Supplementary Material*

Ross EL, Vijan S, Miller EM, et al. The cost-effectiveness of cognitive behavioral therapy versus second-generation antidepressants for initial treatment of major depressive disorder in the United States. A decision analytic model. Ann Intern Med. 29 October 2019. doi:10.7326/M18-1480

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* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

Where modeling methods are identical, parts of this appendix are adapted from:

Ross EL, Zivin K, Maixner DM. The cost-effectiveness of electroconvulsive therapy vs. pharmacotherapy/psychotherapy for treatment-resistant depression in the United States. JAMA Psychiatry. 2018; published online ahead of print, May 9.

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 (40).

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 (31). 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 –b**. Note that clinical trials of depression treatment – as well as our model – treat remission as a subset of response; hence, to determine the fraction of patients who will achieve response but not remission, the model must subtract the remission probability, **a**, from the response probability, **b** (Figure 1).

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 (31). 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.

Discontinuation due to adverse events

Patients in the remission or response states may also discontinue a treatment line due to adverse effects, resulting in progression to initiation of the subsequent line. Each line of treatment is characterized by a probability of discontinuation for those in remission, $\mathbf{k_R}$, and a probability of discontinuation for those with response, $\mathbf{k_S}$; these probabilities are applied in every model time-step. Of note, studies of initial treatment efficacy generally categorize early discontinuation due to adverse events as non-response (31); thus, to avoid double counting, patients in the initiation state are not subject to an independent probability of discontinuation due to adverse events.

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, discontinuation due to adverse events, 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. To handle death and state-transitions during cycles, the model implements a cycle-tree half-cycle correction within each model time-step.

Input parameter derivations

Remission and response probabilities

Remission and response probabilities for patients receiving first-line SGA in our model were derived from re-analysis of the SSRI group of a meta-analysis assessing the efficacy of venlafaxine vs. SSRIs (32). For consistency, we excluded studies which did not assess both remission and response. We performed a restricted maximum likelihood random-effects meta-analysis on the logit-transformed probabilities of remission and response using the underlying studies in the above meta-analysis; this approach yielded estimates (95% CIs) of 39.7% (32.1-47.8) for remission and 63.1% (55.3-70.3) for response (Appendix Figure 2).

Remission and response probabilities for treatment lines 2-9 in our model were derived from Steps 1-4 of the STAR*D trial (31). The number of patients assessed at Steps 1-4 were 3671, 1439, 390, and 123. Reported remission/response probabilities for Steps 1-4 were: 36.8/48.6%, 30.6/28.5%, 13.7/16.8%, and 13.0/16.3%. Of note, remission and response probabilities are input into the model independently, and the likelihood of patients achieving response-but-not-remission is set to equal the difference between the two probabilities; whenever the remission probability is greater than or equal to the response probability (as in Step 2 of the STAR*D trial), the likelihood of response-but-not-remission is set to 0.

Remission and response probabilities for all treatment lines except first-line pharmacotherapy are expressed in the model as relative risks compared with first-line pharmacotherapy. The relative risks (95% CIs) of remission and response for first-line CBT were calculated by inverting the values reported in Gartlehner et al.'s meta-analysis (7), providing estimates of 1.02 (0.76-1.37) for remission and 1.11 (0.93-1.32) for response.

Relative risks of remission and response for treatment lines 2-5 (based on STAR*D Steps 1-4) were calculated based on the remission and response probabilities and sample sizes above. This yielded relative risks for remission (95% CIs) for lines 2-5 compared to first-line SGA of 0.93 (0.86-1.00), 0.77 (0.70-0.85), 0.35 (0.27-0.45), and 0.33 (0.21-0.52). For response, the values were 0.77 (0.73-0.81), 0.48 (0.44-0.53), 0.27 (0.21-0.33), and 0.26 (0.17-0.39). Given the stabilization of remission and response probabilities from lines 4 through 5, we made the assumption that the probabilities used for line 5 would also apply to lines 6-9.

Relapse probabilities

In contrast with remission and response probabilities, which are assessed only once for any given treatment line, relapse and treatment discontinuation probabilities are assessed each model cycle. Thus, it is necessary to evaluate the time-frame over which these probabilities are reported and convert the values to monthly probabilities for consistency with the model's cycle-length.

To derive relapse probabilities for first-line SGA, we used data from an individual patient-level meta-analysis of relapse trajectories in patients treated with duloxetine or fluoxetine (33). Of 960 patients, 204

(21.3%) met clinical criteria for relapse ($HRSD_{17} \geq 14$) at 26 weeks. This corresponds to an annual probability of 38.1%, or a monthly probability of 3.9%.

Two studies which evaluated risk of relapse with CBT vs. SGA were identified in Gartlehner et al.'s meta-analysis (34, 35), but a pooled relative risk of relapse was not estimated. We re-evaluated these two studies and pooled their data to generate an estimate of the relative risk of relapse with CBT vs. SGA.

In David et al.'s study (34), 72 patients treated with rational emotive behavioral therapy or cognitive therapy had achieved remission or response at 14 weeks of treatment; at 6 months, 4 of these patients had relapsed. For comparison, 33 patients treated with pharmacotherapy achieved remission or response, of whom 5 subsequently relapsed. In Dobson et al.'s study (35), among 47 patients who initially remitted after treatment with behavioral activation or cognitive therapy, 18 had relapsed 52 weeks later; for comparison 9 of 26 patients treated with paroxetine relapsed.

Replicating Gartlehner et al.'s methods (7), we calculated an overall relative risk using a restricted maximum likelihood model in OpenMetaAnalyst. This yielded a relative risk (95% CI) of 0.729 (0.255-2.082) (Appendix Figure 2).

Treatment discontinuation probabilities

Gartlehner et al. identified three studies which evaluated the risk of treatment discontinuation due to adverse events with CBT vs. SGA (36-38). We used the SGA arms of these trials to generate an estimate of the probability of treatment discontinuation due to adverse events for patients receiving first-line SGA.

In the study by DeRubeis et al. (36), of 119 patients treated with paroxetine, 8 discontinued treatment due to adverse events by 16 weeks. In the study by Dimidjian et al. (37), of 78 patients treated with paroxetine, 9 discontinued treatment due to adverse events by 16 weeks. Finally, in the study by Mynors-Wallis et al. (38), of 36 patients treated with fluvoxamine or paroxetine, 2 discontinued treatment due to adverse events before 52 weeks; we made the assumption that one of these events occurred prior to 12 weeks. As in our analysis of SGA efficacy, we performed a restricted maximum likelihood random-effects meta-analysis on the logit-transformed probability of discontinuation due to adverse events; this approach yielded an estimated probability (95% CI) of 8.1% (4.7-13.6). The weighted average of the time-points at which this probability was evaluated in the three studies was 15.4 weeks; hence, this value corresponds to an annual probability of 24.9% or a monthly probability of 2.4%.

Finally, the relative risk (95% CI) of treatment discontinuation due to adverse events for first-line CBT was calculated by inverting the values reported in Gartlehner et al.'s meta-analysis (7), providing an estimate of 0.40 (0.06-2.50).

Supplement Table 1. Impact Inventory

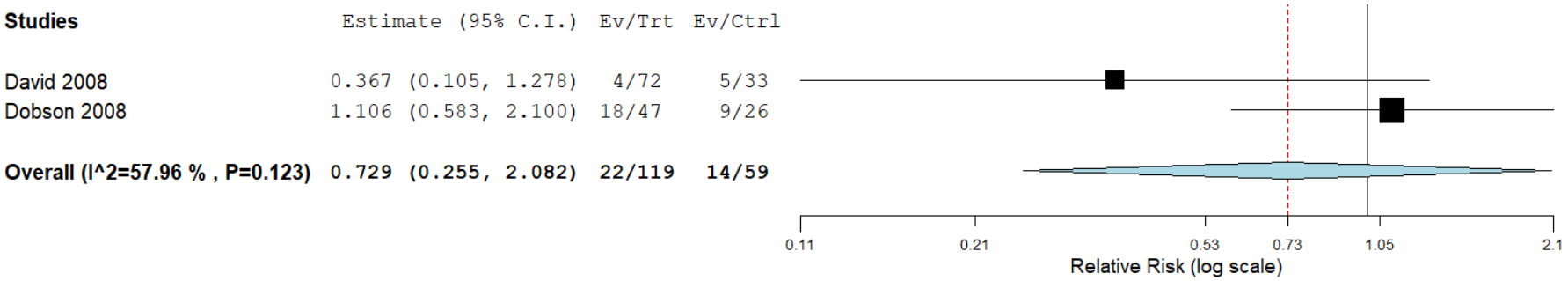
Sector	Type of impact	Included in this analysis from given perspective?	
		Healthcare sector	**Societal**
Formal healthcare sector			
Health	<u>Health outcomes</u>		
	Longevity effects	No	No
	Health-related quality of life effects	**Yes**	**Yes**
	Other health effects (e.g. adverse effects)	**Yes**	**Yes**
	<u>Medical costs</u>		
	Third-party payers	**Yes**	**Yes**
	Out-of-pocket	**Yes**	**Yes**
	Future related medical costs	**Yes**	**Yes**
	Future unrelated medical costs	**Yes**	**Yes**
Informal healthcare sector			
Health	Patient-time costs	No	**Yes**
	Caregiver-time costs	No	No
	Transportation costs	No	No
Non-healthcare sector			
Productivity	Productivity lost due to illness	No	**Yes**

Supplement Table 2. Second-Generation Antidepressant Costs

Medication name	Dose	NADAC per day (14) (2017 USD)	Patients prescribed medication (13)	Annual cost (4853) (2014 USD)
Citalopram	40 mg	0.042	11,995	14.73
Escitalopram	10 mg	0.078	6,229	27.47
Fluoxetine	40 mg	0.137	7,692	48.41
Fluvoxamine	200 mg	0.670	202	237.42
Paroxetine	40 mg	0.123	4,706	43.54
Sertraline	100 mg	0.054	10,791	19.16
Vilazodone	20 mg	7.238	648	2563.74
Duloxetine	60 mg	0.234	6,808	82.73
Venlafaxine	150 mg	0.175	6,345	61.85
Mirtazapine	30 mg	0.129	4,323	45.64
Bupropion	150 mg x2	0.304	8,479	107.72
Weighted average excluding vilazodone				48.04
Weighted average including vilazodone				71.94

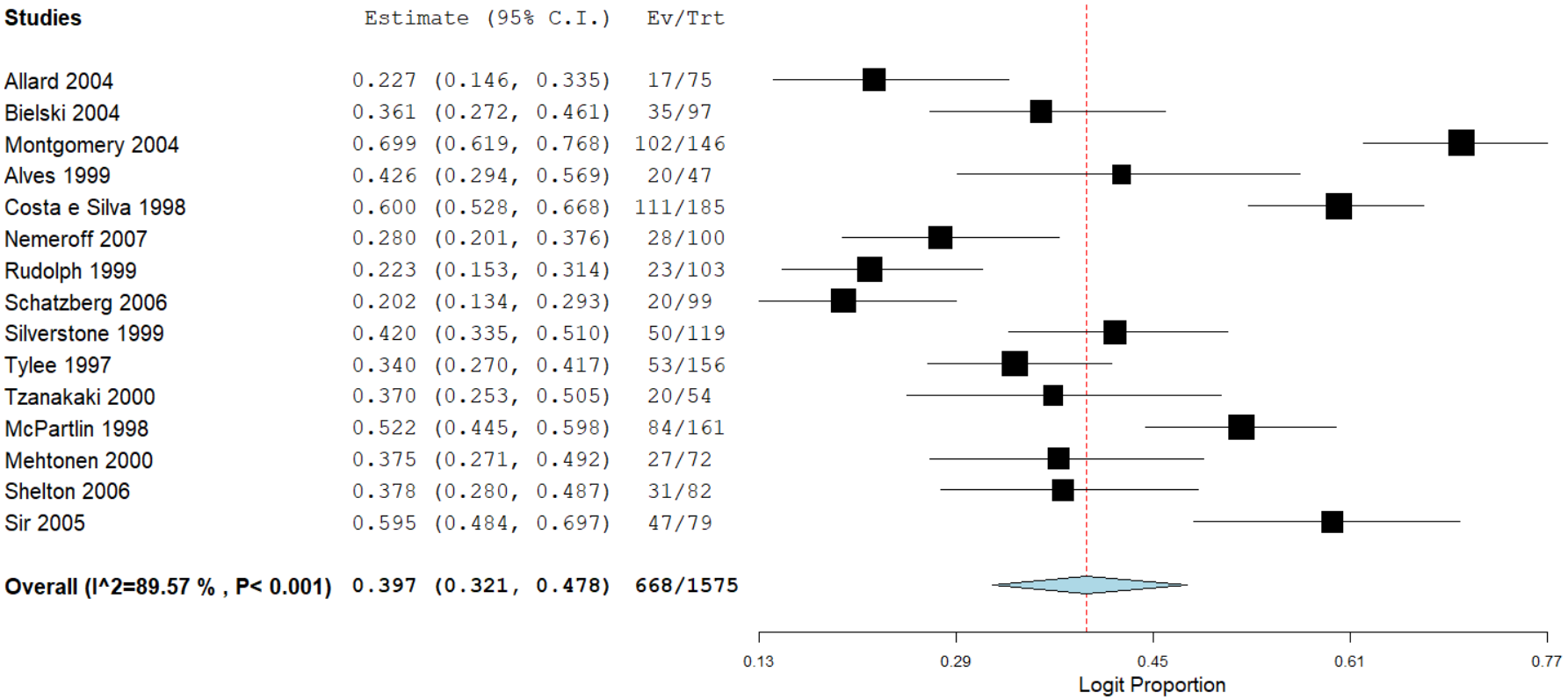
NADAC, National Average Drug Acquisition Cost; USD, United States Dollars

Supplement Figure 1. Relapse rates with cognitive behavioral therapy compared with second-generation antidepressants.



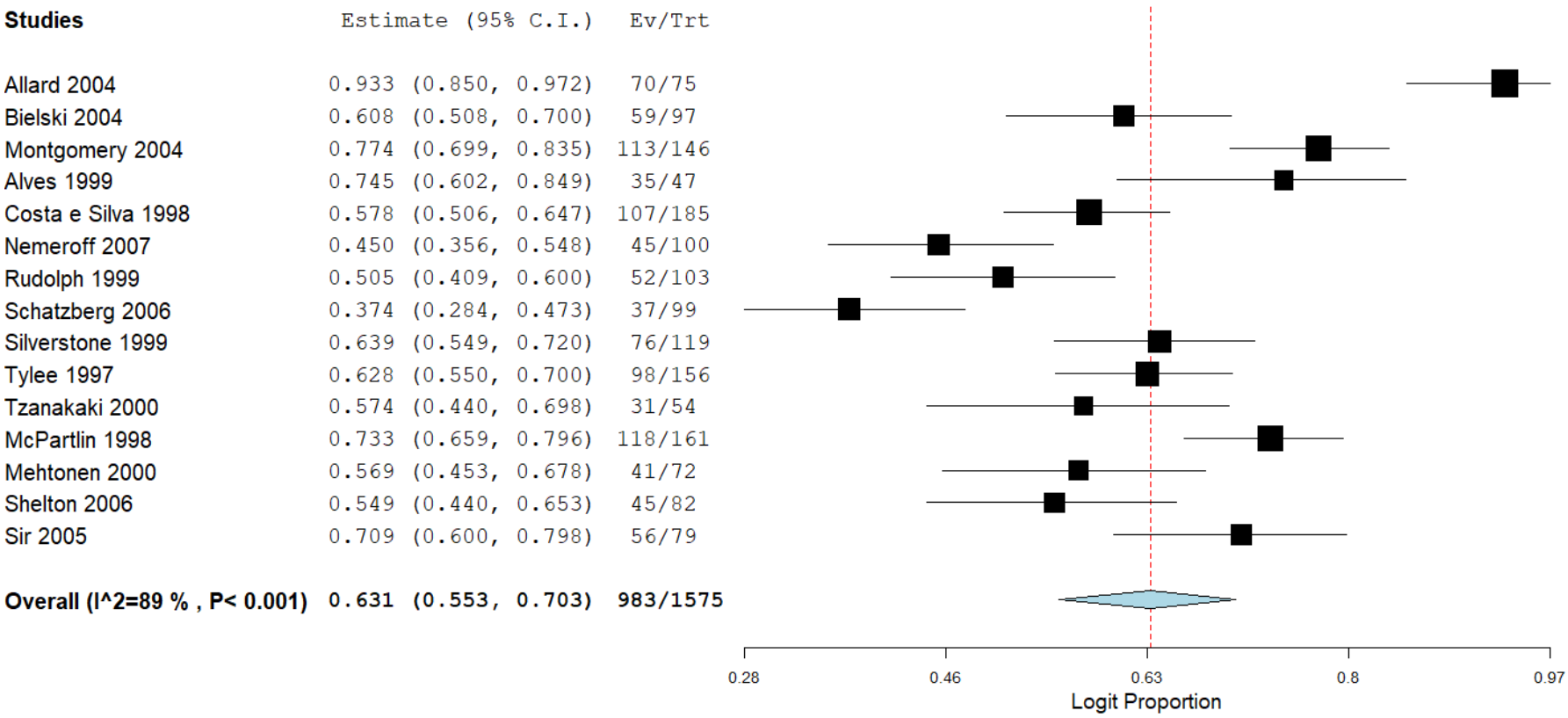
Forest plot showing the estimated relative risks of relapse of depression from two randomized controlled trials of cognitive behavioral therapy vs. second-generation antidepressants.

Supplement Figure 2a. Remission rates with selective serotonin reuptake inhibitors.



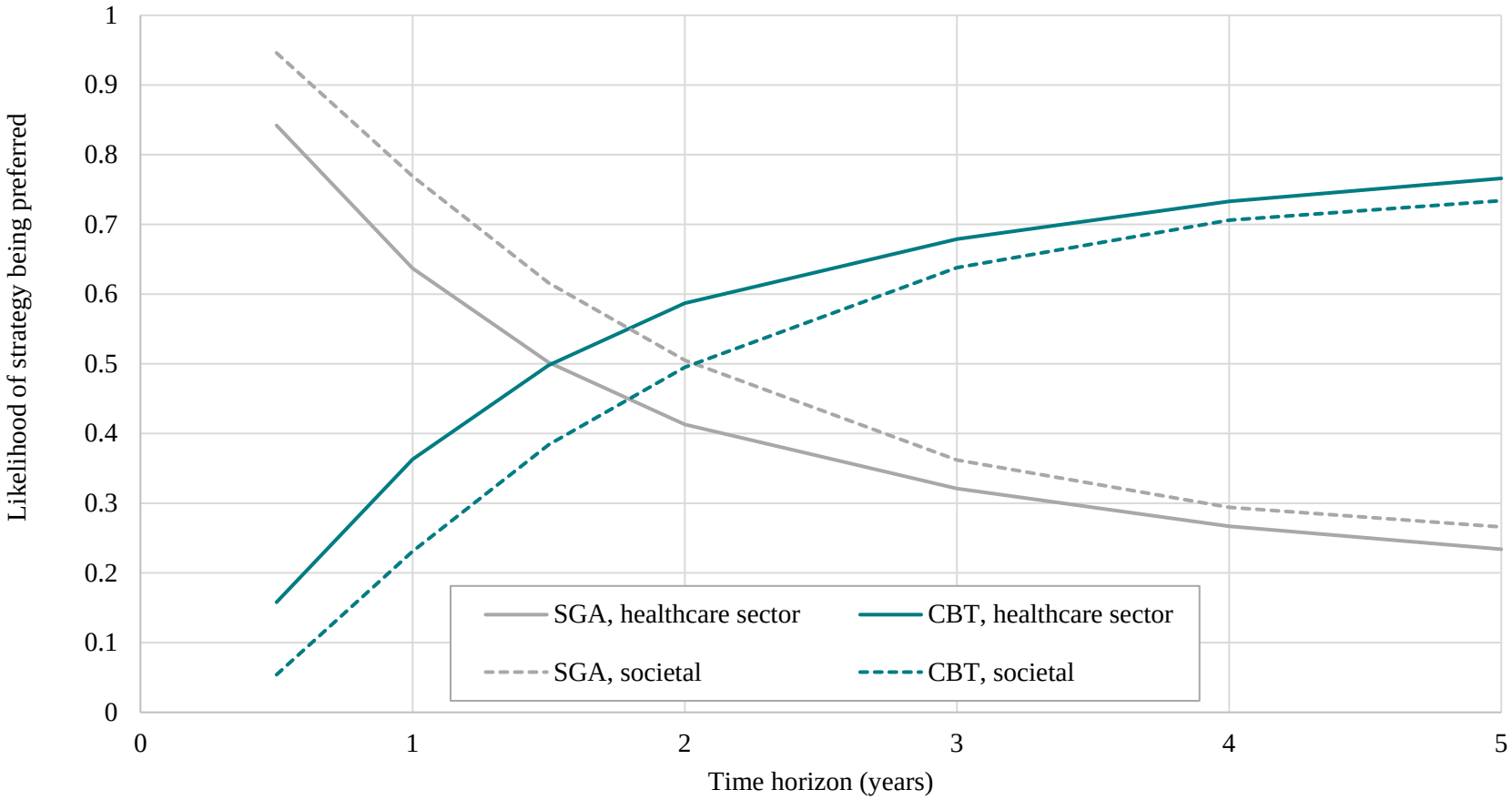
Forest plot showing the estimated probability of remission from randomized controlled trials of selective serotonin reuptake inhibitors in patients with major depressive disorder.

Supplement Figure 2b. Response rates with selective serotonin reuptake inhibitors.



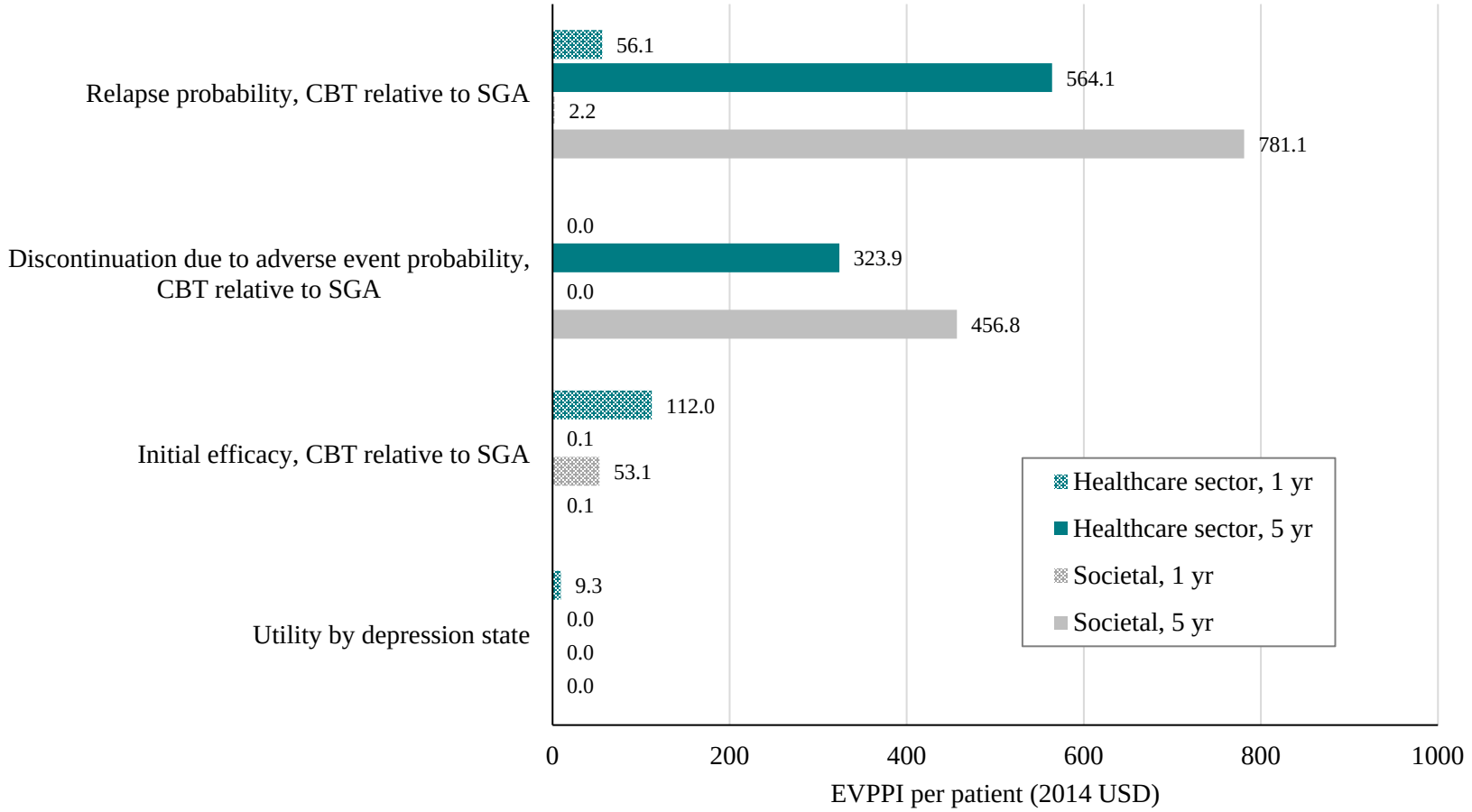
Forest plot showing the estimated probability of response from randomized controlled trials of selective serotonin reuptake inhibitors in patients with major depressive disorder.

Supplement Figure 3. Probabilistic sensitivity analysis with varying time horizon.



The vertical axis shows the fraction of 10,000 probabilistic model runs in which either CBT (green) or SGA (gray) is the preferred strategy (i.e. is the strategy that produces the greatest net monetary benefit). The horizontal axis shows the time horizon at which health-economic outcomes of the two treatment strategies are evaluated. Results from a healthcare sector perspective are shown in solid lines; results from a societal perspective are shown in dashed lines.

Supplement Figure 4. Expected value of partial perfect information analysis.



Horizontal bars indicate the expected value of partial perfect information (EVPPI) for parameter groups displayed on the vertical axis. EVPPI is displayed for healthcare sector (green) and societal (gray) perspectives at both one-year (dotted) and five-year (solid) horizons. All parameter groups with an EVPPI of ≥$10 for at least one perspective/time-horizon are shown. Additional parameter groups which were evaluated but did not produce an EVPPI ≥$10 include: annual mortality probability; 1st-line CBT cost; 1st-line SGA cost; other depression costs; initial efficacy of treatment lines 2-9; and the initial efficacy, relapse probability, and discontinuation due to adverse event probability of 1st-line SGA, as evaluated independently from the RR of these outcomes for CBT vs. SGA.