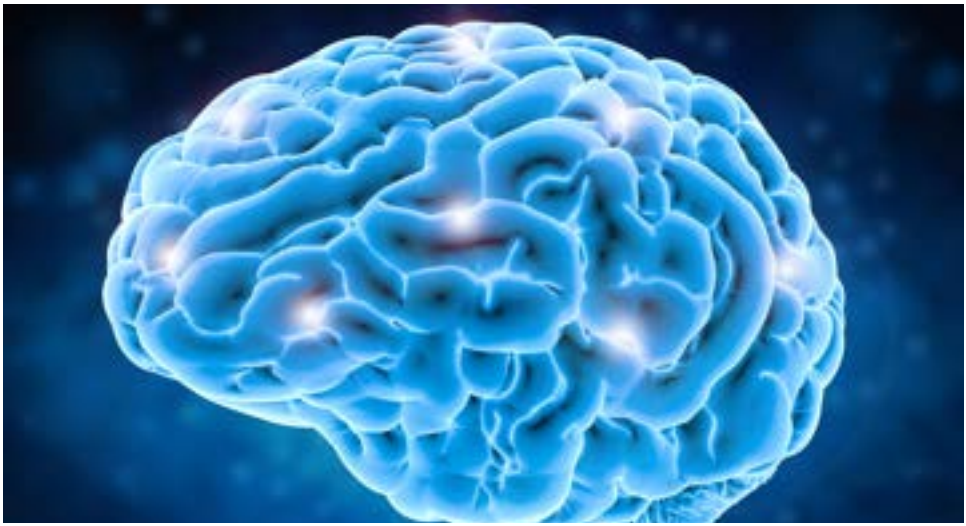
MARCH 2026 / ISSUE 57

PULSE

A Monthly Update on Advances in Neuromodulation



Produced by the Neuromodulation Division of the Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA

Anthony Jang, MD, Managing Editor | AlJang@mednet.ucla.edu
Aaron Slan, MD, Editor-in-Chief | aslan@mednet.ucla.edu

rTMS and Esketamine Demonstrate Comparable Suicide-Related Outcomes with Differing Safety Profiles in TRD

Praveen P. Rajaguru MD, MPH reviewing Chen et al., Journal of Affective Disorders, 2026 Apr

In this target trial emulation, intranasal esketamine and rTMS exhibited largely comparable suicide-related outcomes in adults with TRD over one year follow-up. rTMS was associated with significantly lower risks of hospitalization, arrhythmia, and injury compared with esketamine, while esketamine showed lower risk of suicide-related outcomes during the 30–90-day interval.

TRD, or MDD that does not respond to two adequate antidepressant trials, has high rates of morbidity, mortality, and healthcare costs. Both intranasal esketamine and rTMS are FDA approved for TRD. However, direct randomized

IN THIS ISSUE:

Clinical Updates

- *rTMS and Esketamine Demonstrate Comparable Suicide-Related Outcomes with Differing Safety Profiles in TRD*
- *TMS Improves Treatment-Resistant OCD Symptoms Independently of Concurrent Changes in Depression*
- *A Pilot Study Suggests That rTMS Is Feasible And Acceptable, With Preliminary Evidence of Efficacy, For The Treatment Of Comorbid Chronic Low Back Pain And Insomnia.*

Emerging Technologies

- *Home-Based,Non-Invasive Afferent Stimulation Of Occipital And Trigeminal Nerves Is Safe And Effective For TRD*

Glossary

comparisons of these interventions remain limited. This study sought to approximate this knowledge gap by employing a large-scale target trial emulation framework to compare clinical outcomes and safety following initiation of rTMS versus esketamine in adults with TRD.

This study used deidentified data from the TriNetX US Collaborative Network, including adults aged 18–65 years with TRD who initiated any protocol of either rTMS or intranasal esketamine between 2019 and 2025. An a priori hypothetical randomized study protocol was established, and real-world data was used to emulate each element. Propensity-score matching was performed across 50 demographic, psychiatric, and medical variables, yielding 1,690 included and matched patients in each treatment group. Outcomes included psychiatric care utilization (i.e. hospitalizations, ED visits), suicide-related events (suicide attempt, suicidal ideation, or self-harm), and safety outcomes including adverse events such as cardiovascular complications or seizures. Outcomes were assessed across various follow-up windows up to 12 months using hazard ratios (HRs) and 95% confidence intervals (CIs).

Baseline characteristics were balanced after matching between rTMS and esketamine cohorts; before matching, the rTMS group had higher prior rates of SI and self-harm while the esketamine group had higher rates of SUD, various medical comorbidities (e.g., diabetes, epilepsy), and ER/inpatient encounters. Over the full one-year follow-up period, rTMS was associated with a non-significant higher risk of suicide-related outcomes relative to esketamine (HR 1.199, 95% CI 0.943–1.526); however in the 30-90 day interval, rTMS exhibited a significantly higher suicide-related risk (HR 1.496, 95% CI 1.031–2.170). rTMS was also associated with significantly lower risks of hospitalization (HR 0.746, 95% CI 0.646–0.861), arrhythmia (HR 0.677, 95% CI 0.485–0.943), and any injury (HR 0.745, 95% CI 0.627–0.885). There were no significant differences in risk of adverse events such as hypertension or seizure across treatments. Subgroup analyses indicated stronger risk of suicide-related outcomes with rTMS, particularly in patients aged 45–65 years (HR 1.558, 95% CI 1.027–2.365).

Impact: This target trial emulation suggests that rTMS and esketamine have broadly comparable long-term suicide-related effectiveness in adults with TRD. However, there are nuanced temporal and safety considerations that may inform precision approaches to treatment. Specifically, esketamine was more efficacious in the acute 30–90-day interval in mitigating suicide risk. However, this study did have limitations given reliance on electronic health records, lack of baseline depression measurements, and lack of control for rTMS and esketamine protocols. While rTMS was associated with decreased rates of hospitalization, authors note that hospitalizations and ER visits could not be confirmed as psychiatric in origin. Prospective RCTs will be necessary to establish robust recommendations in the utilization of esketamine versus rTMS for TRD.

Chen JP, Hsu CW, Chen YT, et al. Comparison of rTMS and esketamine for treatment-resistant depression: A target trial emulation. J Affect Disord. 2026;399:121132. doi:10.1016/j.jad.2025.121132

TMS Improves Treatment-Resistant OCD Symptoms Independently of Concurrent Changes in Depression

Meghan Y. Reddy, MD reviewing Breiger et al., Transcranial Magnetic Stimulation, Apr 2025

This naturalistic study of patients with treatment-resistant OCD found that deep TMS using the BrainsWay H7 coil led to a 28.9% response rate for patients who completed a full course of at least 29 treatments. The reduction in OCD symptoms occurred independently of improvements in comorbid depressive symptoms, suggesting a direct therapeutic effect on OCD-specific neural circuitry.

While TMS is approved for the treatment of OCD, data regarding its effectiveness and the influence of comorbid MDD remain limited making it unclear whether OCD symptom relief is a direct result of the treatment or secondary to improvements in mood. This study sought to quantify response rates and determine if OCD improvement occurs as an independent phenomenon.

Researchers at McLean Hospital analyzed a naturalistic sample of 130 patients referred for TMS consultation for treatment-resistant OCD between 2019 and 2024. Following established protocols, each session included symptom provocation. Treatment utilized the BrainsWay H7 coil at 20 Hz at 100% RMT, with up to 36 treatments, targeting the

DMPFC. Each treatment delivered 50 trains with a 20-second intertrain interval, for 2000 total pulses. Symptom changes were tracked using YBOCS and QIDS. Of note, the primary analysis focused on the 45 patients who completed a full course of at least 29 sessions. Secondary analyses exploring response rates and trajectory of response focused on the 74 patients who received at least 10 treatments. Treatment response rates were calculated using unpaired t-tests. Linear regression models were used to investigate predictors of treatment response.

In the primary cohort, 28.9% of patients achieved clinical response (≥30% reduction in YBOCS) and 40.0% achieved a partial response (≥20% reduction in YBOCS). The average reduction in YBOCS scores was 4.78 points or 17.4%. Both obsessions and compulsions showed significant and comparable decreases with no significant difference in the magnitude of reduction. Regression analysis confirmed that YBOCS scores improved significantly over time when controlling for QIDS scores (p 0.0048), whereas depressive symptoms did not show a significant independent change when controlling for OCD improvement (p=0.82). When analyzing a subgroup of patients who also met clinical criteria for depression (N = 41), OCD responders (N = 11) experienced a larger reduction in their QIDS scores compared to OCD non-responders (N = 30; p=0.003). The depression response and remission rates for the OCD responders were also higher than the depression response and remission rates of the OCD non-responders. Predictors of a more robust OCD response included higher baseline YBOCS scores and lower baseline QIDS scores when considered in combination. In the secondary post hoc analysis, 23.0% of patients achieved clinical response. The average reduction in YBOCS scores at session 10 was 7.16% and 16.6% at session 36.

Impact: These findings provide evidence that the H7 TMS protocol is an effective intervention for treatment-resistant OCD. OCD response was independent of depressive symptom changes, suggesting that this protocol directly modulates the circuits associated with OCD pathophysiology. A notable limitation was the high rate of treatment noncompletion (41 of 86 participants; 48%), which may reflect the distress associated with symptom provocation during stimulation and which highlights important practical considerations for the real-world implementation and tolerability of TMS-based interventions for OCD.

Breiger M, Baldi S, Perlo S, et al. Patterns, predictors, and effectiveness of TMS for treatment-resistant OCD: A naturalistic study. Transcranial Magnetic Stimulation. 2025;4:100096. doi:10.1016/j.transm.2025.100096

A Pilot Study Suggests That rTMS Is Feasible And Acceptable, With Preliminary Evidence of Efficacy, For The Treatment Of Comorbid Chronic Low Back Pain And Insomnia.

Sheyna M. Nathwani, MD, reviewing Chang et al., J Pain. 2025 Dec.

This double-blind, sham-controlled RCT evaluated M1- and DLPFC-rTMS for patients with comorbid insomnia and chronic low back pain and demonstrated both feasibility and acceptability of rTMS. Preliminary evidence suggested superior benefits of DLPFC stimulation on sleep disturbance and pain processing.

Insomnia and sleep disturbances occur in over 70% of patients with chronic low back pain (CLBP). While cognitive behavioral therapy is the primary treatment for comorbid CLBP and insomnia, it may insufficiently address neurophysiological mechanisms and is often limited by adherence. Low-frequency rTMS targeting the DLPFC has been linked to sleep improvements, whereas high-frequency rTMS over M1 is tied to pain modulation. This study is the first to directly compare the feasibility and acceptability of these rTMS approaches with each other and sham stimulation, and to examine their preliminary effects on pain and sleep in individuals with comorbid CLBP and insomnia.

This double-blinded, three-arm, sham-controlled RCT involved 36 adult participants with CLBP, defined as scoring >3 points on the Numerical Pain Rating Scale. Participants also met criteria for insomnia after screening with the Brief Insomnia Questionnaire and with Pittsburgh Sleep Quality Index of > 5. Participants were randomized to one of three study arms: M1-rTMS, DLPFC-rTMS, or sham-rTMS. In the M1-rTMS group, 10 Hz with a total of 1500

pulses over 15 mins were applied to the left M1 (50 pulses per train, inter-train interval of 25 seconds, 30 trains per session). For the DLPFC-rTMS treatment group, 1 Hz with a total of 1500 pulses over 30 min were applied to the right DLPFC (150 trains of 10 pulses, inter-train interval of 2 seconds). Sham stimulation used identical parameters as the DLPFC treatment but was delivered via a sham coil. All participants underwent 10 treatment sessions over 2 weeks, with subsequent one-month follow up. Primary outcomes of treatment were feasibility and acceptability. Feasibility was measured by recruitment of at least 15 participants/week and >30% eligibility rate, while acceptability was measured by adherence rate > 70% and attrition rate < 20%. Secondary preliminary outcomes of pain and insomnia parameters were assessed at baseline, following treatment, and one month after treatment.

The study recruited an average of 19.2 participants per week over 16 weeks, screening 307 candidates, of whom 38.4% were eligible. Thirty-six participants were enrolled (n = 36), with 100% adherence and 0% attrition, thereby demonstrating both feasibility and acceptability of this treatment. At post-treatment, both M1-rTMS ($p_{corrected}$ = 0.001) and DLPFC-rTMS ($p_{corrected}$ < 0.001) significantly reduced pain intensity compared with sham stimulation, although only DLPFC-rTMS maintained this effect at one-month follow-up. No differences in insomnia outcomes were observed between M1-rTMS and sham-rTMS. In contrast, DLPFC-rTMS significantly reduced insomnia severity at post-treatment ($p_{corrected}$ = 0.030) and one-month follow-up ($p_{corrected}$ < 0.001) and resulted in lower wake after sleep onset compared with sham-rTMS ($p_{corrected}$ = 0.016) and M1-rTMS ($p_{corrected}$ = 0.038). Authors found that improvement in pain intensity correlated with reduction in insomnia severity post-treatment (r = 0.51, p = 0.002) and at one-month follow-up (r = 0.38, p = 0.022). Mild adverse events (e.g. headaches, dizziness, scalp pain, etc.) were reported by 11 participants (30.6%), with no serious adverse events and no group differences in event incidence (χ^2 = 1.83, p = 0.400).

Impact: This pilot randomized, double-blind trial demonstrates that rTMS is a feasible, safe, and acceptable intervention for adults with comorbid chronic low back pain and insomnia. Active stimulation over M1 or DLPFC reduced post-treatment pain intensity compared with sham, with DLPFC-rTMS showing more durable improvements in sleep disturbance and pain at one-month follow-up. These findings suggest rTMS—particularly DLPFC stimulation—may address both pain and sleep symptoms in this comorbid population and warrants evaluation in larger, fully powered randomized trials. Dual-site treatment (R DLPFC + M1) would be an interesting arm to include in future study to assess for additive effects. Limitations include the small pilot sample, short treatment and follow-up duration, lack of direct comparison of stimulation parameters, and limited generalizability due to exclusion criteria.

Chang JR, Sun ER, Jin M, Lin LG, Li SX, Lee JL, Huang FF, Kwan RL, Zheng DK, Samartzis D, Fu SN, Wong AY. The efficacy and safety of repetitive transcranial magnetic stimulation for comorbid chronic low back pain and insomnia: A randomized, double-blind, sham-controlled pilot trial. J Pain. 2025 Dec 31;40:106180. doi: 10.1016/j.jpain.2025.106180. Epub ahead of print. PMID: 41482216.

Home-Based, Non-Invasive Afferent Stimulation Of Occipital And Trigeminal Nerves Is Safe And Effective For TRD

Kaleab Tessema, MD PhD, reviewing Carpenter et al., Brain Stim., 2025 Aug

In this double-blind RCT (n=124 participants total), home-based external combined occipital and trigeminal afferent stimulation (eCOT-AS) demonstrated safety and superior efficacy over sham in treating moderate to severe TRD.

While neuromodulation approaches like ECT and TMS can be effective for management of TRD, they are often less accessible to patients due to limitations related to distance, time, and monitoring burden. Home-based devices that can deliver self-administered treatment could help address some of these barriers. The ProlivRx system (Neurolief Inc) is a wearable eCOT-AS device that delivers stimulation to branches of the occipital and trigeminal nerves using three pairs of electrodes. Given the putative roles of occipital nerve stimulation and trigeminal nerve stimulation in regulating brain regions related to depression (e.g., dorsal rostral pons, ACC, nucleus tractus solitarius), the authors aimed to investigate the safety and efficacy of eCOT-AS for treatment of TRD.

This double-blind, sham-controlled RCT was conducted across 13 sites and included 124 patients with moderate to severe MDD and unsuccessful antidepressant trials due to either insufficient response or poor tolerability. Patients were on stable antidepressant therapy for at least 4 weeks at baseline and remained on their regimen throughout the study. Patients were randomized to active or sham treatment for 8 weeks, with treatment consisting of self-administered eCOT-AS via the ProlivRx system (Neurolief Inc) twice per day on at least 5 days per week. Active treatment parameters were 130-300 μs phase duration, 80Hz pulse frequency, and 6.7mA-18mA peak current; sham parameters were 100 μs duration, 0.33 Hz frequency, and 5-10mA peak current for 3 minutes followed by a taper to 0.2mA. The double-blind phase was followed by an 8-week open-label phase consisting of active treatment with either the same regimen as above or less frequent treatment (3-4 sessions per week) for patients who experienced remission. Clinical status was assessed via HDRS, MADRS, CGI for illness severity (CGI-S) and improvement (CGI-I), and adverse event logging.

Data from a total of 124 patients comprised the ITT set and were analyzed for safety. Adverse events were largely non-severe and temporary, without any unexpected serious events. Data from 97 patients (47 active, 50 sham) who completed at least 70% of the prescribed treatment in the randomized phase comprised the modified ITT (mITT) set and were analyzed for efficacy. Active treatment was significantly superior to sham at week 8 in terms of HDRS17 decrease from baseline (difference=-2.61, CI [-4.79, -0.43], p=0.0196, Cohen's D 0.74), clinically significant improvement of at least 7 points in HDRS17 score (difference=29.7%, p=0.0034, NNT=3.4), and remission rate (difference=15.3%, p=0.0273). Analysis of the subsequent 8-week open-label phase revealed further improvement in HDRS17 response rate (48.8%, p=0.0215), conversion of 9 of 28 non-responders to responders (32.1%, CI [15.88%, 52.35%]), response maintenance in 11 of 13 responders (84.6%), numerically higher remission rate (difference=9.5%, p=0.2329), and conversion of 8 of 32 non-remitters to remitters (25%, CI [11.46%, 43.4%]). Active treatment also demonstrated greater improvement in CGI-S, CGI-I, and Q-LES-Q scores compared to sham, with further improvement during the open label phase.

Impact: This study suggests that home-based eCOT-AS may represent a more accessible neuromodulation approach that can safely and effectively improve depressive symptoms and quality of life in patients with MDD after unsuccessful antidepressant trials. Additional investigation could focus on, among many other areas, the role of antidepressants in the outcomes observed here, the treatment effects in more and less treatment-resistant populations, and the durability of benefits. Of note, this device has now gained FDA approval (as of January 2026) for home-based treatment of MDD that is unresponsive to antidepressant therapy.

Carpenter LL, George MS, Navarro N, Deutsch L, Leuchter AF. A Novel Home-Based, Combined Occipital and Trigeminal Afferent Stimulation Therapy for Major Depressive Disorder: Efficacy and Safety Results from a Double-Blind Multicenter Randomized Sham-Controlled Study. Brain stimulation. 2025;18(5):1695-1704. doi:10.1016/j.brs.2025.08.022

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
ECT (electroconvulsive therapy)
HFL (high frequency left, 10 Hz stimulation to left DLPFC)
HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent theta burst stimulation)
MST (magnetic seizure therapy)
TBS (theta-burst stimulation; TMS delivered as triplet burst pulses at 50 Hz, repeated at 5 Hz)
TENS (transcutaneous electrical nerve stimulation)
TMS (transcranial magnetic stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tDCS (transcranial direct current stimulation)
tACS (transcranial alternating current stimulation)
TPS (transcranial pulse stimulation)

BOLD (blood oxygen level dependent)
DTI (diffusion tensor imaging)
EEG (electroencephalography)
EMG (electromyography)
fMRI (functional magnetic resonance imaging)
MRI (magnetic resonance imaging)
MT (motor threshold)
RMT (resting MT)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
PTSD (post-traumatic stress disorder)
SUD (substance use disorder)
TRD (treatment resistant depression)

BAI (Beck Anxiety Inventory)
BDI (Beck Depression Inventory)
CGI (clinical global impression scale)
HAM-A (Hamilton Anxiety Rating Scale)
HAM-D / HDRS (Hamilton Depression Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)
MoCA (Montreal Cognitive Assessment)
PANSS (Positive and Negative Symptom Scale)
QIDS (Quick Inventory of Depressive Symptomatology)
YBOCS (Yale-Brown Obsessive Compulsive Scale)

ANOVA (analysis of variance)
AUC (area under the curve)
CI (confidence interval)
FDA (United States Food and Drug Administration)
ICA (independent component analysis)
ITT (intention to treat)
OR (odds ratio)
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)
SMD (standard mean difference)

BA (Brodmann area)
DLPFC (dorsolateral prefrontal cortex)
DMPFC (dorsomedial prefrontal cortex)
M1 (primary motor cortex)
mPFC (medial prefrontal cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)