

# Toward Better Measurement of Anxiety in ASD: Outline

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# Disclosures

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  - Roche

# Toward Better Measurement of Anxiety in ASD: Outline

- General issues on outcome measurement
- Autism Speaks Task Force
- Patient (Parent) Reported Outcomes
- Building an outcome measure: Current NIMH grant

## NIH Multisite Trials in Children with ASDs past 16 years

| Study                                | N   | Target                           | Ages   | Published, date                   |
|--------------------------------------|-----|----------------------------------|--------|-----------------------------------|
| Risperidone vs placebo               | 101 | Irritability                     | 5-17   | NEJM, 2002                        |
| Methylphenidate vs placebo           | 72  | Hyperactivity                    | 5-14   | Arch Gen Psych, 2005              |
| Citalopram vs placebo                | 149 | Repetitive Behavior              | 5-17   | Arch Gen Psych, 2009              |
| Risperidone vs RIS + Parent Training | 124 | Irritability & Adaptive Behavior | 4.5-13 | J Am Acad Child Psych, 2009; 2012 |
| Parent Training vs Parent Education  | 180 | Irritability & Adaptive Behavior | 3-7    | Enrollment completed              |
| Guanfacine vs placebo                | 62  | Hyperactivity                    | 5-14   | Enrollment completed              |

# Characteristics of a good outcome measure

- Relevant (clinically meaningful)
- Measures a separate & definable construct
- Orderly distribution (Mean  $\pm$  SD)\*
- Has “normative” data (to interpret Mean  $\pm$  SD)\*
- Solid Internal Consistency (a little noise is ok)
- Good test-retest
- Not: too long, too brief, too narrow, too broad
- Sensitive to change

\* In ASD: consider  $\geq 70 < 70$

# Autism Speaks Task Force

Lecavalier, L., Wood, J.J., Halladay, A.K., Jones, N.E., Aman, M.G., Cook, E.H., Handen, B.L., King, B.H., Pearson, D.A., Hallett, V., Sullivan, K.S., Grondhuis, S., Bishop, S.L., Horrigan, J.P., Dawson, G., Scahill, L. (2014).

Measuring Anxiety as a Treatment Endpoint in Youth with Autism Spectrum Disorder.

*JAutism Developmental Disorders*, 44(5): 1128-1143

# Measures Dubbed *Appropriate with Conditions*

| Measure                    | Type                  | Rel & Valid      | Sensitivity to Change | Comment                  |
|----------------------------|-----------------------|------------------|-----------------------|--------------------------|
| CASI-Anxiety               | parent                | yes              | yes (pilot)           | Incomplete coverage      |
| MASC                       | Parent                | yes <sup>a</sup> | yes <sup>a</sup>      | ↑ reliance on language   |
| Pediatric Anx Rating Scale | Clinician (interview) | yes <sup>a</sup> | yes <sup>a</sup>      | ↑ ↑ reliance on language |
| a=high functioning samples |                       |                  |                       |                          |

# FDA Monograph, 2009

## **Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims**

# Conceptual Problems:

## Co-morbidity vs Complication vs Convergent

### Co-morbidity model

- ASD and Anxiety Disorders are independent
  - Anxiety disorders in ASD same as TD children

### Complication model

- ASD ↑ risk of anxiety & complicates the picture
  - Anxiety symptoms blend & amplify ASD picture

### Convergent Model

- Anxiety is part of ASD condition
  - Insistence on routines, social avoidance = anxiety

# Practical Problems

- Disentangling anxiety from ASD
  - Social avoidance in ASD vs Social Anxiety Disorder
  - Protest on separation from mother: insistence on sameness, Separation Anxiety or both
- Cognitive & Language Delay
  - Difficulty expressing worries, interpreting physiological signals and sorting emotions
- Anxiety in ASD may be different
  - Insistence on routines: all about predictability → vigilance & over-reaction

# Blurry Boundaries

- In typically developing children:
  - Anxiety is dimensional and categorical
  - Boundaries between anxiety disorders are not sharply drawn
- Boundary problems are  in ASD

# Three-site NIMH grant

- Aim # 1: Six focus groups with parents of children with ASD on manifestations of anxiety in ASD.
  - ➔ Draft parent-rated anxiety measure (based on focus group data).
- Aim # 2: Draft measure on the web, obtain 900 children with ASD.
  - ➔ Evaluate the distribution, factors, item analysis to refine draft.
- Aim # 3: Conduct clinical assessments on 90 children with ASD.
  - ➔ Evaluate validity and test-retest reliability of new parent-rated scale and the Pediatric Anxiety Rating Scale (PARS).
- Aim # 4: Compare heart rate variability in 30 subjects with ASD + elevated anxiety to 30 subjects with ASD + low anxiety.
  - ➔ potential biomarker

# Six Focus Groups: 600 pages of transcripts

- Triggers (specific stimulus)
  - Loud noises
  - Crowds
  - New Situations
- Observable Behaviors
  - Request for reassurance
  - Avoidance with distress
- Child Coping Behaviors
  - Withdrawal
  - Self-soothing behavior
  - Breakdown in coping → emotional outbursts

# Draft Items

- Selected from new 52 items + 20 existing items

|   |   |   |   |   |
|---|---|---|---|---|
|   | 0 | 1 | 2 | 3 |
| Requires frequent reassurance about upcoming events                     |   |   |   |   |
| Uneasy in noisy situations (e.g., school cafeteria, malls)              | 0 | 1 | 2 | 3 |
| Gets upset if someone breaks the rules                                  | 0 | 1 | 2 | 3 |
| Overly fearful of weather events (e.g., storms, hurricanes or tornados) | 0 | 1 | 2 | 3 |
| Uncomfortable in social situations                                      | 0 | 1 | 2 | 3 |
| Gets stuck on what might go wrong                                       | 0 | 1 | 2 | 3 |
| Compares self to others in a negative manner                            | 0 | 1 | 2 | 3 |
| Over-reacts when things do not go as planned                            | 0 | 1 | 2 | 3 |
| Needs a lot of reassurance that things will work out                    | 0 | 1 | 2 | 3 |
| Gets upset when routine is not followed                                 | 0 | 1 | 2 | 3 |
| On the look-out for any change in routine                               | 0 | 1 | 2 | 3 |
| Worries about being left home alone or with a sitter                    | 0 | 1 | 2 | 3 |
| Anxious about upcoming events   | 0 | 1 | 2 | 3 |

# Plan

- Put 72 items on the web; factor/item analysis

Goal: dimensional parent measure

- Assess 90 subjects (30 per site) in person: new parent measure, revised PARS, CYBOCS-ASD

Goal: establish reliability & validity

- 30 Hi ANX vs 30 Low ANX on HRV

Goal: validate HRV as a biomarker

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