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Model to assess the cost-effectiveness of new treatments for depression

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Objectives: The objective of this study was to develop a model to assess the cost-effectiveness of a new treatment for patients with depression.
Methods: A Markov simulation model was constructed to evaluate standard care for depression as performed in clinical practice compared with a new treatment for depression. Costs and effects were estimated for time horizons of 6 months to 5 years. A naturalistic longitudinal observational study provided data on costs, quality of life, and transition probabilities. Data on long-term consequences of depression and mortality risks were collected from the literature. Cost-effectiveness was quantified as quality-adjusted life-years (QALYs) gained from the new treatment compared with standard care, and the societal perspective was taken. Probabilistic analyses were conducted to present the uncertainty in the results, and sensitivity analyses were conducted on key parameters used in the model.
Results: Compared with standard care, the new hypothetical therapy was predicted to substantially decrease costs and was also associated with gains in QALYs. With an improved treatment effect of 50 percent on achieving full remission, the net cost savings were 20,000 Swedish kronor over a 5-year follow-up time, given equal costs of treatments. Patients gained .073 QALYs over 5 years. The results are sensitive to changes in assigned treatment effects.
Conclusions: The present study provides a new model for assessing the cost-effectiveness of treatments for depression by incorporating full remission as the treatment goal and QALYs as the primary outcome measure. Moreover, we show the usefulness of naturalistic real-life data on costs and quality of life and transition probabilities when modeling the disease over time.

Keywords: Depression, Cost-effectiveness, Cost-utility, Model, QALY

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Depression imposes a disability burden and also a substantial financial burden on society (24). Improving the management of depression in primary care is a public health priority. It has been argued that up to half of the primary care patients with depressive disorders either are unrecognized or receive no specific treatment (10;29). The primary objectives of interventions for depression are to alleviate symptoms and to prevent relapses. However, it has become increasingly important to also consider the cost-effectiveness of different treatment alternatives. Health economic evaluations and guidelines on the use of pharmacological therapies have been initiated as a result of increasing drug costs and strained healthcare budgets in many countries.

Newer antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), affect neurotransmitters selectively. Apart from SSRIs, there are several new selective antidepressants, for example, reversible inhibitors of monoamine oxidase A (RIMAs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). In primary care treatment for depression, SSRIs and SNRIs currently are used mostly and are proven effective (19–22). However, the currently marketed antidepressants are not effective in all patients with depression and have other limitations, including a delayed onset of action of 3–6 weeks and adverse side effects, which reduce treatment compliance (17). With an increased understanding of the neurobiological causes of depression and new clinical substances under development for treating depression, it is likely that better onset of action will be provided in the near future. Hence, economic evaluations of treatments for depression under development will have to be more focused on the time parameter in the treatment, especially so the time to remission, and thereby prevention of relapses and recurrences.

Previous economic evaluations of treatments for depression have been focused mainly on newer generations of antidepressant drugs (SSRI/SNRI). In a recently published review, Barrett et al. found fifty-eight economic evaluations conducted on different interventions for depression, and twenty-seven of these were specifically evaluating drug treatments (4). Most guidelines on how to assess cost-effectiveness for medical technologies recommend the use of quality of life as the primary outcome measure and to include all relevant costs. Among the twenty-seven published studies evaluating drug treatments for depression, four were based on measures of quality of life and ten included costs relevant from the societal perspective. Hence, only a minority of the previously published economic evaluations use a generic quality of life measure as primary outcome, which makes comparison of results between studies difficult. By only considering direct treatment costs in the analysis, it neglects the major bulk of the cost of depression and the potentially important impact of a treatment for depression on employment and productivity (4).

It seems reasonable to assume that the economic costs of care are minimized when patients receive quality care quickly and adequately (5). However, few economic evaluations have considered this aspect in their analyses. Previous findings show that patients reaching full remission are associated with a significantly lower cost compared with non-remitting patients (23;27). This finding suggests that time to remission is a key parameter when evaluating treatments for depression from a health economic perspective, especially as depression is a disabling disease with negative consequences on working ability.

The objective of this study is to develop an approach to model long-term consequences from a hypothetical therapy for depression and to conduct cost-effectiveness analyses based on a patient population from the recent health economic study Health Economic Aspects of Depression in Sweden (HEADIS) (27).

MATERIALS AND METHODS

Cost-effectiveness analysis in depression generally requires modeling, as all the required data are seldom available from a single data set over the relevant timeframe. The current analysis is mainly based on the HEADIS study, which was a naturalistic observational study investigating the health economics consequences from antidepressant treatment in patients treated in a primary care setting. The HEADIS study provided data on costs, utilities, and transition probabilities for standard care to the present modeling study. Complementary assumptions were retrieved from the literature.

The intervention that is evaluated is a hypothetical antidepressant therapy compared with standard care, as it is currently provided to depressed patients in Swedish primary care. The treatment effect of standard care included antidepressant therapy (83 percent were initially prescribed an SSRI drug, 9 percent SNRI [venlafaxine], and 8 percent other antidepressants [monoamine oxidase or tricyclic antidepressant {TCA}]), counseling, and psychotherapy (10 percent of the study population received psychotherapy). Both the costs and the effects of standard care were based on the results from the HEADIS study (27). The treatment effect from the hypothetical treatment was applied as a percentage increase in the probability of achieving remission. In base case, the effect of the hypothetical treatment had no impact on relapse rates, but this finding was tested for in a sensitivity analysis.

The Model

A Markov simulation model (28) was constructed to simulate the course of events for subjects treated for depression over varying time periods (6 months to 5 years). The possible health states defined in the model were divided into: well, remission, episode, and dead. Patients are simulated individually in the model and start out with a current episode from depression. A patient starts the simulation at a given

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age and moves through the states of the model according to a set of transition probabilities that occur at monthly cycles. Patients can remit from the initial episode with a certain probability, and once remitted, the patient can either relapse or remain remitted. After 6 months of remission, the patient is considered to be free from depression (well), which is an assumption based on previous research (15). Patients being well can recur and, hence, return to an episode. The model allows for multiple episodes throughout the timeframe of the analysis. Patients also have a risk of dying in all states, and the mortality was taken from general population life tables. Depressive episodes, however, are associated with higher mortality. Remission was defined as clinical remission as judged by treating physicians in clinical praxis and rated improvement measured with the Clinical Global Impression Improvement scale (CGI-I) (11). Costs were assigned for each Markov state in the model, as well as health utilities for estimation of quality-adjusted life-years (QALYs). The model was programmed in TreeAge Pro Suite 8.2 (TreeAge Software, Inc., Williamstown, MA).

Patient Group and Setting

The cost-effectiveness analysis was based on a patient group followed naturalistically for 6 months (HEADIS study) (27). The study included 447 patients with depression who were treated with antidepressant therapy in the Swedish primary care setting. The study population had a mean age of 47 years (SD 14.3), 67 percent were women, and 67 percent were working (with an age below 65). A total of 24 percent of the patients were mildly depressed (assessed with the Clinical Global Impression Severity Scale [CGI-S]) (11), 61 percent moderately depressed, and 15 percent severely depressed at inclusion. Fifty-nine percent of the population had a physical or psychiatric comorbidity. For a more detailed description of the patient population and the observational study, see previous publication (27).

Cost Data

The present study adopted the societal perspective, including costs of care occurring both in the outpatient and inpatient setting. Moreover, costs due to sickness absence were included. Cost of care and productivity losses in the different states of the model were estimated using data from the observational study HEADIS (27). Data on resource use included primary care visits, hospital visits, and visits to other health professionals (e.g., psychologists and counselors). Costs were calculated by combining the resource-use data and sickness absence information with current unit prices for Sweden (26). In the model, all future costs were discounted to present value at 3 percent annually (which is recommended by the Swedish Pharmaceutical Benefits Board) and were presented for year 2005 in Swedish kronor (SEK) (US$1≈7.5; €1≈9.3). The cost data assigned to the different health states are summarized in Table 1.

Table 1. Input Data for the Model

Parameter	Data (95% CI)	Source
Costs by states	(SEK/month)	
Well	0	
Episode		
Direct healthcare costs	3,247 (2,864–3,888)	(27)
Indirect costs	7,036 (5,808–8,313)	(27)
Cost of antidepressants	385 (309–507)	(27)
Remission		
Direct healthcare costs	2,044 (1,175–2,559)	(27)
Indirect costs	4,165 (3,278–5,111)	(27)
Cost of antidepressants	323 (267–405)	(27)
Dead	0	
Health utility weights		
Well	.86 (SE .009)	(6)
Episode	.57 (.52–.61)	(27)
Remission	.81 (.78–.84)	(27)
Dead	0	
Transition probabilities		
Relapse rate (for 6 months)	.15	(9)
Remission rate	Survival function	(27)
Recurrence (episodes/year)	.20	(2)
Increased risk of recurrence with previous episodes (hazard ratio)	1.15 (1.11–1.18)	(14)
Suicide risk (SMR)	20.4 (SE 1.1)	(12)
Duration of treatment	Until 6 months after remission	(1;3)

CI, confidence interval; SEK, Swedish kronor; SMR, standard mortality ratio; SE, standard error.

Health Utilities

Quality of life was measured with the EuroQoL (EQ-5D) health status questionnaire and was used to estimate QALYs for the model (25). The data from the HEADIS study showed that remission was an important predictor of health-related quality of life, whereas other demographic and clinical variables were not statistically significant (25). The results from the HEADIS study, were used for the health states "Episode" and "Remission" in the Markov model (27). For the health state "Well," a utility score was taken from a recent study of the health-related quality of life in the general population conducted by Burström et al. (7). The utility scores applied in the model are summarized in Table 1.

Transition Probabilities

The relapse risk of a new episode could not be based on the HEADIS since the follow-up period was too short, but it was instead retrieved from published sources. Geddes et al. (9) have conducted a thorough meta-analysis based on clinical trials, and estimated the risk of relapse to be .15 during 6 months of treatment with antidepressants. Once the patient

Table 2. Weibull Survival Function on Time to Remission (Months), No Hazard

$N = 398$	Coefficient	SE	Z	$p > z$	95% CI	
Age (year)	.0037	.0053	.69	.49	−.007	.014
Male	−.0286	.1521	−.19	.851	−.327	.270
Disease severity[a]	−.9538	.2802	−3.4	.001	−1.503	−.405
New episode	−.2450	.1739	−1.41	.159	−.586	.096
Comorbidity	−.0761	.1494	−.51	.611	−.369	.217
Psychotherapy	.0640	.2207	.29	.772	−.368	.496
Constant	−2.9207	.3555	−8.22	0	−3.618	−2.224

Note. Likelihood ratio, $\chi_6^2 = 19.73$; $p = .0031$.
[a] 1, severe depression; 0, mild/moderate depression.
SE, standard error; CI, confidence interval.

had remained symptom-free (i.e., the remission state in the model) for 6 months, the patient was considered well (recovered). The risk of recurring was set to .20 per year (2). However, the risk was assumed to increase with number of previous episodes (hazard ratio 1.15) (14). Mortality rates were taken from the general population in Sweden, and based on the literature, it was assumed that patients having a depressive episode had an increased relative risk of dying due to suicide of 20.4 (12).

Transition probabilities for remission were based on data from the HEADIS study (27). A Weibull regression model (27) was estimated on survival data measuring time to remission, and transition probabilities were calculated from the survival function (see Table 2). The Weibull distribution is suitable for modeling data with hazard rates that increase or decrease over time and allows for the estimation of the probability of an event in different time intervals after the starting point, for example, the probability of achieving remission within 4 months after the start of the episode. These types of calculations are not possible with other nonparametric survival analysis methods (e.g. Kaplan–Meier functions). The Weibull survival function was used to estimate the monthly remission rate based on data from the HEADIS. The estimated parameter values in the Weibull survivor function are given in Table 2. To estimate the remission rate (r) for a certain month (t = 1, 2, 3, etc.) after the depression episode, the following formula was used:

$$r = 1 - \frac{\hat{S}(t)}{\hat{S}(t-1)} = 1 - \frac{e^{-(e^{(\hat{\alpha}+\hat{\beta}\times age)}t^{\hat{p}})}}{e^{-(e^{(\hat{\alpha}+\hat{\beta}\times age)}(t-1)^{\hat{p}})}}$$

where the ratio between the survivor functions is equal to the hazard function integrated between t − 1 and t.

Analysis of Uncertainty

All patient-level data (costs, utility, transition probabilities) were entered as distributions rather than point estimates. This strategy allowed for stochastic evaluation of the model and estimation of confidence intervals that take into account the uncertainty in the estimates of the data used in the model. Key input parameters were also varied in sensitivity analysis.

RESULTS

Simulated Transitions, Costs, and QALYs over Time in Standard Care

Patients were simulated through the developed Markov model over a 5-year time frame. The patient cohort simulated is treated for an acute depression episode and, thus, all patients start in this health state. In consequence with the transitions of patients over time, the costs are increasing most heavily during the first year after the index episode and the accumulated cost for the first year amounts to SEK95,300. As patients are turning symptom free over the longer-term, costs occur only due to relapses and recurrences and, hence, costs are declining over the following years. At 5 years, the total accumulated cost is SEK157,700. In terms of QALYs, the pattern is more linear, as the differences in utility are not as great between the health state of remission and when patients are recovered completely from the episode. During the first year, the total number of QALYs is .70, compared with 1.46 at the end of the second year and 3.62 after 5 years.

Cost Savings and QALY Gains with New Treatment

As a base case scenario, a hypothetical effect of the new treatment is modeled as a 50 percent relative improved remission rate. In base case, the cost of the new treatment was, moreover, set equal to that of standard care. All patients were assumed to start the simulation in the state "Episode," and 10,000 patients were simulated stochastically through the model. The time horizon was varied from 6 months (equaling the follow-up length of the HEADIS study) to 5 years.

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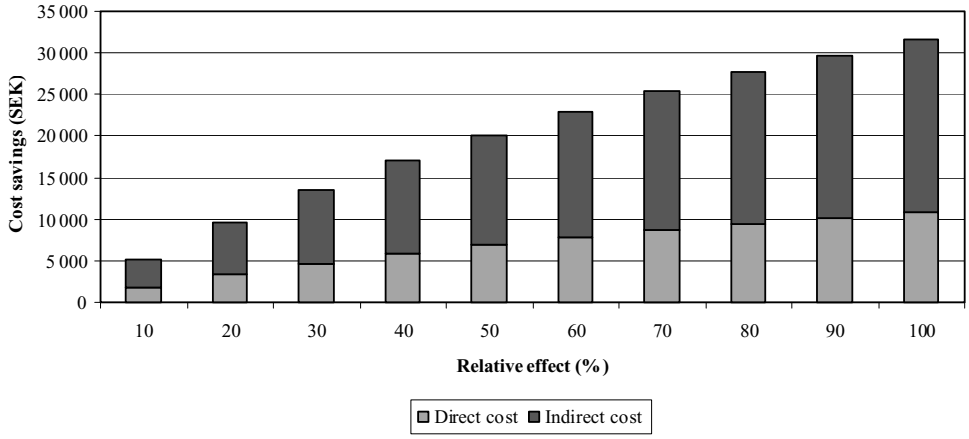

Figure 1. Estimated cost savings for different relative effect sizes (time frame, 5 years). Differences are statistically significant at the 5 percent level. SEK, Swedish kronor.

The new treatment produces statistically significant cost savings even for the shortest time frame (6 months). The total cost savings ranged from SEK2,300 to 20,100. There were both cost reductions in healthcare costs as well as indirect costs. With a time frame of 5 years, the total direct cost for patients with standard care resulted in SEK52,900, compared with SEK46,000 for the intervention arm, corresponding to a difference of SEK6,900. However, the main cost saving was observed in indirect costs, where the intervention produced a cost reduction of SEK13,200.

In terms of QALYs, the results simulated over three different simulation time frames, the new treatment generated improvements by .011–.073 QALYs over the time frame of half a year up to 5 years.

Varying the relative treatment effect size of the new treatment has a dramatic impact on the potential cost savings (given the same cost of the intervention as for standard care). With only a marginal increased effect of 10 percent, the cost saving is SEK5,200 over 5 years, and with 100 percent improved effect compared with standard care, it amounts to SEK31,600 (see Figure 1).

Similarly to the simulations of cost savings with the new intervention, analysis of potential improvements in quality-of-life was conducted. Figure 2 presents the results over three different simulation time frames, where the new treatment generated improvements by .002–.12 QALYs, depending on the relative effect improvement on the remission rate and the time frame given.

Intervention Cost Threshold

By introducing a premium price for the hypothetical intervention, we can assess at what levels of effect it is not cost saving to treat anymore. These levels can be considered threshold values for when the hypothetical intervention is just not cost saving compared with standard care. Figure 3 presents the results from this analysis and shows that even a small relative effect size allows for rather considerable premium prices for

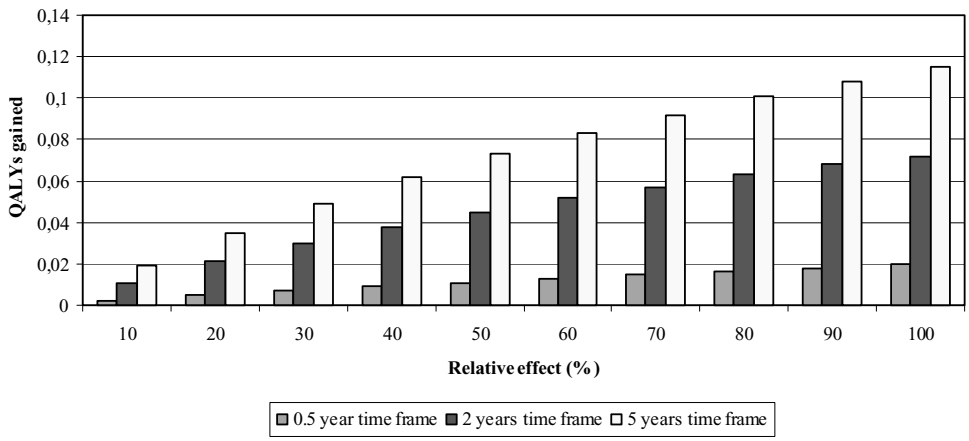

Figure 2. Quality-adjusted life-years (QALY) gained with hypothetical treatment. Differences are statistically significant at the 5 percent level.

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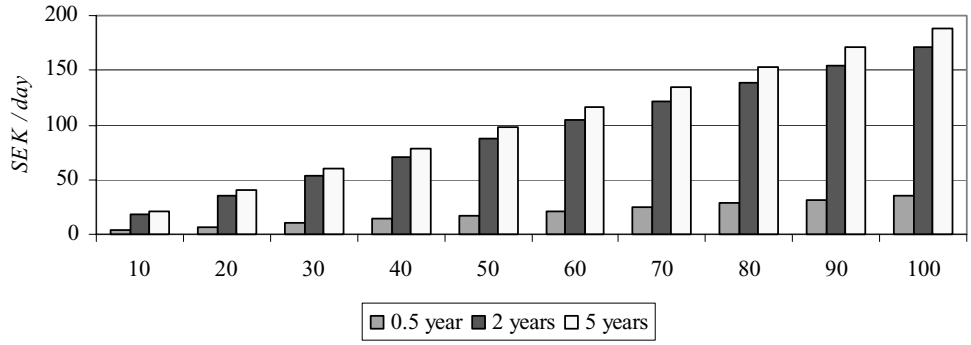

Figure 3. Threshold intervention cost at different effect levels and time frames (premium cost in Swedish kronor [SEK]/day). Differences are statistically significant at the 5 percent level.

the new intervention. The daily treatment cost of standard care was estimated at SEK10. At a relative effect improvement of 50 percent, the premium price for the new intervention would be SEK17 per day at a time frame of 6 months and up to almost SEK100 when following patients over a 5-year time frame. The premium price, however, varies highly when reducing or increasing the relative effect size of the new intervention.

Sensitivity Analysis

In our base case assessment of the new treatment, we have used a conservative effect assumption, by suggesting that the new treatment only had effect on the remission rate from the initial depressive episode and no impact on the relapse and recurrence risk. By assigning the same relative treatment effect of 50 percent also to the risk of relapses, the cost savings would increase to SEK23,700, and QALYs gained increase to .08 over a 5-year time frame. If we further were to assume that the same treatment effect would reduce the risk of recurrence by the same amount, the result would be cost savings of SEK36,400 (see Table 3).

We restricted our base case simulations to a follow-up period of up to 5 years. As sensitivity analysis, we ran simulations for up to 30 years follow-up from the index episode. With a 5-year time frame, we have already shown a cost saving of SEK20,100 and a QALY gain of .07. The results improve quite substantially up until a follow-up period of approximately 15 years (cost saving of SEK26,100 and .21 QALYs gained), whereas it changes marginally thereafter (see Table 3). At 30 years, the total accumulated cost of a depressed patient who has received standard care reaches SEK313,000 and 14.6 QALYs.

In base case, the new treatment was assumed to have the same adverse effects as antidepressant drugs prescribed today. By assuming an increased average cost due to drug-related adverse effects, the cost savings decrease slightly (see Table 3).

In our base case scenario, we assumed no reduction in mortality risk for the new treatment compared with standard care. It is likely, however, that a new therapy has the potential to reduce the mortality risk further. The sensitivity analysis shows that a reduction of the mortality risk for those patients on new treatment leads to gains in QALYs compared with standard care, whereas the cost savings with the new treatment is slightly decreased (Table 3). Moreover, in base case, we assumed a mortality risk of 20 times the general population risk when having a depression episode. The sensitivity analysis shows that varying this risk rate for both treatment arms has little impact on the cost-effectiveness results (see Table 3), presumably because the base mortality risk is very low in a middle-aged population.

Costs and effects were discounted with a factor of 3 percent in the base case analysis. Higher discount rates for both costs and effects slightly decrease the cost savings and QALY gains shown for the new treatment (see Table 3).

DISCUSSION

Our results show that new treatments for depression, having a relatively better effect, easily can produce cost savings for society compared with standard care for depression. With a 5-year time perspective, a 50 percent improved remission rate with a new antidepressant treatment would result in cost savings of more than SEK20,000 per patient with depression, and over a course of an episode (approximated to 6 months), the corresponding cost savings would be SEK2,300 per patient.

The present study is a novel approach to assessing the cost-effectiveness of treatment for depression in several ways. First, the model developed for the analysis allows for estimations of costs and effects from treatment over the longer term. Second, the assessment is based on cost and effect data from a naturalistic observational study carried out in primary care settings in Sweden and, hence, captures the consequences from standard care as they occur in clinical practice. Third, the model uses full remission as an important driver of costs and effects in depression (27), in contrast to partial response to treatment, and primary data from

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Table 3. Sensitivity Analysis (5-Year Time Frame)

	ΔCosts	ΔQALYs
Hypothetical treatment effects		
Relapse risk reduction		
10%	21,106	.075
20%	21,936	.077
30%	22,634	.079
40%	23,229	.08
50%	23,742	.081
Relapse and recurrence risk reduction		
10%	24,482	.080
20%	28,169	.086
30%	31,317	.091
40%	34,035	.096
50%	36,405	.10
Mortality risk reduction		
10%	19,838	.08
20%	19,573	.088
30%	19,307	.095
40%	19,041	.103
50%	18,773	.11
Additional cost of AE with new treatment (SEK/month)		
25	19,938	.073
50	19,774	.073
75	19,610	.073
100	19,446	.073
Non–treatment-specific parameters		
Simulation time frame		
5 years	20,102	.073
10 years	24,327	.119
15 years	26,128	.165
20 years	26,674	.208
25 years	26,621	.248
30 years	26,327	.280
Increased mortality risk		
0 (general population)	21,057	.052
10	20,413	.062
20[a]	19,800	.073
30	19,214	.083
Discount rate (costs and effects)		
0%	21,057	.077
3%[a]	20,102	.073
5%	19,503	.070
10%	18,120	.064

[a] Base case assumptions.
QALYs, quality-adjusted life-years; AE, adverse event; SEK, Swedish kronor.

the HEADIS study allowed for estimations of a probability of remitting over time. Fourth, the study takes the societal perspective into account in the cost inclusion and effect is measured in terms of QALYs.

Our results indicate that there is a substantial health economic potential for future therapeutic developments in depression, especially for new treatments that may shorten the time until achieving remission. As patients who remain depressed (in a depression episode) are both associated with significantly higher costs as well as reduced quality of life (27), it is highly important for future therapies to reduce the time elapsing from the start of treatment until the patients are completely symptom-free. We have shown that only marginal relative effect improvements in newer treatments can reduce most notably the cost of the disease, with increasing gains over longer time periods of follow-up.

To our knowledge, there are only three previous model-based cost-effectiveness assessments previously conducted in the area of depression in Sweden. Löthgren et al. (16) conducted a cost-effectiveness analysis of escitalopram versus citalopram and venlafaxine over a 6-month time frame. The input data in the study by Löthgren et al. were mainly based on international literature and expert opinion; the definition of remission applied was response to treatment as measured in the clinical trials (Montgomery–Asberg Depression Rating Scale score below or equal to 12 at 8 weeks) rather than reflecting full remission; and the outcome measure for effectiveness was not QALYs. An older study by Norinder et al. (18) evaluated mirtazapine and amitriptyline as first-line treatment for major depressive disorder. A decision-analytic model was used, and costs and effects (measured in terms of symptom-free patient) were estimated over a 6-month time frame. The analyses were based on literature data, Swedish registry data, and the authors' own assumptions. Casciano et al. (8) conducted a multinational assessment of the cost-effectiveness of antidepressants (venlafaxine, SSRIs, and TCAs), for which Sweden was included. The study was based, however, on secondary data and assumptions.

A model of the consequences of treatments for depression is necessary in the present study as we are investigating a hypothetical treatment with better effects than the alternatives available today. However, more long-term observational studies are necessary to follow-up and confirm the assumptions used in model studies and, moreover, to record the development of costs and health effects as they evolve over time. Peveler et al. (19) recently completed a clinical trial in a UK primary care setting, evaluating which antidepressants are best value for money when treating depressed subjects. Long-term consequences of depression have until today surprisingly seldom been thoroughly investigated. Angst et al. (2) have performed an impressive life-long follow-up study of a group of patients with bipolar and unipolar depression in Switzerland, on which we based our assumption of risk of recurrence. However, it should be noted that the patient cohort studied by Angst et al. consists of more severe cases, and as a consequence, we might overestimate the number of recurrences over time as the patient cohort used in the present study had milder symptoms. Risk of relapses was based on a thorough systematic review by Geddes et al. (9), which did include a somewhat more severe patient population than what was included in the present study.

There are several limitations that should be considered when interpreting our results. First, since the model analysis in the present study is based mainly on data from a Swedish observational study, HEADIS, the generalizability of the

results is limited to the primary care setting. Second, long-term consequences in patients with depression have not been studied sufficiently to date, and assumptions about risks for relapses and recurrences need to be verified for the Swedish setting. Third, there is an inherent potential risk of double-counting in cost-utility analyses (13). We have shown that treating patients to full remission with a new therapy primarily produces gains in costs but also in health (QALYs) and that bringing the patient back to the workplace is of importance. In an earlier article, it was shown that there is a strong association between health-related utility and working ability in depressed patients (25); thus, there is a potential double-counting in the valuation of health gains and costs in our analysis.

The model developed in the present study is fully applicable to international settings, due to the fact that its structure is not strictly based on a specific treatment setting or geographical setting, but rather is structured in line with the natural course of depression. The results presented from our cost-effectiveness assessment are based on a Swedish primary care setting, as costs and health-related utilities were taken from a Swedish observational study. By adjusting these input parameters, the analyses could easily be transferred to other geographical or treatment settings.

CONCLUSION

We have shown a new approach for assessing the cost-effectiveness of treatments for depression. Our study demonstrates the importance of designing and conducting naturalistic observational studies providing information about cost and health-related quality of life as input for the economic evaluation. We also have shown the importance of defining response in a way that is in line with how depression is treated in clinical practice and to incorporate this definition when modeling the disease over time.

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