Autism Spectrum Disorders & Attention Deficit Disorder in PEDIATRIC PRIMARY CARE

TIPS Conference
March 22, 2019

Benjamin L. Handen, PhD, BCBA-D
Professor of Psychiatry and Pediatrics
Western Psychiatric Institute and Clinic
University of Pittsburgh School of Medicine

Abigail Schlesinger MD
Associate Professor Psychiatry and Pediatrics
Western Psychiatric Hospital
University of Pittsburgh School of Medicine

Disclosures

<table>
<thead>
<tr>
<th>Disclosures</th>
<th>Ben Handen</th>
<th>Abigail Schlesinger</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIA</td>
<td></td>
<td>DDAP</td>
</tr>
<tr>
<td>NICHD</td>
<td></td>
<td>CVS</td>
</tr>
<tr>
<td>Autism Speaks</td>
<td></td>
<td>DHS</td>
</tr>
<tr>
<td>Roche</td>
<td></td>
<td>AAP</td>
</tr>
</tbody>
</table>

NIA
NICHD
Autism Speaks
Roche
DDAP
CVS
DHS
AAP
Here's the Plan

Discuss
- Differences and Similarities between ADHD and ASD

Review
- Importance of clarifying symptoms and identifying treatment targets when treating ADHD & ASD
- Pharmacologic & Nonpharmacologic Options for ADHD and ASD

Is There an ADHD-ASD Spectrum?
Autism Spectrum Disorder (ASD) - DSM-5

A. Persistent deficits in social communication and social interaction, manifested by all three:
   - Deficits in social-emotional reciprocity
   - Deficits in nonverbal communicative behaviors used for social interaction
   - Deficits in developing, maintaining, and understanding relationships

B. Restricted, repetitive patterns of behavior, interests, or activities, manifested by at least two:
   - Stereotyped or repetitive motor movements, use of objects, or speech
   - Insistence on sameness, inflexible adherence to routines, or ritualized patterns
   - Highly restricted, fixated interests that are abnormal in intensity or focus
   - Hyper- or hypo-reactivity to sensory input
Attention-Deficit/Hyperactivity Disorder

Inattentive (6 of 9)
- Fidgets
- Leaves seat
- Runs about or climbs
- Unable to play or engage in Leisure activities
- “Driven by a motor”
- Talks excessively
- Blurts out
- Difficulty waiting turn
- Interrupts or intrudes

Hyperactive/Impulsivity (6 of 9)
- Careless mistakes
- Sustaining attention
- Does not seem to listen
- Does not follow through
- Difficulty organizing
- Avoids tasks that require sustained mental effort
- Loses things
- Easily distracted
- Forgetful
- Interrupts or intrudes
• Sara is 5 ½ years old and comes in because her private kindergarten has threatened to “kick her out” if her behavior doesn’t improve quickly. She’s had a behavioral health therapist in the school for the last 2 months, and a there is a behavioral management plan in place, but her behaviors are still a significant concern. Mom brought an email from the school for you to read

• “Sara never stops moving, she runs and climbs during quiet time, she’s got no friends. She doesn’t look at us when we ask her to listen. She doesn’t understand personal space. She talks nonstop. She interrupts her peers to make points. She doesn’t want to wait for lunch and runs away from the lunch room to her teachers room. Since the therapist came she is more likely to follow directions – if she realizes that we have asked her to do something. She is disruptive when it’s time to transition from free play to circle time. When she does start circle time she moves her hands excessively, can’t sit on her spot and continually interrupts her peers repeats portions of songs over and over. It is hard to judge her abilities due to her behavior.”
<table>
<thead>
<tr>
<th>ADHD Hyperactive(6)</th>
<th>ADHD Inattentive(6)</th>
<th>Autism Spectrum Disorder(6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>fidgets</td>
<td>careless mistakes</td>
<td></td>
</tr>
<tr>
<td>leaves seat</td>
<td>sustaining attention</td>
<td></td>
</tr>
<tr>
<td>runs about or climbs</td>
<td>does not seem to listen</td>
<td></td>
</tr>
<tr>
<td>unable to play or engage in leisure activities</td>
<td>does not follow through</td>
<td></td>
</tr>
<tr>
<td>“driven by a motor”</td>
<td>difficulty organizing</td>
<td></td>
</tr>
<tr>
<td>talks excessively</td>
<td>avoids tasks that require sustained mental effort</td>
<td></td>
</tr>
<tr>
<td>blurs out</td>
<td>loses things</td>
<td></td>
</tr>
<tr>
<td>difficulty waiting turn</td>
<td>easily distracted</td>
<td></td>
</tr>
<tr>
<td>interrupts or intrudes</td>
<td>Forgetful</td>
<td></td>
</tr>
<tr>
<td></td>
<td>interrupts or intrudes</td>
<td></td>
</tr>
</tbody>
</table>

**ALL 3 - social communication and social interaction**
- Deficits in **social-emotional reciprocity**
- Deficits in **nonverbal communicative behaviors** used for social interaction
- Deficits in **developing, maintaining, and understanding** relationships

**AT LEAST 2 - Restricted, repetitive patterns of behavior, interests, or activities**
- Stereotyped or repetitive motor movements, use of objects, or speech
- Insistence on sameness, inflexible adherence to routines, or ritualized patterns
- Highly restricted, fixated interests that are abnormal in intensity or focus
- Hyper- or hypo-reactivity to sensory input

---

**How many kids are we talking about anyway?**

- 1 in 59 children diagnosed with ASD
  - Variation by location, gender, SES & race
- 23% - 74% of kids with ADHD may have ASD
- 31% of kids with ASD have ADHD
- Comorbidity higher in clinically referred than community-based studies
Why is it hard to distinguish ADHD from ASD?

• Common symptoms/behaviors:
  – Social skills deficits
  – Inattention
  – Learning problems
  – Both occurs more frequently in males than females

ADHD & ASD Presentation Overlap

• Some common symptoms (e.g., poor peer relations, does not seem to listen when spoken to)
• Some common neuropsychological deficits (e.g., problems with planning, working memory, inhibition, mental flexibility)
• Diagnosed at early age; symptoms often chronic and persist into adulthood
• Many children diagnosed with Autism Spectrum (including the diagnosis formally known as Asperger’s and High Functioning Autism) are first diagnosed (or misdiagnosed) with ADHD
Problems with Diagnosing ADHD in ASD

- Challenge in discriminating between symptoms due to ASD vs. ADHD
- ADHD symptoms must be “inconsistent with developmental level”
- How to “control for” intellectual disability
- ADHD often the first diagnosis in "high functioning kids"
- Few available diagnostic tools for assessing ADHD in ASD

Considerations Making Diagnosis

- Impact of language
  - Some symptoms not appropriate for children with limited language (e.g., “often talks excessively,” “often blurts out answers”).
- Considering Mental Age
  - Connors does not require adjustment
- Is tool normed for ID and ASD Population
  - Hyperactivity subscale of Aberrant Behavior Checklist
Comorbidities in ASD

- Specific phobia 44% (one-third of which were fear of needles or crowds)
- Obsessive-compulsive disorder (OCD): 37%
- ADHD: 31% (two-thirds inattentive type)
- Separation anxiety disorder: 12%
- Major depressive episode: 10%
- The study was limited by a sample that was mostly male, verbal, and higher functioning as well as by the use of parental reports as the sole data source.
Assessment model

- Ideally want information from three sources
  - Parents (history and standardized questionnaires)
  - Teachers (history and standardized questionnaires)
  - Observation (either from school, wrap agency or in clinic)
- As with typically developing children with ADHD, may not necessarily see symptoms in clinic
- But ideally would like to document clinically significant concerns in at least two different settings

Impact of ADHD symptoms on functioning


<table>
<thead>
<tr>
<th></th>
<th>Autistic/ADHD (N=57)</th>
<th>Autistic (N=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication</td>
<td>68.5</td>
<td>87.0</td>
</tr>
<tr>
<td>Daily Living</td>
<td>56.6</td>
<td>78.7</td>
</tr>
<tr>
<td>Socialization</td>
<td>58.0</td>
<td>85.9</td>
</tr>
</tbody>
</table>
ADHD Symptoms in ASD

More severe impairment

Potentially altered response to treatment

Longterm outcome is worse

Take Home point

- Must treat ADHD symptoms in ASD Aggressively
  
- Start Low...
  - Go Slow...
  - Don't Stop Thinking!
Treatment options

How many children with autism are prescribed psychotropic medication to Treat ADHD?
ASD Psychotropic Rates in Ohio (Witwer & Lecavalier, 2005)

Medications Within The Last 12 Months Among Nonreferred Children With ASD, Ages 3-21 (n=353)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Number</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>stimulants</td>
<td>86</td>
<td>(24.0)</td>
</tr>
<tr>
<td>antidepressants</td>
<td>76</td>
<td>(21.2)</td>
</tr>
<tr>
<td>antipsychotics</td>
<td>69</td>
<td>(19.5)</td>
</tr>
<tr>
<td>alpha agonists</td>
<td>39</td>
<td>(10.9)</td>
</tr>
<tr>
<td>mood stabilizers</td>
<td>15</td>
<td>(4.2 )</td>
</tr>
<tr>
<td>anxiolitic/hypnotics</td>
<td>10</td>
<td>(2.8 )</td>
</tr>
<tr>
<td>noradrenergic agonists</td>
<td>6</td>
<td>(1.7 )</td>
</tr>
<tr>
<td>opiate blockers</td>
<td>5</td>
<td>(1.4 )</td>
</tr>
<tr>
<td>antihistamines</td>
<td>3</td>
<td>(0.9 )</td>
</tr>
<tr>
<td>beta blocker</td>
<td>1</td>
<td>(0.3 )</td>
</tr>
</tbody>
</table>

Do Stimulants Work in Autism?

- Prior to 1995, many thought stimulants didn’t work in Autism
- Most studies were not well controlled
- Until 2005, largest controlled study had only 13 children
- In 2005, a double-blind study of 72 children was published (RUPP)
Handen, Johnson & Lubetsky, 2000
Ritalin and Autism

- 8 of 13 children had a >50% on Conners scale
- No change in primary symptoms of ASD (based upon the CARS)
- Side Effects: increased sadness, drowsiness

Handen, Johnson & Lubetsky, 2000 Ritalin and Autism (n=13)
RUPP MPH Study, 2005

- Cross-over design: placebo, low, medium and high MPH doses (1 week per condition)
- N=72; 74% Autistic Disorder 26% PDD NOS or Asperger’s Disorder
- Doses given b.i.d. (0.125, 0.25, 0.50 mg/kg per dose) with smaller third dose in late afternoon
- Dependent Measures: Aberrant Behavior Checklist, CGI

RUPP MPH Study Results

- 13 (18%) subjects discontinued - side effects
- 35 (49%) classified as responders (decrease of >25% on the ABC Hyper-activity subscale and CGI-I of 1 or 2)
- Effects sizes, $d$, of 0.29, 0.54, and 0.40
- Age, IQ and ASD subtype not found to influence outcome
Preschoolers with PDD and ADHD (Ghuman et al., 2009)

- 14 preschoolers, 3-5 years
- 12 with PDD; 2 with ID
- Mean IQ: 75 (SD 18)
- 1-week placebo lead-in; single-blind MPH titration; 4 week D-B crossover (2 weeks placebo, 2 weeks MPH)
- Dependent Measures: Conners, Nisonger, CGI

Recommendation

- There is Strong Support for the use of Ritalin in ASD
- There are no studies involving other stimulants, such as Adderall, although likely have a similar response rate.
- Stimulants are FDA approved for treatment of ADHD in children and adults
### Stimulant Alternatives/Adjuncts

<table>
<thead>
<tr>
<th></th>
<th>Short Acting</th>
<th>Long Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha-2 Agonists</strong></td>
<td>Clonidine (Catapres)</td>
<td>Clonidine ER (Kapvay)</td>
</tr>
<tr>
<td>Guanfacine (Tenex)</td>
<td>Guanfacine ER (Intuniv)</td>
<td></td>
</tr>
<tr>
<td>Atomoxetine (Strattera)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clonidine (Catapres/Kapvay) & Guanfacine (Tenex/Intuniv)**

- Action in Prefrontal Cortex helps ADHD
- Action in Brain Stem can decrease sympathetic activity, decrease blood pressure
  - Side effects are largely from decreased sympathetic activity (i.e., dry mouth, sedation)
  - Hypotension
- Takes weeks to see full effect
Alpha-2 Agonists

Clonidine (Catapres/Kapvay) & Guanfacine (Tenex/Intuniv)

- **Pros:**
  - Moderately effective (hyperactivity & impulsivity, insomnia, treatment emergent tics, & aggression)

- **Cons:**
  - Side Effects: Rebound HTN/tachycardia, hypotension, sedation, dizziness, constipation, H/A, fatigue, sudden death in combination with stimulants
  - Contraindications: CAD, impaired liver/renal function

---

**Alpha-2 Agonists**

- Routine PE/VS prior to initiation of Rx
- Contraindications: CAD, impaired liver/renal function
- Side Effects: Rebound HTN/tachycardia, hypotension, sedation, dizziness, constipation, H/A, fatigue
- Dosage: Start with HS and titrate toward morning (or afternoon)
- Monitor BP, but ECG not routinely necessary
Guanfacine (Tenex)

<45 kg start 0.5mg at bedtime >45 kg start 1mg at bedtime

Can increase to 0.5 bid-tid for total of 2mg (<40kg); 3 mg (<45kg); 4mg (>45kg)

Guanfacine ER(Intuniv)

1 mg to 7mg (0.05-0.12 mg/kg) once daily
- 6-12 not much data over 4mg
- 13 and above not much data over 7mg

Begin at a dose of 1 mg once daily at night and adjust 1 mg/week.
Can change to AM once child/adolescent adjusts to dose
**Guanfacine ER (Intuniv)**

**Do not**
- Crush, chew or break tablets before swallowing.
- Administer with high-fat meals,
- Substitute with short acting guanfacine 1-1 (different pharmacokinetic profiles)
- Cross titrate with short acting (stop short acting then start long-acting)

**Do:** discontinue with a taper (1 mg every 3 to 7 days to avoid rebound hypertension.)

---

**Clonidine (Catapres)**

- Start - <45kg 0.05mg at bedtime
  >45kg 0.1mg at bedtime
- Titrate – <40kg 0.2mg; <45 0.3mg; >45 0.4mg
- Sedation decreases with time
- Often only given at bedtime, but can be given more than once a day
- Additional evidence in Tourette's
### Kapvay (Clonidine ER)

- Dosing 0.1-0.2 bid at am and bedtime – increase by 0.1 every week
- More common side effects may include: drowsiness, tiredness, irritability, nightmares, sleeplessness, constipation, dry mouth, decreased appetite, dizziness.
- Less common side effects may include: low blood pressure, low heart rate
- Tablets should not be crushed, chewed or broken before swallowing.
- Do not substitute for other clonidine products on a mg-per-mg basis, because of differing pharmacokinetic profiles.
- When discontinuing, taper the dose in decrements of no more than 0.1 mg every 3 to 7 days.

### Atomoxetine (Strattera): Efficacy in Children & Adolescents

- 24-hour duration of action with once-daily dosing
- Incidence of insomnia comparable with placebo (for children/adolescents)
- Not contraindicated in patients with tics and anxiety
- Nonstimulant/noncontrolled substance
- May improve some measures of functional outcome (not just core ADHD symptoms)
- **DOSING:**
  - 0.5 mg/kg qam (e.g. 10mg x4d, then double)
  - 1.4mg/kg or 100mg
Atomoxetine (Strattera): Side Effects

- Children and Adolescents:
  - Decreased appetite (15%)
    - Average weight loss of 2 – 4 LB in first 3 months, then resume normal growth
  - Dizziness (5%)
  - Dyspepsia (5%)
  - Sedation
  - BP/HR
- Liver Toxicity – rare side effect
- Has black box warning for suicidality.

When to consider Atomoxetine (Strattera)

- History of adverse effect to stimulants
- Comorbid anxiety, depression, tics, enuresis or Tourette’s
- Require 24 hour symptom relief
- Severe stimulant rebound
- Personal or family history of substance abuse
- Concern about insomnia or appetite suppression
Atypical Antipsychotics

- Activate dopamine neurons in prefrontal cortex and limbic regions
- Decrease agitation/irritability, but also affects hyperactivity
- Not an option unless have additional co-morbid diagnoses (or dangerous ADHD symptoms)
- Risperidone, quetiapine, ziprasidone, aripiprazole and olanzapine

RUPP-PI Design

- 24-week, D-B trial
- N=49 for Med alone; N=75 for Med + PMT
- Age: 4-13 years, IQ>35, ABC Irritability subscale>18
- Autistic, PDD-NOS, or Asperger’s Disorder
- Taking no other psychotropic medications
Acute Risperidone Trial: RUPP (N=101)

Response criteria: ≥25% improvement in the Aberrant Behavior Checklist Irritability score, and a rating of “much improved” or “very much improved” on the CGI-I


Risperidone Hyperactivity Effects in ASD (RUPP)

Mean ABC Hyperactivity Subscale (p<0.001)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>31.8±9.6</td>
<td>17.0±9.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>32.3±8.5</td>
<td>27.6±10.6</td>
</tr>
</tbody>
</table>
Using Risperidone – by the Book (PDR)

Autism
• Irritability associated with autistic disorder in children aged 5-16 years
  – 5-16 years (<20 kg): 0.25 mg/day PO initially; may be increased after ≥4 days to recommended dosage of 0.5 mg/day
  – 5-16 years (≥20 kg): 0.5 mg/day PO initially; may be increased after ≥4 days to recommended dosage of 1 mg/day
• Insufficient response to recommended dosage
  – dosage may be adjusted after minimum of 14 days and at least every 2 weeks thereafter
    • <20 kg: Adjusted in increments of 0.25 mg/day; not to exceed 1 mg/day
    • ≥20 kg: Adjusted in increments of 0.5 mg/day; not to exceed 2.5 mg/day

Using Aripiprazole – by the Book (PDR)

Autism
• Indicated for irritability associated with autistic disorder
• <6 years: Safety and efficacy not established
• 6-17 years: 2 mg/day PO initially; increase gradually at ≥1 week intervals to target dosage of 5 mg/day; may gradually be further increase PRN to 10 mg/day or higher; not to exceed 15 mg/day
Parent training

Parent Management Training

- Eleven core sessions within first 16 weeks
  - (Basics of ABA, Prevention Strategies, Reinforcement, Planned Ignoring, Compliance Training)
- Five optional sessions (e.g., time out, sleep problems)
- Twice monthly booster sessions from weeks 16-24
RUPP-PI Study of Risperidone and Parent Training

E.S. = .55
Risperidone dose and parent training

- Risperidone dose was 12% lower with combined treatment
- 2.26 mg/day vs 1.98 mg/day (p=.04)
Summary

• A large number of children with ASD display ADHD symptoms
• Strong support for stimulants and risperidone (risperidone should be limited to more severe cases)
• Moderate support for atomoxetine, clonidine and guanfacine
• Children with ASD are more prone to side effects and response rates tend to be lower in comparison to typically developing children (especially for stimulants, atomoxetine, and clonidine/guanfacine)

Thank You