

Conflicts of Interest

- **Vanessa Perez Patel** and **Elizabeth Merikle** are employees of Covance by Labcorp which conducted the research
- **Nancy Tich, Terri Sebree** and **Joseph Palumbo** are employees of Zynerba Pharmaceuticals
- **Randi Hagerman** has received research support from Zynerba Pharmaceuticals
- Research was funded by Zynerba Pharmaceuticals

Disclaimers

This presentation is intended to communicate scientific and medical information about data from clinical trials involving ZYN002. ZYN002 is an experimental treatment which has not been approved by any government regulatory bodies, including the United States Food and Drug Administration (FDA) and has not been determined by the FDA to be a safe or effective treatment for any disease or condition. This presentation is not designed or intended to promote the use of a ZYN002 or any other Company product in order to impact prescribing.

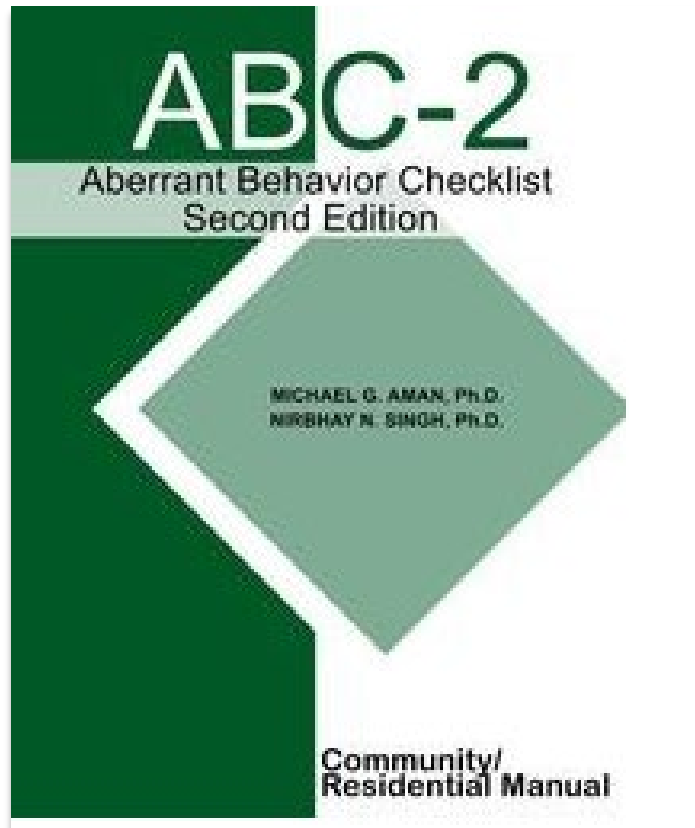
Caregiver-Perceived Behavioral Challenges in Fragile X Syndrome (FXS) and their Measurement using the Aberrant Behavior Checklist-Community FXS Specific Scoring

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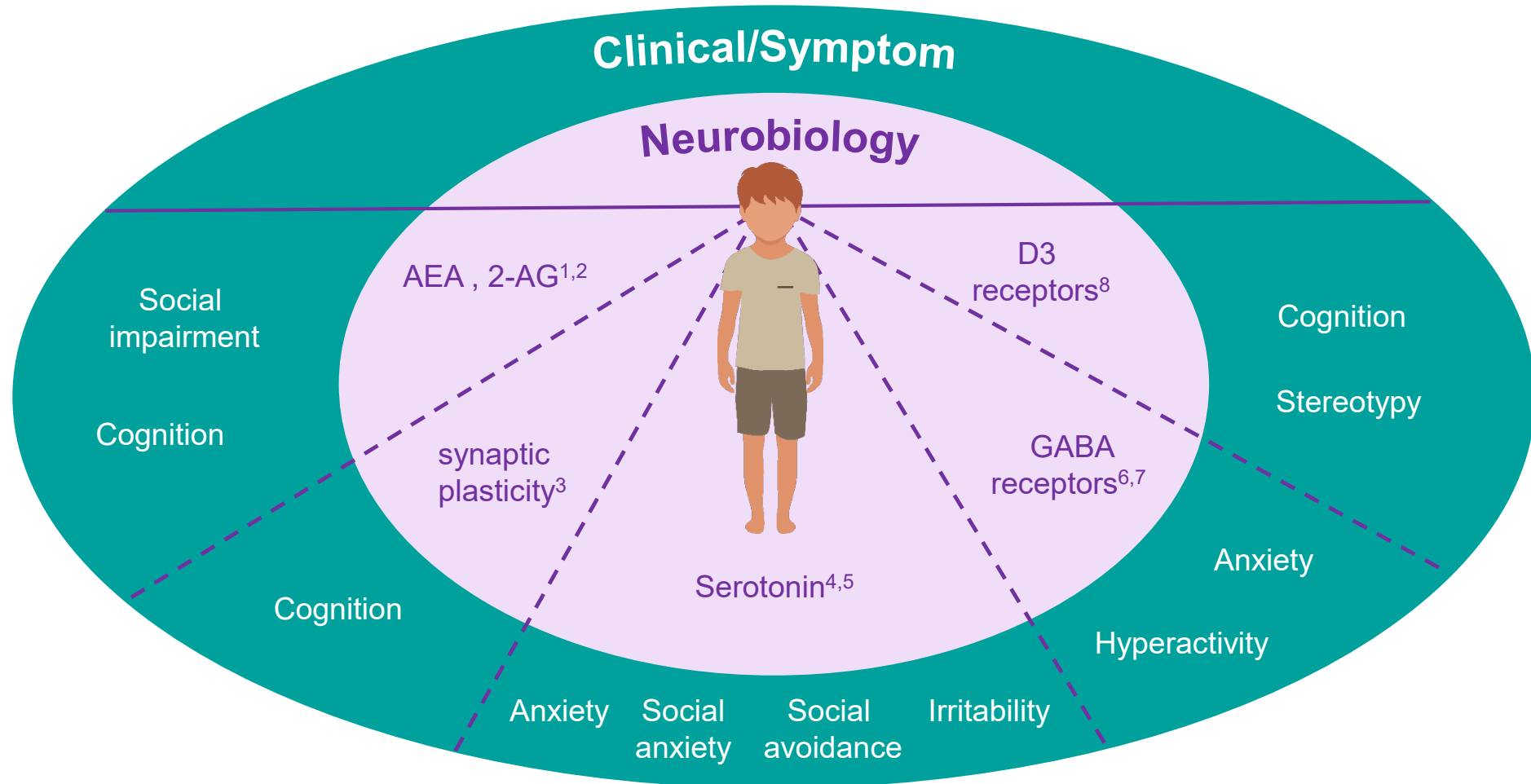


Aberrant Behavior Checklist-Community (ABC-C)



- Designed to monitor behavioral outcomes in individuals with intellectual disabilities
- 58 items assessing 5 behavioral domains
 - Irritability (15 items)
 - Social Withdrawal (16 items)
 - Stereotypic Behavior (6 items)
 - Hyperactivity (16 items)
 - Inappropriate Speech (4 items)
- Used in development programs for antipsychotics approved for the treatment of Autism Spectrum Disorder

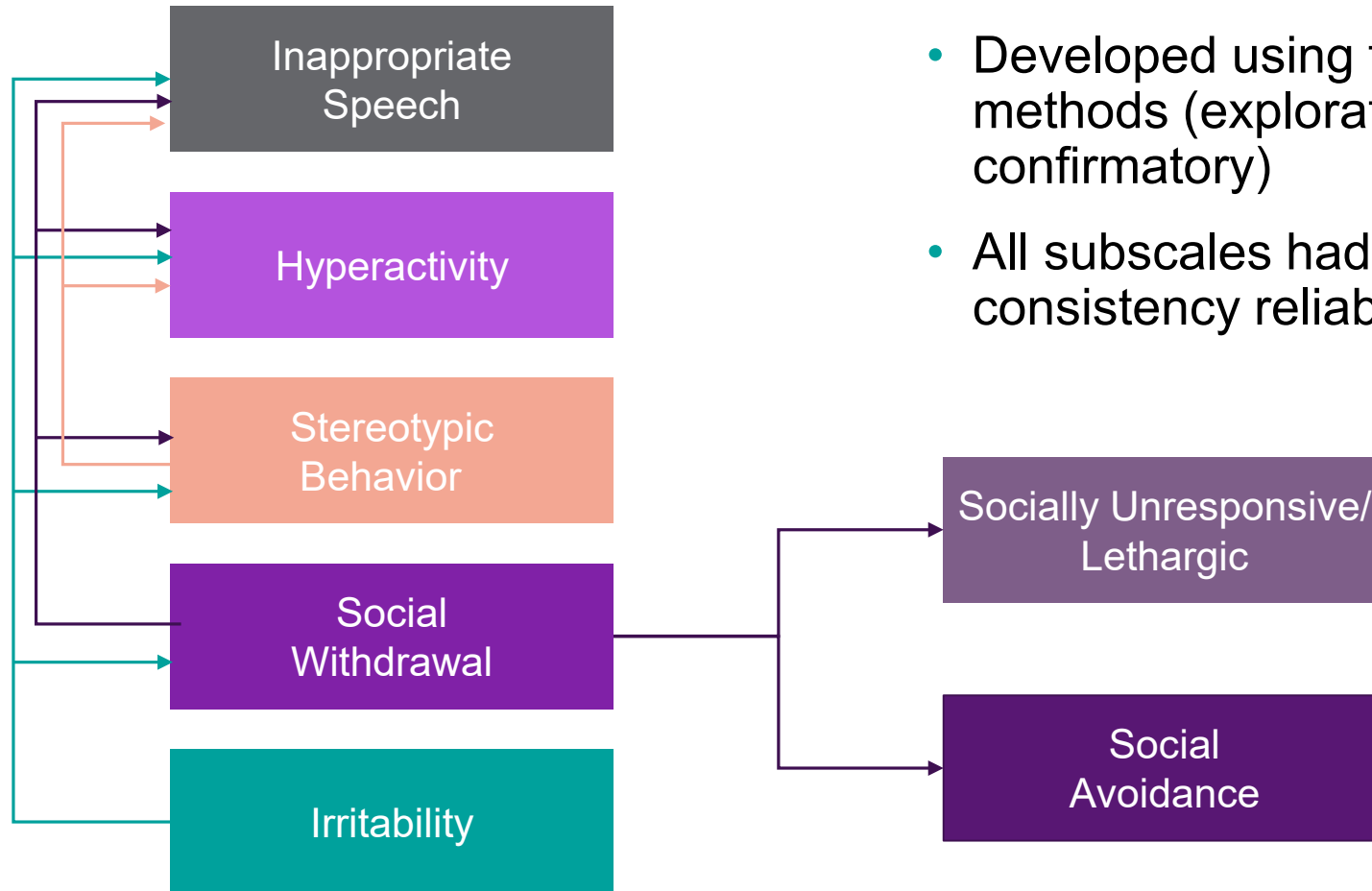
FXS Neurobiology and Behavioral Phenotypes



1. Jung KM, Nat Commun. 2012;3:1080; 2. Maione S. Br J Pharmacol. 2011;162: 584–596; 3. Huber KM, Proc Natl Acad Sci U S A. 2002;99:7746–7750; 4. Blessing EM, Neurotherapeutics. 2015;12: 825–836.

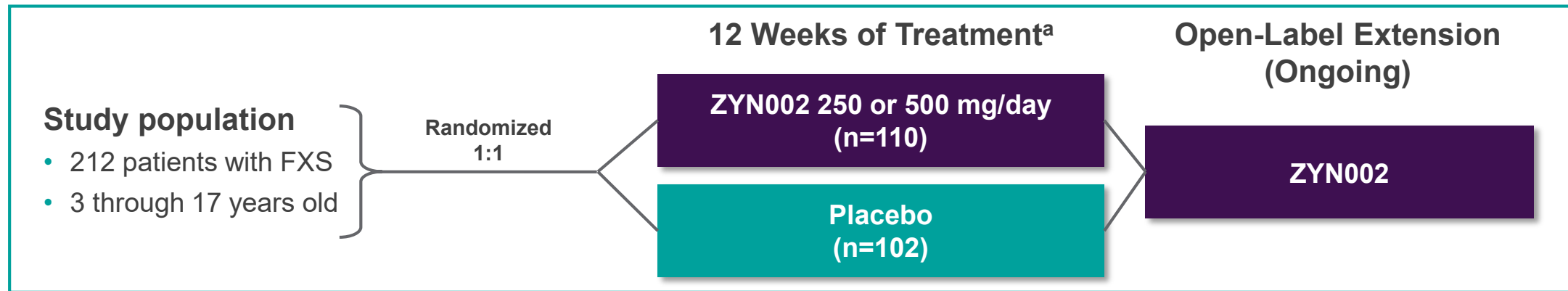
5. Bergamaschi. Neuropsychopharmacology. 2011;36:1219–1226; 6. Lozano R, Curr Pharm Des. 2015;21:4972–4979; 7. Bakas T. Pharmacol Res. 2017;119:358–370; 8. Bian Y Acta Pharmacol Sini.2019;40:374-86.

ABC-C_{FXS}: FXS specific scoring algorithm better captures FXS behavioral phenotype



- Developed using factor analytic methods (exploratory and confirmatory)
- All subscales had acceptable internal consistency reliability

CONNECT-FX: Clinical study Of CaNNabidiol (CBD) in ChildrEn and AdolesCenTs with Fragile X



- ZYN002 is a pharmaceutically produced CBD gel for transdermal delivery
- Primary Endpoint:
 - Change from baseline to end of treatment in ABC-C_{FXS} Social Avoidance subscale
- Key Secondary Endpoints
 - Change from baseline to end of treatment in ABC-C_{FXS} Irritability subscale
 - Change from baseline to end of treatment in ABC-C_{FXS} Socially Unresponsive/ Lethargy subscale

^a2-week placebo period followed by 12 weeks of treatment.

Qualitative Research Objectives

- To support the use of the ABC-C_{FXS} as a measure of endpoints in clinical trials of FXS
 - Demonstrate that the ABC-C_{FXS} subscales measuring the primary and key secondary endpoints in CONNECT-FX capture behavioral challenges of relevance to patients with FXS and their families
 - Evaluate the comprehension, relevance of the ABC-C_{FXS} in caregivers of patient with FXS

Qualitative Methods



Concept Elicitation Interviews (N=10)

- 1 hour semi-structured telephone interviews with caregivers of children with FXS
- Interviews transcribed and coded for analysis
- Concept saturation¹ assessed



Cognitive Interviews (N=25)

- 1.5 hour semi-structured video interviews with caregivers of children with FXS
- Interviews transcribed and coded for analysis
- Comprehension formally assessed



CONNECT-FX Caregiver Survey (N=212)

- Open-ended question at entry into CONNECT-FX regarding the five behavioral, social or emotional problems most impactful to child and family

¹Saturation is the point at which no new information is elicited

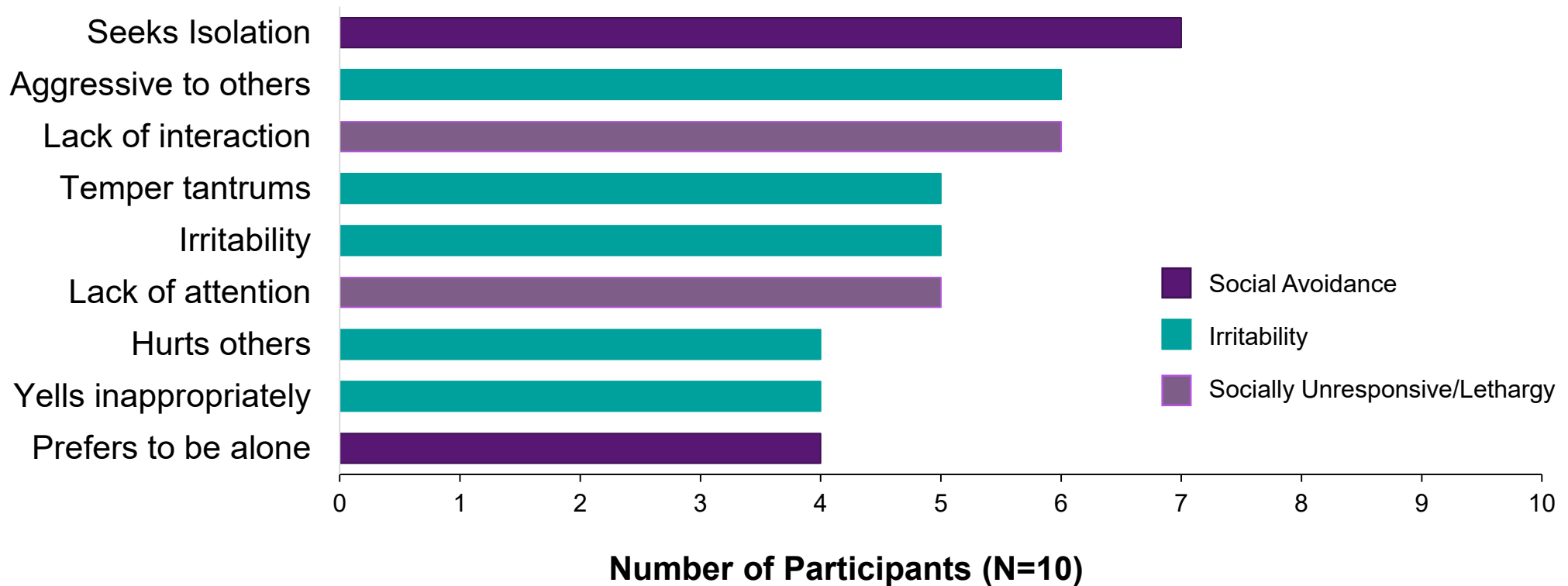
Demographics

Participant characteristics were similar across the studies

	Concept Elicitation	Cognitive Interviews	Caregiver Survey (CONNECT-FX randomized)
N	10	25	212
Age-Years, Mean (range)	(3-18)	10.3 (3-18)	9.7 (3-17)
Sex – Males, N (%)	8 (80)	22 (88)	159 (75)
Parent Education – College or above, N (%)	N/A	21 (84)	N/A

Concept Elicitation

Behaviors related to Social Avoidance, Irritability and Social Unresponsiveness most frequently reported



Saturation achieved after 8 interviews

Concept Elicitation: Representative Caregiver Quotes

“ **[Seeks Isolation]**...He would stay up in his room. He didn't want to come downstairs. He **didn't want to be around people.**”

“ **[Prefers to be alone]** She will at all costs avoid any type of new social engagement.”

“ **[Lack of interaction]** Children her own age try to play with her and she **doesn't want anything to do with them.**”

“ **[Aggressive to others]** It became where our daughter, his sister would walk by him and he'd **hit her for no reason.**”



Cognitive Debriefing: Comprehension

All participants comprehended ABC-C Instructions and Items

“ **[Instructions]** ...it's basically consider [sic] the past week's behavior and decide on a scale of zero to three, zero not a problem at all and then increasing in severity of problems. ”

“ **[Q5, Seeks isolation]** I'm thinking doesn't want to participate with peers or in a group setting, would rather just go and be alone in his room or other places away from others. ”

“ **[Q58, Few social reactions]** Well, I guess I was looking at even if they prefer to be isolated, if they go out in public, will they at least make eye contact or those similar where how you affected when you're with other people. ”



Cognitive Debriefing: Ease of Completion

Vast majority of participants reported that the ABC-C was easy to complete

	N (%)
Easy to understand and answer	22 (88)
No difficulty interpreting response options	25 (100)
Recall period easy to remember	18 (72)
Recall period appropriate	19 (76)

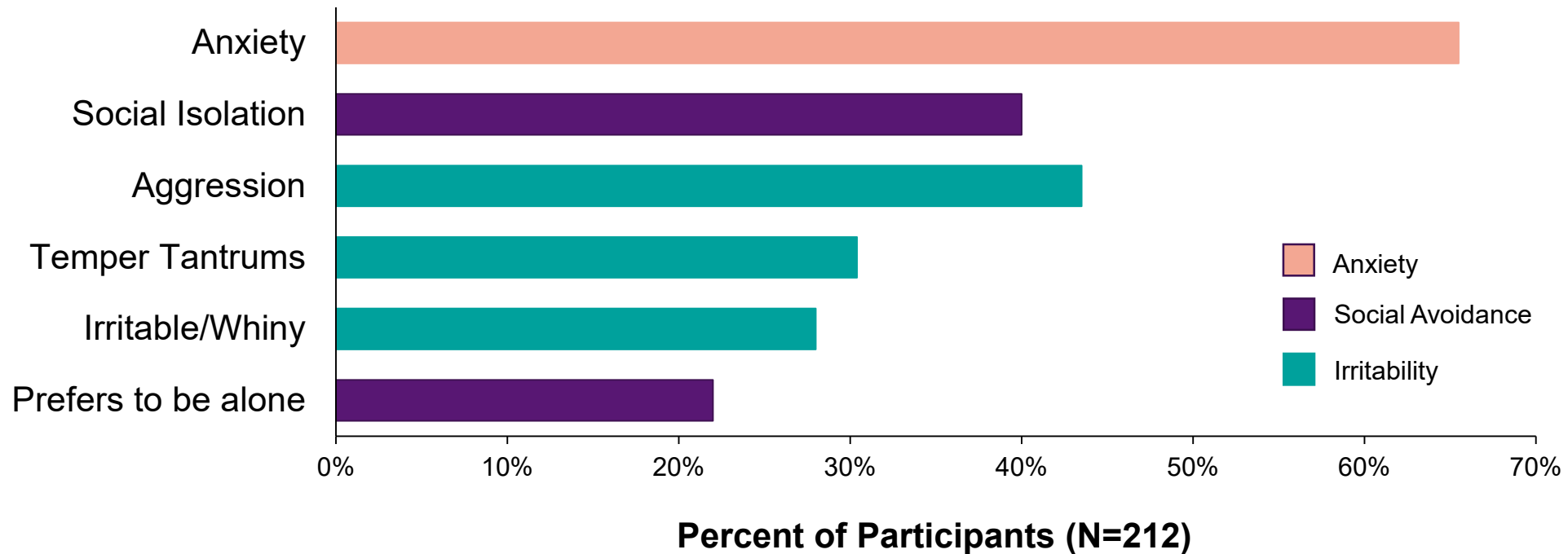
“**[Easy to Answer]** *It was pretty easy to answer, so much applies to him that I understood the question, because they were things I was familiar with.*”

“**[Response Options]** *Yes, I mean I think overall they’re looking at how much of an issue, does it have—how much of an impact does it have on the child’s and your life..*”

“**[Recall Period]**... *I think you can get a good snapshot of your child in a seven-day period*”

Caregiver Survey

Behaviors related to Social Avoidance and Irritability were most frequently reported as impactful by caregivers of children with FXS



Summary of Qualitative Evidence

ABC-C_{FXS} is fit for purpose for measuring clinical trial endpoints in FXS



Concept Elicitation Interviews (N=10)

- Behavioral challenges reported by caregivers were consistent with the ABC-C_{FXS} Social Avoidance, Irritability and Socially Unresponsive/Lethargy subscales and their items



Cognitive Interviews (N=25)

- Caregivers demonstrated comprehension of the ABC-C and reported that it was easy to complete and its content relevant

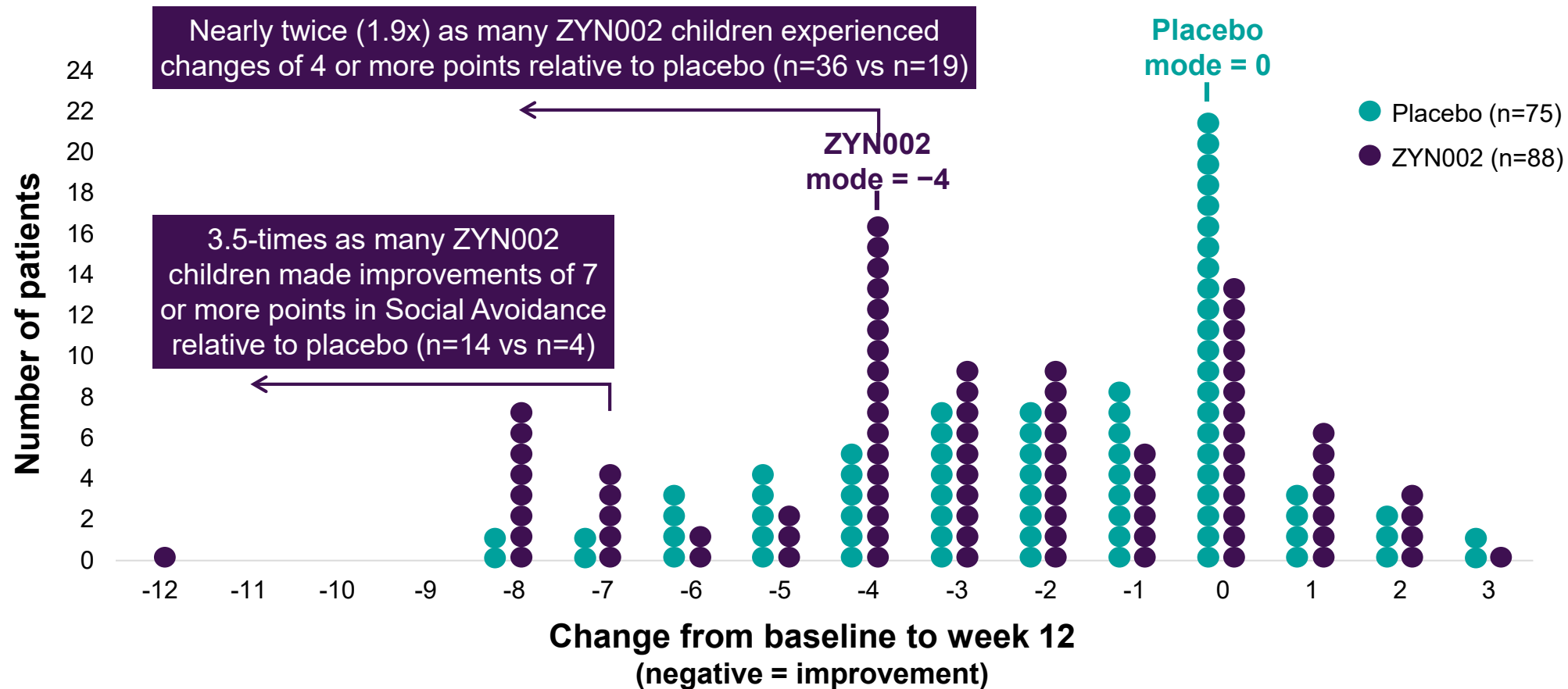


ZYN2-CL-016 Caregiver Survey (N=212)

- Caregivers of participants in CONNECT-FX reported behavior problems consistent with the content and domains of the ABC-C_{FXS} at study entry

ABC-C_{FXS} Social Avoidance: Sensitive to change in CONNECT-FX

ZYN002 demonstrated greater improvement in patients with $\geq 90\%$ methylation of the *FMR1* gene



Observed cases: 4 patients did not have a Week-12 assessment. Data from a pre-specified ad hoc analysis of patients with $\geq 90\%$ methylation of the *FMR1* gene representing 80% of the overall population.

Advancing Science



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Thank-you

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