Clustering of Medication Adherence Trajectories

Pironet A[1], Demonceau J[1], Vera M[2], Blahova Z[3], Reuteman-Fowler C[4], Bajc M[2], Vrijens B[1]

[1]AARDEX Group, Belgium
[2]Boehringer Ingelheim Canada, Ontario
[3]Boehringer Ingelheim RCV GmbH & Co KG, Austria
[4]Boehringer Ingelheim International, Germany
Contact: antoine.pironet@aardexgroup.com

Introduction

- Electronic monitoring of medication adherence can be performed using smart packages, which record each time a participant removes a pill.
- This fine-grained longitudinal data is difficult to process visually and to translate into action when many participants are involved.

Aim

- Selecting and validating clustering techniques that can reliably and objectively categorize complex, longitudinal medication adherence behaviors in large datasets.
- To enable better data visualizations and clinical decision-making.

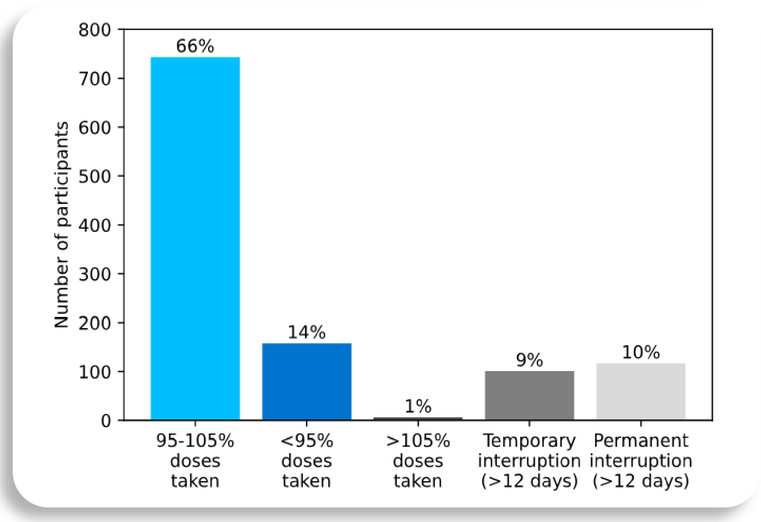
Method

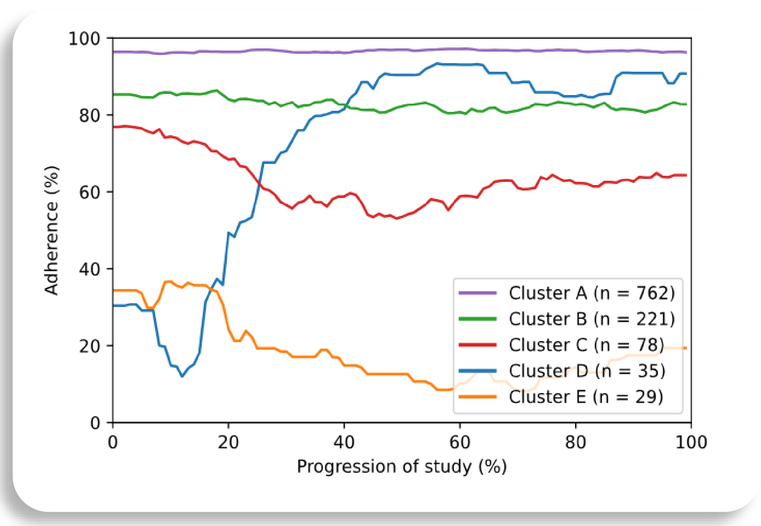
- The CONNEX-X trial (NCT05211947) involved participants with schizophrenia taking iclepertin once daily for 365 days.
- Medication adherence was monitored using smart blisters (Schreiner Group, Germany).
- Blister data was collected at site visits using MEMS® Adherence Software (AARDEX Group, Belgium).
- For each participant, the daily number of medication intakes was computed from the blister data.
- Daily medication adherence was computed as a 0/1 variable indicating whether exactly one dose was taken on a given day.
- Two clustering algorithms were applied to the daily medication adherence data:
  1. Classification rules from the Non-Adherence Research Consortium (NARC) [1], based on
     - the proportion of doses taken
     - the duration of treatment interruptions.
  2. *k*-means (with 2 to 10 clusters) applied to smoothed daily medication adherence curves.
- Cluster consistency was evaluated using the silhouette coefficient.
- Cluster stability was evaluated by separately clustering the two halves of the dataset [2].

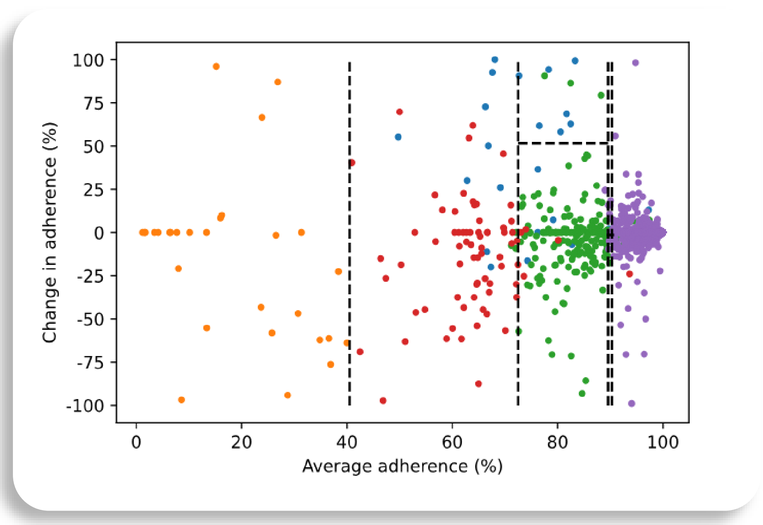
Results

- The trial ran from August 2022 to January 2025.
- Adherence data from 1,125 participants were available for analysis.
- The median follow-up duration was 294 days (Q1: 148, Q3: 365).
- A total of 265,972 medication intakes were recorded and analyzed.
- The results of the NARC classification are displayed in the upper Figure.
- The NARC clusters are easily interpretable, but do not allow to visualize the temporal evolution of adherence.
- The results of the *k*-means clustering are displayed in the central Figure.
- The *k*-means clusters have to be interpreted, which can be automated using a decision tree with 2 simple features:
  - Cluster A (N = 762): average adherence > 90%
  - Cluster B (N = 221): average adherence between 73% and 90%, with change < 52 % (mostly stable)
  - Cluster C (N = 78): average adherence between 40% and 73%
  - Cluster D (N = 35): average adherence between 73% and 90%, with change > 52 % (increasing)
  - Cluster E (N = 29): average adherence < 40%
- The results produced by the decision tree are shown in the bottom Figure.
- The concordance between *k*-means and decision tree labels was 95%, meaning that the simple decision tree can reproduce *k*-means labels.
- Cluster consistency, measured using silhouette coefficient:
  - NARC: 0.26 (weak)
  - *k*-means: 0.46 (reasonable)

  The silhouette coefficients indicate that there is no strong cluster structure in the data, as visible in the bottom Figure.
- Stability of the clusters:
  - NARC: 27% (meaning that the NARC clusters do not naturally emerge when using subsets of the data)
  - *k*-means: 100% (meaning that *k*-means clusters remain identical when using subsets of the data).







Conclusion

- Electronic monitoring of medication adherence provides fine-grained data on participants' medication-taking behavior.
- This rich data (265,972 medication intakes) is not easy to process visually and to translate into action.
- A standard clustering algorithm produced consistent, stable, and visually clear clusters of trajectories (central Figure).
- In addition, using a decision tree also made these clusters interpretable (bottom Figure).
- This approach makes electronic medication adherence data more actionable.

References

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2. Tibshirani, R., & Walther, G. (2005). Cluster validation by prediction strength. *Journal of Computational and Graphical Statistics*, *14*(3), 511-528.

Disclosures

- One or more authors report potential conflicts which are described in the program