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VIAGRA: WHAT'S THE STORY... ?

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I. INTRODUCTION

The emergence of sildenafil (Viagra) and orlistat (Xenical) has prompted widespread debate on the limits of NHS coverage, in particular with respect to "lifestyle drugs". Thoughts from both sides of the debate were summarised at a recent King's Fund discussion[1]:

> *"The NHS should not provide Viagra or other treatments which threaten to turn the NHS into a national happiness service... Personal sadness and emotional distress are not diseases to be relieved on taxpayers' money."*
>
> *"The role of the NHS has changed since its inception. It is about enhancing people's quality of life as well as extending it... Obesity, impotence and baldness cause anxiety, loss of self image and even suicide. New treatments are effective and modern doctors must have these breakthrough therapies at their disposal to use wisely."*[1]

The debate is far from resolved, and the number of new technologies which improve quality of life in its widest sense without effect on longevity will only increase. If health economists are to contribute constructively to policy debates around new technologies such as these, we need to separate policy debate from media hype and scientific fact from moral opinion.

As part of the West Midlands Development and Evaluation Service (DEC), researchers at the University of Birmingham conducted a systematic review of the effectiveness of sildenafil citrate for the treatment of male erectile dysfunction (ED)[2]. In this paper we summarise the main findings of the review in terms of the epidemiology of ED and the effect of sildenafil citrate on both erectile function and health related quality of life. The full report is available from the Department of Public Health and Epidemiology at the University of Birmingham.

Since the licensing of Viagra in the USA at the end of March this year, the buzz of media attention, hype and debate around the drug has spread across the globe. Sildenafil was depicted as the herald of "the new era of lifestyle drugs", set to reach annual worldwide sales of over $5bn and "ultimately.. turn the pharmaceutical industry into an engine of growth for the entire economy."[3] From a cross-section of the media, we aim to summarise the debate so far around sildenafil and the NHS, and to draw out the apparent key concerns.

Finally, we address how these concerns could or should be interpreted by health economists. Is the sildenafil debate a political arena, where evidence based medicine takes a back seat to affordability concerns and media morality? Or do we have theories and frameworks with which to structure the debate and draw out key recommendations for policy and research? In this paper we investigate the evidence

around key concerns, and suggest two possibilities for explaining the apparent conflict between relative cost-effectiveness and (suggested) NHS priority:

- that the DEC review has misrepresented the effectiveness of sildenafil in terms of health related quality of life, and
- that the ongoing debate is simply evidence of social disability weightings which are misrepresented by individually derived health state valuation tariffs

II. BACKGROUND

Epidemiology[2]

Male erectile dysfunction is defined as the persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection[4]. The degree of ED varies and may range from a partial decrease in penile rigidity or ability to sustain an erection to complete erectile failure[5,6]. The US NIH Consensus Development Panel on Impotence concluded that the term erectile dysfunction should replace the more general term impotence, which can carry pejorative connotations and is also used to refer to libidinal, orgasmic and ejaculatory problems[7].

Erectile dysfunction is often broadly classified as *organic* or *psychogenic*[6]: *organic* refers to ED with a clear physical cause (e.g. spinal cord injury) or occurring in conjunction with a condition known to be a risk factor for ED (e.g. diabetes); *psychogenic* refers to all other forms of ED. The usefulness of this simple dichotomy is limited, as psychogenic as described above subsumes both ED with a clear psychogenic cause and that where no physical cause has been established, and ignores that ED is often multifactorial in origin[8,9]. The common viewpoint until the late 1970s was that the vast majority of ED was psychogenic[9]. However, advances in our understanding of the pharmacology and physiology of erections have identified an increasing list of organic causes, accounting for roughly 75% of ED[10,11]. The prevalence of ED is particularly high in men with diabetes and other endocrine disorders, heart disease, hypertension and neurological disorders[12,13] and in those with penile anomalies or after pelvic injury or surgery[14]. Around one quarter of ED seen in clinic patients is caused by medication, especially thiazide diuretics[9,15]. The role of lifestyle-related risk factors is less well defined[13], although many "recreational" drugs interfere with sexual function[16,17] and, at least within disease groups, smoking may well have an additional effect on prevalence of ED[18].

The prevalence of erectile dysfunction increases progressively with age, although it is not an inevitable consequence of aging[7,5]. The aetiology of erectile dysfunction to some extent explains this age-dependency as many organic causes are age-related diseases (e.g. diabetes (NIDDM))[19]. As such, organic and

particularly mixed cause chronic ED is more commonly found in older men, whilst psychogenic factors are the most likely cause of intermittent ED in young men[20].

ED is not only non-life-threatening, it is also bounded by cultural, religious and legal issues and is therefore often under-reported[14]. There are a limited number of studies that attempt to estimate ED prevalence, although inconsistent or non-existent definitions of erectile dysfunction make comparison difficult; these studies are summarised elsewhere[2]. The classic work of Kinsey[21] and the more recent Massachusetts Male Aging Study[18] remain the key sources of epidemiological data on erectile dysfunction, although neither are based on strictly representative samples. These estimate the prevalence of complete ED increases with age, from less than 1% of under-30s to over 50% of over-80s. For the English adult male population, this equates to a prevalence of 9.45%, or 1.84 million men.

Over 85% of this total is men over the age of 50; men over 60 account for 70% of the total, and the over-70s alone form 49% of all men with ED. It is clear from this that estimates of the impact of sildenafil on the NHS will be very sensitive to assumptions made concerning the prevalence of erectile dysfunction and the sexual behaviour of elderly men. It is unfortunately in precisely these older age groups that evidence on sexual behaviour is weak.

Current Treatment Options

Current treatment options for erectile dysfunction include: psychological management, vacuum constriction devices, intracavernosal injection (ICI) therapy, transurethral drug delivery (MUSE), penile prostheses and surgery. A number of other products for the treatment of erectile dysfunction are in active development[2]. A summary of the key trials of ICI and MUSE shows the proportion of men achieving satisfactory response ranges from 50-80% for ICI and from 50-60% for MUSE; however, pain is reported by around 20% of men[2]. Vacuum devices are the cheapest form of treatment for ED in the longer term, and provide a safe method of obtaining adequate erections in up to 90% of patients[22,23]. However, the devices can be difficult to use and the interference with spontaneity[24] and other effects may be unacceptable to many men or their partners[25].

Currently, most treatments for erectile dysfunction are initiated in secondary care; this has to a large extent been due to the nature of the treatments and the need to train patients in how to use them[2]. Although many health authorities require men to purchase their own vacuum pumps, all other treatments are currently available on the NHS. In 1997 the NHS spent £6m on ICI prescriptions; this look set to double with the introduction of MUSE in February 1998. This increase matches recent experience of urologists and psychosexual medicine specialists in the West Midlands, who have seen rapidly increasing numbers of men presenting in clinics in recent months, with clinic waiting lists by September of up to 12 months[2].

PACT prescription data do not provide associated patient numbers, so the number of men in England currently treated for erectile dysfunction under the NHS with ICI and MUSE needs to be estimated from realistic dosage rates. A weekly dose of between 0.6 and 1 equates to between 12,000 and 20,000 men treated in 1997, and up to double that by the end of 1998. At most, this represents 2% of men with ED. There are no data on the number of men using vacuum devices.

There are also no data available on the number of men currently treated privately for erectile dysfunction. The 1997 Impotence Association survey found that the majority of men surveyed took independent action concerning their condition before visiting their GP. 13% of men surveyed contacted a private clinic before seeing their GP, 10% visited a private specialist and 41% purchased items privately, with half of these men spending over £100 and 8% spending over £1,000[26]. Whilst the survey does not represent a random sample of the total ED population, it provides extensive information on the experience of men with erectile dysfunction (and their partners) who have sought treatment for their condition.

The Story so far: Viagra Debate March-December 1998

Ongoing debates over "lifestyle drugs" in general and Viagra in particular suggest that dominant concerns of health care professionals and the general public extend beyond those of evidence on effectiveness and cost-effectiveness. A précis of media coverage of sildenafil is given here:

March - April	FDA licenses sildenafil and publishes clinical review (27/3/98)[27] Launch of Viagra in USA, on a sexual function disorder market where 1997 sales were $157m, of which MUSE accounted for 69%[28] After four weeks, the sexual function disorder market has increased to over 10 times its previous size, and Viagra has captured 97.5% of the market[29]
May	For its first five weeks, Viagra is the top product launch ever; prescriptions continue to increase[30] First trial results are published in the New England Journal of Medicine[31,32] Business Week announces the "new era of lifestyle drugs" and sets out the main issues: the uncertainty around potential demand, both from true sufferers and those looking for enhanced performance; the opportunity for detecting underlying disease; and when treatments are life-enhancing[3] and patients "not severely impaired" can insurers pay for treatments but not enhancements, and how bad does your condition have to be before you are "impaired"?[33] The European Agency for the Evaluation of Medicinal Products (EMEA) adopts a positive opinion on the marketing authorisation application for the EU. Sildenafil citrate is indicated for men over 18 following medical history and examination and without any of the listed contraindications or causes for caution[34]
June	News of the "Pfizer riser" hits the UK media as a "fully fledged social phenomena"; with media interest itself fuelling claims that inappropriate demand will swamp the NHS for what "is clearly a lifestyle drug rather than a treatment for a life-threatening condition"[35] Tessa Jowell states that sildenafil "will be available on NHS prescription to meet identified clinical need"[36] but Frank Dobson stresses that prescription will be tightly controlled; such

	indications of "firm national guidance" are welcomed[37]
July - August	Speakers at the BMA annual conference claim Viagra could add £1bn pa to the NHS drugs bill and lead to "sex by postcode"[38,39,40] whilst consultant-only prescribing would cause chaos[41]. Others highlight the severity of impotence, leading "to depression, alcoholism and even suicide, affecting wives and children as well as men"[42] In a House of Commons debate on the prescribing of Viagra, Evan Harris sets out the special characteristics of Viagra as: publicity, potential demand for recreational use, majority of demand from currently untreated men, and no clear future savings. He claims arguments for £1bn cost, secondary care prescribing and ED as a non-health issue are false, and calls for public debate on rationing[43]. In response, Alan Milburn suggests secondary care prescribing for a limited group of men with ED[43] Some journalists begin to set out groups for whom Viagra is unlikely to work[44] Meanwhile, Viagra sales in the US fall from their May peak but demand remains high despite low third-party coverage and total sales for the first year are forecasted to reach $1bn[45] Sildenafil is approved by the EU states' representatives[46]
September	Programmes on Viagra are screened by all five television channels Letters to the NEJM highlight possible side-effects of sildenafil treatment and "emphasize the need for physicians to consider the cardiovascular status of men with erectile dysfunction before any treatment is prescribed"[47] The UK price of £4.84 for 50mg dose is announced and Pfizer claim that the annual drugs bill from sildenafil treatment will be no more than £50m[39] The day before it is licensed, GPs and Health Authorities are informed that "as an interim measure, SMAC has advised that doctors should not prescribe sildenafil"[48]. Frank Dobson argues too-high expectations and health service priorities[49]; the media sees a Viagra ban but welcomes signs of an explicit approach to rationing[50,51,52,53]. North Nottinghamshire Health Authority goes a step further by restricting sildenafil, if approved, to secondary care prescribing for at least one year[49] The UK move is welcomed though criticised overseas[54], where funding decisions over sildenafil vary[55] GPs agree with the moratorium but worry over increased workload[56,57] The media increasingly discuss rationing and NHS priorities[58,59]
October - November	Seroxat joins Viagra and Xenical as the new lifestyle drug when it is approved for social phobia and interpreted by the media as the "pill for shyness"[60] It is suggested that the government want to limit expenditure on Viagra to the £10-12m currently spent on alternative treatments[61] Calls are made to allow private prescription by NHS GPs[62,63] The King's Fund debates lifestyle drugs and rationing[1] FDA post-marketing surveillance data leads to new warnings advising caution before prescribing sildenafil to men with certain health problems[64] Viagra sales for the third quarter (July-Sept.) are $115m for the US and $26m for the rest of the world, bringing total sales since launch to $524m for the US and $27m for the rest of the world. Viagra is now launched in 27 countries, this will reach 50 (including EU countries) by the end of 1998[65] The first Viagra-heist: a lorry-load of Viagra is stolen in the Netherlands[66]
December	A decision on sildenafil is expected before Christmas

Whilst the media coverage detailed above has provided Pfizer with a near perfect substitute for direct to consumer marketing, and at a fraction of the cost, it has also heightened concerns:

- that the size of potential demand for Viagra will result in exorbitant cost to the NHS, such that Viagra should not be prescribed on the NHS as it is unaffordable
- that the size of potential demand for Viagra will result in unmanageable increases in workload for GPs and, depending on delivery route, for secondary care clinics
- related to both the above, that the potential for abuse of Viagra means it should be prescribed only in secondary care, or that it should not be prescribed on the NHS
- that reported severe side-effects suggest Viagra should not be available on the NHS until further evidence on safety is available
- that Viagra treats a lifestyle condition, and should not be prescribed on the NHS as it is an enhancement rather than a treatment
- that Viagra treats a personal condition which does not represent a health problem, and should not be treated on the NHS
- that in the context of expected cost impact and severity of condition addressed, Viagra should be given relatively low priority in NHS funding, such that its availability on the NHS is limited

Safety concerns are addressed in the following section. Concerns over potential demand, affordability and workload are addressed in section IV, and issues relating to definitions of health and relative priority are addressed in the final section.

III. EFFECTIVENESS AND COST-EFFECTIVENESS OF SILDENAFIL

Effectiveness

The systematic review of sildenafil identified twenty-one randomised controlled trials comparing sildenafil to placebo. Three of these have been published[31,67] and twenty are summarised in the new drug application (NDA) submission to the FDA[27]. Sildenafil has been evaluated in approximately 4,500 men, of whom 560 received treatment for at least one year. All trials showed a statistically significant improvement in erectile function with men using sildenafil compared to placebo.

The outcome measures used in sildenafil trials vary. Eight phase II trials measured penile rigidity following oral treatment with sildenafil or placebo. Rigidity of 70% of maximal is considered satisfactory for sexual intercourse, while rigidity less than 60% is an indication of organic impotence[68]. In all studies

an increased duration of rigidity >60% was seen with increasing doses of sildenafil*; the clinical significance of this is difficult to quantify[2].

Nine phase II trials and seven phase III trials evaluated erectile and sexual function. Doses ranged between 25mg and 200mg up to once per day for periods of 4 to 26 weeks. Nine trials evaluated fixed doses and seven were variable dose studies with titration according to response and toleration. Eight trials investigated men with broad spectrum ED, two trials studied men with diabetes, two studied men with spinal cord injury, three enrolled only men with ED of no established organic cause and one men with ED wholly or substantially organic. All trials included a treatment-free run-in period prior to randomisation during which baseline data on sexual and erectile function was collected. Trial populations were men over 18 with ED of over six months duration in established heterosexual relationships who had attempted sexual activity during the run-in period. Medical exclusion criteria are listed below; trial results may well not be generalisable to excluded groups. Where provided, baseline sexual activity data show between a third and a half of participants had successful intercourse during the run-in period[69]. The combination of baseline function and exclusion criteria used in the trials suggests that the effectiveness of sildenafil treatment in clinical practice will be below that seen in clinical trials.

Medical exclusion criteria for clinical trials:[69]

anatomical deformities such as severe penile fibrosis
other sexual disorders such as hypoactive sexual desire
major uncontrolled psychiatric disorder
history of drug or alcohol abuse
elevated prolactin or low free testosterone
need for nitrates, androgens, anticoagulants or trazodone
need for aspirin or NSAIDs and history of peptic ulcer disease
history of major haematologic, renal or hepatic disorder
history of bleeding or active peptic ulcer disease
stroke or myocardial infarction within 6 months
cardiac failure, unstable angina, ECG ischaemia or life-threatening cardiac arrhythmia within 6 months
postural hypotension, or blood pressure outside 90/50 to 170/100 mmHg
other experimental drug use within 1 to 3 months
uncontrolled diabetes or diabetic retinopathy
history of retinitis pigmentosa
any clinically significant baseline laboratory abnormality
spinal cord injury (except trials 358 and 367)

The primary endpoint used in most trials was responses to two questions of the International Index of Erectile Function (IIEF), an instrument specifically developed for the evaluation of sildenafil[70,71]. Question 3 asks for the proportion of successful attempts at penetration and question 4 asks for the proportion of

* In the seven studies which calculated a p-value, the response to sildenafil at doses above 25mg was consistently statistically significantly greater than placebo.

successfully maintained erections after penetration, with response to both questions on a five point likert scale: 0 (no attempt), 1 (almost never or never), 2 (a few times, much less than ½), 3 (sometimes, about ½), 4 (most times, much more than ½), 5 (almost always or always). Responses were analysed as continuous data and the number of men not attempting intercourse is not given; this can make the interpretation of findings difficult. Secondary endpoints included remaining questions of the IIEF, a "global efficiency question" (GEQ) ("Did treatment improve your erections?"), an event log or diary and an optional partner questionnaire.

Over 90% of participants completed these studies, with drop-out rates varying between trials from 1% to 22%[27]. In the eight dose titration studies, over half of participants migrated to 100mg[27]. Primary outcome data are available for nine trials: mean response to question 3 ranged from 3.1-3.8 (for dose 25mg-100mg) compared to 2.2 for placebo; the corresponding range of mean response to question 4 was 3.0-3.7 compared to 2.0 for placebo[2]. Available secondary outcome data shows dose-related statistically significant increases in mean scores for IIEF questions relating to frequency of adequate erections, ease of maintaining erections and satisfaction with erections and overall sexual relationship, but show no treatment effect on sexual desire or libido. GEQ data are provided for all trials and also show a dose response relationship over the dose range 25-100mg, with 65-82% of men treated with sildenafil reporting improved erections compared to around 18-25% of men treated with placebo[2]. Event log data are available for nine trials: for fixed dose studies these show 38-50% of attempts at intercourse were successful for men receiving sildenafil compared to 13-24% with placebo; for dose titration studies 50-60% of attempts were successful with sildenafil compared to 0-25% with placebo. Sildenafil had no effect on rates of attempted intercourse, despite increased success rates[72]. Response rates appear to be lower for men with diabetes than for the overall group, however this applies both to sildenafil and placebo groups and may be related to a lower rate of baseline successful function[2]. Effectiveness does not appear to vary by age[2].

The results of a 'battery of quality of life instruments' completed by 940 men participating in three European trials are available so far only in abstract form[73]. The study reports quality of life scores for men with broad-spectrum aetiology ED at baseline and at 12 weeks using SF-12 mental and physical health summaries, Psychological General Well-being Index (PGWBI), Rosenberg Self Esteem Scale, Medical Outcomes Study Family Interaction Survey, Impact of Erectile Problems Scale (IEPS), and questions on satisfaction with relationship with partner and general health compared to three months ago. Those receiving sildenafil treatment showed significant improvement at 12 weeks compared to placebo on SF-12 mental health summary, positive well-being, self-control and depression dimensions of PGWBI, IEPS and questions on satisfaction with relationship with partner and general health (mean improvement varied across measures from 0 to 30%, compared to -4 to 7% for placebo). The placebo group showed a

significant improvement over sildenafil on SF-12 physical health summary score, other instruments showed no significant effect[73]. The authors conclude that sildenafil treatment results in significant improvements in key quality of life parameters, although assessment of these findings awaits the availability of the full results[2]. Response rates to the optional partner questionnaires were low and response data are currently unavailable[2].

Safety

Sildenafil has a relatively safe side-effect profile. Adverse events were reported by around 60% of men receiving sildenafil in trials and 40% of men on placebo but were responsible for drug withdrawal in only 2.5% and 2.3% respectively[72]. A further 1.9% withdrew due to adverse events during open label extensions[74]. Adverse events were mainly transient, mild or moderate in nature and dose related[75]. The most common adverse events associated with sildenafil are related to vasodilation (headache, flushing, nasal congestion); dyspepsia and abnormal vision are also reported. All these events reflect the known pharmacological properties of sildenafil[75]. The safety data from trials show no clinically significant changes in blood pressure, heart rate or ECG with sildenafil treatment[74], and there was no difference in the incidence of serious cardiovascular events (myocardial infarction, angina and coronary artery disorder) between sildenafil and placebo groups[75].

FDA monitoring of the post-marketing safety of sildenafil reports 130 US deaths over the period late March to mid-November 1998[64]. These have occurred in the context of over 6 million prescriptions issued over this period. Of the US deaths, 128 were possibly related to use of Viagra; only twelve of these had no history of cardiac disease or risk factors, and at least 16 had used nitrates (contraindicated with sildenafil). The report draws attention to the background risk of sudden cardiac death in this age and risk factor population and the additional risk associated with sexual activity[64].

Sildenafil is licensed as a prescription-only medicine for the treatment of erectile dysfunction in a sub-group of the adult male population. This sub-group is defined as men who[34]: (a) are over 18 and have undergone a medical history and examination by a physician to diagnose ED, determine potential underlying causes and decide if pharmacological treatment is appropriate; (b) are not using nitrates, either regularly or intermittently, in any form; (c) have not recently had a stroke or heart attack, do not have low blood pressure, severe heart or liver problems, or certain rare inherited eye disease. In addition, caution is recommended before prescribing sildenafil to patients with sickle cell anaemia, leukaemia, multiple myeloma, bleeding disorders, active peptic ulceration or any disease or deformity of the penis. Sildenafil must not be used together with other treatments for ED. Caution is also advised before prescribing sildenafil to men with hypertension or "underlying cardiovascular disease which could be affected adversely by .. vasodilatory effects, especially in combination with sexual activity"[76].

Cost-effectiveness

Sildenafil has not been directly compared with current treatments for erectile dysfunction, although comparative trials with alprostadil (used in ICI therapy and MUSE) are due to commence in 1998[2]. These two drugs have different mechanisms of action: alprostadil is a vasodilator which acts to relax smooth muscle directly and therefore produces erections in the absence of sexual arousal; sildenafil enhances the effects of nitric oxide, which is released in response to sexual stimulation, and is therefore ineffective in the absence of arousal[2]. Different mechanisms of action mean that sildenafil may be effective in men in whom alprostadil is ineffective and vice versa, although it is anticipated that there will be a group of men with ED for whom neither treatment is effective[32].

Trials of alprostadil and sildenafil are not directly comparable, due to differences in study subjects, assessments and duration. A summary of the key trials of ICI and MUSE[2] suggest that sildenafil is at least as effective as these alternatives in the major patient groups under study in terms of clinical outcome measures. In addition, sildenafil does not require uncomfortable insertion or injection, has fewer side-effects than alprostadil and, if effective, produces an erection only when sexually aroused rather than automatically, whether desired or not. At a cost of £4.84-£5.87 per dose, the drugs cost of sildenafil is 50-60% that of alprostadil; the suitability of sildenafil for primary care prescribing, due to the lack of perceived side-effect problems and lack of need for specialist diagnosis and monitoring, may further reduce treatment costs relative to ICI therapy or MUSE. If these tentative comparisons of effectiveness are supported by comparative trials, sildenafil will be shown to dominate both ICI and MUSE in a cost-effectiveness analysis, being less costly and at least as effective[2]. Vacuum devices are the cheapest form of treatment for ED in the longer term, and appear at least as effective as other options[22,23], but may be unacceptable to many men[25].

All current predictions of the patient population for sildenafil extend far beyond those currently receiving alprostadil treatment, so whilst for some the relevant comparison will be between sildenafil and current treatment options, for the majority the appropriate comparator is no treatment. In this case, sildenafil treatment under the NHS represents an additional resource burden, and should be evaluated against alternative uses of such additional funds. In comparison to no treatment, sildenafil treatment in primary care is likely to cost around £310 per annum[2]. Treatment results in improved erectile function in at least 50% of men treated, and this improvement is likely to be reflected in improved satisfaction with sexual and overall relationships, self-esteem and overall mental health[73].

Available data do not allow QALY gain from sildenafil treatment to be calculated with confidence, although a rough estimate can be taken from existing tariffs of health state values such as that calculated

for the EuroQol EQ-5D classification[77], where the reduction in anxiety or depression associated with successful sildenafil treatment for one year would be translated into a QALY gain of 0.071. This provides a 'ball-park' cost-utility estimate of £7,000 per QALY gained; the figure is highly sensitive to the assumed degree of improvement in health-related quality of life associated with successful sildenafil treatment[2]. Three urological studies[78,79,80] have estimated utility values for erectile dysfunction, all in the context of prostate cancer; these provide a range of values for the annual QALY gain from successful treatment of 0.05-0.15 QALYs. This range provides cost-utility estimates of £3,000 to £20,000 per additional QALY gained; whilst this range may be too broad to be useful policy information, it fits a current DEC decision band that would result in the introduction of sildenafil treatment in the NHS being "strongly supported"[2].

IV. POTENTIAL DEMAND AND AFFORDABILITY

Potential Demand

The potential demand for sildenafil is difficult to gauge. Given that an oral treatment is far more acceptable than self-injection or urethral insertion, demand will be greater than the current 2% of men with ED. Low satisfaction with current treatments[26] suggests many of the presenting 2% will switch to sildenafil when, as promised, it becomes available on the NHS[36†]. The uncertain extent of hidden demand for sildenafil treatment is the main factor behind the range of publicised cost impact estimates from £50m[81] to £1bn[39] per annum drugs costs.

Unfortunately, there is no information on what proportion of men with erectile dysfunction are interested in seeking treatment for their condition. Estimates can be based on sexual functioning studies and survey findings on acceptance of ED, although changing attitudes towards human sexuality in recent years and increased awareness of erectile dysfunction in recent months may well prompt men who previously accepted or tolerated ED to seek treatment.

A Danish study of 51 year old men found that, whilst 40% reported erectile problems, only 7% thought this abnormal for their age and only 5% intended to seek treatment[82]. Erectile dysfunction has a devastating effect on some men, whilst others tolerate it as an accepted part of the ageing process[83]. The proportion of men with erectile dysfunction that are interested in treatment will be low if it is true that:

> *"In many older persons, erectile impotence is, fortunately, accompanied by a decline in and usually complete cessation of erotic response"*[21]

However, the proportion of men with ED presenting for treatment will be high if:

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† Men currently treated by the NHS presumably have "identified clinical need"

"Knowing that one has the capacity to perform sexually is an important part of the sexual self-image of any person, and adjusting to the loss of sexual capability is rarely a "non-event", even in celibate individuals"[84]

Existing research on the sexual behaviour of older men is limited. The classic study of human male sexual behaviour is that of Kinsey and Pomeroy, carried out in the 1930s and 1940s in the USA[21]. Kinsey's work showed that age was by far the most important factor affecting frequency of sexual outlet in the sexual history of the male. Whilst frequency of intercourse was bound up in the social context of the time (and place), data on total sexual outlet showed:

"There are no calculations in all of the material in human sexuality which give straighter slopes than the data showing the decline with age in the total outlet of .. males. Starting from a high point of 3.2 for the single males, or 4.8 for the married males, in the middle teens, the means for both groups drops steadily to about the same point, 1.8 per week at 50 years of age, to 1.3 per week at 60 years, and to 0.9 per week at 70 years .. there is a more or less corresponding decrease in frequency for each type of outlet"[21]

The suggested reasons for this decline were physical and psychological, although:

"How much of the overall decline in the rate for the older male is physiologic, how much is based on psychologic situations, how much is based on the reduced availability of contacts, and how much is, among educated people, dependent upon preoccupation with other social or business functions in the professionally most active period of the male's life, it is impossible to say at the present time"[21]

Further studies since Kinsey have added to the descriptive data on human sexual function and may provide an illustration of changes in behaviour, especially in the unmarried population, with changing social mores, but have neither altered the essential relationship between age and sexual activity nor gone further in attributing its cause between Kinsey's possible explanatory factors of physical and physiologic decline, psychologic fatigue and pressures of social responsibilities.

One of the weaknesses of the Kinsey data is the small number of men over 60 years old included in the study. Further studies in the 1960s and 1970s added to the frequency data for both men in general and for the elderly in particular[85,86] but was largely focused on men of particular ages or with particular conditions, and as such is restricted in scope. The Massachusetts Male Aging Study[18], conducted in 1987-89 and based on a sample of 1,709 men aged between 40 and 70, provides the main source of population-based data on frequency of sexual activity in older men. The main study of sexual behaviour in the UK used an age cut-off at 59, due both to the finding in pilot work that older people found the study more intrusive, with associated lower response rates, and to the study focus on issues of more relevance to

younger than older groups (infertility, unwanted pregnancy, sexual risk behaviour and HIV)[87]. A similar study provides local data for the West Midlands[88]. The government is to commission a second UK survey, but this will be restricted to people aged 16-44[89].

Given estimates of ED prevalence by age, these studies suggest that the proportion of men without ED who are sexually active falls from near 100% of men under 60 to 75-85% of men in their 60s, 60-70% of men in their 70s and 40-60% of men in their 80s. These estimates are very tentative, and require further evidence on the breakdown of sexual inactivity between ED and other causes. Very little is known about the reasons for sexual inactivity in the general population, and inactivity in men without ED may be due to a combination of factors surrounding interest, opportunity and, perhaps most importantly, interest and dysfunction of partner. Treatments for ED will only restore sexual functioning to couples where the man's ED is the only factor preventing current activity; the future availability of similar treatments for women may well have a far larger impact on demand, as these will enable couples to overcome sexual dysfunction, whichever party is affected.

Of course, embarrassment and lack of knowledge of available interventions may continue to prevent many men seeking treatment. The extent to which this will occur is difficult to predict. The Impotence Association survey findings suggest that up to a quarter of men currently interested in treatment for erectile dysfunction have not visited their GP, due largely to embarrassment, belief that the condition was incurable or self-resolving, or that their GP would think their condition unimportant or had more important problems to deal with[26]. If the proportion of men with ED interested in treatment falls from all of those under 60 to 40% of those over 80, and if 15% of interested men never present (due to embarrassment, etc.), then the potential demand for sildenafil may be up to 65% of men with ED, or 1.2 million men in England. Pfizer estimates a lower presentation rate of nearly 40%, or 0.7 million men[90].

Data from the US may provide some indication of potential demand in England, although social and cultural differences as well as important differences in health system funding mean that US presentation rates are unlikely to be replicated here. Applying the above estimates of ED prevalence by age, levels of interest in sexual activity, etc. to US population data[91] suggests a potential US demand of between 3.4 and 5.7 million men, for the higher and lower presentation rates above. Not all men will be suitable for treatment; a treatment rate of 70% of men presenting would result in between 2.4 and 4 million men prescribed sildenafil. By the end of September, over 3 million men had been prescribed Viagra in the USA[65]. If all these men were true ED sufferers, this figure supports the above range of presentation estimates and suggests sufferers will present quickly. Some proportion of US prescriptions may well have been to men with only mild to moderate ED; defining ED as a persistent or recurrent condition[4] would exclude such men from prescription on the NHS.

Unlike many medications, there is no set dosage for sildenafil. The rate at which sildenafil tablets are prescribed may be set by national guidance, by GP views on appropriate prescribing levels, or by men's desired usage rates. The existing US studies of sexual behaviour suggest that frequency of intercourse in active males declines with age, with median frequency per week falling from 1-2 for men in their 30s and 40s to 0.8-1 for men in their 50s and below this for men over 60[21,85,86]. Available data for the UK support the US estimates[87,88]. Clearly, men presenting for sildenafil treatment will form a distribution around these median values, from those with a low frequency of activity desiring the ability to perform if the opportunity arose ("just in case packet of 3") to those who, were it not for their ED, would be in highly active sexual relationships.

If the average prescribing rate is one dose per week, this equates to an annual drugs cost of around £250-300, depending on dosage. As such, the driving factor in affordability concerns is not unit cost but numbers of currently untreated men presenting. This may be different to technologies at the centre of other rationing debates, where presenting numbers are small but unit cost is high.

Workload

Currently, most treatments for erectile dysfunction are initiated in secondary care; this has to a large extent been due to the nature of the treatments and the need to train patients in how to use them. The relative safety and ease of use of sildenafil suggests that it is entirely appropriate for primary care prescribing. Indeed, there is wide agreement among urologists, pharmacists and GPs that the primary diagnosis of ED and its treatment with sildenafil can be undertaken safely and more efficiently in the primary care sector. A GP is more likely to be aware of co-morbidity or medications that may be the cause of ED, and of cardiovascular status, family situation and other factors that may influence appropriate treatment. The assessment of a patient with ED is thought to be well within the competencies of a GP, with specialist referral required only if diagnosis or underlying cause is uncertain or if first-line treatment fails[2].

The above estimates of potential demand translate to a presentation rate of 1,430-2,410 men per 100,000 total population, of which 1,000-1,690 men will receive sildenafil treatment and 600-1015 are likely to continue treatment. Potential increases to clinic workload can be calculated as multiples of the above, according to population coverage. If a GP serves a population of 2,000, the respective figures will be 28-48 men presenting, of which 20-34 will be treated and 12-20 of these continue treatment. With one consultation per man presenting, two more for treatment and two more to continue treatment over a year, this equates to an expected additional GP workload of 93-156 additional consultations, spread over the time period taken for all presentation to occur. Many of these men will be current patients with known risk factors for erectile dysfunction. Others will need clinical assessment for heart disease, diabetes, etc.,

with referral to secondary care if there is either no clear diagnosis or a need for specialist treatment (e.g. psychosexual counselling). If prescribing is limited to secondary care, the addition to GPs workload will be related to numbers presenting, with men requiring assessment for referral and perhaps follow-up care whilst on clinic waiting lists.

Whether this constitutes an unmanageable increase in workload depends, for GPs, on the timing of presentation for treatment, and for clinics on the total population served. The opportunity cost of both GP consultations and clinic appointments needs to be considered. A survey of clinics in the West Midlands in August 1998 suggested that many were already operating at more than full capacity[2]. The unit cost of treatment will also be related to the prescribing policy chosen. In the Commons debate, Evan Harris argued that "there are no immediately obvious down-the-line savings through the prevention of either in-patient admission or a worsening in health that would require more expensive treatment"[43]. However, the availability of sildenafil is likely to lead to many men with undetected co-morbidity presenting in primary care. This offers an opportunity to increase detection of diseases which are the cause of considerable morbidity and mortality as well as cost to the NHS, namely diabetes[92,93] and coronary heart disease[94]. If detection leads to improved management of such conditions, there will be undoubted future benefits and savings[95,93] although also additional treatment costs.

Inappropriate Demand

In practical terms, there is no clear diagnosis for erectile dysfunction. Epidemiological data measuring mild to moderate impotence in addition to the persistent erectile problems covered by the definition of ED suggest that the total population affected to some degree by erectile difficulties may be up to five times that of the ED population[18]. For England, this means that whilst 1.84 million men are likely to suffer from complete erectile dysfunction, up to 10 million are likely to experience erectile problems of some degree. Sildenafil may therefore be wanted by a population up to five times that of men in clinical need. Any presentation of men with only mild to moderate impotence will increase demand and workload above those shown above.

The potential for abuse of NHS provision of sildenafil raises concerns for all involved in developing a strategy for the introduction of this drug to the NHS. These concerns have been exacerbated by the volume of media attention that has been paid to this new technology. Calls for secondary care prescribing have often been based on fears over inappropriate use of new health technologies. However, it is unclear how secondary care prescribing can do more to restrict inappropriate use than primary care prescribing if there is clear guidance on restrictions and if education is provided to GPs, to ensure a consistent approach to sildenafil prescribing, as well as to the public and/via the media to dissuade inappropriate requests.

V. REMAINING ISSUES

The systematic review of sildenafil in the treatment of erectile dysfunction concluded that this was a highly effective and seemingly cost-effective technology, whose introduction to the NHS would be supported on current criteria[2]. This assessment is far more positive than that emanating from the majority of debate detailed above. Two possible explanations of this apparent conflict are: (a) that the effectiveness of sildenafil in terms of health related quality of life is far lower than that estimated by the review; or (b) that the measurement of benefit is appropriate, but should be weighted by some value $\alpha < 1$ to reflect social preferences for the relative priority attached to conditions and/or beneficiaries such as apply here.

(a) Sexual Functioning, Health and Health Related Quality of Life

The primary question here is whether sexual function is part of health. 'Sexual health' is now a widely adopted term, and:

> *"... most definitions of health include reference to adequate function of all organs of the body, without discrimination, and the ability to perform most functions, without discrimination, that people and professional doctors would consider to be normal"*[43]

Acceptance of sexual health as part of health care objectives implies the acceptance of a range of conditions as 'disease', including erectile dysfunction. New technologies which address these conditions should therefore be accepted as treatments rather than lifestyle enhancements. Erectile dysfunction is clearly not a life-threatening condition, and may be described as a condition "somewhere between painful and uncomfortable"[3], however it is a recognised medical condition that is currently treated by the NHS. Arguments of lifestyle drugs and enhancements rather than treatments may well apply for men with only mild to moderate erectile problems, but not for men with ED defined as a persistent or recurrent condition[4]. For at least three-quarters of sufferers ED is related to underlying chronic organic disease, and for others may well be related to psychological problems.

The importance of quality of life outcomes in urology was highlighted by a US study which showed that men were willing to trade survival for maintenance of sexual function[96]. Yet until recently, there had been relatively little research carried out on the assessment of health related quality of life of patients with urological conditions. The last few years have seen the development of a substantial body of research regarding health-related quality of life in patients with genitourinary malignancies (especially prostate cancer) and benign prostatic hyperplasia (BPH). This has included the development and validation of disease-specific quality of life instruments, as well as the use of generic quality of life questionnaires such as the Nottingham Health Profile, SF-36 and EuroQol EQ-5D[97,98]. In contrast, there remains little

research examining health related quality of life in patients with other urological conditions, such as incontinence and sexual dysfunction[‡]. Incontinence and erectile dysfunction are typically assessed by traditional outcome measures i.e. questions on degree and frequency of incontinence or on frequency and satisfaction of sexual activity. However, assessing the impact of these conditions on quality of life also requires subjective measures of severity[97].

Ofman[84] provides a detailed discussion of the possible quality of life impact of male erectile dysfunction and highlights the shortcomings of current attempts at its measurement:

> *"Possibly because of the difficulty of assessing the complex question of sexual functioning in the context of quality of life, it is usually measured as a sub-category of physical functioning.. Often, no clear definitions of what constitutes dysfunction are given... [and questions do not] take into account the possibility that even if no intercourse occurs, there may be erectile functioning, sexual desire and other sexual behaviour. The systematic assessment of sexual functioning would require a structured interview or questionnaire in which the following dimensions were evaluated: sexual interest (thoughts about sex, wish for sexual activity, auto-eroticism), sexual arousal (sensation of feeling sexually aroused, occurrence of erection, volume and rigidity of the erection both in situations with partner and without), orgasm (premature ejaculation, difficulty ejaculating, sensation), pain & discomfort during or after sexual activity, body image, and masculine self-image."*[84]

A recent review of studies addressing quality of life effects of ED notes that the lack of high quality information in this field could be expected given that ED was until recently a relatively little-studied condition with few treatments and scarce epidemiological data[99].

Several observational studies have found a negative association between (severity of) erectile dysfunction and general quality of life scores[100,101,102]. The Massachusetts Male Aging Study[18] found a significant positive association between erectile dysfunction and both depression and anger expression or suppression. The absence of control groups in such studies makes interpretation of these findings difficult, and some authors note that such associations may well be due to the influence of co-morbid disease and/or of uncertain causality[101,18].

The impact of erectile dysfunction on health related quality of life has been assessed in several recent clinical trials of ICI, MUSE and sildenafil[103,104,105,106,73]. An immediate problem for any attempt to summarise these findings is that each trial used a different combination of general and disease-specific

[‡] Although research on BPH and prostate cancer can provide information on ED and other sexual dysfunction as side-effects of treatment

quality of life instruments. Two studies of men on ICI therapy show significant improvements in sexual functioning and in mental health and self-esteem dimensions of the Duke Health Profile[103,104]; however the small number of participants in one study[103] and lack of control group in either make interpretation of these findings difficult. Results from trials of MUSE including quality of life instruments are currently available only in abstract form[105,106]; these found significant improvements in emotional well-being and in relationship with partner for men successfully treated with MUSE, although these results should be treated with caution until publication allows the quality of the trials to be assessed[2]. The results of the study investigating effects of sildenafil on health-related quality of life, as discussed earlier, are also available only in abstract form[73], showing significant improvement on SF-12 mental health summary, the positive well-being, self-control and depression dimensions of Psychological General Well-being Index, Impact of Erectile Problems Scale and questions on satisfaction with relationship with partner and general health.

Whilst the IIEF is now the internationally accepted measure of clinical effectiveness in erectile dysfunction treatment, there exists no comparable single measure to capture the impact of erectile dysfunction on sufferers' quality of life. The above assessments of the impact of ED on health related quality of life have used a variety of generic and disease-specific measures, however generic measures used thus far do not include multi-attribute utility scales which can be used to construct QALYs. The only estimates of the impact of ED in QALY terms are from three studies of prostate cancer treatment which estimated utility values for major adverse effects, including erectile dysfunction. The estimated reduction in health related quality of life due to erectile dysfunction ranged from 0.05 to 0.15[78,79,80].

On balance, the quality of life research concerning erectile dysfunction suggests that such an improvement will be associated with a significant improvement in satisfaction with sexual and overall relationships, self-esteem and overall mental health. How this can be translated into QALY improvement will depend on the dimensions of the multi-attribute utility scale used. Only the 15D measure explicitly includes sexual activity as one of its fifteen dimensions[107]; although the Quality of Well Being scale includes a symptom/problem complex of "problems with sexual interest or performance"[108]. The estimated reduction in health related quality of life (HRQL) due to erectile dysfunction using these measures would be 0.018 and 0.257 respectively. For all HRQL measures, the impact of erectile dysfunction on relationships and mental health can be expressed as a reduction in social and/or psychological function. However, the number of levels per attribute on many instruments means that a one level reduction in social and/or psychological function may well overestimate the degree of reduction in HRQL resulting from ED. Estimating the expected health gain from sildenafil treatment in terms comparable with other health interventions is, therefore, both difficult and inevitably subjective given available data. Cost-utility estimates in the review are in the range £3,000 to £20,000 per QALY, relating to expected health gain of

between 0.013 and 0.082 QALYs[2]. With no direct data on health improvement in QALY terms from sildenafil treatment, it is possible to argue that the true QALY gain is below this range.

(b) QALY gains and social preference weights

The final concern of the ongoing Viagra debate addresses the priority that should be accorded to sildenafil as an NHS provided treatment, in the context of its predicted cost impact, effectiveness and cost-effectiveness. An additional consideration appears to be that the condition to be treated is one causing relatively small reductions in quality of life for people who are otherwise relatively healthy. What weight each of these considerations should have in the decision-making process is less clear, as recognised by Alan Milburn:

> *"Weighing up all those factors - the evidence on clinical and cost effectiveness and the needs of individual patients while keeping a reasonable view on priorities - is a complex affair, involving a range of competing judgements. At the moment, decisions.. ..are taken more or less on an ad hoc basis"*[43]

However, the complexity of the problem should be the reason for promoting, rather than avoiding, the use of transparent frameworks for decision-making.

The tone of debate around relative priority for sildenafil treatment appears to fit the notion of social preferences for health care resource allocation that produce a different set of health state valuations than measures of individual preference. This difference could be due to the inclusion of equity concerns over the condition, treatment, and/or beneficiary group concerned.

Sildenafil is a new health care technology that offers a small quality of life improvement at the top end of the 0-1 scale. If social preferences dictate that lower priority should be given to improvements in quality of life as compared to improvements in length of life, to quality of life improvements in relatively healthy individuals (i.e. at the top end of the scale) in comparison to improvements of similar degree at lower levels of health-related quality of life, and/or to health improvements to groups with certain characteristics compared to others, then QALY gains need to be weighted before estimates of cost-effectiveness reflect social benefits of alternative resource allocation decisions. There is little data on public preferences for such alternative health improvements, although studies by Nord[109,110,111] and others[112,113,114,115] suggest that the public give priority to life-saving interventions over those that improve quality of life, and to QoL-improving interventions at lower levels of QoL over those at higher levels. Clearly more research is needed into the views of the UK population over matters of this sort, under the implication that

interventions for conditions accorded low priority may not be available free (or at prescription cost) on the NHS.

VI. CONCLUSIONS

Just the word Viagra causes most people to smirk. The discovery of an effective and acceptable treatment for erectile dysfunction has led to widespread media coverage of a previously hidden condition, and provided cartoonists with months of material. However, Viagra provides an opportunity to debate some key issues for the NHS, for example:

- what is covered by the terms 'health' and 'disease', and what is not?
- should all treatments for disease be provided publicly, and if not, what factors determine the public/private boundary, and/or the relative priority a treatment receives on the NHS?

Additional issues for health economists are not original but include:

- how to measure benefits of sexual health technologies
- the appropriateness of existing valuation data for priority setting debates
- the need for formal exploration of social values and preferences

The danger is that collective refusal to treat the issue seriously will result in a lack of intelligent debate and missed opportunities for further research.

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