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Research article

Oral sildenafil (Viagra™) in male erectile dysfunction: use, efficacy and safety profile in an unselected cohort presenting to a British district general hospital.

Krishnamurthy Sairam*[1], Elena Kulinskaya[2], Damian Hanbury[1], Gregory Boustead[1] and Thomas McNicholas[1]

Address: [1]Department of Urology, Lister Hospital Coreys Mill Lane, Stevenage SG1 4AB, UK and [2]Reader in Medical Statistics, Health Reasearch & Development Support Unit (HRDSU) Faculty of Health & Human Sciences, University of Hertfordshire, Hatfield AL10 9AB, UK

E-mail: Krishnamurthy Sairam* - ksairam@baus.org.uk; Elena Kulinskaya - E.Kulinskaya@herts.ac.uk; Damian Hanbury - dchanbury@doctors.net.uk; Gregory Boustead - gboustead@lister.org.uk; Thomas McNicholas - mcnic@globalnet.co.uk

*Corresponding author

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Abstract

Introduction: Sildenafil (Viagra®) is one of the drugs used in the first line therapy of male erectile dysfunction (MED). We have recorded outcomes, adverse events and acceptability of Sildenafil (Viagra) therapy in an unselected group of men presenting with ED to a British district general hospital.

Methods: In this prospective observational study, 147 men with ED were seen since Oct 1999. Study patients were reviewed at 4, 12 and 52 weeks. All the patients filled the International Index of Erectile Function (IIEF) questionnaire and were asked about their willingness to pay (WTP) for treatment.

Results: All suitable men accepted Viagra as first line therapy. 91% of our patients found sildenafil treatment successful. 80% of these patients were willing to continue with sildenafil therapy. Side effect profile of sildenafil was different in this study with much higher incidence of headache, dyspepsia, flushing and abnormal vision. 92% of men with ED expect to be treated by the NHS. Of those men eligible for treatment in the NHS, 30% qualify under the clinical categories and 18% under the 'distress' category. Only 55% of those with cardiovascular risk factors qualify for NHS treatment.

Conclusions: Sildenafil is widely accepted as first line therapy among British men with ED and has a success rate of 91%. Nearly half of men with ED qualify for NHS treatment. Nearly half of those with vascular risk factors do not qualify for NHS treatment. Most men with ED could possibly be managed in primary care.

Background

Male erectile dysfunction (MED) (or impotence) has been defined as the persistent inability to attain and maintain an erection adequate to permit satisfactory sexual performance [1]. The Massachusetts Male Aging Study reported a combined prevalence of 52% for minimal, moderate,

and complete impotence in non-institutionalised 40 to 70 years old men [2].

Over the last decade, a substantial body of evidence has accumulated demonstrating the beneficial effects of phentolamine, papaverine, and prostaglandin E1 (PGE1) when injected intracavernously. However, both the method of administration (self-injection) and the risks of major adverse events, such as intracorporeal fibrosis and priapism [3], strongly suggested the need for further therapeutic advances in the treatment of impotence. Transurethral alprostadil (as MUSE™) was the next to arrive on the scene, but the response rate has been variable and enthusiasm has waned [4]. The introduction of Sildenafil (Viagra) provided the possibility of an acceptable, effective oral therapy [5]. Sildenafil works by blocking the effects of the enzyme Phosphodiesterase 5 (PDE-5), so prolonging the effects of Nitric Oxide (NO) released in the penile cavernosal tissues from relevant nerve endings. The profile of oral sildenafil (Viagra™) to date is that of an effective and well tolerated on-demand pharmacological treatment for men with erectile dysfunction [6].

With its unprecedented level of popularity and media hype, Viagra brought it's own set of problems. The Government released its initial guidelines on treatment of impotence [7] "to find a sensible balance between treating men with the distressing condition of impotence, and protecting the resources of the NHS to deal with other patients". This was subsequently revised in June 1999 [8] and serves as the current guideline for NHS prescription of impotence treatments (Table. 1). It is of note that the Department of Health included a non-clinical category – 'severe distress' – eligible for treatment under the NHS. In determining whether a patient is suffering from severe distress due to their ED[9], the following criteria were recommended to be taken into account:

• Significant disruption to normal social and occupational activity

• Marked effect on mood, behaviour, social and environmental awareness

• Marked effect on interpersonal relationships

We receive multiple referrals of men with MED who appear suitable for sildenafil (Viagra) and assess them and offer the full range of therapies. Many more men are presenting to their GP's, some of whom are sufficiently experienced and interested in MED to be able to offer treatment themselves or in consultation with a specialist. However, published data on most clinical trials involving sildenafil included only select groups of men with stringent exclusion criteria. We have recorded outcomes, adverse events and the acceptability of Sildenafil (Viagra) therapy in an unselected group of men presenting with ED to a British district general hospital.

Table 1: Government guidelines on the categories of patients 'eligible' for treatment of their ED under the NHS. Column 2 represents the number (percentage within parentheses) of patients with ED eligible for NHS treatment in this study.

Category eligible for NHS treatment	No. (percent)
Distress	26 (17.6%)
Diabetes mellitus	22 (15%)
ED treatment prior to / on 14/09/1998	8 (5.4%)
Prostatectomy	5 (3.4%)
Prostate cancer	2 (1.4%)
Radical Pelvic Surgery	2 (1.4%)
Spinal Cord Injury	3 (2%)
Parkinson's Disease	1 (0.7%)
Multiple sclerosis	0
Poliomyelitis	0
Renal failure treated by dialysis or transplant	0
Severe pelvic injury	0
Single gene neurological disease	1 (0.7%)
Spina bifida	0
Total – eligible for NHS treatment	70 (47.6%)
Distress ('specialist' prescriptions required)	17.6%
Other categories (GP can prescribe)	30%

Methods

In this prospective study, which was approved by the local ethical committee, all the patients referred to this unit with ED as their primary complaint were seen in a dedicated andrology outpatient clinic. The self-administered International Index of Erectile Function (IIEF) [10] questionnaire was filled prior to the consultation. Patient's height and weight were measured followed by dipstick testing of their urine (Bayer Multistix™). This was followed by the consultation, which included a detailed history and focussed physical examination (Visit 1). Suitable treatment options were then discussed and patients were provided information about this study. Patients taking nitrates, those with uncontrolled (or newly diagnosed) cardiovascular disease and those already on sildenafil or who had tried sildenafil and found it unsuccessful received alternative treatments to sildenafil. If eligible, they were started on 50 mg of sildenafil. Elderly men or those with a significant cardiovascular history were started at the lower dose of 25 mg. All men were advised on self-escalation of the dose to a maximum of 100 mg, provided they did not have a significant improvement in their erectile

quality at the original dose and were able to tolerate the possible side effects.

Patients were reviewed at 4, 12 and 52 weeks. The IIEF questionnaire was administered at each visit and the global score (GS – sum of responses to questions 1 – 15) and erectile domain score (EDS – sum of responses to questions 1 – 5 and 15) calculated. At the first review (Visit 2), side effects were recorded and patients were categorised as 'success' or 'failure' based on their response to the end of treatment global efficacy question (GEQ) in the IIEF questionnaire – "Has the treatment you have been taking over the past study interval improved your erections?" If any of the patients had problems with dosing this was adjusted at this review and they were seen again at 12 weeks (Visit 3). Those succeeding with treatment continued in the study until the 52-week review (Visit 4) and were asked to report any clinical problems in the interim. All the patients were questioned about the return of spontaneous erectile activity at each review.

All the men underwent urine dipstick testing followed by fasting blood glucose, testosterone and prolactin estimation. Further tests were carried out where indicated on an individual basis.

Table 2: Willingness-to-pay (WTP) for treatment of ED. (GBP – Great Britain pounds)

1	I want to be treated by the NHS	Free
2	I want to be treated by the NHS, but if I had to pay (considering what I can afford) I would pay – in GBP per week	1 – 5 6 – 10 11 – 15 16 – 20 21 – 30 31 – 50
3	I don't think the NHS should pay for my treatment; I am willing to pay – in GBP per week	1 – 5 6 – 10 11 – 15 16 – 20 21 – 30 31 – 50

As part of this study patients were asked about their willingness to pay (WTP) for the treatment of their ED (all options, not just sildenafil alone) at baseline and at each review. The options presented to the patients is illustrated in Table 2. The proportions of men in the various categories eligible for treatment under the NHS were recorded prospectively (see Table 1). Results were analysed using the SPSS software.

Results

A total of 147 men with ED were seen in the Andrology Clinic between October 1999 and March 2000. Figure 1 provides a flow chart of the study's progress. Thirty-four men were not included in the study. Their details are provided in Table 3. Thus, 113 men were enrolled in the study. Of the 147 men, 117 were suitable for taking sildenafil out of whom 2 declined treatment with it, amounting to an acceptance rate of 98.3%. Nineteen men had already tried Viagra (13 successes and 6 failures) by the time they were seen in the Andrology Clinic. At Visit 2, 14 men dropped out of the study (8 – lost to follow-up, 6 – not interested in study anymore). Out of the remaining 99 men, 7 dropped out of the study by Visit 3 (1 – ejaculatory dysfunction, 1 – unable to tolerate sildenafil, 1 – lost to follow-up, 4 – not interested) and 8 (8.7% – 8/92) had failed with sildenafil. After Visit 3, 84 men continued with sildenafil, out of whom 10 dropped out of the study by Visit 4 (6 – lost to follow-up, 1 – lack of partner, 2 – prostate cancer surgery undertaken, 1 – not interested). All these 10 were 'successes' with sildenafil therapy (at Visit 3) and for the purposes of this study they were included in the final analysis on an intention-to-treat basis. This was achieved by using the last observation carried forward (LOCF) method. The median follow-up period was 11 months (mean 9.1, range 1 – 14 months). Thus, 91.3% (84/92) of men reported sildenafil therapy as successful.

The reported frequency of sexual intercourse in this population was between 0.25 – 10 per week (mean 2.4). Evaluation of sexual function log revealed that there was good concordance between the pre-study reported frequency and logged frequency during the study period. Of the 113 men in the study, only 33 (29%) reported having some amount of spontaneous erection, but not suitable for enjoyable intercourse at Visit 1. Following sildenafil therapy, 82/99 (82.8%) men had improved erections (based on GEQ) suitable for intercourse. Seventeen (17.2%) failed treatment. There were no differences in the response rates between the various aetiological groups. A total of 33/99 (33.3%) men reported return of spontaneous erections suitable for penetrative intercourse, at least once, following treatment, of whom 14 (42.4%) did not have any spontaneous erections suitable for intercourse prior to therapy. Of the 74 men reviewed at Visit 4, 59 reported that they would continue using Viagra on a long-term basis (79.7%). Three men had reported complete return of spontaneous erections and had stopped using Viagra (1 at Visit 2 and 2 at Visit 4).

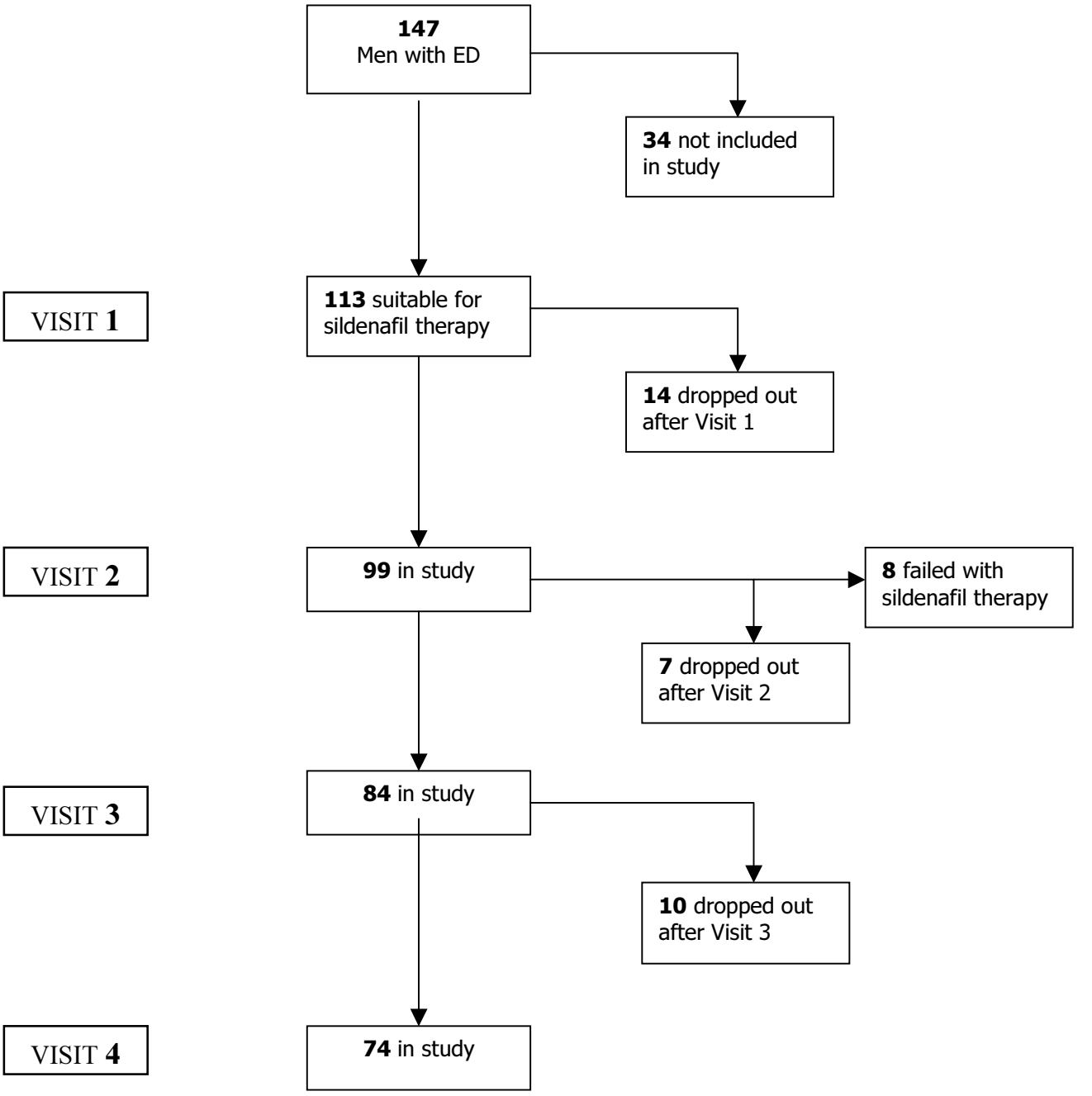

Figure 1
Flow diagram of patient population in the study.

Table 3: Details of men not included in the study.

Men presenting with ED as main complaint	147
Already using Viagra successfully	13
Already tried Viagra and failed	6
On nitrates	6
Cardiac opinion – Not suitable	2
Suspected venous leak	1
Rapid ejaculation	1
Psychological counselling required	1
Not interested	2
No partner – patient declined treatment	1
Declined Viagra specifically	1
Total no. of patients **not** included in study	34

The mean IIEF GS at Visit 1 was 25.7 (median 22, range 5 – 64), at Visit 3, 56.9 (median 62, range 7 – 73) and at Visit 4, 59.3 (median 60, range 18 – 73). The respective mean IIEF EDS was 8.2 (median 6, range 0 – 28), 23.5 (median 27, range 1 – 30) and 25.2 (median 25, range 6 – 30). There was no correlation between age and response to Viagra, although older men had relatively lower IIEF scores.

Of the 99 men reviewed, the optimal dose for achieving erection satisfactory for sexual intercourse was: 25 mg – 6 (6.1%), 50 mg – 44 (44.4%), 75 mg – 1 (1%) and 100 mg – 38 (38.4%). The side effects most commonly encountered were headache (24%), flushing (16%), dyspepsia (12%), nasal congestion (10%), abnormal vision (5%), thirst (2%) and dazed feeling (2%). Uncommon side effects included palpitations (1), dizziness (1) and penile pain (1). Severe side effects necessitated withdrawal of Viagra in 2 patients (1 was a 'success' and the other a 'failure'). Out of 53 men who reported lack of side effects at Visit 2, 6 developed some side effects at Visit 3. Conversely, 11 men who had side effects at Visit 2 reported lack of them at Visit 3. There were no changes in the side effect profile between Visit 3 and Visit 4. Four men with Peyronie's disease had used sildenafil – two reported success with therapy while the other two failed. There were 2 isolated reports of prolonged erection (lasting 20 – 30 minutes) that were painless, which did not recur. There were no serious adverse events or deaths recorded during the trial period.

Of the 147 men seen, 141 had expressed an option when asked about their willingness-to-pay (WTP) for treatment. Thirty men (21.3%) wanted ED treatment completely free of charge (i.e., on the NHS), 100 (70.9%) wanted it free, but were willing to pay some cost if required to do so and 11 (7.8%) felt that it was inappropriate for ED to be treated in the NHS and were willing to pay for it 'at cost'. Following treatment with sildenafil, those who failed to have better erections were not willing to pay any amount, while in those who succeeded there were no statistically significant changes i.e. the 3 WTP groups did not show any significant upward or downward trend following success with sildenafil therapy.

Under the current Government guidelines, only 47.6% of men with ED are eligible for treatment under the NHS (see Table 1). Out of the 147, 58 patients (40%) had one or more cardiovascular risk factors (hypertension, ischaemic heart disease, arrrythmia, congestive heart failure, dyslipidaemia or peripheral vascular disease). Only 32 of these patients (i.e. 55% of those with CVS risk factors) qualified for NHS treatment based on other grounds.

Discussion

Sildenafil, a potent PDE-5 inhibitor has been studied extensively in the context of clinical trials. To date its profile as a safe treatment option in the management of ED remains unchanged. This study aimed mainly at recording the acceptance of the drug, its efficacy and safety profile outside the scope of a trial i.e., in a study without any stringent exclusion criteria.

Out of 117 men who were suitable for taking sildenafil, the acceptance of sildenafil as a treatment option is high, 98.3% (115/117). Sildenafil was successful in treating ED in 91.3% (84/92) of this study population. At the end of the study period, 79.7% (59/74) of men wanted to continue treatment with sildenafil. The side effect profile of sildenafil in this study would appear to be different from previous published data [6] in that the incidence of headache, flushing, dyspepsia and abnormal vision is higher, but in the absence of a control group the significance of this is uncertain. It must be noted that 13% of men who reported side effects at Visit 2 reported complete lack of them at Visit 3. It is of interest that there is a 2% incidence each of thirst and 'dazed feeling' (reported by patients as a 'muzzy head'). The physiology underlying this is unclear, although it could be related to PDE inhibition in the brain, where the various PDE isoenzymes are in abundance [11].

During the period following the licensing of sildenafil for use in ED, an increase in the number of patients seeking treatment for heretofore-untreated ED was widely anticipated. This institution did not find an increase in the number of men referred with ED in the year following 14 September 1998, compared to the year preceding this date. It is not clear though, if this anticipated increase in the number of men with ED have been dealt with in the primary care. Considering that the referral pattern from

Table 4: Patient demographics. Ranges and percentages are provided in parentheses.

Mean age of patients in years	56.3 (18 – 85)
Race	
Caucasians	137
Blacks	5
Asians	5
Sexual orientation	
Heterosexuals	142
Homosexuals	5
Mean duration of ED in years	4.7 (0.5 – 20)
Lack of libido	9 (6.1%)
Lack of nocturnal tumescence or early morning erections	43 (29.3%)
Reported frequency of sexual intercourse (per week) – mean	2.4 (0.25 – 10)
Aetiological groups	
Vasculogenic	39 (26.5%)
Psychogenic	42 (28.6%)
Neurogenic	4 (2.7%)
Mixed	42 (28.6%)
Diabetes	17 (11.6%)
Hypogonadism	2 (1.4%)
Drug induced	1 (0.7%)
Comorbidity	
Known diabetics	22 (15%)
Known hypertension	27 (18.4%)
Ischaemic heart disease (known angina / MI / treated for IHD)	15 (10.2%)
Known arrythmia (with or without treatment)	8 (5.4%)
Peripheral vascular disease	15 (10.2%)
Congestive heart failure	2 (1.4%)
Low testosterone (proven on fasting sample; below normal or treated by GP with androgens for hypogonadism)	40 (31%, n = 129)
Dyslipidemia (proven by blood test or on prophylactic statins)	18 (12.2%)
Alcohol consumption > 21 units per week	13 (8.8%)
Smokers	45 (30.6%)
Ex-smokers	65 (44.2%)
Non-smokers	37 (25.2%)

primary to secondary care has not changed in this institution, we do not feel that this has happened.

Willingness-to-pay is a tool used to assess health benefits perceived to be due to a health measure [12] – [13]. In this study, there were no significant changes in the WTP within or between the 3 WTP groups, in those who succeeded with sildenafil therapy. This lack of change / trend in the WTP seems more to reflect the perception of healthcare delivery by the NHS, in that, in spite of successful treatment of their ED, the patients were unwilling to change their WTP category. The other possibility is that the gradations or categories in WTP in this study were probably not sufficiently wide to detect the changes. This study is based in the real world and hence could not include further gradations. It is also likely that if the condition were something more serious, for example, cancer, then the treatment measure and its success may have impacted differently on the perception.

It is of note that the mean frequency of intercourse in this cohort of patients is higher than that quoted in the guidelines issued by the Department of Health [9]. Fifteen patients (10.2%) (Table 3, rows 2 – 5) would have required specialist opinion (e.g. would have required a cardiologist, urologist or an andrologist in a tertiary referral centre to have seen them prior to starting therapy for their ED), while the rest could have been managed in primary care.

Conclusions

Oral sildenafil appears to be safe in the treatment of erectile dysfunction in the real world. It is accepted widely by our patients as first line treatment and is successful in 91% of our patients. At the end of the study period 80% of the patients were willing to continue with sildenafil therapy. In our part of the United Kingdom, there is a large expectation for ED to be treated in the NHS. Of those men eligible for treatment of their ED in the NHS, 30% qualify under the clinical categories and 18% under the 'distress' category. This has implications on the local prescribing policies and resources. Under the current guidelines, only 55% of men with one or more cardiovascular risk factors qualify for treatment in the NHS. The majority of men presenting with ED could be managed in primary care.

Competing interests

We are grateful to Pfizer plc for providing an independent educational grant towards the Research Fellowship of KS. Pfizer plc have neither contributed nor influenced the material data or conclusions of this study.

Author contributions

K Sairam and T McNicholas are the principal authors. E Kulinskaya provided statistical support. D Hanbury and G Boustead edited and revised the manuscript.

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