**Brief Report**

**Improving prognostic prediction in depression: The utility of pre-treatment symptom variability and trajectory**

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**Statement of Ethics:**

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by University of Haifa IRB committee. All adult participants provided written informed consent to participate in this study. Written informed consent was obtained from the individuals for publication of the details of their medical case and any accompanying images.

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**Introduction**

One of the empirical findings with greatest impact on clinical practice is that baseline depressive symptom severity predicts treatment outcomes. For instance, pooled individual patient data from 16 studies indicated that higher initial severity is significantly associated with lower remission rates across both medication and psychotherapy treatments [1]. The finding on the importance of baseline symptom severity for determining treatment outcomes has substantial implications for clinical practice, directly influencing critical treatment decisions such as whether to initiate treatment, determining expected prognosis, and selecting appropriate therapeutic approaches. Clinical guidelines worldwide, including those from the United States [2], Canada [3], and the United Kingdom [4], consistently use baseline depression severity as a determinant of treatment recommendations.

In recent years, the clinical utility of baseline depressive symptom severity as a predictor of treatment outcome has been increasingly questioned, as conflicting findings have begun to accumulate. It has even been suggested that current clinical guidelines for best practice may contradict recent scientific evidence [5]. Classic findings suggesting that baseline severity predicts differential success for specific treatments have failed to receive consistent empirical support [5]. Not less critical, severity may not even reliably predict general treatment outcomes. For instance, a comprehensive meta-analysis of 132 controlled psychotherapy studies with over 10,000 patients, found no evidence that higher baseline symptom severity predicted poorer response relative to controls [6].

These findings, casting doubt on the clinical utility of using baseline symptom severity as a predictor of clinical prognosis, seem counterintuitive to what many clinicians view as fundamental truths guiding their daily decision-making in treating depression. Indeed, clinicians conducting initial assessments for depression treatment routinely rely on their clinical impressions of symptom severity to determine clinical prognosis. *But could it be that clinicians gather a richer, more nuanced understanding of depression than what baseline severity scores—the cornerstone of much clinical research—can offer?*

Recent findings on the psychopathology of depression characterize mental health, and particularly depression, as highly dynamic and person-specific [7]. In other words, patients' depressive states before treatment initiation are not necessarily stable: some individuals show worsening symptoms pre-treatment, others demonstrate stability, and some even exhibit improvement. Patients differ not only in their symptom trajectories but also in the degree of symptom variability. Some show substantial day-to-day fluctuations in their depression severity, while others experience minimal or no fluctuations at all. This raises an important question: can this pre-treatment symptom dynamic (as manifested in trajectory and variability) provide clinically valuable prognostic information about a patient's likelihood of improvement, above and beyond what existing assessments (such as baseline Hamilton scores) are able to predict?

In the current study, we focused on the dynamics of depression (trajectory and variability) just prior to treatment commencement, as this period is most clinically relevant and immediately accessible for assessment by clinicians before starting treatment. We used a daily digital depression-assessment app, previously shown to have approximately 90% agreement with clinicians' Hamilton Depression Rating Scale evaluations, to capture depression dynamics during the week before treatment initiation (Days 1-7). We then examined whether these pre-treatment depression dynamics offer additional clinical utility by predicting treatment prognosis, above and beyond what baseline Hamilton scores alone could indicate.

**Methods**

Study setting and participants are described in details elsewhere [8, 9, and at clinicaltrials.gov Identifiers: NCT02728557 and NCT04576182]. Patients diagnosed with MDD (n=77) participated in one of two clinical trials of short-term psychotherapies for depression of 16 weeks; those with at least 3 daily assessments of pre-treatment depression were included in the analyses. The study was approved by the Institutional Review Board, and all patients gave informed consent in writing before screening.

The dynamic of depression was measured with the digital format of the Hamilton depression rating scale [10], and the HRSD itself [11] was administered at baseline and then weekly for the 16 weeks of treatment.

**Statistical Analysis**

To characterize pre-treatment individual dynamics, two within-patient binary parameters were computed: (a) linear trajectory (categorized as "improving" if slope < 0, or "worsening" if slope ≥ 0), and (b) variability, measured by the standard deviation (SD) and categorized as "low variability" (SD ≤ median of the sample’s SD) or "high variability" (SD > median).

The intersection of these two parameters yielded four distinct dynamic types for patient classification:

1. Improving + Low Variability
2. Improving + High Variability
3. Worsening + Low Variability
4. Worsening + High Variability

To predict HRSD severity across treatment, a linear mixed-effects model was fitted with fixed effects for session, dynamic type, and their interaction. Baseline HRSD score was included as a covariate. A random intercept was specified for each patient. All analyses were conducted using R (version 4.4.0).

**Results**

The distribution of pre-treatment dynamic types was as follows: Improving + Low Variability (n = 19, 24.7%), Improving + High Variability (n = 15, 19.5%), Worsening + Low Variability (n = 20, 26.0%), and Worsening + High Variability (n = 23, 29.9%).

Table 1 summarizes results from the linear mixed-effects model predicting changes in HRSD scores across treatment sessions. A significant interaction was observed between session and the Worsening + High Variability group (β = –0.22, 95% CI: –0.33 to –0.10, p < .001), indicating a significantly steeper improvement trajectory compared to the reference group (Improving + Low Variability).

Simple slope analyses (Table 2, Figure 1) revealed that all four trajectory groups significantly improved over time (all slopes negative, p < .001). Notably, patients characterized by initially worsening symptoms and high variability demonstrated the fastest improvement, significantly outperforming the other groups. No significant differences were found among the remaining three groups, which showed broadly similar rates of symptom reduction.

These findings indicate that while all groups improved significantly, individuals with initially worsening and highly variable depressive symptom dynamics exhibited the strongest response.

**Discussion**

The results suggest that individuals entering treatment with initially worsening and unstable depressive symptom patterns (high variability) demonstrated the greatest treatment efficacy. The contribution of these findings extends beyond what could be inferred solely from baseline Hamilton scores. Clinically, these findings highlight the importance of assessing not only the severity but also the dynamic nature (trajectory and variability) of depressive symptoms shortly before treatment initiation, offering clinicians valuable prognostic information to guide treatment decisions.

Since we aimed to provide analyses that could directly inform clinicians' decision-making based on the short timeframe immediately preceding treatment initiation for individuals undergoing treatment for depression, our study focused exclusively on participants exhibiting clinical depression, specifically during the week prior to treatment onset. Future research could extend the assessment period to evaluate depressive symptom dynamics over longer durations and include a broader spectrum of participants, encompassing subclinical populations and individuals without depression, to further enhance the generalizability and clinical relevance of these findings. Future studies utilizing larger datasets could explore additional, more complex patterns of depression dynamics, as well as their potential role in predicting and moderating treatment outcomes.

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**Table 1. Linear mixed-effects model predicting HRSD change across treatment**

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictor** | **β** | **95% CI** | ***p*** |
| Session | –0.32 | –0.41 , –0.24 | <.001 |
| Trajectory Type (ref: Improving + Low Variability) |  |  |  |
|   Improving + High Variability  | 0.18 | –2.50 , 2.80 | .90 |
|   Worsening + Low Variability | 1.50 | –1.00 , 4.00 | .20 |
|   Worsening + High Variability  | 0.23 | –2.20 , 2.60 | .80 |
| Baseline HRSD | 0.44 | 0.26 , 0.62 | <.001 |
| Session × Trajectory Type |  |  |  |
|   Session × Improving + High Variability  | 0.01 | –0.13 , 0.15 | >.90 |
|   Session × Worsening + Low Variability | 0.00 | –0.13 , 0.13 | >.90 |
|   Session × Worsening + High Variability  | –0.22 | –0.33 , –0.10 | <.001 |

**Table 2. Estimated slopes by trajectory type**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trajectory Type** | **Estimated Slope** | **SE** | ***t*** | ***p*** |
| Improving + Low Variability | –0.32 | 0.04 | –7.38 | <.001 |
| Improving + High Variability  | –0.32 | 0.06 | –5.43 | <.001 |
| Worsening + Low Variability | –0.33 | 0.05 | –6.54 | <.001 |
| Worsening + High Variability  | –0.54 | 0.04 | –13.37 | <.001 |

**Figure 1. Depressive symptom reduction over treatment sessions by pre-treatment symptom dynamics**

