

Convergence of Active and Passive Digital Phenotyping of changes in physical activity in Younger and Older Adults with Schizophrenia In a 52-Week, Open-Label Clinical Trial Of Xanomeline and Trospium Chloride

Philip D. Harvey,^{1,2} Soumya A. Chaturvedi,³ William P. Horan^{3*} Amy Claxton,^{3*} Colin Sauder,^{3*} Tejendra R Patel,^{3*} Inder Kaul^{3*}, John N. Saber²

¹University of Miami Miller School of Medicine, Miami, FL, USA ²EMA Wellness, Boston, MA, USA; ³Bristol Myers Squibb, Princeton, NJ, USA



Methodological Issues Addressed:

- Digital phenotyping, including active assessments with remote ecological momentary assessment (EMA) and passive measures such as facial and vocal expression, GPS, and actigraphy, are being used more commonly in clinical trials.
- Although these measures appear to have a number of positive features, EMA surveys are essentially unsupervised self-reports.
- As self-report is challenging in schizophrenia, strategies for evaluation of convergent validity of these EMA reports are important.
- Further, treatment studies targeting cognition and negative symptoms have sometimes included an upper age limit; in this study we examine the treatment related effects and convergence of active and passive digital phenotyping in older (Age>44) and younger participants with schizophrenia
- We address convergence of active and passive digital indices of physical activity and age-related differences in baseline and treatment related changes in physical activity variables.

Background:

- Previous research has suggested that negative symptoms may worsen with age in schizophrenia.
- Elements of negative symptoms, such as avolition, anergia, and amotivation, are defined in part by reduced physical activity.
- Thus, we examined age-related differences in physical activity with active and passive digital phenotyping in a 12-month open-label trial with xanomeline/trospium chloride (X/T).
- We also report month x month changes across in outcomes across older and younger age groups in an effort to understand age-related differences in baseline performance and changes with treatment.

Study Over-View:

- In a 12-month study of xanomeline/trospium (XT) in schizophrenia, ecological momentary assessment (EMA) and fit bit actigraphy were used to capture active and passive digital phenotyping information.
- We examined changes in behavioral topography indexed by the frequencies of activities such as sleeping or resting (recumbent), sitting, standing, and moving, as well as step counts from the actigraphy.

Data Analysis Strategy

Hierarchical Linear Modeling, in a mixed models repeated-measures design

- Random Subject Intercept
- Repeated measures effects of survey month
- Analyses for proportion of surveys in which each experience was engaged
- Different activity types could occur at each survey
 - Proportion of surveys with each activity was the outcome
- Dynamic covariate analyses were used to examine convergence of the course of different activities and steps, as well as Mood variables

Participants:

- Participants with schizophrenia were:
 - Taking antipsychotic medication currently
 - Willing to change to X/T
 - Willing to participate for 12 months
- **EMA Survey Strategy:**
- Participants answered 3 EMA surveys per day delivered by a smartphone,
- 7 days a week, one week per month for 12 months
- Participants were paid \$1.00 per survey and their running total compensation was displayed on the device
- Participants wore a fit bit actigraph on all EMA survey days
- **EMA Survey Content:**

Surveys occurred in a fixed order and were in three forms based on location and social context:

- Home alone
- Home with someone
- Away

Mood states were assessed at each survey

- Happy and relaxed defined Positive Affect (PA)
- Sad and Anxious defined Negative Affect (NA)

EMA Activity Definitions:

- Recumbent Sleeping, Resting
- Seated Sitting alone, watching television, listening to music, reading, talking, joint social activities
- Standing Cooking, grooming,
- Moving Exercise, all activities that required leaving home and traveling

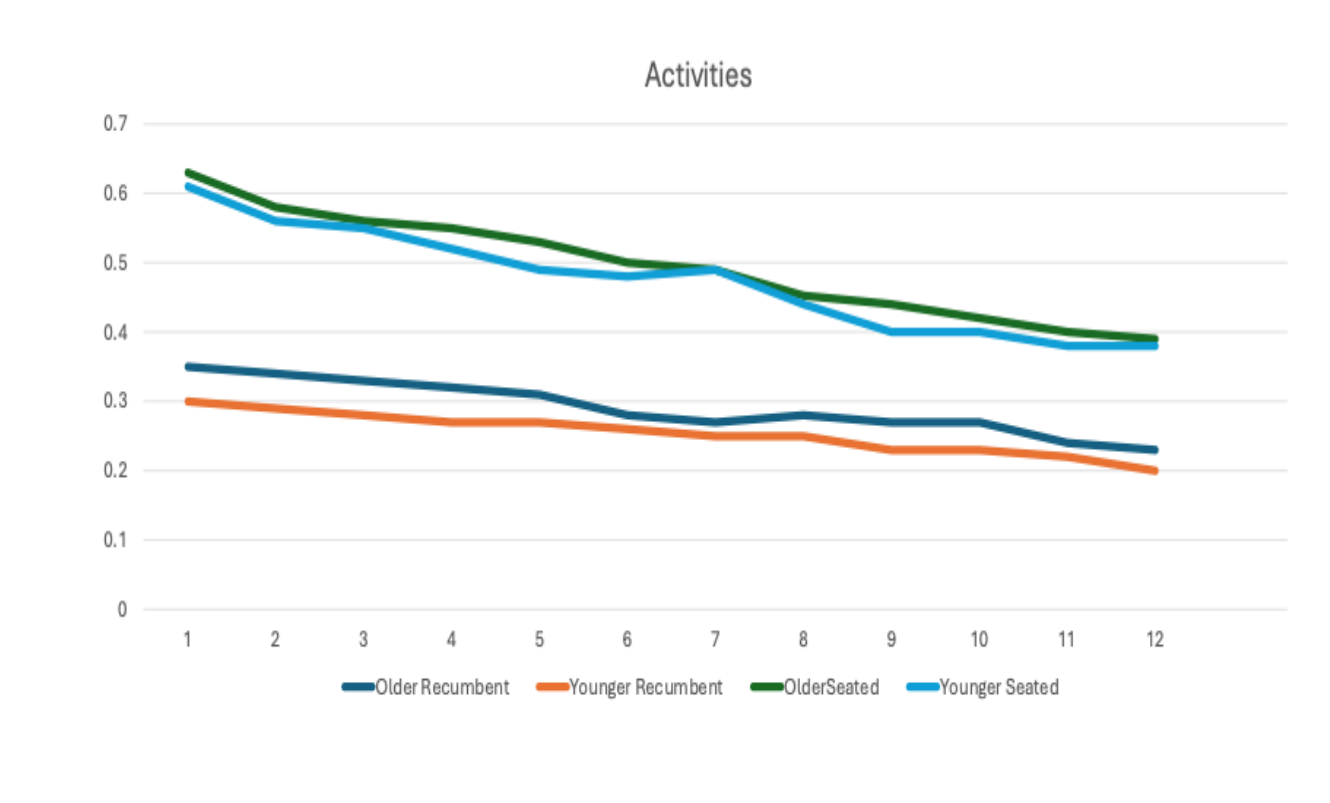
Actigraphy Dependent Variable

Total Daily Step counts on EMA days

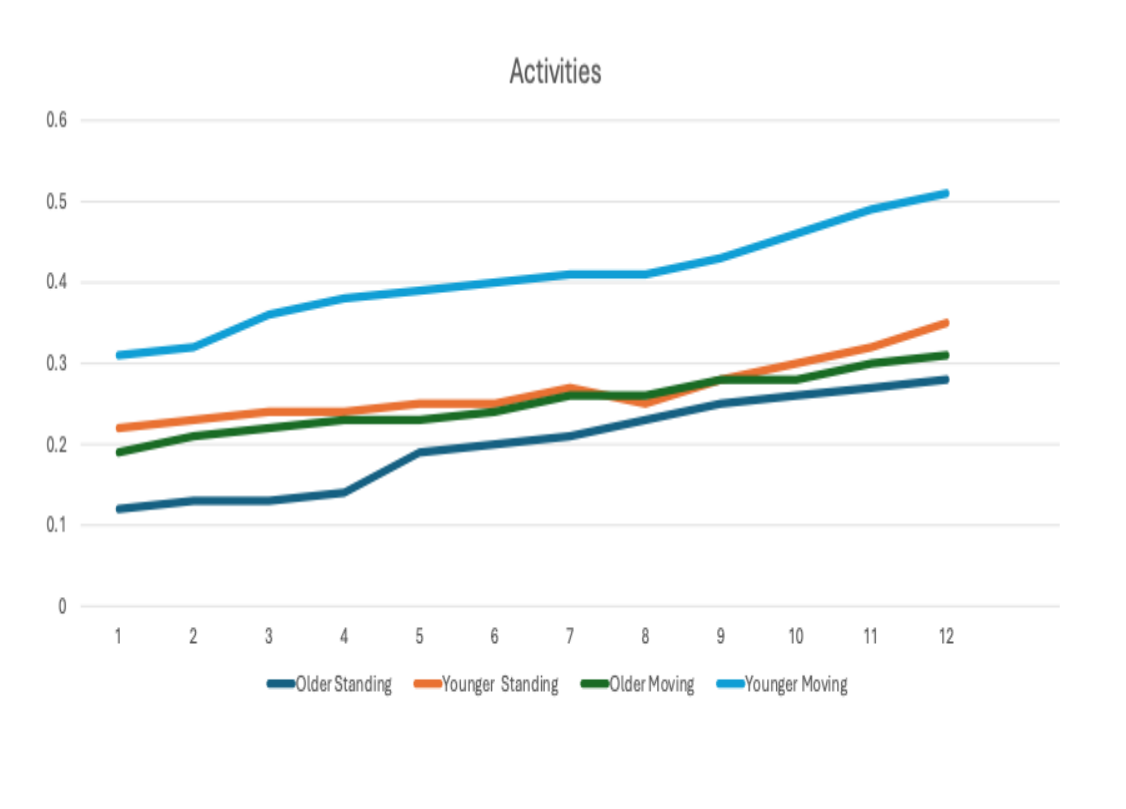
Results

- There were 350 participants who met the predetermined 33% EMA daily adherence criteria during the baseline period and 312 (89%) who also provided actigraphy data on their EMA days.
- These participants had overall adherence to EMA surveys of 75% during their study participation.
- The 312 doubly adherent participants answered 33,657 EMA surveys and provided 7957 participant-days of actigraphy.
- At baseline, older participants were home more frequently ($p<.001$), had lower step counts, ($p<.001$), more recumbent and seated activities (both $p<.001$) and fewer standing and moving activities (both $p<.01$).
- There were treatment-related reductions in recumbent and seated activities, increases in standing and moving activities, ($p<.001$) and daily steps over 12 months, ($p<.001$).
- Step counts were correlated with answering more surveys at home ($p<.001$) and the frequency of all 4 activities at baseline ($p<.001$).
- Changes in step counts correlated with changes in all 4 activities in the expected direction, with the significance levels all less than 1×10^{-6} .

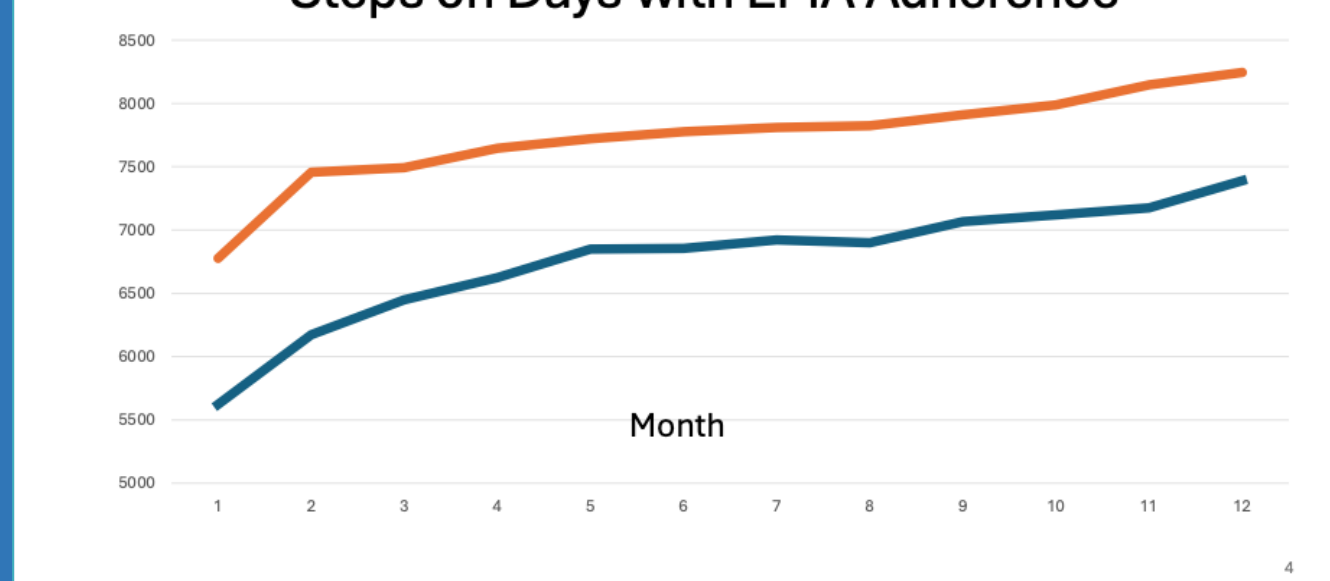
Activity Frequency per Survey over 12 Months: Sedentary activities



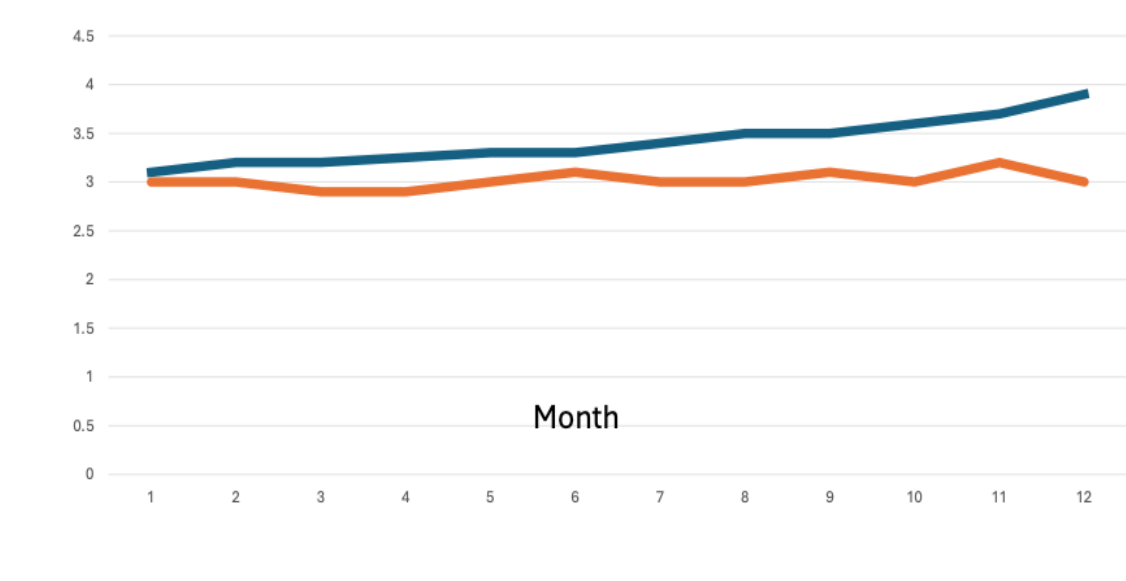
Activity Frequency per Survey over 12 Months: Standing and Moving activities



Number of Daily Steps per Month: Steps on Days with EMA Adherence



Positive Affect by Month



Differences in Daily Step Counts Associated with Momentary Frequencies of Sedentary and Physically Demanding Activities

Increase in Steps Associated with a Momentary Difference Of one activity

Activity	LS Mean	SE	X ²	p
Decrease in Recumbent	557.59	95.15	50.63	<.001
Decrease in Seated	862.14	90.69	108.00	<.001
Increase in Standing	734.51	119.25	52.63	<.001
Increase in Moving	1181.46	97.70	238.60	<.001

Conclusions:

- Active and passive digital phenotyping indices were highly correlated at baseline and improved in concert with treatment, suggesting substantial convergent validity.
- A previous study similar convergence between GPS data and reports of geo-location.
- There were age-related differences in physical activities related to negative symptoms in schizophrenia, but these features changed with treatment, the potential to lead to improvements in health outcomes as well as everyday functioning.
- These data add to the rapidly growing validity database for active and passive digital phenotyping as clinical trials outcomes measures.

