Challenges to Patient Identification in Clinical Trials for the Treatment of Autism Spectrum Disorder

Laura M. Gault, M.D., Ph.D.
Disclosures

- Employee of AbbVie
Outline

• Clinical Presentation of ASD
• Diagnostic Criteria for ASD
• Common Comorbidities in ASD
• Current Treatment
• Approach to novel treatments
CLINICAL PRESENTATION
Autistic Disturbances of Affective Contact – Leo Kanner, 1943

• Described unusual communication and behavior in 11 children
• “extreme autistic aloneness”, delayed echolalia, “anxiously obsessive desire for maintenance of sameness”
• Viewed as “inborn”, little role for psychoanalytic interpretation
• Recognition of milder forms of these behaviors in family members
Autism Spectrum Disorder (ASD)

• Neurodevelopmental disorder involving deficits in social communication and repetitive behaviors

• Symptoms manifest during early development


• Prevalence estimates suggest ASD 1:48 to 1:68, with ~4:1 male:female

CDC 2011-2013, 2014
Risk Factors for ASD

• Strong genetic component
  – Monozygotic twins have 37-90% concordance rate vs 10-30% in dizygotic twins
  – Risk for parents who have one child with autism for having a second is 2-19%
  – Likely multigenic etiology in about 85% of cases
  – In 15%, ASD attributable to single gene mutation (e.g., Rett syndrome (MeCP2), Fragile X, Neurofibromatosis) or chromosomal deletion and/or duplication (16p11, 15q11-13)

• Environmental risk factors
  – Prenatal or Perinatal factors
  – Other?
DIAGNOSTIC CRITERIA
Recent Diagnostic Changes in ASD

**DSM-IV-TR**

Three main disorders...

- Autistic Disorder
- Asperger’s Disorder
- Pervasive Dev. Disorder NOS (PDD-NOS)

Genetic disorders w/ autistic features

- Fragile X Disorder
- Rett’s Syndrome

**DSM-V**

Two new disorders...

- Autism Spectrum Disorder *(specify if there is a known genetic cause...)*
- Social (Pragmatic) Communication Disorder *(social communication deficit w/o repetitive behavior)*
# ASD – DSM-V Diagnostic Criteria

## Social communication & interaction (all 3):
- Deficits in social-emotional reciprocity
- Deficits in non-verbal communicative behaviors used for social interaction
- Deficits in developing, maintaining, and understanding relationships

## Restricted, repetitive behavior, interests, activities (2+):
- Stereotyped or repetitive motor movements, use of objects, or speech
- Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior
- Restricted, fixated interests, abnormal in intensity
- Sensory hyper-/hypo-reactivity, unusual interest in sensory environment (new!)
Examples

Social Communication
• Sam, aged 12
• Normal IQ

Repetitive Behaviors
• Jake, aged 12
• Normal IQ

13 yo boy with ID and ASD

https://www.youtube.com/watch?v=yGtI3oI8D-o
Potential Impact of Diagnostic Revision

• What is the impact of the new diagnostic criteria on the use of screening and assessment tools?
• What will the impact be globally?
  – DSM-IV and ICD-10 are aligned
  – Will DSM-V and ICD-11 be aligned?
• How will implementation of new criteria in clinical research affect comparability of data with datasets generated using previous diagnostic criteria?
• How will new criteria be used in clinical practice?
• How will application of revised criteria impact access to services?
COMORBIDITIES
ASD Symptoms & Comorbidities

Social / Communication Deficits
- Hyperactivity
- Inattention

Repetitive / Restricted Behaviors
- Self Injury
- Tantrums

Intellectual Disability

Other Comorbidities
- GI Problems
- Seizures

Anxiety
- Mood
- Sleep Deficits

Aggression
- Irritability
CURRENT TREATMENT
Treatment of ASD

Treatment is multimodal, with two goals

- Communication, social-emotional function, adaptive behavior
- Decrease maladaptive, comorbid and core repetitive behavior

PARENT Coordinates Care!

- Pediatrician
- Psychiatrist
- Psychologist
- Neurologist
- Speech, PT, OT
- Feeding Therapy
- Behavior Therapist
- Special Education

Treatment “team”
Treatment of Autism

**Primary**
- Social/communication
- Irritability
- Repetitive Behavior
- ADHD
- Sleep
- Mood
- Seizures

**Medications**
- None
- Atypical antipsychotics (e.g., RIS, ARI)
- None (SSRIs?)
- Stimulants, Alpha 2 agonists, SNRIs
- Hypnotics, OTC?
- SSRIs
- AEDs

**Other Tx**
- Common
  - Psychotherapy
  - Social skills training
  - Parent training
  - School-based tx
  - Feeding therapy
  - Speech, OT, PT
- ? Evidence?
  - Sensory training
  - CATs (DHA, ...)
  - Dietary treatments (for GI, behavior)
  - Recreational tx

APPROACH TO NOVEL TREATMENT
Where is the clinical need for medicines?

Social / Communication Deficits

- Hyper-activity
- Inattention

Repetitive / Restricted Behaviors

- Self Injury
- Tantrums
- Aggression
- Mood
- Anxiety
- Sleep Deficits
- Irritability

Other Comorbidities

- GI Problems
- Seizures

Intellectual Disability
Considerations for ASD Drug Development

- Greatest benefits likely derived from treating early in development
  - Need to consider potential interaction of target with normal growth and development
  - Traditional drug development approaches define safety and efficacy first in adult populations, but how predictive are these results for those in children?

- Nearly all drug development programs will be ‘add-on’
  - Ongoing behavioral therapy
  - DDIs (especially considering medications for comorbidities)

- How to define population for initial efficacy study?
  - Currently, a homogeneous population cannot be defined based on biochemical or imaging biomarkers
  - If single gene disorder, how applicable are results to broader population of ASD?

- Many currently used scales were not developed as outcome measures and have poor psychometric properties
  - Scales not necessarily useful across a broad range of intellectual abilities or ages
Collaboration Across Key Stakeholders to Provide an Improved Understanding of Biomarkers, Trial Design and Regulatory Path Will Support Design of Future ASD Trials

**CHALLENGES OF TODAY**

- No biomarkers available to permit selection of homogeneous population or predict clinical effect
- Clinical assessments to identify population and measure change over time often developed for other purposes and not validated for use
- No formal regulatory path or guidance and little industry-agency interaction

**BUILDING FOR THE FUTURE**

- Ongoing work in public-private partnerships such as EU-AIMS and ABC-CT characterize biomarkers for use in clinical trials
- Ongoing work by ABC-CT and other public-private partnerships will better define appropriate inclusion and outcome measures for clinical trials
- Increased discussions across key stakeholders will further refine potential regulatory paths and increase industry engagement for ASD
BACKUPS

- description of 4 boys: "lack of empathy, little ability to form friendships, one-sided conversations, intense absorption in a special interest, and clumsy movements"
- "extreme variant of the male character"
- "little professors"
- Also noted similar characteristics in relatives
DSM-V Criteria for ASD

• **A. Persistent deficits in social communication and social interaction:**

  1. **Deficits in social-emotional reciprocity**, ranging from
     • abnormal social approach
     • failure of normal back-and-forth conversation
     • reduced sharing of interests, emotions, or affect
     • failure to initiate or respond to social interactions.

  2. **Deficits in nonverbal communicative behaviors used for social interaction**, ranging from
     • poorly integrated verbal and nonverbal communication
     • abnormalities in eye contact and body-language or deficits in understanding and use of gestures
     • a total lack of facial expression and nonverbal communication.

  3. **Deficits in developing, maintaining, and understanding relationships**, ranging from
     • difficulties adjusting behavior to suit various social contexts
     • difficulties in sharing imaginative play or in making friends
     • absence of interest in peers
DSM-V Criteria for ASD

• B. **Restricted, repetitive patterns of behavior, interests, or activities**, as manifested by at **least two** of the following:
  1. **Stereotyped or repetitive motor movements, or use of objects, or speech** (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
  2. **Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior** (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
  3. **Highly restricted, fixated interests that are abnormal in intensity or focus** (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
  4. **Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment** (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).
Comparison of DSM-IV and DSM-V Diagnostic Criteria in Clinical Samples

Huerta et al., 2012
• Video clips
  • https://www.youtube.com/watch?v=8jrqpnn60d4A
  • https://www.youtube.com/watch?v=lbXjW-cX9kQ
  • https://www.youtube.com/watch?v=w_23z9yJAq0
  • https://www.youtube.com/watch?v=j4PTf7LgsIEe.com/watch?v=3w1c4sF4ZTg
  • https://www.youtube.com/watch?v=l7fdv1q9-m8
  • https://www.youtube.com/watch?v=yGtl3ol8D-o
Neurobiology of ASD

• Enlarged head sized
  – Originally noted by Kanner
  – Not enlarged at birth, but may be enlarged by 10% in toddlers, though not as pronounced by adolescence
    • Suggests possible failure of normal pruning

• Abnormalities in limbic system
  – Reduced density, cell size and dendritic arborization
  – Hypoactive in fMRI studies

• Peripheral serotoninemia

• Possible role for dopaminergic and opioid systems
Approaches to Understanding the Neurobiology of ASD

• Human genetics
  – Common inherited variation (GWAS, SNPs)
  – Rare inherited variation
  – De Novo variation (CNVs and SNVs)

• Neuroanatomical
  – Neuropathological findings (macroscopic and microscopic)
  – Structural imaging (MRI, DTI)

• Systems level
  – Functional Imaging (EEG, fMRI)

• Cellular and Molecular level
  – Synapse formation
  – Excitatory/Inhibitory Neurotransmission
  – Neuropeptide signaling
Emerging Evidence for Biological Convergence in ASD

Chen et al., 2015
a tremendous **UNMET NEED**...

...and novel molecular targets **exist**

...what is holding us back?

**Current Model is TOO RISKY**
- There is no "autism doctor;" care is uncoordinated
- Research tools are subjective & not sensitive to measuring change
- ASD population is heterogeneous – who do we select for PoC studies?

**What Do We NEED?**
- A way to organize and access data easily across providers
- New sensitive, objective endpoints
- Better data to inform PoC subpopulation selection
Increasing collaboration among academia, industry, research foundations and regulators is advancing our ability to conduct trials in ASD

- Autism Speaks (Paul Wang)
- Simons Research Foundation (Steve Zukin)
- J&J (Gahan Pandina)
- EU-AIMs (Declan Murphy)
- NIMH and ABC-CT (Linda Brady)
- FDA (Tiffany Farchione)