Saturday 19 September 1998

BMJ

Viagra: on release

Evidence on the effectiveness of sildenafil is good

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The popular interest in Viagra (sildenafil) is not solely the result of media hype and the drug's association with sex: the demand for treatment has been enormous. Since its launch in the United States in March it has become the fastest selling drug ever.[1] The demand is being met by prescription in the United States and globally through the internet and on the street, which in Europe precedes its licensing for prescription by doctors.

The level of demand was predictable, given a prevalence of erectile dysfunction of over 50% in men aged 50-70, and the unacceptability, poor effectiveness, or unavailability of existing treatments, such as implants, intracavernosal injection, intraurethral pellets, vacuum devices, and sex therapy.[2] To most sufferers a tablet treatment must have seemed too good to be true.

A localised effect after oral administration is possible because of sildenafil's specificity of action. The final common pathway for sexual arousal and stimulation leading to erection is the production in cavernosal tissues of cyclic guanosine monophosphate (GMP), which relaxes the smooth muscle and permits swelling of the corpora with blood. Sildenafil is a potent and specific inhibitor of cyclic GMP specific phosphodiesterase type 5, the isoenzyme responsible for breakdown of cyclic GMP in the corpus cavernosum. Thus its effect is contingent on sexual arousal or stimulation, giving a more "natural" erectile response.

Sildenafil treatment has been evaluated in 21 randomised, double blind, placebo controlled trials and 10 open label extension studies (continued non-blind treatment after trials),[3] but only three randomised controlled trials and one open label study have so far reached peer reviewed publication. Objective and subjective measures show that sildenafil improves rigidity and the number of erections in men with erectile dysfunction.[4] Two large studies have shown significant and considerable improvement over placebo in quality of erections, proportion of successful attempts at sexual intercourse, and overall satisfaction with treatment.[5] Orgasmic function, satisfaction with intercourse, and overall sexual satisfaction also improved, but there was no effect on sexual drive. Placebo effects tended to be slight. Effectiveness over 32 weeks is shown by an open label extension study from which only 3% of men withdrew as a result of insufficient response, but no more detail than this is currently available.[5]

Pooled safety data from 18 of the 21 studies, totalling over 3700 men aged 18-87 years (equivalent to 1631 years of exposure), showed no evidence of serious adverse effects attributable to sildenafil.[3] The most common side effects are headaches, flushing, dyspepsia, nasal congestion, and transient disturbance of colour discrimination. Up to 30% of participants experienced a side effect, but the authors described these as transient, and in the published randomised controlled trials only 2% of participants discontinued treatment as a result.[5] There were no significant changes in pulse, blood pressure, electrocardiographic findings, or results of laboratory tests (unspecified), and no cases of priapism. The US Food and Drug Administration has reported details of 69 deaths in people taking sildenafil during March to July 1998—during which 3.6 million prescriptions were dispensed—but has not found any need to take regulatory action.[6] The only important drug interaction so far described is the potentially dangerous potentiation of the hypotensive effect of nitrates.[3] This contraindication is important as erectile dysfunction is commonly associated with cardiovascular disease but also because amyl nitrates ("poppers") are drugs of misuse, particularly in the homosexual community.[7]

A long list of exclusion criteria were applied in the studies, including history of alcohol or substance misuse, poorly controlled diabetes, and stroke or myocardial infarction within six months. Samples are therefore not representative of all those who will seek treatment, and we cannot generalise the effectiveness and safety findings to these groups. Nevertheless, there are considerably more data on this treatment than for the treatment options previously available.[8]

The research evidence does not extend to use by women, in whom it may also enhance genital arousal. Some doctors in the United States are already prescribing sildenafil to women, and a trial is currently under way. Sildenafil has also been adopted as an enhancer of sexual performance by men without sexual dysfunction, sometimes in combination with stimulants. This amounts to inappropriate use, or misuse, for which no information on safety or dependency currently exists. Researchers must continue to examine effectiveness and safety in long term use and in patient groups excluded from previous studies. Interesting questions also arise about who the drug does not work for, who would benefit from potentially curative treatments such as surgery or therapy, and what impact

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successful treatment has on quality of life as well as on mental and physical health.

The immediate challenge posed by sildenafil in the United Kingdom involves the need for rational decision making about availability on the NHS or from medical insurers. The challenge for clinicians, mainly general practitioners, is to be adequately informed, which will require urgent availability of information and education, usually sadly lacking in the field of sexual health. Although sildenafil seems to be a simple solution to a common problem, it should not be prescribed without assessment of the patient's physical and mental health and his sexual and general relationships, followed by management of underlying causes, such as diabetes, cardiovascular disease, or change to antihypertensive, antipsychotic, or antidepressant drug treatment. Smoking and alcohol consumption can have a profound adverse effect on erections. Patients may have severe relationship or personal difficulties, requiring counselling or therapy. The various treatment alternatives[9] need to be discussed with the patient and preferably his partner before one is chosen.

Erectile dysfunction is a cause of misery, relationship difficulties, and significantly reduced quality of life for many men and their partners. Whatever the availability of sildenafil in the NHS, the effectiveness of this treatment and the high prevalence of this distressing disorder make it inevitable that it will be taken by large numbers of men. The medical profession must respond with acceptable standards of assessment, followed by regular monitoring of continued effectiveness, appropriateness, and, above all, safety.

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Viagra and rationing

Let the sunlight in, let the people speak

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The inability of Britain's government to come to terms with rationing is exposed by this week's "interim guidance" that doctors should not prescribe sildenafil (Viagra) (pp 000, 000).[1 2] The government should use this opportunity to lead the debate that Britain needs on what will be provided on the NHS, who will decide, and how.

The fiction of the NHS, encouraged by this government and the last, is that the NHS can provide a comprehensive, high quality service that is free at the point of delivery and covers everybody. The reality, well recognised by most of those working in the service, is that health systems cannot meet all four principles.[3] Something has to give. The United States has never had universal coverage. Britain has had continuing slippage in comprehensiveness, quality, and free access at the point of delivery, and now comprehensiveness is abandoned to a blare of trumpets.

"Media coverage of this drug to date," said Frank Dobson, secretary of state for health (recognising an opportunity to try and pin the blame elsewhere), "has created expectations that could prove a serious drain on the funds of the NHS. If this were to happen, other patients could be denied the treatment they need. I cannot allow this to happen." The reality is that patients are denied the treatment they need every day of the week. What's more, coming through the pipeline are a series of "lifestyle" drugs that will be attractive to those who want to be thinner or to soup up their slowing brains. Recognising that the founding principles of the NHS cannot be maintained, many would opt for abandoning comprehensiveness rather than universal coverage, quality, and free access at the point of delivery.

Mr Dobson might thus find considerable support for the painful decisions that have to be made. What is unacceptable is that these decisions are made piecemeal, on the hoof, behind closed doors, according to unknown criteria. We need a comprehensive, transparent, continuing debate that is based on evidence and values. Almost certainly Britain needs an institution—perhaps a version of the Royal College of Physicians' National Council for Health Care Priorities[4]—that can hold the debate. There will be no end to the debate and no neat resolution, but the process will be of vital and continuing importance.

Instead, Mr Dobson is seeking "further expert advice" and "discussions with the manufacturer." No doubt he will try to bully the manufacturer into reducing the price. Good luck. But this won't solve the problem. Nor will "expert advice." There are no technical fixes for rationing. No expert can trade a man's impotence against a couple's infertility against adequate care for psychogeriatric patients against chemotherapy for childhood cancer. These trade offs depend on the values of our society, the agreed purposes of the NHS, and many other issues laid out in the agenda for the rationing debate published by the Rationing Agenda Group in the *BMJ*.[5] The government has never taken up the agenda offered by the Rationing Agenda group, but now would be a good time to do so. The government cannot be blamed for failing to provide, but it can be blamed for obscuring and avoiding the debate.

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