Management of ADHD in the Context of Autism Spectrum Disorder

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Disclosures 2018-2019

- My spouse/partner and I have the following relevant financial relationships with commercial interests to disclose:
  - Consulting fees: Akili, Jazz Pharma, and Shire.
  - Royalties paid to the Department of Psychiatry at MGH, for a copyrighted ADHD rating scale used for ADHD diagnoses: Bracket Global, Ingenix, Prophase, Shire, Sunovion, and Theravance.
  - Financial interest: Avekshan LLC, a company that develops treatments for ADHD. My interests were reviewed and are managed by MGH and Partners HealthCare in accordance with their COI policies.
# Features of Autism

## Impaired Social-Emotional Competence

<table>
<thead>
<tr>
<th>I. Non-verbal communication (NVC)</th>
<th>II. Verbal communication</th>
<th>III. Emotional processing</th>
<th>IV. Social (inter-personal) processing</th>
<th>V. Abstracting ability</th>
<th>VI. Introspective/Introceptive ability</th>
<th>VII. Executive Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Eye contact (joint-attention)</td>
<td>- Level of verbal communication</td>
<td>- Emotional awareness, recognition</td>
<td>- Social motivation &amp; awareness</td>
<td>- Black &amp; white/concrete/literal thinking</td>
<td>(self awareness of cognitions, emotions, &amp; physiological state)</td>
<td>(moderation of emotions, motivations, interests)</td>
</tr>
<tr>
<td>- Receptive and Expressive emotional NVC</td>
<td>- Atypical style of speech (pedantic, professorial)</td>
<td>- Emotional expression (verbal &amp; non-verbal)</td>
<td>- Sharing (activities, affect, back &amp; forth conversations)</td>
<td>- Tolerance for ambiguity</td>
<td>- Psychological mindedness</td>
<td>- All or none approach (lack moderation)</td>
</tr>
<tr>
<td>(facial expression, verbal tone, touch)</td>
<td></td>
<td></td>
<td>- Contextual understanding (social adaptability)</td>
<td></td>
<td></td>
<td>- Abnormal intensity of interests</td>
</tr>
</tbody>
</table>

## Restricted/Repetitive Behaviors (RRBs)

<table>
<thead>
<tr>
<th>VIII. Cognitive/Behavioral Rigidity</th>
<th>IX. Repetitive patterns</th>
<th>X. Atypical Salience</th>
<th>XI. Sensory Dysregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Routines (routine-bound)</td>
<td>- Speech (delayed echolalia, scripting, idiosyncratic phrases)</td>
<td>- Interests (odd/idiosyncratic)</td>
<td>- Atypical sensory perceptions/responses</td>
</tr>
<tr>
<td>- Rituals (verbal &amp; motor)</td>
<td>- Motor mannerisms (flapping, clapping, rocking, swaying)</td>
<td>- Social-emotional stimuli</td>
<td></td>
</tr>
<tr>
<td>- Resistance to change (transitional difficulties)</td>
<td>- Interests (non-progressive, non-social)</td>
<td>- Atypical fears</td>
<td></td>
</tr>
<tr>
<td>- Rigid pattern of thinking (rule-bound/highly opinionated)</td>
<td>- Lack spontaneity/tolerance for unstructured time</td>
<td>- Social inflexibility</td>
<td></td>
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</tr>
</tbody>
</table>

## ASSOCIATED Features

- Intellectual disability
- Novelty averse behaviors
- Poor motor co-ordination
Population-Based Prevalence of ASD

Children with ASD

ADDM Network
- Children 8 years old
- Medical records reviewed by trained clinicians

Prevalence of ASD has more than DOUBLED between 2002 & 2012

# Neurodevelopmental Disorders ASD and ADHD

## Shared Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence in Children</td>
<td>6-8%</td>
<td>2%</td>
</tr>
<tr>
<td>Heritability Estimates</td>
<td>75%</td>
<td>90%</td>
</tr>
<tr>
<td>Male:Female Ratio</td>
<td>2.5:1</td>
<td>4:1</td>
</tr>
<tr>
<td>Manifest early in life</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lifelong Disorders</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Neurodevelopmental Disorders ASD and ADHD

## Distinct Symptom Triad

<table>
<thead>
<tr>
<th>ASD</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Impaired social interaction</td>
<td>- Inattention</td>
</tr>
<tr>
<td>- Impaired social communication</td>
<td>- Hyperactivity</td>
</tr>
<tr>
<td>- Restricted Repetitive Behaviors</td>
<td>- Impulsivity</td>
</tr>
</tbody>
</table>

References:
Prevalence of ASD Traits vs. Diagnosis in Referred Populations with ADHD

**ASD Traits**

- Clark et al., 1999
- *Kochhar et al., 2011
- *Cooper et al., 2014
- *Grzadzinski et al., 2011
- *Mulligan et al., 2009
- Reirsen et al., 2007
- *Kotte et al., 2013

Percentage: 0 - 20 - 30 - 40 - 50 - 60 - 70

18% - 63%

**ASD Diagnosis**

- Joshi et al., 2013
- Jensen & Steinhausen, 2014
- Faber et al., 2010
- Larson et al., 2011
- Smalley et al., 2007

Percentage: 0 - 2 - 4 - 6 - 8 - 10 - 12 - 14 - 16

2% - 15%

*ADHD Youth with no prior diagnosis of ASD

**Comorbid ASD in up to 15% of the ADHD Populations**
Prevalence of ADHD Symptoms and Diagnosis in Individuals with ASD

**ADHD Symptoms**

- Sverd et al., 1995: 49% - 88%
- Lee & Ousley, 2006: 49% - 75%
- Sturm, et al., 2004: 49% - 75%
- Tani et al., 2006: 49% - 75%
- Yoshida & Uchiyama, 2004: 49% - 75%
- Holtmann et al., 2005: 49% - 75%
- Goldstein & Schwebach, 2004: 49% - 75%
- Gadow et al., 2004: 49% - 75%

**ADHD Diagnosis**

- Joshi et al., 2014: 28% - 75%
- Sinzig et al., 2009: 28% - 75%
- DeBruin et al., 2007: 28% - 75%
- Mattila et al., 2010: 28% - 75%
- Leyfer et al., 2006: 28% - 75%
- Gjevik et al., 2011: 28% - 75%
- Simonoff et al., 2008: 28% - 75%

Comorbid ADHD in up to 75% of the ASD Populations
ADHD Symptom Profile in ASD

Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

Joshi et al., 2014
Neuropsychological Correlates of HF-ASD

Processing Speed
Wechsler Adult Intelligence Scale (WAIS-III)

<table>
<thead>
<tr>
<th></th>
<th>Processing Speed Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC [N=52]</td>
<td>109</td>
</tr>
<tr>
<td>ADHD [N=52]</td>
<td>103  <strong>AB</strong> 89</td>
</tr>
<tr>
<td>ASD [N=26]</td>
<td>89</td>
</tr>
</tbody>
</table>

Cognitive Flexibility
Delis Kaplan Executive Function System (D-KEFS)

<table>
<thead>
<tr>
<th></th>
<th>Mean Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number-Letter Switching Trail Making Subtest</td>
<td>11</td>
</tr>
<tr>
<td>Inhibition Colour-Word Interference Subtest</td>
<td>12</td>
</tr>
<tr>
<td>Switching Colour-Word Interference Subtest</td>
<td>11</td>
</tr>
</tbody>
</table>

HC=Healthy Controls; A=Versus HC, B=Versus ADHD; Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

Fried, Joshi, Biederman et al., 2016
Distribution of ADHD by ASD Subtype

- Autistic Disorder (N=185): 79%
- Asperger's Disorder (N=44): 77%
- PDD-NOS (N=42): 76%

Joshi et al., 2014
ADHD Treatment History in ASD

Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

ADHD undertreated in youth with ASD

Joshi et al., 2014
Increasingly greater recognition of ASD in intellectually capable populations

Under-recognition of ASD in psychiatrically referred populations

Psychiatrically referred populations predominantly suffer from broader phenotype of high-functioning autism

ADHD is the most common psychopathology associated with ASD

The clinical presentation of ADHD in ASD youth is typical of the disorder

ASD youth with ADHD are significantly more impaired in their various indices of psychosocial functioning

Significantly fewer ASD youth receive targeted treatment for ADHD
Stimulants
• Methylphenidate formulations

SNRI
• Atomoxetine

Alpha-2 Adrenergic Agonists
• Guanfacine
• Clonidine

RUPP Autism Network, 2002, 2005; Pearson et al., 2013; Harfterkamp et al., 2012; Handen et al., 2008; Fankhauser et al., 1992; Jaselskis et al., 1992; Owen et al., 2009
Problems with Treatment Trials for ADHD in Autism

Age group: Children and Adults
IQ: Low and High-functioning
Tx. Target: Symptoms Versus Syndrome
- Hyperactivity vs. agitation
- Irritability / Aggression
- Repetitive Behaviors
- Anxiety symptoms
- Sleep dysregulation
Example: MPH-RUPP Trial

Rate of Response (CGI-I≤2+ABC-H ↓↓≥25-30%)

- TD: 70%
- ASD: 50%

Magnitude of Response:
ES=0.20 – 0.54 (vs. 0.35 – 1.3 in MTA trial)

False Conclusions: MPH is less effective than typically expected for treatment of ADHD in children with ASD

RUPP Autism Network, 2005; Jahromi et al., 2009*
Example: Guanfacine ER – Efficacy

Significant improvement in:
- Repetitive behaviors (ABC-Stereotypy)
- Communication (ABC-Inappropriate speech)

Scahill et al., 2015; *Biederman et al., 2008
Clinical Trials of ADHD in Autism

• Severe problems with interpretation of previous clinical trials findings

• What does it mean to suffer from ADHD in low functioning, non verbal Autism?

• Treatment targets were largely agitated states

• Mood and anxiety disorders were not considered for exclusion

RUPP Autism Network, 2005; Pearson et al., 2013; Harfterkamp et al., 2012; Fankhauser et al., 1992; Jaselskis et al., 1992; Scahill et al., 2015
The MGH Study of Methylphenidate Extended-Release Liquid Formulation (Quillivant XR) in High Functioning Adults with ASD

Joshi, et al. 2019
6-week Open-label Trial of Methylphenidate Extended-release Liquid Formulation (Quillivant XR) for the Treatment of ADHD in Adults with HF-ASD

- Clinical Trials Registration @ ClinicalTrials.gov
- Registration Number: NCT02096952
- URL: https://clinicaltrials.gov/ct2/show/NCT02096952?term=NCT02096952
- Study Approved by: Partners Human Research Committee Institutional Review Board
- Study Funded by: Pfizer, Inc.

Joshi, et al. 2019
### Demographic Characteristics

<table>
<thead>
<tr>
<th>Participants</th>
<th></th>
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<tbody>
<tr>
<td>Total participants</td>
<td>11</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>09 (82%)</td>
</tr>
<tr>
<td>Ethnicity (Caucasian)</td>
<td>10 (91%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Mean</td>
<td>24 ±3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Full Scale IQ</th>
<th></th>
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<tbody>
<tr>
<td>Mean</td>
<td>117 ±16</td>
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</tbody>
</table>

### Diagnoses (DSM-V)

- **Autism Spectrum Disorder**: 11 (100%)
- **ADHD-Combined Type**: 07 (64%)
- **ADHD-Inattentive Type**: 04 (36%)

### Baseline Severity

(Respective CGI-Severity ≥4 [moderately ill])

- **ASD [SRS-2 Adult Self-Report Score]**: 105 ±25
- **ADHD [AISRS Clinician-Rated Score]**: 35 ±3.5

### Global Assessment of Functioning

- **Mean score**: 56 ±2
- **Range**: 53-60

### Adjunctive Medications

- **# of Participants**: 08 (73%)
  - SSRI/SSRI/DNA: 06 (55%)
  - Atypical Antipsychotic: 01 (09%)

Joshi, et al. 2019
Study Medication

- Methylphenidate Hydrochloride Extended-Release Liquid Formulation: 25mg/5mL
- Taken QAM

**Study Medication (MPH-ER)**

<table>
<thead>
<tr>
<th>Mean dose</th>
<th>49 ±16 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose range</td>
<td>20-60 mg/day</td>
</tr>
</tbody>
</table>

At Dose:
- 60 mg/day 06 (55%)
- 50 mg/day 02 (18%)
- 20-40 mg/day 03 (27%)

**Concomitant Medications**

- Melatonin (3 mg QHS [PRN])* 1 (9%)
- Benadryl (50-100 mg QHS [PRN])* 1 (9%)

*For insomnia

Joshi, et al. 2019
Treatment Response: ADHD Symptoms

Clinician-Rated Measure:
Adult ADHD Investigator Symptom Report Scale (AISRS)

Mean AISRS Score

Weeks

MC=Mean Change

Joshi, et al. 2019
Treatment Response: ADHD Symptoms

Self-Rated Measure:
Adult ADHD Self-Report Scale (ASRS)

Mean ASRS Score vs. Weeks

MC = Mean Change

LOCF [34 ±10.6]

33 ±10

[MC = -9 ±11; Z = -2; p=0.03]

Joshi, et al. 2019
Treatment Response: Outcome Measures

- ADHD-CGI-I ≤2: 82%
- AISRS-Total Reduction ≥30%: 91%
- ADHD-CGI-I ≤2 + AISRS Reduction ≥30%: 82%

Joshi, et al. 2019
Treatment Response: ASD Symptoms

Self-Rated Measure:
Adult Self-Report Social Responsiveness Scale-2 (SRS-2)

MC = Mean Change

LOCF [97 ±28]

[MC = -8 ±17; Z=1; p=0.33]

Joshi, et al. 2019
**Adverse Events**

*Adverse Events (reported >1 visit)*

- **Headache**
- **Insomnia**
- **Decreased appetite**
- **Anxiety/Panic**
- **Musculoskeletal**
- **Nausea**
- **Tachycardia**
- **Palpitations**

**Experienced any AEs:** 09 (82%)

**Serious AEs:** N=1  *(Report of OD on Benadryl [suicide attempt] at wk-6. Prior h/o SI. [Upon completion continued tx. with study medication]*)

**Treatment Limiting AEs:** N=1  *(Terminated at week-3 @ 20 mg/day d/t AEs: headaches, palpitations, jaw pain, & insomnia [resolved on d/c]*)

Joshi, et al. 2019
Conclusion

• Treatment with stimulants in high functioning adults with ADHD is highly effective and well tolerated
• More studies are needed in assessing efficacy of medicines for ADHD in ASD
• These studies should be limited to high functioning ASD with appropriate attention to exclusions of mood and anxiety comorbid disorders