Pharmacologic Treatment of Challenging Behaviors in Autism Spectrum Disorders: A Lifespan Approach

Jessica A. Hellings, MB.BCh., M.Med (Psych) S.A., FAPA
The Ohio State University Nisonger Center
USA
Disclosures:

• Current, non-reimbursed international collaboration with Roche

• Prior study drug and placebo provided by Janssen Pharmaceuticals

• Prior consultant to Ferring Pharmaceuticals and Abbott Laboratories

• Study investigator for Shire, Forest, Autism Speaks-ATN, NIMH
Introduction:

• Medications may reduce irritability, impulsivity, inattention and improve development, learning and behavior in individuals with Autism Spectrum Disorders (ASD).

• Medications should always be used together with behavioral interventions, parent training, social skills groups and educational interventions.
But:

• No medications are as yet accepted to reverse the core symptoms of ASD.

• Combinations of medications are frequently needed for optimal outcomes, yet combination studies are lacking.

• In general, lower doses are needed for tolerability reasons.
Also:

- "Start low and go slow", but "go up before you give up!"

- Average number of all diagnoses for an adult with developmental disabilities is 10; average number of medications is 10.
Complementary and Alternative Medicines (CAM)

- Alternative treatments are commonly used, yet efficacy and safety studies are lacking; including the gluten-free casein-free diet, vitamin B6, magnesium, probiotics, omega-3 fatty acids and many others.
Impulsivity:

• Impulsivity is associated with repeated hitting, kicking, biting, pinching, cussing and running off, and may be a component of self-injury.

• Bipolar disorders in ASD are often atypical, chronic, rapid cycling or mixed.

• Two common causes of impulsivity are ADHD and Bipolar mania. ADHD is common in childhood and often missed in adults with ASD.
Try to gradually taper off:

- Benzodiazepines: disinhibition


- Long-acting stimulants: shorter-acting preferable (studies are needed)

- Antidepressants: SSRIs, others: activation, behavioral worsening may occur; benefits published with fluoxetine in isolated cases (Cook et al., 1992).
Symptom and Diagnosis-Driven Treatments:

• Preschool-aged and school-aged children and adolescents with ASD often manifest Impulsivity-Hyperactivity-Inattention, accompanied by aggression and/or self-injury and OCD symptoms.

• The above are symptoms of Attention Deficit Hyperactivity Disorder (ADHD) and appropriate medications indicated for ADHD may be helpful; including stimulants and non-stimulant ADHD medications (atomoxetine, amitriptyline, clonidine, guanfacine). (Mahajan et al. 2012, Pediatrics; Bhatti et al. 2013, JADD).
But:

• Co-occurring symptoms of behavioral rigidity and repetitive behaviors (Obsessive-Compulsive-like) may be worsened by ADHD medications, and low dose antipsychotics including risperidone or aripiprazole may be helpful.

• Adults with a childhood history of Hyperactivity-Impulsivity-Inattention when young, may benefit from atomoxetine or other ADHD treatments, not uncommonly with a low dose of an antipsychotic agent.
Hellings & Younas (2012 NCDEU Poster Abstract):

- Performed a retrospective chart review of 20 consecutive patients with ASD treated with ATX.
  - Mean age 17.6 years (range 5-50); 19 (95%) were aggressive, 12 (60%) had self-injury.
  - 14 (70%): Severe intellectual disability (ID) clinically, uncooperative with IQ testing; 2 (10%) profound ID; 1 (5%) severe ID, 3 (15%) mild ID, 1 gifted.
• 71.8% (mean) had 50% or more of follow-up visits with Clinical Global Impressions-Improved (CGI-I) rating of Much Improved or Very Much Improved (range 0-100).

• ATX doses were lower than those recommended in the package insert: mean 0.7 mg/kg/day (range 0.4-1.2) versus maximum of 1.4 mg/day or 100 mg daily.

• Side effects included tachycardia in 5(25%), behavioral worsening in 3(15%), headache: 1(5%) appetite decrease in 1(5%).
Individuals with Prominent Self-Injury:

- Stimulants often worsen self-injury (Arnold et al., 2006).

- Non-stimulant medications for ADHD symptoms may be preferred in such cases with self-injury.

- Low dose antipsychotics such as risperidone may be used first, before trying atomoxetine, for example (Hellings & Younas) [2012 NCDEU Poster Abstract].
Stimulants in ASD: Evidence Base

- Methylphenidate (MPH): RUPP study, 2005: Double-blind, placebo-controlled. MPH superior to placebo, but only 49% of 72 responded (versus 70-80% in normally developing youth).

- Adverse events were more frequent, notably in 18% versus 1.4% in youth without ASD.

- Similar findings in 2 smaller, randomized controlled trials (Handen et al., 2000; Quintana et al., 1995).
Dextroamphetamine (DEX):

- Campbell & coworkers' early small studies (1972, 1976); preschoolers aged 3-6 years; poor tolerability and efficacy; negative.

- Hellings et al. (2010 NCDEU Poster) chart review of 20 subjects aged 5-16 years, median age 10 years. DEX in ultra-low to low doses, mostly in combination showed good efficacy and tolerability (0.2-0.5 mg/kg/day); median dose 20 mg/day (range 5-35 mg/day); mean treatment duration 17.1 months (range 2-51 months).

- Prospective studies are warranted.
Non-Stimulant ADHD Medications in ASD: Evidence Base

• Atomoxetine (ATX): Arnold et al. 2006; double-blind placebo-controlled pilot crossover study: 3 weeks of each, 12 boys and 4 girls.
  – Primary outcome was Hyperactivity Subscale of Aberrant Behavior Checklist; ATX was superior to placebo (p=0.043, effect size d=0.90).
  – ATX also superior on a 0 to 3 rating of 9 DSM-IV ADHD hyperactive/impulsive symptoms.
Non-Stimulant ADHD Medications in ASD: Evidence Base, cont’d.

- Atomoxetine, cont’d.
  - No significant difference on 9 inattentive DSM-IV symptoms.
  - Posey et al. (2006), 8-weeks open-label ATX trial in 16 children and adolescents with ADHD symptoms and High-Functioning ASD: 12 (75%) subjects were "Much Improved" or "Very Much Improved" on CGI ratings: mean dose $1.2 \pm 0.3\text{mg/kg/day}$. 

The Ohio State University
Nisonger Center
non-stimulant ADHD medications in ASD: evidence base, cont’d.

- amitriptyline (AMI): chart review, n=50 (Hellings et al. 2013, JADD):
  - low doses (mean dose 1.3 ± 0.6 mg/kg/day, mean level 114.1 ± 50.5, mean duration 3.4 years);
  - mostly in combinations often with stimulants, e.g. DEX, + low dose risperidone or aripiprazole and low dose AMI.
Non-Stimulant ADHD Medications in ASD: Evidence Base, cont’d.

- Amitriptyline (AMI): chart review, n=50 (Hellings et al. 2013, JADD), cont’d:
  - CGI-I ≤ 2 in 60% of patients at the final visit; in 82% of patients for at least 50% of follow-up visits.
  - Need EKGs, blood levels quarterly; warn parents of overdose toxicity and to lock AMI away.
  - AMI may benefit sleep, appetite, anxiety, impulsivity and hyperactivity.
Alpha agonists in ASD:

Two studies:

- Frankenhauser et al. (1992): placebo versus clonidine patch in 7 males, ages 5 to 33 years. Significant improvement in clinician, parent global ratings but not parent Conners rating.

- Jaselskis et al. (1992) performed a crossover trial of placebo and clonidine in 8 boys with Autistic Disorder and hyperactivity: Improvements significant in Parent, Teacher rating on one of two scales.
Alpha agonists in ASD, cont’d:

- Posey & McDougle (2007): A retrospective chart review of guanfacine in 80 children with ASD; 19 of 80 (24%) were responders.

Other Medications:

• Selective serotonin reuptake inhibitors:
  
  – Problems of activation and behavioral worsening; negative double-blind, placebo-controlled citalopram study for repetitive behaviors in ASD (King et al., 2009).
Other Medications:

• Trials to target core social impairments in ASD: All with mixed results.
  – Memantine, amantadine, cycloserine, lamotrigine, secretin, naltrexone.
  – Oxytocin nasal spray: FDA has expressed serious concerns about safety, developmental effects; no systematic data collection on cases it has been used in so far.
Antipsychotic Medications:

Risperidone (RIS):
• FDA-approved in USA for irritability in children aged 6 years and older with Autistic Disorder.
• Most extensively studied of the antipsychotics in ASD
• Side effects of increased appetite, weight gain, metabolic syndrome, Type II diabetes (Correll et al., 2007; Hellings et al., 2001), prolactin elevation (Findling et al., 2003; Hellings et al., 2005), worse in females.
Antipsychotic Medications, cont'd.

Risperidone (RIS), cont’d:

- Elevated prolactin may be countered using low dose aripiprazole, e.g., 1mg/day.
- Divide RIS into 3 low doses per day to minimize side effects.
- May be best antipsychotic for self-injury: Studies are needed; also of the active metabolite paliperidone.
Antipsychotic Medications, cont’d.

• Aripiprazole: FDA-approved for same indication as RIS.
  – Normalizes prolactin (Shores, 2005).
  – Industry-sponsored study by Marcus et al. (2009) showed significantly greater improvement over placebo for irritability.
Antipsychotic Medications, cont’d.

• Loxapine: Designer drug from 1980s based on clozapine: Further study needed in adolescents and adults with ASD and irritability.
  – 7-OH loxapine, 8-OH loxapine and amoxapine are active metabolites (Kapur, 1997).
  – Ultra-low doses of 5-15 mg/day may be beneficial for adolescents and adults with ASDs, irritability and aggression (Hellings et al., 2009 chart review of 21 patients).
  – Weight gain, neuromotor side effects may be less than with atypicals or other typical antipsychotics.
  – Amoxapine metabolite marketed separately as an antidepressant.
LAASDAI: Loxapine Add-on for Adolescents and Adults with Autism Spectrum Disorders, Aggression and Irritability.

J.A. Hellings¹, J.C. Han², G.I. Palaguachi², G. Reed³, S.E. Cain³, X. Zhou³, F.X. Barth³, M.G. Aman¹, R. Andridge¹, M. Logan³, J. Hayes³ and M.G. Butler³.

(1) McCampbell Hall, The Ohio State University Nisonger Center, Columbus, OH (2) Eunice Kennedy Shriver NICHD, NIH, Bethesda, MD, (3) University of Kansas Medical Center, Kansas City, KS.
Methods:

• 12-week prospective, add-on open trial
• Loxapine added at 5mg on a Mon, Weds, Fri and Sat (to minimize akathisia) and titrated openly up to 15mg daily, by response, as needed during the first 6 weeks.
• Concomitant medications were reduced as tolerated in the first 6 weeks.
• All medication doses were held stable in weeks 6 through 12.
• Fasting, morning blood draws were obtained at baseline and study end for CBC and diff, CMP, Fasting lipids, prolactin, HbA1c, BDNF, and loxapine and metabolite levels at study end.
### Table 1: Primary Outcome Measure of CGI-I

<table>
<thead>
<tr>
<th>Week</th>
<th>N</th>
<th>Responder</th>
<th>Non-Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>16</td>
<td>2 (13%)</td>
<td>14 (88%)</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>7 (47%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>12 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>12</td>
<td>14</td>
<td>14 (100%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Figure 1: Secondary Outcome Measure of CGI-S

![Graph showing the least squares means of CGI-S over weeks 0 to 12. The p-value is <.0001.]
Figure 2: Secondary Outcome Measures, contd.
BDNF concentration was significantly higher following loxapine treatment, both unadjusted and adjusted for delta-platelets and delta-BMI-z.
Bipolar-like symptoms are likely to be more chronic, mixed or rapid cycling in individuals with ASD (Lowry, 1998)

<table>
<thead>
<tr>
<th>Depressive Disorders</th>
<th>Bipolar Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood, crying</td>
<td>Irritability, most common</td>
</tr>
<tr>
<td>usual interests</td>
<td>Laughing spells/crying spells/lability</td>
</tr>
<tr>
<td>Isolative, withdrawn</td>
<td>intrusive, <strong>impulsive</strong></td>
</tr>
<tr>
<td>activity; work, outings</td>
<td>active, pace, walk far</td>
</tr>
<tr>
<td>/ appetite</td>
<td>/ appetite</td>
</tr>
<tr>
<td>/ sleep</td>
<td>/ sleep</td>
</tr>
<tr>
<td>aggression, self-injury</td>
<td>aggression, self-injury</td>
</tr>
<tr>
<td>Morbid thoughts/death/suicide</td>
<td>Grandiose, hypersexual</td>
</tr>
<tr>
<td>prone to abuse</td>
<td>prone to abuse, injuries</td>
</tr>
</tbody>
</table>
For Bipolar-like Disorders, try:

• Valproic Acid (VPA), negative placebo-controlled trial for aggression in children and adolescents with ASD by Hellings et al., 2005), BUT: Behavioral benefits in seizure disorders.

• Gabapentin: Add-on antiseizure medication, good response together with VPA; doses were 900-1800 mg/day; an alternative to lithium (Hellings, 2006).
For Bipolar-like Disorders, cont’:

• Lithium for severe cases, often together with VPA, and an antipsychotic in low dose.

• Antipsychotics: low doses may be used as a mood stabilizer, or if accompanying psychosis is present (Lowry, 1998; Hellings, 1999).
Summary:

• Several new and old medications may be extremely helpful for behavioral comorbidity in ASD.

• Combinations of low doses of medications are often required; studies are needed.

• Close side effect monitoring is essential.

• Choose medications not only for anticipated beneficial effects but also to minimize unwanted side effects.

Thank you!
Table Mountain as seen from Bloubergstrand, South Africa