

## Efficacy and safety of sildenafil citrate in the treatment of men with mild to moderate erectile dysfunction

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**Background** Erectile dysfunction is a common, multi-factorial disorder.

**Aims** To evaluate the efficacy, tolerability and frequency of use of sildenafil citrate in men with mild to moderate erectile dysfunction of no established organic cause.

**Method** This double-blind, randomised, placebo-controlled, flexible-dose, two-way crossover study was conducted at four centres in the UK in 44 men with mild to moderate erectile dysfunction of no clinically obvious organic cause. The study included two 28-day treatment periods, during which time sildenafil or placebo (25–75 mg, based on efficacy) was taken as required.

**Results** Compared with placebo, sildenafil was associated with increases in frequency of use, erections adequate for sexual intercourse and level of sexual satisfaction ( $P < 0.0001$ ). More patients receiving sildenafil stated they would use the treatment again compared with those receiving placebo ( $P < 0.0001$ ). There were no discontinuations due to sildenafil treatment.

**Conclusions** Sildenafil is effective and well tolerated in men with mild to moderate erectile dysfunction of no clinically identifiable organic cause.

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Surveys conducted in the UK indicate that 32% of men aged 16 years or older have difficulty in achieving an erection, and 20% have difficulty maintaining an erection; however, few men with erectile dysfunction have obtained the help they would like to receive (Spector & Boyle, 1986; Dunn *et al*, 1998). A multi-factorial disorder, erectile dysfunction is broadly defined as being of organic, psychogenic or mixed causes. Sildenafil citrate has been shown to be effective and well tolerated in men with erectile dysfunction of broad-spectrum aetiology (Goldstein *et al*, 1998; Morales *et al*, 1998; Padma-Nathan *et al*, 1998). This study investigated the efficacy, tolerability and frequency of use of sildenafil in men with erectile dysfunction for which an organic cause was not evident or sufficiently established to permit diagnosis.

### METHOD

#### Study participants

Men aged 18–70 years with clinically diagnosed erectile dysfunction of more than 6 months duration were eligible for study inclusion if, as determined by a medical history supplied by the patient's general practitioner, a physical examination conducted by the study investigator and other diagnostic procedures, their erectile dysfunction was of no established organic (i.e. vascular or neurogenic) cause. The patients were also required to be engaged in a stable relationship with a female partner, provide written informed consent and have residual erectile function (at least one Grade 3 or 4 erection (see grading scale in Assessment section)) or a positive response to papaverine (up to a 40 mg dose) or prostaglandin E<sub>1</sub> (20 µg dose) injection within 4 weeks of study entry. Exclusion criteria included: having two successful penetrative sexual intercourse acts per week; a history of alcohol misuse; regular treatment with nitrates, anticoagulants or aspirin within 2

weeks before study entry; treatment with antidepressants or major tranquillisers for psychoses or related conditions; continued use of other erectile dysfunction treatments.

#### Study design

This double-blind, placebo-controlled, flexible-dose, randomised, two-way crossover study of sildenafil, taken as needed, was conducted at four centres in the UK. The study included two 28-day, double-blind treatment periods not separated by a washout period, and a 2-week follow-up period.

#### Randomisation and blinding

Randomisation to one of the two treatment sequences was undertaken in a double-blinded fashion prior to the study start date. Subjects were allocated to a treatment sequence group, and blocks were assigned to each centre to ensure adequate balance of subjects to sequences within each centre. Other than the project statistician and the pharmacist who packaged the study drug, all study investigators and other staff were blinded to the sequence allocation.

#### Dosing

Patients received 25 mg doses of sildenafil or matching placebo, and were instructed to take the study drug 30 to 60 minutes before anticipated sexual activity, but not more than once daily, and to record the actual time of dosing in the patient diary. Dose could be increased incrementally to a total of three 25 mg tablets to increase efficacy if necessary. Patients were instructed to decrease the dose if the study drug was not well tolerated.

#### Clinical assessments

For assessment of efficacy, patients completed a detailed daily diary recording erectile activity for 7 days before the first treatment period and for the two consecutive 28-day treatment periods. Data from patients' logs were used as a primary source of assessment because sexual function is best assessed in a natural setting with self-report techniques (Andersen & Broffitt, 1988). Based on recommendations by the National Institutes of Health Consensus Conference on Impotence (1993), records included information deemed important in the assessment of patients with erectile dysfunction, such as timing and number of

doses of study drug taken; time of onset, duration and quality of erections; whether the erection was associated with sexual stimulation; occurrence of satisfactory sexual intercourse; and whether other sexual activity occurred. The quality of erections was graded on a four-point scale: 1, increase in size but not hard; 2, hard but not hard enough for penetration; 3, hard enough for penetration (but not completely hard); 4, completely hard.

Erectile activity was also assessed by yes/no responses to a two-item global efficacy questionnaire (GEQ; Goldstein *et al*, 1998) administered at the end of each 28-day treatment period: (GEQ1) "Has the treatment you have been taking over the last 28 days improved the quality of your erections?" and (GEQ2) "If this treatment were available would you want to take it?" As part of the patient diary, patients' partners were asked if treatment improved their partner's erections and, if so, were they satisfied with the quality of the patient's erections during the 28-day treatment period.

### Safety assessments

All observed and volunteered adverse events were recorded by the investigator and assessed for severity and relationship to study medication. Objective test findings, including standard laboratory tests (haematology, biochemistry and urinalysis) and physical examinations (supine blood pressure and pulse rate) were performed at each clinic visit (screening, Day 0, Day 28 of both first- and second-treatment periods and follow-up); a 12-lead electrocardiogram was performed at the screening and follow-up visits.

### Statistical analysis

Sample size was based on the primary efficacy variable and used data from a previous study that had compared multiple doses of sildenafil with placebo and indicated that a sample size of 36 subjects was sufficient to detect a 60% difference in weekly erection count with probability 0.80 when testing at the 5% level of significance. All analyses were controlled for the differing effects between centres. The interaction effect of centre with both treatment and sequence was assessed when the analysis was able to do so; these effects were found to be not significant, and therefore were removed from the model. Intent-to-treat analyses were performed on efficacy

variables and included all randomised patients who had a baseline measurement of erectile dysfunction and at least one efficacy assessment after the start of each treatment. All tests of significance were two-sided and evaluated at the 5% significance level. The mean number of Grade 3 or 4 erections was log transformed and analysed using an analysis of variance model and included appropriate terms for sequence, subject, period and treatment. The mean number of doses per week was also subjected to an analysis of variance model. The number of occurrences of satisfactory sexual intercourse as a proportion of the number of doses taken and the number of satisfactory Grade 3 or 4 erections as a proportion of doses taken were analysed using logistic regression. The odds of a satisfactory event were calculated as  $a/b$ , with  $a=X/(100-X)$  where  $X$  is the percentage of satisfactory events with sildenafil treatment, and  $b=Y/(100-Y)$  where  $Y$  is the percentage of satisfactory events with placebo treatment. The results of the investigator questionnaire and the partner question were analysed using the Mainland-Gart test for contingency tables (Mainland, 1963; Gart, 1969), which investigated each 28-day period and treatment effects. No interim analysis was undertaken.

## RESULTS

### Demographics

Of the 47 patients screened for the study, 44 were randomised to treatment, with 15, 13, 13 and 3 study participants at the four treatment centres. The demographic characteristics were similar in the two treatment groups (see Table 1). The overall mean age was 53 years and the overall mean duration of erectile dysfunction was 2.9 years. Of the 44 patients who received at least one dose of study drug, 40 (91%) completed the study and were included in

the intent-to-treat population. The median duration of treatment was 29 days for both sildenafil and placebo.

### Efficacy of treatment

As assessed from the patients' diary data, analyses of the frequency of study drug use included the distribution of number of doses taken over the entire study period and the average number of doses taken per week by the intent-to-treat population (see Table 2). Whereas the distribution of dosages of study drug showed little variability in the number of doses of sildenafil taken for the overall study period, more doses of placebo were taken at the higher dosage level. The average number of doses taken per week was significantly higher for treatment with sildenafil compared with placebo ( $P=0.001$ ). The mean values of time between doses showed a shorter median time for sildenafil compared with placebo (50.2 *v.* 56.7 hours, respectively). A similar pattern was observed for the minimum time between doses, with a lower mean for sildenafil than placebo (23.9 and 32.7 hours, respectively).

The geometric mean number of Grade 3 or 4 erections per week was significantly higher for treatment with sildenafil compared with placebo ( $P<0.0001$ , see Fig. 1). The average number of Grade 3 or 4 sexually stimulated erections was also higher for patients receiving sildenafil than for patients receiving placebo (see Fig. 1). Of all responders to sildenafil, 85% were able to have intercourse more than 75% of the time. The majority of non-sexually stimulated erections were nocturnal or early morning erections for both treatments.

The estimated proportion of occurrences of satisfactory Grade 3 or 4 erections per number of doses was 94% for sildenafil and 68% for placebo, with a highly significant overall treatment effect for sildenafil

**Table 1** Baseline demographic data of patients with erectile dysfunction of no known organic origin

Characteristic	Sildenafil—Placebo	Placebo—Sildenafil
Number of patients	24	20
Age range (years)	33–69	36–69
Mean age (years)	53	53
Range of erectile dysfunction duration since first diagnosis (years)	0.5–10	0.5–10
Mean duration of erectile dysfunction (years)	2.8	3.1

**Table 2** Treatment dosage based on diary data

	Sildenafil			Placebo		
	25 mg	50 mg	75 mg	25 mg	50 mg	75 mg
Distribution of number of doses taken ( $n=44$ )	109	105	106	33	48	122
Average number of doses (S.E.M.) per week ( $n=40$ )	3.4 (0.3)*			2.6 (0.3)		

\* $P=0.001$  sildenafil v. placebo.

( $P<0.0001$ , see Fig. 2). The odds of achieving a satisfactory erection while taking sildenafil were 7.9 times greater than the corresponding odds for placebo ( $P<0.05$ ). The estimated occurrence of satisfactory sexual intercourse per number of doses was 62% for sildenafil and 12% for placebo ( $P<0.0001$ , see Fig. 2). Thus, the odds of having satisfactory sexual intercourse while taking sildenafil were on average 12 times greater than the corresponding odds for placebo ( $P<0.02$ ).

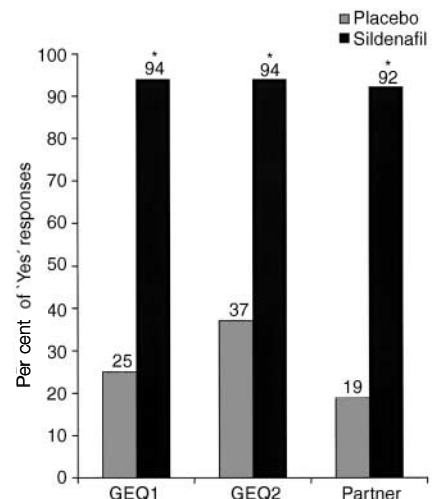
Of the 36 patients included in the analysis of GEQ1, responders to treatment included 34 (94%) who recorded improved erections while taking sildenafil, and nine (25%) while taking placebo ( $P<0.0001$ , Fig. 3). This analysis included patients who recorded improvement with sildenafil but not placebo ( $n=25$ ), both treatments ( $n=9$ ) or neither treatment ( $n=2$ ). Of the 35 patients included in the analysis of GEQ2, 33 (94%) stated they would take sildenafil if it was available, and 13 (37%) stated they would take placebo ( $P<0.0001$  for treatment effect). This

analysis included patients who stated they would take sildenafil but not placebo ( $n=20$ ), both treatments ( $n=13$ ) or neither treatment ( $n=2$ ).

Partners' opinions of the effect of each 28-day treatment on the patient's erections also showed a highly significant positive response for sildenafil compared with placebo ( $P<0.0001$ , see Fig. 3). Of the 37 partners included in this analysis, 34 (92%) recorded that the patient's erections had improved while taking sildenafil and seven (19%) reported improved erections while the partner was taking placebo. Overall, 28 partners recorded improvement with sildenafil but not placebo, one recorded improvement with placebo but not sildenafil, and six recorded improvement with both sildenafil and placebo.

### Safety and tolerability

Treatment with sildenafil was well tolerated during the two 28-day periods. Twenty-three patients receiving sildenafil



**Fig. 3** Patients' and partners' opinions on erections at the end of each treatment period. Percentage of patients who reported that treatment improved their erections (GEQ1) and that they would continue with treatment after the study if the study drug was available (GEQ2). Percentage of partners who reported improved erections (Partner). \* $P<0.0001$  sildenafil v. placebo. GEQ, global efficacy questionnaire.

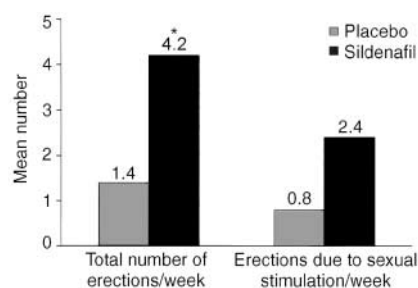
and 14 receiving placebo reported adverse events of all causes. Most treatment-emergent adverse events were mild to moderate in nature (see Table 3). Two severe adverse events (palpitations and flushing) were reported with sildenafil, both of which resolved without treatment.

Of the five discontinuations in this study, four were due to protocol violation or because the patient was lost to follow-up. The only discontinuation due to a serious adverse event involved a patient who suffered a myocardial infarction while receiving placebo during the second 28-day treatment period. Clinical laboratory test abnormalities were reported for eight of the 43 patients on sildenafil and six of 41 patients on placebo. However, there were no discontinuations due to laboratory test abnormalities.

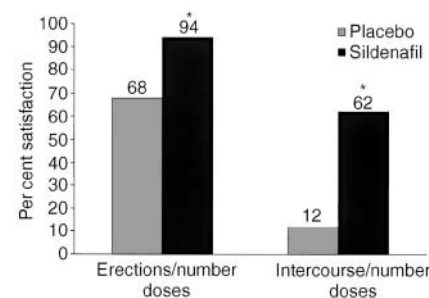
## DISCUSSION

### Background

Erectile dysfunction, the consistent inability to achieve and maintain an erection sufficient for satisfactory sexual activity, affects up to 30 million men in the USA (National Institutes of Health Consensus Development Panel on Impotence, 1993). This estimate includes the combined prevalence of



**Fig. 1** Effect of treatment on the average number of Grade 3 or 4 erections per week (the geometric mean). The geometric mean and the average number of erections associated with sexual stimulation per week were derived for each treatment from the patient logs. Patients used sildenafil 31% more often per week than placebo. \* $P<0.0001$  sildenafil v. placebo.



**Fig. 2** Efficacy of treatment on satisfaction of erections and intercourse. The odds ratio for number of satisfactory erections (Grade 3 or 4) as a proportion of the number of doses was 7.9 ( $P=0.039$ ) and the odds ratio for number of occurrences of satisfactory sexual intercourse taken as a proportion of the number of doses was 12.0 ( $P=0.013$ ). \* $P<0.0001$  sildenafil v. placebo.

**Table 3** Summary of adverse events for 43 patients on sildenafil and 43 on placebo

	Sildenafil, n (%)	Placebo, n (%)
Number of patients		
Reporting adverse events	23 (53)	14 (33)
Discontinuations due to adverse events	0 (0)	1 (2)
Treatment-emergent adverse events		
Headache	11 (26)	0 (0)
Flushing	4 (9)	0 (0)
Dyspepsia	3 (7)	1 (2)
Arthralgia	3 (7)	2 (5)

mild, moderate and severe erectile dysfunction, the categories described in the extensive Massachusetts Male Aging Study (MMAS; Feldman *et al*, 1994).

Erectile dysfunction has been associated with a number of organic, psychogenic and lifestyle factors that can show varying degrees of interdependence. Indeed, numerous psychogenic and other 'non-organic' factors may contribute to or be associated with erectile dysfunction. Various psychological processes can impair erectile function by reducing erotic focus or awareness of sensory experience. Stress and anxiety, resulting from work-related problems, relationship conflict or performance fears, can cause increased sympathetic outflow and elevated catecholamine levels, thereby increasing penile smooth muscle tone and opposing the smooth muscle relaxation required for erection (Krane *et al*, 1989). Conversely, problems with erectile function, as may result from subtle but significant organic changes, can generate varying degrees of anxiety (Smith, 1988). Not only is clinical depression a well-recognised cause of decreased sexual desire and of erectile dysfunction (Feldman *et al*, 1994), but erectile dysfunction itself may result in depression (Shabsigh *et al*, 1998). Compounding this complex, dynamic and bidirectional relationship, erectile dysfunction can be induced as a side-effect of medications used to treat depression (e.g. tricyclic antidepressants, lithium, monoamine oxidase inhibitors and serotonin reuptake inhibitors) and other classes of psychotropics (e.g., phenothiazines, butyrophenones, opiates and amphetamines) (Bennett & Melman, 1995; Margolese & Assalian, 1996). Suppression and expression of anger, overrestrictive upbringing and substance misuse have also been associated with the development of erectile dysfunction (Smith, 1988; Feldman

*et al*, 1994; Bennett & Melman, 1995). Regardless of its aetiology, erectile dysfunction can adversely affect quality of life, self-esteem and partner relationships if the condition is not successfully treated, that is, effectively and with minimal adverse effects (National Institutes of Health Consensus Development Panel on Impotence, 1993; Hanson-Divers *et al*, 1996).

Sildenafil, a selective inhibitor of phosphodiesterase type 5, enables a natural erection after sexual stimulation (Boolell *et al*, 1996). The efficacy, safety and tolerability of sildenafil have been demonstrated in large clinical trials (Goldstein *et al*, 1998; Morales *et al*, 1998; Padma-Nathan *et al*, 1998), in which a therapeutic response of similar magnitude was observed in men with erectile dysfunction of various aetiologies. To date, evaluations of sildenafil in patient subsets have predominantly focused on men with erectile dysfunction due to an organic cause, for example radical prostatectomy (Zippe *et al*, 1998), diabetes (Rendell *et al*, 1999), cardiovascular disease (Cheitlin *et al*, 1999) and spinal cord injury (Maytom *et al*, 1999).

Our study assessed the efficacy and safety of sildenafil in men with mild to moderate erectile dysfunction associated with no detectable organic cause and an age distribution similar to that of men with erectile dysfunction from the general population (Feldman *et al*, 1994). The patients' medical histories, the findings on physical examination and the results of diagnostic tests suggested that many of these men had erectile dysfunction of predominantly psychogenic origin. However, men with a history of depression were excluded from the study owing to the chronic nature of this disorder and the propensity of many medications used in the treatment of depression to induce erectile dysfunction.

## Study findings

In our study, sildenafil was associated with significant improvements in the quality and quantity of erections and levels of satisfactory intercourse. The average number of sexually stimulated erections adequate for intercourse were three-fold greater, and satisfactory sexual intercourse occurred more frequently with sildenafil. Similar results were reported for patients with erectile dysfunction of broad-spectrum aetiology (Goldstein *et al*, 1998). Both the patients and partners in our study strongly agreed that sildenafil was effective in improving erections, and most patients indicated that they would continue treatment with sildenafil, if it was available.

In general, sildenafil was well tolerated, with no discontinuations due to adverse events. The majority of adverse events were mild to moderate. The frequency of the most common adverse events associated with sildenafil was consistent with other published studies of men with erectile dysfunction of broad-spectrum aetiology (Goldstein *et al*, 1998; Morales *et al*, 1998; Padma-Nathan *et al*, 1998).

## Limitations

Several limitations of this study merit acknowledgement. Although the identification of an organic abnormality does not establish it as the cause of erectile dysfunction in every individual (Riley & Athanasiadis, 1997), mild organic disease causing changes in erectile function of study participants may not have been detectable by the methods used at screening. Moreover, the study was performed in a natural environment, requiring a reliance on the study participants' own reports of efficacy; although of great value, self-reported sexual function and symptomatology may not be accurate in all settings.

The patients in our study preferred sildenafil and used this treatment 31% more frequently than placebo, which may have artificially increased the number of erections per week with sildenafil treatment. Additionally, not all erections recorded in this study were related to sexual intercourse, which likely explains why the odds ratio of achieving satisfactory intercourse with sildenafil was higher than that of achieving satisfactory erections. Indeed, the high number of nocturnal and early morning erections reported in this study suggests erectile dysfunction of predominant psychogenic aetiology. However, the



study participants were not required to undergo a formal psychiatric evaluation, and presence of psychogenic factors contributing to the patients' erectile dysfunction was not confirmed.

### Clinical implications

Erectile dysfunction is a multi-factorial disorder, and failure to identify an organic cause does not prove a psychogenic origin (Goldstein *et al*, 1998), but is generally associated with mild to moderate dysfunction. Although emphasis has shifted to the role of organic factors in the aetiology of erectile dysfunction, this should not reduce the importance of assessment of erectile dysfunction in men with mild to moderate dysfunction that may be of psychogenic origin or of no obvious organic cause. In the MMAS (Feldman *et al*, 1994), the largest population-based epidemiological survey of erectile dysfunction in current literature, the majority of men with erectile dysfunction fell into this category. In these men, the condition is likely to progress to severe erectile dysfunction if an untreated psychogenic factor is contributing to the pathology (Bennett & Melman, 1995).

Obviously, for optimal outcomes, the assessment and treatment of a multi-factorial disorder such as erectile dysfunction may require the participation of professionals who are trained and skilled in diverse disciplines. The purpose of performing pharmaceutical intervention studies is to help men with erectile dysfunction as part of a multi-disciplinary approach. It is not to promote drug use in place of cognitive-behavioural strategies for treating erectile dysfunction that is not due to a chronic illness, disease or surgery.

Although a presumptive diagnosis of psychogenic erectile dysfunction requires a medical assessment for organic factors that may contribute to the aetiology of the disorder and require treatment, the study findings cannot be interpreted to apply to all men who have clinically diagnosed erectile dysfunction of psychogenic origin. Rather, confirming and extending the findings of a smaller study undertaken in a similar population (Boolell *et al*, 1996), our study showed that oral sildenafil is an effective and well-tolerated treatment for men with erectile dysfunction that is mild to moderate in severity and may be either predominantly psychogenic or has an organic cause that has not been sufficiently established to be clinically manifest.

### CLINICAL IMPLICATIONS

- Mild to moderate erectile dysfunction that may be of psychogenic origin or no clinically obvious organic cause affects a large and important segment of men with erectile dysfunction.
- Oral sildenafil is an effective and well-tolerated treatment in men with mild to moderate erectile dysfunction for which an organic cause is not evident or sufficiently established to permit diagnosis.
- Adequate assessment and successful treatment of erectile dysfunction, a multi-factorial disorder, may require the participation of skilled professionals trained in diverse disciplines.

### LIMITATIONS

- Mild organic disease, not detected by the methods used at screening, may have contributed to the study participants' erectile dysfunction.
- Although the study participants' medical histories, findings on physical examination and results of specific diagnostic procedures suggested that many of these men had erectile dysfunction of predominantly psychogenic aetiology, the study protocol did not require the participants to undergo a formal evaluation for potential psychogenic factors.
- The more frequent use of sildenafil compared with placebo may have artificially increased the mean number of erections per week during sildenafil treatment.

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