Medications in Autism: What We Know and Don't Know

Jeremy Veenstra-VanderWeele, M.D.
Mortimer D. Sackler, M.D., Associate Professor
Center for Autism and the Developing Brain
Sackler Institute for Developmental Psychobiology
Columbia University / New York State Psychiatric Institute
Disclosures: Grants and Contracts

- National Institute of Mental Health
- National Institute of Child Health and Development
- Autism Speaks
- American Academy of Child and Adolescent Psychiatry
- Brain and Behavior Research Foundation (NARSAD)
- Agency for Health Care Research and Quality
- Springer
- Wiley
- Seaside Therapeutics
- Roche Pharmaceuticals
- Novartis
- Forest
- SynapDx
Outline

• What is autism spectrum disorder (ASD)?
• What do we know about medications in ASD?
• How do we approach common co-occurring psychiatric conditions?
• The ultimate goal: combined medical and behavioral treatment
Outline

• What is autism spectrum disorder (ASD)?
• What do we know about medications in ASD?
• How do we approach common co-occurring psychiatric conditions?
• The ultimate goal: combined medical and behavioral treatment
What is Autism Spectrum Disorder?

“Autism is not a disease.” – Isabelle Rapin
It is certainly not a single disease.
Core autism spectrum disorder symptoms

- Impaired social communication/interaction (3/3):
  - Social reciprocity
  - Nonverbal communication
  - Relationships

- Restricted/repetitive behavior (2/4):
  - Repetitive speech/behavior
  - Insistence on sameness
  - Restricted interests
  - Sensory abnormalities

**BEHAVIORAL COMORBIDITIES**
- Hyperactivity/impulsivity
- Agitation/aggression
- Anxiety
- Severe constipation
- Seizure disorder

**COGNITIVE COMORBIDITIES**
- Language impairment
- Intellectual disability

**GENETICS**
- Simple genetic disorders: fragile X, TS, Rett, etc.
- Copy number variants: 16p11-p12, 15q11-q13, 22q13, etc.
- Rare variants: NRXN1, NLGN4, Shank3, Sert, etc.

**MEDICAL COMORBIDITIES**
- Abnormal EEG
- Developmental macrocephaly
- Neuroimaging: altered brain region size
- Neuroserotonemia
- Altered immune/mitochondrial indices

**BIOMARKERS**
Core autism spectrum disorder symptoms

Impaired social communication/interaction (3/3):
- Social reciprocity
- Nonverbal communication
- Relationships

Restricted/repetitive behavior (2/4):
- Repetitive speech/behavior
- Insistence on sameness
- Restricted interests
- Sensory abnormalities

Genetics
- Copy number variants: 16p11-p12, 15q11-q13, 22q13, etc.
- Rare variants: NRXN1, NLGN4, Shank3, Sert, etc.

Behavioral comorbidities
- Hyperactivity/impulsivity
- Agitation/aggression
- Anxiety

Cognitive comorbidities
- Language impairment
- Intellectual disability

Medical comorbidities
- Seizure disorder
- Abnormal EEG
- Developmental macrocephaly
- Neuroimaging: altered brain region size
- Altered immune/mitochondrial indices

Biomarkers
- Hyper-serotonemia

Medication
- Severe constipation
Core autism spectrum disorder symptoms

Impaired social communication/interaction (3/3):
- Social reciprocity
- Nonverbal communication
- Relationships

Restricted/repetitive behavior (2/4):
- Repetitive speech/behavior
- Insistence on sameness
- Restricted interests
- Sensory abnormalities

BEHAVIORAL COMORBIDITIES
- Hyperactivity/impulsivity
- Agitation/aggression
- Anxiety
- Severe constipation
- Seizure disorder

COGNITIVE COMORBIDITIES
- Language impairment
- Intellectual disability

GENETICS
- Simple genetic disorders: fragile X, TS, Rett, etc.
- Copy number variants: 16p11-p12, 15q11-q13, 22q13, etc.
- Rare variants: NRXN1, NLGN4, Shank3, Sert, etc.

MEDICAL COMORBIDITIES
- Seizure disorder
- Abnormal EEG
- Developmental macrocephaly
- Abnormal immune/mitochondrial indices
- Neuroimaging: altered brain region size

BIOMARKERS
- Hyperserotonemia
- Altered immune/mitochondrial indices
Outline

• What is autism spectrum disorder (ASD)?
• What do we know about medications in ASD?
• How do we approach common co-occurring psychiatric conditions?
• The ultimate goal: combined medical and behavioral treatment
Context

- Comparative Effectiveness of Therapies for Children with Autism Spectrum Disorders
- Vanderbilt Evidence-Based Practice Center
- Strength of evidence ≠ degree of benefit
Behavioral Interventions
Behavioral Interventions

- Early Intensive Behavioral / Developmental Interventions
  - Improve cognitive, language, and adaptive outcomes in certain subgroups of children.
    - Strength of evidence: Moderate

- Other behavioral interventions
  - Cognitive behavioral therapy for anxiety: Moderate
  - Social skills training: Mixed
Medications
Key point

There are no medications for the core symptoms of Autism Spectrum Disorder.
FDA-approved Medications

Strength of Evidence

• Aripiprazole (Abilify) = high
• Risperidone (Risperdal) = high
• Primary target symptoms: ‘Irritability’ subscale of Aberrant Behavior Checklist
  – Originally ‘irritability/agitation/crying’

• Also show benefit for ‘hyperactivity’ and ‘stereotyped behavior’ subscales
  – But not the treatment target

Example: Risperidone

![Graph showing the percentage of much improved or very much improved patients over 8 weeks of treatment with Risperidone and Placebo.](image)

RUPP. NEJM. 2002.
Risperidone and aripiprazole

• Significant side effects
  – Weight gain
  – Sedation
  – Motor symptoms

Metformin for weight gain due to risperidone or aripiprazole

- 6-17 year olds with ASD taking risperidone, aripiprazole, or other medicines in this class

- No significant difference in side effects
  - More days with gastrointestinal side effects with metformin
Δ = 2.7 kg

Anagnostou et al., *JAMA Psychiatry*, 2016
Medications for Attention Deficit Hyperactivity Disorder (ADHD) Symptoms
Law of 50%
Stimulants

- Methylphenidate (Ritalin, Concerta)
  - Largest study suggests less benefit, more side effects than in ADHD [without ASD]
    - 49% “much” or “very much improved” + 30% symptom reduction
    - 18% could not tolerate even lowest dose due to side effects
      - Irritability prominent

Atomoxetine (Strattera)  
Study 1

• 6-17 year olds with ASD + ADHD
• Atomoxetine $1.2 \text{ mg/kg} \times 8\text{ weeks}$
  • Only 21% of patients rated as “very much” or “much improved”
    – 9% on placebo
• Only 1 patient stopped atomoxetine due to side effects (fatigue)

Atomoxetine Study 2

• 5-14 year olds with ASD + ADHD
• Atomoxetine up to 1.8 mg/kg (split) +/- parent training (PT) x 10 weeks
  • 47-48% “much improved” on atomoxetine
    – 19% on placebo, 29% on placebo + PT
• Decreased appetite

Guanfacine (Tenex, Intuniv)

- 5-14 year olds with ASD + ADHD
- Guanfacine extended-release (ER) 1-4mg x 8 weeks
  - 50% “much improved” on guanfacine ER
    - 9.4% on placebo
- Well-tolerated
  - Sedation, decreased appetite, dry mouth

Repetitive Behavior Symptoms
Serotonin Reuptake Inhibitors

• Insufficient Strength of Evidence
  – Citalopram (Celexa) shows no benefit for repetitive behaviors lumped together
  • Differential response to placebo in less affected children
  • Activation very common (almost 50%)

Disclosure: Off-label use of medication

What is Meant By ‘Activation’?

• Increased energy
• Decreased need for sleep
• Impulsivity
• Mood changes
  – Lability
  – Irritability
  – Aggression

Disclosure: Off-label use of medication
Differences in Adults?

- Fluoxetine (Prozac) study for Obsessive Compulsive Disorder symptoms
  - Mean age = 34 years old
  - Mean IQ = 103

- Similar data with fluvoxamine (Luvox)
  - McDougle, et al. 1996

- Less activation in adults

Disclosure: Off-label use of medication

What medication has been best studied in Autism Spectrum Disorder?
Secretin

• Best-studied medication in ASD
• Strength of Evidence = high for lack of benefit
• Lessons to be learned:
  – Hesitate to draw conclusions without randomized, placebo-controlled trials
  – Placebo effect can be powerful in ASD
    • 30-45%

Off-Label Use of Medication
Secretin

Bodfish et al., *NEJM*, 1999
Secretin

“After they were told the results, 69 percent of the parents of the children in this study said they remained interested in secretin as a treatment for their children.”

Bodfish et al., *NEJM*, 1999
Many current medical treatments have similar evidence to secretin before the randomized, placebo-controlled trials.
Happy to take questions…
Outline

• What is autism spectrum disorder (ASD)?
• What do we know about medications in ASD?
• How do we approach common co-occurring psychiatric conditions?
• The ultimate goal: combined medical and behavioral treatment
Important Note

Most children with ASD either do not need or will not benefit from available medications.
Many Possible Targets for Treatment in ASD

- Medical comorbidity (start here)
- Core symptoms (behavioral treatment)
- Communication (behavioral and speech treatment)
- Psychosocial stress (structure and family treatment)
- Psychiatric comorbidity
General Principles

• Form a partnership: parent, child, and clinician.
• First, do no harm.
  – Avoid chronic response to acute problem.
  – Manage benefit:risk (side effect) ratio.
  – Aim for least restrictive environment.
    • Avoid hospitalization if safe.
• Target a clear symptom.
• Start low, go slow.
General Principles (Cont’d)

• Follow up within expected response period.

• Change one thing at a time.
  – Know the effects of each treatment.

• Maximize response to one treatment before adding another.

• Monitor side effects as closely as benefits.
  – Anticipate and contract for stopping.
    • “We’ll stop if he gains 10 lbs in the first 2 months.”
Frequently, the Presenting Problem is Non-Specific: Irritability/Agitation/Aggression
Evaluating and Treating Irritability/Agitation/Aggression in ASD

• Address psychosocial stressors
• Medical/sleep work-up
• Improve communication
• Differential reinforcement of other behavior (ABA)
• Treat co-occurring psychiatric symptoms first!
  – Will come back to this non-specific category
Treatment of Co-Occurring Psychiatric Symptoms in ASD
Attention Deficit Hyperactivity Disorder
Evaluation Pathway for ADHD in ASD

1. Sleep or medical problems
   - Insomnia
   - Seizure disorder

2. Co-occurring psychiatric symptoms
   - Mood
   - Anxiety

3. Evaluation of setting/structure
   - Communication tools
   - Schedule
   - Predictable reinforcement

Disclosure: Off-label use of medication

Medication Pathway for ADHD in ASD

1. Guanfacine / clonidine (lower risk)
2. Methylphenidate / amphetamines (more risk, larger effect size)
3. Atomoxetine (smaller effect size)
4. Risperidone or aripiprazole for SEVERE impulsivity conferring risk of injury, elopement

Disclosure: Off-label use of medication

Anxiety

• Most kids have some anxiety, especially kids with ASD.
• Only consider medications if a child has an anxiety disorder diagnosis:
  – Separation anxiety disorder
  – Generalized anxiety disorder
  – Social anxiety disorder / social phobia
  – Panic disorder (teens or adults)
Pathway for Anxiety in ASD

- LIMITED DATA!

1. Social stories/communication/structure
2. Exposure and response-prevention
   - Cognitive behavioral therapy (CBT)
3. After diagnosis, consider shorter half-life serotonin reuptake inhibitor (sertraline [Zoloft], fluvoxamine [Luvox])

Disclosure: Off-label use of medication
Repetitive Behavior

• Repetitive behavior is necessary to make a diagnosis of ASD
  – Can sometimes feed significant irritability/agitation/aggression

• Repetitive behavior can also include co-occurring Obsessive Compulsive Disorder (OCD)
Pathway for Repetitive Behavior

- LIMITED DATA!
  1. Replacement/differential reinforcement of other behavior (ABA)
  2. If high-functioning: Exposure and Response-Prevention (CBT)
  3. For OCD: Shorter half-life serotonin reuptake inhibitor (sertraline [Zoloft], fluvoxamine [Luvox])
  4. For repetitive self-injury, skin picking, hair pulling: N-acetylcysteine (Pharma-NAC)

Disclosure: Off-label use of medication
Depression

• Very common, particularly in high-functioning adolescents with ASD
• Next to nothing known about treatment
Pathway for Depression in ASD

- LIMITED DATA!
  1. Behavioral activation/structure/therapy
  2. Shorter half-life serotonin reuptake inhibitor

Disclosure: Off-label use of medication
Pathway for Insomnia in ASD

A topic for another day…

Disclosure: Off-label use of medication
If other approaches don’t work for irritability/agitation/aggression...
Pathway for Medication for Irritability/Agitation/Aggression in ASD

1. Guanfacine / clonidine (usually fail when severe)
2. Risperidone / aripiprazole
3. Haloperidol or other medicine in this class

Disclosure: Off-label use of medication
Outline

• What is autism spectrum disorder (ASD)?
• What do we know about medications in ASD?
• How do we approach common co-occurring psychiatric conditions?
• The ultimate goal: combined medical and behavioral treatment
Additive Effects of Behavioral Therapy and Risperidone?

Summary

• Real world treatment targets symptoms rather than ASD, draws on data across disorders.
• Risperidone and aripiprazole can help with irritability/agitation.
• ADHD meds can help but have more side effects and less benefit in ASD.
• The ultimate goal: combined medical and behavioral treatment.
Happy to take questions...