

Cost utility analysis of sildenafil compared with papaverine-phentolamine injections

Elly A Stolk, Jan J V Busschbach, Max Caffa, Eric J H Meuleman, Frans F H Rutten

Abstract

Objective To compare the cost effectiveness of sildenafil and papaverine-phentolamine injections for treating erectile dysfunction.

Design Cost utility analysis comparing treatment with sildenafil (allowing a switch to injection therapy) and treatment with papaverine-phentolamine (no switch allowed). Costs and effects were estimated from the societal perspective. Using time trade-off, a sample of the general public (n = 169) valued health states relating to erectile dysfunction. These values were used to estimate health related quality of life by converting the clinical outcomes of a trial into quality adjusted life years (QALYs).

Participants 169 residents of Rotterdam.

Main outcome measures Cost per quality adjusted life year.

Results Participants thought that erectile dysfunction limits quality of life considerably: the mean utility gain attributable to sildenafil is 0.11. Overall, treatment with sildenafil gained more QALYs, but the total costs were higher. The incremental cost effectiveness ratio for the introduction of sildenafil was £3639 in the first year and fell in following years. Doubling the frequency of use of sildenafil almost doubled the cost per additional QALY.

Conclusions Treatment with sildenafil is cost effective. When considering funding sildenafil, healthcare systems should take into account that the frequency of use affects cost effectiveness.

Introduction

The registration of sildenafil has initiated debate about the socioeconomic aspects of this treatment for erectile dysfunction. Generally, governments are concerned about the affordability of sildenafil.¹ It is not known whether sildenafil is cost effective. Although the clinical effects of sildenafil have been proved, uncertainty remains about the value of sildenafil to both patients and society.

We performed an economic evaluation of sildenafil using cost utility analysis, a form of cost effectiveness analysis in which clinical outcomes are converted into quality adjusted life years (QALYs) gained.² Both costs and effects were measured from the societal perspective. This means that treatment outcomes were valued by the general public and that all costs were considered—that is,

medical costs, costs of patients, and costs in other sectors of society. Costs and effects were analysed over five years.

Participants and methods

We compared the costs of treatment with sildenafil with that of conventional treatment. Before the introduction of sildenafil, injection therapy was the treatment of choice for erectile dysfunction.¹ Many patients, however, were unwilling to receive injection therapy and accordingly did not seek treatment. We therefore assumed that injection therapy with papaverine-phentolamine was accepted by 10% of patients (Pfizer, Netherlands, personal communication, 1998, based on market research).

We estimated utility values for different states of erectile dysfunction. These utilities were applied to the clinical outcomes before and after treatment in a clinical trial of sildenafil by Goldstein et al.³ A detailed description of our methods to analyse costs and effects is available.⁴

Clinical effects

The study by Goldstein et al is the largest dose escalation study reported.³ It was placebo controlled and the patient population consisted of men with erectile dysfunction due to various causes. Efficacy was assessed with the international index of erectile function.⁵ The difference between the mean utility before and after treatment (controlled for placebo) is the mean gain in utility.

Determining utilities for erectile dysfunction states

From a randomly selected sample of 45 000 people obtained from the Rotterdam telephone directory we recruited 354 people to participate in the valuation task. Participants valued 24 erectile dysfunction states on a scale from 0 to 1 using time trade-off.⁶ Subjects had to value the health states “for a person like yourself.” The exception was that women were asked to imagine being a man with erectile dysfunction. For example, a respondent might be asked the following: “If during the past four weeks, your condition was such that you were sometimes able to attain an erection, and you were (almost) never able to maintain your erection, how many years would you be willing to trade off to restore your erectile function?” This also implies that erectile function is valued the same in patients with different levels of sexual activity.

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Institute for Medical
Technology
Assessment,
Erasmus University
Rotterdam, PO Box
1738, 3000 DR
Rotterdam,
Netherlands
Elly A Stolk
research fellow

Jan J V Busschbach
senior researcher
Frans F H Rutten
professor

Department of
Urology, Hospital St
Antoniusshove,
Leidschendam,
Netherlands
Max Caffa
urologist

Department of
Urology, University
Medical Centre St
Radboud,
Nijmegen,
Netherlands
Eric J H Meuleman
urologist

Correspondence to:
E A Stolk
stolk@bmg.eur.nl

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Costs

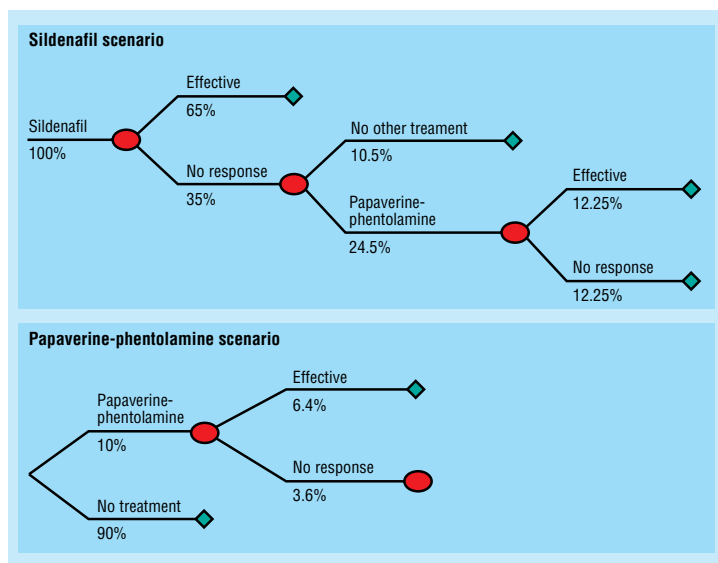
All costs are expressed in 1999 British pounds (£1 = 1.62 euro). We used 1999 data to determine the Dutch cost prices. To determine the medical costs, we estimated resource use—for example, consultations and prescription charges (a lump sum charge to refund pharmacy costs and medicines) and multiplied the quantities by the unit prices. We estimated resource use of sildenafil and papaverine-phenolamine injections on the basis of consensus statements on both treatments.⁷ Costs outside the healthcare sector and productivity costs were assumed to be negligible.

The cost of sildenafil was based on observational data from the first quarter that sildenafil was available in the Netherlands.⁸ An appropriate share of the costs of supporting departments was reflected in the cost of a visit to a urologist. The physician's costs were calculated on the basis of the estimated duration of an outpatient visit. The analysis included all costs related to the hospital, such as costs of salaries and supplies, costs of supporting departments, and overhead costs.

Cost effectiveness

We compared two scenarios: treatment with sildenafil and treatment with papaverine-phenolamine (figure). In the sildenafil scenario, we allowed patients to switch to papaverine-phenolamine injections, as these injections may be effective in patients in whom sildenafil has failed. Since sildenafil has already become the treatment of choice, although its cost is not reimbursed in the Netherlands, patients are unlikely to switch from injections to sildenafil. A switch was therefore not allowed in the papaverine-phenolamine scenario.

We compared the sildenafil and papaverine-phenolamine scenarios assuming use once a week. The maximum recommended frequency of papaverine-phenolamine injections is once a week, but use of sildenafil is not limited for medical reasons. Nevertheless, we believe that the assumption was appropriate as the utility values were elicited independently of the frequency of intercourse.



Patient flow for scenarios of treatment of erectile dysfunction with sildenafil or papaverine-phenolamine injections

The cost effectiveness of the different scenarios was analysed in a model comprising acceptability of treatment, probability of successful treatment, switching or discontinuation of treatment, and the duration of successful treatment. The patient flows in the model were determined on the basis of secondary data and clinical experience in the two participating hospitals.⁸⁻¹³ We performed an incremental analysis of the costs and effects of sildenafil compared with papaverine-phenolamine. The results are presented as cost per QALY.

We also conducted a sensitivity analysis including acceptance rate of papaverine-phenolamine treatment, resource use, values, effectiveness of treatment, and frequency of use (see *BMJ's* website for details).

Results

Respondents

A total of 184 subjects (52%) failed to attend the interview sessions. This was probably because of extremely bad weather at the time of interview, which made it difficult for participants to reach the university. One person withdrew from the study after he was informed about the subject. A sample of 169 subjects valued the erectile dysfunction states; 89% (150) of the responses were valid. Age ranged from 18 to 80 years (mean age of 45.8 (SD 15.4) years). There were 81 men (54%) and 69 women, which is close to the sex distribution in the general population.

Effects

In Goldstein et al's study the international index of erectile function among men receiving sildenafil rose from 2.0 at baseline to 3.9 at end of treatment for ability to penetrate (placebo group 2.1 to 2.3) and from 1.5 to 3.6 for satisfactory sexual intercourse (placebo group 1.6 to 1.8).³ The mean utilities elicited for the 24 erectile dysfunction states described by these two questions ranged from 0.74 to 0.94 (see *BMJ's* website for details). When these values are combined with trial data, the mean utility increased from 0.807 at baseline to 0.915 at end of treatment for men receiving sildenafil and from 0.819 to 0.821 for men receiving placebo. Therefore, the mean utility gain attributable to sildenafil is 0.11.

The values of the general public were not influenced by age, sex, availability of a partner, sexual activity, and sexual satisfaction. Participants with children considered erectile dysfunction less of a problem than subjects without children. More extensive description of this analysis is available.¹⁴

Costs

The resource use and the costs attributable to treatment of erectile dysfunction with sildenafil or papaverine-phenolamine injections are given on the *BMJ's* website. Papaverine-phenolamine is cheaper per dose, but it has to be prescribed by a urologist and therefore has higher initial costs (£484 versus £407 for sildenafil). Sildenafil has higher running costs: yearly treatment costs are £254 versus £233 for papaverine-phenolamine. The higher initial costs of papaverine-phenolamine are recovered after seven years.

Cost effectiveness

Overall, sildenafil creates more benefits and more costs because more patients are treated (figure). Therefore, the main issue is whether the additional effects of silde-

Costs and effects of treatment with sildenafil and papaverine-phenolamine injection and difference between two treatments

Year	Successfully treated patients (%)		Incremental cumulative effects (QALY)	Incremental cumulative costs (£)	Incremental cost utility ratio (£/QALY)
	Sildenafil	Injection			
1	77.25	6.40	7.79	28 368	3639
2	69.53	5.50	14.84	44 773	3017
3	66.05	5.23	21.53	60 356	2803
4	62.75	4.97	27.88	75 161	2695
5	59.61	4.72	33.92	89 226	2630
∞*					2329

*In year N the incremental cost utility ratio is a function of the incremental cumulative costs divided by incremental cumulative effects over these N years. But if you look at the cost utility ratios in the first and second year separately, you get an incremental cost utility ratio of £3639 per QALY in the first year and £2329 per QALY in the second year. The incremental cost utility ratio is constant from the second year on: £2329 per QALY. So, in the long term, the influence of the first year treatment costs is diminishing and the incremental cost utility ratio approaches £2329 per QALY.

nafil are worth the additional costs. This question is addressed in the incremental analysis shown in the table. The incremental cost utility ratio of sildenafil compared with papaverine-phenolamine is £3639 per QALY in the first year, decreasing to £2630 per QALY after five years.

Sensitivity analysis

The frequency of use influences the outcomes considerably. Doubling the frequency of use of sildenafil increases the cost per additional QALY by 45% in the first year and 85% in each following year. The initial costs are relatively high because the costs of non-responders are added to the costs of responders. Hence, the effect of the frequency of use on the cost per additional QALY is moderated in the first year. In the long term, however, the main cost driver with sildenafil is the drug.

Assuming a lower utility gain (0.08) than observed in the valuation study, resulted in a 37.5% increase in cost per additional QALY.⁴ Effectiveness and acceptability also influenced the results significantly. The cost per additional QALY increased 38% with a lower effectiveness of sildenafil (50%), but decreased (1%) in each following year. Changes in acceptability had an opposite effect: when acceptability of papaverine-phenolamine injections is increased to 70%, the incremental cost utility ratio is 25% lower in the first year, but 10% higher from the second year onwards. Uncertainty about resource use did not influence the outcomes significantly; in the analysis of different cost scenarios (based on the number of visits and duration of visits), a high cost scenario increased the costs per additional QALY by only 8%.

When the uncertainty of all variables is combined into a worst case model (low utility gain and effectiveness and high costs, dropout, and acceptability), the incremental cost utility ratio is £9343 per QALY in the first year (156% increase), and £4691 in each following year (101% increase).

Discussion

The mean incremental cost utility ratio of sildenafil compared with papaverine-phenolamine was £3639 per QALY in the first year and improved in the following years. This cost utility ratio is generally favourable, as suggested acceptable thresholds of cost utility vary between £8000 and £25 000.^{15 16} Moreover, many interventions with less favourable cost utility ratios are currently being funded, such as breast cancer screening (£5780 per QALY) and kidney transplantation (£4710 per QALY).¹⁷

Validity of assumptions

We made several assumptions that could be viewed as unfavourable to sildenafil. For instance, we underestimated the effects by not including partner satisfaction and we assumed the effects of oral and injection treatment to be equal. Furthermore, we used a relatively low rate of drop out for injection therapy, which results in a more favourable cost effectiveness ratio for injection therapy.¹¹⁻¹³ Although such assumptions might introduce bias, the interpretation of the results is not greatly affected because the assumptions in the economic appraisal of sildenafil were conservative.

The utility values we elicited for erectile dysfunction did not take into account possible comorbidity. As in most cases total disutility is less than the sum of parts,¹⁸ we might have overestimated the effect. However, the sensitivity analysis showed that sildenafil remained cost effective with lower utility gains.

The subjective nature of the value of erectile functioning again raises issues about whose values should be used in economic appraisal of health care: the values of the general public or those of people at risk (in our case ageing men). However, we found that the utility values for sexual functioning were independent of background variables such as age, sex, and sexual activity. Therefore, neither the limitations in the representativeness of our sample, nor our choice to elicit values from the general public has influenced the results.

Implications

These findings should be interpreted in the light of the discussion about the affordability and value of sildenafil.

What is already known on this topic

Clinical research suggests that sildenafil is an effective treatment for erectile dysfunction

Economic appraisal of sildenafil is needed given the prevalence of the disorder and controversy regarding funding of treatment

What this study adds

Erectile dysfunction is generally perceived as a disease that limits quality of life considerably

The clinical effect of sildenafil is derived at reasonable costs

Health service funding of sildenafil should be considered

fil to society. Firstly, we have shown that erectile dysfunction limits quality of life considerably, in the eyes of the general public. Furthermore, our study shows that sildenafil is cost effective, and its reimbursement should therefore be considered. However, as frequency of use greatly affects cost, such reimbursement should not be unconditional.

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Contributors: FFHR initiated the research, discussed core ideas, commented on drafts of the manuscript, and is guarantor of this study. JJVB designed the study, particularly the collection of quality of life data. He also contributed to data analysis and interpretation and writing the paper. EAS carried out the data collection, performed the data analysis, and produced the main drafts of the paper. MC and EJHM developed the treatment scenarios, contributed to the data collection and interpretation, and commented on drafts of the manuscript. All authors approved the final version of the article.

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Scientific, ethical, and logistical considerations in introducing a new operation: a retrospective cohort study from paediatric cardiac surgery

Catherine Bull, R Yates, D Sarkar, J Deanfield, M de Leval



Cardiothoracic Unit, Great Ormond Street Hospital NHS Trust, London WC1N 3JH

Catherine Bull
senior lecturer in paediatric cardiology

R Yates
consultant paediatric cardiologist

D Sarkar
registrar in paediatric cardiology

J Deanfield
professor of cardiology

M de Leval
professor of cardiac surgery

Correspondence to:
C Bull
C.Bull@gosh-tr.nthames.nhs.uk

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Abstract

Objective To review the initial impact on mortality of infants with congenital heart disease of a new surgical technique that is now taken for granted.

Design Retrospective cohort study.

Setting A tertiary paediatric cardiology centre.

Subjects 325 consecutive neonates with simple transposition of the great arteries admitted before, during, and after the preferred management changed from the Senning operation to the arterial switch (1978-98); and 100 consecutive neonates requiring a different neonatal open heart operation that did not change in that period.

Main outcome measures Mortality before and early after operation reconstructed sequentially as the series evolved and retrospectively once the series was complete; actuarial survival associated with the different treatment strategies.

Results For both the transposition and the comparison group, early mortality in 1998 was lower

than in 1978. During that period, however, there was a phase temporally related to the adoption of the switch operation in which early mortality for transposition increased. Actuarial survival of recent patients with "intention to treat" with arterial switch is superior to those with intention to treat with the Senning operation, as predicted when the switch operation was first adopted.

Conclusions A period of increased hazard for individual patients may occur when a specialist community, a particular unit, and an individual surgeon are all learning a new technique concurrently. Obtaining informed consent during this time of uncertainty is helped by clarity about the objectives of treatment and availability of relevant local and international data.

Introduction

The introduction of a new management strategy to a group of patients for whom a long established