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Cost-Effectiveness of Repetitive Transcranial Magnetic Stimulation versus Antidepressant Therapy for Treatment-Resistant Depression

*Kim-Huong Nguyen, PhD, Louisa G. Gordon, PhD**

Center for Applied Health Economics, Menzies Health Institute Queensland, Griffith University, Australia

ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) therapy is a clinically safe, noninvasive, nonsystemic treatment for major depressive disorder. **Objective:** We evaluated the cost-effectiveness of rTMS versus pharmacotherapy for the treatment of patients with major depressive disorder who have failed at least two adequate courses of antidepressant medications. **Methods:** A 3-year Markov microsimulation model with 2-monthly cycles was used to compare the costs and quality-adjusted life-years (QALYs) of rTMS and a mix of antidepressant medications (including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclics, noradrenergic and specific serotonergic antidepressants, and monoamine oxidase inhibitors). The model synthesized data sourced from published literature, national cost reports, and expert opinions. Incremental cost-utility ratios were calculated, and uncertainty of the results was assessed using univariate and multivariate probabilistic sensitivity analyses. **Results:** Compared with pharmacotherapy, rTMS is a dominant/cost-effective alternative for patients with treatment-resistant depressive disorder. The model predicted that QALYs gained with rTMS were higher than those gained with antidepressant medications (1.25 vs. 1.18 QALYs) while costs were slightly less (AU $31,003 vs. AU $31,190). In the Australian context, at the willingness-to-pay threshold of AU $50,000 per QALY gain, the probability that rTMS was cost-effective was 73%. Sensitivity analyses confirmed the superiority of rTMS in terms of value for money compared with antidepressant medications. **Conclusions:** Although both pharmacotherapy and rTMS are clinically effective treatments for major depressive disorder, rTMS is shown to outperform antidepressants in terms of cost-effectiveness for patients who have failed at least two adequate courses of antidepressant medications.

Keywords: antidepressant, cost effectiveness analysis, economic evaluation, Markov model, microsimulation, repetitive transcranial magnetic stimulation.

Introduction

Major depressive disorder (MDD) is a significant burden to many health care systems. It is a chronic and debilitating disease, and it significantly decreases quality of life [1,2]. It is one of the most common of all psychiatric disorders and ranks among the leading causes of disability worldwide [3]. Although many patients with depression respond to first-line medication and psychotherapy treatments, an estimated 20% to 40% of the patients are unable to tolerate pharmacotherapy or do not benefit from these treatments after repeated attempts [3]. In addition, even with successful acute treatment outcomes, the long-term durability of response among treatment-resistant patients is poor. A recent review reported that the rate of recurrence of MDD, treated in specialized mental health settings, was very high: 60% after 5 years, 67% after 10 years, and 85% after 15 years [1]. Patients with treatment-resistant depression (TRD) contribute to a disproportionately high burden of illness than do patients who respond to treatment; they are twice as likely to be hospitalized and have higher treatment costs [2].

Repetitive transcranial magnetic stimulation (rTMS) therapy is a noninvasive, nonsystemic therapeutic device offering treatment that uses pulsed magnetic fields at magnetic resonance imaging strength to induce an electric current in a localized region of the cerebral cortex. During the rTMS session, the patient is conscious and there is no requirement for an anesthetic or muscle relaxants. A treatment session usually lasts approximately 40 minutes and is normally performed three to five times a week over a period of 4 to 6 weeks. After each session, patients may continue with their daily work or other routines. rTMS produces a clinical benefit without the systemic adverse effects typical of oral medications and appears to have no adverse effects on cognition [4–7]. rTMS involves an electromagnetic coil and is not suitable in patients with metal items such as cochlear implants and implanted electrodes. It is also not recommended for patients who are at risk of epileptic seizures, who are

* *Address correspondence to:* Louisa G. Gordon, Center for Applied Health Economics, Menzies Health Institute Queensland, Griffith University, University Drive, Meadowbrook, Logan, QLD 4131, Australia.

E-mail: louisa.gordon@griffith.edu.au.

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withdrawing from drugs or alcohol, or who have drug or alcohol dependence [5].

Clinical practice guidelines stipulate that current options for TRD are antidepressant medications, rTMS, and electroconvulsive therapy (ECT). In dozens of small trials, however, rTMS has been compared only with ECT mostly because they are both classified as physical therapies. ECT, however, is commonly used in emergency settings for psychotic patients, whereas rTMS is indicated for a wider range of mild to severe MDD. In addition, many patients with MDD are unable to tolerate the adverse effects of ECT or refuse to have ECT because of the associated stigma or fear about potential adverse effects (e.g., cognitive impairment). As such, it has been suggested that ECT is complementary, rather than a replaceable treatment, to rTMS and standard pharmacotherapies [8].

Simpson et al. [9] is the only study that compared pharmacotherapies and rTMS in the treatment of MDD. It concluded that rTMS provided a net cost saving compared with antidepressant medications [9]. Two studies compared rTMS with ECT and arrived at different conclusions [10,11]. Kozel et al. [11] (US-based) suggested that rTMS would be a cost-effective treatment for patients with MDD compared with ECT alone over 12 months, whereas Knapp et al. [10] (UK-based) found that rTMS has a very low probability of being a cost-effective alternative to ECT over 6 months.

Because of the paucity of health economic assessments of rTMS for health service decision making, the purpose of this study was to investigate the cost-effectiveness of rTMS compared with pharmacotherapies for patients with TRD within the context of the Australian health system. We sought to use updated evidence to populate our economic model and ascertain whether our results corroborated the short-term findings from Simpson et al. [9].

Methods

Overview

A hypothetical health state transition (Markov) model was used to combine data on the health care costs and health effects of rTMS and antidepressants over 3 years. The study population was patients with MDD who have failed two adequate medication trials from two different classes of drugs. Using a health system perspective, the key outcome was the incremental cost per quality-adjusted life-year (QALY), which represents the additional cost of rTMS per additional QALY compared with antidepressants. The stability of the results was thoroughly tested in sensitivity analyses.

Treatment Strategies

Two main treatment strategies were considered: rTMS and pharmacotherapies (standard antidepressant medications). The model considers a mix of pharmacotherapies because in practice, a large variety of antidepressants are prescribed for patients with MDD depending on previous treatments, medication tolerance, and resistance. The antidepressant mix includes selective serotonin reuptake inhibitors, which account for a large share of MDD medications in Australia, followed by serotonin and norepinephrine reuptake inhibitors, tricyclics, noradrenergic and specific serotonergic antidepressants, reversible inhibitor of monoamine oxidase A, and monoamine oxidase inhibitors [12].

The model assumed that other standard psychotherapies (i.e., talking therapies) were maintained during both treatment options. ECT, augmentation (e.g., lithium and atypical antipsychotic medications), and hospitalizations were available for those who failed the two main treatments.

Model Structure

A Markov microsimulation model was constructed and analyzed in TreeAge Pro 2014 software. The model duration was 3 years with 2-monthly cycles. Eight health states were used to account for acute or continuing treatments, combinations of responsiveness to treatment and relapse options, and deaths (see File 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.04.004). The MDD health states were based on the 17-item Hamilton Depression Rating Scale (HAM-D17), which is one of the most widely used and accepted measures for rating the severity of depression symptoms. In the absence of long-term clinical data, the duration of 3 years was chosen to track several courses of treatment per patient, which is typical of clinical practice.

Patients entered the model and moved between the various health states according to their treatments, their response to therapies, and their chance of remission or relapse. The probability of gaining remission or regressing varied according to the strategy under analysis (either rTMS or antidepressant). After this point, the model for both strategies was identical in incorporating the probabilities of receiving salvage treatments and their efficacy outcomes (ECT, augmentation, and hospitalization) and the probability of having adverse events during treatment.

Data Inputs and Sources

To identify relevant evidence to populate the model, the Cochrane Library and Medline databases were searched. In both instances, a basic search strategy was used with key words (and their combinations) such as major depressive disorder, major depression, rTMS, antidepressant, ECT, treatment resistant. A manual search of the references of each identified article of interest was also completed for further information. Other sources of information included national epidemiological reports and hospital cost reports (Table 1).

Probabilities

The treatment effects (probabilities of gaining response or remission) for rTMS are extensively reported in the literature. The range is wide, however, due to trial design and sample size variations. Meta-analyses also report varying response and remission rates, depending on the comparators, treatment frequency (low vs. high), and frontal side (left, right, or bifrontal) [13–16]. To calculate the pooled estimate of the treatment effect for all relevant studies, meta-analyses were performed using the random-effect inverse variance–weighted method for binary outcomes (see File 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.04.004). The response and remission rates for rTMS were estimated as 37.5% and 21.5%, respectively. The efficacy outcome for antidepressant medication was derived from the STAR*D trial [17,18]. This study reported major outcomes (remission, response, and adverse effects) for different patient groups including patients who failed two adequate antidepressant courses in their current illness episode. The reported response and remission rates for antidepressant medications were 16.8% and 13.6%, respectively.

The probabilities of regressing after a period of remission for both rTMS and antidepressant medications are not reported in the literature. Studies, however, have reported information on worsening and relapse rates for rTMS [6,19], antidepressants [17], and ECT treatment [20]. These rates were converted to probabilities of losing remission (regressing). Treatment efficacy tends to decrease if patients develop resistance [9,18,21]; however, the decrement rate is not reported quantitatively in the literature. The rates of efficacy decrement (for each subsequent treatment) were therefore assumed to be 20% and 15% of remission and response rates, respectively. It was also assumed that 75% of the

Table 1 – Summary of variables used in the economic model.

Description	Base case	Distribution	Low	High	Sources and assumptions
Transition probabilities					
rTMS					
Remission: First treatment	21.5%	Beta	19.7%	31.2%	Meta-analysis (File 1 in Supplemental Materials)
Response: First treatment	37.5%	Beta	33.2%	48.7%	Meta-analysis (File 1 in Supplemental Materials)
Start maintenance	10.0%	Beta	5.0%	15.0%	Expert opinion*
Lose remission (no maintenance)	16.6%	Beta	10.0%	20.0%	[6,17–20]
Lose remission with maintenance	12.0%	Beta	8.0%	16.0%	[6,17–20]
Antidepressant medications					
Remission: First treatment	13.6%	Beta	13.0%	36.8%	[17,18]
Response: First treatment	16.8%	Beta	16.0%	48.6%	[17,18]
Lose remission	28.1%	Beta	20.0%	40.0%	[17,18]
ECT (after failing rTMS or antidepressants)					
Remission: First treatment	46.3%	Beta	20.0%	70.0%	Meta-analysis (File 1 in Supplemental Materials)
Response: First treatment	60.9%	Beta	40.0%	80.0%	Meta-analysis (File 1 in Supplemental Materials)
Lose remission	22.3%	Beta	15.0%	35.0%	[20]
For all treatment arms					
Hospitalization	10.4%	Beta	8.0%	12.0%	Calculated from literature
Gaining REM after hospitalization	35.0%	Beta	20.0%	50.0%	Assumption
REM: % decrement for each subsequent treatment	20.0%	Triangular	15.0%	25.0%	Assumption
RESP: % decrement for each subsequent treatment	15.0%	Triangular	10.0%	20.0%	Assumption
Retreatment after relapse	36.2%	Beta	25.0%	45.0%	Expert opinion*
Relapse from partial remission	50.0%	Beta	40.0%	71.0%	[17]
Relapse: % increase for each subsequent treatment	10.0%	Triangular	8.0%	12.0%	[17]
Getting ECT after failing the main treatment	25.0%	Beta	20.0%	30.0%	Assumption
Having adverse events during treatment	5.80%	Beta	4.0%	8.0%	[17]
Health utilities					
Remission (HAM-D17 score <8)	0.860	Beta	0.750	0.900	[22,23]
Partial remission (mild-moderate $8 \leq$ HAM-D17 score <20)	0.710	Beta	0.650	0.820	[22,23]
No response (severe-very severe HAM-D17 score ≥ 20)	0.520	Beta	0.250	0.580	[22,23]
Disutility for antidepressant treatment	0.066	Triangular	0.040	0.100	[22,23]
Disutility for rTMS treatment	0.101	Triangular	0.050	0.150	Estimation
Disutility for ECT treatment	0.104	Triangular	0.500	0.150	Estimation
Hospitalization (severe-very severe with suicidal risk HAM-D17 score ≥ 20)	0.300	Beta	0.090	0.400	[22,23]
Resources and cost components (2013–2014 AUD)					
rTMS					
Number of acute sessions	28.3	Triangular	20.0	30.0	[4]; Expert opinion*
Number of maintenance sessions	4.0	Triangular	3.0	5.0	Expert opinion*
Cost per session	$150.00	Gamma	$120.00	$180.00	Assumption ± 20%
Antidepressant					
Months per course of treatment	3.0	Triangular	2.0	6.0	Expert opinion*
Cost per month	$17.27	Gamma	$13.82	$20.72	Calculation ± 20%
ECT					
Number of sessions	10.0	Triangular	6.0	12.0	ECT literature
Cost per session	$814.00	Gamma	$651.20	$976.80	AR-DRG v.6 ± 20%
Augmentation					
Cost per course treatment	$235.19	Gamma	204.1	359.0	Expert opinion* and calculation
Hospitalization					
Average cost per hospitalization	$14,021	Gamma	$13,106	$20,484	AR-DRG v.6
Adverse events					
Antidepressant	$80.95	Gamma	$64.76	$97.14	Calculation ± 20%

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Table 1 – *continued*

Description	Base case	Distribution	Low	High	Sources and assumptions
rTMS	$81.79	Gamma	$65.43	$98.15	Calculation ± 20%
ECT	$72.53	Gamma	$58.03	$87.04	Calculation ± 20%

AR-DRG, Australian refined diagnosis-related groups; AUD, Australian dollar; ECT, electroconvulsive therapy; HAM-D, Hamilton Depression Rating Scale; REM, remission; RESP, response; rTMS, repetitive transcranial magnetic stimulation.
* The expert was a university professor in psychiatry and a practicing physician, and had no conflicts of interest to declare.

patients who failed either rTMS or (acute) antidepressants would start augmentation medication. In Australia, lithium is indicated (and approved by the Pharmaceutical Benefit Schedule) to augment antidepressants for patients with MDD. Off-label use, however, includes atypical antipsychotic drugs such as aripiprazole, quetiapine, and olanzapine. The model used lithium augmentation as the base case, and tested a mix of augmentation therapies in the sensitivity analysis. Last, mortality risk was assumed to be higher for patients in acute depression or in mild/moderate depression than in the general population.

Resources and Costs

Costs related to all health care resource items for the economic model are summarized in Table 1. All costs were converted to monthly values to accommodate the 2-monthly cycle calculation. For simplicity, cost per treatment course (for both rTMS and antidepressant) was assumed to occur within one cycle. Psychiatric consultation for treatment and a management plan incurred a cost for each treatment course. Subsequent psychiatric consultations and short visits were part of regular MDD monitoring.

Each rTMS session was estimated to cost approximately AU $150 covering the professional component and practice components. Each acute rTMS course consists of an average number of 28 sessions [4] and lasts for a period of 4 to 6 weeks. Patients who respond positively to treatment (i.e., observed reduction in HAM-D17 score) will proceed to rTMS maintenance until potential relapse or dropout. For rTMS maintenance, the average number of sessions was estimated to be 26 per annum, equivalent to an average of two rTMS sessions per month.

Each antidepressant (acute) treatment course was recommended for at least 3 months. The monthly cost was calculated as the weighted average of most commonly used antidepressant drugs prescribed by Australian doctors (Table 1) [12]. This resulted in a monthly cost of AU $17.30, equivalent to AU $52 per 3-monthly (acute) treatment course. If a patient's condition improved to full remission, further medication was not required unless the patient had a relapse later.

For each treatment option, patients who failed two consecutive courses would move to either augmentation or ECT. Augmentation agents included lithium and atypical antipsychotic agents (e.g., quetiapine, aripiprazole, and olanzapine). The total cost for augmentation included at least 2-month supply of the medication, regular monitoring tests, and one psychiatrist consultation in addition to standard antidepressant medications. The ECT treatment cost covered 10 sessions with one psychiatric visit. The costs for hospitalizations and individual adverse events were identified by Sullivan et al. [22] and valued using Australian national cost schedules (Table 1).

Health State Utility Values

To calculate QALYs, patient utility values were assigned to each health state in the model. Fourteen published studies were identified from a systematic review of clinical trials and economic evaluations of MDD treatment (limited to publications after January 2000). Hawthorne et al.'s [23] estimates were used for the model base case because they reported the utility weights for Australians but still aligned with values reported in the wider literature. There is limited information on the disutility from adverse events associated with each treatment. The most relevant study for this topic is Sullivan et al. [22] on the cost-effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions in the United States. For the economic model, the weighted averages of the disutilities of adverse events relevant to each treatment were calculated, with the utility values taken directly from Sullivan et al. [22].

Analyses

The main outcomes of the model were costs and quality-adjusted life-years (QALYs), both discounted at 5% to reflect time preferences. For the base case, microsimulations were performed with 50,000 trials to achieve stable results. Mean costs and QALYs for each treatment arm were produced to calculate the incremental cost-effectiveness ratio (ICER). Univariate and multivariate probabilistic sensitivity analyses were undertaken for key variables. The 95% confidence intervals or the high and low values, where available, were used to reflect wide variation in the base values. Beta distributions were assigned for utilities and probabilities, whereas gamma distributions were assigned for costs. All sensitivity analyses were performed with 50,000 trials for result stability and consistency with the base case. An upper threshold of AU $50,000 per QALY was used to indicate cost-effective results.

Results

Estimates of cost, effect, and ICER for the base case (3-year horizon) are presented in Table 2 and on the cost-effectiveness plane in Figure 1. The model predicted that QALYs gained with rTMS were higher than QALYs gained with pharmacotherapy (1.25 vs. 1.18 QALYs) while costs were slightly less (AU $31,003 vs. AU $31,190). Therefore, in the base case, the rTMS option was considered the superior alternative compared with pharmacotherapy for the treatment of treatment-resistant patients with MDD. At a threshold of AU $50,000 per QALY gain, the probability that rTMS was dominant was 32% and the probability that rTMS was cost-effective compared with antidepressants was 41%.

Table 3 presents the effect of parameter changes on the ICER. The analytical model was very robust with respect to all parameters. Univariate sensitivity analyses identified the most influential variables in the model: the probabilities of gaining and losing remission after antidepressant treatment; the probability of losing remission without rTMS maintenance; the probability of losing remission after treatment; and the doses and costs per session of rTMS and ECT. The model was not sensitive to the utility values, and for most probability and cost variables rTMS was a dominant alternative to antidepressant medication. The multivariate analyses showed that the model results were

Table 2 – Costs, effects, cost-effectiveness ratios, and net monetary benefit (2013–2014 AUD).

Mean values	3 y (base case)		5 y (sensitivity analysis)	
	Antidepressant	rTMS	Antidepressant	rTMS
Total cost	$31,190	$31,003	$41,009	$39,693
Incremental total cost	–	–$187	–	–$1,316
Total QALYs	1.18	1.25	1.53	1.63
Incremental total QALYS	–	0.07	–	0.10
Cost/QALY	$26,432	$24,803	$26,803	$24,352
Incremental cost per QALY	–	Dominant	–	Dominant

AUD, Australian dollar; QALY, quality-adjusted life-year; rTMS, repetitive transcranial magnetic stimulation.

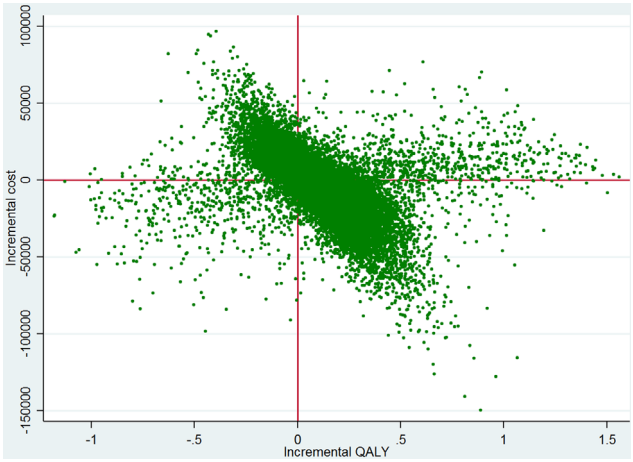

Fig. 1 – Microsimulation results in the Base case (3 year horizon with 50,000 trials.) QALYs, quality-adjusted life-years.

stable to variations in model values, with the likelihood of rTMS being dominant or cost-effective compared with antidepressants exceeding 70%.

Additional sensitivity analyses were also performed on the discount rates and model duration. When a longer time horizon was applied (5 instead of 3 years), the average cost saving increased to $1316 and the average QALY gain per patient was 0.10. This implies increasing cost-effectiveness in the medium term for rTMS treatment versus standard pharmacotherapies. The use of different discount rates had little impact on this overall conclusion. At a 3% discount rate, rTMS was a superior strategy, less costly, and more effective, compared with the antidepressant medication. At a 7% discount rate, the ICER was AU $127 per QALY gained, well below a willingness-to-pay threshold of AU $50,000.

Discussion

A cost-effective treatment for treatment-resistant patients with depression is an important challenge today because MDD is a chronic and debilitating disease that significantly decreases one's quality of life, and is a leading cause of disability worldwide [2,3]. rTMS has been received as a clinically effective and safe option for treatment-resistant patients with MDD [4–7,24]. In this economic evaluation, we have shown that rTMS is a cost-effective alternative to pharmacotherapy over 3 years. In general, patients with treatment-resistant MDD gain slightly more quality of life at a lower cost when treated with rTMS than with pharmacotherapies. The results of the analyses suggest that there is a low probability of antidepressant medications being cost-effective compared with rTMS at a willingness-to-pay level of AU $50,000 per QALY gain.

To date, rTMS therapy appears to have a high degree of safety and acceptability among patients and clinicians [25]. The magnetic pulse produces an audible high-frequency clicking sound, and ear protection (earplugs) is used during rTMS treatments. Common adverse events observed with rTMS are mild to moderate posttreatment headache and mild pain or discomfort at the treatment area. The most significant medical risk associated with the use of rTMS therapy is the inadvertent induction of a seizure. No seizures, however, were reported in the clinical research trials of the NeuroStar rTMS Therapy System [25,26]. In postmarket use, the prevalence of seizure with the NeuroStar rTMS Therapy System, under recommended operating conditions, is estimated to be less than 0.1% per patient and lower than what is typically seen with routine antidepressant medications. There has also been no evidence of emergent suicidal ideation during acute treatment with the NeuroStar rTMS Therapy System.

In the time of fiscal challenge and rising burden of mental illness, this cost-effectiveness evidence is timely and useful for both policymakers and service providers in resource allocation. Incorporating rTMS into the standard treatment algorithm for MDD expands the choice set available for patients, especially for those who develop intolerance to and/or fail pharmacotherapies. rTMS can also replace ECT in a subgroup of patients without psychotic symptoms or acute risks who are traditionally referred for ECT. As a substitution therapy, rTMS will be a cost-saving device for government budgets if more treatment-resistant patients with MDD switch from antidepressant medication and/or ECT to rTMS. That is, subsidizing rTMS is potentially an efficiency-improvement strategy for the health system.

The findings from our model are consistent with conclusions from the Simpson et al. [9] study despite significant differences in modeling approaches. Simpson et al. used a Markov cohort model to compare rTMS with sham and pharmacotherapies under open-label conditions and for patients who were exposed to at least one but no more than four antidepressant medications. Based on the data derived from the published STAR*D study [17] and on a multicentre randomized controlled trial [21], the study found that rTMS provided a net cost saving of US $1123 per QALY gained compared with the current antidepressant medication therapies [9]. Although our model relies on the same STAR*D study for the clinical efficacy of pharmacotherapies (in patients with TRD), the efficacy for rTMS was derived from a large meta-analysis rather than one single study. This might better reflect the effectiveness of rTMS in practice. In addition, Simpson et al.'s model did not take into account the subsequent and rescue treatments (i.e., ECT, augmentation, and hospitalization) when patients failed either rTMS or standard pharmacotherapies. Our model closely mimics this pathway and thus better reflects the treatment algorithm for MDD in "real" practice.

Table 3 – Summary of sensitivity analysis results (2013–2014 AUD).

Variables	Antidepressants		rTMS		Cost-effectiveness results of rTMS vs. antidepressants
	Cost ($)	QALY	Cost ($)	QALY	
Utilities					
Univariate	28,921–28,947	1.19–1.23	28,434–28,466	1.23–1.30	Dominant = 100%
Multivariate (all utility values)	28,911	1.16	28,431	1.24	Dominant = 97%; ICER < 50,000 = 3%
Transition probabilities					
Gaining remission after treated with antidepressant	29,145	1.19	28,518	1.27	ICER > 50,000 = 10%; Dominated = 1%
Losing remission without rTMS maintenance	28,923	1.19	28,483	1.27	ICER > 50,000 = 7%
Losing remission after treated with antidepressant	28,577	1.20	28,441	1.27	ICER > 50,000 = 13%; Dominated = 7%
Other transition probabilities (univariate)	28,833–29,400	1.19	28,388–28,951	1.26–1.27	Dominant = 60%–100%; ICER < 50,000 = 0%–40%
Multivariate (all probabilities)	31,103	1.18	30,423	1.25	Dominant = 57%; ICER < 50,000 = 34%; Dominated = 9%
Costs					
rTMS dose for acute treatment	28,917	1.19	28,418	1.27	Dominant = 98%; ICER < 50,000 = 2%
rTMS cost per session	28,937	1.19	28,491	1.27	Dominant = 67%; ICER < 50,000 = 33%
ECT dose	28,876	1.19	28,400	1.27	Dominant = 97%; ICER < 50,000 = 3%
ECT cost per session	28,945	1.19	28,457	1.27	Dominant = 89%; ICER < 50,000 11%
Augmentation (including lithium, atypical antipsychotic drugs)	28,976	1.19	28,489	1.27	Dominant 100%
Other cost variables	28,919–28,945	1.19	28,437–28,459	1.27	Dominant = 100%
Multivariate (all cost variables)	28,915	1.19	28,452	1.27	Dominant = 71%; ICER < 50,000 = 29%
All variables (1,000 simulations with 50,000 trials each)	30,528	1.20	30,071	1.27	Dominant = 56%; ICER < 50,000 = 15%; ICER > 50,000 = 17%; Dominated = 12%

AUD, Australian dollar; ECT, electroconvulsive therapy; ICER, incremental cost-effectiveness ratio; rTMS, repetitive transcranial magnetic stimulation.

We did not consider psychotherapies in this model because of a lack of clinical evidence of rTMS versus psychotherapy (both efficacy and safety). Psychotherapies for patients with TRD currently do not show definitive benefits to warrant their use as a comparator for these difficult-to-treat patients. In addition, no clinical studies have directly compared the efficacy of rTMS treatment to any form of psychotherapy. There are also no high-quality studies comparing psychotherapies to pharmacotherapy or rTMS or placebo that are relevant for this article, that is, those who failed to respond to two previous medication treatments. Although an assessment of effectiveness or safety between psychotherapy and rTMS is not possible within the scope of this research, this option cannot be ruled out as being potentially beneficial to some patients.

Despite using the best available evidence to use in the model, a number of assumptions were necessary. First, we have made various assumptions in the decrements of efficacy for subsequent courses of the same treatment. We also calculated the probabilities of losing remission from relapse rates (for the respective treatments) under an assumption that the rate of losing remission is constant over time. Second, utility weights were all sourced from the literature on patients with depression and may be different to the modeled population (i.e. treatment-resistant patients). Third, some cost estimates relied on expert advice, which might not fully represent those of all clinicians in current practice. The sensitivity analyses, however, showed that the effect of the above assumptions was small, and, if present, there was approximately 10% chance that antidepressants were a cost-effective treatment compared with rTMS. Finally, our analyses took an Australian perspective with the use of Australian-specific costs, utilities, and background mortality. Generalizability to other countries may be in question, but we believe that the relativities of the unit costs for the different treatments would likely be similar across jurisdictions.

Conclusions

The study shows that rTMS is a cost-effective treatment alternative for patients with MDD who have failed at least two adequate courses of antidepressant medications. This result supports providers in deciding to subsidize rTMS to increase the diversity of treatment options. This finding also has wider implications in relation of improving cost efficiency within the health system.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2015.04.004 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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