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Suicidal Ideation as Specific rTMS Target

According to a post-hoc analysis of clinical-trial data, bilateral repetitive transcranial magnetic stimulation (rTMS) reduced suicidal ideation independently of its effects on depressive symptoms.[1] This observation suggests rTMS may be a useful alternative to ECT in reducing suicidal ideation.

Background: Although ECT has been shown to reduce suicidality in patients with mood disorders, many patients may prefer to receive rTMS because it is less invasive, does not require anesthesia, carries less stigma, and does not have adverse cognitive effects. However, the effects of rTMS on suicidal ideation have only been studied in 2 small trials.[2,3] The present analysis combines data from these studies in order to clarify the antisuicide effects of rTMS.

Methods: Data were combined from 2 previously published studies that compared bilateral, unilateral, and sham rTMS in patients with treatment-resistant depression that had not responded to ≥2 antidepressant medications of different classes in the current episode. Suicidal ideation was measured using the suicide item on the Hamilton Rating Scale for Depression (HAM-D), which is scored from 0 (absent) to 4 (any serious suicide attempt). Both studies excluded patients with active suicidality, thus no eligible patient had a suicidal ideation score of >3. The primary study outcome was resolution of suicidal ideation, defined as a decrease from any nonzero score to 0 at the study endpoint, which could be 3–6 weeks after baseline depending on the patient's response. Change in depressive symptoms was evaluated using the 16 non-suicide items of the HAM-D.

Results: After exclusion of patients who had a suicide score of 0 at baseline, the sample consisted of 156 patients who received treatment with bilateral (n=52), unilateral (n=56), or sham (n=48) rTMS. The mean baseline suicide score was nearly 2 in all groups. Suicidal ideation resolved in 40% of patients who received bilateral rTMS, 27% of patients who received unilateral treatment, and 19% of those who received sham treatment. Patients who received bilateral treatment had a significantly higher likelihood of resolution than the sham

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group (odds ratio,* 3.03; p=0.02). Resolution of suicidal ideation was not significantly more likely with unilateral versus sham treatment despite an odds ratio of 1.59.

The level of correlation between changes in depressive symptoms and in suicidal ideation was modest but significant (correlation coefficient,* 0.038; p<0.001). The degree of HAM-D improvement did not differ significantly between those whose suicidal ideation did and did not remit, and improvement in depression accounted for about 15% of the change in suicidal ideation.

Of the 33 patients in the initial studies excluded from the analysis because of a suicide score of 0 at baseline, new suicidal ideation developed in 1 of 14 patients receiving bilateral rTMS, 2 of 6 in the unilateral group, and 4 of 13 in the sham group.

Discussion: The rate of remission of suicidal ideation in this pooled sample was higher than the rate of remission for depression (40% vs 26% with bilateral rTMS). These results support the emerging idea that suicide may be its own transdiagnostic entity; and bilateral rTMS may be a specific treatment for suicidality. Future studies should evaluate different neuroanatomic targets and the potential of rTMS in suicidal ideation related to other disorders such as borderline personality disorder or PTSD.

[1]Weissman C, Blumberger D, Brown P, Isserles M, et al: Bilateral repetitive transcranial magnetic stimulation decreases suicidal ideation in depression. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11692. From the University of Toronto, Canada; and other institutions. **This analysis was performed without specific funding. Six study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

[2]Blumberger D, et al: A randomized double-blind sham-controlled comparison of unilateral and bilateral transcranial magnetic stimulation for treatment-resistant major depression. *World Journal of Biological Psychiatry* 2012;13:423–435.

[3]Blumberger D, et al: Unilateral and bilateral MRI-targeted repetitive transcranial magnetic stimulation for treatment-resistant depression: a randomized controlled study. *Journal of Psychiatry & Neuroscience* 2016;41:E58–E66.

***See Reference Guide.**

Deep Brain Stimulation for Depression

According to results of a systematic review and meta-analysis, evidence is insufficient at this time to support the clinical use of deep brain stimulation (DBS) for refractory depression. While the treatment shows promise, it also comes with significant risks and burdens, and less invasive brain stimulation approaches are available.

Methods: A comprehensive literature search was undertaken to identify single- or double-blind, crossover or parallel-group studies published before December 2017 in which DBS was compared with sham treatment using a validated depression scale. For crossover trials, only the first phase of treatment was included, whenever possible, to avoid carryover effects. Meta-analysis compared rates of response based on study-defined improvements on the Hamilton Rating Scale for Depression (HAM-D), Beck Depression Inventory, or Montgomery-Asberg Depression Rating Scale, generally a ≥50% reduction in score or a final HAM-D score of <8.

Results: A total of 9 studies were included in the analysis: 7 double-blind randomized controlled trials, 1 single-blind sham stimulation trial before and after 24 weeks of active stimulation, and 1 single-blind study of sham treatment for 4 weeks before crossing over to active DBS. Intervention sites were the subcallosal cingulate gyrus in 5 studies, the medial forebrain bundle in 2, and the anterior limb of the internal capsule or ventral capsule/striatum in 2. Treatment duration ranged from 1 day to 26 weeks. The studies enrolled a total of 200 patients, 23 of whom dropped out, most often for reasons relating to their underlying illness, not the device.

The pooled odds ratio* for response, measured at 16 weeks, was 5.5 (p<0.00001). However, the odds ratio for response was reduced to 2.5 and was no longer statistically significant after exclusion of the 5 crossover studies. In the 8 studies that reported mean reductions in depression score compared with sham stimulation, the mean reduction was -0.42 standard deviations

(p=0.006). Differences in secondary outcomes, including global functioning and quality of life, did not differ significantly between the groups.

A total of 131 serious adverse events occurred in 84 patients. These included worsening depression or anxiety in 29 patients, suicidal ideation in 12, and infection in 7. It was not always clear whether these effects were related to the surgery or to brain stimulation. Many other adverse effects were transient and related to the stimulation, including hypomanic symptoms, sleep disturbance, disinhibition, agitation/restlessness, nausea/vomiting, and headache.

Discussion: Based on the limited number of studies available, each with important methodological limitations, DBS may be an effective treatment for depression. However, serious adverse effects appear to be common. The authors recommend using other less-invasive brain stimulation procedures such as repetitive transcranial magnetic stimulation, magnetic seizure therapy, or vagus nerve stimulation, all of which are associated with fewer adverse effects.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Kisely S, Li A, Warren N, Siskind D: A systematic review and meta-analysis of deep brain stimulation for depression. *Depression and Anxiety* 2018;35 (May):468–480. From the University of Queensland Southern Clinical School, Australia; and other institutions. **Funded by the University of Queensland; and the National Health and Medical Research Council. The authors declared no competing interests.**

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Dementia Risk After ECT

Several small studies and case reports have raised concern about the potential for an increased risk of dementia following ECT. However, results of a large registry-based cohort study do not support the association.

Methods: The study cohort, drawn from the Danish National Patient Registry, consisted of all individuals aged ≥10 years who received an affective disorder diagnosis between 2005 and 2015. A subsample of the population consisted of men evaluated for the military draft between 1939 and 1959 who received the affective disorder diagnosis after 2004. This subcohort provided information for a separate analysis that included baseline cognitive function. The number of ECT treatments was dichotomized as ≤10 and >10, based on the median number of sessions necessary for remission. The study outcome was an incident diagnosis of dementia between 2005 and 2016. To minimize possible biases, alternative analyses were conducted using adjustment for a long list of covariates, propensity score matching,* and a 2-year lag time between the last ECT and a dementia diagnosis, to eliminate the chance of mistaking post-ECT cognitive deficits for dementia. A competing mortality risk analysis was also conducted to account for the possibility that early death might preclude a diagnosis of dementia.

Results: More than 168,000 patients with a mean age of 47 years were included in the analysis, of whom 5901 (3.5%) received ECT. The military sample consisted of nearly 13,600 men with an affective disorder, of whom 925 (6.8%) received treatment with ECT. A total of 5204 patients in the full cohort (3.1%) had onset of dementia during the study years. Rates of dementia diagnosis ranged from 0.1% of patients aged <50 years to 12.5% of those aged ≥70 years.

The incidence of dementia was higher in patients who had undergone ECT (70 vs 59 cases per 10,000 person-years), but this difference was eliminated after adjustment for covariates and in the propensity score-matched model. In the propensity score-matched analysis, in patients aged ≥70 years, undergoing >10 ECT treatments was associated with significantly reduced dementia incidence (hazard ratio,* 0.59; p=0.003). In the sample of military draftees, ECT was associated with dementia risk only in those with the lowest premorbid cognitive ability, but this observation was based on a very small number of cases.

Discussion: Although the incidence of dementia in this study population with affective disorders was 2–3 times higher than the general population, undergoing ECT did not appear to confer additional risk. The data from the military subsample suggest that reduced cognitive reserve is not likely to influence dementia risk, except perhaps at the lowest level of premorbid cognitive function.

Osler M, Rozing M, Christensen G, Andersen P, et al: Electroconvulsive therapy and risk of dementia in patients with affective disorders: a cohort study. *Lancet Psychiatry* 2018;5 (April):348–356. From Bispebjerg and Frederiksberg Hospitals, Denmark; and other institutions. **Funded by the Danish Council for Independent Research; and other sources. The authors declared no competing interests.**

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Preventive Cognitive Therapy and Depression Relapse

In a randomized trial, adding preventive cognitive therapy (PCT) to maintenance antidepressant therapy provided better relapse prevention than either antidepressants alone or PCT with an antidepressant taper.

Background: Many patients at risk for depressive relapse are not willing to continue antidepressants for long periods of time, and there is evidence that some patients may become resistant to the preventive effects of antidepressants over time. Results of previous studies of PCT suggest it may have relapse-preventive effects that are equivalent to antidepressant maintenance, but it is unclear whether adding PCT would allow for antidepressant taper and if combining the treatments would have greater efficacy.

Methods: Study participants were adults with a history of multiple major depressive episodes whose symptoms were currently in remission (i.e., Hamilton Rating Scale for Depression [HAM-D] score ≤10) for between 8 weeks and 2 years. To be eligible for the study, patients had to have achieved remission using antidepressant medications and to have been receiving pharmacotherapy for ≥6 months. PCT is a manualized program consisting of 8 weekly sessions, aimed at identifying dysfunctional attitudes, enhancing memories of positive experiences, and formulating preventive strategies. PCT was initially offered in a group format, but individual therapy was added because many patients could not attend group sessions. Participants were randomly assigned to receive PCT with an antidepressant taper, PCT with ongoing maintenance antidepressants, or antidepressant maintenance alone. Outcomes were assessed after 3, 9, 15, and 24 months by blinded raters. The primary study outcome was the time to recurrence of depression over 24 months.

Results: The study enrolled 289 participants over a 6-year period. Before randomization, 69% had ≥4 months of sustained remission. A total of 209 patients with available follow-up data were included in the analysis. Of patients still in the study after 6 months, about 60% were compliant with their continued medication or with the taper. Most who received PCT completed 5 of the 8 sessions: 68 (88%) in the combined-treatment group and 57 (90%) who tapered antidepressants.

PCT with taper and antidepressant maintenance had similar results, while the treatment combination was superior to both. (See table.) The estimated cumulative incidence of relapse over 2 years was similar in the group receiving PCT with antidepressant tapering and the group receiving antidepressant

Relapse Risk Over 2 years			
Treatment	**Comparison**	**Hazard Ratio***	**Significance**
Antidepressants alone	PCT with taper	0.86	p=ns
Combined treatment	Antidepressants alone	0.59	p=0.026
Combined treatment	PCT with taper	0.54	p=0.011

maintenance alone (63% and 60%, respectively), although relapses tended to occur more often in the first 140 days in patients whose antidepressant was tapered. The estimated recurrence rate in patients receiving both PCT and continued antidepressants was 43%. Combining PCT with maintenance antidepressants also had positive effects on secondary outcomes, including a reduced number and shorter duration of recurrences.

Discussion: Results of this study suggest PCT should be offered to patients who have recovered after recurrent depression and who wish to stop their antidepressants, as well as to those who intend to continue their medication.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Bockting C, Klein N, Elgersma H, van Rijsbergen G, et al: Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial. *Lancet Psychiatry* 2018;5 (May):401–410. From the University of Amsterdam, the Netherlands; and other institutions. **Funded by the Netherlands Organisation for Health Research and Development. Two of 13 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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Depression, Anxiety, and Thyroid Disease

A systematic review and meta-analysis found significant associations between presence of autoimmune thyroid disease and depression and anxiety. Although the study could not confirm the association as causal, there is evidence to support an autoimmune basis for some psychiatric disorders.

Methods: A comprehensive literature search identified studies published between 1992 and 2017 evaluating depression and/or anxiety using standardized measures in patients with and without autoimmune or Hashimoto's thyroiditis, overt hypothyroidism, or latent or subclinical hypothyroidism.

Results: Meta-analysis of the 19 identified studies (>36,000 patients) found thyroid disease significantly increased risk for both depression and anxiety disorders. Risk for depression was increased >3-fold (odds ratio,* 3.56; $p<0.001$). Most studies that examined anxiety used a self-report instrument such as the State-Trait Anxiety Inventory, the Beck Anxiety Inventory, or the Hospital Anxiety and Depression Scale. As a result, it was not possible to analyze the association of autoimmune thyroiditis with specific anxiety disorders. However, risk for anxiety disorders overall was increased >2-fold (odds ratio, 2.32; $p<0.001$) in patients with autoimmune thyroiditis.

Discussion: These results suggest that thyroid disease and depression/anxiety are likely to co-occur. Laboratory testing for thyroid disease, including levels of thyroid stimulating hormone, free T3 and T4, as well as thyroid peroxidase antibodies (a more sensitive indicator of autoimmune disease), may be useful in patients presenting with depression or anxiety, as those with autoimmune thyroiditis require an adapted treatment approach. Levothyroxine treatment and selenium supplementation can improve mood symptoms. Thyroid function affects the serotonin system, making SSRIs an appropriate option when antidepressants are required. TCAs may not be suitable for patients with autoimmune thyroiditis who are already likely to gain weight.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis. However, the authors did not disclose the study's source of funding.

Siegmann E, Muller H, Luecke C, Philipsen A, et al: Association of depression and anxiety disorders with autoimmune thyroiditis: a systematic review and meta-analysis. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.0190. From Friedrich-Alexander University Erlangen-Nuremberg, Germany; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

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Correlation Coefficient (r): A measure of the closeness of the relationship between 2 variables. The value of r can range from -1 to 1. An r value near 1 indicates a strong positive relationship. An r-value close to zero indicates no relationship, and a negative r-value indicates a negative relationship.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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