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ORIGINAL RESEARCH
Economic Evaluation

Core Discrete Event Simulation Model for the Evaluation of Health Care Technologies in Major Depressive Disorder

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ABSTRACT

Objective: A review of existing economic models in major depressive disorder (MDD) highlighted the need for models with longer time horizons that also account for heterogeneity in treatment pathways between patients. A core discrete event simulation model was developed to estimate health and cost outcomes associated with alternative treatment strategies. **Methods:** This model simulated short- and long-term clinical events (partial response, remission, relapse, recovery, and recurrence), adverse events, and treatment changes (titration, switch, addition, and discontinuation) over up to 5 years. Several treatment pathways were defined on the basis of fictitious antidepressants with three levels of efficacy, tolerability, and price (low, medium, and high) from first line to third line. The model was populated with input data from the literature for the UK setting. Model outputs include time in different health states, quality-adjusted life-years (QALYs), and costs from National Health Service and societal perspectives. The codes are open source. **Results:** Predicted costs and QALYs from this model are within the range of results from previous economic evaluations. The largest cost components from the payer perspective were physician visits and hospitalizations. Key parameters driving the predicted costs and QALYs were utility values, effectiveness, and frequency of physician visits. Differences in QALYs and costs between two strategies with different effectiveness increased approximately twofold when the time horizon increased from 1 to 5 years. **Conclusion:** The discrete event simulation model can provide a more comprehensive evaluation of different therapeutic options in MDD, compared with existing Markov models, and can be used to compare a wide range of health care technologies in various groups of patients with MDD.

Keywords: antidepressants, cost-effectiveness, depression, discrete event simulation.

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Introduction

Major depressive disorder (MDD) is a complex public health problem associated with significant medical, social, and economic burden. The lifetime prevalence of MDD ranges from 10% to 15% [1]. The disease remains highly recurrent despite therapeutic progress [2]. Both unipolar and bipolar depression are associated with an increased risk of suicide, which is overall about 20 times higher than in the general population [3]. In 2004, the total costs of MDD reached €118 billion in Europe, with 25% outpatient care and drug costs, 8% hospitalization costs, and 64% indirect costs resulting from lost productivity and mortality [4]. MDD is predicted to become the second leading contributor to the global disease burden by 2020 [5].

There are a large number of antidepressant drugs on the market, for instance, 27 in the British National Formulary, with different efficacy and tolerability profiles, as well as different costs. In this context, a cost-effectiveness model would be useful to inform the choice between alternative treatment strategies. Decision tree (DT) models have been applied to assess the cost-effectiveness of MDD treatments. They have the main limitation of being inflexible when covering the disease's long-term events [6]. Events such as recurrence and its corresponding health states are missed by DT models because the model time horizon covers only the acute phase of depression, although treatment continues after remission to prevent relapse and recurrence. Representing these missed events is technically possible within the DT models. This would, however, result in broadening the number of corresponding health states. The use of a Markov model is another alternative. Simple Markov models, however, lack memory [7] because they neither consider previous depressive

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episodes nor previously received treatments. Tracking treatment history would necessitate broadening the number of health states, which, as in DT models, may impede model implementation and analysis, or using patient-level simulation [6].

The discrete event simulation (DES) approach overcomes these limitations of DT models or simple Markov models and is more flexible and less computing intensive than Markov models running at the patient level [8]. DES models conceptualize the course of patients in terms of experienced events and their effect on current and future health, medical resource use, and other components, continuously in time. Patient characteristics, so-called attributes, which affect event occurrence, can be updated accordingly.

This article presents a core DES model, accounting for long-term clinical events and treatment pathways, to estimate health and cost outcomes associated with alternative treatments in different groups of patients with MDD. Analyses were conducted with fictitious treatment strategies to identify the main drivers of incremental costs and quality-adjusted life-years (QALYs) between alternative treatment strategies in MDD, including patient and treatment characteristics, and to assess the validity of the model.

This is an open-source model, and the code is available at www.open-model-mdd.org. This approach aims at transparency, at facilitating the use of the model by researchers from academia, health technology assessment agencies, or industry, and at enabling other researchers to contribute to the development of the model, for example, by sharing enhancements in the programs or by providing new input data.

Methods

After reviewing existing models in MDD, we developed a structure capturing the main aspects of treatment, related to effectiveness and tolerability. Three meetings were organized with coauthors and two additional health economic experts to review successive versions of the model. Contributors came from six countries (Canada, France, The Netherlands, Spain, Sweden, and the United Kingdom) and commented on requirements for adapting the model to their country. The model was then implemented, taking into consideration the recommendations made during the first two meetings, and a third meeting was organized to review the model and discuss results of the initial analyses.

Model Overview

The model simulates the evolution of depression status, treatment-related adverse events (AEs), and changes in treatment in a cohort of adult patients with a new episode of MDD. These patients could have been treated for previous episodes earlier in their life and have subsequently recovered.

Depression is a long-term disease that often requires several lines of treatment [9,10]. This model predicts health outcomes and costs associated with alternative treatment strategies. Each strategy does not correspond to a single treatment option but consists of four lines of pharmacological treatment, with two options at each switch, according to the reason for switch: either lack of efficacy or AEs. Thus, a treatment strategy can be represented as a tree diagram, as illustrated in Figure 1. The model has the flexibility of specifying a treatment line as a specific drug or as a combination of several treatments.

The time horizon is flexible in the model. Costs can be estimated from societal and payer perspectives, as detailed below.

Attributes

Several attributes are generated randomly for each patient individually at the beginning: age, sex, number of previous depression episodes, and working status. The model user can specify proportions at baseline for these different attributes to

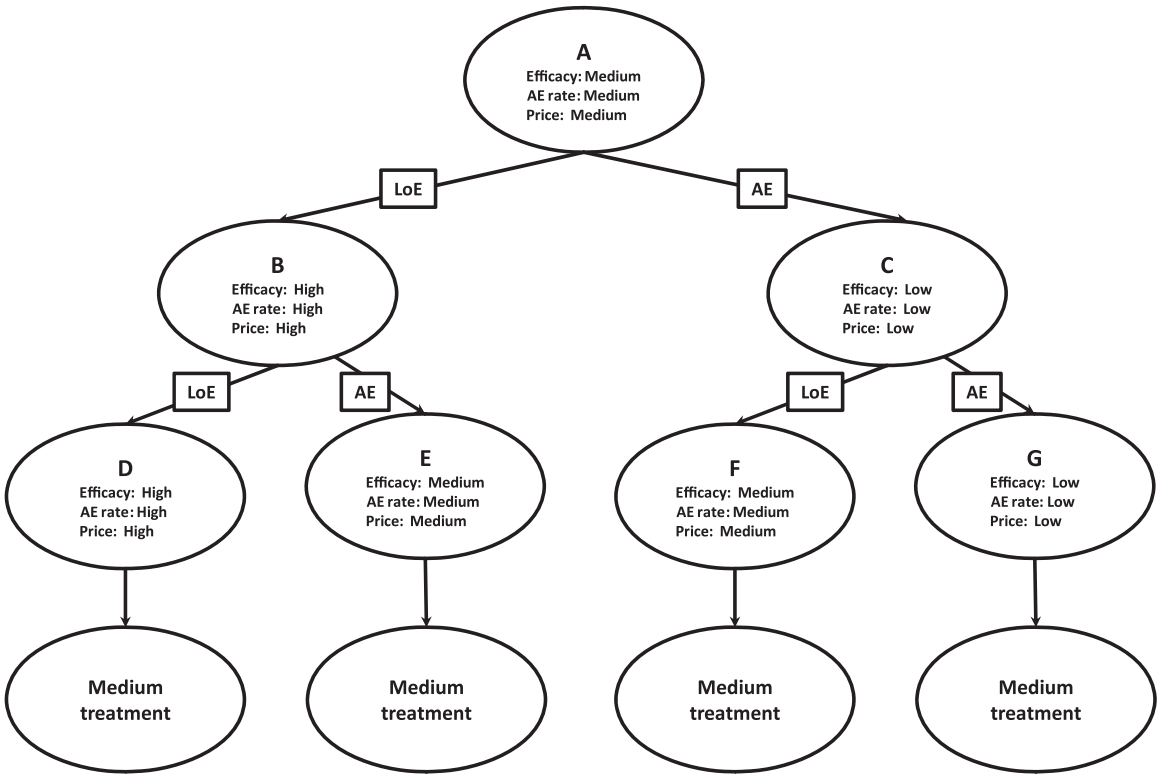

Fig. 1 – Example of treatment strategy ("medium treatment strategy"). AE, adverse event; LoE, lack of efficacy.

generate a patient cohort representative of patients in a particular setting. Other attributes are updated during the simulation according to clinical events that occur. These include depression status, current treatment, treatment line, treatment dose, presence or absence of long-term AEs, and presence or absence of residual symptoms after remission, as well as the number of previous episodes.

Events

Patient pathways are represented in Figure 2. To simplify, several events (death due to suicide or other causes, suicide attempt, hospitalization for MDD, and sick leave related to depression) are not represented in the figure, although they can occur at any time.

Disease-related events

All events identified in previous models were included in this model. The model also included a "partial response" event (defined as a $\geq$25% decrease in severity scale from the beginning of the episode for analyses reported herein), because in real practice treatment modification (titration, switch, addition) is possible in case of lack of improvement after 1 month of treatment. In addition,

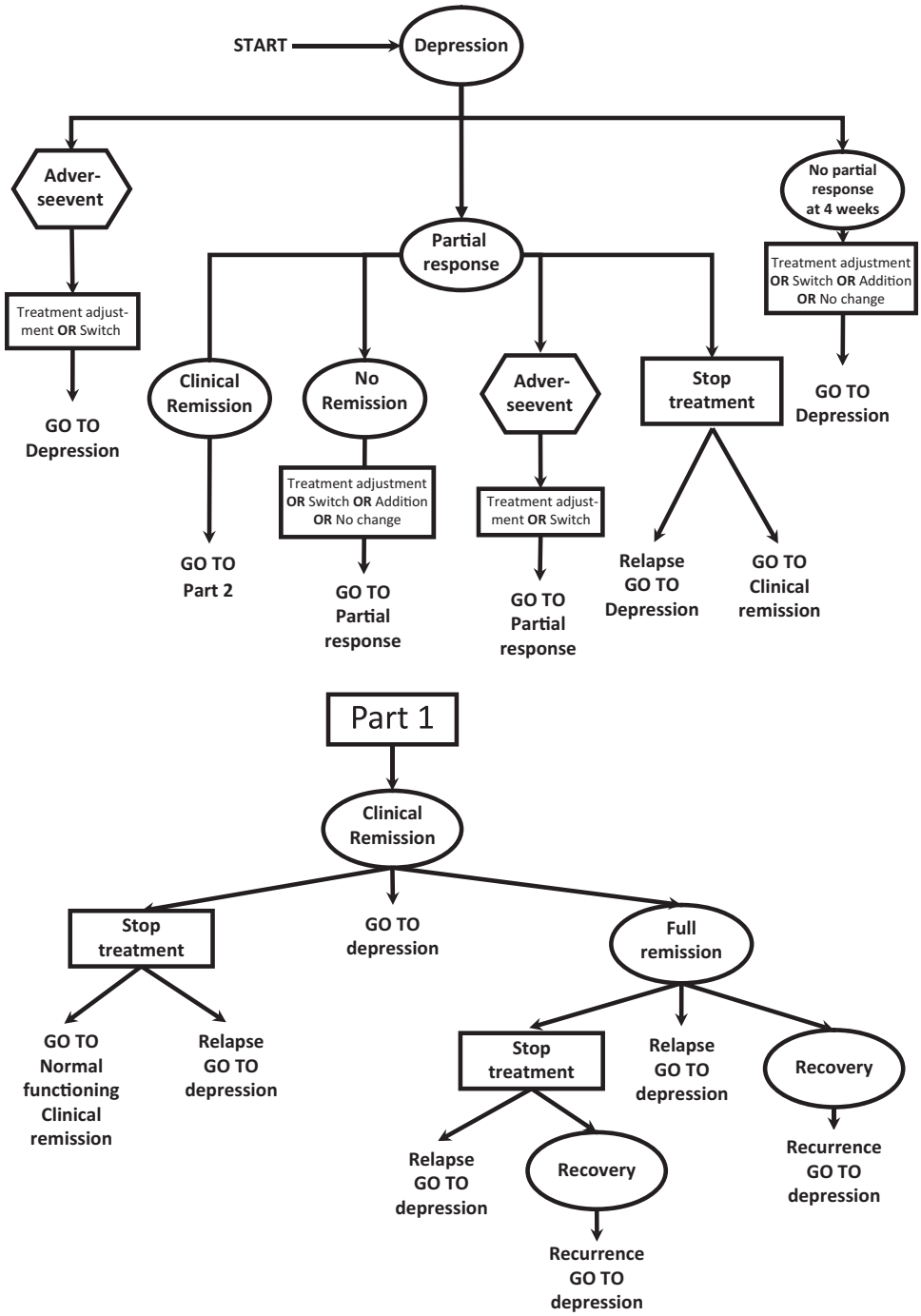

Fig. 2 – Model structure.

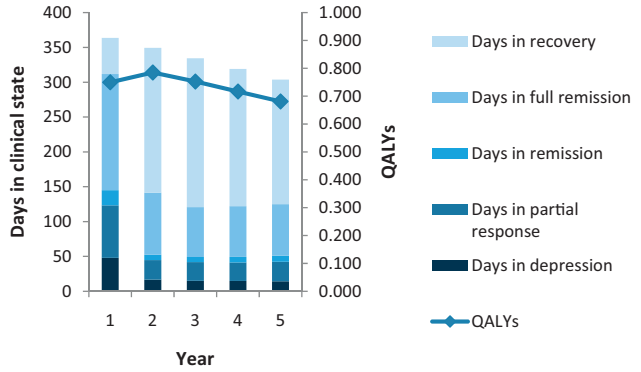

Fig. 3 – Distribution of average number of days and costs by year and clinical status. QALYs, quality-adjusted life-years.

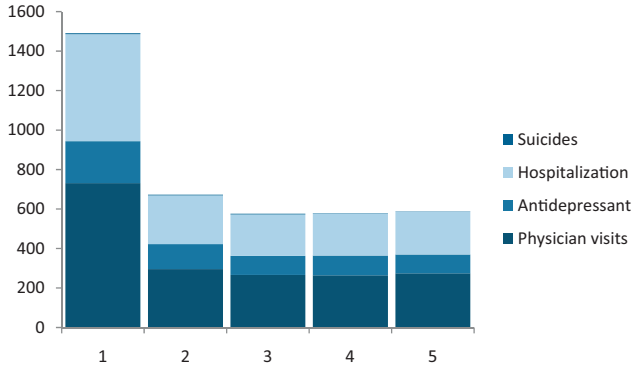

Fig. 4 – Distribution of costs by year and clinical status.

two types of remission were considered: "clinical remission," which is symptom remission as defined in a clinical trial, based on the Montgomery and Asberg Depression Rating Scale (MADRS) score (MADRS total score $\leq$10), and "full remission," which is a combination of clinical remission and normal functioning. This is to account for the fact that functioning may remain impaired for some time after clinical remission [8] because of residual symptoms. Among patients in remission, the time to normal functioning is assumed to be dependent on the presence of residual symptoms and antidepressants may differ in the time to resolution of residual symptoms.

After 6 months in full remission, the patient is considered to reach a state of "recovery." Thus, different categories of depression status in the model are new depressive episode, partial response, clinical remission, full remission, and recovery. A new episode is designated as a relapse if it occurs after response and before recovery, and as a recurrence if it occurs after recovery; the monthly risk of relapse is greater than the monthly risk of recurrence.

Residual symptoms extend the time from clinical remission to full remission. The model allows for an interaction between treatments and residual symptoms on time to normal functioning.

Adverse events

Compared with the models in the review, the proposed model has a high level of detail relating to AEs. Rather than combining all AEs into one type of event, the most frequent types of AEs are considered (nausea, diarrhea, and sexual dysfunction, for selective serotonin reuptake inhibitors; headache, insomnia, and others for other antidepressants) to account for specific tolerability profiles associated with different classes of antidepressants [11]. Treatment-related AEs are considered as short-term AEs with the exception of sexual dysfunction, which is considered as a long-term AE. Short-term AEs occur during the first month of treatment line [12] and do not last beyond treatment discontinuation. For each short-term AE, a cost increment and a QALY decrement were applied. Sexual dysfunction is assumed to be a long-term AE because it was thought less distressful and less impairing when a patient is acutely depressed. When the patient is getting better (in clinical remission), however, this AE starts to have an effect on quality of life during the simulated length of this AE.

Treatment Pathway

A treatment modification can occur in case of either an AE or lack of efficacy (no partial response, no clinical remission, or relapse). In case of an AE, two options were defined: switch or dose reduction. In case of lack of efficacy, the options considered were treatment switch, dose increase, and addition of an antipsychotic. Combinations of antidepressants were not explicitly considered but can be entered in the model as switches. Patients developing a new episode after recovery are assumed to be treated with the same treatment as that to which they responded earlier.

Patients normally discontinue treatment 6 months after remission, that is, when reaching recovery. Persistence to

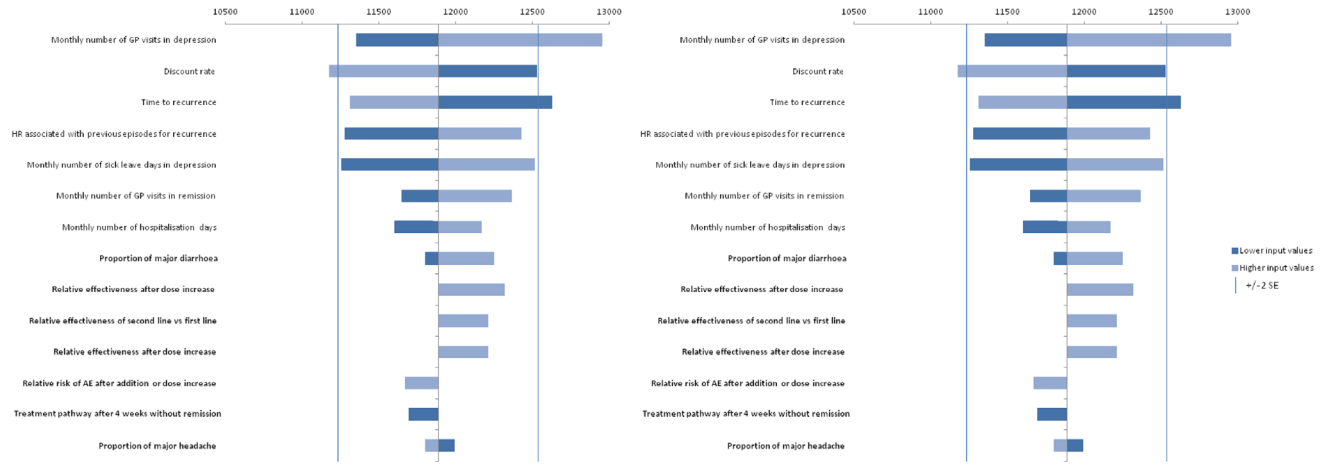

Fig. 5 – Tornado charts for non–treatment-relative parameters. QALYs, quality-adjusted life-years. Each bar represents the variation of the difference in QALYs and societal costs when the input values are changed according to scenarios specified in the Table 1. The vertical line represents the base case. Assumptions are shown in bold font.

treatment, however, is relatively low in reality, and the model accounts for the fact that patients can discontinue earlier.

Simulation Algorithm

All patients enter the model with a moderate to severe MDD episode. Several attributes (mentioned above) and the time to death (due to all-cause mortality) are simulated at the start. The simulation then follows a recursive process. Times to the occurrence of potential new events are simulated after each event, until the time horizon has been reached or death occurs, whichever comes first. Patient attributes are updated at each event. For example, when the patient reaches clinical remission, times to full remission and to relapse are simulated. If the time to full remission is shorter than the time to relapse, the next event is full remission, and new times to events are generated (e.g., time to recovery). If the time to relapse is shorter than the time to full remission, the next event is relapse. At remission, the presence or absence of residual symptoms is simulated on the basis of a fixed probability and treatment-emergent sexual dysfunction is simulated on the basis of a probability depending on treatment.

Probabilities of Events

Times to each AE and most MDD-related events (partial response, clinical remission, full remission, and relapse) were assumed to be exponentially distributed. This implies that the probability of these events was the same every day as long as the patient attributes are unchanged (as in a Markov model). In case of dose adjustment (reduction or increase) or addition of an antipsychotic, these probabilities were adjusted by applying a multiplicative factor on the time to event. The line of treatment was assumed to have an effect only on response, remission, and full remission and was also taken into account by means of a multiplicative factor. The effect of residual symptoms on full remission was implemented in the same manner. The time to recurrence was assigned a Weibull distribution, with a scale parameter dependent on the number of previous depressive episodes.

Costs

The following types of costs were included in the model, expressed in 2011 British pounds (GBP):

- Costs of antidepressant and antipsychotic medication;
- General practitioner visits including regular visits in the acute phase and additional visits for AEs or lack of efficacy;
- Psychiatrist visits including regular visits and additional visits;
- Hospitalization for depression;
- Productivity lost related to absenteeism or presenteeism; and
- Suicide and suicide attempts.

Costs can be estimated from two different perspectives. All costs listed above are included from the societal perspective, while productivity costs are not considered from the health care payer perspective. Unit costs of resources may also differ between these two perspectives and can be defined according to local context.

For most resource categories, the cost is simply obtained as the product of the amount of resource used per patient and the corresponding unit cost. For hospitalization, the cost is calculated as the number of days in hospital multiplied by the daily cost. The number of inpatient days per month is assumed to be dependent on depression status [25]. The model allows estimation of the productivity costs due to depression using either the human capital approach or the friction cost approach. In the human capital approach, the cost is estimated as the gross daily wage multiplied by the average number of days of absence per month depending on depression status, and by the number of months spent in each disease state. For the friction cost approach, events corresponding to the beginning and end of sick leave periods are simulated. The cost of a sick leave is then calculated as the minimum of the sick leave period and the friction cost period, multiplied by gross wage and elasticity of production [13].

The cost of presenteeism was calculated as the product of the number of underproductive days at work, a coefficient of presenteeism, and gross daily wage.

Quality-Adjusted Life-Years

QALYs are obtained by weighting the time spent in each disease state by a utility dependent on depression status. Utility values were taken from the study by Sapin et al. [14] based on the EuroQol five-dimensional questionnaire health-related quality-of-life assessment as recommended in the National Institute for Clinical Excellence methodological guidance [15]. In case of short-term AEs, a QALY decrement was subtracted from the previously cumulated number of QALYs. For sexual dysfunction, a QALY loss, calculated as the product of a fixed disutility by the simulated duration of sexual dysfunction, was subtracted. Utility values for AEs were obtained from the study by Sullivan et al. [16].

Analyses

The model was implemented by using Scilab (www.scilab.org), an open-source mathematical software package. It was populated with data representing fictitious treatments for the purpose of testing the model and identifying parameters with the greatest influence/effect on results. Three possible values were considered for all treatment-dependent input parameters (e.g., mean times to disease-related events or AEs, unit cost): low, medium, and high. These values covered the range of efficacy and tolerability estimates from a mixed treatment comparison previously published, and the range of current unit costs for antidepressants in the United Kingdom [17]. Other input data sources are presented in Table 1.

Cost and QALYs were simulated initially for a "base-case" treatment strategy, represented in Figure 1, with medium efficacy, medium tolerability, and medium price in first line. Treatment characteristics in second and third lines depend on the reasons for switch:

- Switch for lack of efficacy: The patient switches to a more effective treatment with more side effects.
- Switch for AEs: The patient switches to a less effective treatment with fewer side effects.

From the fourth line, a medium treatment is assumed to be prescribed, independent of previously received treatments.

To identify the key drivers of costs and effectiveness (QALYs), sensitivity analyses were implemented. For each treatment-specific parameter, two strategies with low and high values were compared, with all other parameters at medium value. For non–treatment-specific parameters, each value was successively substituted by lower and high estimates and results were compared with the base case, for the medium strategy represented in Figure 1. Finally, incremental cost-effectiveness ratios were estimated for a comparison between two strategies: an existing strategy, as represented in Figure 1, and a new strategy with a drug with high effectiveness and high price in first line. The effect of the time horizon on the incremental cost-effectiveness ratio was examined.

The history of a cohort of 1000 patients was simulated over 5 years. The same cohort was used for all analyses to ensure

Table 1 – Model parameters and input values.

Parameter	Source	Dependent on	Base-case value						Scenarios
Age (y) (percentages by age category)	Adult psychiatric morbidity in England, 2007			18–34	35–44	45–54	55–64	65–74	–
			Male	23%	22%	24%	20%	11%	
			Female	24%	18%	26%	16%	16%	
Sex (percentage of women in the MDD population)	Adult psychiatric morbidity in England, 2007		63% of females						–
General mortality	UK Office of National Statistics	Sex, age	Gompertz law						
			Men $\alpha = 0.0000370$ and $\beta = 0.0925091$ Women $\alpha = 0.0000144$, and $\beta = 0.0999890$						
Work status (percentage of workers in the MDD population)	Borghi and Guest [25]		52.2% of workers						–
Number of previous episodes	Mueller et al. [26]		0: 37%/1: 23%/2: 13%/3 and +: 27%						–
Residual symptoms (percentage of patients having residual symptoms)	Assumption		20%						–
Treatment impact on prominent symptoms	Assumption	Treatment	HR = 1 for all treatments						HR = 0.5 HR = 1
Probabilities of sexual dysfunction at remission	Cochrane review [24]	Treatment	High rate: 9% Medium rate: 6.5% Low rate: 4%						Treatment A: low rate Treatment B: high rate
Duration of sexual dysfunction	Assumption	Treatment	High duration: 60 d Medium duration: 45 d Low duration: 30 d						Treatment A: short duration Treatment B: long duration
Probabilities of AEs over 8 wk: nausea	Cochrane review [24]	Treatment	High rate: 26% Medium rate: 19% Low rate: 12%						Treatment A: low rate Treatment B: high rate
Probabilities of AEs over 8 wk: headache	Cochrane review [24]	Treatment	High rate: 20% Medium rate: 15.5% Low rate: 11%						Treatment A: low rate Treatment B: high rate
Probabilities of AEs over 8 wk: diarrhea	Cochrane review [24]	Treatment	High rate: 18% Medium rate: 12% Low rate 6%						Treatment A: low rate Treatment B: high rate
Probabilities of AEs over 8 wk: insomnia	Cochrane review [24]	Treatment	High rate: 14% Medium rate: 10.5% Low rate: 7%						Treatment A: low rate Treatment B: high rate
Probabilities of AEs over 8 wk: Other AEs	Cochrane review [24]	Treatment	High rate: 37% Medium rate: 29% Low rate: 21%						Treatment A: low rate Treatment B: high rate
	Assumption		5%						

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Proportion of major sexual dysfunction				Proportion of major sexual dysfunction = 0% Proportion of major sexual dysfunction = 10%
Proportion of major nausea	Assumption		1%	Proportion of major nausea = 0% Proportion of major nausea = 2%
Proportion of major headache	Assumption		2%	Proportion of major headache = 0% Proportion of major headache = 4%
Proportion of major diarrhea	Assumption		1%	Proportion of major diarrhea = 0% Proportion of major diarrhea = 2%
Proportion of major insomnia	Assumption		3%	Proportion of major insomnia = 0% Proportion of major insomnia = 6%
Proportion of other major AEs	Assumption		3%	Proportion of other major AEs = 0% Proportion of other major AEs = 6%
Partial response rate at 4 wk	Assumption	Treatment	High rate: 70% Medium rate: 55% Low rate: 40%	Treatment A: high rate Treatment B: low rate
Clinical remission rate 4 wk after partial response	Assumption	Treatment	High rate: 50% Medium rate: 40% Low rate: 30%	Treatment A: high rate Treatment B: low rate
Normal functioning after 2 wk clinical remission	Assumption	Treatment	High rate: 80% Medium rate: 60% Low rate: 40%	Treatment A: high rate Treatment B: low rate
Relapse rate at 6 mo	Gilchrist and Gunn [27]	Treatment	High rate: 46% Medium rate: 20% Low rate: 10%	Treatment A: low rate Treatment B: high rate
Time to recurrence	Mueller et al. [26]	Number of previous episodes	Weibull law ($\mu = 7.33$ and $\sigma = 1.33$)	Time to recurrence reduced by 20% Time to recurrence increased by 20%
Treatment duration	GPRD analysis	Line of treatment	First line: 201 d Second line: 157d Third line: 161 d Fourth line: 143 d	Treatment duration reduced by 20% Treatment duration increased by 20%
Time to suicide attempt	GPRD analyses		Rate per 100,000 at 1 mo: Depression: 49.38	Time to suicide attempt reduced by 20%

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Table 1 – *continued*

Parameter	Source	Dependent on	Base-case value	Scenarios
				Time to suicide attempt increased by 20%
			Full remission and recovery: 10.35	
Risk of dying of suicide attempts	Khan et al. [28]		10%	Risk of dying = 5% Risk of dying = 15%
Variation of time to side effect after treatment adjustment for AE	Assumption		No variation	Risk of AE decreased by 20%
Variation of time to side effect after treatment adjustment or addition	Assumption		No variation	Risk of AE after adjustment and after addition increased by 20%
Relative effectiveness after addition	Assumption		No variation	Time to events decreased by 20%
Relative effectiveness after treatment adjustment for AE	Assumption		No variation	Time to events increased by 20%
Relative effectiveness after treatment adjustment or addition for lack of efficacy	Assumption		No variation	Time to events increased by 20%
Relative effectiveness first line vs. second line	Assumption		No variation	Time to events for second line increased by 20%
Treatment pathway after no partial response or no remission at 4 wk	Assumption		Switch: 7.5%	Switch: 25%
			Treatment adjustment: 37.5% Addition: 5% No change: 50%	Treatment adjustment: 25% Addition: 25% No change: 25%
Treatment pathway after no partial response at 4 wk	Assumption		Switch: 7.5% Treatment adjustment: 37.5% Addition: 5% No change: 50%	Switch: 25% Treatment adjustment: 25% Addition: 25% No change: 25%
Treatment pathway after no remission at 4 wk after partial response	Assumption		Switch: 7.5% Treatment adjustment: 37.5% Addition: 5% No change: 50%	Switch: 25% Treatment adjustment: 25% Addition: 25% No change: 25%
Utility of depression	Sapin et al. [14]		0.33 (moderate depression, baseline)	Utility = 0.15 (severe depression baseline) Utility = 0.44 (moderate depression, 8 wk)
Utility of partial response	Sapin et al. [14]		0.72	

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				Utility = 0.58 (nonresponder, 8 wk) Utility = 0.79 (clinical remission)
Utility of clinical remission	Sapin et al. [14]		0.79	Utility = 0.72 (partial response) Utility = 0.86 (full remission)
Utility of full remission	Assumed identical to recovery		0.86	None
Utility of recovery	Sapin et al. [14]		0.86	None
General practitioner visits/ psychiatrist visits	NICE guideline [15]	Depression status	Acute period: one GP/specialist visit every 2 wk Maintenance period: one GP/specialist visit every 2 mo 75% of GP/25% of specialist	Visit multiplied by 2 in the acute phase Visit divided by 2 in the acute phase Visit multiplied by 2 in the maintenance phase Visit divided by 2 in the maintenance phase
Mean number of sick leave days	Borghi and Guest [25]	Depression status	2.67 d per month 0 in recovery	Mean number reduced 20% Mean number increased 20%
Mean number of hospitalization days	Borghi and Guest [25]	Depression status	0.225 d per month 0 in recovery	Mean number reduced 20% Mean number increased 20%
Additional GP visit for treatment adjustment, addition or switch	Clinical practice		1 additional GP visit	Additional GP visits = 2
Additional GP visit for treatment adjustment	Clinical practice		1 additional GP visit	Additional GP visits = 2
Additional GP visit for addition	Clinical practice		1 additional GP visit	Additional GP visits = 2
Additional GP visit for switch	Clinical practice		1 additional GP visit	Additional GP visits = 2
Discount rate	NICE guideline [15]		3.5% for cost and outcomes	Discount of outcomes = 0% and discount of cost = 0% Discount of outcomes = 8% and discount of cost = 8%

AE, adverse effects; GPRD, General Practice Research Database; HR, hazard ratio; MDD, major depressive disorder; NICE, National Institute for Health and Care Excellence.

comparability, and the baseline demographic characteristics were representative of patients with MDD in the United Kingdom. Inputs reflecting the UK setting were chosen because of the good availability of data in the United Kingdom and because this would allow comparisons with results of previous models. Costs were estimated from the perspective of the National Health Service (NHS) and Personal Social Services (NHS&PSS) and from the societal perspective. The human capital approach was used for estimating the costs of lost productivity, and presenteeism was ignored. Costs and QALYs after the first year were discounted to present value at an annual rate of 3.5% per annum.

All input data and associated data sources are shown in Table 1.

Results

Disease Status

In the first year, an average patient treated with the "medium strategy" spent 145 days in depression (defined as not in full remission or recovery), 167 days in full remission, and 52 days in recovery (Fig. 3). The number of days in recovery increased to 214 in the third year and then decreased each year because of mortality and discounting.

Cost Estimates

The total cost for the medium strategy over 5 years was £3,892 (standard error [SE] £60) per patient from the NHS&PSS perspective and £11,885 (SE £325) from the societal perspective. Total costs per year decreased substantially over the first 2 years, as the number of days in depression decreased, and remained stable afterwards (Fig. 4).

From the NHS&PSS perspective, the costs of physician visits accounted for 47% of the total costs over 5 years, followed by hospitalization costs (37%) and antidepressant costs (16%). From the societal perspective, lost productivity accounted for 68% of total costs.

Key parameters affecting costs included treatment effectiveness. The cost of a strategy with high effectiveness in first line was lower than the cost of a strategy with low effectiveness in first line by £602 per patient over 5 years from the NHS&PSS perspective and £1400 from the societal perspective (Table 2). Non–treatment-specific parameters for which the effect on results exceeded twice the SE included physician visits in the acute phase, parameters related to the time to recurrence, and discount rate (Fig. 5).

QALY Estimates

The total number of QALYs over 5 years for the medium strategy was 3.684 (SE 0.014). The number of QALYs by year peaked at 0.785 (SE 0.003) in the second year, because the number of days in recovery was high during that year, and decreased subsequently over time because of mortality and discounting.

Differences between treatments in time to partial response, time to remission, and time to relapse had a significant effect on QALYs (Table 2). The number of QALYs for a strategy with high effectiveness in first line exceeded that of a strategy with low effectiveness by 0.078 over 5 years. Among different parameters related to effectiveness, the partial response rate had the greatest effect. The difference in QALYs between two strategies with different safety profiles in first line (low rates for all AEs vs. high rates for all AEs) was 0.007 over 5 years. However, the effect of each AE taken individually was lower than the SE. Among

Table 2 – Results of comparisons between different treatment strategies.

Comparison	QALYs (A − B)			NHS&PSS costs (A − B)			Societal costs (A − B)		
	Year 1	Year 5	Total	Year 1	Year 5	Total	Year 1	Year 5	Total
Effectiveness: A, high effectiveness B, low effectiveness	0.060	−0.001	0.078	−363	−2	−602	−780	−42	−1400
Partial response rate at 4 wk: A, high rate B, low rate	0.040	0.006	0.066	−105	−35	−245	−192	−114	−542
Clinical remission rate 4 wk after partial response: A, high rate B, low rate	0.008	0.002	0.021	−91	−18	−238	−193	−51	−815
Normal functioning after 2 wk in clinical remission: A, high rate B, low rate	0.003	0.001	0.005	−26	−2	−31	−54	−110	−278
Relapse rate: A, low rate B, high rate	0.014	−0.004	0.010	−171	−11	−341	−348	21	−609
Probabilities of AEs: A, low rate of all AEs B, high rate of all AEs	−0.005	0.002	−0.007	24	−32	74	8	−47	336
Probabilities nausea: A, low rate B, high rate	0.002	−0.001	0.007	−36	−16	−172	−92	−99	−669
Probabilities of headache: A, low rate B, high rate	0.001	−0.002	0.000	−13	4	−112	−35	−9	−316
Probabilities of diarrhea: A, low rate B, high rate	−0.005	−0.003	−0.008	10	26	27	30	135	343
Probabilities of insomnia: A, low rate B, high rate	0.003	0.001	−0.005	0	−32	20	26	−5	251
Probabilities of other AEs: A, low rate B, high rate	0.001	0.000	−0.001	−11	6	83	−11	−68	88
Probabilities of sexual dysfunction A, low rate B, high rate	−0.005	−0.003	−0.008	10	26	27	30	135	343
Impact of residual symptom A, HR = 1/2 B, HR = 1	0.000	−0.001	0.001	3	−1	−71	17	130	53

AE, adverse event; HR, hazard ratio; QALYs, quality-adjusted life-year; NHS&PSS, National Health Service and Personal Social Services.

non–treatment-related parameters, utilities and discount rates are the key drivers of QALYs. The discount rate, however, would have less effect on incremental costs and QALYs, as well as the incremental cost-effectiveness ratio, because incremental costs and QALYs decrease over time.

Incremental Cost-Effectiveness

When comparing two strategies with high effectiveness and high price versus low effectiveness and low price in first line, the first strategy was estimated to be less expensive by £243 from the NHS&PSS perspective for a gain of 0.078 QALYs over 5 years. The SE around incremental costs was £75, that is, 30% of the mean, and the SE around incremental QALYs was 0.010, or 13% of the mean. Reducing the time horizon to 3 years reduced incremental costs by 33%.

Assuming a cost-effectiveness threshold of £30,000, the parameters with the most effect on net monetary benefit were treatment effectiveness and especially treatment partial response rate and treatment relapse rate (see Figure in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.11.012).

Discussion

This article proposes an innovative core disease model for MDD aiming to simulate patient pathways in a flexible and realistic manner, and to facilitate the economic evaluation of different treatment strategies in MDD, taking into account health technology assessment requirements from different countries where models are used.

This model was tested for fictitious treatment strategies, based on data from the literature and UK unit costs. The analyses showed that costs were highest in the first year and remained significant in subsequent years. The largest cost components were productivity costs from the societal perspective and costs of physician visits and hospitalizations from the NHS&PSS perspective. Costs were strongly dependent on treatment effectiveness, as well as frequency of physician visits and parameters related to recurrence. The parameters driving estimates of QALYs included treatment effectiveness, health state utilities, and discount rates. A time horizon shorter than 3 years was not long enough to capture the full incremental costs and incremental QALYs between two strategies with different effectiveness in first line. This stems from the assumption that patients who achieved recovery with a given treatment would receive it again as first-line treatment in case of recurrence.

Cost estimates appeared plausible in the light of previously published studies for the United Kingdom. Previous economic models for the United Kingdom estimated the costs of MDD from the NHS&PSS perspective at £486 over 12 months for selective serotonin reuptake inhibitors in primary care, £516 to £585 for serotonin–norepinephrine reuptake inhibitors in primary care and £1622 to £1667 for serotonin–norepinephrine reuptake inhibitors in secondary care over 12 months [18], £376 to £465 over 6 months for escitalopram [19], and £1459 to £2177 over 14 months [20]. Thus, our base-case estimate of £1486 over 12 months for a strategy with "medium treatment" in first line lies in the range of previous model estimates. In addition, the cost structure is also consistent with previous studies. A review of productivity costs found that they accounted for approximately 60% of total costs in MDD [17], which is comparable to the proportion of 68% estimated here.

According to new International Society for Pharmacoeconomics and Outcomes Research guidelines, the validation of the model involves five steps: face validity, verification, cross validity, external validation, and predictive validation. As mentioned above, we performed the first three of these: the face validity with expert board meetings to validate the structure and assumptions on the model, the verification in performing quality control of the programming, and the cross validation with comparisons with previously published UK models.

Compared with previous models, the proposed model has several advantages, such as a longer time horizon. As noted above, using a shorter time horizon led to a reduction in incremental costs and incremental QALYs. In addition, this model considers a state of partial response before remission, whereas existing models had a response state followed by remission, or a remission state only. Data on clinical response are more widely available from clinical trials, but we believe that the partial response state provides a more realistic representation of clinical practice: the lack of partial response at 4 weeks may require a switch, whereas patients with significant symptomatic improvement who did not reach the usual response criteria are unlikely to switch (unless they also experience AEs). This state is important, as shown by the fact that the utility in partial response was among the parameters with the greatest effect on the number of QALYs. Furthermore, the time to partial response was the treatment-related parameter with the largest effect on incremental QALYs. Another important characteristic of this model is the level of detail related to AEs. We found that one AE had a relatively small effect on costs and QALYs, but changing the probability of all AEs had a significant effect. Depending on the situation in which the model is applied, this level of detail may not be required, and it could be sufficient to consider different types of AEs as one event. Having different types of events, however, will allow comparisons between treatments with different effectiveness profiles.

Other improvements made in this model appeared to have little effect on results, for example, the distinction between "clinical remission" and "full remission," or adjustments of efficacy and safety after dose changes or switch. Also, it may be possible to simplify the model for future adaptation. It should be noted, however, that these findings are dependent on the set of input values used for the reported analyses. For example, the utilities entered for clinical remission and full remission were very similar.

The disease states in our model are similar to those in the conceptual structure of the DES model previously proposed by Haji Ali Afzali et al. [21], except for the partial response state (a response state was considered in the previous model). At the time of writing, no result of that model was published, and so no comparison was possible. As concerns the model structure, a major difference concerns AEs, which did not appear explicitly in the previous structure. In addition, the treatment pathway was not presented; thus, it was not clear when dose changes or switches would occur, and how their effect on future events would be captured.

Now that model programs have been made available, the usefulness of the model will depend on the availability of data to populate it. The Prospective Epidemiological Research on Functioning Outcomes Related to Major depressive disorder study is a 2-year prospective cohort study currently ongoing in Europe (ct number: NCT01427439). This study aims at assessing the link between depression and functioning and includes assessment tools that will provide relevant data to improve the model including information on therapeutic management of depressed patients, resource utilization, and utilities. It will also be possible to estimate the multiplicative factors applied to times to events in case of dose adjustment (reduction or increase), addition of an antipsychotic, or switching to the next treatment line, as well as the correlations between attributes. The first communication of baseline results is planned in 2014. Although utility data already exist, the only source of EuroQol five-dimensional questionnaire utilities by MDD state is the article of Sapin et al. [14], which is

based on a clinical trial. We believe that it would be useful to estimate new utilities, matching exactly the health states of the model, from the observational study. Adaptations of the model for different countries will require collecting local unit costs, as well as collecting local resource utilization data or adapting estimates from other countries with local clinical experts. Treatment patterns and probabilities of dose titration, switching, and discontinuation should also be revised in model adaptations. Administrative or medical records databases may provide useful data for this purpose; however, obtaining probabilities of switch or discontinuation (AE or lack of efficacy) will be challenging. A possibility would be to adjust the probabilities estimated from the observational study according to the difference in overall probabilities of switch and discontinuation. When the model is to be adapted for new products, we would recommend conducting network meta-analyses to obtain estimates of efficacy and safety parameters that are comparable to those for existing products, and take into consideration all the evidence available for each product. As explained below, however, this may limit the choice of statistical distributions for simulating times to events.

As concerns limitations of this model, comorbidities of MDD were not considered. There is much comorbidity associated with MDD. Some belong to the central nervous system therapeutic area, for example, insomnia or anxiety, but other diseases such as diabetes or cancer could also be considered as comorbidities of MDD. It would not be feasible to consider all of them in one model. It may be required, however, to incorporate comorbidities when treatment strategies targeting patients with specific comorbidities are developed. The most important comorbidities to consider would be those interacting with the efficacy or safety of treatments. Another limitation is that no effect of residual symptoms on relapse or recurrence was integrated, although several publications report that patients with residual symptoms are more likely to have a relapse or recurrence [22,23]. Although this would be possible with our model structure, this relationship was not incorporated in the model, because the data found in the literature were not sufficiently detailed for that purpose.

Other improvements may also be considered in future versions. A differentiation between levels of severity of depression, with different health state utilities, would be appropriate, in particular because the severity of depression following a relapse may differ from the initial severity. The possibility to reach normal functioning before clinical remission could also be taken into account. AEs of antipsychotics could be added, especially weight gain. Furthermore, the times to AEs were simulated by using exponential distributions, which imply that the probability of occurrence of those events was the same every day. Most AEs, however, have a greater probability of occurrence in the first weeks of treatment. Other distributions should be considered according to available data. A difficulty is that all the evidence available about existing products should ideally be used; that is, users should refer to meta-analyses on response rates, relapse rates, or probabilities of AEs, for example. Meta-analyses, however, generally provide only one data point for each parameter; for example, only response rates at 8 weeks are reported in Cipriani et al. [24]. The only type of distribution that may be fitted with one data point is the exponential one. A Weibull distribution would require at least two data points, for example, response rates at two different time points. In addition, the model would ideally consider the fact that patients who experienced AEs with one treatment may be more likely than others to experience the same events with other treatments. We have no empirical data, however, to confirm this hypothesis or quantify the effect of experience of AEs on the risk of future events.

Another limitation of our model is that switches can occur because of AEs or because of lack of efficacy. In real life, the decision to switch is often based on an assessment of symptom improvement relative to AEs; that is, AEs may be better accepted and less likely to lead to switch if symptoms are much improved.

Another important addition for some countries, such as the United Kingdom or The Netherlands, would be psychotherapies. There is wide variability among psychotherapeutic approaches. In the current model, short psychotherapies, such as cognitive-behavioral therapies, can be implemented in the model as a pharmacological treatment or as an addition to conventional antidepressants. The methods for incorporating psychotherapies in the model, however, could be improved, and this will be one of the priorities for future developments of the model.

Another possible improvement could be to include hospitalization as a treatment option. In the current version, we considered the costs of hospitalization, but not their effect on disease status. An average treatment was assumed in our analyses for resistant patients (with at least three previous lines of treatment). These patients, however, are often hospitalized. Taking into consideration other medications prescribed in combination with antidepressants, without restriction to antipsychotics, for example, thyroid hormones or lithium, would not necessitate any change in the model structure.

The model running time was 12 minutes for two strategies over 5 years, with 1000 patients. This number of patients provided SEs representing 40% of incremental costs and 10% of incremental QALYs when comparing two strategies with different effectiveness and price in first line. This variability may reflect the heterogeneity in patient pathways in reality and is not an indicator of the quality of the model. It has implications, however, for the number of patients to be defined in such analyses based on this model. For example, to detect a difference of 0.078 in QALYs (as observed in our analyses of incremental effectiveness) with an SE of 5% of that value, the number of patients would have to be about 6000. The running time will also be a hurdle at the time of conducting probabilistic sensitivity analysis to assess second-order uncertainty. We are currently considering ways to improve the running time, such as reprogramming the model by using alternative software.

To conclude, we have developed a model that provides the potential to assess the cost-effectiveness of alternative treatment strategies in MDD with more accuracy than do existing models. It is a flexible model and can be adapted for the evaluation of a wide range of different treatment strategies. This is not intended to be a definitive model, and we expect that it will be improved over time, but we believe that it can already be useful in its current version.

By choosing to make it open-source and freely available on the Internet, we hope to foster the research community to develop, implement, and share new data and functions to populate, enhance, and validate the model.

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Supplemental Materials

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