Using Active and Passive Digital Phenotyping to Increase Signals in Early-Stage Drug Development Trials

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Background:

- Clinician reported outcomes (ClinROs) in CNS and Neurological Disorders are subjective, highly dependent on experience and expertise of clinical raters, and can be impacted by poor reliability from a range of potential sources of error.
- Early phase CNS studies are often underpowered for statistical significance on ClinROs (i.e., MADRS in MDD); as a result, blinded trials may not be feasible because of the risk/benefit analysis.
- An alternative strategy is dense sampling with ecological momentary assessments (EMAs) that include active and passive data collection. This approach could increase statistical power, reduce the risk of potential placebo effects, and help validate beneficial elements of a novel compound.

Methodological Issues Addressed :

- A strategy to reduce the risk of placebo effects and enhance the ability to capture beneficial elements of novel compounds is to increase the volume of data collected and collect data that uses technology-based approaches collecting densely sampled data actively and passively.
- EMA surveys examining activities and symptoms have shown significant convergence with primary endpoints in negative symptoms of schizophrenia[1] (p<.001 for NSA-16 total and item scores) and depression[2] (p<.001, change on clinician rated HAMD-6 over 6 weeks).
- Adherence rates to daily EMAs has been over 70% in previous studies[3].
- EMA derived symptom scores appear to be efficient and valid measures to track daily symptomatic change in clinical trials, repeatedly predicting results of later in person clinical ratings. [1,2]

Results:

- In a small, unblinded study, passive and active digital phenotyping assessments converged with and predicted later clinical ratings on the MADRS and HAM-A, with high levels of adherence observed
- Digital phenotyping content that is not an obvious element of an efficacy assessment (productive activities, nighttime sleep, step counts) correlated with concurrent ratings and anticipated later clinical ratings.
- EMA assessments are an accurate reflection of symptoms and behaviors leading up to the dispersed clinical ratings.
- EMAs as a cost-effective, technology-based assessments can generate robust, dense data that could not be feasibly collected with traditional, in person clinical ratings. To obtain 658 data points for an in-person study with 6 assessments, over 100 participants would be required.

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Methods:

- 13 participants were treated with ANC-501 50mg, a Vib receptor antagonist, adjunctive to ongoing AD medication in a non-blinded design for 8 weeks,
- Non-blinded design that included 8 weeks of clinical ratings of depression (MADRS) and anxiety (HAM-A), collected at days 1, 8, 15, 29, 43, and 56.
- EMA sampling conducted three times daily over the course of the study, totaling 658 unique assessments using a downloadable app and BYOD.
- EMAs included a HAMD-6, modified GAD-7, and validated survey of daily activities which included location, social context, productive and unproductive home-based activities and away from home activities. A smart watch also measured daily steps.
- Adherence to individual EMA surveys was 65%, with over 75% of participants completing at least survey per day.

Analysis and Results

Data analyses included changes in symptoms based on in-person and EMA assessments of symptoms as well as EMA-based assessments of activities and daily steps. Concurrent and lagged analyses were used to determine if EMA and actigraphy-based assessments both converged with and predicted symptoms assessments (MADRS and HAM-A)

Figure 1: Pooled EMA (HAMD-6) weekly analysis and MADRS mean at time points of administration..

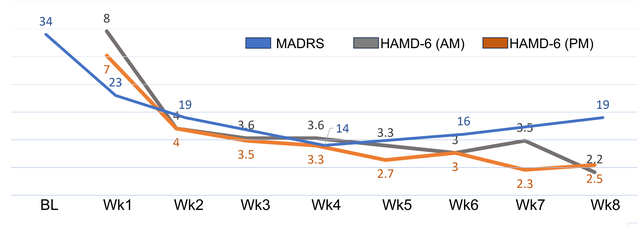

Figure 2: Pooled EMA (modified GAD-7) weekly analysis and HAM-A mean at time points of administration..

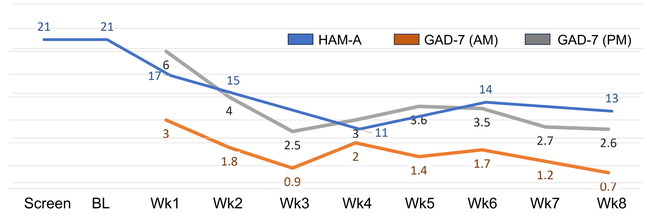

Figure 3: Effect size, Week 8 (Paired sample t-tests). * = p < .02.
Strong convergence of MADRS and HAM-A clinician ratings with daily EMA HAMD-6.

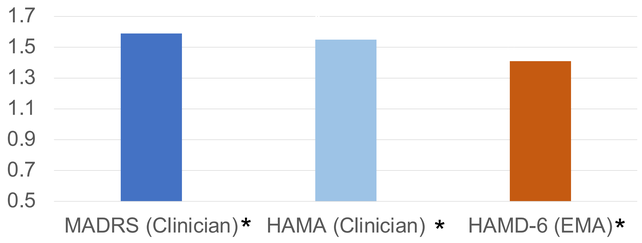

Figure 4, Correlation Twice daily EMA assessments (HAMD-6) averaged across week and in clinic MADRS ratings were highly correlated at all study visits evaluated (all r>.05)

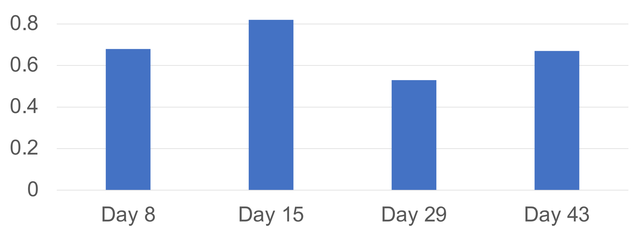

Figure 5, Lagged correlation of EMAs and MADRS:
Changes in daily EMA-rated depression (HAMD-6) up to day 15 predicted MADRS clinical ratings at day 29. EMA changes (HAMD-6) up to days 15 and 29 predicted changes in clinical MADRS ratings at day 43. (all r>.45)

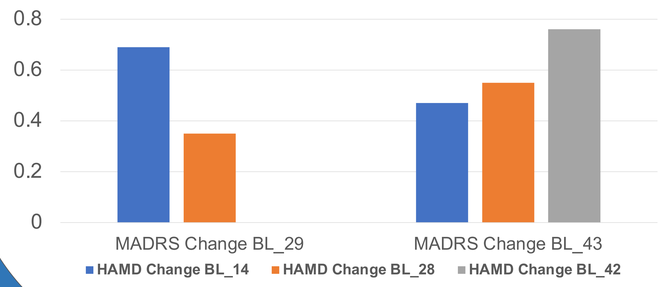

Figure 6. Lagged correlation of productive activities and MADRS:
Productive activities reported on EMAs increased significantly over time during the study (p=.02). Productive activities from baseline to days 8, 15, and 29 predicted MADRS ratings of depression at the later timepoints in the study.