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ORIGINAL RESEARCH
Economic Evaluation

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

***Anne-Lise Vataire, MSc*[1,]*, *Samuel Aballéa, MSc*[1], *Fernando Antonanzas, Pr*[2], *Leona Hakkaart-van Roijen, MD*[3], *Raymond W. Lam, MD*[4], *Paul McCrone, PhD*[5], *Ulf Persson, PhD*[6], *Mondher Toumi, PhD*[7]**

[1]Creativ-Ceutical, Paris, France; [2]University of La Rioja, Logrono, Spain; [3]Erasmus University Rotterdam, Rotterdam, The Netherlands; [4]University of British Columbia, Vancouver, Canada; [5]King's College, London, UK; [6]The Swedish Institute for Health Economics, Lund, Sweden; [7]University of Lyon, Lyon, France

A B S T R A C T

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.

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

* *Address correspondence to:* Anne-Lise Vataire, Health Economics and Outcomes Research, Creativ-Ceutical, 215 rue du Faubourg Saint-Honoré, Paris 75008, France.

E-mail: ava@creativ-ceutical.com.

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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

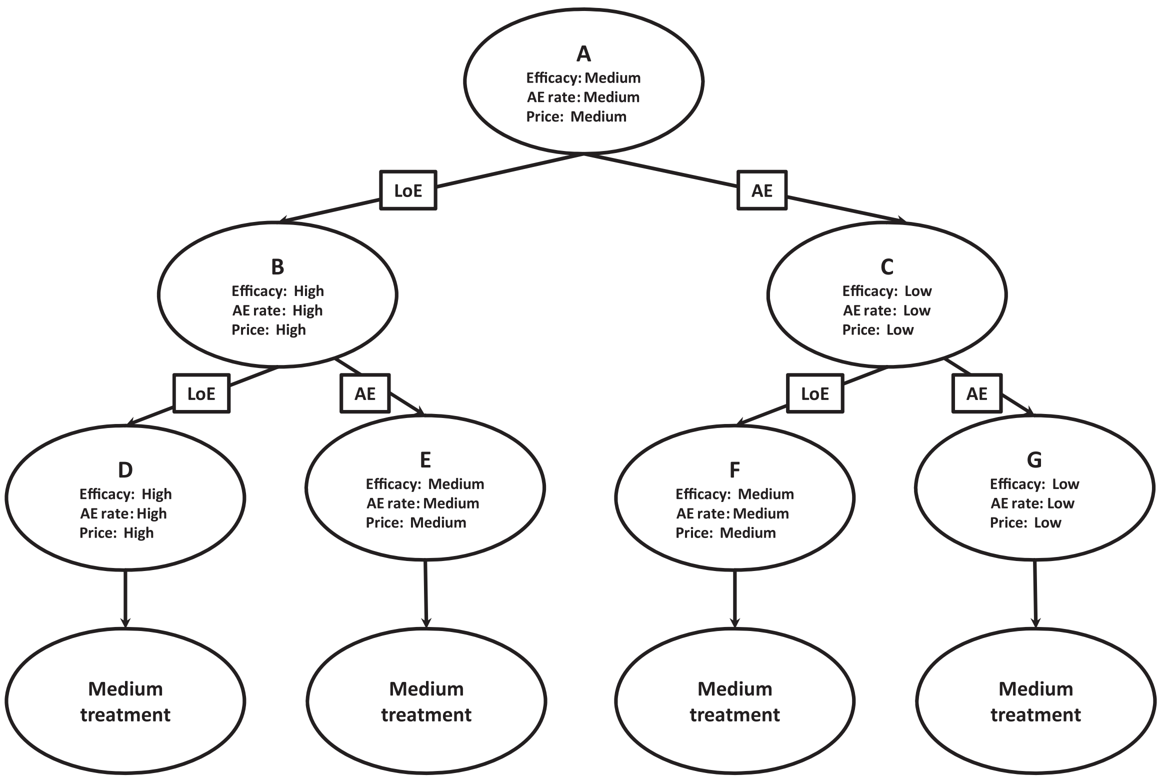

Fig. 1 – Example of treatment strategy ("medium treatment strategy"). AE, adverse event; LoE, lack of efficacy.