Longitudinal Convergence Between Dispersed In-Person Clinical Ratings and Remote Ecological Momentary Assessments (EMAs) of Negative Symptoms in Schizophrenia

ISCTM

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Methodological Issue Being Addressed

- Traditional clinical trials for negative symptoms involve dispersed in-person assessments that can occur several months apart, posing a substantial recall burden
- The ecological momentary assessment (EMA) method has the potential to capture rich, in-the-moment reports of emotions and experiences related to negative symptoms while minimizing recall demands
- In the context of a 12-month open-label trial, this convergent validity study evaluated the relation between monthly burst EMA assessments and interspersed in-person clinical ratings of negative symptoms

Introduction

- The behavioral indicators of reduced emotional experience negative symptoms include attenuated emotional responses and increased amounts of being home, alone, and engaging in unproductive and asocial activities
- Previous treatment studies have suggested that increases in positive mood states (positive affect [PA]) are associated with reductions in other elements of negative symptoms[1]
  - Those previous studies also found that clinical assessments of social functioning conducted every 12 weeks did not identify these changes
- The current trial used a more comprehensive clinical assessment of negative symptoms, but assessments were still dispersed by approximately 4 months, requiring an extended recall period

Aims

- We evaluated whether EMA surveys assessing behavioral indicators of reduced experiential negative symptoms correlated with subsequent clinical ratings on the Negative Symptoms Assessment (NSA)[2]
- To evaluate the potential impact of attrition, we separately examined EMA predictors of the month 4 NSA assessment and the final NSA assessment available for each participant

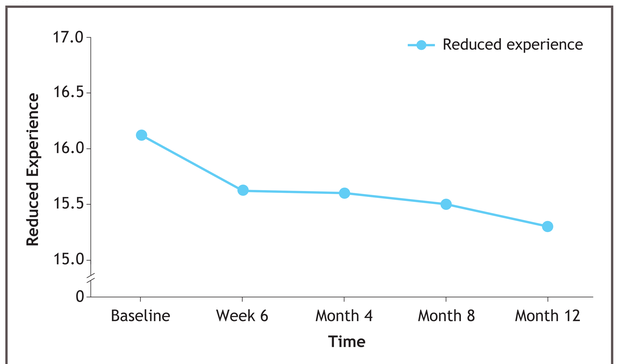
Methods

- During the 12-month, open-label EMERGENT-5 trial (NCT04820309) of KarXT (xanomeline and trospium chloride) in schizophrenia, the NSA was administered at week 6 and months 4, 8, and 12 (or final assessment)
- We were interested in reduced emotional experience, defined on the NSA by the sum of the following items: reduced interest in intimacy, reduced social drive, reduced sense of purpose, reduced productive activities, and reduced interest in hobbies
- Participants completed EMA surveys 3× per day, 7 days per week, 1 week per month for up to a year. Hierarchical linear modeling (HLM) using full information maximum likelihood procedures examined whether EMA variables predicted subsequent NSA scores at the early (month 4) and final (last available) time points
- The proportion of EMA surveys answered at home, alone, and while engaging in productive, passive, or unproductive activities were the negative symptom indicators extracted from EMA
- Concurrent momentary PA (happy and relaxed) level was also used as a predictor
- Time since baseline defined the repeated-measures factor, and baseline NSA scores were included as a covariate in the HLM

Results

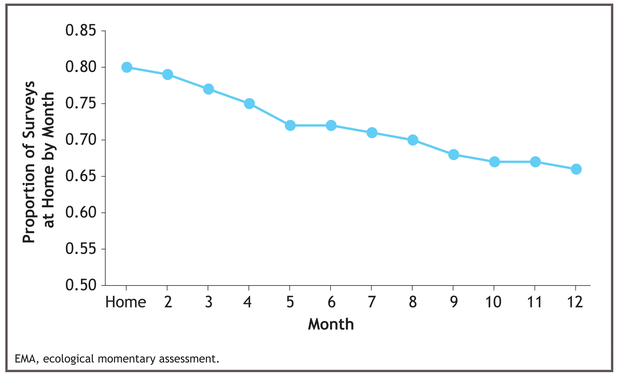
- Of a total 450 enrolled participants, 70% completed a month 4 NSA assessment; 12-month NSA completion rates were slightly above 50%
- 12,636 EMA surveys were completed by participants prior to their month 4 NSA analyses, and 25,548 surveys were completed by participants who had an NSA endpoint assessment
- Across the overall 12-month trial period, there were significant changes from baseline, with both NSA ratings and EMA variables improving over time. Changes from baseline for NSA reduced emotional experience were significant at both 4 months (P<0.001, d=0.22; **Figure 1**) and the final assessment (P<0.001, d=0.40)
- During the first 4 months of EMA data collection, significant time effects on EMA variables reflected decreases in surveys answered when home (P<0.001; **Figure 2**) and alone (P<0.001; **Figure 3**) as well as for increased productive (all P<0.01; **Figure 4**), reduced passive and unproductive activities (both P<0.009; **Figure 4**), and higher PA (P<0.001; **Figure 5**) compared with baseline. During the entire protocol, using the final NSA available for each participant, the significance of the EMA effects was essentially identical to that seen in the first 4 months

Figure 1. Course of NSA reduced experience over assessments



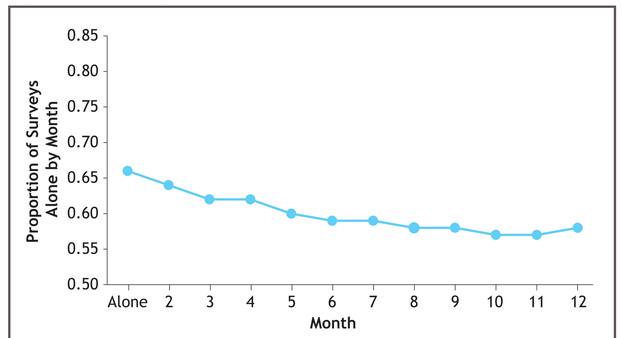
NSA, Negative Symptoms Assessment.

Figure 2. EMA surveys answered at home



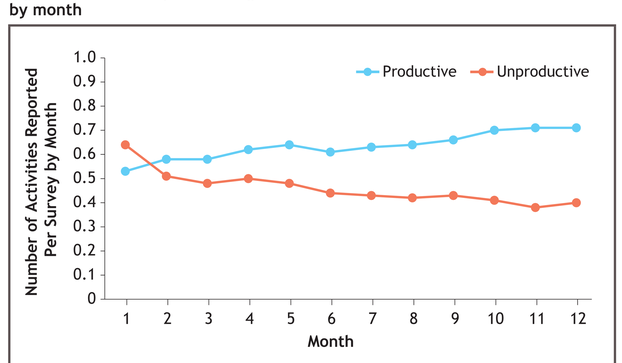
EMA, ecological momentary assessment.

Figure 3. EMA surveys answered alone



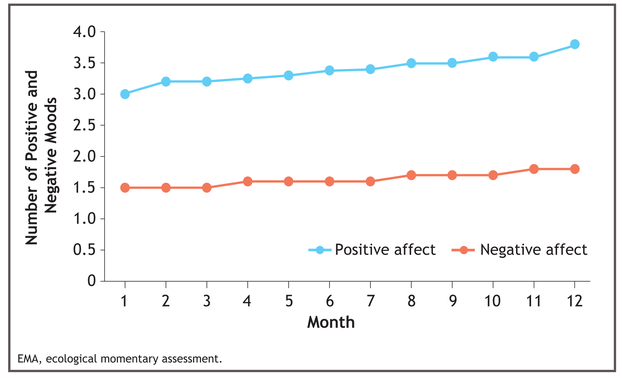
EMA, ecological momentary assessment.

Figure 4. EMA surveys reporting productive and unproductive activities by month



EMA, ecological momentary assessment.

Figure 5. Positive and negative moods intensity assessed by EMA per month



EMA, ecological momentary assessment.

- Baseline NSA ratings were significantly correlated with the set of EMA variables collected at month 4. The time course of the EMA variables jointly predicted lower month 4 NSA ratings (P<0.0001); only the number of surveys answered at home was not an independent significant predictor (all P<0.012). Similarly, analyses on the final NSA available for each participant indicated that the time course of all of the EMA variables predicted NSA ratings collectively (P<0.00001) and individually (P<0.001) (**Table 1**)
- Shared variance was similar for EMA predictions of month 4 and final NSA ratings (**Table 2**)
- As baseline NSA scores share 17% of the variance with month 1 EMA scores, the overlap between EMA scores and repeated NSA assessments is larger than the shared variance estimates presented

Table 1. Prediction of NSA reduced emotional experience scores at month 4 and final postbaseline reassessments

	Month 4 Reassessment			Final Reassessment		
Predictor	χ^2	df	*P* value	*P* value	df	*P* value
Omnibus	4525.06	26	<0.001	9731.36	62	<0.001
Intercept	314.61	1	<0.001	772.64	1	<0.001
Home	0.08	1	0.77	178.43	1	<0.001
Alone	13.92	1	<0.001	98.10	1	<0.001
Month	5.67	3	0.13	5.98	11	0.20
Unproductive	76.07	6	0.009	152.54	6	<0.001
Passive	12.67	2	<0.001	76.54	2	<0.001
Productive	10.91	3	0.012	151.75	3	<0.001
Positive affect	262.70	5	<0.001	330.63	5	<0.001
Baseline covariate	5132.27	1	<0.001	9207.52	1	<0.001

NSA, Negative Symptoms Assessment.

Table 2. NSA reduced experience ratings with EMA variables and baseline NSA scores

NSA Time Point	EMA Variable (%)	Baseline Reduced Emotional Experience (%)
Baseline (month 1)	17	-
Month 4 (months 1-4)	15	28
Endpoint (month 1-endpoint)	12	29

EMA, ecological momentary assessment; NSA, Negative Symptoms Assessment.

Discussion and Conclusions

- NSA ratings and EMA indices of experiential negative symptoms both improved during a 12-month open-label trial of KarXT. Further, the EMA indicators significantly predicted subsequent NSA scores across early and late phases of the trial, suggesting that EMA-related changes are meaningfully related to NSA changes detected by clinical raters
- These findings support the validity of EMA as a negative symptom assessment method that minimizes burdens associated with recall and with in-person clinical assessments

References

1. Browne J, et al. *Behav Sci (Basel)*. 2022;12(3):60.
2. Alphs LD, et al. *Psychopharmacol Bull*. 1989;25(2):159-163.

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Declaration of interests

WPH, SAC, AC, TRP, and **IK** are employees of Bristol Myers Squibb. **PDH** is a consultant for Alkermes, Boehringer-Ingelheim, BioXcel, Karuna Therapeutics, a Bristol Myers Squibb company, Merck, Minerva Pharmaceuticals, SK Pharma, and Sunovion/DSP and has received royalties from VeraSci.

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