Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

Model states and transitions

We develop a deterministic Markov model with discrete one-month time-steps to simulate the treatment of major depressive disorder in the United States. The structure of the model is diagrammed in **Figure 1** of the main text. The disease states within the model and transitions between them are described below.

Initiation

Upon starting a new line of treatment, simulated patients spend one time-step in the initiation state before the outcome of that treatment is determined. These states are denoted by $\mathbf{I_1}$ for first-line initiation, $\mathbf{I_2}$ for second-line initiation, etc. This state is intended to capture the delayed onset of treatment efficacy, as well as the time needed to ensure an adequate trial of a treatment before switching to a different treatment.[1–3]

Remission, response, non-response

After spending one time-step in initiation, patients transition to one of three states intended to capture their acute response to treatment. Remission ($\mathbf{R_1}$, $\mathbf{R_2}$, etc.) indicates a near-complete resolution of depressive symptoms, as measured by one of several commonly-used rating scales; response ($\mathbf{S_1}$, $\mathbf{S_2}$, etc.) indicates ≥ 50% resolution of depressive symptoms; and non-response ($\mathbf{F_1}$, $\mathbf{F_2}$, etc.) indicates < 50% resolution of depressive symptoms.[4,5] To determine the proportion of patients entering each outcome state, each line of treatment is characterized by a probability of remission, **a**, a probability of response, **b**, and a probability of non-response, **1 – a – b**.

Relapse

Patients who have achieved remission or response on a given line of treatment may subsequently transition into the relapse state ($\mathbf{E_1}$, $\mathbf{E_2}$, etc.), reflecting a return of depressive symptoms.[4] Each line of treatment is characterized by a probability of relapse for those with initial remission, $\mathbf{d_R}$, and a probability of relapse for those with initial response, $\mathbf{d_S}$; patients in remission (**R**) or response (**S**) are subject to these relapse probabilities during every model time-step. Those patients in the non-response (**F**) or relapse (**E**) states for treatment lines 1-8 transition to initiation (**I**) of the subsequent treatment line during the next model time-step.

Mortality and competing risks

The population of patients in the model is characterized by a probability of mortality per time-step, **μ**. Patients in all model states are subject to this mortality probability; for clarity, mortality probabilities are not shown in **Figure 1**. As mortality is possible in any model state, patients in a given state are subject to competing risks; for example, a patient in remission on 1st-line antidepressant treatment is subject to probabilities of death, relapse, and continued remission. To handle this, we treat mortality as an overriding risk; that is, only those patients who don't die in a time-step are subject to risks of relapse or other such transitions within the model.

Cost inflation

There are several nationally representative indices that can be used to inflate/deflate healthcare costs to a given year; in this analysis, we use an index called the medical care expenditure index (MCE).[6,7] The MCE has two main benefits over other available indices. First, disease-specific inflation estimates are available, which show a different inflation rate for treatment of mental illness as compared with e.g.

infectious diseases. Second, the MCE indices are designed to reflect changes in both unit costs and patterns of treatment for a given illness over time, rather than the change in price of a static bundle of goods and services.

Prior research has shown that, in the case of depression, using the MCE approach to evaluate inflation produces more conservative estimates of cost growth than other approaches do.[8] In our analysis, we find that our model's cost outcomes are well-validated by recent, independent data on overall costs of depression care, which lends support to the decision to use the more conservative MCE index.

Parameter covariance in probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) produces an estimate of the aggregate uncertainty in a model's outcomes, given the individual uncertainty distributions surrounding each parameter within the model. Along with the uncertainty in each parameter's value, the covariance between parameters may be an important factor in determining overall uncertainty in outcomes. Prior research has shown that in some cases, treating probabilistic inputs as independent from one another may underestimate overall uncertainty.[9] To address this, we perform two separate PSAs. In the PSA with *independent parameter variance*, the value of each parameter is based on an independently drawn random variable between 0 and 1 applied to its probability distribution. In the PSA with *linked parameter variance*, a single random variable between 0 and 1 is drawn and applied in concert for every parameter within each of the following groups: depression costs for lines 1-9, initial remission and response probabilities for lines 1-9, relapse probabilities for lines 1-9, and initial and maintenance costs of ECT. The latter approach likely overestimates the degree of covariance between these parameters, but can help establish an upper bound on overall uncertainty.

References

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Supplementary tables

eTable 1: Scenario sensitivity analysis results

	Pharmacotherapy efficacy data from Weinmann et al. and Amsterdam et al.			Pharmacotherapy efficacy data from STAR*D trial only			Depression cost data from Gibson et al.		
Strategy	***Costs (2013 USD)***	***QALYs***	***ICER (USD/QALY)***	***Costs (2013 USD)***	***QALYs***	***ICER (USD/QALY)***	***Costs (2013 USD)***	***QALYs***	***ICER (USD/QALY)***
No ECT	40,210	2.71	–	46,220	2.53	–	37,820	2.63	–
6th-line ECT	46,670	2.79	Dominated	55,440	2.68	Dominated	44,900	2.75	Dominated
5th-line ECT	47,170	2.80	81,000	54,920	2.69	Dominated	45,120	2.76	Dominated
4th-line ECT	48,910	2.81	Dominated	55,790	2.70	Dominated	45,460	2.76	Dominated
3rd-line ECT	48,630	2.81	90,000	53,610	2.71	43,000	45,800	2.77	58,000
2nd-line ECT	50,980	2.82	484,000	54,470	2.71	152,000	47,770	2.77	513,000
1st-line ECT	53,500	2.82	815,000	56,630	2.71	716,000	50,280	2.78	809,000

USD, United States dollars; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; ECT, electroconvulsive therapy

eTable 1 (continued): Scenario sensitivity analysis results

	Suicide mortality reduced with remission or response of depression			First ECT course provided without maintenance ECT		
Strategy	***Costs (2013 USD)***	***QALYs***	***ICER (USD/QALY)***	***Costs (2013 USD)***	***QALYs***	***ICER (USD/QALY)***
No ECT	42,420	2.64	–	42,490	2.63	–
6th-line ECT	50,130	2.75	Dominated	50,210	2.79	Dominated
5th-line ECT	49,890	2.76	Dominated	49,930	2.80	Dominated
4th-line ECT	50,950	2.77	Dominated	50,340	2.81	Dominated
3rd-line ECT	49,880	2.77	54,000	50,410	2.82	42,000
2nd-line ECT	52,050	2.78	557,000	51,700	2.82	335,000
1st-line ECT	54,560	2.78	802,000	54,660	2.83	1,035,000

USD, United States dollars; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; ECT, electroconvulsive therapy