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Clément François, Harri Sintonen & Mondher Toumi

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Introduction of escitalopram, a new SSRI in Finland: comparison of cost-effectiveness between the other SSRIs and SNRI for the treatment of depression and estimation of the budgetary impact

Clément François[1], Harri Sintonen[2], Mondher Toumi[1]

Summary

A cost-effectiveness study of major depressive disorder was undertaken to compare escitalopram, a new SSRI, with citalopram, fluoxetine, and venlafaxine in Finland. A decision-tree model with a 6-month horizon was constructed using probabilities issued from comparative trial data, a standardised literature review and an expert panel. The therapeutic success (remission) and the treatment costs were the main outcomes. The expected success rate was 51.4% for escitalopram, 45.6% for citalopram, 45.6% for fluoxetine, and 49.6% for venlafaxine. Average expected total costs per patient are similar for escitalopram (EUR 857) and venlafaxine (EUR 876), and higher for citalopram (EUR 990) and fluoxetine (EUR 959). The budgetary impact shows a decrease in the total healthcare budget estimated at EUR 11.7 million. Escitalopram is a more cost-effective treatment than citalopram, fluoxetine, and venlafaxine in the treatment of depression and its increased utilisation would reduce healthcare costs for the treatment of depression in Finland.

Key words: depression, escitalopram, models, economic, pharmacoeconomic analysis

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[1] International Department of Health-Economy, Epidemiology and Pricing, Lundbeck A/S, Paris, France
[2] Department of Public Health, University of Helsinki, Finland

Address for correspondence: Clément François, Lundbeck, 37 Avenue Pierre 1er de Serbie, 75008 Paris, France, e-mail: cfr@lundbeck.com.

Introduction

Major depressive disorder (MDD) is a significant public health problem, presenting a considerable burden of illness to patients, healthcare providers and payers. Tricyclic antidepressants (TCAs) were the first truly effective antidepressants used to treat this disorder and they have remained the principal form of pharmacotherapy for three decades. The introduction of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) was noteworthy, but there are still patients who do not receive the full benefit of these drugs. A new SSRI, escitalopram, has been developed and results from controlled clinical trials (data on file, 99001, 99002, 99003, Lundbeck; data on file MD-01, MD02, Forest Laboratories), of both escitalopram and citalopram versus placebo show the benefit of escitalopram relative to citalopram in the treatment of patients with MDD.

Increasing costs for pharmaceuticals has resulted in the development and application of pharmacoeconomic analyses as well as guidelines for their use[1, 2]. The introduction of newer antidepressants with higher acquisition costs than traditional drugs has prompted several pharmacoeconomic analyses of antidepressants[3–6].

Since economic data are needed for these pharmacoeconomic analyses, and clinical trials were not designed to provide this data, a modelling approach is typically used to extrapolate the clinical trial results and to estimate the costs and outcomes of treatment with escitalopram in clinical practice, i.e in real-world conditions[7].

We have attempted to study the economic aspects of depression in two complementary ways: by developing this model that permits the calculation of the cost-effectiveness of treatment with different pharmacological agents, and by estimating the overall budgetary impact of the introduction of escitalopram in Finland. To test the model we compared the new antidepressant escitalopram with current standards of care for MDD as well as with the SSRIs citalopram and fluoxetine and the SNRI venlafaxine.

Methods

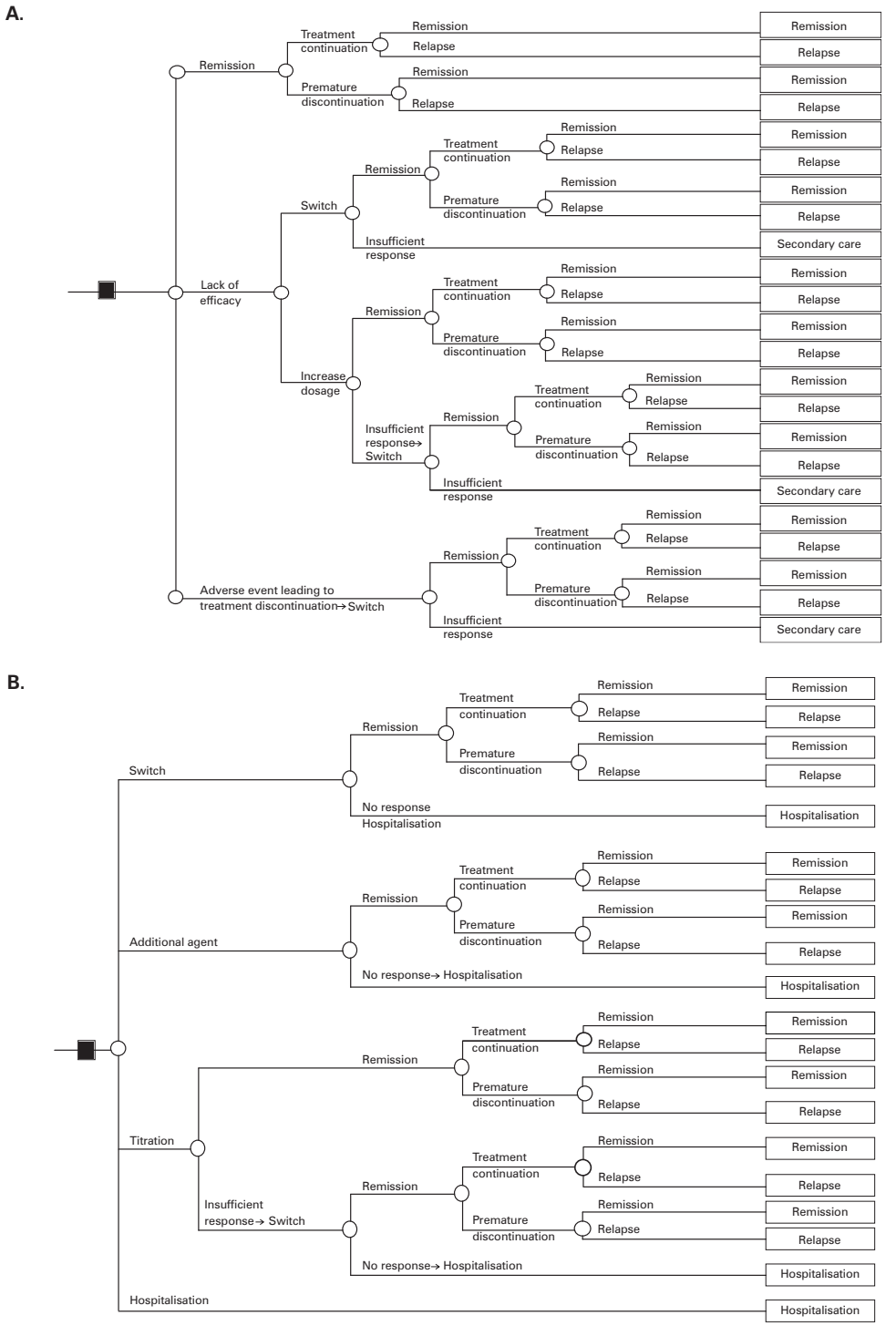
A pharmacoeconomic decision-analytic model was developed to estimate the comparative cost-effectiveness and cost-utility of escitalopram, citalopram, fluoxetine and venlafaxine in patients with depression. In addition to the results of randomised clinical trials for escitalopram versus citalopram (data on file, 99001, 99002, 99003, Lundbeck; data on file MD-01, MD02, Forest Laboratories) and data from published studies on fluoxetine and venlafaxine we also used information from the literature and advice from a panel of experts in the treatment of depression.

Pharmacoeconomic model

Model design

The decision tree used in the model is shown in Figure 1. It is divided into two sections: the primary care path, where all patients start and the secondary care path,

Figure 1. The decision model. A: Primary care model; B: Secondary care model.



where patients with insufficient response and after switching treatment are referred to a healthcare specialist. The model examines a period of 6 months from the start of treatment of patients exhibiting a Major Depressive Episode (MDE). Outcomes for the acute phase of treatment are based on the results of flexible-dose comparative clinical trials. The subsequent management of patients for the continuation phase of treatment to 6 months is based on clinical practice patterns and expert opinion. The duration of treatment reflects current guidelines and recommendations throughout Europe and the US[8, 9]. The model allows for patients who have insufficient response or suffer adverse events to receive an increased dosage of the same antidepressant and/or to be switched to another antidepressant. The model also allows for referral of patients who experienced insufficient response after increasing dose and/or switching antidepressant to secondary care. Suicide attempts, not shown in the decision tree for the sake of simplicity, are applied at a constant rate across the primary care model and do not discriminate between drugs. The main outcome measure, which indicates success of treatment, is remission of symptoms (defined as a Montgomery Åsberg Depression Rating Scale (MADRS) score </=12) 6 months after the start of treatment. The costs of treatment are assessed from the resources used associated with each different treatment path. Cost-effectiveness can thus be expressed as cost per successfully treated patient.

Treatments compared

Escitalopram 10–20 mg was compared with the following antidepressants:

- Citalopram (branded and generic) 20–40 mg. Citalopram was chosen as the reference comparator because: (i) it is the market leader in Finland and in most European countries (IMS Data view); (ii) it is the only drug for which direct comparison is available in randomised controlled trials; (iii) escitalopram is the active enantiomer of citalopram.
- Fluoxetine (branded and generic) 20–40 mg. Available as a generic, fluoxetine can demonstrate the potential lower price of generics.
- Venlafaxine 75–150 mg, a promising new antidepressant with increasing market penetration.

The subsequent assumption was made: patients start on a recommended initial daily dose which can be doubled if remission is not achieved.

Perspective

The adopted analytic perspective was the societal perspective.

Data sources

The necessary data that was used in the decision model can be divided into four categories: (i) clinical data; (ii) transition probabilities; (iii) medical resource use; and (iv) associated costs.

Clinical data

Data were derived from comparative clinical trials on: the percentage of patients in remission; and from the percentage of patients in remission after titration. An overview of these figures for escitalopram, citalopram, fluoxetine and

Table 1. Drug specific probabilities

Probability	*Baseline value*	*Range for sensitivity analysis*	*Basis for assumption*
Remission rate			MADRS ≤ 12,
Escitalopram	52.1	44.0–60.0	8-week flexible-dose European study, data on file, 99003, Lundbeck
Citalopram	42.8	35.1–50.8	
Fluoxetine	42.3	33.6–44.6	8-week flexible-dose European study[11-16]
Venlafaxine	48.3	39.1–55.3	
Remission rate after titration			
Escitalopram	36.2	23–49.4	Same as remission rate
Citalopram	23.8	12.5–35.5	
Fluoxetine	23.8	12.5–35.5	
Venlafaxine	37.4	32.7–64.9	
Relapse rate			
Escitalopram,	12.5	8.3–16.7	Refs 17-19
Citalopram, fluoxetine, venlafaxine	15.5	6.2–15.8	

venlafaxine obtained in clinical trials is presented in Table 1.

Clinical data for escitalopram and citalopram

Two trials clearly established the efficacy of escitalopram versus citalopram in treating MDD at the doses tested. The 8-week fixed-dose US study compared escitalopram 10–20 mg to citalopram 40 mg[10]. Since 40 mg is not the starting recommended dose for citalopram, this study was not used in the model. Only the 8-week flexible-dose European study (data on file, 99003, Lundbeck) was used in the model.

8-week flexible-dose European study

In this double-blind randomised controlled flexible-dose study carried out in the General Practitioner (GP) setting, an increase in dose was permitted no earlier than week 4 (Table 2). The study found escitalopram in doses of 10 mg or 20 mg per day to be more effective than citalopram in the treatment of depression of patients responding to treatment and reaching full remission:

- The percentage of responders (defined as ≥ 50% reduction in MADRS score) was higher in patients treated with escitalopram (63.7%) than in patients treated with citalopram (52.6%). The difference of 11.1% was statistically significant (p=0.021).
- The percentage of patients who reached full remission after 8 weeks of treatment (defined as a MADRS score £12) was also significantly higher (p=0.036) among those treated with escitalopram (52.1%) than for those patients treated with citalopram (42.8%).

The average dose at week 8 was 14.1 mg in the escitalopram group and 28.6 mg in the citalopram group. When considering only those patients who had their dosage

Table 2. Efficacy results of 8-week flexible-dose European study, week 8

Arm	*No. patients*	*Responders (≥ 50% reduction in MADRS)*	*Remitters (MADRS ≤ 12)*	*Increase of dose at week 4 or 6*
	Week 0/8	%	%	%
Escitalopram 10–20 mg	155/146	63.7	52.1	41
Citalopram 20–40 mg	159/152	52.6	42.8	43
Difference	--	11.1	9.3	2
P-value	--	0.021	0.036	NS

NS, nonsignificant.

increased at week 4 and who were not responders at this time, 36% of the escitalopram patients achieved response at the end of the study as compared with only 24% of citalopram patients (p=0.08). These results indicate that for patients not satisfactorily treated with the initial dose, increasing the escitalopram dose from 10 mg to 20 mg provided greater benefit than increasing the dose of citalopram from 20 mg to 40 mg.

The drop out rate due to adverse events was not significantly different between treatment groups (2.6% for escitalopram and 3.8% for citalopram). (Data on file, 99003, Lundbeck)

Clinical data for fluoxetine and venlafaxine

The probabilities of fluoxetine and venlafaxine were derived from indirect comparisons of escitalopram using the results of an 8-week flexible-dose European study and also by comparing them with results of studies reported in the literature. For fluoxetine these comparisons were made using citalopram as a common reference. The difference in outcomes of two comparative trials of fluoxetine and citalopram reported by Patris *et al*[11] and Bougerol *et al*[12] were added to the difference between citalopram and escitalopram in the 8-week flexible-dose European study. For venlafaxine, probabilities comparable to those for escitalopram were derived using fluoxetine as a common reference, as reported in comparative trials (by Silva[13], Rudolph and Feiger[14], Dierick *et al*[15] and Diaz-Martinez *et al*[16]), with the exception of the calculation of the relapse rate described below. The difference in outcomes for comparative trials of venlafaxine and fluoxetine was added to the results for fluoxetine. A similar methodology was used to calculate withdrawal due to adverse events.

Clinical data for relapse rates

Percentages of patients relapsing after achieving remission were taken from 24-week placebo-controlled trials of citalopram reported by Montgomery *et al*[17] and Robert and Montgomery[18]. As these were the only well-designed trials, a conservative approach was adopted and this remission rate was used for escitalopram, citalopram and fluoxetine. Studies of relapse with fluoxetine (Reimherr *et al*[19]) showed a very high rate, probably due to inclusion of patients suffering from new episodes, and

were not therefore considered comparable or appropriate for use in the model. In the case of venlafaxine, an indirect comparison was made with escitalopram, using the difference between placebo and venlafaxine for the pooled analysis of relapse rate reported by Entsuah *et al*[20], and adding this to the difference from placebo for the average relapse rate of citalopram recorded across the two long-term trials[17, 18].

Utility data

In order to present outcomes in terms of quality-adjusted life years (QALYs), utility values (i.e. the relative desirability of a health state where 1 represents perfect health and 0 represents death) were determined for each state experienced in the treatment pathways. These were based on the utilities estimated in a Lundbeck ad-hoc study (data on file, Quality of Life Prospective Study, Lundbeck).

Transition probabilities

Data on practice pattern inputs: non-drug-specific

Data that were not considered as being drug-specific included: (i) premature discontinuation rate; (ii) relapse rate after premature discontinuation; (iii) percentage of patients requiring a doubling of dose; (iv) remission rate following switch of antidepressants; (v) relapse rate following switch of antidepressants; (vi) failed suicide attempts; and (vii) suicide attempt resulting in death. There are no detailed studies about pharmacotherapy of depression conducted in naturalistic settings in primary care in Finland. Thus, non-drug specific input into the clinical practice pattern were derived from the literature, consultation with clinical experts in Finland (clinical expert panel in Finland) and an observational study of citalopram in France (data on file, observational study of Seropram®, Lundbeck). The study used for estimation of probabilities was an observational pharmaco-epidemiological study with a multicentre, prospective, noncomparative cohort design, involving 1,020 patients treated with citalopram by GPs and psychiatrists in France. Details of demographics, diagnosis, treatment, resource utilisation and sick leave were recorded prospectively for a 5-month period. The study was used to estimate the probability of premature discontinuation. The remission and relapse rates following switch were based on evidence from Posternak that they are the same rates as for first-line treatment[21]. The remission rate was taken as a weighted average of the four most commonly used antidepressants in Finland (citalopram, fluoxetine and mirtazapine) (IMS DATAview). The probability of suicide attempts which did and did not result in death came from the literature[22-24].

Resource use

The quantities of medical resource use in relation to each branch of the decision tree were estimated. Estimates of resource use in terms of the number of physician (GP and psychiatrist) visits were determined through literature and consultation with clinical experts (clinical expert panel in Finland). The data on sickness absence was based on the observational study of Seropram® (citalopram) in France (data on file, Lundbeck) and information obtained from the Social Insurance Institution in Finland[25]. In assessing drug costs, it was

Table 3. Cost of resource use in model

Cost item	*Price for 2000 (EUR)*	*Sources*
Physician service		
GP (outpatient)	73.8	Heikkinen *et al*, 2001[26]
Psychiatrist visit	100.9	Heikkinen *et al*, 2001[26]
Cost per sickness absence day	161	Statistics Finland[27]
Hospitalisation	235.5	Heikkinen *et al*, 2001[26]
Suicide	542	Palmer *et al*,1998[30]
Suicide attempt	4,422	Runeson *et al*, 1992[31]
Secondary care		Secondary care model
Medical costs	1,982	
Nonmedical costs	3,479	

assumed that consultations at which treatment changes took place occurred at monthly intervals.

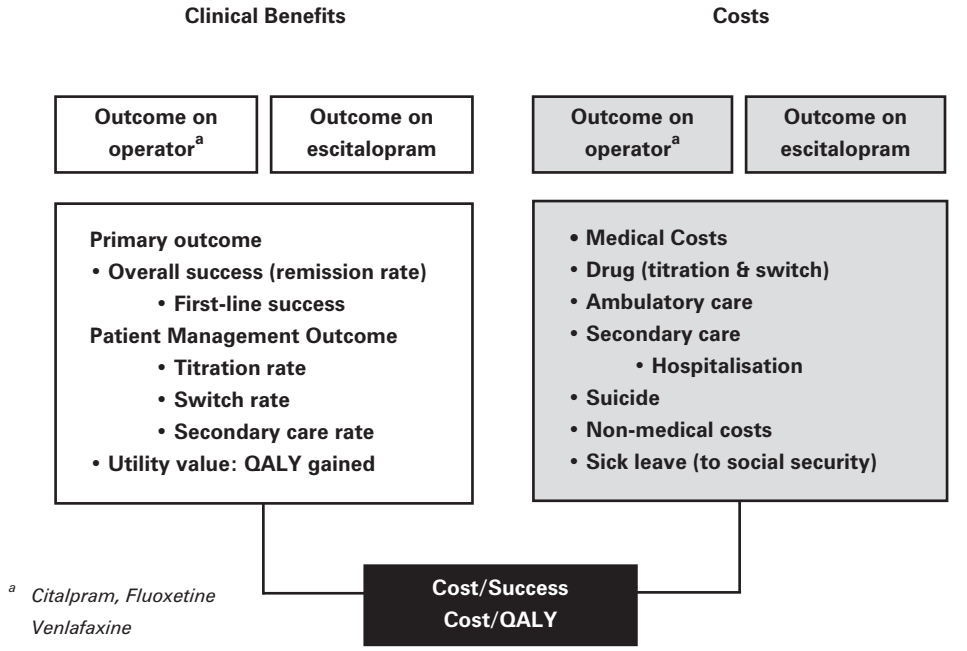
Cost data

Standard costs as expressed in Euro (EUR) in 2000 were used in all analyses. Unit costs were determined from cost data for Finland[25, 26] and are shown in Tables 3 and 4. The price for escitalopram represents a 15% increase over the price of citalopram, as requested. The cost of antidepressant after switching to another antidepressant was based on the weighted cost of the defined daily dose of the three most widely used antidepressants in Finland (20 mg citalopram, 20 mg fluoxetine, 30 mg mirtazapine) (IMS dataview). The human capital method was applied to value production losses due to depression.

Table 4. Unit cost of each antidepressant (Price/DDD Eur)

Cost item	*DDD (mg/day)*	*Packs size*	*Price/DDD (E)*	*Corresponding price for double dose*
Escitalopram	10	28	1.52	2.87
		100	1.29	2.37
Branded citalopram	20	28	1.321	2.496
		100	1.122	2.058
Generic citalopram	20	28	0.92	1.75
		100	0.79	1.44
Venlaflaxine	75	28	1.429	2.593
		98	1.248	2.200
Fluoxetine	20	30	0.963	1.926
		100	0.842	1.684
Generic fluoxetine	20	30	0.837	1.674
		100	0.695	1.390
Mirtazapine	30	30	1.724	3.448
		100	1.444	2.888

Figure 2. Clinical benefits and costs



Analysis

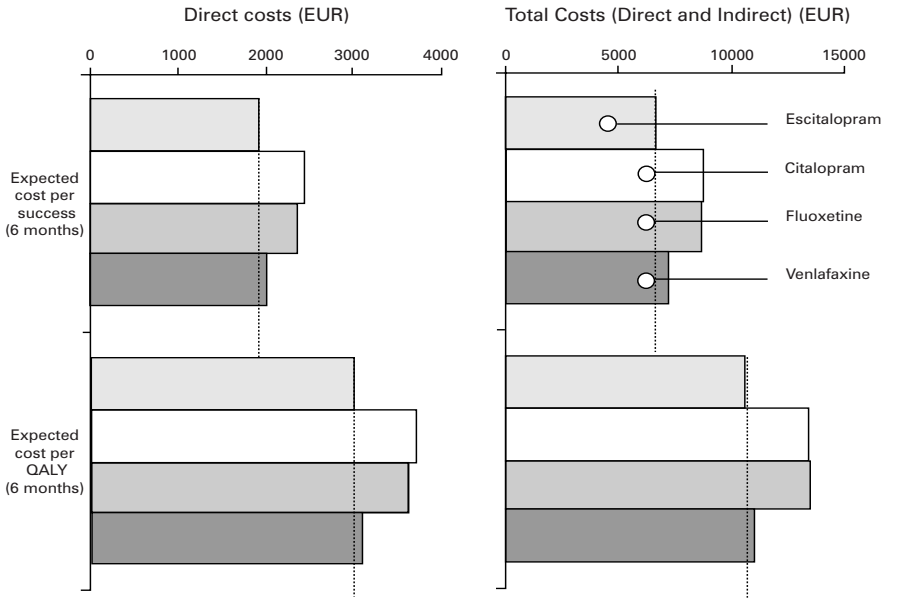
Cost-effectiveness and cost-utility analyses

The pharmacoeconomic analysis employed two analytic types: cost-effectiveness and cost utility analyses. The average cost-effectiveness and cost-utility ratios have been calculated by dividing the cost of treatment by the outcome measure. This has been done for total costs and the primary outcome measure to give the expected cost per successfully treated patient. The detail of outcomes and costs can be viewed in Figure 2.

Table 5. Average costs, average base case effectiveness and QALY per patient for 6-months treatment

	Escitalopram	*Citalopram*	*Fluoxetine*	*Venlafaxine*
Overall success (includes switch) %	51.4	45.6	45.6	49.6
First-line success (without switch) %	42.4	32.7	32.7	40.1
Titration rate %	37.2	33.7	35.6	40.7
Switch rate %	33	47.5	47.5	35
Secondary care rate %	19.4	28	28	20.5
QALY	0.33	0.30	0.30	0.32
Antidepressant drug cost (EUR)	205	170	137	197
Ambulatory care (EUR)	271	271	272	275
Secondary care (EUR)	381	549	550	404
Total direct costs (EUR)	857	990	959	876

Figure 3. Cost-effectiveness and cost-utility (QALY) ratios: comparison of escitalopram versus other antidepressants



Sensitivity analysis

Two sets of sensitivity analyses were performed to test assumptions and the robustness of the results. Univariate analyses were conducted by varying key parameters and direct costs. Break-even analyses were conducted on antidepressant drug prices, total direct costs, escitalopram cost per daily defined dose (DDD) and the remission rate for escitalopram.

Global budget impact

The effect of the introduction of escitalopram on the antidepressant drug budget was estimated. This was done by making projections of the market share under base case scenario (escitalopram only takes market share from branded citalopram) and by using IMS volume sales (defined daily doses, DDDs) and cash sales (EUR) projected between 2002 and 2004. The estimated number of patient episodes during each drug treatment (using IMS volume sales) are combined with the average 6-month per-patient expected costs of treatment (total direct costs) to estimate the effect of the introduction of escitalopram on the overall healthcare budget.

Results

Pharmacoeconomic analysis

The following results were obtained after considering the benefits and costs of escitalopram in comparison with citalopram, fluoxetine and venlafaxine.

The overall success rate with or without taking a switch into consideration (i.e. first- or second-line antidepressant) was higher for escitalopram than for the other antidepressants (Table 5). Patient management outcomes were improved with escitalopram. The titration, switch, secondary care and hospitalisation rates were lower than for other antidepressants,

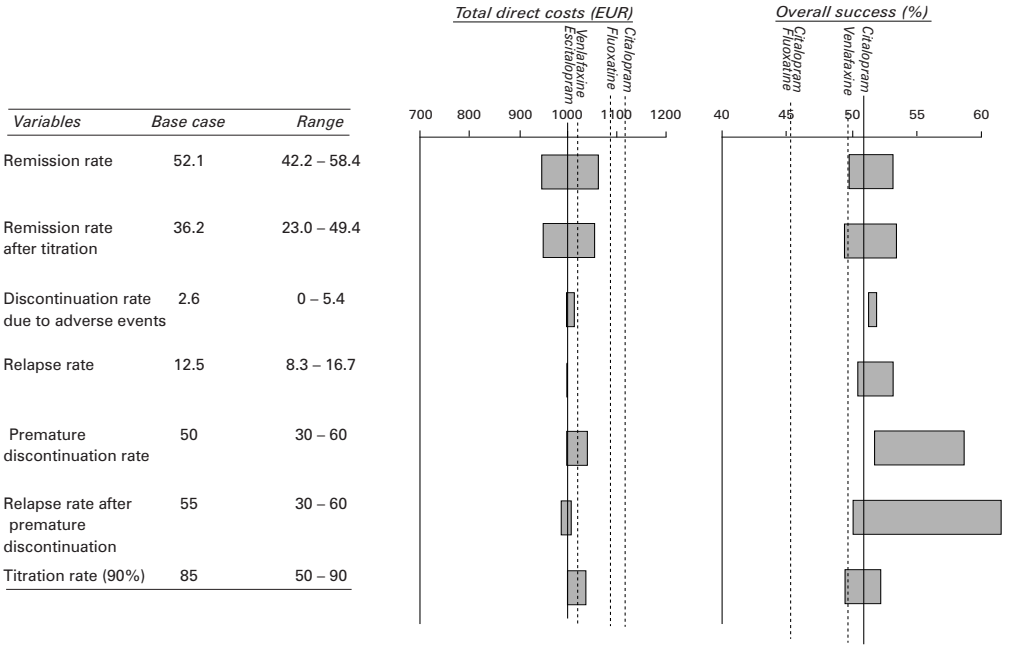
Table 6. Cost per success and cost per QALY, for direct, indirect and total costs

	Escitalopram	*Citalopram*	*Fluoxetine*	*Venlafaxine*
Costs/success direct	1,667	2,171	2,103	1,766
Costs/success indirect	4,848	6,384	6,439	5,218
Costs/success total	6,516	8,555	8,542	6,984
Costs/QALY direct	2,597	3,300	3,197	2,738
Costs/QALY indirect	7,552	9,703	9,787	8,088
Costs/QALY total	10,148	13,003	12,983	10,825

which can be viewed in Table 5. Direct costs (including drug costs, ambulatory care, secondary care) were lower for escitalopram as compared to other antidepressants (Figure 3). Indirect costs associated with patients taking sick leave due to depression were lower for escitalopram than for other antidepressants (Figure 3).

The average costs, average base case effectiveness and QALYs per patient for 6 months of treatment are shown in Table 5. Overall success is higher with escitalopram as compared to other antidepressants. Furthermore, more QALYs are produced and total direct cost is lower.

Figure 4.



Shaded area represents 95% confidence intervals for total direct costs and overall success when the different variables are varied within the ranges indicated.

Cost-effectiveness and cost-utility ratios

Treatment with escitalopram is the dominant strategy since it leads to better clinical outcomes and lower overall costs. Figure 3 shows the average cost-effectiveness ratios, expressed as the cost per successfully treated patient and the average cost-utility ratios expressed as the cost per QALY for escitalopram, citalopram, fluoxetine and venlafaxine. This shows that the expected costs per success or expected costs per QALY are lower with escitalopram as compared to citalopram, fluoxetine and venlafaxine. This is the case when total, direct or indirect costs are considered (Table 6).

Sensitivity analyses

The robustness of the results were tested in univariate sensitivity analyses for escitalopram versus the base case values for citalopram, fluoxetine and venlafaxine. The results are shown in Figure 4 and represent 95% confidence intervals or feasible ranges for the specified variables based on indirect comparisons using the literature. At the extreme values of probabilities tested, escitalopram is still associated with lower costs and a higher success rate than citalopram, or fluoxetine. The impact of antidepressant price variations on drug costs and total direct costs was tested in the sensitivity analyses. Regarding citalopram and fluoxetine, it was assumed that the lower and the upper prices used in the sensitivity analyses corresponded, respectively, to the generic price (forecast generic price for citalopram) and the branded price. Values of price corresponding to generic citalopram and generic fluoxetine, escitalopram were still associated with lower costs than citalopram or fluoxetine. A break-even analysis was also performed to assess the threshold value of escitalopram cost per DDD, for which escitalopram remained the dominant strategy. Thus, increasing the cost per DDD of escitalopram from EUR 1.52 up to EUR 2.63, EUR 2.37 and EUR 1.67 still gives a similar average cost-effectiveness ratio (total direct cost per successfully treated patient) to citalopram, fluoxetine and venlafaxine, respectively. Break-even analyses were also performed to assess the threshold values of remission rate for escitalopram at which the costs per successfully treated patient were similar to those of citalopram, fluoxetine and venlafaxine. The remission rate and remission rate after titration on escitalopram would both have to be reduced from 52.1% to 38% and 36.2% to 25.0%, respectively, to give a similar cost-effectiveness ratio as for citalopram and fluoxetine. Compared to venlafaxine, rates would both have to be reduced to 46.0% and 32.0% to give a similar cost-effectiveness ratio.

Global budget impact

The introduction of escitalopram at the market penetration levels indicated for 2004 as a base-case scenario would lead to an increase in the drug budget of EUR 2,895,000 in 2004. This corresponds to a 4.2% increase in the antidepressant budget (Table 7).

The impact of the introduction of escitalopram on the overall healthcare costs indicated for 2004 as a base-case scenario

Table 7. Budgetary impact of escitalopram (drug budget)

000s EUR	*2002*		*2003*		*2004*	
	Budget	*% Increase*	*Budget*	*% Increase*	*Budget*	*% Increase*
Without escitalopram	64,432		65,875		69,746	
With escitalopram Base-case scenario	63,553	1.8 %	67,904	3.1%	72,641	4.2%

would lead to a 3.7% reduction in the total healthcare costs of EUR 11.7 million (from EUR 359.6 million to EUR 346.5 million, Table 8).

The small projected increase in the drug budget is thus confirmed by this method of calculation and is more than compensated by the decrease in other healthcare costs.

Discussion

Although selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants, data comparing the effectiveness of the members of this class of antidepressants are limited[25]. When studied, the effectiveness between SSRIs appears to be similar[26], though not interchangeable, because patients who discontinue one SSRI for lack of tolerability or response can generally be treated effectively with another. Escitalopram is clearly more effective than citalopram, as it shows a significantly higher rate of remission, which is the primary criteria for physicians. This higher remission rate (both at recommended dose and at double dose for non-responding patients) is the greatest driver of the decision analytic model. Though the higher remission rate was significant in only one study, it was numerically significant in all the studies comparing escitalopram with citalopram at comparable dosage.

Also, by taking into account factors other than the clinical trials (such as premature discontinuation, switch, referral to secondary care) the decision analytic model allows for a greater external validity of the findings. As in all decision analytic models,

Table 8. Breakdown of global budget impact into drug and non-drug impacts

000s EUR	*2002*			*2003*			*2004*		
	Total	*% reduction*	*Drug*	*Total budget*	*% reduction*	*Drug*	*Total budget*	*% reduction*	*Drug*
Without escitalopram	302,633	–	49,560	322,901	–	52,408	349,743	–	55,747
With escitalopram Base-case scenario	298,083	1.5%	50,758	314,668	2.5%	54,575	337,994	3.3%	58,838

different sources of data were used. This may have led to bias.

We attempted to reduce these potential biases by building the model on local data collected through a standardised literature review, and not only relying on expert opinion. However, an expert panel composed of clinicians and a local health economist was consulted to insure that the structure of the model and the assumptions made reflected the current treatment of MDD in Finland. Assumptions were based on weak data: for example, the hospitalisation rate may have been overestimated as it is assumed that all patients were hospitalised if they experienced a 'no response' either after a switch, adding an agent, or a titration plus a switch in secondary care. In clinical practice, hospitalisation may not take place as frequently.

Another limitation was the absence of comparative clinical trial data between escitalopram, fluoxetine and venlafaxine. Indirect comparisons were made based on a structured review of the literature.

Since there is no clear consensus on the measurement of indirect costs, the human capital method was applied to value production losses due to depression. This approach might overestimate costs, as it assumes that potential production is equal to indirect costs. Another method we considered was the friction costs. This assumes that within the production process everyone is replaceable and therefore indirect costs are restricted to the amount of production lost due to disease and depends on the time-span necessary to restore the initial production level. However, as the length of time of absence from work is relatively short, estimations using both methods should not differ significantly.

All the assumptions as well as the uncertainty around the variables were tested in extensive sensitivity analyses to verify the validity of the conclusions, estimates and different hypotheses. The results confirm that none has been judged to significantly affect the primary outcome and costs resulting from the model.

Conclusions

The evaluation of a new antidepressant treatment, such as escitalopram, is subject to budgetary restrictions imposed by Public Health Authorities. The choices to be made are therefore guided by comparative studies, preferably those which allow analysing the therapeutic attributes according to their immediate costs, but also to their respective medical advantages (the effectiveness and utility of treatments). This pharmacoeconomic analysis demonstrated the importance of considering all aspects of patient management and health-state rather than just simply drug prices alone in determining which drugs should be used in the treatment of depression. Based on a decision model this analysis concludes that escitalopram is a more cost-effective treatment alternative than citalopram, fluoxetine, and venlafaxine in the treatment of depression. The cost-

effectiveness of escitalopram versus fluoxetine and venlafaxine will be further validated with data from ongoing head-to-head comparison trials. The results of this study suggest that increased utilisation and prescription of escitalopram will reduce the overall healthcare costs in the treatment of depression in Finland.

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References

1. CCOHTA. *Guidelines for economic evaluation of pharmaceuticals: Canada*. 2nd edn. 1997; Ottawa, Canadian Coordinating Office for Health Technology Assessment (CCOHTA).
2. Finnish Pharmaceuticals Pricing Board. *Guidelines for the Preparation of an account of health-economic aspects* (an unofficial translation). 1999.
3. EinarsonTR, Arikian S, Sweeney S *et al*. A model to evaluate the cost-effectiveness of oral therapies in the management of patients with major depressive disorders. *Clinical Therapeutics* 1995; **17**: 136–153.
4. Lapierre Y, Bentkover J, Schainbaum, S *et al*. Direct cost of depression: analysis of treatment costs of paroxetine versus Imipramine in Canada. *Canadian Journal of Psychiatry* 1995; **40**: 370–377.
5. Nuijten MJ, Hardens M, Souetre E. A Markov process analysis comparing the cost effectiveness of maintenance therapy with citalopram versus standard therapy in major depression. *Pharmacoeconomics* 1995; **8**: 159–168.
6. Einarson TR, Addis A, Iskedjian M. Pharmacoeconomic analysis of venlafaxine in the treatment of major depressive disorder. *Pharmacoeconomics* 1997; **12**: 286–296.
7. Buxton MJ, Drummond MF, Van Hout BA *et al*. Modelling in economic evaluation: an unavoidable fact of life [editorial] [see comments]. *Health Economics* 1997; **6**: 217–227.
8. Practice guideline for the treatment of patients with major depressive disorder (revision). *American Journal of Psychiatry* 2000; **157** (Suppl): 1-45.
9. Anderson IM, Nutt DJ, Deakin JFW. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology* 2000; **14**: 3-20.
10. Burke WJ, Gergel, Bose A. Fixed dose trial of the single isomer SSRI escitalopram in dpressed outpatients. *Journal of Clinical Psychiatry* 2002; **63**: 331-336.
11. Patris M, Bouchard JM, Bougerol T *et al*. Citalopram versus fluoxetine: a double-blind, controlled, multicentre, phase III trial in patients with unipolar major depression treated in general practice. *International Clinical Psychopharmacology* 1996 ; **11**: 129–136.
12. Bougerol T, Scotto JC, Patris M. Citalopram and fluoxetine in major depression: comparison of two clinical trials in a psychiatrist setting and in general practice. *Clinical Drug Investigation* 1997; **14**: 77–89.
13. Silva J. Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression [see comments]. *Journal of Clinical Psychiatry* 1998; **59**: 352–357.
14. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *Journal of Affective Disorders* 1999; **56**: 171–181.

15. Dierick M, Ravizza L, Realini R *et al*. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. *Progress in Neuropsychopharmacology and Biological Psychiatry* 1996; **20**: 57–71.

16. Diaz-Martinez A, Benassinni O, Ontiveros A *et al*. A randomized, open-label comparison of venlafaxine and fluoxetine in depressed outpatients. *Clinical Therapeutics* 1998; **20**: 467–476.

17. Montgomery SA, Rasmussen JG, Tanghoj P. A 24-week study of 20 mg citalopram, 40 mg citalopram, and placebo in the prevention of relapse of major depression. *International Clinical Psychopharmacology* 1993; **8**: 181–188.

18. Robert P, Montgomery SA. Citalopram in doses of 20-60 mg is effective in depression relapse prevention: a placebo-controlled 6 month study. *International Clinical Psychopharmacology* 1995; **10** (Suppl. 1): 29–35.

19. Reimherr FW, Amsterdam JD, Quitkin FM *et al*. Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. *American Journal of Psychiatry* 1998; **155**: 1247–1253.

20. Entsuah AR, Rudolph RL, Hackett D *et al*. Efficacy of venlafaxine and placebo during long-term treatment of depression: a pooled analysis of relapse rates. *International Clinical Psychopharmacology* 1996; **11**: 137–145.

21. Posternak MA, Zimmerman M. Switching versus augmentation: a prospective, naturalistic comparison in depressed, treatment-resistant patients. *Journal of Clinical Psychiatry* 2001; **62**: 135–142.

22. Kiloh LG, Andrews G, Neilson M. The long-term outcome of depressive illness. *British Journal of Psychiatry* 1988; **153**: 752–775.

23. Thornicroft G, Sartorius N. The course and outcome of depression in different cultures: 10-year follow-up of the WHO Collaborative Study on the Assessment of Depressive Disorders. *Psychological Medicine* 1993; **23**: 1023–1032.

24. Angst J, Preisig M. Outcome of a clinical cohort of unipolar, bipolar and schizoaffective patients. Results of a prospective study from 1959 to 1985. Schweiz. *Archives of Neurology and Psychiatry* 1995; **146**: 17–23.

25. Statistical yearbook of the Social Insurance Institution, Finland 2000. Publication T1:36, Helsinki 2001.

26. Heikkinen *et al*. Terveydenhuollon yksikkökustannukset Suomessa vuonna 2000. Stakes Aiheita 23/2001, Helsinki 2001.

27. Statistics Finland, http://statfin.stat.fi/statweb/

28. Straton JB, Cronholm P. Are paroxetine, fluoxetine, and sertraline equally effective for depression? *Journal of Family Practice* 2002; **51**: 285.

29. Kroenke K, West SL, Swindle R *et al*. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. *Journal of the American Medical Association* 2001; **286**: 2947–2955.

30. Palmer CS, Revicki DA, Genduso LA *et al*. A cost-effectiveness clinical decision analysis model for schizophrenia. *American Journal of Managed Care* 1998; **4**: 345–355.

31. Runeson B, Wasserman D. Management of suicide attempters: what are the routines and the costs? *Acta Psychiatrica Scandinavica* 1994; **90**: 222–228.

Appendix

Randomised Controlled Clinical Trials – unpublished studies

99001: H. Lundbeck A/S. A double-blind, randomised, placebo-controlled trial evaluating the efficacy and safety of 10 mg Lu 26-054 in outpatients with Major Depressive Disorder. 2001; Report No. 215/311.

99002: H. Lundbeck A/S. An open long-term safety follow-up study of Lu 26-054 in the treatment of Major Depressive Disorder 2002; Report No 225/311.

99003: H. Lundbeck A/S. A double-blind, randomised, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of Lu 26-054 and citalopram in outpatients with Major Depressive Disorder 2001; Report No. 221/311.

MD-01: Forest Laboratories. Fixed Dose Comparison of the Safety and Efficacy of Lu 26-054, Citalopram and Placebo in the Treatment of Major Depressive Disorder. 2001; Report No. SCT-MD-01.

MD-02: Forest Laboratories. Flexible Dose Comparison of the Safety and Efficacy of Lu 26-054. Citalopram, and Placebo in the Treatment of Major Depressive Disorder. 2000; Report No. SCT-MD-02.