

# PSYCHIATRY ALERTS NOS

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## Theta Burst Brain Stimulation for PTSD

In a preliminary study, intermittent theta-burst transcranial magnetic stimulation (TBS) improved symptoms of posttraumatic stress disorder. Theta-burst stimulation offers the advantages of brevity, which allows for potential combination with psychotherapy, and consistency with a theoretical model of PTSD. In addition, pretreatment neuroimaging findings were predictive of treatment effects.

**Methods:** The study was conducted in veterans with DSM-5 chronic PTSD who were symptomatic despite ongoing treatment. Patients were randomly assigned to receive active or sham TBS for 10 consecutive weekdays. TBS was administered to the right dorsolateral prefrontal cortex in 9.5-minute sessions. After double-blind treatment, all patients could receive an additional 2 weeks of unblinded active TBS to explore the effects of longer-term treatment. The main efficacy outcome was change in PTSD symptoms using the Clinician-Administered PTSD Scale for DSM-5 (CAPS).

A convenience sample of 26 patients underwent resting-state functional MRI within 5 days before the start of treatment. MRI studies sought predictors of response after 2 weeks of real or sham TBS. MRI focused on brain areas involved in functional networks of interest in PTSD: the default mode network (self-referential processing and episodic memory), the executive control network (emotion regulation and working memory), and the salience network (threat detection).

**Results:** Of 50 patients randomized, 1 in each treatment group withdrew because of emergent headaches and 1, in the sham TBS group, withdrew after developing homicidal ideation. A total of 47 patients completed the first 2 weeks and 43 completed the additional 2 weeks of unblinded treatment. After 2 weeks, active TBS was associated with a modest, statistically nonsignificant improvement in CAPS score, relative to placebo (effect size,\* 0.12). TBS was associated with better outcomes on the Social and Occupational Functioning Assessment Scale (effect size, 0.39;  $p=0.04$ ). Average improvements on the self-reported PTSD Checklist for DSM-5 and the Inventory of Depressive Symptomatology were judged to be clinically meaningful (effect sizes, 0.39 and 0.45, respectively), although they were not statistically significant.

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Outcomes were more favorable in an analysis that included the additional 2 weeks of open-label TBS, with medium to large effect sizes for most measures. (See table.) Improvements in most areas occurred during the first week of active stimulation and were sustained with little additional change. At the 4-week assessment, clinically meaningful improvement (i.e., decrease in CAPS score of  $\geq 12$  points) was evident in 81% of patients initially assigned to active treatment and in 67% of those who received 2 weeks of sham treatment (number needed to treat,\* 7).

| Clinical outcomes of active versus sham TBS in PTSD after 1 month of follow-up |                          |              |
|--------------------------------------------------------------------------------|--------------------------|--------------|
| Instrument                                                                     | Net change (effect size) | Significance |
| Clinician-Administered PTSD Scale for DSM-5                                    | 0.74                     | p<0.001      |
| PTSD Checklist for DSM-5                                                       | 0.63                     | p<0.001      |
| Social and Occupational Functioning Scale                                      | 0.93                     | p<0.001      |
| Quality of Life Enjoyment and Satisfaction                                     | 0.02                     | p=0.01       |
| Inventory of Depressive Symptomatology                                         | 0.47                     | p<0.001      |

Neuroimaging analyses indicated that baseline functional connectivity predicted changes that would occur with active TBS. Improvement was associated with stronger baseline functional connectivity within the default mode network and between this network and externally oriented networks. Improvement in depression was also associated with stronger within-default mode network connectivity. Improvement was also associated with greater negative connectivity between networks.

**Discussion:** These results suggest that intermittent TBS may be a promising new treatment that can produce rapid improvement within 1 week in patients with PTSD. However, because of the modest sample size, these results must be considered preliminary and require replication.

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

Philip N, Barredo J, Aiken E, Larson V, et al: Theta-burst transcranial magnetic stimulation for posttraumatic stress disorder. *American Journal of Psychiatry* 2019; doi 10.1176/appi.ajp.2019.18101160. From Providence VA Medical Center; and Brown University, RI. **Funded by the Department of Veterans Affairs. One of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

\*See Reference Guide.

## Intestinal Microbiota and Anxiety

According to the results of a systematic literature review, regulating intestinal microbiota may reduce anxiety symptoms. Nonprobiotic methods appear to be more effective than probiotic supplementation.

**Background:** Some evidence has suggested that gut microbiota could impact hypothalamic-pituitary-adrenal (HPA) axis function, and clinical studies have shown that intestinal flora can alter communication between the gut and the brain via the gut-brain axis. However, whether regulating intestinal microbiota has positive effects on anxiety symptoms is unclear.

**Methods:** A comprehensive search of English and Chinese literature databases was undertaken to identify controlled trials evaluating regulation of intestinal flora in patients with anxiety with or without comorbid medical conditions. Active treatments could include probiotic supplementation or nonprobiotic interventions including dietary changes and prebiotic supplements. Anxiety symptoms were evaluated using validated scales.

**Results:** A total of 21 studies including 1503 patients were identified: 10 evaluated patients with comorbid irritable bowel syndrome, 5 included patients with other chronic conditions (e.g. rheumatoid arthritis, diabetes, obesity), and 6 evaluated medically healthy patients. Probiotic interventions, either alone or in combination with treatment as usual, were used in 15 studies, and 7 studies evaluated nonprobiotic interventions. The most commonly used probiotic was *Lactobacillus*, which could be used alone or in combination with other probiotic supplements. Anxiety symptoms were improved in actively-treated patients in 11 of the 21 studies (52%). Nonprobiotic measures appeared to be more effective, with 6 of 7 studies showing positive results, compared with 5 of 14 using probiotics (86% vs 36%). Improvements were evident regardless of the anxiety assessment measure used. Two serious adverse events were reported in the studies (major depressive episode and deep vein thrombosis), but neither was determined to be related to study treatment. Mild adverse effects of treatment included dry mouth, cenesthopathy, and diarrhea.

**Discussion:** Differences in research designs, study subjects, interventions, and anxiety assessment scales resulted in heterogeneity that was too great for the planned meta-analysis to be conducted. Nevertheless, the results support regulating intestinal flora via probiotic and/or nonprobiotic measures to alleviate anxiety. This approach may be particularly useful for patients with somatic diseases that make them unsuitable candidates for psychiatric medications.

Yang B, Wei J, Ju P, Chen J: Effects of regulating intestinal microbiota on anxiety symptoms: a systematic review. *General Psychiatry* 2019;32:e100056. doi 10.1136/gpsych-2019-100056. From Shanghai Jiao Tong University School of Medicine, China. Funded by the National Natural Science Foundation of China; and other sources. The authors declared no competing interests.

## Online Treatment of Suicidal Ideation

An online self-help program reduced suicidal ideation in a population-based randomized trial. The program, Think Life, was based mainly on cognitive-behavioral therapy and also used elements of dialectical behavior therapy, problem solving therapy, and mindfulness-based cognitive therapy. The high enrollment demonstrates considerable interest from the general public in such a program, but attrition rates were also high.

**Methods:** The study was conducted in a Flemish region in Belgium, a population the authors characterize as highly culturally susceptible to stigma about psychological problems and treatment. Participants were recruited via media coverage and the Flemish suicide help line. The only requirements for participation were age  $\geq 18$  years, at least mild suicidal thoughts, fluency in Dutch, an active email address, and internet access. Using mental health or support services did not preclude participation. The intervention consisted of 6 weekly modules incorporating psychoeducation, an assignment, and exercises. Participants were randomly assigned to receive access to the program immediately or to a waiting list, which granted access after 12 weeks. The primary study outcome measure, administered after 6 and 12 weeks, was the Beck Scale for Suicidal Ideation (BSS), which has a score range of 0–38 points. Safety procedures at weeks 2 and 4 included standardized measures of suicidal ideation, telephone risk assessment for participants scoring above cutoff levels, and contact with the patient's general practitioner or psychiatrist if suicide risk was high. Because of these procedures, participants could not be completely anonymous. Secondary outcomes, measured with validated scales, included depression, hopelessness, worry, and anxiety.

**Results:** Of nearly 1,700 persons who signed up for the program, more than half did not provide informed consent or were excluded for other reasons. The remaining 724 patients were randomized to the active program (n=365) or the waiting list (n=359). In the active treatment group, 73% of patients completed the 2-stage baseline assessment, 26% completed the post-treatment

evaluation, and 22% completed follow-up. Rates were 63%, 48%, and 46%, respectively in the control group. Attrition between baseline and the 6-week evaluation was nearly double in the active-treatment group: 64% vs 33% in the control group. The mean age of participants was 36 years, nearly 60% were women, and 60% were receiving treatment from a psychiatrist or psychologist. About half had a history of suicide attempts.

In the intent-to-treat analysis,\* BSS scores indicating suicidal ideation were reduced by a significantly larger margin in Think Life participants than in controls (see table) at both the 6 and 12-week evaluations. By 6 weeks, safety procedures had been performed more often in the control group than in treatment participants (30% vs 16%;  $p=0.011$ ). Rates at 12 weeks were 25% and 17%, respectively. About 8% of each group reported a suicide attempt.

| BSS Suicidal Ideation Scores |           |         |             |              |
|------------------------------|-----------|---------|-------------|--------------|
| Assessment Time              | ThinkLife | Control | Effect Size | Significance |
| Baseline                     | 19.49     | 19.92   | —           | —            |
| 6 Weeks                      | 12.82     | 15.93   | 0.34        | $p=0.001$    |
| 12 Weeks                     | 11.55     | 13.88   | 0.25        | $p=0.03$     |

At baseline, participants showed severe depressive symptoms, moderate hopelessness, high levels of worry, and severe anxiety symptoms. For all secondary outcomes the Think Life group demonstrated significantly greater reductions than the control group at 6 weeks with effect sizes ranging from 0.37 to 0.46 ( $p\leq 0.006$  for all). The effects persisted at 12-week follow-up with effect sizes of 0.38–0.6 ( $p\leq 0.001$  for all).

**Discussion:** High attrition rates are an important limitation of online interventions, including the Think Life program. However, given the program's positive effects on suicidal ideation and on secondary outcomes of hopelessness, worrying, depression, and anxiety, the Think Life intervention appears to be useful in prevention of suicide, at least during the gap between crisis help and face-to-face treatment.

**Study Rating\*—15 (88%):** This study met most criteria for a randomized controlled trial; however, because outcome measures were self-ratings, blinding was not possible.

De Jaegere E, van Landschoot R, van Heeringen K, van Spijker B, et al: The online treatment of suicidal ideation: a randomised controlled trial of an unguided web-based intervention. *Behaviour Research and Therapy* 2019; doi 10.1016/j.brat.2019.05.003. From Ghent University, Belgium; and other institutions. **Funded by the Flemish Government. Two of 7 study authors disclosed potentially relevant financial relationships.**

\*See Reference Guide.

## Brief Contact Intervention for Suicide Prevention

In persons who attempted suicide, a personalized brief contact intervention (BCI) did not reduce the risk of repeated suicide attempts when compared with treatment as usual. The simple intervention, based on crisis cards, phone calls, and mailed postcards, did not include any therapeutic elements.

**Background:** BCIs offer a nonintrusive way to maintain contact with patients in the immediate postdischarge period when risk of repeat suicide attempt is high. While few studies indicate BCIs are effective in preventing suicide reattempts, some research suggests specific BCIs may be useful in certain patient groups. The present study examined an algorithm targeting specific BCIs to groups in which they have been shown to be effective.

**Methods:** Study participants were treated for a suicide attempt in 25 emergency departments or crisis centers in France over a 3-year period. All received treatment as usual, consisting of an emergency follow-up appointment and a referral to a psychiatrist or physician. In addition, randomly selected patients received BCIs according to the algorithm. Crisis cards with the emergency department phone number were offered during discharge after a first attempt. Patients with a previous suicide attempt received a phone call offering psychological support and encouraging them to make new contacts. Those from the telephone group who could not be contacted or who declined follow-up care were sent a series of 4 monthly handwritten postcards. The primary study outcome was the proportion of patients with a repeat suicide attempt in the 6 months postdischarge.

**Results:** A total of 1040 patients were discharged after a suicide attempt. In the algorithm group, 263 first attempters received a crisis card. Of 230 with a previous attempt allocated to receive a phone call, 155 (67%) were contacted by phone, and 139 were eventually mailed postcards.

After 6 months, repeat suicide attempts occurred in 13% of the intervention group and 17% of the control group, a statistically nonsignificant difference (number needed to treat,\* 25). There were 3 deaths by suicide in the algorithm group and 8 in the controls, also a nonsignificant difference. The only significant study finding was that more patients in the control group were lost to follow-up after 13 months: 18.4% vs 13.6% in the intervention group (p=0.038). Subgroup analyses, although limited by small sample size, suggest personalized BCI is less effective in men and in younger patients.

**Discussion:** The authors suggest that new media such as text messages and smartphone apps may be useful in reaching a wider group of patients, and incorporating therapeutic elements could improve outcomes.

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

Valva G, Berrouiguet S, Walter M, Courtet P, et al: Combining postcards, crisis cards, and telephone contact into a decision-making algorithm to reduce suicide reattempt: a randomized clinical trial of a personalized brief contact intervention. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11631. From the University Hospital of Lille, France; and other institutions. **Funded by the French Health Ministry. The authors declared no competing interests.**

\*See Reference Guide.

## CPAP and Depression/Anxiety

In patients with obstructive sleep apnea and cardiovascular disease, continuous positive airway pressure (CPAP) improved symptoms of depression but not anxiety. Effects were larger in patients with baseline depression, appeared within several months of starting treatment, and were independent of improvement in daytime sleepiness.

**Background:** This report describes a secondary analysis of the SAVE study, which evaluated the effects of CPAP on cardiovascular outcomes. Because the SAVE study found improved scores on the Hospital Anxiety and Depression Scale (HADS), the present analysis was conducted to examine these effects in greater detail.

**Methods:** The SAVE study recruited patients with a history of cardiovascular disease and moderate-to-severe obstructive sleep apnea. They were randomly assigned to receive CPAP in addition to usual care or usual care alone. Usual care included management of cardiovascular risk factors and advice about sleep hygiene and lifestyle changes supporting better sleep. Mood symptoms were assessed throughout the 7-year study using the HADS, which consists of subscales for anxiety and depression, each with 7 items and a maximum score of 21. Participants were considered to have depression and/or anxiety based on HADS subscale

scores of  $\geq 8$ . To further clarify the effects, a systematic review and meta-analysis of published clinical trials of the effects of CPAP on depressive or anxiety symptoms in patients with obstructive sleep apnea was also conducted.

**Results:** The analysis was based on 2410 patients, followed for a mean of 3.7 years. At study end, 18.1% of the CPAP group and 24.8% of the control group met criteria for depression. The unadjusted odds ratio\* was 0.67 ( $p < 0.001$ ). After adjustment for improvement in the Epworth Sleepiness Scale (ESS), measuring daytime sleepiness, improvement in depression remained significant (odds ratio, 0.80;  $p = 0.031$ ). Rates of depression in the CPAP group were lower than in controls at nearly all study time points beginning at the 6-month assessment. The number needed to treat\* with CPAP to prevent 1 case of depression was 15. Analysis of the individual questions on the HADS depression subscale showed a broad effect across all symptoms, and patients with preexisting depression symptoms experienced significant symptom reduction. CPAP had a small, statistically nonsignificant positive effect on anxiety.

The systematic review and meta-analysis supported the findings from the SAVE study. In the 20 identified studies (4,255 participants) comparing CPAP with standard care, an oral placebo, or sham CPAP, the overall standardized mean difference\* in depression scores for CPAP versus control was 0.18. Effects of CPAP on anxiety were small and not statistically significant.

Zheng D, Xu Y, You S, Hackett M, et al: Effect of continuous positive airway pressure on depression and anxiety symptoms in patients with obstructive sleep apnoea: results from the sleep apnoea cardiovascular endpoint randomised trial and meta-analysis. *EClinicalMedicine* 2019; doi 10.1016/j.eclinm.2019.05.012. From the University of New South Wales, Sydney, Australia. **Funded by the National Health and Medical Research Council of Australia; and other sources. Four of 24 authors disclosed potentially relevant financial relationships. The remaining authors declared no competing interests.**

\*See Reference Guide.

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**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**Intent-to-Treat (ITT) Analysis:** An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an ITT analysis, everyone who begins treatment is included regardless of treatment completion. ITT analyses are done to avoid the effects of crossover, drop-out, and other factors that could alter the results or inflate the magnitude of effects.

**Number Needed to Treat (NNT):** Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

**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  $> 1$  indicates that the event is more likely to occur in that group than in the comparison group.

**Standardized Mean Difference:** The difference between two normalized means. Used for comparison of data obtained using different scales, a value of 0–0.2 is considered a negligible effect, 0.2–0.5 a small effect, 0.5–0.8 a medium effect, and  $> 0.8$  a large effect.

**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](http://www.alertpubs.com).

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