

Content Validity in Support of the ABC-C_{FXS} and Subscales in Fragile X Syndrome

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INTRODUCTION

- Fragile X Syndrome (FXS) is a genetic condition caused by a mutation in the Fragile X mental retardation 1 (FMR1) gene and is among the leading causes of autism spectrum disorder¹
- Children with FXS exhibit autism-like symptoms — such as social anxiety, social avoidance, social withdrawal, and deficits in socially relevant communication, as well as restricted/repetitive behaviours and irritability — that have been shown to impair social and school functioning²
- It is important to make sure the Aberrant Behavior Checklist-Community (ABC-C) is sensitive enough, as an understandable questionnaire, to generate reliable and reproducible data
- Because patients cannot reliably report their symptoms due to the intellectual limitations associated with FXS, a parent/caregiver-reported measure focused on problematic behaviours is needed to better align outcomes in clinical trials with symptoms that are clinically meaningful to patients
- The ABC-C is a 58-item observer-reported rating scale of inappropriate and maladaptive behaviour in individuals with intellectual and developmental disabilities comprised of five subscales: Irritability, Social Withdrawal, Stereotypic Behavior, Hyperactivity and Inappropriate Speech
- A factor analysis of the ABC-C in children, adolescents, and adults with FXS resulted in modifications to the subscale structure of the ABC-C, hereafter referred to as the ABC-C_{FXS}; a sixth factor (Social Avoidance) emerged comprised of items related to socially avoidant behaviours that are core aspects of FXS³
- The content of the items of the ABC-C_{FXS} in relation to the caregiver experience has not been systematically evaluated

OBJECTIVE

- The objective of this study was to establish the content validity of the ABC-C_{FXS} using qualitative methods to support the use of 3 ABC-C_{FXS} subscales (Social Avoidance, Irritability and Socially Unresponsive/Lethargic) to measure primary and/or secondary endpoints in clinical trials evaluating therapeutic interventions

METHODS

- The study involved two stages of qualitative data collection:
 - A web-based journal
 - In-depth individual interviews with caregivers of children formally diagnosed with FXS
- Caregivers were recruited via online invitation through the National Fragile X Foundation (NFXF) website
- To be eligible, participants had to reside in the US, be the primary caregiver for a child (aged 3-18 years) with a confirmed diagnosis of FXS, and have the primary role in making treatment decisions for the child
- Caregivers were instructed to use an online journal for five consecutive days to summarize the experiences that shaped their patient-related decisions and actions
- After completing the five-day journal, participants underwent an in-depth interview using a semi-structured guide that covered the following areas:
 - Background and presentation of diagnosis
 - Healthcare professional management and symptomatology
 - Emotional journal
 - Treatment experience
 - Reaction to a hypothetical new medication for FXS
- Responses were independently coded by two researchers using a codebook that was:
 - Developed from the interview guide based on the framework shown in Table 1
 - Updated after each round of coding as new concepts emerged

Table 1. Coding Categories

Category	Description
Symptom	Any outstanding characteristic that can be traced as a definitive sign of known Fragile X symptoms, including but not limited to physical features, delay in speech, cognitive delay, and delay in physical development or motor functioning
Behaviour	Any negative or positive patient act that is reported by the caregiver

RESULTS

PATIENTS

- All participants (10/10, 100%) were parents of patients with FXS
- Other characteristics of the sample, as reported at the time of the interview, are provided in Table 2

Table 2. Caregiver and Child Characteristics

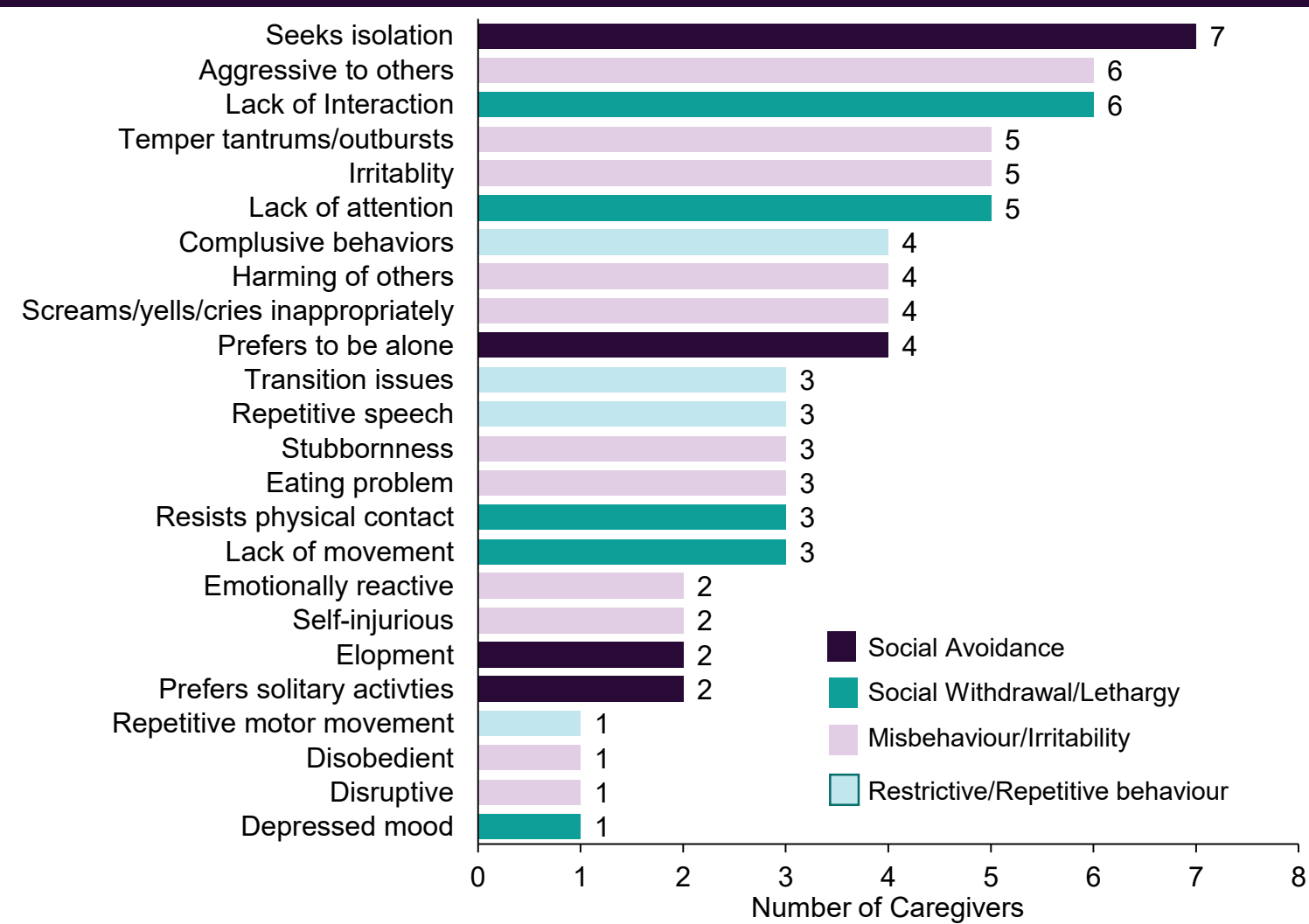
Characteristic	N (%)
Caregiver relationship	
Parent	10 (100)
Other	0 (0)
Age of caregiver, years	
25–34	3 (30)
35–44	4 (40)
45–54+	3 (30)
US region of residence	
Northeast	2 (20)
South	4 (40)
Midwest	0 (0)
West	4 (40)
Child age, years	
3–7	3 (30)
8–12	4 (40)
13–18	3 (30)
Child sex	
Male	8 (80)
Female	2 (20)
Time since FXS diagnosis, years	
≤2	3 (30)
3–7	3 (30)
8–15	4 (30)
Severity of FXS	
Mild	1 (10)
Moderate	5 (50)
Severe	3 (30)
Don't know/Unsure	1 (10)

RESULTS cont.

BEHAVIOURAL SYMPTOMS OF FXS

- The most frequently identified behavioural symptoms are shown in Figure 1
- When grouped by domains of social avoidance, the two categories of social withdrawal/lethargy and misbehaviour/irritability were often mentioned together and alongside communication, suggesting that they are both interrelated and meaningful to caregivers of children with FXS

Figure 1. Frequency of FXS-related Symptoms and Behaviours



- Although the study was not conducted with the goal of demonstrating saturation for the concepts included in the ABC-C_{FXS}, saturation was reached for three of the ABC-C_{FXS} subscales: Social Avoidance, Irritability, and Socially Unresponsive/Lethargic
- Altogether, 90% of caregivers reported at least one behaviour that was representative of social avoidance, socially unresponsive/lethargic, and irritability

EXPERIENCE CORRESPONDS WITH ABC-C_{FXS} SUBSCALES

SOCIAL AVOIDANCE

- It was common for their children with FXS to prefer the company of single family members to groups of people, even friends, and to seek isolation from others either via physical setting (staying in their room or in the car) or blocking out the world (using headphones)
- Social avoidance had a negative impact on important activities, such as travel, schooling, or visits to the doctor, and it could manifest as elopement
- The social-avoidant behaviours reported by caregivers (seeks isolation from others [70%], prefers to be alone [40%], and prefers solitary activities [20%]) corresponded to items on the Social Avoidance subscale, including **seeks isolation from others** and **isolates himself/herself from other children or adults**

Caregiver Verbatim

- We just need to pick up a few things, we're going to the store," he's okay. He'll go with me, he'll go with his dad. He'll go with his sister. But if it's more than one of us, no.* **Caregiver 4**
- Yes, that would probably be the biggest thing. . . just doesn't like being around other people or other kids except for her sister.* **Caregiver 9**

IRRITABILITY

- Irritability was with a broad spectrum of verbal (talk-back, hollering, articulate yelling, non-verbal screams) and physical behaviours (hitting siblings, overturning furniture) at inappropriate times
- Frequently reported aspects of misbehaviour and irritability mapped onto items of the Irritability subscale, specifically **aggressive to others** (60%), **irritability** (50%), **temper tantrums/outbursts** (50%), **screaming/yelling inappropriately** (40%), **harming of others** (40%), and **stubbornness** (30%)
- Less aggressive, but still inappropriate, behaviours identified by caregivers (eg, boisterousness, quickly-changing moods) were similarly concordant with items on the ABC-C_{FXS} Irritability subscale

Caregiver Verbatim

- It could be anything from just cursing to overturning furniture. There's a broad spectrum there.* **Caregiver 6**
- Him being so stubborn impedes him from. . . I know it just goes in circles, but I know that part of his aggression or anger is because he can't explain himself. If he was a little bit more patient, then he would be able to explain himself.* **Caregiver 1**

SOCIALLY UNRESPONSIVE/LETHARGIC

- Lack of interaction and attention were frequently reported by caregivers.
- Depressive symptoms were less frequently reported than other elements of social withdrawal and, along with other negative behaviours, compounded communication problems
- Caregiver reports of lack of interaction (60%) and lack of attention (50%) mapped to subscale items, such as **preoccupied**, **stares into space**, **does nothing but sit and watch others**, **unresponsive to structured activities (does not react)**, and **shows few social reactions to others**
- Items on the subscale pertaining to communication — **is difficult to reach, contact, or get through to**; **pays no attention when spoken to**; and **deliberately ignores directions** — were identified as important by caregivers, particularly with respect to how they may exacerbate other syndrome-related behaviours

Caregiver Verbatim

- He didn't want to eat. He just wanted to sleep. What else? He just wanted to have his blanket, and sometimes he begins to feel like something comes over him. He looks scared and begins to scream.* **Caregiver 3**
- He didn't want to go outside and swing anymore. . . He didn't want to become active.* **Caregiver 4**

Conclusions

- This study further validates the appropriateness of the Social Avoidance, Irritability and Socially Unresponsive/Lethargic subscales of the ABC-C_{FXS} to assess core behavioral symptoms of FXS in clinical trials
- Findings further validate social avoidance, irritability, and socially unresponsive/lethargic as core behavioral symptoms from the perspective of caregivers of children with FXS

