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ORIGINAL RESEARCH

Cost-Effectiveness of Transcranial Magnetic Stimulation in the Treatment of Major Depression: a Health Economics Analysis

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ABSTRACT

Introduction: Transcranial magnetic stimulation (TMS) is a novel antidepressant therapy shown to be effective and safe in pharmacotherapy-resistant major depression. The incremental cost-effectiveness and the direct cost burden compared with sham treatment were estimated, and compared with the current standard of care. ***Methods:*** Healthcare resource utilization data were collected during a multicenter study (n=301) and a decision analysis was used to stratify the 9-week treatment outcomes. A Markov model with an acute-outcome severity-based risk of relapse was used to estimate the illness course over a full year of treatment follow-up. These model estimates were also compared to best estimates of outcomes and costs of pharmacotherapy treatment, using the published STAR*D outcomes. The cost-effectiveness of TMS was described using an incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained and on a direct cost per patient basis across a varying range of assumptions. The model's sensitivities to costs due to losses in work productivity and to caregiver time were also examined. ***Results:*** Compared with sham treatment and at a cost of US$300 per treatment session, TMS provides an ICER of US$34,999 per QALY, which is less than the "willingness-to-pay" standard of US$50,000 per QALY for a new treatment for major depression. When productivity gains due to clinical recovery were included, the ICER was reduced to US$6667 per QALY. In open-label conditions, TMS provided a net cost saving of US$1123 per QALY when compared with the current standard of care. In the open-label condition, cost savings increased further when the costs for productivity losses

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were included in the model (net savings of US$7621). The overall cost benefits of treating MD using TMS were greater in those patients at the earliest levels of treatment resistance in the overall sample. ***Conclusion:*** TMS is a cost-effective treatment for patients who have failed to receive sufficient benefit from initial antidepressant pharmacotherapy. When used at earlier levels of treatment resistance, significant cost savings may be expected relative to the current standard of care.

Keywords: antidepressant; clinical trial; cost-effectiveness; efficacy; health economics; major depression; TMS; transcranial magnetic stimulation

INTRODUCTION

In the US, only 3.2 million of the 14 million patients with depression receive adequate pharmacotherapy.[1-3] Even in those who are treated, the success rate with pharmacological treatments is not high,[4] and short-term antidepressant drugs are only moderately effective when compared with placebo.[5] The recently published results of the Sequenced Treatment Alternatives to Relieve Depression trial (STAR*D)[6] illustrate a pattern of diminishing clinical returns: each successive pharmacological treatment failure predicted a worse prognosis of a subsequent trial. The STAR*D study showed that after three successive pharmacological treatment strategies the cumulative remission rate is at best only 67%.[6]

Compared with 50 years ago, the diagnosis of major depressive disorders is made more frequently and the availability and options for drug treatment of depression has greatly expanded. Despite these changes in treatment practice, the clinical impact of depression itself and of treatment resistance is growing. The World Health Organization (WHO) estimates that by the year 2020, unipolar depression alone[5,7] will be second only to ischemic heart disease in medical burden.[8] This somber prospect urges us to look for more effective and economically sound antidepressant treatments.

Nonpharmacological neuromodulation therapies (NMTs) have emerged in the last decade as potentially efficacious treatments.[9] NMTs subconvulsively modulate discrete networks with repetitive electrical stimulation. In contrast, the therapeutic efficacy of electroconvulsive therapy (ECT)[10] is dependent on the patient having an adequate major motor seizure. Transcranial magnetic stimulation (TMS) is a type of NMT whereby electrical stimulation is produced by a rapid oscillation in electrical energy that is converted to magnetic energy.[11] If activated over the skull and directed towards the brain, anatomically and functionally related brain regions are stimulated through cortical-subcortical neuronal circuits.[12] Prefrontal TMS, repeated over several weeks, has a clinically significant acute antidepressant effect.[13]

TMS has been shown to be safe and effective in the treatment of patients with major depression.[13-23] Two reports have already discussed the health economic impact of TMS in patients with depression.[15,16] Both analyses were conducted using either historical estimates of TMS efficacy,[15] or based on the results of a limited, fixed-dose treatment paradigm conducted in a small sample.[13,16] Since those reports, the results of the first large, multisite, randomized, controlled study of TMS used as monotherapy in patients with pharmacotherapy-resistant depression have been published.[17] This clinical development program also included two open-label extension studies that provided information on

acute efficacy[17] and the long-term durability of the acute response to TMS.

The present report aims to estimate the incremental cost-effectiveness ratio (ICER) for the NeuroStar TMS Therapy System (Neuronetics Inc., Malvern, PA, USA) compared with sham treatment and with current, standard care, using a decision analysis modeling approach. The model is structured to accommodate the clinical data obtained in the recently completed Neuronetics trials referred to here as Studies 101,[14] 102,[17] and 103[18] (see below for details), and combines these data with cost and utility weights derived from published data, and mean costs from large archival billing databases for patients with depression.

Quality-adjusted life year gained (QALY) quantifies the impact of a medical treatment both in terms of the quality and the quantity of life lived. The ICER is another term used to measure the benefit of a treatment. Although, there is no defined cost-effectiveness threshold value for the US, an ICER below US$50,000 is generally considered highly cost-effective.[19] A de-facto value for pharmaceuticals has been proposed to lie somewhere between US$50,000 and US$100,000 per QALY.[19] The WHO suggests a limit for cost-effectiveness of three times a country's gross domestic product (GDP) per capita, which would set the upper limit at US$140,000 for the US.[20,21] However, acceptable ICER values may vary with time and depend on the burden of the condition being treated, the size of the patient population affected, and health equity considerations.[19] In this economic modeling study, we tested the ICER for TMS compared with sham or compared with standard treatments. We hypothesized the incremental cost of TMS treatment would be lower than the societal willingness-to-pay threshold.

METHODS

Overview of Clinical Development Program

Patient Population

Patients included in the study met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria for unipolar, nonpsychotic major depressive disorder, confirmed by a structured psychiatric interview.[14] Patients were moderately to severely ill by symptom measures at baseline and moderately to severely resistant to pharmaceutical antidepressant treatment in the current illness episode as measured by the Antidepressant Treatment History Form (ATHF; Table 1).[22] The ATHF quantifies the adequacy of the antidepressant trial for research purposes. By protocol definition all study patients had to have failed to receive clinical benefit from at least one, but no more than four, ATHF-verified adequate antidepressant exposures in their current depressive episode. In this study, age was not a predictor of response to TMS (*P* value for interaction = 0.509).

Synopsis of Study Designs and Clinical Outcomes

Study 101 was a 6-week, randomized, sham-controlled trial that examined the efficacy of the Neuronetics' NeuroStar TMS Therapy System compared with a sham TMS treatment condition.[14] Patients who achieved clinical remission (defined below) in Study 101 underwent a 3-week taper phase, which transitioned participants off TMS and onto a stable regimen of single-drug antidepressant maintenance pharmacotherapy.

Study 102 was an open-label trial that was available for all patients who had participated

Table 1. Demographic and clinical features and baseline symptom severity of the study population.

	Active TMS (*n*=155)	Sham TMS (*n*=146)	*P* value
Demographic variables			
Females, *n* (%)	86 (55.5)	74 (50.7)	0.421
Age, years, mean ± SD	47.9±11.0	48.7±10.6	0.509
Ethnic origin, *n* (%)			
Caucasian	146 (94.2)	131 (89.7)	
Other	9 (5.8)	15 (10.3)	0.201
Employment status, *n* (%)			
Full-time	55 (35.5)	41 (28.1)	
Part-time	26 (16.8)	29 (19.8)	
Unemployed	74 (47.8)	76 (52.1)	
Receiving disability compensation	28 (18.0)	31 (23.2)	
Disease history			
Recurrent illness course, *n* (%)	149 (96.1)	136 (93.2)	0.611
Mean duration of current episode, months (SD)	13.6 (9.9)	13.2 (9.5)	0.728
Number (%) of population with current episode >2 years	36 (23.2)	23 (15.8)	0.112
Prior antidepressant treatment			
Number of antidepressant treatment attempts in current illness episode, mean (SD)	5.5 (3.4)	5.4 (3.6)	0.774
Number of dose/duration adequate antidepressant treatments in current episode, mean (SD)	1.6 (0.9)	1.6 (0.8)	0.905
Baseline symptom scores			
MADRS, total score (SD)	32.8 (6.0)	33.9 (5.7)	0.036
HAMD17, total score (SD)	22.6 (3.3)	22.9 (3.5)	0.508
HAMD24, total score (SD)	30.1 (5.0)	30.5 (4.9)	0.568
CGI severity (SD)	4.7 (0.6)	4.7 (0.7)	0.197
IDS-SR, total score (SD)	42 (9.4)	43.4 (9.9)	0.197

CGI=Clinical Global Impression; HAMD17=17-item Hamilton Depression Rating Scale; HAMD24=24-item Hamilton Depression Rating Scale; IDS-SR=Inventory of Depressive Symptomology - Self-Related; MADRS=Montgomery-Asberg Depression Rating Scale; TMS=transcranial magnetic stimulation.

in the first study for at least 4 weeks and had not achieved sufficient clinical improvement from their randomized assignment.[17] Patients in Study 102 followed the same treatment sequence as the active arm on Study 101.

Study 103 was an open-label, 24-week durability of effect study[18] available to all patients who participated in either Study 101 or 102 and who met criteria for clinical remission and had successfully transitioned to maintenance pharmacotherapy. Additional treatment with TMS using the active treatment protocol was permitted in Study 103 if patients experienced symptom recurrence.

In all studies, the active TMS treatment session consisted of a fixed-dose parameter set involving stimulation at 120% of the patient's observed motor threshold, with a repetition rate of 10 pulses per second, a 4-second stimulation train, and a 26-second intertrain interval for 75 trains, totaling 3000 pulses delivered in each treatment session. Complete details of the study design and efficacy/safety outcomes for all proto-

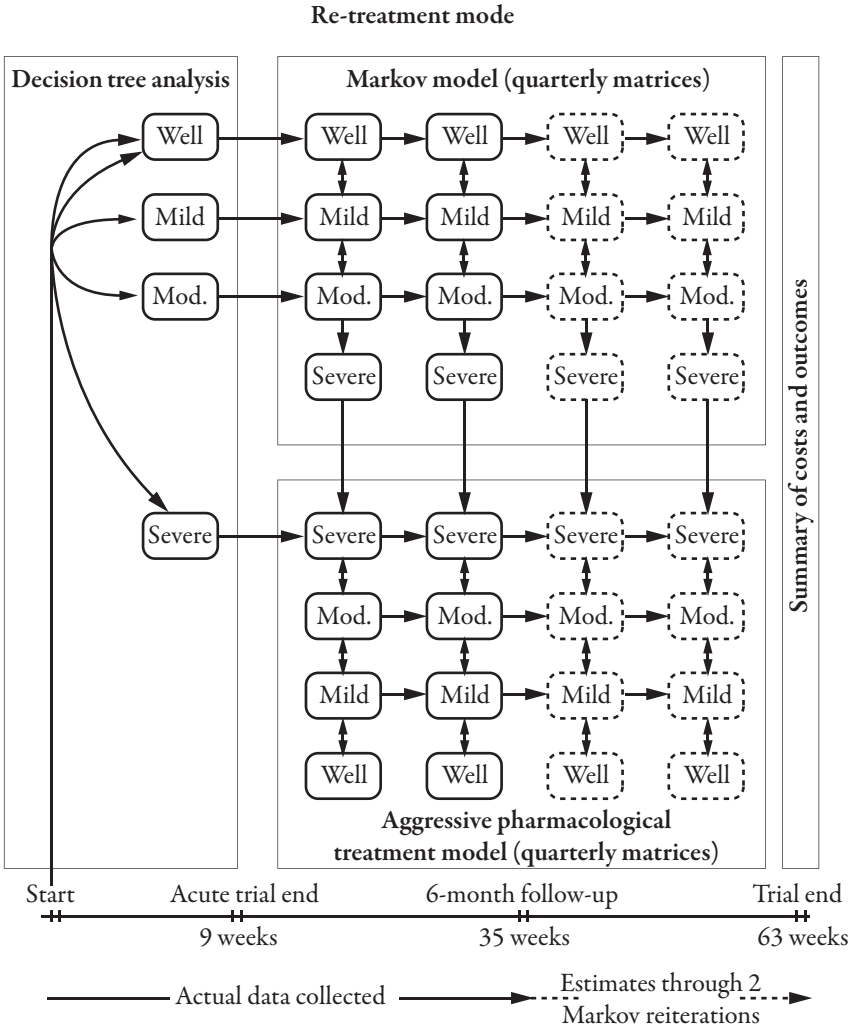
cols have been reported elsewhere[14,17,18,23] In the randomized, controlled trial Study 101,[14] the a-priori-defined primary efficacy outcome was the difference between active and sham TMS using the last visit Montgomery-Asberg Depression Rating Scale (MADRS) score through week 4 of the acute treatment phase. In the overall patient population (n=301), the standardized effect size for the outcome on the MADRS was 0.39. The strongest predictor of response to TMS was a lower score on the ATHF indicating that the patient had failed fewer previous adequate antidepressant trials.[23] That is, patients who were less treatment-resistant showed a significantly better response to acute TMS. In the patients who had failed only one antidepressant treatment at an ATHF-verified level of treatment exposure (referred to here as ATHF=1; n=164 or 54.5% of the overall patient population), the standardized effect size for the outcome on the MADRS was 0.94. As prior antidepressant treatment resistance appears to be an important moderator of clinical outcome to TMS, the economic model in this report is provided for both the overall patient population and for the subset of patients within the overall group who failed to receive clinical benefit from only one ATHF-verified treatment during the current episode.

Description of Decision Analysis Model

In this study, a decision tree was used as the structural framework for organizing the efficacy outcome data for the 6-week acute treatment and the 3-week treatment taper phases. The general structure of the model is depicted in Figure 1. The tree segregated patients into groups who completed the 6 weeks of treatment in Study 101 or 102 and those who did not finish. It then categorized patients into those who participated in the planned 3-week tapering phase and those who did not. Within each of these groups we characterized the distribution of patients using outcome criteria defined according to a final MADRS score as follows: (1) "MADRS 0", no depression (total score 0-9); (2) "MADRS 1", mild depression (total score 10-17); (3) "MADRS 2", moderate depression (total score 18-27); and (4) "MADRS 3", severe depression (total score >27).

Patients who completed all 9 weeks of treatment in either Study 101 or 102, were then further classified into two groups: MADRS 0-2 included those patients who met criteria for MADRS 0, 1, or 2 at the end of 9 weeks of treatment, and MADRS 3. Patients who were classified as MADRS 3 at the end of acute treatment were moved into a separate Markov model. These patients were assumed to have an illness severity where they would be treated with a new drug regimen combination consisting of a new antidepressant, a mood stabilizer, and an atypical antipsychotic. Note that the patients in the MADRS 3 group can be presumed to have demonstrated failure to benefit from at least two prior antidepressant treatments (ie, ATHF-verified failure of antidepressant pharmacotherapy prior to study entry, and subsequently prospectively demonstrated failure to benefit from TMS during the TMS study itself). Therefore, the estimates of the potential efficacy of future antidepressant treatment for the MADRS 3 group in the Markov model were based on the results reported for levels 3 and 4 in the STAR*D study,[6] ie, the groups in that study who had also failed to benefit from at least two antidepressant treatment exposures. The decision analysis model was programmed in Excel (Microsoft Corp., Seattle, WA, USA).

Figure 1. Structure of the decision analysis model. See text for complete description of decision analysis model. Well=MADRS 0, total score 0-9; Mild=MADRS 1, total score 10-17; Mod.=MADRS 2, total score 18-27; Severe=MADRS 3, total score >27.



Data Analysis Methods and Model Parameters

An analytical economic dataset was constructed from the original locked clinical and health economics outcomes dataset obtained from the Neuronetics clinical development program (full dataset access provided by Neuronetics, Inc., Malvern, PA, USA). The specific model parameters specifying acute treatment outcome and severity-specific relapse rates estimated over 1 year of follow-up that were used in the decision analysis model were, therefore, derived from our analysis of the actual raw clinical efficacy outcome data from the Neuronetics Studies 101,[14] 102,[17] and 103.[18] Health resource utilization was obtained for all patients in the clinical trial at entry into Study 101 and again at their point of exit from Study 103. This utilization information was obtained using a self-report questionnaire designed specifically for use in this study (Appendix 1). The information covered three major domains of information (productivity/work loss [nine items]; healthcare utilization and cost [18 items]; and caregiver support [four items]).

The overall clinical and health outcomes information was then combined with standard cost weights drawn from large national databases[24] and are discussed further in the sections below. Detailed cost weights were estimated for subgroups of patients with similar clinical severity, where the clinical severity was defined by the MADRS criteria described above in the decision analysis model. These subgroups were used to define the outcomes for patients at the end of the acute efficacy treatment in the respective clinical trial (ie, either the Neuronetics studies or the STAR*D study), and to link the trial results to cost and quality of life weights reported in the literature.[25-27] The results of the clinical trial data analysis were linked to health state-specific relapse rates estimated over a 1-year period following their acute treatment, using the actual follow-up data from Study 103 to estimate this 1-year interval.[26,28-30] The 6-month data were used to estimate 1-year outcome using a slope.

As noted above, the mean utilization values estimated from the study data were combined with unit cost weights derived from the analysis of a large sample of 2004 Medicaid billing data for patients with depression (SC Office of Research and Statistics, personal communication). The 2004 mean costs (not charges) were then inflated to equivalent 2006 cost weights using the medical care consumer price index over that interval of time. In the model outputs reported here that include the cost of lost productivity, 2 hours of lost time per treatment received was assumed. As a base case, each TMS session was estimated to cost US$300. The ICER for all reported model estimates was calculated as the difference in the 1-year cost of treating 100 patients with TMS minus the difference in the cost expected for treating 100 patients in the control group (sham TMS or pharmacotherapy, depending upon the specific model being considered), divided by the difference in the QALYs produced by the two treatments over 1 year. The model parameters and cost weights are provided in Table 2. The costs of the various pharmacotherapy regimens considered for the models are summarized in Tables 2 and 3. Final analyses utilized costs from antidepressant treatment regimen 2 (antidepressant: sertraline; mood stabilizer: valproic acid; atypical antipsychotic: aripiprazole) for the re-treatment part of the model (Table 3).

The model first estimated outcomes for TMS compared with sham treatment using the Study 101 overall population data.[14] As the experience in a blinded, randomized, controlled trial and a comparison to sham are not fully reflective of the expected clinical outcomes with TMS in ordinary clinical practice, where other actual treatments options would be considered, three additional model estimates were performed to place these results in context, comparing these model estimates to the best estimates of outcomes and costs of pharmacotherapy treatment, using the published STAR*D outcomes for this comparison. These three additional model estimates included: (1) a comparison of 1-year outcomes for the overall patient population treated with TMS in the open-label Study 102 data versus a synthetic comparison group of clinical outcomes observed in the published results from the STAR*D trial for levels 2 and 3 combined in that study; (2) the impact of prior antidepressant treatment resistance was also examined by performing a comparison of the Study 101 active TMS versus sham using only data from patients where ATHF=1; and finally, (3) the open-label Study 102 clinical outcomes restricted to those patients within the overall study population who failed only one ade-

Table 2. Model parameters and cost weights.

Parameter/variables	Base model value	Range for sensitivity analysis	Data sources
MADRS 0 utility weight	0.83	0.80-0.86	Revicki 1995[30]; NICE 2006[31]
MADRS 1 utility weight	0.73	0.70-0.76	Revicki 1995[30]; NICE 2006[31]
MADRS 2 utility weight	0.63	0.60-0.66	Revicki 1995[30]; NICE 2006[31]
MADRS 3 utility weight	0.30	0.27-0.33	Revicki 1995[30]; NICE 2006[31]
In-hospital failure	0.09	0.06-0.12	Kamlet 1995[28]; NICE 2006[31]
Decision tree mode			
TMS treatment (base case)	US$300.00	±10%	Neuronetics studies[14,17,18]
MADRS 0 medical care/day	US$2.16	±10%	Neuronetics studies[14,17,18]
MADRS 1 medical care/day	US$2.16	±10%	Neuronetics studies[14,17,18]
MADRS 2 medical care/day	US$3.01	±10%	Neuronetics studies[14,17,18]
MADRS 3 medical care/day	US$3.94	±10%	Neuronetics studies[14,17,18]
MADRS 0 productivity/day	US$33.37	±10%	Neuronetics studies[14,17,18]
MADRS 1 productivity/day	US$43.80	±10%	Neuronetics studies[14,17,18]
MADRS 2 productivity/day	US$99.40	±10%	Neuronetics studies[14,17,18]
MADRS 3 productivity/day	US$128.59	±10%	Neuronetics studies[14,17,18]
Median hourly wage for patient during treatment	US$12.00	±10%	Neuronetics studies[14,17,18]
Lost wages per treatment	US$509.04	±10%	Neuronetics studies[14,17,18]
Markov model			
Hospital cost/day	US$880.00	±10%	Medicaid 2004*
ER cost/visit	US$426.00	±10%	Medicaid 2004*
MD office visit	US$129.00		Medicaid 2004*
Antidepressant maintenance drug cost/day	US$1.53.00	±10%	Red Book 2006[32]
Follow-up drug cost to treat failure/day	US$2.20	±10%	Red Book 2006[32]
Re-treatment cost for patients in severe health state	US$22.63	See Table 3	Red Book 2006[32]
Marginal cost of hospital care for suicide	US$852.00	US$40,000	Medicaid 2004*
24-week failure	TMS	Sham	
MADRS 0	30%	33%	Neuronetics Study 103[18]
MADRS 1	23%	50%	Neuronetics Study 103[18]
MADRS 2	33%	50%	Neuronetics Study 103[18]
MADRS 3	33%	50%	Neuronetics Study 103[18]
Efficacy of pharmaceutical treatment regimens used for DRS 3 patients	14%	14%	Rush et al. 2006[6]

*SC Office of Research and Statistics, personal communication.
ER=emergency room; MADRS=Montgomery-Asberg Depression Rating Scale; MADRS 0=total score 0-9; MADRS 1=total score 10-17; MADRS 2=total score 18-27; MADRS 3=total score >27; MD=medical doctor; TMS=transcranial magnetic stimulation.

quate prior antidepressant treatment in their current illness episode (ATHF=1) were compared with a STAR*D synthetic comparison group restricted to the level 2 outcomes only. We tested the sensitivities of the model estimate to variations in the assumptions, cost weights, and quality-of-life adjustments used for each estimate. Specifically, the impact of two key model parameters alone and in combination were tested: (1) either excluding or including indirect costs in the model; and (2) varying the estimated cost of a suicide attempt. Clinical outcomes in the STAR*D comparison datasets are reported using the

Table 3. Model cost of pharmaceutical treatment regimens for patients with severe depression.

Drug type	Drug name	Daily dose, mg	Cost per day*, US$	Cost per week, US$
Regimen 1				
Antidepressant	Fluoxetine	20	2.66	
Mood stabilizer	Carbamazepine	100	0.43	
Atypical antipsychotic	Olanzapine	5	11.76	
			[14.85]	[103.95]
Regimen 2				
Antidepressant	Sertraline	150	4.21	
Mood stabilizer	Valproic acid	1500	6.87	
Atypical antipsychotic	Aripiprazole	10	11.55	
			[22.63]	[158.41]
Regimen 3				
Antidepressant	Venlafaxine	37.5	2.07	
Mood stabilizer	Lamotrigine	200	3.83	
Atypical antipsychotic	Olanzapine	20	23.50	
			[29.40]	[205.80]

Costs in brackets represent total costs per day or per week.
*Red Book 2006.[32]

Hamilton Depression Rating Scale (HDRS). Information provided on the IDS/QIDS web site[33] was used to establish clinically equivalent rating comparisons of the HDRS data to the MADRS scores used in the Neuronetics dataset. All statistical analyses were performed with SAS version 8.1 (Cary, NC, USA).

RESULTS

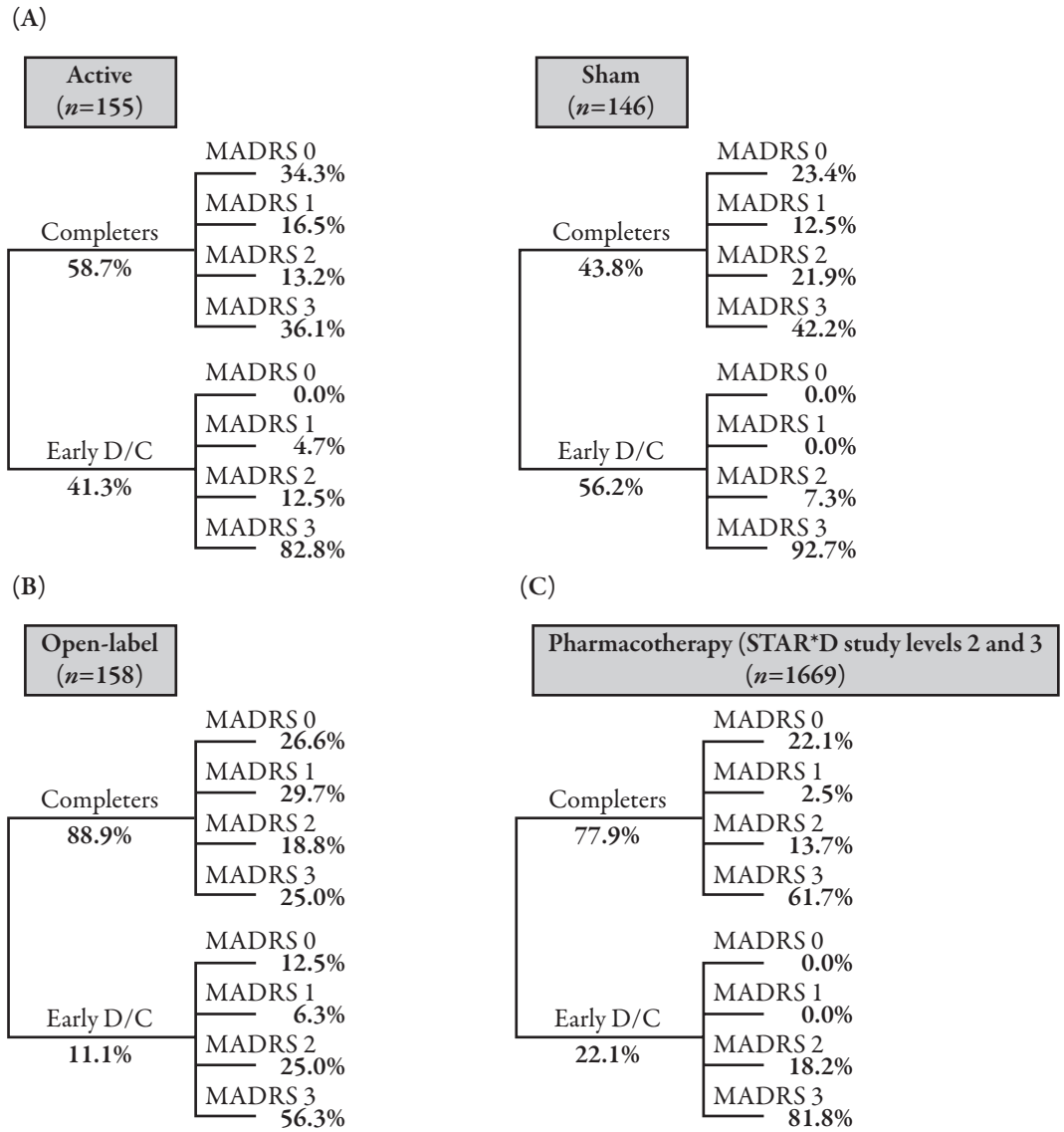
Summary of Acute Efficacy Outcomes in Decision Analysis Model

Results of the decision analysis for the acute treatment phase in both the active TMS (n=155) and sham TMS (n=146) randomized groups in Study 101 are shown in Figure 2A. In the active TMS treatment group, 58.7% of patients who completed the acute treatment phase proceeded through the 3-week TMS taper phase and entered long-term follow-up in Study 103. Similarly, in the sham TMS treatment group, 43.8% of patients who completed the acute treatment phase proceeded through the 3-week TMS taper phase and entered long-term follow-up in Study 103.

Results for the decision analysis for the acute treatment phase of all patients (n=158) in the open-label Study 102 are shown in Figure 2B. Of those patients who received open-label TMS treatment in Study 102 and completed the acute treatment phase, 88.9% of them proceeded through the 3-week TMS taper phase and entered long-term follow-up in Study 103.

A similar decision analysis model was applied to the outcomes from the STAR*D study to establish a comparison benchmark for pharmaceutical treatment of patients who had failed initial antidepressant pharmacotherapy. As noted above, the STAR*D results for levels 2 and 3 combined were used as a comparison for the overall population in the Neuronetics studies, whereas the results for the level 2 STAR*D group alone were used as a comparison for the subgroup of patients in the Neuronetics studies who failed only one

Figure 2. (**A**) Decision tree outcomes for acute-phase (6-week) treatment in Study 101: overall study population. (**B**) Decision tree outcomes for acute-phase (6-week) treatment in Study 102: overall study population. (**C**) Decision tree outcomes for acute-phase pharmacotherapy treatment. Data adapted from the published results of the STAR*D study.[6] See text for complete description of decision analysis model. D/C=discontinuation; MADRS 0=total score 0-9; MADRS 1=total score 10-17; MADRS 2=total score 18-27; MADRS 3=total score >27; TMS=transcranial magnetic stimulation.



adequate prior antidepressant treatment in their current illness episode (ATHF=1). This method of comparison between the two study populations provides the closest correspondence of the actual antidepressant treatment failure history of the differing patient groups compared in the models. Results of this analysis are shown in Figure 2C. Of the patients who completed either level 2 or 3 treatment in STAR*D, 77.9% proceeded into long-term follow-up in that study.

Summary of Healthcare Cost Estimates

The health economics analysis model estimated the mean expected costs of treatment

for a population of 100 patients treated and followed for 1 year of therapy. The mean expected costs for the different treatment groups in the model varied greatly, depending on the composition of the population, treatment efficacy, and the costing assumptions used. As a starting point, the ICER of active TMS compared with sham TMS in the randomized, controlled trial Study 101 was examined, and the resulting ICER was found to be acceptable from an economic perspective. However, although of interest, this type of comparison has limited practical meaning for comparison of cost of care for actual patients treated in a real-world clinical setting as none would provide billable sham treatments. For that reason, annual cost estimates for patients who were treated according to the treatment algorithms described in the STAR*D trial protocol were used as a standard pharmacotherapy comparison group. The STAR*D study regimens and their outcomes are reasonable proxies for commonly used pharmacotherapy regimens in ordinary clinical practice, and the sample size (n=2876, including levels 1-4) in that study is large and definitive.

Using this costing approach, the model estimated a mean annual cost per patient that could vary from as low as US$4379 for STAR*D patients who responded to the initial drug therapy to as much as US$26,546 for STAR*D patients who were nonresponders, and thus required emergency room and hospital care and multidrug treatment before responding. Similarly, the mean annual costs estimated for the overall TMS study population in the model (excluding the cost of the TMS treatments themselves) ranged from US$3683 for responders to US$26,599 for nonresponders that required emergency room visits, hospitalization, and multidrug therapy. At an assumed base case cost of US$300 per TMS treatment, the mean cost for this therapy was US$7792 per patient.

However, the differences in the distribution of responders between the TMS and the STAR*D arms of the model were large enough for the ATHF=1 study population in the TMS sample that the added cost of the TMS therapy was more than offset by the reduction in the proportion of costly nonresponders.

The economic estimates for such populations are usually described as being economically "dominant" because a treatment is expected to result in both improvement in health outcomes and generating overall savings. This condition of economic "dominance" was predicted for estimates comparing the use of active TMS to sham TMS for patients in the ATHF=1 study population alone based on the outcomes in Study 101. The dominance of TMS was also observed for estimates that compared active TMS outcomes in both Study 101 and Study 102 for the ATHF=1 population versus STAR*D drug therapy outcomes for the level 2 sample. For example, assuming a base case cost of US$300 per TMS treatment, the model predicted savings ranging from US$2406 per treated patient when Study 102 responses in the ATHF=1 patient subgroup were compared with the STAR*D level 2 estimates, to savings of US$10,516 per treated patient when the ATHF=1 study population results from Study 102 were compared with the STAR*D level 2 study estimates and the costs of lost patient productivity and caregiver time were included. When these productivity gains are excluded from the model for a comparison of the Study 102 ATHF=1 study population outcomes with the STAR*D level 2 study outcomes, the model still reports an economically dominant cost saving of US$1123 per patient per year of treatment.

ICER Analysis or Cost Savings

Data for the ICERs or the economically dominant model estimates of cost savings for the various models discussed in this section for the base case alone are summarized in Table 4.

Study 101 Data

TMS Versus Sham (Overall Study Population, n=301)

Using an estimated base case cost of US$300 per session for TMS, the cost per QALY of TMS studied in the overall study population under the conditions of a randomized, sham-controlled, double-blind, clinical trial (Study 101 data) was US$6667/QALY when productivity costs due to work loss and increased caregiver burden were included in the model, and US$34,999/QALY excluding these additional costs. However, increasing the cost of suicide from US$40,000 to US$60,000 only slightly changed the cost per QALY from US$6667/QALY to US$6428/QALY, indicating that the model is robust but sensitive to the omission of productivity costs.

The effect on the model of varying the per-session cost of TMS across a range from US$250 to US$450 per treatment session, administered under the same controlled Study 101 conditions, and without productivity costs included, resulted in a range of ICERs from US$23,382/QALY to US$69,847/QALY. Similarly, varying the per-session cost of TMS while including productivity costs predicted a range of ICERs from a dominant saving of US$4950/QALY to a cost of US$41,515/QALY.

TMS Versus Sham (ATHF=1 Study Population, n=164)

Using an estimated base case cost of US$300 per-session for TMS, the cost per QALY of TMS studied under the conditions of a randomized, sham-controlled, double-blind, clinical trial (Study 101 data) in the ATHF=1 study population only was a saving of US$747/QALY (dominant) and a cost of US$29,556/QALY,

Table 4. ICER (incremental cost per quality-adjusted life year [QALY] gained) or dominant cost savings (per treated patient per year) for the various economic models examined: base case cost assumptions.

		ICER or [dominant cost savings]	
Model structure	**Study population**	**With productivity costs included in the model, US$**	**Without productivity costs included in the model, US$**
Acute TMS vs. sham (randomized, controlled trial)	Overall (*n*=301)	3,544	36,551
	ATHF=1 (*n*=164)	[5,092]	29,556
Acute TMS (open-label study) vs. pharmacotherapy treatment as usual (STAR*D study)	Overall (*n*=301)	[7,243]	[746]
	ATHF=1 (*n*=164)	[9,844]	[2,243]

Costs in brackets represent economically dominant model estimates for TMS, and are reported as cost savings per treated patient per year. All other costs represent incremental cost per QALY gained (ICER).
ICER=incremental cost-effectiveness ratio; STAR*D=Sequenced Treatment Alternatives to Relieve Depression trial; TMS=transcranial magnetic stimulation.

when reported either including or excluding productivity costs in the model, respectively. Similar to the findings in the overall study population, increasing the cost of suicide from US$40,000 to US$60,000 only slightly changed the savings or the ICER.

In the ATHF=1 study population alone, the effect on the model of varying the per-session cost of TMS across a range from US$250 to US$450, without productivity costs included in the model predicted a range of ICERs US$18,758/QALY to US$61,948/QALY. In this sensitivity analysis, the cost of TMS needed to exceed US$400/treatment session before the most stringent willingness-to-pay threshold of US$50,000/QALY was exceeded.

Study 102 Data

In all the base case model estimates for Study 102 data, economic dominance of TMS treatment was shown, so results discussed in this section are reported in terms of the cost savings per treated patient per year of follow-up that were observed in the model estimates.

TMS Alone Versus Drug Therapy (Overall Study Population, n=*301; ATHF=1 Subset,* n=*164)*

The use of TMS in the overall patient population of patients treated under open-label study conditions (Study 102 data), compared to the corresponding STAR*D study outcomes (levels 2 and 3) presented a saving of US$1123 per patient per year and US$7621 per patient per year, when productivity costs were either excluded or included in the model, respectively. Increasing the cost of suicide from US$40,000 to US$60,000 changed the estimates from a saving US$1123 per patient per year to US$1184 per patient per year.

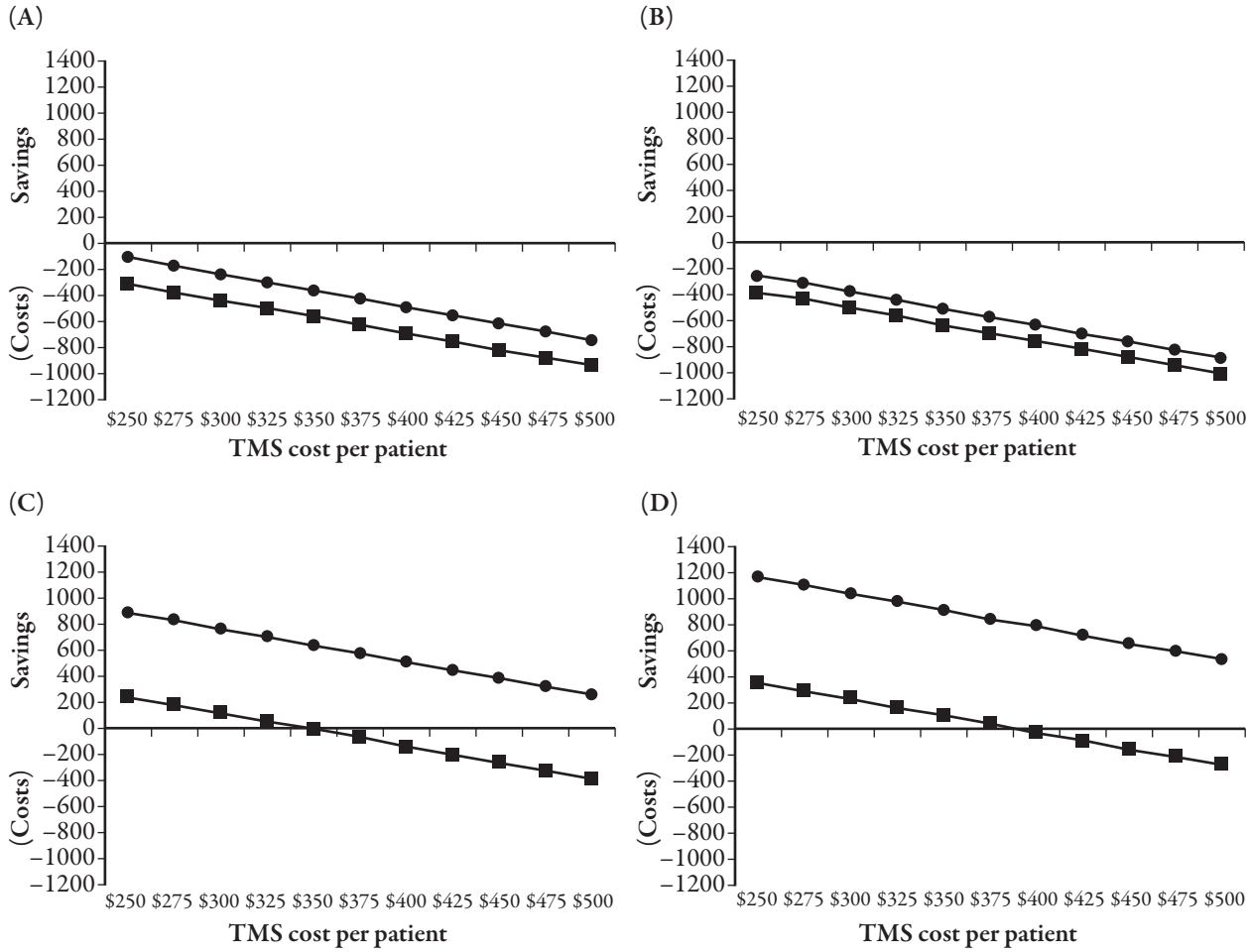
When the Study 102 outcomes for the ATHF=1 patient population alone were compared to STAR*D level 2 outcomes alone (ie, those patients in the STAR*D study who, similar to the ATHF=1 subgroup, had failed to benefit from only one antidepressant treatment in their current episode) varying the cost of TMS treatment from US$250 to US$450 with health gains only included in the model, predicted a range of cost savings from US$3671 per patient per year to US$1389 per patient per year. If caregiver and work loss costs are added to the model, in addition to health gains alone, the corresponding savings range from US$11,781 per patient per year to US$6721 per patient per year.

Cost Savings per Year of Treatment: Summary of Break-Even Time Points

Figure 3 provides a comprehensive summary of the costs or savings per year of treatment for TMS compared with pharmaceutical antidepressant standard care across the conditions of the various models examined. The data are presented based on the outcomes in either the randomized, controlled trial (Study 101) or the open-label trial (Study 102), and in all instances are compared with the open-label outcomes with pharmaceutical standard of care observed in the STAR*D study, as described above. In these graphs, the data for the overall study population and the ATHF=1 study subgroup are reported separately. Within each graph, data for the model's reporting output with productivity costs either included or excluded are shown for comparison.

In these graphs, and in the data reviewed in the previous results, the most relevant economic estimates for payers in today's health insurance environment come from the models that examine the cost and consequences

Figure 3. Savings (costs) per patient per year treated with TMS compared with pharmaceutical antidepressant standard care. (**A**) Randomized, controlled Study 101, overall study population *n*=301; (**B**) Randomized, controlled Study 101, ATHF=1 study population only *n*=164; (**C**) Open-label Study 102, overall study population *n*=301; (**D**) Open-label Study 102, ATHF=1 study population only *n*=164. (●) With and (■) without productivity gains included in model.



for patients treated under similar open-label study conditions, namely the comparison of TMS costs and outcomes observed in Study 102 compared to the costs and outcomes from the patients treated with pharmaceutical antidepressant therapy also under open-label conditions, namely the STAR*D study results. The results of the economic estimates for these specific comparisons are reported in Figure 3C and D for the 12-month time horizon assumed in the model.

As the majority of TMS costs occur in the first 6-9 weeks of therapy, and most insurers have rapidly changing, transient membership in their health plans, some payers may be interested in understanding the estimated time to reaching the economic break-even point when considering the costs of TMS. In other words, the time point at which the cost of TMS is offset by expected savings from the avoidance of additional treatments for depression. To accomplish this, the model was populated using the ATHF=1 study population outcomes from the open-label TMS Study 102, and then these results were compared with the outcomes observed in the STAR*D level 2 study. For this

comparison, the model assumed a base case cost of TMS of US$300 per treatment session. In this analysis, the mean cost for a TMS patient would be completely offset at 29 weeks, when compared with the expenditure flow expected for patients from the STAR*D trial over 12 months of treatment. As expected, this estimate varies with the assumptions about the cost per TMS visit. If a visit cost is assumed to be US$250 then the time to break-even is 24 weeks. If the visit cost is US$450 then the time to break-even is 46 weeks. Using the overall study population in Study 102, not just the ATHF=1 study sample, the time to break-even is 37 weeks compared with patients in the STAR*D study with a similar ATHF distribution at baseline (ie, levels 2 and 3) and a cost per visit of US$300 for TMS.

DISCUSSION

This paper reported the largest, comprehensive, cost-effectiveness study of TMS in patients with pharmacotherapy-resistant major depression. A major strength of this analysis is that it was based on the largest multisite clinical trial dataset of TMS published to date, incorporating evidence from a randomized, double-blind, acute efficacy controlled trial, as well as outcomes from open-label long-term efficacy and durability of effect for TMS that served as an extension study to the randomized, controlled trial.

Even in the most conservative economic model presented here, namely treatment with active TMS at a base case cost of US$300 per treatment session, compared with a sham control condition in the randomized controlled trial Study 101, and with the model restricted to net health gains only, TMS provides an ICER of US$34,999 per QALY. This is below the most stringent willingness-to-pay standard of US$50,000 per QALY for a new treatment. When work productivity gains due to clinical recovery and reduced caregiver costs are included in this model, the ICER is reduced further to US$6667 per QALY.

We believe that the evidence for the overall cost-effectiveness for the use of TMS is more apparent when a more clinically relevant model is considered, namely a comparison of open-label treatment with TMS in Study 102 (overall study population) with the outcomes of standard antidepressant pharmacotherapy in the STAR*D study (levels 2 and 3). In this analysis, using similar per-session TMS cost assumptions, and an economic model restricted to net health gains alone, TMS provides an actual net cost savings of US$1123 per patient per year. Cost savings increase further when the costs of work productivity gains due to clinical recovery and reduced caregiver costs are included in the model. In this latter analysis, the net cost savings are US$7621 per patient per year. The break-even point, where the cost of TMS is offset by expected savings from the avoidance of additional treatments for depression occurs at 37 weeks.

Finally, the overall cost benefits of the antidepressant effect of TMS are greatest in those patients at the earliest levels of treatment resistance in the overall patient sample (ie, the ATHF=1 patient population), as it is expected that these patients are the most likely to demonstrate a better clinical response to any treatment compared with more treatment-resistant patient populations. In these analyses, for open-label treatment with TMS in Study 102 compared with current standard-of-care outcomes in level 2 of the STAR*D study, using economic models that either excluded or included productivity cost gains, cost savings of US$2406 were observed and US$10,516 were realized, respectively. In this patient population the mean break-even time point occurs earlier, at 28 weeks.

Of all the models presented in this report, the comparison of the cost associated with TMS to the cost associated with the pharmacotherapy algorithm described in the STAR*D study is the most realistic and clinically relevant model for several reasons. First, it relies on treatment conditions likely to be implemented in clinical settings, where patients knowingly receive active TMS as a monotherapy, without any adjunctive pharmacotherapy. Furthermore, it uses for comparison one of the largest published clinical trial datasets, the STAR*D study, which examined the sequential benefits of commonly used antidepressant treatment strategies. Moreover, such a model appears to be the most relevant for payers when break-even time points are calculated and for employers when additional costs of productivity are incorporated. Indeed, the majority of the treatment cost of TMS is incurred within the first 6-9 weeks of therapy. It is evident that the direct cost of TMS therapy is higher than the direct costs of acute pharmacotherapy, within the sets of assumptions put forth in our modeling. However, when improved outcomes, durability of effect over time, and greater patient adherence to treatment are factored in, treatment with TMS leads to good economic value per patient treated compared with the economic value associated with the pharmacotherapy alternatives. Furthermore, this benefit is projected to continue over an entire year of follow-up after successful acute treatment, provided that patients undergo simple maintenance pharmacotherapy. It should be noted that productivity gains are significant even when time away from work to receive the treatment (estimated as 2 hours per treatment in our models) is included in the model and deducted from the estimated work productivity gains.

Two other studies have investigated the economic value of TMS. Kozel et al.[15] used an economic decision analysis drawing upon data from a published treatment trial comparing TMS with ECT.[34] This trial was chosen for analysis as it represented outcome data for both modalities randomly assigned from the same study population sample. They compared the costs of three different treatment strategies for nonpsychotic, severe major depression: ECT alone; TMS alone; and TMS followed by ECT for nonresponders (TMS-to-ECT). They calculated 12-month costs and QALYs for all nonpsychotic, severely depressed patients who would have otherwise undergone ECT. In their model, the average TMS session was estimated at US$94.80 whereas the ECT session was estimated at US$969.80. The ECT costs included the cost of treatment (including anesthesia, monitoring, nursing, etc), travel, and the costs of a companion to monitor the patient for 24 hours after each treatment. In that report, ECT alone compared with TMS alone was predicted to add US$460,031 per QALY gained. The strategy of treating with TMS first and then referring nonresponders to ECT revealed that this strategy compared with ECT alone showed cost savings and an increase of US$1538 QALYs gained.

In contrast with the conclusions from the Kozel report, Knapp et al.[16] recently published a cost-effectiveness study that compared ECT and TMS based on a clinical trial[13] where patients were randomized to receive either ECT twice weekly in an adjustable design or TMS on consecutive weekdays at a fixed dose and for a fixed duration of 3 weeks. Costs were calculated for the treatment period and for the subsequent 6 months, and comparisons made between groups after adjustment for any baseline differences. TMS was not as effective as ECT and overall there were no treatment cost

differences acutely or at 6-month follow-up. They also reported that informal care costs were higher for the TMS group. Based on these results, Knapp et al.[16] concluded that TMS was not likely to be chosen by clinicians. Both of these studies, while informative, lacked critical elements that limit the generalizability of their results. Unlike the data reported in the present study, where both clinical outcomes and healthcare resource utilization surveys were collected from a much larger sample enrolled in a three-phase clinical trial, collected across multiple clinical study sites, the report from Kozel et al.[15] relied on the results of a single trial to infer response rates. Knapp et al.[16] developed an economic hypothesis whereby TMS administered in what is now recognized as a clinically suboptimal treatment regimen[35] was, not surprisingly, found to have little economic value. The patient selection criteria used in that study, combined with the suboptimal dosing schedule used (short, fixed duration, and fixed dose of 1000 stimuli/session) may have contributed largely to the clinical shortcomings of the therapy in that report. In addition, a sampling bias in the follow-up economic data collected 6 months after therapy in the report by Knapp et al. (eg, 45% of the ECT group completed the assessment compared with 75% of the TMS group) may also have contributed to the differences in the economic projections. In addition, the authors' assumptions for the calculation of the unit cost of TMS and ECT were not based on an annual patient volume (60 patients for ECT and 25 patients for TMS) which biased the visit cost of TMS upwards. These data did not include the various costs associated with the ECT treatment session itself, including caregiver costs, transportation, and other costs nor did the model include work productivity losses due to the short and long-term cognitive impairments that are well known to be associated with ECT.[36]

The economic model reported here has limitations. A Markov model approach was employed with defined, strict health states at the end of acute treatment, and did not take into consideration multiple, patient-specific sociodemographic characteristics that may influence clinical outcome, with the exception of moderate or severe treatment resistance. Various sources were relied upon to estimate costs; however, the present authors provided robust sensitivity analyses to support the results. In a practical sense, no healthcare provider or payer will pay for the cost of conducting sham treatment. The original double-blind, controlled data were reported so that the reader was aware of the economic impact expected from the results of the blinded, clinical study, which can be considered the most conservative economic analysis. More relevant estimates for payers are the results of modeling the open-label TMS trial outcomes compared to the standard care outcomes for patients treated in the STAR*D study matched for similar levels of prior treatment resistance. Of note is that the STAR*D sample also contained more medical and psychiatric comorbidities than the TMS trial.[6] Also, indirect medical costs savings were not included in the model, although they should be significant as these nondepression-related healthcare costs are known to have a significant influence on the total costs for the healthcare of patients with major depression. Future studies with larger sample sizes may provide even more accurate estimates.

In summary, TMS is a cost-effective treatment for pharmacotherapy-resistant patients with major depression. The data reported here highlight that significant cost savings may be found relative to current standard care pharmaceutical treatment, especially when used

at the earlier levels of treatment resistance. Medical care decisions are complex and should rarely be based on economic results alone. The findings presented in this cost-effectiveness analysis are intended to provide a framework for discussions to inform decisions. Economic studies contribute an important perspective and are meant to supplement information on clinical assessment issues and ethical considerations when access and utilization policy decisions are made. Future studies with prospectively gathered healthcare resource utilization costs will help to further delineate the costs and the overall role for TMS in the psychiatric care of patients with major depression resistant to initial pharmacotherapy.

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APPENDIX 1

Health Resource Questionnaire

PRODUCTIVITY/WORK LOSS

1. What is your current work status?
   - ☐ You work full time for pay (Go to question 5)
   - ☐ You work part time for pay (Go to question 5)
   - ☐ You are not working for pay (Go to question 2)
2. You are not working due to:
   - ☐ Depression
   - ☐ Reason other than depression
3. You are receiving disability insurance payments: ☐ Yes ☐ No
4. Your disability payments are due to:
   - ☐ Depression
   - ☐ Reason other than depression
5. Approximately how much money did you earn in salary and wages in 2003, before taxes and other deductibles?
   - ☐ Less than $15,000
   - ☐ $15,000-$24,999
   - ☐ $25,000-$34,999
   - ☐ $35,000-$49,999
   - ☐ $50,000-$74,999
   - ☐ $75,000-$99,999
   - ☐ More than $100,000
6. Over the past 3 months, how many total hours did you miss from work due to your depression?

   _____ hours in total each week
7. On a scale of 0-10, with "0" representing "not at all impaired" and "10" representing "totally impaired", how much was your productivity at work impaired by your depression in the past 3 months?

   0 1 2 3 4 5 6 7 8 9 10

   Not at all impaired Totally impaired
8. During the past 3 months, about how many days did you stay in bed more than half of the day because of your depression?

   _____ days in total over the past 3 months
9. During the past 3 months, how many days did you cut down on your usual activities more than half of the day because of your depression?

   _____ days in total over the past 3 months

HEALTHCARE UTILIZATION AND COST

Please answer these questions related to physician and hospital visits over the past 3 months.

1. During the past 3 months, did you visit a healthcare provider?

   ☐ Yes ☐ No

2. Was one or more of these visits for your depression?

   ☐ Yes ☐ No, skip to question 4

3. How many times have you visited an outpatient provider for your depression in the last 3 months?

   _____

4. Did you make one or more outpatient visits for any psychiatric or mental health problems other than depression during the past 3 months?

   ☐ Yes ☐ No, skip to question 6

5. How many times have you made an outpatient visit for these other mental health problems?

   _____

6. Excluding depression or other psychiatric problems, did you make one or more outpatient visits during the past 3 months for a medical problem?

   ☐ Yes ☐ No, skip to question 8

7. How many times did you have an outpatient visit for medical problems?

   _____

8. Did you go to an emergency room during the past 3 months for depression, for any other psychiatric or mental health problems, or for general medical problems?

   ☐ Yes ☐ No, skip to question 12

9. How many emergency room visits were for depression?

   _____

10. How many emergency room visits were for other mental health problems?

    _____

11. How many emergency room visits were for a general medical problem?

    _____

12. Did you stay overnight in a hospital during the past 3 months for any reason?

    ☐ Yes ☐ No, skip to end

HEALTHCARE UTILIZATION AND COST (continued)

13. Were you in the hospital for depression?

☐ Yes ☐ No, skip to question 15

14. How many days were you in the hospital for depression?

_____

15. Were you in the hospital for any other mental health problem in the past 3 months?

☐ Yes ☐ No, skip to question 17

16. How many days were you in the hospital for other mental health problem(s)?

_____

17. Were you in the hospital for any medical reason in the past 3 months?

☐ Yes ☐ No, skip to the end

18. How many days were you in the hospital for other medical reasons?

_____

CAREGIVER SUPPORT

1. Do you have someone who acts as your caregiver to assist you with daily activities?

☐ Yes ☐ No, skip to the end

2. Who regularly assists you with daily activities? (Check all that apply)

☐ Your spouse/significant other ☐ Your child

☐ Your friend ☐ Another relative

☐ A professional paid to assist you

3. What activities does your caregiver help you with? (Check all that apply)

☐ Household chores (cleaning, cooking, laundry, shopping, etc)

☐ Personal care (bathing, dressing, grooming, eating, etc)

☐ Transportation (driving)

☐ Other (specify) _____

_____

CAREGIVER SUPPORT (continued)

4. On average, how many hours each week does your caregiver or caregivers usually assist you?

   _____

   hours in total each week