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Cost-effectiveness analysis of deep transcranial magnetic stimulation relative to evidence-based strategies for treatment-refractory obsessive-compulsive disorder

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ABSTRACT

Objective: This study examined the cost-effectiveness of deep transcranial magnetic stimulation (dTMS) for treatment refractory obsessive-compulsive disorder (OCD) relative to other established treatment options, including antidepressant medication (ADM), ADM + antipsychotic augmentation, real-world cognitive-behavioral therapy (ADM + CBT Effectiveness), clinical trial CBT (ADM + CBT), intensive outpatient program (IOP), partial hospitalization program (PHP), and PHP to IOP stepdown.

Methods: A decision analytic model was developed to evaluate the cost-effectiveness of dTMS relative to other established treatment alternatives for adults (18–64 years old) with refractory OCD. Building on Gregory et al. (2018), the model was parameterized with probabilistic and deterministic parameters from the literature and an outcomes database to perform a Monte Carlo simulation of a hypothetical cohort of 100,000 adults with OCD to estimate costs, and incremental cost-effectiveness ratio (ICER) for dTMS relative to each treatment strategy. Encounters took place from 2012 to 2015. Data for dTMS were taken from a recent multisite study.

Results: Although dTMS fit between ADM and ADM + CBT in overall costs, ADM + CBT had the lowest ICER and thus would be chosen before dTMS. dTMS was determined to be more cost effective relative to PHP/IOP step-down, PHP, and IOP.

Conclusion: dTMS is cost-effective, along the treatment continuum from outpatient medication management and CBT to more intensive, facilities-based approaches, and may be an incremental strategy to employ when higher intensity strategies are either not available, not financially feasible, or whilst on extended waits for admission to these higher levels of care.

Obsessive-compulsive disorder (OCD) affects ~1.2% of individuals each year and confers significant impairment (Markarian et al., 2010; Ruscio et al., 2010). Cognitive-behavioral therapy with exposure and response prevention (CBT) and serotonin reuptake inhibitors (SRIs) are established interventions (Pigott and Seay, 1999). Approximately 40–60% of adults respond to SRIs; CBT response rates range from 70 to 85% (Fineberg and Gale, 2005; Öst et al., 2015). However, partial- and non-response is common, resulting in a sizable number of treatment refractory individuals (Fineberg and Gale, 2005). While operational definitions vary, treatment refractory status is characterized by sustained symptomology measured on the Yale-Brown Obsessive--Compulsive Scale following adequate treatment with first-line medications, high fidelity CBT, and augmentation with atypical antipsychotic medication (Kühne et al., 2020; Pallanti et al., 2002; Pallanti and Quercioli, 2006).

After incomplete response to first-line treatments, there are several augmentation strategies with varying levels of support including antipsychotic augmentation of SRI, adding CBT to an established pharmacotherapy regimen, adding pharmacotherapy to CBT, or specialized OCD intensive treatment programs. Until recently, however, there was little guidance about which option to choose from among these. Gregory et al. assessed the cost-effectiveness of seven treatment strategies for treatment-refractory adult OCD (Gregory et al., 2018). Partial hospitalization in an OCD specialty program (PHP) with step-down to an intensive outpatient treatment program (IOP) was the most cost-effective strategy followed by participation in high fidelity

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outpatient CBT and antidepressant treatment, IOP treatment, and PHP treatment, which were not different from one another, but significantly outperformed antidepressant monotherapy and antipsychotic augmentation. These findings were generally replicated among children with treatment refractory OCD with IOP treatment being the most cost-effective strategy followed by PHP treatment and high-fidelity outpatient CBT and antidepressant treatment (Gregory et al., 2020). Importantly, these data provide guidance about the utility of various treatment approaches following incomplete response to first-line interventions.

Deep transcranial magnetic stimulation (dTMS) has emerged as an intervention for individuals with treatment refractory OCD (Carmi et al., 2019). dTMS uses the H-coil (versus a figure- 8 coil), which stimulates 3–5 cm deep and larger volumes relative to standard TMS (Lu and Ueno, 2017). In a recent multisite randomized controlled trial, dTMS demonstrated superiority relative to sham stimulation among 99 treatment-resistant OCD patients (age 22–68) (Carmi et al., 2019). Participants were randomized to either high-frequency (20 Hz) or sham dTMS over six weeks of daily treatment paired with individualized symptom provocation. dTMS was associated with significantly greater improvements in OCD symptomology versus sham treatment at post-treatment (d = 0.69), and 4-weeks follow-up (Carmi et al., 2019). Efficacy of dTMS for OCD in naturalistic practice has been supported (Roth et al., 2021).

dTMS provides an additional intervention option for adults with treatment refractory OCD but the cost-effectiveness of this approach relative to others is unclear making it difficult to determine at what point in the continuum of care this intervention should be utilized and covered by third party payers. Accordingly, we sought to update Gregory et al. by examining the cost-effectiveness of dTMS relative to other intervention strategies for treatment-refractory OCD (Gregory et al., 2018). Current evidence suggests that more intensive CBT, ideally with a step-down from a PHP to IOP, is the most cost-effective approach for individuals with treatment-refractory OCD. Yet, there has been no consideration of how dTMS may factor into this continuum, which has clear implications for understanding at what point clinicians and insurers should recommend and cover this intervention.

1. Method

The aim of this study was to add a new treatment strategy for treatment-refractory OCD in adults (i.e., dTMS), with previously unavailable data, to advance work estimating cost-effectiveness for this disease. We combined two former approaches: (1) denominating the analysis in terms of dollars per unit change in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) for each treatment strategy, and (2) evaluating cost-effectiveness for the 12 months inclusive of the treatment episode (Goodman et al., 1989; Gregory et al., 2018, 2020). While denominating and report results as dollars per Quality-Adjusted Life Year (QALY) and including costs and benefits across the life span was desired, the lack of these parameters for all treatment strategies prohibited this approach. In light of this limitation, the work does deliver important data for clinicians, policymakers, and patients to consider when developing their treatment strategies and making such choices in community. The additional treatment strategy, dTMS, was added to those evaluated in Gregory et al. for adults, and denominated as dollars per unit change in Y-BOCS, following similar work with pediatric treatment strategies (Gregory et al., 2018, 2020). These analyses were developed and executed using standards for decision analytic models, and generally accepted cost-effectiveness techniques, in accordance with CHEERS good practice guidelines for cost-effectiveness analyses (Drummond et al., 2015; Gold et al., 1996; Hunink et al., 2001; Husereau et al., 2013).

The model included parameters (Table 1) from previously published trials and studies, and an outcomes database, maintained by a specialty center providing intensive intervention for treatment-refractory OCD (Brown et al., 2007; Carmi et al., 2019; Gregory et al., 2018; Simpson et al., 2006, 2013; Tundo et al., 2007). The ADM + CBT arm represented clinical trials outcomes when treatment was conducted by expert clinical centers with intensive fidelity checks. The ADM + CBT Effectiveness arm represented an estimate of 'real-world' naturalistic CBT when applied following medication non-response (Tundo et al., 2007). Several parameters, including health utilities, relapse rate and excess mortality associated with OCD, were unavailable in the literature, and thus unable to be incorporated into the model. Specifically, the paucity of evidence

Table 1
Model parameters.

Category	Parameter	Value	SD	Distribution	Source	Study Type
Starting Values	Y-BOCS at Presentation	29.22	7.77	Normal		Outcomes Database
	Q-LESQ at Presentation	0.45	0.17	Normal		Outcomes Database
Effectiveness (Change in Y-BOCS)	Antidepressant Medication (ADM)	2.6	1.484	Normal	[20,21]	Trial
	ADM + Antipsychotic	3.5	1.698	Normal	[20]	Trial
	ADM + CBT	11.2	1.147	Normal	[20,21]	Trial
	ADM + CBT Effectiveness	5.3	0.663	Normal	[22]	Trial
	Intensive Outpatient (IOP)	8.7	6.90	Normal		Outcomes Database
	Partial Hospitalization (PHP)	9.6	6.70	Normal		Outcomes Database
	PHP to IOP	10.9	6.52	Normal		Outcomes Database
	dTMS	6.5	0.733	Normal	[11]	Trial
Costs (2015$)	Antidepressant Medication (ADM) (Annual)	$1576	1173.93	Gamma	[23]	Cost
	ADM + Antipsychotic	$5000		Uniform		
	ADM + CBT Effectiveness	$9540	4388.23	Gamma	[23]	Cost
	ADM + CBT	$11,609	$149.65	Gamma	[22,23]	Author calculations
	Intensive Outpatient (IOP)	$11,744	$9276	Gamma		Outcomes Database
	Partial Hospitalization (PHP)	$14,562	$11,039	Gamma		Outcomes Database
	PHP to IOP	$29,386	$16,638	Gamma		Outcomes Database
	dTMS	$8000	–	–	[11]	Trial
Transition Probabilities	Well →Dead				[30]	U.S. Life Tables
Other	Age	30.51	12.28	Normal		Outcomes Database
	Gender (Female)	0.51	0	Bernoulli		Outcomes Database

Note. Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; Q-LESQ = Quality of Life Enjoyment and Satisfaction Questionnaire; ADM = Antidepressant medication; CBT = Cognitive behavioral therapy; IOP = Intensive Outpatient Program; PHP = Partial Hospitalization Program; dTMS = Deep Transcranial Magnetic Stimulation.

regarding benefits of treatment beyond the initial treatment year limited the analysis 1 year, inclusive of the treatment period, thereby not accounting for possibilities for relapse and changes in subclinical symptomology, and the reemergence of disease in youth, and eventually adulthood for pediatric patients suffering from OCD and receiving any of these therapies. Thus, the model assumed a one-year period of disutility for OCD, during which hypothetical individuals received treatment. Similar to earlier approaches, this model was developed from the payer perspective in the United States, evaluated using Willingness to Pay (WTP) thresholds of $50,000 and $100,000, and constructed commensurate with published analytical and reporting standards (Drummond et al., 2015; Gold et al., 1996; Husereau et al., 2013).

An outcomes database, containing data for treatment effectiveness, quality of life assessments and incurred costs for treatment episodes, for IOP, and PHP, was used to parameterize those treatment strategies (Kay et al., 2016; Storch et al., 2007, 2010). The database, overseen by Rogers Memorial Hospital, contained a total of 819 care episodes between 2012 and 2015, and financial data. Within these data assessments were administered at admission, discharge, and 12-months post-discharge. We estimated distributions for treatment effects, effectiveness, and net reimbursement costs for IOP and PHP treatment strategies.

To estimate cost-effectiveness parameters, we employed an updated decision analytic model to perform a Monte Carlo (MC) simulation of a hypothetical cohort of 100,000 adults with treatment-refractory OCD to estimate costs, effectiveness, and incremental cost-effectiveness ratio (ICER) for each treatment strategy, incorporating both probabilistic and deterministic parameters (Table 1) (Hunink et al., 2001). This cost-effectiveness approach instruments a counterfactual, wherein each simulated individual passes through each treatment strategy and accumulates costs and benefits resulting from each treatment strategy. Then the outcomes (costs and benefits) of each strategy are compared for each simulated individual. The heterogeneity in severity is accounted for in the model, where each of the 100 K draws in the MC simulation have a different starting Y-BOCS (e.g., severity) and each simulated draw results in a unique draw from the treatment and cost distribution for each simulated individual. Each simulated individual has a value of costs and effectiveness for each treatment strategy, and those are used to compute the estimated mean and standard deviation for each of the resulting treatment strategies.

Probabilistic parameters are those where distributional information was available, which allowed the model to draw unique parameters for each of the microsimulation passes (100,000 unique patients), thereby varying the parameters for each hypothetical individual and adding important variance to the parameters. Deterministic parameters were ones in which no distributional data was available, and essentially each simulation draw contained the same value for that parameter, limiting the variation in the model from that parameter. Probabilistic parameters are preferred and allow for incorporation of more variation in the underlying parameter in the model results, thus providing more confidence that the model resembles real world applications wherein individuals would have unique variation in their parameters.

Change in the Y-BOCS was the primary clinical outcome measure and the remission threshold was indicated as a post-treatment value ≤ 14 (Lewin et al., 2011). The threshold of 14 was employed because (1) a higher threshold is more conservative given the high severity of disease among treatment-refractory populations, and (2) to maintain consistency and comparability with previously published work on CEA among treatment-refractory adults (Gregory et al., 2018).

Total direct or reimbursement costs for the 12-months inclusive of the intervention were used to determine the costs of each treatment episode. These costs included costs for continuance of pharmacology beyond the initial course of therapy (~12 weeks), medication management, and any follow-up behavioral therapy. These costs are equivalent those reimbursed by payers (i.e. government, commercial insurance coverages or private pay in the United States). We adjusted for the payer mix reported in the Truven Marketscan database, to estimate direct costs faced by payers. Two treatment cost approaches were used, (1) costs for the seven trial-based strategies were estimated from the literature, as indicated in Table 1, and derived from the Truven Marketscan database (Truven), and (2) for IOP and PHP strategies, we analyzed encounter data from the specified outcomes database. These included net reimbursement costs for the IOP and PHP strategies, and were analogous to the definition of costs derived from analysis of Truven Marketscan data. These cost estimations aligned to the perspective of the analysis – that of a payor in the United States.

We used the outcomes database to estimate distributions for treatment effects and net reimbursement costs for PHP/IOP strategies. The database contained 819 care episodes (discharges) for PHP/IOP. The treatment effect was presumed to be normally distributed, and we parameterized a normal distribution used in the analyses by estimating the mean and standard deviation of those episode. Health care costs are distributed gamma, and the mean and standard deviation estimated from the outcomes database was loaded into TreeAge Pro, which includes a utility to estimate a gamma distribution using the mean and standard deviation of a sample (Greene, 2012; Manning and Mullahy, 2001). Once these distributions were parameterized, they were used, along with distributions for the other parameters and strategies to compute cost-effectiveness estimates. This approach follows previous work, namely Gregory et al. (Gregory et al., 2018, 2020)

The model, and all calculations, were implemented in Tree Age Pro (2020). The model calculates cost-effectiveness estimates for each strategy, and sorts them descending by cost, then effectiveness, in this case unit change in Y-BOCS. With cost-effectiveness results calculated, dominated strategies were eliminated and the surviving strategies were evaluated by ICER.

2. Results

Table 1 summarizes the key parameters used in the analysis. Cost effectiveness parameters as dollars per unit change in Y-BOCS, and carry this forward through the calculations of the ICER, to make conclusions about cost-effectiveness.

2.1. Net health benefits

Table 2 reports the results of the analysis, excluding those treatment arms that are "dominated", meaning that they lie inside of the cost-effectiveness frontier, and do not represent a rational (dollars per unit change in Y-BOCS) next choice in treatment. First, all treatment alternatives are ordered in increasing costs, then the incremental costs and incremental effectiveness are examined. Next, arms that are incrementally more expensive, without the same slope, in terms of effectiveness, are excluded. Those that do not meet this threshold are excluded from the analysis.

dTMS, is more costly than ADM monotherapy, and incrementally more effective (3.9 units of Y-BOCS for $6425 additional dollars). The dTMS strategy fits in between ADM and ADM + CBT from a cost perspective; however, ADM + CBT has the lowest ICER, and therefore would be chosen before dTMS in terms of maximizing cost-effectiveness. Using an ICER logic exclusively, ADM + CBT would be chosen first, then progression to dTMS and ultimately PHP/IOP, forgoing ADM monotherapy. PHP/IOP is more effective than ADM + CBT, but at a much higher cost, namely incremental costs ($17,734) for an additional 1.3 units in incremental effectiveness. This varies from previous work in that PHP/IOP is much more cost-effective in terms of dollars per QALY, the metric used in Gregory et al. (2018). These results suggest an ordering of treatments in cost-effectiveness (ICER) as follows, ADM, ADM + CBT, dTMS and finally progression to PHP/IOP, excluding dominated strategies, those with greater costs and lower effectiveness. Results including dominated strategies are given below in Table 3 for use in comparing to previously reported work in this area.

Table 2
Cost-effectiveness results.

Strategy	Costs ($) Mean	Costs ($) SD	Incremental Costs ($)	Effectiveness Unit Change in Y-BOCS Mean	Effectiveness Unit Change in Y-BOCS SD	Incremental Effectiveness	Incremental Cost Effectiveness Ratio (ICER)
ADM	$1575	39.37		2.6	1.484		
ADM + Antipsychotic	$4994	5.33	$3420	3.5	1.698	1.1	3110
dTMS	$8000	–	$3006	6.5	0.733	3.0	1002
ADM + CBT	$11,610	149.65	$3610	11.2	1.147	4.7	768
PHP/IOP	$29,344	528.76	$17,734	10.9	6.52	1.3	13,641

Note. SD = Standard deviation; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; ICER = Incremental Cost Effectiveness Ratio; ADM = Antidepressant medication; CBT = Cognitive behavioral therapy; IOP = Intensive Outpatient Program; PHP = Partial Hospitalization Program; dTMS = Deep Transcranial Magnetic Stimulation.

Table 3
Cost-Effectiveness (including dominated strategies).

Strategy	Costs ($)	Costs ($) SD	Incremental Costs ($)	Effectiveness Unit Change in Y-BOCS (Mean)	Effectiveness Unit Change in Y-BOCS (SD)	Incremental Effectiveness	Incremental Cost Effectiveness Ratio (ICER)
ADM	$ 1575	39.37		2.6	1.484		
ADM + Antipsychotic	$ 4994	5.33	$ 3420	3.5	1.698	1.1	3110
dTMS	$ 8000	–	$ 4006	6.5	0.733	3.0	1335
[a]ADM + CBTEffectiveness	$ 9529	137.96	$ 4545	5.3	0.663	−1.2	–
ADM + CBT	$11,619	149.65	$ 2070	11.2	1.147	4.7	770
[a]IOP	$11,744	328.46	$ 125	8.7	6.90	−2.5	–
[a]PHP	$14,539	331.13	$ 2930	9.6	6.70	1.1	–
PHP/IOP	$29,344	528.76	$ 17,734	10.9	6.52	1.3	13,626

Note. SD = Standard deviation; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; ICER = Incremental Cost Effectiveness Ratio; ADM = Antidepressant medication; CBT = Cognitive behavioral therapy; IOP = Intensive Outpatient Program; PHP = Partial Hospitalization sProgram; dTMS = Deep Transcranial Magnetic Stimulation.
[a] Dominated strategies.

3. Discussion

Building on past cost-effectiveness analyses in adult OCD, this report contributes by indicating where dTMS falls on the treatment continuum for adults with treatment refractory OCD. Past results prior to the FDA clearance of dTMS indicate that specialized OCD intensive treatment (i.e., PHP with step-down to IOP treatment) was the most cost-effective strategy followed by participation in high fidelity outpatient CBT and antidepressant treatment, intensive outpatient treatment, and partial hospitalization treatment, which were not different from one another, but significantly outperformed antidepressant monotherapy and antipsychotic augmentation (Gregory et al., 2018). Reanalysis of Gregory et al. including dTMS indicate that dTMS outperformed antidepressant monotherapy and antipsychotic augmentation but was less cost-effective relative to high quality CBT provided either on an outpatient basis or intensively (Gregory et al., 2018).

There are important implications of these findings. Despite the robust effects of CBT, access and cost issues, including the limited number of specialty providers who accept commercial insurance, severely limits access. dTMS may provide a treatment alternative when high fidelity CBT is unavailable to augment pharmacotherapy, or an individual cannot relocate for more intensive intervention. Similarly, antipsychotic medications demonstrate modest efficacy together with high frequency of side effects including weight-gain and other metabolic issues (Allison et al., 1999; Allison and Casey, 2001; Kessler et al., 2005). In Carmi et al. patients had failed prior pharmacological and behavioral interventions; dTMS may provide an alternative to antipsychotic treatment that balances safety, efficacy, reduced physical health morbidities, and patient preference (Carmi et al., 2019). We were unable to incorporate excess morbidity associated with the sequela associated with pharmacotherapy, which may favor dTMS even further given the favorable associated side effect profile (Carmi et al., 2019; Roth et al., 2021).

Several limitations should be considered when interpreting these findings. First, cost effectiveness results were included from a broad array of studies characterized by differences in treatment history, period of time sampled, and OCD symptom severity. For example, there may be differences in clinical severity between individuals who participated in clinical trials versus receiving naturalistic intensive treatment. Alternatively, estimates from naturalistic open-label treatment may be greater than those from clinical research studies given the flexibility in treatment of the former (e.g., duration, conconmitment interventions). Second, we were unable to include additional adjustments for health status for individuals receiving antipsychotic treatments, which have documented weight-gain and other metabolic issues (Allison et al., 1999; Allison and Casey, 2001; Kessler et al., 2005). On balance, some of the individuals across clinical trials and higher levels of care would be on conjoint antipsychotic treatment thereby balancing out additional effects. Third, we only had short-term estimates for cost and treatment response, and could not parameterize estimates over longer durations. Fourth, we sourced cost estimates from a variety of sources. Rates within the specialty IOP/PHP programs likely reflected proportionally higher rates than cost estimates derived from Truven, which reflected non-specialty care; this may result in cost effectiveness estimates being biased against the speciality IOP/PHP programs. Fifth, published data examining real-world effectiveness of CBT (relative to that provided in clinical trials) may represent lower estimates of potential effects. Sixth, data on age, race/ethnicity, and other potentially important demographic variables were not consistently available for analysis (Tundo et al., 2007). Finally, the outcomes database relied on consensus diagnostic procedures (versus through structured interviews) and used self-reported Y-BOCS versus the clinician-rated Y-BOCS used in research

studies (Carmi et al., 2019; Simpson et al., 2006, 2013; Tundo et al., 2007).

Within these limitations, this report contributes by evaluating where dTMS should fall on the treatment continuum for adults with intervention refractory OCD. Our results suggest that dTMS is cost-effective, along the treatment trajectory from outpatient medication management and CBT to more intensive, facilities-based approaches, and may afford an incremental strategy to employ when higher intensity strategies are either not available, not financially feasible, or whilst on extended waits for admission to these higher levels of care. In this latter scenario, dTMS may be appropriate for those with significant obsessive-compulsive symptomology to potentially receive benefit while they wait. Future studies should incorporate robust naturalistic data into dTMS estimates to confirm placement on the treatment continuum.

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Author statement

Dr. Gregory was responsible for conceptualizing the project/paper, drafting the manuscript, data analysis, and critical review/revision of the manuscript.

Dr. Goodman was responsible for conceptualizing the project/paper, drafting the manuscript, and critical review/revision of the manuscript.

Dr. Kay was responsible for conceptualizing the project/paper, data analysis, and critical review/revision of the manuscript.

Dr. Riemann was responsible for conceptualizing the project/paper, and critical review/revision of the manuscript.

Dr. Storch was responsible for conceptualizing the project/paper, drafting the manuscript, and critical review/revision of the manuscript.

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