Toward Better Measurement of Anxiety in ASD: Outline

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Disclosures

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  – Roche, Coronado, Neuren, MedAvante, Shire

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  – NIMH
  – 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
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Target</th>
<th>Ages</th>
<th>Published, date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone vs placebo</td>
<td>101</td>
<td>Irritability</td>
<td>5-17</td>
<td>NEJM, 2002</td>
</tr>
<tr>
<td>Methylphenidate vs placebo</td>
<td>72</td>
<td>Hyperactivity</td>
<td>5-14</td>
<td>Arch Gen Psych, 2005</td>
</tr>
<tr>
<td>Citalopram vs placebo</td>
<td>149</td>
<td>Repetitive Behavior</td>
<td>5-17</td>
<td>Arch Gen Psych, 2009</td>
</tr>
<tr>
<td>Parent Training vs Parent Education</td>
<td>180</td>
<td>Irritability &amp; Adaptive Behavior</td>
<td>3-7</td>
<td>Enrollment completed</td>
</tr>
<tr>
<td>Guanfacine vs placebo</td>
<td>62</td>
<td>Hyperactivity</td>
<td>5-14</td>
<td>Enrollment completed</td>
</tr>
</tbody>
</table>
Characteristics of a good outcome measure

- Relevant (clinically meaningful)
- Measures a separate & definable construct
- Orderly distribution (Mean ± SD)*
- Has “normative” data (to interpret Mean ± 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 ≥ 70 < 70
Autism Speaks Task Force

# Measures Dubbed *Appropriate with Conditions*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Type</th>
<th>Rel &amp; Valid</th>
<th>Sensitivity to Change</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASI-Anxiety</td>
<td>parent</td>
<td>yes</td>
<td>yes (pilot)</td>
<td>Incomplete coverage</td>
</tr>
<tr>
<td>MASC</td>
<td>Parent</td>
<td>yes(^a)</td>
<td>yes(^a)</td>
<td>↑ reliance on language</td>
</tr>
<tr>
<td>Pediatric Anx Rating Scale</td>
<td>Clinician (interview)</td>
<td>yes(^a)</td>
<td>yes(^a)</td>
<td>↑ ↑ reliance on language</td>
</tr>
</tbody>
</table>

\(^a\)=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**

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

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