# Absence of early mood improvement as a robust predictor of rTMS non-response in Major Depressive Disorder

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## Background

• Repetitive Transcranial Magnetic Stimulation (rTMS) is a safe, efficacious therapy for treatment-resistant Major Depressive Disorder (MDD) with minimal side effects.[1-4]

• Though numerous rTMS treatment protocols exist, insurers typically approve only 36 sessions for MDD, limiting the time clinicians have to optimize treatment parameters for each individual patient.[5]

• Early, accurate prediction of non-response could allow clinicians to change treatment approach earlier and potentially improve patient outcomes.

• This study evaluated if lack of improvement in *sleep*, *anxiety*, or *mood* as early as one or two weeks into treatment would predict rTMS non-response, defined as <50% improvement.

## Methods

• This retrospective study included 329 patients treated with a full six-week course of rTMS in the UCLA TMS Clinical and Research Program between August 2015 and March 2020 for an episode of non-psychotic MDD.

• Symptoms were assessed at pre-treatment baseline, after approximately every five treatment sessions, and at the end of treatment using the 30-item IDS-SR and Patient Health Questionnaire (PHQ-9).[6-8] S*leep*, *anxiety*, and *mood* measures were calculated at one and two weeks based on validated subscales of the IDS-SR30.[9]

• Multivariate linear regression analyses were performed using percent improvement in *sleep*, *anxiety*, and *mood* at one and two weeks (in separate analyses) as independent variables, baseline IDS-SR score as a covariate, and overall percent improvement in IDS-SR score as the dependent variable.

• We calculated the negative predictive value (NPV) of changes in *mood* and *sleep* across cut-off values ranging from 0-50% improvement at one and two weeks of treatment. We generated separate curves for subjects with moderate (26-38), severe (39-48), and very severe MDD (49-84) as measured by the IDS-SR.

## Results

**Table 1. Characteristics of subjects receiving rTMS**

| Characteristic | Total | Non-responders | Responders | Test statistic | p-value |
|---|---|---|---|---|---|
| N | 423 | 235 | 94 | | |
| Female | 223 (52.7%) | 127 (54.0%) | 54 (57.4%) | $\chi^2 = 2.94$ | 0.23 |
| Age | 46.0 ± 16.5 | 45.1 ± 16.0 | 46.2 ± 16.5 | t = 0.55 | 0.58 |
| Pre-treatment IDS-SR Score | 43.2 ± 11.1 | 44.1 ± 10.8 | 41.0 ± 11.2 | t = 2.36 | 0.02 |
| Pre-treatment PHQ-9 Score | 17.3 ± 5.3 | 17.6 ± 5.0 | 16.2 ± 5.4 | t = 2.17 | 0.03 |
| Pre-treatment *Sleep* Score | 5.5 ± 2.4 (0 - 12) | 5.5 ± 2.4 (0 - 12) | 5.2 ± 2.5 (0 - 12) | t = 0.90 | 0.37 |
| Pre-treatment *Anxiety* Score | 10.1 ± 4.5 (0 - 24) | 10.4 ± 4.6 (0 - 24) | 9.2 ± 4.2 (1 - 19) | t = 2.03 | 0.04 |
| Pre-treatment *Mood* Score | 20.0 ± 5.0 (3 - 32) | 20.4 ± 4.8 (3 - 31) | 19.1 ± 5.0 (3 - 30) | t = 2.21 | 0.03 |
| # of Psychotropic Medications | 2.6 ± 1.8 | 2.6 ± 1.8 | 2.5 ± 1.9 | t = 0.62 | 0.62 |

Data presented as mean ± standard deviation unless otherwise specified. Given the number of comparisons, we used *$p \leq 0.0038$ based on Bonferroni correction to avoid a Type I error.

**Table 2. Linear regressions examining subscale % improvement after treatment weeks one and two as predictors of overall symptom improvement**

| | | After 1 Week | | After 2 Weeks | |
|---|---|---|---|---|---|
| **Predictor** | **Dependent Variable** | **Coefficient** | **p-value** | **Coefficient** | **p-value** |
| Sleep % Improv | IDS-SR | 0.06 | 0.06 | 0.09 | 0.001* |
| | PHQ-9 | 0.02 | 0.70 | 0.04 | 0.32 |
| Mood/Cognition % Improv | IDS-SR | 0.43 | <0.001* | 0.41 | <0.001* |
| | PHQ-9 | 0.45 | <0.001* | 0.48 | <0.001* |
| Anxiety/Arousal % Improv | IDS-SR | 0.06 | 0.23 | 0.05 | 0.24 |
| | PHQ-9 | 0.05 | 0.44 | -0.01 | 0.91 |
| Pre-Treatment Composite IDS-SR Score | IDS-SR | -0.31 | 0.03* | -0.18 | 0.16 |
| | PHQ-9 | -0.26 | 0.20 | -0.18 | 0.35 |

Baseline IDS-SR score is included as a covariate. *$p \leq 0.05$.

**Figure 1. Plot illustrating the relationship between % chance of non-response (NPV) and % improvement in *mood*, stratified by baseline IDS-SR severity, after one (A) or two weeks (B) of treatment**

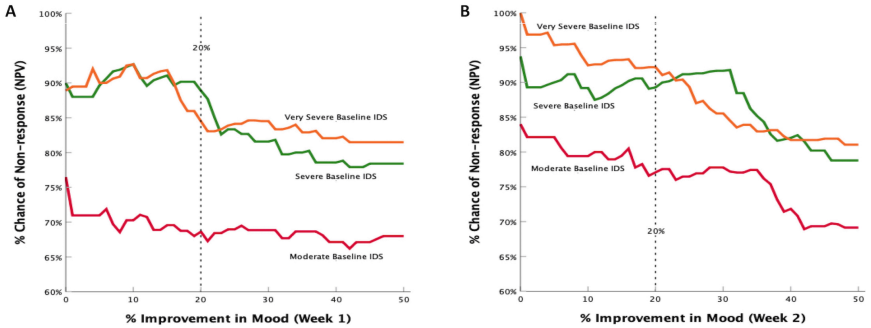
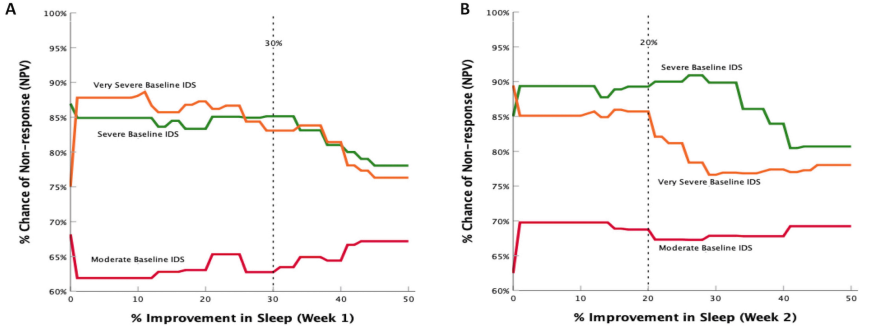



**Figure 2. Plot illustrating the relationship between % chance of non-response (NPV) and % improvement in *sleep*, stratified by baseline IDS-SR severity, after one (A) or two weeks (B) of treatment**




## Conclusions

• Subjects with severe or very severe baseline IDS-SR scores whose mood subscale score improved <20% by week one were highly likely to be non-responders at six weeks.

• Tracking mood items on the IDS-SR is a practical and robust method to predict rTMS non-response as early as one week into the standard six-week course of treatment typically approved by insurers.

## References

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