Psychopharmacology of Co-occurring Conditions in Autism Spectrum Disorders

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Disclosures

• In the past 12 months, I have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that will be discussed in my presentation.

• This presentation will not include discussion of pharmaceuticals or devices that have not been approved by the FDA.

• This presentation will be discussing unapproved or “off-label” uses of pharmaceuticals or devices.
Objectives

- Medications to treat 3 classes of symptoms
  
  - Hyperactivity, impulsivity, inattention: STIMULANTS
  - Aggression, self-injury, irritability: ATYPICAL ANTIPSYCHOTICS
  - Anxiety, repetitive behaviors: SELECTIVE SEROTONIN REUPTAKE INHIBITORS
  
- Review efficacy, side effects, monitoring plan
Psychopharmacological Treatments in ASD

- Randomized placebo controlled trials
- Open label, retrospective reviews, case reports
- Experimental
Interventions

- Speech and language services
- Educational programming
- Behavioral interventions
- Social skills training
- Sensory integration
- Medical treatments
- Psychopharmacological treatments
- Complementary and alternative medicines

The goal of intervention is to maximize adaptation.
North Carolina Survey, N = 1,538

3 to 56 years
Autism Society of North Carolina

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>% Reporting Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant</td>
<td>22</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>17</td>
</tr>
<tr>
<td>Stimulant</td>
<td>14</td>
</tr>
<tr>
<td>Alpha agonist</td>
<td>8</td>
</tr>
<tr>
<td>Sedative</td>
<td>7</td>
</tr>
<tr>
<td>Mood stabilizer</td>
<td>5</td>
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<tr>
<td>Any medication</td>
<td>46</td>
</tr>
<tr>
<td>3 or more medications</td>
<td>8</td>
</tr>
</tbody>
</table>

J Child Adolesc Psychopharmacol, 2002
0 to 21 years
All 50 states plus Washington DC

Medication Type

- Antidepressant: 25
- Stimulant: 22
- Mood stabilizer: 21
- Anxiolytic: 12
- Sedative: 3
- Any medication: 56
- 3 or more medications: 20

Pediatrics, 2008
Interactive Autism Network, N = 5,181

3 to 17 years

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>% Reporting Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulant</td>
<td>15</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>15</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>14</td>
</tr>
<tr>
<td>Alpha agonist</td>
<td>8</td>
</tr>
<tr>
<td>Mood stabilizer</td>
<td>7</td>
</tr>
<tr>
<td>Any medication</td>
<td>35</td>
</tr>
<tr>
<td>3 or more medications</td>
<td>9</td>
</tr>
</tbody>
</table>
Assessment

- 1 - 2 visits
- Multi-informant
- Family history
- What is the primary behavior of concern?
- What might be the cause?
- Do symptoms interfere with functioning?
- Do the parents want to try medications?
- Are other providers aware?
Discussion

• Evidence (sometimes trial and error process)
• Factors to consider
  - risks/benefits of each medication
  - swallow pills/liquid preparation
  - tolerate blood draw/EKG
  - timing
• Plan
  - measurable goals
  - start with well-studied medication
  - ‘start low and go slow’
  - compliance
  - duration of treatment
  - monitoring plan
  - future medication trials
  - polypharmacy
  - coordination of care
ADHD Symptoms

Stimulants

Nonstimulants

Alpha-2 agonists

NRI (atomoxetine)

Neuroleptics
Methylphenidate (MPH) - Ritalin

- 72 subjects, 5 to 14 years
- Double blind placebo cross over trial
- MPH: Low (0.125mg/kg), medium (0.25mg/kg), high (0.5mg/kg)
- Outcome measures: Aberrant Behavior Checklist (ABC)
  Clinician Global Impression Scale

Results: 49% - Improved attention, decreased hyperactivity (versus 69% in typically developing children)

Arch Gen Psychiatry, 2005
Common Adverse Effects*

![Bar chart showing percentages of adverse effects for different doses of MPH.]

- **Appetite decrease**: High dose 24%, Medium dose 12%, Low dose 5%
- **Insomnia**: High dose 11%, Medium dose 18%, Low dose 11%
- **Irritability**: High dose 8%, Medium dose 12%, Low dose 8%
- **Emotional outbursts**: High dose 10%, Medium dose 14%, Low dose 8%

* 18% drop out (versus 1.4% in children without ASD) due to irritability

*Arch Gen Psychiatry, 2005*
Stimulant Side Effects

• Appetite suppression
• Negative mood
• Flat affect
• Worsening anxiety, repetitive behaviors
• Elevated blood pressure/pulse
• Insomnia
• Psychosis
• Disorganizing effects
Stimulant Monitoring

- BP/Pulse
- Appetite suppression
- Height/Weight
- Sleep
- Mood/Anxiety
- Thought processes
- Repetitive behaviors/Tics
Alpha-2 Agonists

• Hyperactivity/impulsivity > Inattention

• Clonidine (Kapvay) – can be sedating, shorter acting, frequent dosing, liquid preparation

• Guanfacine/Tenex (Intuniv) - binds preferentially to postsynaptic 2A-adrenoreceptors in the prefrontal cortex

• Other: aggression, outbursts (prn), anxiety

• Side effects: Low BP, pulse, sedation, mood change

• Consider as first line agent
<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Subjects</th>
<th>Design</th>
<th>Results</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaselskis et al., 1992</td>
<td>Clonidine 0.15 – 0.2 mg/day (tid)</td>
<td>n = 8, 5 to 13 yrs</td>
<td>DBPC 6-week crossover</td>
<td>Clonidine &gt; PBO by parent and teacher report</td>
<td>Hypotension, sedation, irritability</td>
</tr>
<tr>
<td>Fankhauser et al., 1992</td>
<td>Transdermal clonidine 5 μg/kg/day</td>
<td>n = 9, 5 to 33 yrs</td>
<td>DBPC 4-week crossover</td>
<td>Clonidine &gt; PBO by clinician report</td>
<td>Fatigue, sedation</td>
</tr>
<tr>
<td>Scahill et al., 2006</td>
<td>Guanfacine 1.0 – 3.0 mg/day</td>
<td>n = 25, 6 to 9 yrs</td>
<td>8 week open trial</td>
<td>Guanfacine &gt; PBO by parent and teacher report</td>
<td>Mood change, sedation, sleep problems, constipation</td>
</tr>
<tr>
<td>Posey et al., 2004</td>
<td>Guanfacine 0.25 – 9 mg/day</td>
<td>n = 80, 3 to 18 years</td>
<td>Retrospective analysis</td>
<td>Improvement with guanfacine by clinician report</td>
<td></td>
</tr>
</tbody>
</table>
Atomoxetine (ATX) - Strattera

- 16 subjects, 5 to 15 years
- Design: PBO-controlled crossover trial
- ATX: 2.5-40 mg/day
- Outcome: ABC-hyperactivity - 25% improvement
  CGI-I - “very much improved” or “much improved”

Results: 9 subjects (57%) on drug improved
4 subjects (25%) on PBO improved
Appetite suppression (75%), moodiness (88%)

JAACAP, 2006
Aggression/Self-Injury/Irritability

- FDA Approved: Risperidone, Aripiprazole
- Other Atypical Antipsychotics
- Typical antipsychotics: Haloperidol
- Other: Mood Stabilizers, SSRIs
Risperidone

- 101 subjects, 5-17 years, mental age >18 mos.
- Multi-site double blind placebo controlled trial – 8 weeks
- Mean dose = 1.8 mg/day (range 0.5-3.5 mg/day)
- Outcome measures: ABC-irritability, CGI-I

Results: Reduction in irritability cluster
69% Risperidone versus 12% Placebo
30% nonresponders

NEJM, 2002
Figure 1. Mean Scores for Irritability in the Risperidone and Placebo Groups during the Eight-Week Trial. Data are for all 101 children (49 assigned to the risperidone group and 52 assigned to the placebo group). Higher scores indicate greater irritability.

Effect size = 1.2
Risperidone

- Risperidone > Placebo (effect sizes) – BROADER COVERAGE
  
  Irritability – 1.2
  Hyperactivity – 1.0
  Stereotypy – 0.8

- No drop out

- Side effects: Increase in appetite and weight (*2.7kg versus 0.8kg*), drowsiness, dizziness, and drooling were greater in the drug compared to placebo group.

*NEJM, 2002*
FIGURE 1. Scores on the Irritability Subscale of the Aberrant Behavior Checklist for 63 Children With Autism Who Responded to Risperidone in an 8-Week Trial and Participated in a 4-Month Open-Label Extension

Week 0 corresponds to the end of the initial 8 weeks of medication exposure.

For patients who discontinued treatment, the last observation was carried forward.
Risperidone + Parent Management Training

- 124 children, 4 to 13 years, 24 weeks
- Two groups: Medication + Parent Training
  - Medication alone

Results:

Combo > Meds - irritability, stereotypy, hyperactivity

Combo (1.98mg) versus Medication alone (2.26mg)

JAACAP, 2009
Aripiprazole

- 218 subjects, age 6-17 years
- 8 week double-blind, PBO- controlled, parallel-group
- 3 drug groups (fixed dose: 5, 10, or 15 mg/day), PBO
- Outcomes: ABC-Irritability; CGI-I

**Results:** Irritability: Drug (49-56%) > PBO (35%) (about 50% nonresponders)

Also reduction in hyperactivity, stereotypies, inappropriate speech, compulsions

*JAACAP, 2009*
Fig. 2 Mean (95% CI) ABC-Irritability subscale score by week (LOCF; efficacy sample). Treatment difference (95% CI) (aripiprazole–placebo): aripiprazole 5 mg/day, –4.0 (–7.7, –0.4); aripiprazole 10 mg/day, –4.8 (–8.4, –1.3); aripiprazole 15 mg/day, –6.0 (–9.6, –2.3). ABC = Aberrant Behavior Checklist; LOCF = last observation carried forward; CI = confidence interval. \(*p < .05; \ **p < .01; \ ***p \leq .001\) versus placebo.
Aripiprazole

- 98 subjects, age 6-17 years
- 8 week double-blind, randomized, PBO-controlled
- Flexible dosing (target: 5, 10, 15mg)
- Outcome measures: ABC-Irritability and other subscales

Results: Irritability: 52% on drug vs 14% on PBO

Also reduction in hyperactivity, stereotypies, inappropriate speech, compulsive behavior

Pediatrics, 2009
FIGURE 2
Mean ABC irritability subscale score according to week (LOCF; efficacy sample).  
\(^a P < .05, \quad ^b P < .005, \quad ^c P < .001\) versus placebo.
<table>
<thead>
<tr>
<th>Promising</th>
<th>Not suitable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Olanzapine</strong></td>
<td><strong>Quetiapine</strong></td>
</tr>
<tr>
<td>(Malone et al., 2001; Hollander et al., 2006)</td>
<td>(Martin et al., 1999; Corson et al., 2004)</td>
</tr>
<tr>
<td><strong>Ziprasidone</strong></td>
<td><strong>Clozapine</strong></td>
</tr>
<tr>
<td>(McDougle et al., 2002; Cohen et al., 2004)</td>
<td>(e.g., Beherec et al., 2011; Lambrey et al., 2010; Chen et al., 2001; Zuddas et al., 1996)</td>
</tr>
</tbody>
</table>
Atypical Antipsychotic Side Effects

- Weight gain/metabolic sequelae
- Elevated prolactin
- Sedation/fatigue
- Extrapyramidal symptoms/NMS
- Prolonged QTc
- Elevated LFTs
- Blood dyscrasias
- Thyroid dysfunction
- Reduction of seizure threshold
## Monitoring Protocol for Patients Taking Atypical Antipsychotics*

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>Baseline</th>
<th>4 wks.</th>
<th>8 wks.</th>
<th>12 wks.</th>
<th>Quarterly</th>
<th>Annually</th>
<th>Every 5 years</th>
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</thead>
<tbody>
<tr>
<td>Personal/family history</td>
<td>✓</td>
<td></td>
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<td></td>
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<td>✓</td>
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<tr>
<td>Weight (BMI)</td>
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<td>✓</td>
<td>✓</td>
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<td>✓</td>
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</tr>
<tr>
<td>Waist circumference</td>
<td>✓</td>
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<td></td>
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<td></td>
<td>✓</td>
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<tr>
<td>Blood pressure</td>
<td>✓</td>
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<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*From the Consensus Development Conference on Antipsychotic Drugs and Obesity in Diabetes. Diabetes Care 2004; 27:599.*
Anxiety/Stereotypic and Repetitive Behavior

- Selective Serotonin Reuptake Inhibitors
- Atypical Antipsychotics
- SNRIs, Benzodiazepines, Buspirone, Valproic acid
Anxiety

• Steingard et al., 1997 (n = 9)
  – Transition-induced anxiety, separation anxiety, generalized fears
  – Sertraline 25-50mg, one case using 150mg
  – Short term improvement

• Ozbayrak, 1997 (n = 2)
  – Anxiety and repetitive behavior
  – Sertraline 25-50mg
  – Both cases showed improvement

• Buitelaar et al., 1998 (n = 22)
  – Anxiety, irritability
  – Buspirione, mean dose = 29.3mg
  – 76% had reduction in anxiety

• Bhardwaj et al., 2005 (n = 1)
  – Separation anxiety
  – Sertraline 75 mg
  – Improvement in 6 months
Stereotypic and Repetitive Behavior

- Citalopram (Celexa) = Placebo (largest study)
- Fluoxetine (Prozac) > Placebo
- Fluvoxamine (Luvox) = Placebo
- Not studied: Sertraline (Zoloft), Escitalopram (Lexapro), Paroxetine (Paxil)
Fluoxetine

- Benefits in adults and children in reducing repetitive behaviors

- Adolescents/Adults (Hollander et al., 2012)
  - mean dose = 64.8mg
  - superior to PBO

- Children (Hollander et al., 2005)
  - mean dose = 9.9mg
  - superior to PBO
  - side effects comparable in the two groups
Citalopram

- 12 weeks, double blind placebo controlled
- N= 149 children and adolescents
- Mean dose = 16.5mg
- Outcome measure: CGI-I, CYBOCS

Results: Drug (33%) versus PBO (34%)

More side effects in the drug group: hyperactivity, impulsivity, insomnia, decreased concentration, diarrhea, seizures

Arch Gen Psychiatry, 2009
Citalopram

![Graph showing the effect of Citalopram hydrobromide and placebo on CYBOCS-PDD Score over weeks.](image)

- **Placebo**
- **Citalopram hydrobromide**

Arch Gen Psychiatry, 2009
## SSRI Side Effects

<table>
<thead>
<tr>
<th>Somatic</th>
<th>Behavioral</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI disturbance</td>
<td>Activation</td>
</tr>
<tr>
<td>Changes in appetite</td>
<td>Manic switching</td>
</tr>
<tr>
<td>Headache</td>
<td>Amotivational syndrome</td>
</tr>
<tr>
<td>Abnormal bleeding</td>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td></td>
</tr>
<tr>
<td>Toxic serotonin syndrome</td>
<td></td>
</tr>
<tr>
<td>Serotonin withdrawal syndrome</td>
<td></td>
</tr>
</tbody>
</table>
SSRI Monitoring

- Weekly monitoring for 4 weeks
- Biweekly monitoring for 2 to 4 weeks
- Monthly monitoring thereafter
- Crisis plan
- Avoid abrupt discontinuation
Risperidone and Aripiprazole

- Reduce stereotypies (effect size = 0.8)
- Require metabolic, neurologic, cardiac monitoring

- Atypicals versus SSRIs for repetitive behavior? consider symptom severity, blood draw, family history (metabolic, bipolar)
Some large well-designed studies of psychiatric medications for problematic behavior

Evidence for the following:

- Inattention/hyperactivity: Methylphenidate, Clonidine/guanfacine
- Irritability/Aggression/Self-injury: Risperidone, Aripiprazole
- Repetitive behaviors: Fluoxetine

Low doses and close monitoring of side effects