Feasibility, Reproducibility, and Clinical Validity of the Pediatric Anxiety Rating Scale, Revised (PARS-R) in Fragile X Syndrome

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Fragile X syndrome (FXS)

- Leading inherited cause of intellectual disability
- Most common single gene cause of autism spectrum disorder
- Anxiety is a core feature of FXS in both males and females
- Numerous impending targeted pharmaceutical trials are directed at underlying biological defects and core symptoms in FXS
- A valid outcome measure for anxiety in FXS is lacking

Anxiety Measurement

- Validity and consistency can be difficult to assess in lower functioning and nonverbal populations
- Common methods include self-report, third-party report (parents, teachers, clinician)
- Clinician administration is advantageous to provide anchors and minimize responder bias and misunderstanding of item intent in perception of anxiety

Pediatric Anxiety Rating Scale-Revised (PARS-R)

J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 41:9, SEPTEMBER 2002

- Clinician-administered anxiety scale that has potential as an outcome measure for FXS studies
- Evaluates both presence and severity of symptoms in multiple anxiety domains
  - *Social*
  - *Separation*
  - *Generalized*
  - *Specific Phobia*
  - *Panic*
  - *Obsessive-Compulsive*
  - *Health/Illness Concerns*
  - *Other symptoms*

Objectives

- To evaluate the PARS-R for rating anxiety in FXS
    1. Feasibility
    2. Clinical validity
    3. Reproducibility (test-retest)
    4. Reliability (inter-rater and cross-site)

Methods

- 49 total participants with FXS
  - 5-35 years old with varying functional levels
  - Mean IQ = 53.26 ± 13.95 (subset, n = 27)
  - 29 young (21 males, 8 females)
  - 20 adult (12 males, 8 females)
  - FMR1 DNA testing demonstrating the full mutation associated with FXS

- Data was collected at 2 sites to study cross-site reliability
  - 43 data sets (RUMC)
  - 6 data sets (UC Davis)

Clinical Validity

- Parent report on the Anxiety, Depression, and Mood Scale (ADAMS)

- Clinician rating on the Clinical Global Impression-Severity scale (CGI-S) rating for anxiety level was obtained independently from treating physician (EBK) for RUMC participants

Reproducibility & Reliability

- Test-retest data (n = 38; M = 8.23 ± 5.64 weeks gap)
  - No change in treatment from Time 1 to Time 2

- Inter-rater reliability of 14 video-recorded administrations was assessed for two non-physician clinical raters (JY/NRP) and between non-physician raters and a clinical psychologist (DH)

Feasibility

- No refusal to participate
- Caregivers were able to report on presence/absence and severity of anxiety symptoms

	Minimum	Maximum	Mean (SD)
Time 1 (n=49)			
Total Items Endorsed	0	25	7.51 (6.86)
5 Item Scale	0	21	8.41 (5.63)
7 Item Scale	0	30	13.47 (8.16)
Time 2 (n=38)			
Total Items Endorsed	0	22	5.08 (5.94)
5 Item Scale	0	22	7.50 (5.50)
7 Item Scale	0	31	12.11 (7.74)

No significant differences in Total Number of Items Endorsed or Severity Indices between age groups ($t \leq 1.936$, $p \geq .097$, all comparisons) or between males and females ($t \leq .746$, $p \geq .467$, all comparisons)

Clinical Validity: PARS-R vs ADAMS (Pearson's correlations)

	Manic/ Hyperactive Behavior r-value	Depressed Mood r-value	Social Avoidance r -value	Generalized Anxiety r -value	Obsessive Compulsive Behavior r -value
5 Item Scale	.44*	.25	.41*	.60***	.56**
7 Item Scale	.38*	.26	.47**	.61***	.54**

Severity scores on the PARS-R were significantly correlated with the ADAMS for the entire group and all subgroups
(* p≤.05, **p≤.01, ***p≤.001)

Clinical Validity: PARS vs CGI (Pearson's correlations)

Group	5 Items Scale r (p-value)	7 Items Scale r (p-value)
Entire Sample (n=43)	.60***	.55***
Young (0-17y)	.97***	.46*
Adult (18+)	.65**	.60**
Male	.96***	.66***
Female	.53*	.47

Severity scores on the PARS-R were significantly correlated with the clinician-rated CGI for anxiety for the entire group and all subgroups (*p≤.05, **p≤.01, ***p≤.001)

Test-retest Reliability (intraclass correlations)

Group	N	Total Items Endorsed	5 Item Scale	7 Item Scale
All Subjects	38	.90	.86	.86
Young (0-17y)	20	.90	.79	.85
Adult (18+)	18	.90	.90	.90
Male	25	.90	.76	.81
Female	13	.94	.94	.94

The PARS exhibited very good reproducibility (T1:T2) for the entire group and all subgroups ($p \leq .001$, all comparisons)

Inter-rater and Cross-site Reliability

	Scale Analysis 61 Symptoms Checklist Items (κ)	61 Symptoms Checklist (α)	5 Item Severity Index (α)	7 Item Severity Index (α)
Inter-rater Reliability				
JY:NR	.87	.93	.98	.99
Cross-site Reliability				
JY:NRP:DH	-	.96	.97	.97
JY:DH	.90	.95	.96	.93
NRP:DH	.85	.92	.96	.94

Administrations and coding of the PARS-R by trained medical student (JY), doctorate level researcher (NR), and clinician (DH) were reliable and consistent within and across sites.

Conclusions

- PARS-R is promising as a *feasible* and *reproducible* measure of *clinically-relevant* anxiety in FXS
- Future work should assess the PARS-R as a useful outcome measure in clinical trials of interventions targeted to the core anxiety phenotype or the underlying disorder in FXS

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