Cost-effectiveness of repetitive transcranial magnetic stimulation versus antidepressant therapy for treatment-resistant depression

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ABSTRACT [FIRST-LEVEL HEADER]

Objective: Repetitive Transcranial Magnetic Stimulation (rTMS) therapy is a clinically safe, non-invasive, non-systemic treatment for major depressive disorder. 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 three-year Markov microsimulation model with two-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 was higher than that for antidepressant medications (1.25 vs. 1.18 QALYs) while costs were slightly less (AUD 31,003 vs. AUD 31,190). In the Australian context at the willingness-to-pay threshold of AUD 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.

Conclusion: While both pharmacotherapy and rTMS are clinically effective treatments for major depressive disorder, rTMS is shown to out-perform antidepressants in terms of cost-effectiveness for patients who have failed at least two adequate courses of antidepressant medications.

INTRODUCTION [FIRST-LEVEL HEADER]

Major depressive disorder (MDD) is a significant burden to many health care systems. It is a chronic and debilitating disease, and significantly decreases quality of life (1, 2). It is one of the most common of all psychiatric disorders and ranks among the leading cause of disability worldwide (3). While many patients with depression respond to first-line medication and psychotherapy treatments, an estimated 20-40% of patients are unable to tolerate pharmacotherapy or do not benefit from them 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 specialised 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 contribute to a disproportionately high burden of illness compared with patients who respond to treatment; they are twice as likely to be hospitalised and have higher treatment costs (2).

Repetitive transcranial magnetic stimulation (rTMS) therapy is a non-invasive, non-systemic therapeutic device offering treatment that uses pulsed, magnetic fields at magnetic resonance imaging strength, to induce an electric current in a localised region of the cerebral cortex. During the rTMS session, the patient is conscious and there is no requirement for anaesthetic 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 four to six weeks. Following each session, patients may continue with their daily work or other routines. rTMS produces a clinical benefit without the systemic side-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 withdrawing from drugs or alcohol, or who have drug or alcohol dependence (5).

Clinical practice guidelines stipulate that current options for treatment resistant depression (TRD) are antidepressant medications, rTMS and electroconvulsive therapy (ECT). In dozens of small trials, however, rTMS has only been compared with ECT mostly because they are both classified as physical therapies. ECT, however, is commonly used in emergency settings for psychotic patients while rTMS is indicated for a wider range of mild to severe MDD. Additionally, many MDD patients are unable to tolerate the side-effects of ECT or refuse to have ECT because of the associated stigma or fear about

potential side-effects (e.g., cognitive impairment). As such, it has been suggested that ECT is a complementary, rather than a replaceable treatment for rTMS and standard pharmacotherapies (8).

Simpson et al., 2009 is the only study that compared pharmacotherapies to rTMS in the treatment of MDD (9). It concluded that rTMS provided a net cost saving compared with antidepressant medications (9). Two studies compared rTMS with electroconvulsive therapy (ECT) and arrived at different conclusions (10, 11). Kozel et al., 2004 (US-based) suggested that rTMS would be a cost-effective treatment MDD patients compared to the ECT alone over 12 months while Knapp et al., 2008 (UK-based) found that rTMS has a very low probability of being a cost-effective alternative to ECT over 6 months (10, 11).

Due to 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 treatment-resistant depression 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 with those short-term findings from Simpson et al., 2009 (9).

METHODS [FIRST-LEVEL HEADER]

OVERVIEW [SECOND-LEVEL HEADER]

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 three years. The study population were 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 [SECOND-LEVEL HEADER]

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 is prescribed for MDD patients depending on prior 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 hospitalisations were available for those who failed the two main treatments.

MODEL STRUCTURE [SECOND-LEVEL HEADER]

A Markov microsimulation model was constructed and analysed in TreeAge Pro 2014 software. The model duration was three years with two-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 Fig. 1). The MDD health states were based on the Hamilton Depression Rating Scale 17 (HAM-D 17) which is one of the most widely-used and accepted measures for severity of depression symptoms. In the absence of long-term clinical data, the duration of three 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 hospitalisation), and the probability of having adverse events during treatment.

DATA INPUTS AND SOURCES [SECOND-LEVEL HEADER]

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 [SECOND-LEVEL HEADER]

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 bi-frontal) (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 (File 1 in Supplemental Materials at: XXX). 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 side 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 developed 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 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. Lastly, 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 [Second-level Header]

Costs related to all health care resource items for the economic model are summarised in Table 1. All costs were converted to monthly values to accommodate the two-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 AUD150 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 four to six weeks. Patients who respond positively to treatment (i.e. observed reduction in HAM-D 17) will proceed to rTMS maintenance until potential relapse or drop-out. 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 three 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 AUD 17.30, equivalent to AUD 52 per three-month (acute) treatment course. If a patient's condition improved to full remission, further medication was not required unless they later relapsed.

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 two-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 hospitalisations and individual adverse events were identified by Sullivan et al. 2004 (22) and valued using Australian national cost schedules (Table 1).

HEALTH STATE UTILITY VALUES [SECOND-LEVEL HEADER]

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., 2009's estimates were used for the model base case (23) 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., 2004 on the cost effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions in

the US (22). 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., 2004 (22).

Analyses [Second-level Header]

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, micro-simulations 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 while gamma distributions 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 AUD 50,000 per QALY was used to indicate cost-effective results.

Results [First-level Header]

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

Table 3 shows 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 were: 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 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 (five instead of three years), the average cost saving increased to $1,316 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 AUD 127 per QALY gained, well below a willingness-to-pay threshold of AUD 50,000.

DISCUSSION [FIRST-LEVEL HEADER]

A cost-effective treatment for treatment-resistant depressive patients is an important challenge today as 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 MDD patients (4-7, 24). In this economic evaluation, we have shown that rTMS is a cost-effective alternative to pharmacotherapy over three years. In general, patients with treatment-resistant MDD gain slightly more quality of life at a lower cost when treated with rTMS compared 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 AUD 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 post-treatment 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 post-market 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 policy makers 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 MDD patients switch from antidepressant medication and/or ECT to rTMS. That is, subsidising rTMS is potentially an efficiency-improvement strategy for the health system.

The findings from our model are consistent with the conclusions by Simpson *et al.,* 2009 study despite significant differences in modelling approaches (9). Simpson et al*.,* 2009 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$1,123 per QALY gained compared with the current antidepressant medication therapies (9). While 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. Additionally, Simpson et al*.,* 2009's model did not take into account the subsequent and rescue treatments (i.e. ECT, augmentation and hospitalisation) 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.

We did not consider psychotherapies in this model due to 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. Additionally, 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 paper, 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 modelled 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 ~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.

CONCLUSION [FIRST-LEVEL HEADER]

The study shows that rTMS is a cost-effective treatment alternative for patients with major depressive disorder who have failed at least two adequate courses of antidepressant medications. This result supports providers in deciding to subsidise 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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TABLE 1: SUMMARY OF VARIABLES USED IN THE ECONOMIC MODEL

Description	Base case	Distribution	Low	High	Sources and assumptions
Transition probabilities					
rTMS					
Remission: 1st treatment	21.5%	Beta	19.7%	31.2%	Meta-analysis (Supplementary File 1)
Response: 1st treatment	37.5%	Beta	33.2%	48.7%	Meta-analysis (Supplementary File 1)
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: 1st treatment	13.6%	Beta	13.0%	36.8%	(17, 18)
Response: 1st 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: 1st treatment	46.3%	Beta	20.0%	70.0%	Meta-analysis (Supplementary File 1)
Response: 1st treatment	60.9%	Beta	40.0%	80.0%	Meta-analysis (Supplementary File 1)
Lose remission	22.3%	Beta	15.0%	35.0%	(20)
For all treatment arms					
Hospitalisation	10.4%	Beta	8.0%	12.0%	Calculated from literature
Gaining REM after hospitalisation	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%	(21)
Health utilities					
Remission (HAMD17 < 8)	0.860	Beta	0.750	0.900	(22, 23)
Partial remission (mild-moderate 8<=HAMD17 <20)	0.710	Beta	0.650	0.820	(22, 23)
No response (severe-very severe HAMD17>=20)	0.520	Beta	0.250	0.580	(22, 23)
Disutility for AntiDep 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
Hospitalisation (severe-very severe with suicidal risk HAMD17>=20)	0.300	Beta	0.090	0.400	(22, 23)
Resources and cost components (2013/14 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
Hospitalisation					
Average cost per hospitalisation	$14,021	Gamma	$13,106	$20,484	AR-DRG v.6
Adverse events					
Antidepressant	$80.95	Gamma	$64.76	$97.14	Calculation ± 20%
rTMS	$81.79	Gamma	$65.43	$98.15	Calculation ± 20%
ECT	$72.53	Gamma	$58.03	$87.04	Calculation ± 20%

** The expert was a University Professor in Psychiatry and a practising physician, and had no conflicts of interest to declare.*

TABLE 2: COSTS, EFFECTS, COST-EFFECTIVENESS RATIOS AND NET MONETARY BENEFIT (2013/14 AUD)

Mean values	3 years (Base case)		5 years (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**

TABLE 3: SUMMARY OF SENSITIVITY ANALYSIS RESULTS (2013/14 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%