Clusters of psychiatric comorbidities and concomitant medications of participants in three randomized controlled trials (VANILLA, V1aduct, aV1ation) with autism spectrum disorder

Yajing Zhu[1], Teresa Gleissl[2], Kevin Sanders[2], Lisa Squassante[2], Lorraine Murtagh[2], Silke Ahlers[2], Asif Jan[2], Janice Smith[1]

[1] F. Hoffmann-La Roche Ltd, Welwyn Garden City, UK; [2] F. Hoffmann-La Roche Ltd, Basel, Switzerland

Disclosures

YZ, TG, KS, LS, LM, SA, AJ, and JS are employees of F. Hoffmann-La Roche.

Sponsored by F. Hoffmann-La Roche Ltd; writing and editorial assistance was provided by Nikki Black of Articulate Science, UK.

Background

- Autism spectrum disorder (ASD) is a complex heterogenous neurodevelopmental condition with the core symptoms of challenges in social communication and interaction, and restricted and repetitive patterns of behavior[1]
- Concomitant psychiatric comorbidities are common in children with ASD with a 2006 study of 109 children reporting 72% of children having at least one co-occurring psychiatric comorbidity[2]
- Polypharmacy is also common amongst individuals with ASD; in a study of 33,565 children with ASD, 35% had evidence of psychotropic polypharmacy (≥2 classes), and 15% used medications from ≥3 classes concurrently[3]
- Individuals with ASD with similar psychiatric comorbidities and concomitant medications may have a similar level of disease complexity, treatment experience, and clinical outcomes
- Latent class analysis (LCA) can be used to identify groups or subtypes of cases in multivariate categorical data and various simulation studies have shown it to be superior than traditional hierarchical clustering methods[4,5]
- By using LCA we can increase our understanding of subpopulations within individuals with ASD to better inform clinical decision-making and clinical trial study design

Objective

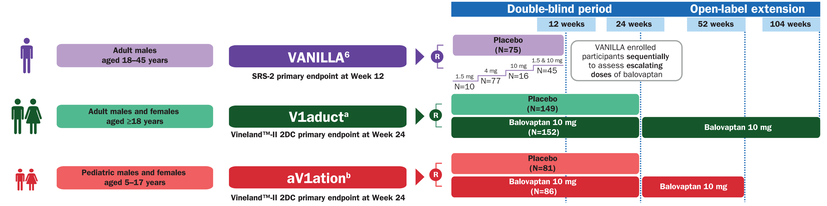
- The aim of this analysis was to understand whether **psychiatric comorbidities** and **concomitant medications** can be used to identify clusters and characterize participants with ASD enrolled in three randomized controlled trials for balovaptan

Conclusions

- **Consistent cluster profiles of psychiatric comorbidities and concomitant medications were found in three balovaptan studies at baseline, with differential distributions of participant characteristics**
  - **Two psychiatric comorbidity clusters at baseline were identified (VANILLA, V1aduct, aV1ation)**
  - **Three concomitant medications clusters at baseline were identified (VANILLA, V1aduct)**
- **Findings of this exploratory analysis indicate that future clinical trials should consider the psychiatric comorbidities and concomitant medications that were observed in the most dominant clusters when stratifying recruitment arms**

Methods

Data were sourced from three balovaptan trials including adults and pediatrics

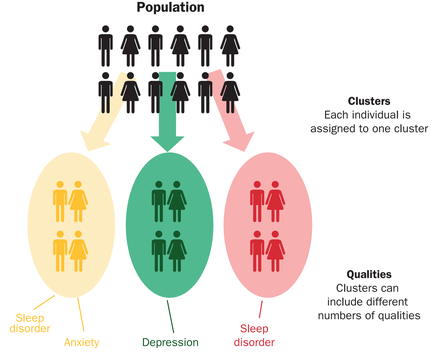


[a]Numbers shown are the V1aduct total population at the interim analysis. [b]Numbers shown are the aV1ation efficacy inferential population at primary analysis. 2DC, two-domain composite score of communication and socialization domains; R, randomization; SRS-2, Social Responsiveness Scale, Second Edition.

- Population data from three balovaptan trials including children, adolescents, and adults with ASD were used in this analysis:
  - VANILLA[6] (N=223; NCT01793441) total population data
  - V1aduct (N=301; NCT03504917) interim analysis (data status April 15, 2020)
  - aV1ation (N=337; NCT02901431) primary analysis (data status April 15, 2020)

Latent class analysis can be used to identify clusters within a population and define their qualities

- LCA (Finite Mixture Model)[4] was used to assign all individuals from each trial to discrete clusters for psychiatric comorbidities and concomitant medications in a data-driven approach using medical histories recorded during trial screening
  - Individuals within clusters have similar response patterns of qualities
  - Clusters were named based on their observed qualities
- The relationship between clusters, individuals' baseline characteristics and key study endpoints was analyzed by exploratory analysis of statistical variance without additional covariate adjustments
- This was a post hoc analysis and results and P-values presented are exploratory
  - Fisher's exact test was used for categorical variables and t-test for continuous variables for comparison of baseline scales between clusters
  - No multiple testing correction was applied

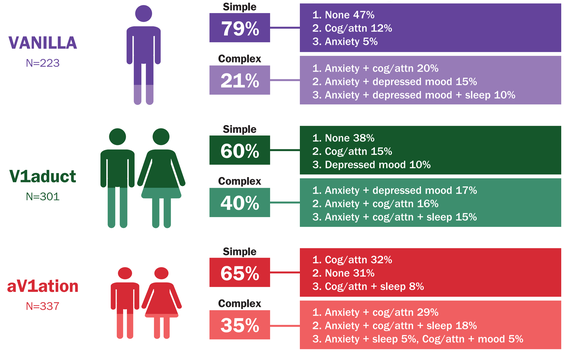


LCA identifies subgroups/clusters within a population and can inform what qualities categorize these groups

Results

Two psychiatric comorbidity clusters were identified: 'Simple' and 'Complex'

- The two distinct clusters were given names based on the qualities that were highly prevalent:
  - **Simple** = 'No comorbidities' or only a single comorbidity are the most prevalent qualities associated with the cluster
  - **Complex** = cluster with two or more concurrent comorbidities and anxiety was highly prevalent
- Across the three trial cohorts:
  - The 'Simple' profile cluster is the majority cluster in all three studies
  - VANILLA cohort contains more 'Simple' cluster profile individuals (79% vs 60–65% in V1aduct and aV1ation trials)
  - Within each cluster there is a similar set of comorbidity combinations
- The classification quality was high, entropy = 0.85



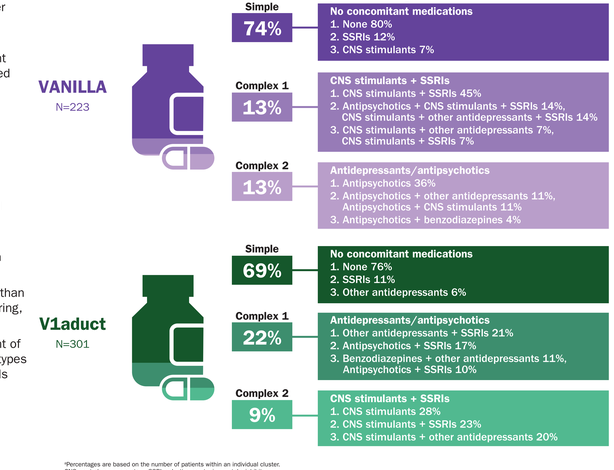
[a]Percentages are based on the number of patients within an individual cluster. Cog/attn, cognitive and attention disorders and disturbances.

Differences between clinical scales and baseline characteristics in psychiatric comorbidity clusters

- Differences between clusters were identified by exploratory analysis (P<0.05)
  - Across all three studies the 'number of comorbidities' varied between clusters
  - In V1aduct, sex, country, Vineland™-II daily living skills (DLS) score, and Pediatric Quality of Life™ Inventory (PedsQL™) were identified as different between clusters
  - In aV1ation, Clinical Global Impression - Severity (CGI-S) score differed between clusters
- Randomized treatment of balovaptan and placebo was well balanced within the clusters
- There were no further differences in the following primary endpoints, secondary endpoints, and other measures tested:
  - Age, country, race, CGI-S, intelligence quotient (IQ), Vineland™-II (Adaptive Behavior Composite [ABC] score, two-domain composite score of communication and socialization domains [2DC], communication, socialization, DLS), Social Responsiveness Scale, Second Edition (SRS-2), PedsQL™, Repetitive Behavior Scale – Revised (RBS-R)
- The 'Complex' profile has higher Vineland™-II daily living scores than the 'Simple' profile (median [IQR]: 71 [65, 79] versus 75 [68, 85], respectively; P=0.027), indicating that individuals may be better at performing everyday practical tasks
- However, PedsQL™ scores are lower (mean ± SD: 66.27 ± 14.89 versus 61.89 ± 16.29, respectively; P=0.017), suggesting that 'Complex' profile individuals may have a lower health-related quality of life
- Please see the poster handout for the corresponding data tables

Three concomitant medications clusters were identified: 'Simple', 'Complex 1', and 'Complex 2'

- Across the two adult cohorts (VANILLA and V1aduct), three cluster profiles were identified:
  - **Simple** = 'No concomitant medications' is the most prevalent medication combination associated with the cluster
  - **Complex 1** = 'CNS stimulants + SSRIs' are the most prevalent medications associated with the cluster
  - **Complex 2** = 'Antidepressants/ antipsychotics' are the most prevalent medications associated with the cluster
- The 'Simple' cluster is the most prevalent cluster profile across both studies
- The classification quality was lower than the psychiatric comorbidities clustering, entropy = 0.63
  - This may be due to a large amount of heterogeneity in the number and types of medications taken by individuals



[a]Percentages are based on the number of patients within an individual cluster. CNS, central nervous system; SSRI, selective serotonin reuptake inhibitor.

Differences between clinical scales and baseline characteristics in concomitant medications clusters

- Differences between clusters were identified by exploratory analysis (P<0.05)
  - Across both of the adult studies (V1aduct and VANILLA), the variable 'number of concomitant medications' differed
  - In VANILLA, IQ and RBS-R (IQR) were identified as different between clusters
- Randomized treatment of balovaptan and placebo was well balanced within the clusters
- There were no differences in the following primary endpoints, secondary endpoints, and other measures tested:
  - Age, country, race, CGI-S, Vineland™-II (ABC, 2DC, communication, socialization, DLS), SRS-2, PedsQL™
- Please see the poster handout for the corresponding data tables

References

1. Sharma SR, *et al. Pharmacol Ther.* 2018;190:91–104.
2. Leyfer OT, *et al. J Autism Dev Disord.* 2006;36:849–861.
3. Spencer D, *et al. Pediatrics.* 2013;132:833–840.
4. Hagenaars JA and McCutcheon AL. Applied latent class analysis. Cambridge University Press, 2002.
5. Prados-Torres A, *et al. J Clin Epidemiol.* 2014;67:254–266.
6. Bolognani F, *et al. Sci Transl Med.* 2019;11:eaat7838.

Presented at the American Academy of Child & Adolescent Psychiatry Virtual Annual Meeting, October 12–24, 2020

Scan code to receive PDF file of poster