Psychopharmacology of Autism Spectrum Disorder

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Conflict of Interest Disclosure

- I have no relevant financial relationships to report with a commercial interest.
Off-Label Use of Medication

• In this presentation, all discussion of use of medication refers to “off-label” use other than risperidone and aripiprazole for irritability in children and adolescents with autistic disorder.
Target symptom domains

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Mood disorders
5. Anxiety disorders
6. Social impairment
Target symptom domains

1. **Motor hyperactivity and inattention**
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Mood disorders
5. Anxiety disorders
6. Social impairment
Medications for hyperactivity and inattention in ASD

- Psychostimulants
- Atomoxetine
- Alpha-2 Agonists
PSYCHOSTIMULANTS IN ASD
RUPP Autism Network Study of MPH in Children With ASD + Hyperactivity

- 72 Children (age, 5–14 y) with autism, Asperger’s Disorder, or PDD NOS and significant “ADHD” symptoms

- Study design
  - 7-day test-dose period
  - 4-week double-blind trial of 3 dose levels (0.125, 0.25, 0.50 mg/kg/dose) of MPH TID and placebo in random order

*MPH = Methylphenidate.*
*ASD = autism spectrum disorder.*
*PDD NOS = pervasive developmental disorder not otherwise specified.*
*ADHD = attention deficit/hyperactivity disorder.*
Test-dose phase

- 6 out of 72 subjects were unable to tolerate ≥ 2 dose levels of MPH and were dropped from the study
- 16 out of the remaining 66 subjects had intolerable adverse events at the highest dose of MPH; entered modified crossover phase
- Irritability was the most common reason for intolerability

Cross-over phase

- 58/66 subjects completed the crossover phase
- 7 subjects dropped out due to intolerable adverse events
- There was a statistically significant main effect of dose of MPH on the ABC Hyperactivity subscale score as rated by both teacher (Primary Outcome Measure; P = .009) and parent (P < .001)

ABC = Aberrant Behavior Checklist.
Categorical response

- 44 subjects were rated as responders to at least 1 week of treatment (MPH or placebo)
  - MPH (n = 35), Placebo (n=9)
- Subject age, IQ, *diagnosis (trend, P = .07), and weight did not moderate treatment response
- *Subjects diagnosed with Asperger’s disorder and PDD NOS were more likely to be classified as responders to both placebo and MPH than those with autism

### Categorical Response

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
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</thead>
<tbody>
<tr>
<td>Asperger’s disorder/</td>
<td>6 (32%)</td>
<td>7 (37%)</td>
<td>7 (37%)</td>
<td>6 (32%)</td>
</tr>
<tr>
<td>PDD NOS (n=19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autism (n=47)</td>
<td>6 (13%)</td>
<td>13 (28%)</td>
<td>15 (32%)</td>
<td>12 (26%)</td>
</tr>
</tbody>
</table>

Response to each dose of MPH was superior to placebo for autism subgroup (P < .001), but not for the Asperger’s disorder/PDD NOS subgroup (P > .05)

MPH Summary

• 35/72 subjects (49%) responded to MPH

• 13/72 (18%) exposed to MPH dropped out due to adverse events

ATOMOXETINE IN ASD
DB, PC Trial of ATX for ADHD Symptoms in Children with ASD

- 8-week study
- 97 subjects (age range: 6-17 yrs; mean 9-10 yrs) (IQ > 60)
- 3-week titration (0.5 mg/kg/day; 0.8 mg/kg/day; 1.2 mg/kg/day)
- Primary outcome measure – ADHD-RS

ATX = Atomoxetine.
### DB, PC Trial of ATX for ADHD Symptoms in Children with ASD

<table>
<thead>
<tr>
<th>Primary Outcome Measure</th>
<th>ATX = 48</th>
<th>PLA = 49</th>
<th>p Value</th>
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<tbody>
<tr>
<td>ADHD-RS (Total)</td>
<td>40.7</td>
<td>38.6</td>
<td>&lt; .001</td>
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<tr>
<td></td>
<td>31.6</td>
<td>38.3</td>
<td></td>
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<tr>
<td>ADHD-RS (Inattention)</td>
<td>20.7</td>
<td>20.6</td>
<td>.003</td>
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<td></td>
<td>17.2</td>
<td>19.9</td>
<td></td>
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<tr>
<td>ADHD-RS (Hyperactivity)</td>
<td>20.0</td>
<td>17.9</td>
<td>&lt; .001</td>
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<tr>
<td></td>
<td>14.5</td>
<td>18.4</td>
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</table>

<table>
<thead>
<tr>
<th>CGI-I (ADHD)</th>
<th>p Value 0.14</th>
<th>ATX = 48</th>
<th>PLA = 49</th>
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<tbody>
<tr>
<td>Very Much Improved</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Much Improved</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Minimally Improved</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>No Change</td>
<td>16</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Minimally Worse</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Much Worse</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Very Much Worse</td>
<td>0</td>
<td>0</td>
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<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>ATX = 48</th>
<th>PLA = 49</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>14</td>
<td>4</td>
<td>.009</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>13</td>
<td>3</td>
<td>.006</td>
</tr>
<tr>
<td>Early Morning Awakening</td>
<td>5</td>
<td>0</td>
<td>.027</td>
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</table>

DB, PC Trial of ATX for ADHD Symptoms in Children with ASD

• Summary

• Effects on Hyperactivity > Inattention in ASD

• Effects on Hyperactivity = Inattention in ADHD

• Magnitude of effect (ADHD-RS) in ASD (8.2), in ADHD (13 to 19)

• Concerns

• Duration of Study

• Starting dose (0.5 mg/kg/day) and rate of upward titration

ALPHA-2 AGONISTS IN ASD
Study of Extended-Release Guanfacine (XR-G) in Children with ASD + Hyperactivity

• 62 Children (age, 5-14 y) with ASD and significant ADHD symptoms (ABC Hyperactivity subscale score > 24)

• Study design
  – 8-week, randomized, db, pc, fixed-flexible dose, clinical trial

ASD = Autism Spectrum Disorder
ADHD = Attention-Deficit/Hyperactivity Disorder
Study of Extended-Release Guanfacine (XR-G) in Children with ASD + Hyperactivity

- XR-G Group (n = 30):
  - 43.6% decline in ABC-H subscale score – 34.2 to 19.3
- Placebo Group (n = 32):
  - 13.2% decline in ABC-H subscale score – 34.2 to 29.7
    (P < 0.0001; effect size = 1.67)

Study of Extended-Release Guanfacine (XR-G) in Children with ASD + Hyperactivity

Least squares means on Aberrant Behavior Checklist–Hyperactivity subscale scores for XR-guanfacine and placebo groups during the eight week trial. Higher scores reflect greater hyperactivity.

Study of Extended-Release Guanfacine (XR-G) in Children with ASD + Hyperactivity

- Rate of Positive Response
  - XR-G Group: 15/30 = 50%
  - Placebo Group: 3/32 = 9.4%
  - (P = 0.001)
- Modal dose for XR-G = 3 mg/day for drug and placebo groups.

Study of Extended-Release Guanfacine (XR-G) in Children with ASD + Hyperactivity

- Most common adverse events
  - drowsiness
  - fatigue
  - emotional fragility
  - tearfulness
  - irritability
- B/P readings returned to baseline measures by Week 8
- HR remained 10 points below baseline measures at Week 8
- No clinically significant changes on electrocardiogram

Target symptom domains

1. Motor hyperactivity and inattention
2. **Irritability** (agression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Mood disorders
5. Anxiety disorders
6. Social impairment
Medications for irritability in ASD

- Antipsychotics
- Mood Stabilizers
ANTIPSYCHOTICS IN ASD
Atypical Antipsychotics

- Serotonin antagonism in addition to dopamine antagonism
- Lower risk of dyskinesias
- Individual drugs include
  - Risperidone
  - Aripiprazole
  - Paliperidone
  - Olanzapine
  - Quetiapine
  - Ziprasidone
  - Clozapine
Risperidone in Children With Autism and Serious Behavioral Problems

RUPP Autism Network

Indiana University (Christopher J. McDougle, MD)
Kennedy-Kreiger, Johns Hopkins (Elaine Tierney, MD)
Ohio State University (Michael G. Aman, PhD; L. Eugene Arnold, MD)
Yale Child Study Center (Larry Scahill, MSN, PhD)
UCLA (James T. McCracken, MD)
NIMH (Benedetto Vitiello, MD)
Risperidone in Children and Adolescents with autism

• 101 subjects (82 boys, 19 girls)
• Diagnosis: autistic disorder
• Significant irritability (ABC Irritability ≥18)
• 8 weeks, double-blind, placebo-controlled, parallel groups
• Mean age = 8.8 ± 2.7 y; range = 5–17 y
• Risperidone 1.8 mg/d; range = 0.5–3.5 mg/d

8-week Risperidone Trial

Response criteria: ≥25% improvement in the ABC–I score, and a rating of “much improved” or “very much improved” on the CGI–I

CGI–I = Clinical Global Impressions–Improvement.
## Baseline and Endpoint ABC Scores by Group

<table>
<thead>
<tr>
<th>ABC</th>
<th>Risperidone</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Endpoint</td>
</tr>
<tr>
<td>Irritability</td>
<td>26.2 (7.9)</td>
<td>11.3 (7.4)</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social Withdrawal</td>
<td>16.4 (8.2)</td>
<td>8.9 (6.4)</td>
</tr>
<tr>
<td>( P = 0.03/NS )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stereotypy</td>
<td>10.6 (4.9)</td>
<td>5.8 (4.6)</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>31.8 (9.6)</td>
<td>17.0 (9.7)</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappropriate Speech</td>
<td>4.8 (4.1)</td>
<td>3.0 (3.1)</td>
</tr>
<tr>
<td>( P = 0.03/NS )</td>
<td></td>
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8-week Risperidone Trial

- Adverse effects
- Mean increase in weight
  - Risperidone, 2.7 ± 2.9 kg
  - Placebo, 0.8 ± 2.2 kg; P < 0.001
- Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group; all P < 0.05
- AIMS and Simpson-Angus: no EPS

AIMS = Abnormal Involuntary Movement Scale.
EPS = extrapyramidal symptoms.
RUPP Risperidone – Parent Management Training Trial

- 124 children (4 to 13 years) with PDDs and significant irritability
- 24-week, three-site, randomized, parallel groups trial
- Children randomized 3:2 to COMB (n=75) or MED (n=49)
- Parents in COMB received a mean of 10.9 PMT sessions

RUPP Risperidone – Parent Management Training Trial

• Primary Outcome Measure (Home Situations Questionnaire [HSQ]); COMB > MED (P=.006)

• COMB > MED on ABC Irritability (P=.01), Stereotypic Behavior (P=.04), and Hyperactivity/Noncompliance (P=.04)

• Final Risperidone dose for MED (2.26 mg/day) vs. COMB (1.98 mg/day) (P=.04)

ABC = Aberrant Behavior Checklist.
Aripiprazole in Autism – Flexible Dose Study

- 98 children and adolescents with autism (age 6-17 years) with significant irritability
- 8-week, double-blind, placebo-controlled, parallel groups, flexibly-dosed (2-15 mg/day) trial
- Aripiprazole (8.5 mg/day) more efficacious than placebo on Aberrant Behavior Checklist Irritability subscale (P<.001)
- Discontinuation rates: PLA=5.9% Aripiprazole=10.6%
- Most common AEs with aripiprazole were fatigue and somnolence
- Weight gain PLA=1.0 kg Aripiprazole=2.1 kg

Aripiprazole in Autism – Fixed Dose Study

- 218 children and adolescents with autism (age 6-17 years) with significant irritability
- 8-week, double-blind, placebo-controlled, parallel groups, fixed-dose (5 mg, 10 mg, 15 mg) trial
- Aripiprazole (5 mg, 10 mg, 15 mg) more efficacious than placebo on Aberrant Behavior Checklist Irritability subscale (P<.05 for all)
- Discontinuation rates: PLA=7.7%, 5 mg=9.4%, 10 mg=13.6%, 15 mg=7.4%
- Common AEs leading to discontinuation: sedation, drooling, tremor, akathisia, EPS
- Weight gain PLA=0.3 kg, 5+10 mg=1.3 kg, 15 mg=1.4 kg

MOOD STABILIZERS IN ASD
Mood stabilizers in ASD

• There are no large-scale DB, PC trials of any mood stabilizer demonstrating efficacy for irritability in autism.
Target symptom domains

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. **Restricted, repetitive patterns of behavior**
4. Mood disorders
5. Anxiety disorders
6. Social impairment
Medications for Restricted, Repetitive Patterns of Behavior in ASD

• SSRIs
SSRIS IN CHILDREN AND ADOLESCENTS WITH ASD
12-week DB, PC study: Fluvoxamine and Placebo

34 children and adolescents (mean age 9.5 years) with ASD

Fluvoxamine started at 25 mg/day every other day, mean dose = 106.9 mg/day

Responders: Fluvoxamine 1/18, Placebo 0/16

Prominent adverse events: insomnia, motor hyperactivity, agitation and aggression

McDougle CJ et al. Unpublished data.
DB, PC Crossover Trial of Liquid Fluoxetine in Children and Adolescents with ASD

• Crossover study: 8 weeks of Fluoxetine and Placebo
• 45 children and adolescents (8.18 ± 3.0 years) with ASD; IQ 63.65 ± 27.9
• Starting dose 2.5 mg/day, mean dose 9.9 ± 4.35 mg/day
• Fluoxetine > Placebo on CY-BOCS Compulsion scale; No difference on global autism measure
• No difference between Fluoxetine and Placebo in reported adverse events

Citalopram in ASD

- 149 children (9.4 ± 3.1 years) with PDDs and significant repetitive behavior
- 12-week, double-blind, placebo-controlled, parallel groups design
- Citalopram started at 2.5 mg/day; max dose = 20 mg/day; (mean dose = 16.5 ± 6.5 mg/day)
- No drug-placebo difference in response on CGI-I or in score reduction on CY-BOCS-PDD
- Significantly more adverse events with citalopram than placebo: increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, and dry skin or pruritus

ACTN Study of Fluoxetine in ASD: S O F I A

- 14-week, double-blind, placebo-controlled
- Largest trial of SSRI in autism to date
- 158 subjects, ages 5-17 y
- Fluoxetine not effective for repetitive behaviors in youth with autism vs. placebo

ACTN = Autism Clinical Trials Network
Autism Speaks, press release 2009
Target symptom domains

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Mood disorders
5. Anxiety disorders
6. Social impairment
Medications for mood disorders in ASD

• Antidepressants
• Mood Stabilizers
Antidepressants in ASD

- There are no published DB, PC trials of medication for treating depression in autism.
- Challenges of diagnosing depression in autism.
Mood stabilizers in ASD

• There are no published DB, PC trials of medication for treating bipolar disorder in autism.
Target symptom domains

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Mood disorders
5. **Anxiety disorders**
6. Social impairment
Medications for Anxiety in ASD

- Buspirone
- Mirtazapine
- Low-dose SSRIs
Prospective, Open-Label Trial of Buspirone in Children and Adolescents with ASD

- 8-week study
- 22 subjects, age range = 6-16 yrs, majority inpatients
- 4 subjects on concomitant behavioral medications
- Target symptoms: Anxiety = 14, Irritability = 1, Anxiety and Irritability = 7

Prospective, Open-Label Trial of Buspirone in Children and Adolescents with ASD

• Starting dose = 5 mg t.i.d.
• Maximum dose = 45 mg/day (reached within 3 weeks)
• Mean dose = 29.3 mg/day
• 9 subjects had a marked response; 7 subjects had a moderate response
• Adverse events: initial sedation = 2, slight agitation = 2, initial nausea = 1

Prospective, Open-Label Trial of Buspirone in Children and Adolescents with ASD

- The 16 responders were followed up for 12-months (mean = 5.4 months)
- Therapeutic benefits were sustained in all subjects
- One subject (10 y.o. boy) developed an oro-facial-lingual dyskinesia (after 10 months) that resolved when drug was discontinued

Naturalistic Open-Label Trial of Mirtazapine in ASD

• Treatment duration ≥ 4 weeks (mean = 150 ± 103 days)

• 26 subjects; age range = 3.8 to 23.5 years, mean age = 10.1 ± 4.8 years; 20 had intellectual disability

• 17 subjects were taking concomitant behavioral medications; mean number of previous adequate medication trials equal 5.5 ± 5.4

Naturalistic Open-Label Trial of Mirtazapine in ASD

- Starting dose = 7.5 mg/day with weekly increases of 7.5 mg based on response and tolerability
- Final mean dose = 30.3 ± 12.6 mg/day
- Nine out of 26 (34.6%) subjects responded (Sleep Disturbance, Irritability, Hyperactivity)
- Most frequent adverse events = increased appetite, sedation, irritability

Low-dose SSRIs for anxiety in ASD

• There are no published DB, PC trials of low-dose SSRIs for treating anxiety in autism.
Target symptom domains

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Mood disorders
5. Anxiety disorders
6. Social impairment
Medications Studied for Social Impairment in ASD

- Not effective
  - Fenfluramine
  - Naltrexone
  - Lamotrigine
  - Amantadine
  - Risperidone
  - Fluoxetine
  - Citalopram
D-Cycloserine in Children with Autism

- 80 children (6.5 ± 2.8 years; range 3-12 years) with autistic disorder and significant social withdrawal
- 8-week, double-blind, placebo-controlled, parallel groups design
- D-cycloserine 1.7 mg/kg/day divided twice daily or placebo
- No drug-placebo difference on the CGI-I, ABC Social Withdrawal subscale, or Social Responsiveness Scale
- D-cycloserine generally well-tolerated
- Majority of responders maintained response during 16-week open-label extension

Questions?