

# Comparison between neurostimulation techniques repetitive transcranial magnetic stimulation vs electroconvulsive therapy for the treatment of resistant depression: patient preference and cost-effectiveness

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**Objectives:** Major depressive disorder (MDD) is a common disorder, widely distributed in the population, and is often associated with severe symptoms and functional impairment. It has been estimated that 30% of MDD patients do not benefit adequately from therapeutic interventions, including pharmacotherapy and psychotherapy. Treatment-resistant depression (TRD) is generally defined as a failure to achieve remission, despite therapeutic interventions.

**Aim:** The most effective treatment alternatives for TRD are hospitalization, electroconvulsive therapy (ECT), and transcranial magnetic stimulation (TMS). Here we compared the clinical effectiveness of ECT and TMS, including success rates, patient responses, side-effect profiles, and financial worthiness.

**Results:** We found that ECT ( $P < 0.0001$ ) was more effective than TMS ( $P < 0.012$ ) (not statistically significant in group effect) in TRD patients. However, ECT patients reported a higher percentage of side effects ( $P < 0.01$ ) and the TMS treatment scored better in terms of patient preference. The cost benefit of ECT was higher than that of TMS (US\$2075 vs US\$814). Patient's preferences for treatment could be more intense in the TMS, if the TMS is included in the Health Maintenance Organization's service list.

**Conclusion:** We propose that both of these treatment options should be available in psychiatric wards, thus expanding the therapeutic toolkit for TRD.

**Keywords:** ECT, TMS, treatment-resistant depression, cost benefit, patient preference

## Introduction

Depression is a common mental disorder, occurring in every decade of life and in all communities of the world.<sup>1-3</sup> Previous Global Burden of Disease (GBD) studies conducted from 1990 to 2010 brought attention to depressive disorders as a leading cause of economic burden. In the 2010 GBD study, depressive disorders were the second most common cause of "years lived with disabilities" (YLDs). Major depressive disorder (MDD) accounted for 8.2% and dysthymia for 1.4% of global YLDs. Depressive disorders were also identified as a major cause of "disability-adjusted life years" (DALYs), with MDD and dysthymia accounting for 2.5% and 0.5% of global DALYs, respectively.<sup>2,3</sup>

Depression can be successfully treated with antidepressant medications and psychotherapy, either alone or in combination. A majority of, but not all, patients

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respond well to these treatments.<sup>1,4,5</sup> Treatment-resistant depression (TRD) is defined as a failure to achieve remission, despite therapeutic interventions. About 30% of depressed patients do not achieve remission after two to four different antidepressant trials, with or without psychological treatment approaches. The three most common clinical treatment approaches in TRD are as follows:<sup>4,5</sup> 1) Patient hospitalization in a day-care unit or psychiatry ward. The average hospitalization time for TRD is 60 days. During this period, the patient receives more intense medications and various forms of psychotherapy. However, hospitalization affects the normal life of the patients, causes difficulties with their circle of life, and can become stigmatic for the patients. All Israeli citizens are mandatorily insured by one of the four insurance companies (Health Maintenance Organizations [HMOs]), according to the Israeli equal health to citizen's plan (1995 law). Thus, the HMOs are responsible for meeting the cost of hospitalizations. The daily payment for hospitalization is set according to the Ministry of Health tariffs. For HMOs per patient, the average expenses arising from hospitalization in a psychiatric ward are greater than 50,000 shekels (US\$12,988), excluding any indirect costs of hospitalization (eg, absence from work and full payment due to medical vacation); 2) Electroconvulsive treatment (ECT) has been an acceptable practice in psychiatry for more than 80 years.<sup>6</sup> Today, ECT is considered acceptable, especially in cases of MDD, and its efficacy and safety are based on well-established clinical experience and research.<sup>6,7</sup> ECT has historically been used to treat depressed patients and this remains the most effective treatment for TRD. However, ECT also benefits patients suffering from hostility, anxiety, and agitation.<sup>8</sup> Each session of ECT costs the HMO up to 1,226 shekels (\$318) and patients receive 8–12 sessions during treatment; 3) Repetitive transcranial magnetic stimulation (rTMS) has been proposed as an alternative treatment method.<sup>9</sup> During rTMS, a rapidly changing electrical current creates a time-varying magnetic field, which passes unimpeded through the hair, scalp, and skull, entering the cortex, where it induces an electrical field that changes the neuronal activity at the site of stimulation and at related neuronal networks. A large number of 3–6-week long, randomized controlled studies have examined the antidepressant properties of rTMS applied over the left dorsolateral prefrontal cortex (LDLPFC).<sup>10,13</sup> Although, the antidepressant properties of the prefrontal rTMS have been clearly demonstrated in patients who did not respond to antidepressant medication in depressive episodes, the response rates in these sham-controlled trials were from modest to moderate.<sup>10,13</sup>

## Study design and theoretical background

Hospitalization, transcranial magnetic stimulation (TMS), and ECT are clinically accepted treatment approaches for resistant depression. We chose not to include the hospitalization arm in our study. This decision was made because of its high cost (direct and indirect costs), as well as the negative effect of hospitalization on routine life. Thus, we compared the effectiveness, patient's preferences, and the associated side effects of ECT and TMS. We also compared the economics involved in these two procedures.

Thus, this study compared the clinical effectiveness of ECT and TMS in order to calculate and compare their success rates, patient responses, side-effect profiles, and financial worthiness, as well as patient's preference.

## Methods and materials

### Subjects

#### TMS sample

Forty-one eligible subjects were included, consisting of depressed outpatients, aged between 18 and 68 years, with a DSM-IV diagnosis of MDD (recurrent episodes). The duration of the current episode was at least 3 months but not more than 5 years. Subjects were required to have a total score of at least 20 on the 21-item Hamilton Depression Rating Scale (HDRS-21) at the screening visit. Subjects were required to have failed at least two adequate antidepressant treatments or to have displayed intolerance to two different antidepressants during a previous depressive episode.

#### ECT sample

Forty ECT patients were referred by their clinician for ECT treatment, due to resistance to the current treatment regime (equal criteria for ECT patients). All patients underwent a physical workout, which included blood tests, neurological and physical examinations, electrocardiogram (ECG), and chest X-ray. Patients signed a consent form to receive ECT treatment. Physicians treating the ECT patients performed a physical examination and an ECG, and a specialist consultation was made every 6 months during the internal medicine-anesthesiologist renewed consultation.

## Overview of study

This was a retrospective medical record review of 81 consecutive patients with treatment-resistant MDD who had received ECT or rTMS. The demographic characteristics of the patients, hospitalization history, the legal status of hospitalization, psychiatric diagnoses and medical

co-morbidities, the reason for ECT–TMS, the treatment regimen, overall duration of ECT–TMS, previous pharmacological therapy, response to ECT or rTMS, and any side effects (including cognitive impairment) were collected from the ECT unit files. Information was also received from the medical staff involved in the treatment.

The severity of the patients' psychopathology pre- and post-ECT–TMS was assessed using a questionnaire. The pre- and posttreatment depression levels of the patients were measured with the HDRS-21<sup>14</sup> (completed by the physician/medical staff), Beck Depression Inventory (BDI-II)<sup>15</sup> (completed by the patient), and Hamilton Anxiety Rating Scale (HARS)<sup>16</sup> (completed by the physician/medical staff). The level of functioning pre- and posttreatment was evaluated using a Visual Analog Scale (VAS)<sup>17</sup> (completed by the physician/medical staff).

Local, Beer Yaakov-Ness Zionah Mental Health Center, Institutional Review Board approval was obtained for the collection and analysis of the treatment data. ECT and rTMS treatments received Ministry of Health approval. We deleted any details from the data that may personally identify the patients.

Patients were recruited by referrals from a treating physician in outpatient clinics and private practice clinics from all over Israel. All subjects signed an informed consent document before undergoing the ECT and rTMS procedures.

## rTMS

Magstim UK (Sheffield, UK) rapid equipment was used for the rTMS treatment.<sup>10,13</sup> The motor threshold (MT) over the left motor cortex (the area controlling the abductor *pollicis brevis* [APB]) was determined by the electromyography (EMG) method, which looks for the lowest machine power output that would provide an motor evoke potential (MEP) of at least 50 mV in five of ten stimulations. The MT was determined daily in all cases. Stimulations were given at 120% MT with continuous EMG monitoring. rTMS was administered over the LDLPFC.<sup>10,13</sup>

Placement of the electrode over the LDLPFC was determined following the method of Grunhaus et al:<sup>9,10</sup> placing the coil 5 cm forward and at an angle of 45° from the vertex, which is the best spot for the APB control. We used a 10 cm wingspan figure-of-eight coil for the rTMS administration. We administered 30 pulses of rTMS at 10 Hz for 10 seconds (a total of 1,500 magnetic pulses per treatment day). rTMS was administered five times per week for 4 weeks (for a total of 20 treatment days).

## ECT

After completing the work-up and signing the treatment consent form, patients were not allowed to eat or drink for 8 hours before the treatment. All patients received 1% intramuscular atropine 20–30 minutes before the treatment. ECT was performed according to the criteria taken from *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging*, and a spECTrum 5000M™ (Mecta, Portland, OR, USA) machine was used to perform the ECT procedure.<sup>18</sup>

The patients received one of three different anesthetics during the ECT: propofol, etomidate, or thiopental. The anesthesiologist selected each patient's anesthetic according to the patient's medical background, additional medications, time taken to recover after the first treatment, and the patient's response to the anesthetic in the past. Thiopental was given at 1.5 mg × body weight, propofol at 0.6 mg × body weight, and etomidate at 0.1 mg × body weight of the patient. Scoline (succinile choline) was added as a muscle relaxant and given as 0.6–0.8 mg × body weight of the patient. The effectiveness of the seizure was defined as 25 seconds minimum of the clinical seizure and 30 seconds minimum of the electroencephalogram-recorded seizure.<sup>19</sup>

## Statistics

In general descriptive and demographics sections (Tables 1 and 2), we performed Student's *t*-tests. For comparison

**Table 1** General description

	N	Male	Female
Number of patients and their sex	81	39	42
Number of patients in ECT	40	21	19
Number of patients in TMS	41	18	23
		<b>Mean</b>	<b>Standard deviation</b>
Age (years)	81	45.642	9.641
Years of education	81	13.148	2.214
Current episode	81	19.457	28.510
Number of lifetime episodes	81	2.395	1.069
Past psychotherapy/cognitive therapy	81	0.741	0.441
HDRS-21 baseline	81	26.802	3.172
HDRS-21 after treatments	81	14.802	13.688
HARS baseline	81	19.642	3.675
HARS after treatments	81	15.518	16.215
BDI baseline	81	25.197	4.247
BDI after treatments	81	11.457	4.093
VAS baseline	81	18.951	10.299
VAS after treatments	81	60.185	16.133

**Abbreviations:** HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; BDI, Beck Depression Inventory; VAS, Visual Analog Scale; ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation.

**Table 2** Student's *t*-test, independent samples

	Mean	N	Standard deviation	<i>t</i> -test	<i>df</i>	Significance (2-tailed)
Age, years (ECT)	47.175	40	8.808	1.422	79	0.159
Age, years (TMS)	44.146	41	10.277			
Years of education (ECT)	12.775	40	1.702	-1.510	79	0.135
Years of education (TMS)	13.512	41	2.589			
Current episode (ECT)	14.175	40	5.697	-1.665	79	0.100
Current episode (TMS)	24.610	41	39.228			
Number of lifetime episodes (ECT)	2.250	40	0.926	-1.210	79	0.230
Number of lifetime episodes (TMS)	2.537	41	1.185			
Past psychotherapy/cognitive therapy (ECT)	0.775	40	0.423	0.688	79	0.493
Past psychotherapy/cognitive therapy (TMS)	0.707	41	0.461			

**Abbreviations:** ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation.

between ECT and TMS, we performed ANOVA multivariate analysis (Figures 1–4).

## Results

Tables 1 and 2 summarize and compare the demographic findings of the ECT and TMS groups.

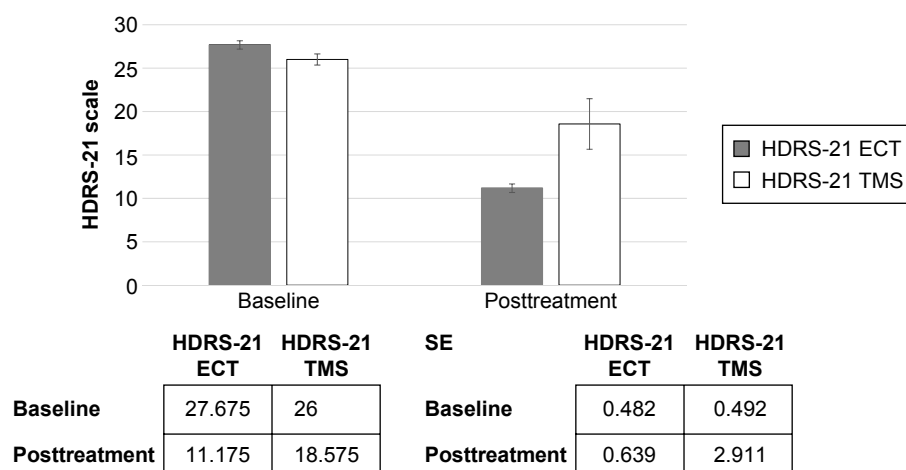
### Effectiveness of treatments

We identified no differences between the two groups in terms of the demographic and baseline questionnaire results. Both groups were defined as TRD patients. Both ECT (*df*: 1; *F*: 32.72; *P*<0.0001) and rTMS (*df*: 1; *F*: 6.85; *P*<0.012) demonstrated their effectiveness in the HDRS-21, although the ECT was superior to rTMS (*df*: 1; *F*: 6.81; *P*<0.012). The ECT (*df*: 1; *F*: 333.5; *P*<0.0001) and rTMS (*df*: 1; *F*: 275.7; *P*<0.0001) both demonstrated their effectiveness in BDI-II. The ECT (*df*: 1; *F*: 423.4; *P*<0.0001) and rTMS (*df*: 1; *F*: 200.7; *P*<0.0001) were also demonstrated to be effective in the VAS improvement scale.

The ECT (*df*: 1; *F*: 70.1; *P*<0.0001), but not rTMS treatment (*df*: 1; *F*: 0.20; *P*<0.889, not significant), was effective in the treatment of anxiety symptoms, as determined by HARS.

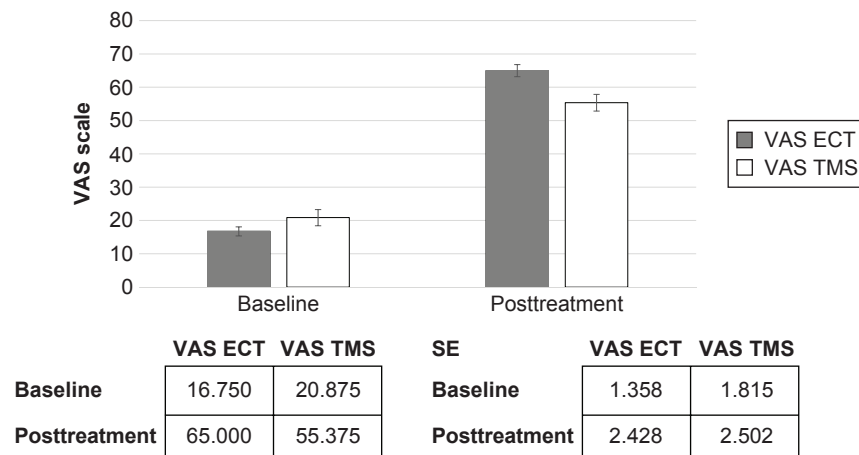
### Patients preferences, treatment effectiveness, and side effects

ECT treatment was superior (more effective) than rTMS in the treatment of TRD: anxiety symptoms did not improve with rTMS, but did improve significantly with ECT; the major disadvantage of ECT is the stigma that continues to surround the treatment, while high cost is the major drawback of TMS and patients who received ECT reported that they would have instead opted for rTMS if it had been financially available to them. They understood that the success rate of rTMS is lower than that of the ECT. This information is based on four basic questions and yes or no [y/n] answers: a) Do you believe that you responded well to ECT treatment? [y/n]; If the answer is yes: b) Would you consider receiving ECT in the future, if needed? [y/n]; c) Would you have considered



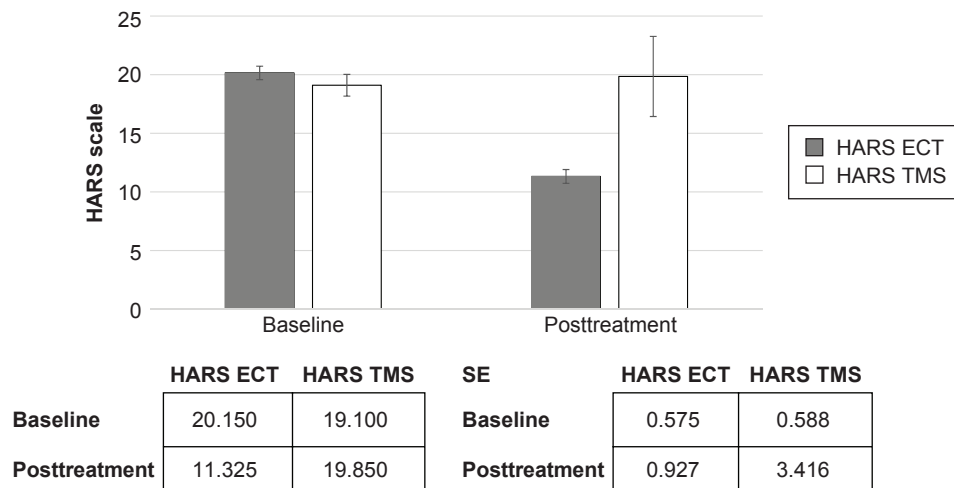
**Figure 1** 21-item Hamilton Rating Scale for Depression (HDRS-21).

**Abbreviations:** ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation; SE, standard error.



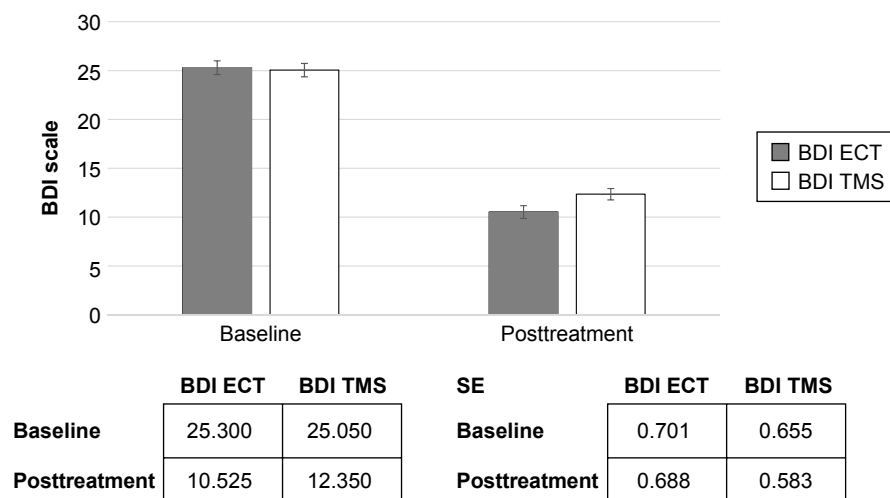
**Figure 2** Visual Analog Scale (VAS).

**Abbreviations:** ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation; SE, standard error.



**Figure 3** Hamilton Anxiety Rating Scale (HARS).

**Abbreviations:** ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation; SE, standard error.



**Figure 4** Beck Depression Inventory (BDI).

**Abbreviations:** ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation; SE, standard error.



**Table 3** Expenses and hospital income from the ECT-TMS treatments

	ECT		TMS	
	Shekels	US\$	Shekels	US\$
Costs to HMO	1,226	318	–	–
Cost to patient (out of pocket)	–	–	450	117
Anesthesiologist expenses	200	52	–	–
Nursing staff expenses	140	36	–	–
Psychiatrist/resident in psychiatry expenses	60	16	60	16
Lease expenses of the TMS machine per day <sup>a</sup>	–	–	125	32
Daily department's expenses <sup>b</sup>	100	26	100	26
Hospital earnings per treatment	726	188	165	43
Final income <sup>c</sup>	7,986	2,075	3,135	814

**Notes:** <sup>a</sup>Lease of the TMS machine costs 10,000 shekels per month. The TMS unit performs 80–120 treatments per month. <sup>b</sup>For ECT, daily department expense (including drugs, monitors, beds, sheets, and an ECT machine) is 15,000 shekels per month. The ECT unit performs 150–250 treatments per month; for TMS, department expense (including the rent and services) is 8,000 shekels per month. The TMS unit performs 80–120 treatments per month. <sup>c</sup>Patients complete  $11.3 \pm 2.3$  ECT treatments and  $19.6 \pm 1.2$  rTMS treatments, with total final income from ECT of  $726 \times 11 = 7,986$  shekels (\$2,074) and from TMS of  $165 \times 19 = 3,135$  shekels (\$814).

**Abbreviations:** ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation; HMO, Health Maintenance Organization; rTMS, repetitive transcranial magnetic stimulation.

receiving rTMS instead of ECT, if needed? [y/n]; d) If you know rTMS is less effective even than consider trying rTMS before ECT if needed? [y/n].

We summarized the income of two procedures for the hospital. Table 3 demonstrates that the hospital's final income is higher with the ECT procedure.

Clinician follow-up charts from patients' medical records found that up to 60% of the ECT sample reported short- and intermediate-term side effects, especially memory loss. The TMS group suffered from relatively fewer (30% reported) and more minor side effects, such as headaches or pressure at the time of treatment, and these were resolved within a few hours after treatment.

## Discussion

MDD is a common disorder that is increasing in prevalence and incidence. TRD is common, occurring in up to one-third of MDD patients,<sup>20</sup> with TRD estimated to account for nearly \$64 billion of the total cost of depression.<sup>21,22</sup> TRD is responsible for a disproportionate amount of the disease burden, due to limited treatment possibilities and its chronic nature.<sup>21,22</sup>

Here we compared the “gold standard” ECT against rTMS during TRD treatment. We found that both the neurostimulation techniques are effective but that ECT is slightly more effective than rTMS. Our results are similar to recently published studies addressing ECT and/or rTMS.<sup>22–24</sup>

The cost-effectiveness of ECT vs rTMS has been explored in previous research, with conflicting results. Kozel et al<sup>25</sup>

published a decision model to evaluate the cost-effectiveness of ECT, rTMS, and rTMS followed by ECT in cases of rTMS failure. They found that rTMS was more cost-effective (in terms of health care and patient costs) than ECT but that rTMS followed by ECT was the most effective and least costly approach. Knapp et al<sup>26</sup> conducted an economic evaluation comparing patients who were randomly treated with either ECT or rTMS in a 6-month follow-up study. Kozel et al<sup>25</sup> found that rTMS had a very low probability of being cost-effective compared to ECT and that rTMS was not as effective as ECT. There were generally no differences between the direct health care costs, whereas the informal care costs were higher in the rTMS population than in the ECT population. Our findings are in line with those of Knapp et al<sup>26</sup> and Vallejo-Torres et al.<sup>27</sup> ECT seems to be more effective than rTMS in the treatment of TRD (but this is not statistically significant). The ECT procedure has more side effects than the rTMS. The ECT treatment is fully covered by the HMO's health care system, whereas the rTMS treatment requires the patient to pay. The hospital earns 2.5 times more from the ECT than from the rTMS, due to expenses and patient fees.

Patients who received ECT reported that, if the rTMS had been financially available to them, they would have opted for this treatment instead, even if they understood that the therapeutic success rate of rTMS is lower than that of ECT.

## Limitations

First, we included patients that were already willing to receive either ECT or TMS. Second, the rTMS population was required to pay for their treatment, which could have affected their willingness to get an effective treatment. Third, many of the ECT patients indicated that they would have preferred the rTMS treatment, if this had been financially viable. Fourth, the ECT treatment has an attached stigma in psychiatry, which makes it difficult to compare between any stigmatizing treatments and more patient-friendly procedures. Fifth, our therapist groups performed both treatments and were, therefore, not blinded to the treatment, although this also has the advantage of no bias between different groups of therapists.

## Conclusion and future plan

The ECT procedure seems to be more effective than the rTMS in the treatment of TRD (but this does not reach statistical significance in this study). The ECT procedure has more side effects than the rTMS. The ECT is fully covered by the HMOs, whereas rTMS is self-funded by the patients. The hospital earns 2.5 times more from ECT than from rTMS.

The majority of patients who received ECT reported that, if rTMS had been financially available to them, they would have opted for rTMS instead of ECT, even if they were aware that the therapeutic success rate of rTMS was lower than that of ECT.

Patients receiving either TMS or ECT responded well to the treatments. However, due to the stigma and relatively high presence of side effects associated with ECT, rTMS was mostly preferred by patients. To make rTMS more widely available, we suggest that this treatment should be included within the HMOs systems and be made available to all TRD patients.

## Disclosure

The authors report no conflict of interest in this study.

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