25–100 mg	IIEF Global efficacy question Quality of life questionnaire Partner questionnaire Pharmacokinetic data	Broad aetiology (excluding spinal cord injury)	Mean age = 59.5 years Mean duration of ED = 4.8 years
104 USA Multi-centre 1996	FDA NDA-20-895[7] Rendell *et al* 1999[16] Pfizer study report	Variable dose Parallel group 4-week treatment free run in	12 weeks	132 136	Placebo Sildenafil 50–100 mg	IIEF Global efficacy question Quality of life questionnaire Partner questionnaire Pharmacokinetic data	Diabetes	Mean age = 57 years Mean duration of ED = 5.6 years Mean duration of diabetes = 12.1 years 18.7% type 1, 81.3 % type 2 diabetes
106 Canada Multi-centre 1996/97	FDA NDA-20-895[7] Pfizer study report	Fixed dose Parallel group 4-week treatment-free run in	12 weeks	122 127 124 124	Placebo Sildenafil 50 mg Sildenafil 100 mg Sildenafil 200 mg	IIEF Global efficacy question Quality of life questionnaire Partner questionnaire Pharmacokinetic data	Broad aetiology (excluding spinal cord injury)	Mean age = 58 years Mean duration of ED = 5.4 years
351 (Part II) UK Single centre 1994	FDA NDA-20-895[7] Boolell *et al* 1996[9]	2-period crossover 7-day washout	7 days	12 12	Placebo Sildenafil 25 mg	Patient diary	No established organic cause	Mean age 48 = (range = 36–63) Mean duration of ED = 3.4 years
353 Europe Multi-centre 1994/95	FDA NDA-20-895[7] Dinsmore *et al* 1996[17] (abstract)	Fixed dose Parallel group 2-week treatment-free run in	4 weeks	95 90 85 81	Placebo Sildenafil 10 mg Sildenafil 25 mg Sildenafil 50 mg	Sexual function questionnaire Global efficacy question Event log	No established organic cause	Mean age = 53 years Mean duration of ED = 4.5 years
355 UK Multi-centre 1994/95	FDA NDA-20-895[7] Eardley *et al* 1996[18] (abstract)	Variable dose crossover 3-week treatment-free run in	4 weeks X 2 no washout	43 44	Placebo Sildenafil 25–75 mg	Global efficacy question Event log	No established organic cause	Mean age = 53 years Mean duration of ED = 3 years
356 Europe Multi-centre 1994/95	FDA NDA-20-895[7] Bailey *et al* 1997[19] (abstract) Virag *et al* 1996[20] (abstract)	Variable dose Parallel group	8 weeks	106 99	Placebo Sildenafil 10–100 mg	Sexual function questionnaire Global efficacy question Event log	Broad aetiology	Mean age = 54 years Mean duration of ED = 4.9 years
357 (Part II) UK Multi-centre 1994/95	FDA NDA-20-895[7] Price *et al* 1998[21]	3 – period crossover 3 – 10 day washout	10 days	21 21 21	Placebo Sildenafil 25 mg Sildenafil 50 mg	Global efficacy question Event log	Diabetes	Mean age = 50 (range = 29-66) Mean duration of ED = 3 years (range = 1-14). Diabetes >5 years
358 (Part II) UK Multi-centre 1995/96	FDA NDA-20-895[7] Maytom MC *et al* 1999[22]	Fixed dose Parallel group	4 weeks	14 12	Placebo Sildenafil 50 mg	Sexual function questionnaire Global efficacy question Event log Partner questionnaire	Spinal cord injury (cord level range T6-L4/5)	Mean age = 33 (range 21-49) Mean duration of ED = 6 years. Erectile response to vibrator
359 UK Multi-centre 1995/96	FDA NDA-20-895[7] Abel *et al* 1997[12] (abstract) Pfizer study report	Variable dose Parallel group 2–4 treatment-free run in period	12 weeks	54 57	Placebo Sildenafil 25–100 mg	IIEF Global efficacy question Event log	Broad aetiology	Mean age = 56 years Mean duration of ED = 4.5 years

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Table 1 (continued). All Phase II and Phase III trials identified.

Study ID, location and date	Source of information	Study design	Duration	*n*	Treatment	Outcomes measured	Cause of ED in trial participants	Patient characteristics
361 Australia Multi-centre 1996	FDA NDA-20-895[7] Pfizer study report	Fixed dose Parallel group 2-week treatment-free run in	12 weeks	59 62 66 67	Placebo Sildenafil 50 mg Sildenafil 100 mg Sildenafil 200 mg	IIEF Global efficacy question Event log	Organic aetiology (excluding spinal cord injury)	Mean age = 57 years Mean duration of ED = 5.2 years
363 Europe Multi-centre 1995/96	FDA NDA-20-895[7] Cuzin *et al* 1997[13] (abstract) Pfizer study report	Variable dose Parallel group 4-week treatment-free run in	26 weeks	156 159	Placebo Sildenafil 25–100 mg	IIEF Global efficacy question Event log Quality of life questionnaire Partner questionnaire	Broad aetiology	Mean age = 54.5 years Mean duration = 4.8 years
364 Europe Multi-centre 1996	FDA NDA-20-895[7] Pfizer study report	Fixed dose Parallel group 4-week treatment-free run in	12 weeks	127 128 132 127	Placebo Sildenafil 25 mg Sildenafil 50 mg Sildenafil 100 mg	IIEF Global efficacy question Event log Quality of life questionnaire Partner questionnaire Pharmacokinetic data	Broad aetiology	Mean age = 55.8 years Duration of ED = 4.8 years
367 Europe & Australia Multi-centre 1996/97	FDA NDA-20-895[7] Giuliano *et al* 1999[14]	Variable dose crossover 4-week treatment -free run in	6 weeks X 2 separated by a 2-week washout	178 178	Placebo Sildenafil 25–100 mg	IIEF Global efficacy question Event log Quality of life questionnaire Partner questionnaire	Spinal cord injury	Mean age = 38 years Mean duration of ED = 11 years

priate, using RevMan version 3.

Results

Number of studies

Twenty randomised controlled trials comparing sildenafil with a placebo were identified. One further trial compared the efficacy of sildenafil with an alternative compound. The placebo trials appear in abstract form in the Center for Drug Evaluation and Research Joint Clinical Review on Viagra® (Sildenafil) NDA-20-895.[6] Of these, only three studies were published in full at the date of searching.[8,9] Pfizer provided further information in the form of trial protocols and unpublished study reports.

Two Phase II Japanese studies exist, one involving 60 patients and one involving 250 patients, but they have not been included, as no outcome data are available.[4]

Type of studies

Trials are described in Table 1. Eight Phase II trials and 13 Phase III trials are included. Fourteen are fixed-dose and seven are titrated-dose studies. They involved approximately 4000 men with ED, of whom over 3000 received sildenafil. There is a discrepancy in the numbers between the two groups because the dose titration studies had two, three or four sildenafil arms and one placebo arm. All trials enrolled only adult males with ED of more than six months' duration, who were in stable heterosexual relationships of more than six months' duration. Exclusion criteria included: deformity; elevated prolactin or low free testosterone; major uncontrolled psychiatric disorders; history of major haematological, renal or hepatic disorder; stroke; myocardial infarction; cardiac failure; unstable angina; electrocardiogram ischaemia or life-threatening arrhythmia within six months; blood pressure outside the range of 90/50 to 170/100 mmHg; active peptic ulcer disease or bleeding disorder; or a need for anticoagulants, nitrates or trazodone.

Quality of studies

All trials were randomised, double-blind and placebo-controlled. More than 80% of patients completed these studies. Data on withdrawals are not consistently reported. Both treatment-related adverse events and insufficient response were responsible for less than 5% of withdrawals. Intention-to-treat analysis was conducted for all outcomes for all randomised patients who had undergone at least one post-randomisation assessment. All these analyses were last observation carried forward.

Questions 3 and 4 of the IIEF were primary endpoints for most studies. The data obtained from these questions were analysed as continuous data, with means calculated including zero (where no attempt at intercourse occurred), making interpretation of findings difficult.

Effectiveness

Sixteen trials measured the primary outcome of sexual function. Table 2 gives the results for all studies using Q3 and Q4 of the IIEF as an endpoint. Table 3 shows the results for trials reporting other clinical endpoints. All trials showed a statistically and clinically significant treatment effect with silde-

Table 2. Results from trials measuring erectile function using IIEF Q3 & Q4.

Study ID	Study design	Date of Measurement	Treatment	IIEF Q3 (frequency of penetration)	*P*-value	IIEF Q4 (maintenance of erection)	*P*-value
102	Fixed dose Parallel group	24 weeks	Placebo	2.2	<0.0001	2.1	<0.0001
			Sildenafil 25 mg	3.2		3.1	
			Sildenafil 50 mg	3.5		3.5	
			Sildenafil 100 mg	4.0		3.9	
103	Variable dose Parallel group	12 weeks	Placebo	2.3	<0.0001	1.8	<0.0001
			Sildenafil 25–100 mg	3.9		3.6	
104	Variable dose Parallel group	12 weeks	Placebo	2.0	<0.0001	1.6	<0.0001
			Sildenafil 50–100 mg	3.2		2.9	
106	Fixed dose Parallel group	12 weeks	Placebo	2.2	<0.0001	1.7	<0.0001
			Sildenafil 50 mg	3.5		3.2	
			Sildenafil 100 mg	3.7		3.6	
			Sildenafil 200 mg	3.5		3.4	
361	Fixed dose Parallel group	12 weeks	Placebo	1.9	<0.0001	1.9	<0.0001
			Sildenafil 50 mg	3.4		3.3	
			Sildenafil 100 mg	3.7		3.7	
			Sildenafil 200 mg	3.7		3.7	
363	Variable dose Parallel group	24 weeks	Placebo	2.2	<0.0001	2.1	<0.0001
			Sildenafil 25–100 mg	3.7		3.6	
364	Fixed dose Parallel group	12 weeks	Placebo	2.2	<0.0001	2.0	<0.0001
			Sildenafil 25 mg	3.2		3.0	
			Sildenafil 50 mg	3.7		3.4	
			Sildenafil 100 mg	3.8		3.6	
367	Variable dose Crossover	6 weeks	Placebo	2.2	<0.0001	1.7	<0.0001
			Sildenafil 25–100 mg	3.8	3.6		

nafil. Increasing improvement was apparent with increasing doses over the range of 25 to 100 mg. One study evaluated a 5 mg dose and one a 200 mg dose. There is less response to 5 mg sildenafil than to larger doses. The data are too limited to indicate whether an improved response can be expected with 200 mg compared with 100 mg.

Data on the global efficacy question is available for 16 trials (Figure 1). In all trials, improvements in erections were reported with sildenafil treatment compared with a placebo. These improvements were statistically significant. Overall, men were 3.57 (95% CI = 2.93–4.34) times as likely to experience improvement on sildenafil. The summary risk difference for all 16 trials was 0.537 (95% CI = 0.484–0.589). The number of men needed to treat with sildenafil for one additional man to experience an improvement in his erections is two (number needed to treat = 1/absolute risk reduction = 1/0.537 = 1.86). As with the primary outcome measures, a dose–response relationship was seen over the dose range of 25 mg to 100 mg.

Eight Phase II trials measured penile rigidity during sexual stimulation following drug administration. They were small trials (n = 173), and most have not been published in full, which prevented further evaluation. Small losses to follow-up were not large enough to alter the conclusions significantly. The results of these trials are summarised in Table 4. Rigidity of 70% of maximal is considered adequate for sexual intercourse, while rigidity of less than 60% is an indication of organic impotence.[11] In all studies an increased duration of rigidity greater than 60% is seen with increasing doses of sildenafil compared with a placebo. Where stated, this increase was statistically significant. The clinical significance of these results is difficult to quantify, but the trial results are consistent with other findings.

Where data are presented, statistically significant (P<0.01) dose-related increases in the mean scores to the other questions on the IIEF were seen with sildenafil treatment compared with a placebo, except for the questions relating to desire, where no treatment effect was seen.[6,8,12-14]

Event log outcome data are inconsistently presented. Data from fixed-dose trials show a dose response in the proportion of successful attempts at intercourse from between 13% to 24% with a placebo, to 38% with sildenafil 25 mg, and 50% with sildenafil 100 mg.[6] In the dose-titration studies, 0% to 25% of attempts at intercourse were successful with a placebo compared with 50% to 60% with sildenafil.[6,8,14] Where reported, this improvement was statistically significant. Six studies presented data on the mean number of erections rigid enough for intercourse achieved per week (grade 3 or 4 when penile response is graded on a four-point scale). In each study an improvement in the number of grade 3 and 4 erections was seen with sildenafil treatment. In five trials it was improved from 0.6 to 0.8 with a placebo to between 1.1 and 1.9 with sildenafil 25 mg to 100 mg. In one study, the mean recorded grade 3 or 4 erections was 1.4 with a placebo and 4.6 with sildenafil 25 mg to 100 mg.[18] A dose–response relationship was apparent.

Results of the optional partner questionnaire were available for seven trials. Response rates ranged from 20% to 94%. Detailed analysis is not possible, owing to the limited data provided. Overall, the responses to the partners' questionnaire corroborated the improvement in the ability to penetrate and maintain erections reported by patients. Generally, increasing partner satisfaction was seen with increasing sildenafil dosage.

A number of the clinical outcome studies included a quality of life questionnaire in the study design. None of the

Table 3. Results from trials with clinical outcomes other than Q3 and Q4 of the IIEF.

Number of study	Study design	Period of measurement	Treatment	Outcome measured	Scale	Result	*P*-value
101	Fixed dose Parallel group	24 weeks	Placebo Sildenafil 5 mg Sildenafil 25 mg Sildenafil 50 mg Sildenafil 100 mg	How often were you able to get an erection?	1 = never/ rarely successful, to 5 = always or almost always successful 0 = no attempts	2.1 2.7 2.9 3.1 3.6	<0.0001
351 (Part II)	2-period crossover 7-day washout	7 days	Placebo Sildenafil 25 mg	Number of patients reporting improved erectile activity		2/12 10/12	0.018
353	Fixed dose Parallel group	4 weeks	Placebo Sildenafil 10 mg Sildenafil 25 mg Sildenafil 50 mg	1. Proportion reporting that treatment improved erections		1. 39%, 64%, 79%, 88% for placebo, 10mg, 25mg and 50mg Sildenafil respectively	Both outcomes <0.0001
			Placebo Sildenafil 10 mg Sildenafil 25 mg Sildenafil 50 mg	2. Proportion interested in continuing treatment		2. 51%, 78%, 84%, 91% for placebo, 10mg, 25mg and 50mg Sildenafil respectively	
355	Variable dose Crossover	4 weeks	Placebo Sildenafil 25–75 mg	Average number of erections adequate for penetration		1.4 4.2	<0.0001
356	Variable dose Parallel group	8 weeks	Placebo Sildenafil 10–100 mg	Proportion interested in continuing treatment		40% 85%	<0.0001
357 (Part II)	3-period crossover 3 – 10 day washout	10 days	Placebo Sildenafil 25 mg Sildenafil 50 mg	Mean number of erections/week		0.6 0.8 1.6	Not stated
358 (Part II)	Fixed dose Parallel group	4 weeks	Placebo Sildenafil 50 mg	1. Proportion reporting that treatment improved erections		1. 7%, 75% for placebo and 50mg Sildenafil respectively	Not stated
			Placebo Sildenafil 50 mg	2. Proportion interested in continuing treatment		2. 15%, 67% for placebo and 50mg Sildenafil respectively	
359	Variable dose Parallel group	12 weeks	Placebo Sildenafil 25–100 mg	Proportion of patients reporting improved erectile activity		18% 81%	Not stated

reports have presented comprehensive data on this questionnaire. In four studies the FDA report identifies statistically significant but small quality of life treatment effects (for health compared with a year ago, satisfaction with relationships, and impact of erectile problems).[6]

Subgroup analyses

The vast majority of patients were Caucasian, and no analysis has been performed on effectiveness according to race. A meta-analysis has been conducted by Pfizer of eight studies considering efficacy in the elderly (≥65 years old, n = 742) and non-elderly men (n = 2240).[23] A statistically significant treatment response of similar magnitude was seen irrespective of age.

Two studies evaluated the effects of sildenafil in diabetic men with ED.[16,21] While a beneficial effect was apparent with sildenafil in both primary and secondary outcomes, the improvements seen were smaller than those recorded with treatment in men with ED of broad aetiology. Statistically significant improvements in mean scores to IIEF Q3 (3.2 versus 2.0) and Q4 (2.9 versus 1.6) were seen with sildenafil compared with a placebo. Improved erections were reported by between 48% and 57% of men treated with sildenafil compared with 10% with a placebo (P<0.005).[16] An abstract report has summarised the pooled efficacy data on sildenafil in diabetic men with ED enrolled in nine trials.[24] A total of 633 men with ED and diabetes were included in the analysis: 388 received sildenafil (5 mg to 200 mg) and 245 a placebo, for between six and 26 weeks. At endpoint, statistically significant improvements in the scores to Q3 (2.9 versus 1.9) and Q4 (2.7 versus 1.5) and in the proportion of patients with improved erections (59% versus 15%) were recorded with sildenafil compared with a placebo. Again, the improvements seen were smaller than those recorded in men with ED of broad aetiology.[24]

Two studies evaluated the effects of sildenafil in 205 men with ED solely attributable to spinal cord injury but with evidence of reflex activity.[14,22] These show the efficacy of sildenafil to be comparable with that in patients with ED of broad spectrum aetiology.

Four per cent of patients enrolled in Phase II and III clinical trials had ED as a result of radical prostatectomy. A subgroup analysis of these patients appears to show lower efficacy with sildenafil, with only 40% to 50% achieving improved erections (personal communication, Pfizer, June 1998).

Open-label extension studies

Ten long-term (usually 52-week) open-label follow-up studies have been undertaken with sildenafil. Outcome data are provided for two studies.[6,25] Ninety per cent of patients expressed satisfaction with treatment at the end of the study, but the data presented are very limited and difficult to evaluate.

Discussion

The above trials show sildenafil to be an effective treatment for ED which is relatively safe in the short term. Long-term safety cannot yet be assessed. A large number of men have been involved in these trials, all of which showed consistent findings, and we believe that there is, therefore, strong justi-

Table 4. Summary of Phase II studies which evaluated penile rigidity with sildenafil treatment followed by visual (or, in study 358, vibratory) sexual stimulation.

Number of study	Treatment	Number of patients	Duration of treatment	Mean duration of 60% (minimum) rigidity of tip of penis	*P*-value versus placebo	Percentage of patients with >60% rigidity
105	Placebo	54	1 dose	0.06[a]	$P = 0.0002$	Not stated
	Sildenafil 25 mg	54	1 dose	0.53[a]		
	Sildenafil 50 mg	53	1 dose	0.39[a]		
	Sildenafil 100 mg	53	1 dose	0.95[a]		
350	Placebo three times daily	16	7 days	7.4 minutes	$P = 0.002$	Not stated
	Sildenafil 25 mg three times daily	16	7 days	36 minutes		
351	Placebo	12	1 dose	2.9	$P<0.001$	Not stated
	Sildenafil 10 mg	12	1 dose	19		
	Sildenafil 25 mg	12	1 dose	26		
	Sildenafil 50 mg	12	1 dose	27		
357	Placebo	21	11 days	1.3, 1.5 (95% CI = 0.7–2.8)[b]	Not significant	Not stated
	Sildenafil 25 mg	21	11 days	2.7, 2.4 (95% CI = 1.3 –4.4)[b]	$P = 0.002$[b]	
	Sildenafil 50 mg	21	11 days	4.3, 7.2 (95% CI = 4.1–12.3)[b]	-	
358	Placebo	27	1 dose	median = 3 minutes (range = 2–4)[b]	$P<0.01$	
	Sildenafil 50 mg	26	1 dose	median = 10 minutes (range = 0.5–72.5)[b]		8 65
360	Placebo	17	1 dose	1.1 (95% CI = 0.4 –2.2)[a]	$P = 0.001$	53
	Sildenafil 50 mg	17	1 dose	5.9 (95% CI = 3.3–10.4)[a]		82
369	Placebo	16	1 dose	Lasted twice as long on sildenafil	*P* not stated	Not stated
	Sildenafil 100 mg	16	1 dose	No further details given[a]		
166–301	Placebo	10	1 dose	0.8		Not stated
	Sildenafil 50 mg	10	1 dose	5.7 (95% CI = 1.7–19.4)	$P = 0.0084$	
	UK-114, 542	10	1 dose	5.6 (95% CI = 1.8–17.3)	$P = 0.0052$	

[a] Mean rigidity of the penis (base or tip not specified). Data are reported in minutes but methods states primary outcome is log transformed duration of 60% rigidity. [b]Penile base rigidity.

fication for this conclusion. The fact that data could not be obtained for the two Japanese trials does not affect this, as the number of participants was small and, even if they had shown no effect, this would not have been sufficient to alter the overall findings.

Sildenafil has not been directly compared with alprostadil in any formulation. Comparative trials are in progress. Owing to their different mechanisms of action, alprostadil may be effective in some patients in whom sildenafil is ineffective.[32] However, for most men, sildenafil will be a more acceptable form of treatment than intracavernosal injection or intraurethral insertion, and should probably be the first treatment of choice for most patients with ED.

All patients in the trials were entered into a two to four-week period free of treatment, which allowed baseline data on ED and sexual function to be collected. One-third to one-half of patients enrolled in these trials had successful intercourse during this period, and therefore had baseline erectile function. Our discussions with experts in this field suggest that men presenting with ED in the National Health Service may be more incapacitated than this. If the effectiveness of ED varies with baseline function, then the number needed to treat may actually be higher in practice than two. In men with diabetes, baseline sexual performance data indicated that only one-fifth of patients had erections sufficient for intercourse. The effectiveness of this drug was also less in this group, although it was still effective. While this may be a consequence of the mechanisms of erectile damage in diabetes, it may be that the drug is just as effective in men with diabetes and that the difference observed is owing to the difference in severity of ED in those recruited.

Conclusion

Sildenafil is an effective oral treatment for erectile dysfunction. All twenty trials reported consistent findings in the improvement of sexual or erectile function.

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