Psychopharmacology and Autism Spectrum Disorder

Bennett L. Leventhal, MD
Professor
Department of Psychiatry
University of California, San Francisco

STAR Center for ASD & NDDs
San Francisco, CA
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Developmental Disabilities: Update for Health Professionals
UCSF
San Francisco, CA

Disclosure of Interests
Bennett L. Leventhal, MD

- Sources of Research Support
  - NIH
  - Simons Foundation
  - Janssen - ended
  - Roche - ended

- Stock and Investments
  - Sadly, no

- Other Financial Interests
  - Regrettably, none

- Speaker Bureaus
  - None

- Consulting Relationships
  - Janssen/J&J

- Family Financial Interest
  - All my children are employed

- Honorarium
  - No

- Off Label Meds
  - Yes, of course

- Travel
  - Too much; no conflict

What is a Neurodevelopmental Disorder? (1)

- Usually Syndromal
- Pediatric Onset
- Affecting Brain Function
- Clinical Effects on
  - Emotion
  - Cognition
  - Behavior

ASD
Autism Spectrum Disorder

The Paradigmatic Neurodevelopmental Disorder
What is a Neurodevelopmental Disorder? (1)

per DSM5

1. Intellectual Disability (ID) (Intellectual Development Disorder)
2. Global Development Delay
3. Unspecified Intellectual Disability (Intellectual Developmental Disorder)
4. Language Disorder
5. Speech Sound Disorder
6. Childhood-Onset Fluency Disorder (Stuttering)
7. Social Pragmatic Communication Disorder (SCD)
8. Unspecified Communication Disorder
9. Autism Spectrum Disorder (ASD)
10. Attention Deficit Hyperactivity Disorder (ADHD)
11. Other Specified Attention-Deficit Hyperactivity Disorder
12. Unspecified Attention-Deficit Hyperactivity Disorder
13. Specific Learning Disorder
14. Developmental Coordination Disorder
15. Stereotypic Movement Disorder
16. Tic Disorder
17. Other Specified Tic Disorder
18. Unspecified Tic Disorder
19. Other Specified Neurodevelopmental Disorder
20. Unspecified Neurodevelopmental Disorder

Consider Other Neurodevelopmental Disorders:
- OCD
- Eating Disorders
- Mood Disorders
  - Bipolar Disorder
  - Major Depressive Disorder
- Substance Abuse
- Schizophrenia
- Trauma related disorders
- Epilepsy
- Alzheimer’s Disease

Autism/ASD – A syndrome

- Syndrome
  - Group of symptoms that tend to cluster together and share a common natural history/course
- Disease
  - A syndrome for which there is:
    - A known etiology (or cause)
    - A known pathophysiological process
    - Both
- ASD is not so unusual because:
  - Like the most medical conditions, ASD is a syndrome
“Autistic Disturbances of Affective Contact”
*The Nervous Child*, 1943

**Leo Kanner**
(1894-1981)

DSM 5: ASD

A. **Persistent deficits in social communication and social interaction across contexts**, not accounted for by general developmental delays

B. **Restricted, repetitive patterns of behavior, interests, or activities**

C. **Symptoms must be present in early childhood**

D. **Symptoms together limit and impair everyday functioning.**
DSM 5 Social Communication Disorder

A. Social Communication Disorder (SCD) is
   - an impairment of **pragmatics**
   - diagnosed based on difficulty in the social uses of verbal and nonverbal communication

B. Low social communication abilities
   - result in functional limitations

C. Rule out Autism Spectrum Disorder

D. Symptoms must be present in early childhood

Autism Spectrum Disorders (ASD)

- A Syndrome
- The 2 “D’s” = Delay & Deviations
- Domains of Impairment
  - a. Social Development
     - Joint Attention
     - Theory of Mind
     - Reciprocity
  - b. Communication Development
  - c. Restricted/Repetitive & Stereotyped Patterns of Interests and Activities (including IS)

Autism & Autistic Spectrum Disorders (ASD)

- Course
  - a. Consistent over time
  - b. Some symptoms decrease
    - a. Stereotypies
    - b. Visual regard
  - c. Some symptoms persist
    - Lack of social reciprocity
    - Language abnormalities
    - Restrictive and repetitive behaviors/IS

What are the Spectra or Axes in Autism Spectrum Disorders (ASD)?

- Few Autism Symptoms
- Lower Cognitive Function
- Fluent Language
- Poor/No Language
- Good Social Skills
- Poor Social Skills
- Higher Cognitive Function
- Many Autism Symptoms
- HIGH Functioning
- LOW Functioning
Autism Etiology
What Causes ASD?

• Chromosomal (syndromic)
  – fragile-X syndrome, tuberous sclerosis
• Genetic - increased risk in twins, siblings
  – small chromosomal deletions or duplications (i.e., copy number variation or CNV.)
• Structural Brain Disruption
  – anatomic, cellular
• Others
  – Environmental/toxic
  – Immunologic
  – gastrointestinal,
  – etc

Appropriate Assessment is the Starting Point for Treatment of Autism

Sources of Information

• Screening
• Clinical Interview
  – History
  – Direct Observation
• Standard Diagnostics
  – ADI
  – ADOS
  – CARS
• Adaptive Function
  – Vineland
  – ABC
• Physical Examination
  – Neurological
  – Sensory Exam
• Laboratory
  – Only as indicated

Factors That Predict Autism Outcome

1. Expressive Language
   - Communicative speech by age 5
2. Language Comprehension
   - Spoken language by age 5
3. Intellectual Capacity
   - Non-verbal intelligence
4. Adaptive Function
5. Severity of Autism symptoms
   a. Social deficits
   b. Restricted, Repetitive Behaviors
   c. Aggression
Environmental Interventions:
How Early? How Often?

- Speech & Language Therapy
- Educational Programming
- Behavior Therapy
  - ABA
  - DTT
  - Pivotal Response Training
  - ESDM
- Family Interventions
  - Education
  - Parent Training
- Individual Psychotherapy
- Pharmacotherapy

RRB’s
Restrictive and Repetitive Behaviors

1. Stereotypies
2. Insistence on sameness
3. “Stimming”
4. Habits
5. Tics

SSRI’s
Serotonin Reuptake Inhibitors*

- fluoxetine (Prozac)
- sertraline (Zoloft)
- paroxetine (Paxil)
- fluvoxamine (Luvox)
- citalopram (Celexa)
- escitalopram (Lexapro)
- clomipramine (Anafranil)

*Note: FDA Warning about suicidality

CY-BOCS Compulsion Score

Symptom Fluoxetine Placebo

Anxiety/Nervousness 15.9% [6/39] 33.3% [12/36]
Insomnia 35.9% [14/39] 47.2% [16/36]
Drowsiness/Fatigue/Sedation 17.9% [7/39] 11.1% [4/36]
Agitation 46.2% [18/39] 44.4% [16/36]
Diarrhea 5.1% [2/39] 19.4% [7/36]
Anorexia 15.4% [6/39] 11.1% [4/36]
LRTI 10.3% [4/39] 19.4% [7/36]
Weight Gain 0% [0/39] 2.8% [1/36]

Traditional Neuroleptics

- haloperidol (Haldol)
- trifluoperazine (Stelazine)
- fluphenazine (Prolixin)
Atypical Neurolpeptics

- clozapine (clozaril)
- risperidone (Risperdal)*
- olanzepine (Zyprexa)
- quetiapine (Seroquel)
- ziprasadone (Geodon)
- aripiprazole (Abilify)*
- Others

*FDA Approved for irritability in ASD

Primary Endpoint Analysis
Aberrant Behavior Checklist - Irritability

After 8 weeks of treatment, the risperidone group had a 56.9% improvement compared to a 14.1% improvement in the placebo group.

Mean ABC Irritability Total Score

Risperidone (n=49)
Placebo (n=52)

*P<0.001 vs. placebo at weeks 4 and 8

Secondary Endpoint Analysis
Aberrant Behavior Checklist Subscales

Change in ABC-Subscale scores from baseline to endpoint

Hyperactivity
- P<0.001 vs placebo
- Risperidone
- Placebo

Stereotypy
- P<0.001 vs placebo
- Risperidone
- Placebo

**RUPP Autism Secondary Endpoint Analysis**

**Aberrant Behavior Checklist (ABC) Scales**

Change in ABC-Subscale scores from baseline to endpoint

- **Social Withdrawal**
  - Risperidone 16.4
  - Placebo 16.1
  - P-value <0.001

- **Inappropriate Speech**
  - Risperidone 4.8
  - Placebo 6.5
  - P-value <0.001

*Scores for Social Withdrawal and Inappropriate Speech did not differ significantly from placebo after the Bonferroni correction (NS indicates not significant)*

**RUPP Autism Study: Adverse Events**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Risperidone n = 49</th>
<th>Placebo n = 52</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased appetite</td>
<td>24 (49)</td>
<td>13 (25)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mild</td>
<td>12 (24)</td>
<td>2 (4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29 (59)</td>
<td>14 (27)</td>
<td>0.003</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>24 (49)</td>
<td>6 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drooling</td>
<td>13 (27)</td>
<td>3 (6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Tremor</td>
<td>7 (14)</td>
<td>1 (2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (16)</td>
<td>2 (4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (29)</td>
<td>6 (12)</td>
<td>0.06</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>6 (12)</td>
<td>1 (2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Weight gain in kg</td>
<td>2.7 ± 2.9</td>
<td>0.8 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Lithium**

Lithium Carbonate

**propranolol**

Inderal

[β-adrenergic blocker]
Attention Deficits

Stimulants

- **Amphetamines**
  - Dexedrine (DEX)
  - Methamphetamine
  - Adderall
  - Adderall XR
  - Vyvanse

- **Methylphenidates (MPH)**
  - Ritalin (and other short acting MPH)
  - Ritalin SR
  - Ritalin LA
  - Concerta
  - Focalin (dex MPH)
  - Metadate CD
  - Methylin ER
  - MPH patch
  - Quillivant XR (liquid)

Non-Stimulant ADHD Treatments

- **Cylert (pemoline)**
- **Tricyclic Antidepressants**
- **Atypical Antidepressants**
  - Buproprion
    - Wellbutrin
  - Venlafaxine
    - Effexor
- **SSRI’s**
- **NE Agents**
  - Atomoxetine (Strattera)

- **Alpha Adrenergic Agonists**
  - Clonodine
    - Catapres
    - Kapvay
  - Guanfacine
    - Tenex
    - Intuniv

- **Atypical Neuroleptics**
  - Risperdal
  - Zyprexa
  - Geodon
Mood Disturbance

Irritability

SSRI’s

Serothonin Reuptake Inhibitors*

- fluoxetine (Prozac)
- sertraline (Zoloft)
- paroxetine (Paxil)
- fluvoxamine (Luvox)
- citalopram (Celexa)
- escitalopram (Lexapro)
- clorimpramine (Anafranil)

*Note: FDA Warning about suicidality

Anticonvulsants
(mood stabilizers)

- valproate (Depakote)
- carbamazepine (Tegretol)
- lamotrigine (Lamictal)
- neurotonin (Neurontin)
- gabapentin (Gabatril)
- Others

Anxiety

1. Anti-anxiety medications
   - Benzodiazepines
2. SSRI’s*
   - fluoxetine (Prozac)
   - sertraline (Zoloft)
   - paroxetine (Paxil)
   - fluvoxamine (Luvox)
   - citalopram (Celexa)
   - escitalopram (Lexapro)
   - clorimpramine (Anafranil)

*Note: FDA Warning about suicidality
New Medications

• GABA – active agents
• mGluR5 agonists and antagonists
• Oxytocin
• Vasopressin 1A antagonist
• Others directed at evolving biology

Cognitive Enhancers?

Arricept (donepezil)
Exelon (rivastigmine)
Namenda (memantine)
Reminyl (galantamine)

Complementary and Alternative/Integrative Treatments - “Off-label”

• Sleep supplements (e.g., melatonin)
• Diets (e.g., gluten free/casein free)
• Supplements (e.g., omega 3 fatty acids)
• Vitamins (e.g., B6 and magnesium)
• Allergies (e.g., lactose)
• Anti-oxidants (e.g., Vit E)
• Neurotransmission Modulators (e.g., NAC)

Other Proposed Treatments

• Vitamins
• Minerals
• Dietary Supplements
• Dietary Restrictions
• Sugar
• Food Dyes
• Chelation
• Secretin
• Steroids
• Eye Tracking
• Sensory Diets
• Facilitated Communication
• Floor Time
• ?
CHELATION

[The Removal of Heavy Metals]

• Benefits
  - Removes toxic heavy metals, when present
  - Measured in blood, tissue, X-Ray
  - NOT measured in hair
  - E.g., lead, strontium

• Risks
  - Chelating chemicals are toxic themselves
    → Sickness & Death
  - Takes a long time
  - Remove toxin but likely will not reverse neural damage

Change in the mean item score on the Children’s Psychiatric Rating Scale-14 (CPRS-14) with risperidone. Each line represents an individual child’s score from baseline to the end of short-term treatment.

All Medications have Side Effects

A special problem in treating ASD
Just because a small amount of medication works well, it does not mean that a lot will work better.

Another special problem in treating ASD is that...

Most children with ASD get better over time!

Our goals are:
Search for etiologies that can be used to
Enhance treatment
Prevent ASD

In the meantime:
Use treatments that help individuals with ASD:
- Acquire skills
- Improve ability to use those skills
- Move toward independent and semi-independent living

QUESTIONS?

THANK YOU

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Developmental Disabilities: Update for Health Professionals
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