ORIGINAL RESEARCH ARTICLE

Pharmacoeconomics 1998 Mar; 13 (3): 317-326
1170-7690/98/0004-0317/$05.00/0

A Short Term Cost-Effectiveness Model For Oral Antidiabetic Medicines in Europe

Sheila C. Hood,[1] *Lieven Annemans*[2] and *Maureen Rutten-van Mölken*[3]

1 Formerly of Global Health Outcomes, Glaxo Wellcome, Uxbridge, Middlesex, England
2 HEDM Research & Consulting, Mechelen, Belgium
3 Institute for Medical Technology Assessment, Erasmus University, Rotterdam, The Netherlands

Summary

A short term (6-month) cost-effectiveness model has been developed to simulate current medical practice and disease progression in patients with type 2 (non–insulin-dependent) diabetes mellitus uncontrolled by diet and exercise. The model is based on decision-analytical techniques and includes probabilities of switching between treatments, the reason for the switch and the most common switch options. Effectiveness and economic measures are the 2 main outcomes.

In order to assess effectiveness, we use symptom-free days with acceptable control (SFDACs), which represent each day of treatment without adverse events or symptoms, and with acceptable control of glucose and lipids. For the economic evaluation, only incremental costs incurred directly by a health insurance system are considered.

This model should prove useful in the evaluation of new oral antidiabetic agents, since the short term aim of antidiabetic therapy is to provide adequate control in the absence of adverse effects and symptoms (a prerequisite for successful long term treatment). Furthermore, short term analysis provides data for comparing initial investment in drug therapy with potential savings over a longer treatment period.

Current treatment algorithms for patients with type 2 (non–insulin-dependent) diabetes mellitus are based on strategies to manage inadequate responses or treatment failures once diet and exercise have proved unsuccessful in meeting glycaemic control targets. First-line drug therapy usually consists of monotherapy with a sulphonylurea, a biguanide or an □-glucosidase inhibitor, while second-line therapy involves a combination of 2 of these oral antihyperglycaemic agents, with or without insulin.[1] Since dyslipidaemias are common in patients with type 2 diabetes, many of these patients will also require lipid-lowering therapies such as fibrates and HMG-CoA reductase inhibitors.[1,2]

A number of undesired effects are associated with the most frequently prescribed antidiabetic agents. These include hypoglycaemia and bodyweight gain (which are particularly associated with the sulphonylureas[3]), gastrointestinal effects (often caused by the biguanides and □-glucosidase inhibitors[4,5]), as well as interactions with other

drugs. Consequently, poor compliance with medication, treatment cessation and alterations in therapy are common during the initial 6 months of treatment. This failure to achieve consistent metabolic control results in increased use of healthcare resources.

Given the pressures on healthcare budgets worldwide, economic outcome models based on decision-analytical techniques have been developed to analyse the consequences (costs and clinical outcomes) of medical decisions.[6,7] Decision algorithm costing methodology has been used in a number of studies calculating the costs of medical procedures for foot infections and retinopathy in patients with diabetes mellitus,[8,9] dyspepsia[10] and inflammatory bowel disease.[11] However, few cost-effectiveness analyses of type 2 diabetes therapy have previously been applied to the initial period of drug therapy.[12] Longer term studies are often somewhat biased towards healthier patients who continue their treatment. In those studies, the most unstable patients, who frequently switch from one treatment to another, are often lost to follow-up.

Short term studies are generally too short to fully assess the cost effectiveness of a new treatment; however, by using a short term model, cost-effectiveness data can be obtained for the initial phase of treatment, which aims to control glucose levels while minimising adverse effects – a prerequisite for long term treatment success. In addition, short term analysis provides information for comparing initial investment against potential savings over a longer treatment period. Hence, such a model would be particularly useful in the evaluation of new oral antidiabetic agents.

A short term cost-effectiveness model to simulate current medical practice in the treatment of patients with type 2 diabetes (whose condition is uncontrolled by diet and exercise) that can be applied to different healthcare insurance systems throughout Europe has been produced, and is described in this article.

Methodology

Patients with type 2 diabetes who were not adequately responding to diet and exercise alone, and needed oral hypoglycaemic agents, were considered in the model.

Study Design

The model was primarily designed to assess the most cost-effective strategy for the short term (6-month) treatment of type 2 diabetes, although it could equally be used to assess the treatment of other diseases. An incremental cost-effectiveness analysis using a decision-analytical model (decision-tree analysis) was selected as the most appropriate tool because of: (i) the wide range of current treatment options for type 2 diabetes; and (ii) the availability of data from several prospective, randomised trials involving those treatment options.

The study was conducted from the perspective of the health insurance system (although the model can be used to assess the most cost-effective strategy from any other perspective, including societal and individual); therefore, only those costs incurred directly by this system were considered. Neither costs nor effects were discounted because of the short term nature of the analysis. The model was programmed using the decision-analytical software DATA 3.0 produced by TreeAge Software Inc. (Williamstown, Massachusetts, USA).

Model Structure and Patient Assessment

A decision tree for first-line antidiabetic therapy was simulated (fig. 1). The first branching point, a decision node, corresponds to the choice of the first-line treatment for a newly diagnosed patient with type 2 diabetes. This treatment will vary according to standard practice in each country. For example, in the UK, the 4 most commonly used oral antihyperglycaemic agents are the sulphonylureas glibenclamide (glyburide) and gliclazide, the biguanide metformin, and the -glucosidase inhibitor acarbose. The branching points that follow these treatment options are chance nodes and

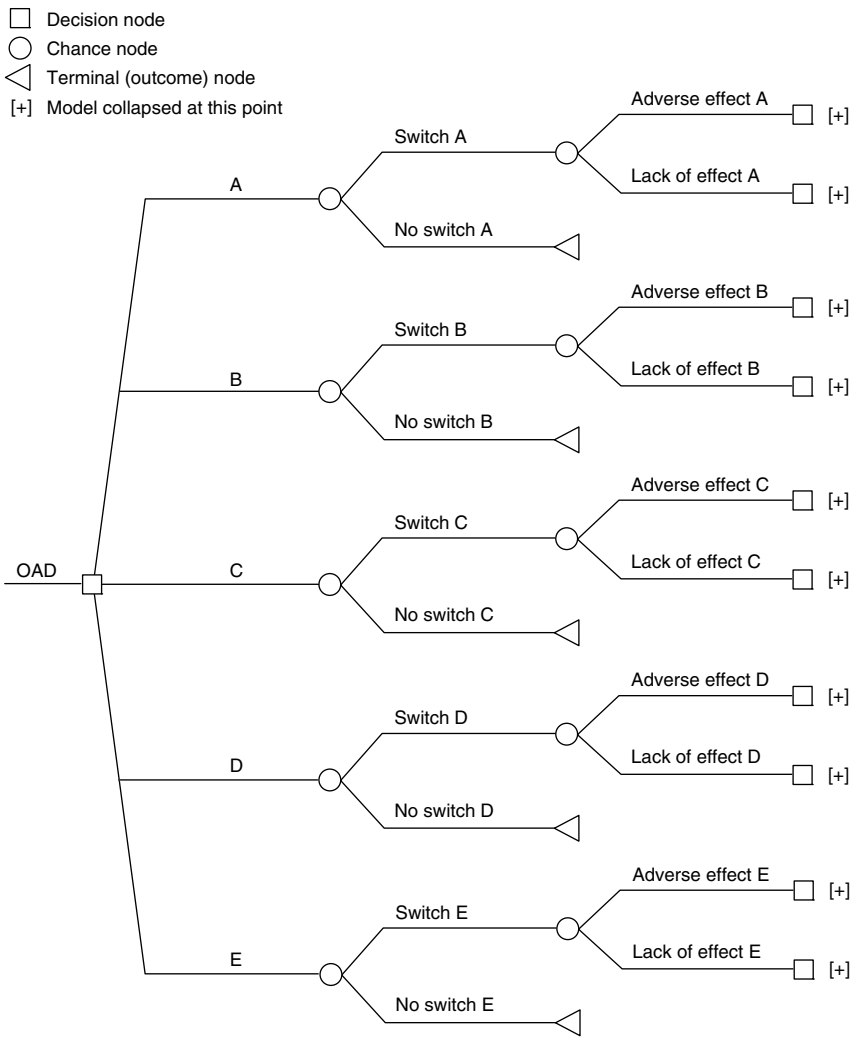

Fig. 1. Basic model structure comparing treatment options (country-dependent) for patients with type 2 diabetes mellitus. *Abbreviation:* OAD = oral antidiabetic drug.

correspond to changes in treatment because of adverse effects or lack of effect. At the next branching point, a decision node, the choice of second-line treatment is made. Again, this choice is country-dependent. Beyond this is another chance node relating to adverse effects or lack of effect of second-line therapy, followed by a decision node that refers to the selection of third-line treatment. At the end of each pathway in the model, there is a final node that represents the outcome at the end of the 6-month study period.

Figure 2 shows an example of a decision tree for glibenclamide treatment in the UK. Gliclazide is not shown as a second-line option in figure 2, as it is not standard practice to co-prescribe 2 sulphonylureas.

In the model, the patients continue first-line treatment unless the physician decides to switch

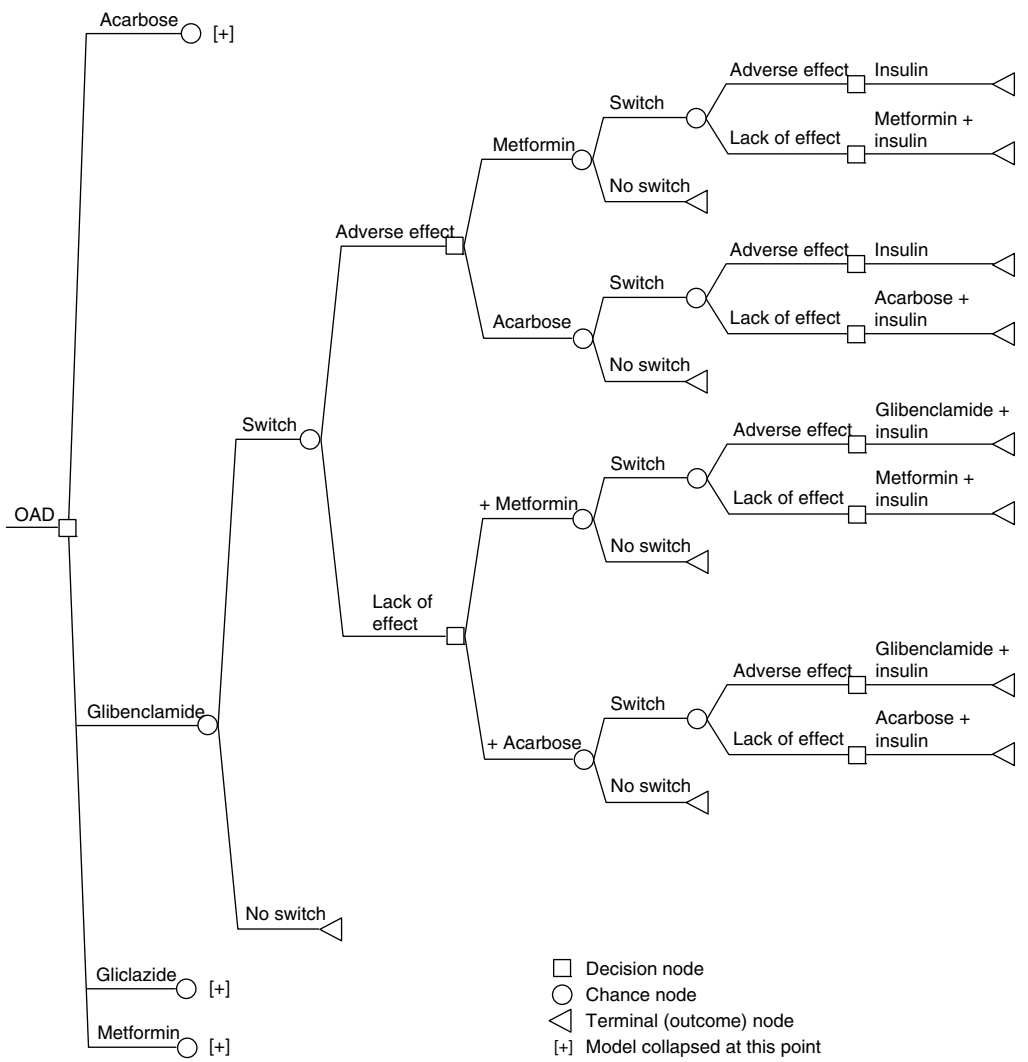

Fig. 2. Example structure of model decision tree for glibenclamide treatment in the UK. A switch [based on Intercontinental Medical Statistics Mediplus data and current guidelines (British Diabetic Association)][13] is defined as a lack of effect, with the subsequent addition of an alternative antidiabetic agent, or the appearance of an adverse effect with a subsequent change in therapy to a different antidiabetic agent. *Abbreviation:* OAD = oral antidiabetic drug.

the patient to a second-line choice because of adverse effects or lack of effect. Patients are reviewed after a defined period or, if adverse effects occur, they have an earlier consultation. A proportion of patients require second-line therapy. Unsuccessful second-line therapy results in a switch to insulin alone or in combination. At the end of the 6-month study period, there are 3 possible outcomes: the patient is on first-line therapy, second-line therapy or third-line therapy.

Probabilities are calculated for the occurrence of treatment change to another agent, and for the

chance that the change results from an adverse effect or lack of effect. These probabilities determine the treatment patterns of patients. The data sources described later in this section provide the basis for the probability calculations.

Variables

At each terminal node in the model, the outcome values assigned to each of the scenarios included in the model (payoff) are defined. There are 2 payoff levels, one for costs and one for effectiveness (table I).

The cost formula takes into account only incremental direct costs influenced by the choice of the treatment option. Costs common to all treatments are disregarded. The cost formula is as follows:

$$\text{Cost} = \text{Cohort} \times (C_{MED1} + C_{SW1} + C_{AE1} + C_{MED2} + C_{SW2} + C_{AE2} + C_{MED3} + C_{AE3} + C_{LIP})$$

Cohort is the number of patients studied; this variable can be set at 1 to calculate the average cost per patient for the 6-month study period or it can be used to calculate the cost of treating a population. C_{MED1}, C_{MED2} and C_{MED3} are the acquisition costs of first-, second-, and third-line therapy, respectively. C_{SW1} and C_{SW2} are the costs associated with switching from first- to second-line therapy and from second- to third-line therapy, respectively. C_{AE1}, C_{AE2} and C_{AE3} are the costs associated with adverse effects (i.e. the incremental costs of co-medication) of first-, second- and third-line therapy, respectively. C_{LIP} is the cost of dyslipidaemia treatment.

A new parameter to express effectiveness – the symptom-free day with acceptable control (SFDAC) – was developed. This represents each day of treatment without adverse effects and with acceptable control of glucose and lipids. This parameter was based on the objectives for type 2 diabetes therapy defined by the European Non-Insulin-Dependent Diabetes Mellitus Policy Group:[1] relief of symptoms; prevention and amelioration of acute and chronic complications; avoidance of factors predisposing to death; control of any accompanying disorders; and improved quality of life.

Each day of the study period is assigned a value. A SFDAC is given a value of 1, whereas if the patient does not meet one or more of the criteria of a SFDAC, the day's score is 0. The total number of SFDACs is calculated for each treatment option. This concept is illustrated by the example of a hypothetical patient starting treatment with glibenclamide as the first-line agent (table II). After 40 days of treatment, glucose control is achieved in the absence of adverse effects and this is maintained during days 41 to 42. The patient then experiences an episode of hypoglycaemia on day 43, followed by a second period of acceptable control with no adverse effects on days 44 to 49. This ends on day 50 with a second episode of hypoglycaemia and a subsequent switch to metformin. The total SFDAC score for glibenclamide during this 50-day period is thus 8 out of a possible 50.

The build-up of the SFDAC formula is as follows:

$$\text{SFDAC} = \text{tot} - \{p_{dyslip} \times [\text{Max}(d_{ae1}; d_{hg1}; d_{hlr1}) + \text{Max}(d_{ae2}; d_{hg2}; d_{hlr2}) + \text{Max}(d_{ae3}; d_{hg3}; d_{hlr3})]\} + \{(1 - p_{dyslip}) \times [\text{Max}(d_{ae1}; d_{hg1}) + \text{Max}(d_{ae2}; d_{hg2}) + \text{Max}(d_{ae3}; d_{hg3})]\}$$

Table I. Costs and effects related to treatment options

Costs
Associated with drug acquisition
Associated with adverse effects
Associated with switching[a]
Associated with dyslipidaemia treatment (statins, fibrates)[b]
Effects
Therapeutic:
control of blood glucose levels
control of plasma lipid levels
Adverse:
bodyweight gain
hypoglycaemia
gastrointestinal (flatulence, diarrhoea, nausea and vomiting)
interactions with other drugs

a Caused by lack of efficacy, severe adverse effects, interactions or additional consultations.

b In patients with dyslipidaemia.

Table II. Hypothetical case illustrating the calculation of symptom-free days with acceptable control (SFDACs)

Day	Event	Score	
First-line glibenclamide			
1-40	Titration time, no acceptable glucose control	40 □ 0 =	0
41-42	Glucose control, no adverse effects	2 □ 1 =	2
43	Hypoglycaemic event	1 □ 0 =	0
44-49	Glucose control, no adverse effects	6 □ 1 =	6
50	Hypoglycaemic event	1 □ 0 =	0
Sub-total number of SFDACs (out of 50 days)			8
Switch to second-line metformin			
51-60	Titration time, no acceptable glucose control and adverse effects	10 □ 0 =	0
61-118	Titration time, no acceptable glucose control	58 □ 0 =	0
Augmentation with insulin			
119-180	Acceptable glucose control, no adverse effects	62 □ 1 =	62
Total number of SFDACs (out of 180 days)			**70**

where: tot is the total number of study days (180 in this case); p_{dyslip} is the proportion of patients with dyslipidaemia; d_{ae1}, d_{ae2} and d_{ae3} are the durations of the periods of adverse effects during first-, second- and third-line therapy, respectively; d_{hg1}, d_{hg2} and d_{hg3} are the durations of the periods of inadequate hyperglycaemia control with first-, second- and third-line therapy, respectively; d_{hlr1}, d_{hlr2} and d_{hlr3} are the durations of the periods of inadequate dyslipidaemia control with first-, second- and third-line therapy, respectively; and Max is the largest value out of the respective d_{ae}, d_{hg} and d_{hlr} values (since adverse effects and lack of control occur at the same time).

The formula is split into 2 parts. The first part relates to the proportion of patients with dyslipidaemia (p_{dyslip}), and thus contains a variable corresponding to the duration of inadequate control of lipids (d_{hlr}). In the second part of the formula, the proportion of patients with normal lipids ($1 - p_{dyslip}$) is considered.

The following should be noted when applying the SFDAC formula: any drug-related adverse effects that occur after the titration period should only contribute to the SFDAC score for patients in whom glucose and lipid levels are adequately controlled. In this case, 'double-counting' is avoided on days on which both adverse effects and lack of control occur.

It is assumed that adverse effects occur shortly after therapy starts, before the achievement of glucose control. However, the late-onset adverse effects of the sulphonylureas (bodyweight gain and hypoglycaemia) are assumed to appear only after glucose levels have been controlled.

An important issue is the definition of 'acceptable control'. One method to calculate acceptable control of glucose is based on data from the UK Prospective Diabetes Study (UKPDS),[14,15] comparing glibenclamide with metformin in patients with type 2 diabetes. It is assumed that blood glucose levels are normally distributed within the population. The glucose level (threshold) at which the physician switches therapy was derived by linking the average glucose level reached in a given period in the UKPDS with the percentage of patients switched because of lack of effect in the same period (i.e. if 30% of patients were switched, the cut-off would be at the 70th centile of blood glucose levels). For other treatment options, average glucose levels reached were used to calculate the percentage of patients with glucose levels higher than the threshold and, hence, the percentage of patients switched because of lack of effect.

The parameters used to assess acceptable lipid control were the number of patients requiring treatment, the number of days taken to achieve lipid control and the percentage of patients effectively treated.

Results Generation and Sensitivity Analysis

The results of the model can be calculated using a Roll Back analysis – the total incremental costs and effectiveness (number of SFDACs) are obtained in reverse order of the decision-tree development (starting from the terminal node and working back to the initial node). The total outcome of a node includes the outcomes of all its branches.

The Roll Back analysis represents the mean of the outcomes of all possible end-points and treatment methods weighted according to the probabilities. The present decision-analysis model aims to assess the optimal (most cost-effective) strategy of short term treatment of type 2 diabetes. Therefore, the calculation of the cost effectiveness of a first-line treatment only considers the most cost-effective subtree following the decision node for second-line treatment.

To verify the robustness of the model, sensitivity analyses must be performed by altering the value of key data or changing outcome probabilities.[16] These include the main cost components (e.g. drug costs), parameters that vary among patient populations (e.g. the proportion of patients receiving additional treatment for dyslipidaemia) and variables for which no empirical data are available (e.g. the assumed proportion of patients with dyslipidaemia). In this way, the conditions that will cause the decision to change can be defined. We used a Tornado Diagram (TreeAge Software Inc.) to identify variables that have a high impact on the study results. A Tornado Diagram compares the impact of all variables or a subset of variables on the outcome by displaying a set of mini sensitivity analyses in one diagram. The key parameters to be tested are those with the widest bars in a Tornado Diagram. If the overall outcome of the Roll Back analysis remains stable over a range of plausible values for the selected parameter, then the model is defined as insensitive to values within the range of that parameter.

The percentage of patients with dyslipidaemia, the percentage of patients receiving treatment for dyslipidaemia, drug costs and drug titration times were all found to have a significant impact on the outcomes of the current model and therefore to be the most relevant variables when considering treatment options for type 2 diabetes.

Data Sources

The model was constructed using clinical data, expert interviews, healthcare databases and cost data that are specific to each country (table III). The clinical trials reviewed were all well designed (randomised, adequately controlled and blinded) and analysed on an intent-to-treat basis. We also interviewed expert physicians (3 per country) who provided qualitative and quantitative information on aspects of medical practice and disease progression. For data on the probability of treatment cessation and switch (and the associated reasons), we consulted country-specific healthcare databases.

Assumptions

It was assumed that the study is conducted in a primary-care setting and has a duration of 6 months. The model allows country-specific data to be applied to a generic list of assumptions (table IV).

Discussion

The short term objectives of antidiabetic treatment, adequate control without extra burden to the patient, are prior conditions for successful long term treatment. However, there is very little information on the cost effectiveness of treatment options during this initial treatment period. The short term cost-effectiveness model for oral antidiabetic drugs that we have developed can be used to provide these data. Importantly, the model can be applied to different healthcare environments by assigning outcome values derived from country-specific

Table III. Data type required for the construction of a short term cost-effectiveness model

Data type	Source
Efficacy	UK Prospective Diabetes Study[14] and published studies (MEDLINE and Health Economic Evaluation Database)[a]
Switches	Country-specific database
Reason for switches	Expert physicians
Average duration of adverse effects	Country-specific database and expert physicians
Dyslipidaemia and percentage of patients treated	Country-specific database and expert physicians
Current direct medical costs	Country-specific pricing guide; health payer capitation fees

a These included Turner et al.,[15] DeFronzo et al.,[17] Ferner and Neil,[18] Tessier et al.,[19] Palmer and Brogden,[20] and Nolan et al.[21]

Table IV. Key assumptions of the model requiring country-specific data

Oral antihyperglycaemic agents
Treatment patterns are based on database searches and expert opinions
Lack of effect of first-line therapy leads to a second-line combination strategy
Adverse effects of first-line therapy leads to monotherapy with a drug from a different class
Experience of adverse effects on both first- and second-line therapy leads to insulin monotherapy;[22] in all other cases, a combination with insulin is considered[23]
Only the 2 most widely used second-line drugs after switch are incorporated in the model
If adverse effects occur, only a proportion of those patients switch to another drug
The decreases in glucose levels were normally distributed
Dyslipidaemias
Percentage of study population that has dyslipidaemia
Percentage of patients with dyslipidaemia who are treated with lipid-regulating drugs
Percentage of patients in which lipid-regulating agents are effective
Period for which lipid-regulating drugs are required
Costs
Patient review tuned to number of days of prescribed drugs (equal to the drug titration time)
Average amount of unused drug after switch because of adverse effects
Patient referral to consultant when insulin prescribed
Patient referral to consultant when treatment switch occurs
Patients started on a lower dosage, which is slowly increased to the final dosage achieved at the end of the titration period
Costs of drugs calculated according to number of boxes, not number of days of treatment

data, and can also incorporate direct medical costs and indirect costs (such as a loss of productivity) incurred by individuals. Future modifications to the model may include extension of the time frame to 1 year to account for variability in disease progression and the appearance of treatment-associated adverse effects.

It has been previously highlighted that as well as establishing an efficacy and adverse-effect profile, the evaluation of a medicine should also include an economic assessment.[24] Simple price comparisons are not considered to be an appropriate measure of the actual cost of the resources consumed to use a medication.[16] Instead, clinical outcomes of treatment and their associated economic consequences need to be analysed.[16,25] Given limited healthcare resources, we suggest that the present model provides a valuable tool to evaluate both established and new treatment options for type 2 diabetes.

We have used a decision-analytical technique in our model, which allows relevant alternatives to be studied at the same time. Thus, an optimal treatment strategy can be found.[26] Furthermore, the model can be used to derive incremental cost effectiveness (extra cost per extra SFDAC) as well as incremental costs (differences in costs between various medications). Both of these parameters are important factors for healthcare policy-makers considering new treatment options.

Results generated from the present short term model can also be integrated into a long term cost-effectiveness analysis. This would allow a comparison of the initial investments in drugs and other healthcare interventions with the potential long term savings associated with glucose and lipid control. For example, it has been suggested that improved glycaemic control would reduce the rate of transition to insulin therapy by patients with type 2 diabetes and may reduce drug and supply costs associated with diabetes.[27]

Recent recommendations point to the following requirements for therapy of type 2 diabetes: optimal control, minimal risk and simplest regimen (with respect to the use of medical resources).[28,29] With regard to the first 2 requirements, physicians

want to achieve adequate control without diabetic symptoms or adverse effects. Therefore, the SFDAC provides an appropriate effectiveness parameter by enabling quantification of the number of days without adverse events or symptoms, and with acceptable control of blood glucose and lipid levels. In addition, the SFDAC has the important advantage that it is easily interpretable and possibly applicable for short term analysis in other disease areas.

The validity of SFDAC assessments may be affected by irregular monitoring of study parameters by patients (e.g. daily blood glucose), or of lipid levels, which would not routinely be measured daily. In these cases, less frequent monitoring (e.g. twice a week) and extrapolation of the data must be employed.

Therapeutic Implications

We have developed a short term cost-effectiveness model to simulate current medical practice in patients with type 2 diabetes, uncontrolled by diet and exercise, which can be applied to different healthcare systems. The model was primarily designed to assess the therapeutic and economic effectiveness of new oral antidiabetic agents; however, the methodology could also be applied to assess both routine and novel treatments in other therapeutic areas. It could also be used to provide data for comparing initial investment in drug therapy with potential savings over an extended treatment period. We intend to apply this model in several European countries in the near future, and submit the results for publication.

Acknowledgements

We would like to thank Phil Siddons [former employee (retired) of Glaxo Wellcome], Fiona Salts (Glaxo Wellcome), Pascal Lecomte (The Lewin Group), Liesbeth Meester (former employee of The Lewin Group) and Gepke Delwel (The Lewin Group) for their assistance. This study was supported by a research grant provided by Glaxo Wellcome.

References

1. Alberti KGMM, Fries FA, Jervell J, et al. A desktop guide for the management of non-insulin-dependent diabetes mellitus (NIDDM): an Update. Diabet Med 1994; 11: 899-909
2. Garg A. Treatment of dyslipidemia in patients with NIDDM. Diabetes Rev 1995; 3 (3): 433-45
3. Groop LC. Sulfonylureas in NIDDM. Diabetes Care 1992; 15 (6): 737-54
4. Clissold ST, Edwards C. Acarbose: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 1988; 35: 214-43
5. Dunn CJ, Peters DH. Metformin: a review of its pharmacological properties and therapeutic use in non–insulin-dependent diabetes mellitus. Drugs 1995; 49 (5): 721-49
6. Pauker SG. Coronary artery surgery: the use of decision analysis. Ann Intern Med 1976; 85: 8-18
7. Weinstein MC, Fineberg HV. Clinical decision analysis. Philadelphia: WB Saunders Co, 1980: 228-65
8. Eckman MH, Greenfield S, Mackey WC, et al. Foot infections in diabetic patients: decision and cost-effectiveness analysis. JAMA 1995; 273: 712-20
9. Javitt JC, Aiello LP. Cost-effectiveness of detecting and treating diabetic retinopathy. Ann Intern Med 1996; 124: 164-9
10. Schipper CK, Rutten FFH, Loffeld FJLF. Kosten en effectiviteit van diagnostiek en behandeling van patiënten met dyspepsie, bepaald met een computermodel. Ned Tijdschr Geneeskd 1993; 137: 1767-71
11. Hay AR, Hay JW. Inflammatory bowel disease: medical cost algorithms. J Clin Gastroenterol 1992; 14: 318-27
12. Zbrozek AS, Whalen E, Smith ME. Cost burden of newly-treated, non–insulin-dependent diabetes mellitus. Am J Managed Care 1997; 3 (3): S27-8
13. Guidelines for good practice in the diagnosis and treatment of non–insulin-dependent diabetes mellitus: report of a joint working party of the British Diabetic Association, the Research Unit of the Royal College of Physicians and the Royal College of General Practitioners. J R Coll Physicians Lond 1993; 27 (3): 259-66
14. UKPDS Group. Relative efficacy of randomly allocated diet, sulphonylurea, insulin or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 1995; 310: 83-8
15. Turner R, Cull C, Holman R, the UK Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomised, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. Ann Intern Med 1996; 124 (1 Pt 2): 136-45
16. Paladino JA. Cost-effectiveness comparison of cefepime and ceftazidime using decision analysis. Pharmacoeconomics 1994; 5 (6): 505-12
17. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1995; 333 (9): 541-9
18. Ferner RE, Neil HA. Sulphonylureas and hypoglycaemia. BMJ 1988; 296: 104-9
19. Tessier D, Dawson K, Tetrault JP, et al. Glibenclamide vs gliclazide in type 2 diabetes of the elderly. Diabet Med 1994; 11: 974-80
20. Palmer KJ, Brogden RN. Gliclazide: an update of its pharmacological properties and therapeutic efficacy in non–insulin-dependent diabetes mellitus. Drugs 1993; 46: 92-125

21. Nolan JJ, Ludvik B, Beerdsen P, et al. Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone. N Engl J Med 1995; 331: 1188-93
22. Colwell JA. The feasibility of intensive insulin management in non-insulin dependent diabetes mellitus. Ann Intern Med 1996; 124: 131-5
23. Johnson JL, Wolf SL, Kabadi UM. Efficacy of insulin and sulfonylurea combination therapy in type II diabetes: a meta-analysis of the randomized placebo-controlled trials. Arch Intern Med 1996; 156 (3): 259-64
24. Drummond M, Rutten F, Brenna A, et al. Economic evaluation of pharmaceuticals: a European perspective. Pharmacoeconomics 1993; 4: 173-86
25. Jolicoeur LM, Jones-Grizzle AJ, Boyer JG. Guidelines for performing a pharmacoeconomic analysis. Am J Hosp Pharm 1992; 49: 1741-7
26. Langley PC. Outcomes research and modelling therapeutic interventions for economic evaluation. Clin Ther 1994; 16: 538-52
27. Brown JB, Glauber HS, Nichols GA, et al. Costs and antihyperglycaemic drug use over 8 years among HMO members newly diagnosed with type 2 diabetes. Am J Managed Care 1997; 3 (3): S45-6
28. Bailey CJ. Biguanides and NIDDM. Diabetes Care 1992; 15 (6): 755-67
29. Henry RR, Genuth S. Forum one: current recommendations about intensification of metabolic control in non-insulin-dependent diabetes mellitus. Ann Intern Med 1996; 124 (1 Pt 2): 175-7

Correspondence and reprints: Dr *Loretto Lacey*, Global Health Outcomes, Glaxo Wellcome, Greenford Road, Greenford, Middlesex UB6 0HE, England.
E-mail: LAL3663@GLAXOWELLCOME.CO.UK