PSYCHIATRY ALERTS NOS

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Highly Concentrated Treatment of OCD

In a naturalistic treatment study, a highly accelerated 4-day exposure and response prevention (ERP) protocol was both feasible and effective in a group of patients with OCD. The results suggest that concentrated therapy has low attrition rates and is at least as effective as longer-term therapy.

Background: In Norway, all patients with OCD are given access to empirically supported treatment by a specialized OCD team. When an unexpected number applied for treatment at Oslo University Hospital, the waiting list grew to 101 patients. In an effort to clear the waitlist, a single clinic employed the Bergen 4-day treatment protocol in 90 consecutive patients over 2 weeks. The accelerated treatment is based on psychoeducation with exposure and response prevention (ERP) and individual treatment in a group setting, with a patient-to-therapist ratio of 1:1 within small groups.

Methods: Study participation criteria were broad: Patients received treatment if they met DSM-5 criteria for OCD, had moderate-to-severe symptoms, and were free of suicidality, psychosis, and substance abuse. Of the 101 waitlisted patients, 11 were excluded for practical reasons or because they did not meet study criteria. Of the remaining 90 patients, all agreed to participate in the accelerated treatment program. Patients were assigned to 1 of 2 cohorts, each consisting of 8 groups of 6 patients; 66 therapists delivered treatment. Therapists met for 8 hours of training on Monday, and sessions with patients were scheduled for the following 4 weekdays. Treatment consisted of a 3-hour day of psychoeducation, followed by 2 days (8–10 hours each) of therapist-assisted individual exposure training and brief group meeting, and a final day of review and planning. An educational meeting for family and friends was also included on day 4. Patients were encouraged to continue with self-administered exposures for the next 3 weeks and to report their experiences daily online. Outcomes were measured after the 4-day treatment and 3 months later. Clinically relevant response was defined as a ≥35% reduction in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score, and remission was defined as a post-treatment Y-BOCS score of ≤12.

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Results: All 90 patients completed the study treatment, and overall, patients experienced a significant reduction in the Y-BOCS score, from a pre-treatment mean of 26 to 10.5 after completing the 4-day protocol ($p<0.001$; effect size,* 4.6). At the end of treatment, 91% of the patients met response criteria and 72% had achieved remission. At the 3-month follow-up, the mean Y-BOCS score remained stable at 10.7 ($p<0.001$; effect size, 4.6), 84% of patients were considered responders, and 68% achieved remission. Of 8 patients who were classified as unchanged after treatment, 4 had achieved remission by the 3-month follow-up. Results did not differ in subgroup analysis of patients with moderate or severe symptoms.

Discussion: The results of this study are similar to previously reported results of the 4-day protocol and are somewhat better than those generally reported for standard ERP treatments. The format is likely to be highly cost-effective, and the 100% completion rate suggests it is acceptable to patients.

Kvale G, Hansen B, Björgvinsson T, Børtveit T, et al: Successfully treating 90 patients with obsessive compulsive disorder in eight days: the Bergen 4-day treatment. *BMC Psychiatry* 2018; doi 10.1186/s12888-018-1887-4. From Haukeland University Hospital, Bergen; and the Norwegian University of Science and Technology, Trondheim, Norway. **Source of funding not stated. The authors declared no competing interests.**

***See Reference Guide.**

Traumatic Brain Injury and Suicide Risk

According to the results of a Danish population-based study, persons with a history of traumatic brain injury (TBI) have twice the risk of suicide as the general population without TBI.[1] Suicide risk was increased across all severity levels of TBI, including mild injuries. The research also identified an important clinical triad that serves as a "red flag" for increased suicide risk: a history of TBI, recent injury (especially with long hospital stays), and multiple post-injury medical contacts for the injury.

Methods: The study cohort consisted of all individuals aged ≥10 years who lived in Denmark beginning January 1, 1980. Through the end of follow-up in 2014, information on medical contacts for TBI, deaths by suicide, and covariates were obtained from linked registries. TBI was categorized as: mild (concussion); skull fracture without documented TBI; or severe (head injury with evidence of structural brain injury).

Results: The dataset included >7.4-million persons, of whom 5.7% had experienced a mild TBI, 0.3% had a skull fracture, and 1.6% had a severe TBI. More than 34,500 suicides occurred, 10.2% of them in persons with a history of TBI.

The absolute rate of suicide in persons with TBI was about twice that of the population with no TBI. (See table.) Risk of suicide increased with increasing TBI severity. A higher suicide rate was associated with an increasing number of medical contacts for likely distinct TBI events ($p<0.001$ for trend). Suicide rates were also increased as a function of the number of days in treatment for TBI ($p<0.001$ for trend) and of recency of contact; suicide risk was highest within the first 6 months after the injury. Suicide rates were elevated in all age groups of TBI patients, but particularly in persons between the ages of 16 and 20 years. Also contributing to

Incidence of suicide in relation to TBI history and severity

Group	Absolute rate per 100,000 person-years	Incidence rate ratio*
No TBI	19.9	reference
Any TBI	40.6	1.90
Mild TBI	38.6	1.81
Skull fracture	42.4	2.01
Severe TBI	50.8	2.38

suicide risk were the onset of a psychiatric disorder after the TBI and engaging in deliberate self-harm after the injury.

Editorial.[2] TBI is a known risk factor for suicide, but only recently have the consequences of mild TBI received recognition. Mild TBI is by far more common than severe TBI and may be associated with depression and impulsivity. There is increasing awareness of chronic traumatic encephalopathy in victims of repetitive head injuries from contact sports and in military veterans with blast exposure, and of lasting brain abnormalities, cognitive deficits, and neuropsychiatric disturbances in persons with mild TBI.

[1]Madsen T, Erlangsen A, Orlovska S, Mofaddy R, et al: Association between traumatic brain injury and risk of suicide. *JAMA* 2018;320 (August 14):580–588. doi 10.1001/jama.2018.10211. From the Danish Research Institute of Suicide Prevention, Copenhagen, Denmark; and other institutions. **Funded by the Mental Health Services Capital Region Denmark; and other sources. One study author disclosed a potentially relevant financial relationship; the remaining 5 authors declared no competing interests.**

[2]Goldstein L, Diaz-Arrastia R: Traumatic brain injury and risk of suicide [editorial]. *JAMA* 2018;320 (August 14):554–556. From Boston University School of Medicine, MA; and other institutions. **The authors declared no competing interests.**

***See Reference Guide.**

rTMS During Pregnancy

In a small controlled trial, repetitive transcranial magnetic stimulation reduced depressive symptoms in women treated in the 2nd or 3rd trimester of pregnancy. Treatment produced few maternal adverse effects and did not appear to affect fetal outcomes; however, there were 3 late preterm births in the active rTMS group, a finding of uncertain significance.

Methods: Study participants were required to be between the ages of 18 and 39 years, 14–34 weeks pregnant, and to have a diagnosis of unipolar major depressive disorder. Also required were minimum scores of 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D) and 3 on the Clinical Global Impression–Severity* (CGI-S) scale. Antidepressant medication was permitted if the dose was stable for 2 weeks before randomization, and women with comorbid anxiety disorder were allowed to enroll. Patients received a total of 20 sessions of active or sham rTMS, administered 5 days per week and targeting the right dorsolateral prefrontal cortex. Primary study outcomes, assessed at the end of treatment, were change from baseline in HAM-D and CGI-S scores.

Results: Of 26 women randomly assigned to treatment, 22 completed ≥17 sessions and 20 completed all 20 sessions. Women who withdrew early did so for reasons unrelated to treatment. During the study, 5 women received pharmacotherapy and 4, all in the control group, had a comorbid anxiety disorder.

At study entry, mean HAM-D and CGI-S scores (23 and 4.6, respectively) did not differ between the active rTMS and sham groups. Women who received active rTMS had larger decreases in depressive symptoms and clinical severity than those who received sham treatment. (See table.)

Outcomes of real vs sham rTMS during pregnancy

Outcome	Active treatment	Sham	Significance
Mean Final HAM-D Score	9.27	13.18	p=0.003
Mean Final CGI-S Score	2.36	3.18	p=0.035
Mean Final EPDS Score	9.55	13.00	p=0.008
Response	82%	45%	p=NS
Remission	27%	18%	P=NS

The number needed to treat* for 1 additional response was 3. Rates of response (≥50% decrease in HAM-D score) and remission (final HAM-D score <8 and CGI-S score ≤1) were numerically, but not significantly, higher with active treatment, possibly because of the small sample size. There were also no significant differences between the groups in patient-rated Beck Depression Inventory and Beck Anxiety Inventory change. Postnatal mean scores on the Edinburgh Postnatal Depression Scale (EPDS) were lower in patients receiving active treatment, but in telephone interviews at 6 weeks, scores did not differ between the groups.

No treatment-related changes in estradiol or progesterone levels were observed, nor were there any clinically relevant cognitive changes. rTMS was associated with few maternal adverse effects other than the expected transient headaches. Fetal growth did not differ between the groups, and there were no significant differences in fetal age at delivery. However, 3 infants in the rTMS group were delivered in gestational weeks 35 or 36. Pre-term birth risk factors unrelated to TMS were present in 2 of these mothers.

Discussion: The high treatment adherence in this study may indicate women's desire for effective alternatives to medication during pregnancy. Patients received right-sided rTMS in this study because of concerns, later shown to be unfounded, that left-sided treatment increases seizure risk. It is likely, although unproven, that left-sided rTMS is equally safe in pregnancy and more effective than right-sided treatment. The dosage of rTMS used in the present study was also conservative, only half the dose considered safe in the general patient population. Larger studies in more varied populations appear to be warranted.

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

Kim D, Wang E, McGeehan B, Snell J, et al: Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder. *Brain Stimulation* 2018; doi 10.1016/j.brs.2018.09.005. From Perelman School of Medicine at the University of Pennsylvania, Philadelphia. **Funded by the NIMH. One of the 9 study authors disclosed a potentially relevant financial relationship; the remaining authors declared no competing interests.**

***See Reference Guide.**

CBT with Heart Rate Variability Biofeedback for PTSD

In an uncontrolled study, patients with noncombat-related PTSD experienced significant benefit from cognitive behavioral therapy with heart rate variability biofeedback.

Methods: Study participants were 30 adults (mean age, 44 years; 22 women) referred for noncombat PTSD treatment. Participants had a wide range of co-occurring conditions, including suicidal ideation and substance abuse, and nearly all had experienced their trauma >10 years in the past, mostly as childhood physical/emotional or sexual abuse. All treatment was provided by a single clinician, who also rated the results. The therapy was organized into distinct modules that taught basic core skills or addressed common PTSD symptoms—i.e., nightmares, dissociation, hyperarousal and reactivity, avoidance, and negative conditions and moods. The initial session included nonspecific practice in distress tolerance, physiological calming, and self-soothing. After completing 2–3 sessions of initial evaluation, patients only used the modules that were most relevant to their symptom profile, completing treatment after a total of 6–14 sessions.

Heart rate variability biofeedback was used as part of the hyperarousal and reactivity module. In the clinic, patients wore a sensor on an earlobe or finger, and heart rate variability was displayed on a computer monitor. They were able to view their heart rate response to skills they were learning, such as paced diaphragmatic breathing. Patients practiced these skills between sessions and were able to test themselves when they returned to the clinic. They were encouraged to practice breathing skills every day to reduce hyperarousal and reactivity.

PTSD symptoms were measured following treatment using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), past-month version, including the Life Events Scale-5. The primary outcome of this observational study was remission, defined as no longer meeting CAPS-5 diagnostic criteria for PTSD.

Results: Of the 30 enrolled patients, 26 completed the protocol and achieved remission of PTSD. In the intent-to-treat analysis,* the remission rate was 87%. Treatment completers experienced an average 43% reduction in CAPS score. The average Clinical Global Impression–Improvement* score was 1.69. A total of 25 patients were reevaluated after 3 months; only 1 patient reported a return of symptoms, which were relatively mild.

Discussion: The remission rate in this study, admittedly a biased estimate, compares favorably with other published reports and meta-analyses of PTSD treatment. The protocol could be easily administered by a range of mental health clinicians and appears to be applicable to patients with persistent PTSD and complex co-occurring issues. However, the positive results require replication in higher quality studies.

Criswell S, Sherman R, Krippner S: Cognitive behavioral therapy with heart rate variability biofeedback for adults with persistent noncombat-related posttraumatic stress disorder. *The Permanente Journal* 2018; doi 10.7812/TPP/17-207. From Kaiser Permanente Northwest, Portland, OR; and other institutions. T**his study was not funded. The authors declared no competing interests.**

***See Reference Guide.**

Habenular Connectivity and Depression Response

The habenula is a small brain structure that interfaces with the basal ganglia and limbic system, influencing multiple neurotransmitter systems with potential effects on motivational and emotional control of behavior. In a large sample of psychiatric inpatients, MRI studies of structural and functional habenular connectivity on admission were predictive of response to treatment for depression.

Methods: Study subjects were consecutively admitted to a psychiatric hospital, where treatment consisted of medication, individual and group psychotherapy, nursing care, health promotion, exercise, and recreation. The typical duration of hospitalization was 4–8 weeks. More than 800 patients, regardless of diagnosis, were invited to volunteer for an MRI study. The sample for the present analysis consisted of 175 patients with scans obtained upon admission and with baseline diagnoses of at least moderately severe depression, defined as a Patient Health Questionnaire depression module (PHQ-9) score of ≥15. Participants were classified as responders or nonresponders based on their discharge PHQ scores, with 127 exhibiting mild or no depression (PHQ-9 score <10) and 48 with at least moderate depression.

Neuroimaging data were extensively modeled to localize the habenula and its connecting tracts to previously described regions of interest. These regions, located downstream of the habenula, were selected based on their known connectivity with the habenula, role in neurotransmitter regulation, and proposed involvement in depression: the dorsal raphe, locus ceruleus, median raphe, substantia nigra, and ventral tegmental area.

Results: The scans identified an overall significant difference in habenular connectivity between responders and nonresponders ($p=0.00016$). Nonresponders had higher functional connectivity of the left habenula to the locus ceruleus ($p=0.003$) and lower structural and functional connectivity of the right habenula to the median raphe ($p=0.011$) and the right habenular afferent fibers ($p=0.025$). No other significant differences between groups were observed. No differences in connectivity between groups were observed for major depression, alcohol dependence, or eating disorder NOS, baseline diagnoses that differed in frequency between

responders and nonresponders. Differences in habenular connectivity explained 28% of the variance in treatment resistance and correctly classified 73% of the patients as responders or nonresponders.

Discussion: The habenula connects with brain regions associated with the dopaminergic, serotonergic, and noradrenergic neurotransmitter systems. The present research suggests studies of habenular connectivity could help identify patients who may require more extreme interventions for depression. The results also support some hypotheses about the pathophysiology of depression. Apparently the dorsal and medial raphe are independently regulated, and the imbalance may contribute to depression severity and resistance. The reduced connectivity with right afferent fibers suggests dysregulation of the median raphe may originate upstream from the habenula.

Gosnell S, Curtis K, Velasquez K, Fowler J, et al: Habenular connectivity may predict treatment response in depressed psychiatric inpatients. *Journal of Affective Disorders* 2019;242:211–219. doi 10.1016/j.jad.2018.08.026. From Baylor College of Medicine; and the Michael E. DeBakey VA Medical Center, Houston, TX. **Funded by the McNair Medical Institute; and other sources. The authors did not include disclosure of potential conflicts of interest.**

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Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

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.

Incidence Rate Ratio: The number of new cases of a condition in a defined (specified) group or population expressed as a ratio. For example, if there are 1000 people and a condition develops in 14 of them, the incidence rate is 14 per 1000 or 1.4%.

Intent-to-Treat Analysis (ITT): 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: 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.

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).