Management of ADHD in the Context of Autism Spectrum Disorder

Tolga Atilla Ceranoglu, MD
# Features of Autism

## CORE Features

### Impaired Social-Emotional Competence

I. **Non-verbal communication (NVC)**
   - Eye contact (joint-attention)
   - Receptive and Expressive emotional NVC (facial expression, verbal tone, touch)

II. **Verbal communication**
    - Level of verbal communication
    - Atypical style of speech (pedantic, professorial)

III. **Emotional processing**
    - Emotional awareness, recognition
    - Emotional expression (verbal & non-verbal)
    - Empathy (ToM)

IV. **Social (inter-personal) processing**
    - Social motivation & awareness
    - Sharing (activities, affect, back & forth conversations)
    - Contextual understanding (social adaptability)

V. **Abstracting ability**
    - Black & white/concrete/literal thinking
    - Tolerance for ambiguity

VI. **Introspective/Introceptive ability**
    (self awareness of cognitions, emotions, & physiological state)
    - Psychological mindedness

VII. **Executive Control**
    (moderation of emotions, motivations, interests)
    - All or none approach (lack moderation)
    - Abnormal intensity of interests

### Restricted/Repetitive Behaviors (RRBs)

VIII. **Cognitive/Behavioral Rigidity**
    - Routines (routine-bound)
    - Rituals (verbal & motor)
    - Resistance to change (transitional difficulties)
    - Rigid pattern of thinking (rule-bound/highly opinionated)
    - Lack spontaneity/tolerance for unstructured time
    - Social inflexibility

IX. **Repetitive patterns**
    - Speech (delayed echolalia, scripting, idiosyncratic phrases)
    - Motor mannerisms (flapping, clapping, rocking, swaying)
    - Interests (non-progressive, non-social)

X. **Atypical Salience**
    - Interests (odd/idiosyncratic)
    - Social-emotional stimuli
    - Atypical fears

XI. **Sensory Dysregulation**
    - Atypical sensory perceptions/responses

## ASSOCIATED Features

- Intellectual disability
- Novelty averse behaviors
- Poor motor co-ordination
DSM Criteria for Autism

Schizophrenic Reaction - Childhood Type

- Psychotic reaction in Children with Autism
  - DSM-I (1952)

Schizophrenia - Childhood Type

- Autistic, Atypical, & Withdrawn Behavior
  - DSM-II (1968)

Infantile Autism

- Infantile Autism
  - DSM-III (1980)

Pervasive Developmental Disorders

- Autistic Disorder
  - DSM-III-R (1987)

- PDD-NOS

Autism Spectrum Disorder

- Autism Spectrum Disorder

- Asperger's Disorder
  - PDD-NOS

- Autism Spectrum Disorder
  - DSM-5 (2013)
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

Prevalence per 1000

7/1000 → 15/1000


Growing proportion of children with HF-ASD
DSM-IV Diagnostic Subtypes of ASD

Prevalence in Children 8 Years Old

- **44%** Autistic Disorder [Narraw Phenotype]
- **56%** Asperger's Disorder / PDD-NOS [Broader Phenotype]

Higher proportion with Broader Phenotype of ASD
Age at Diagnosis of ASD

By DSM-IV Diagnosis (In Children 8 years Old)

- Autistic Disorder: 4 years
- PDD-NOS: 4.5 years
- Asperger's Disorder: 6.25 years

By Age Range

- <3 years: 20%
- 3 - 5 years: 36%
- 6 - 8 years: 17%
- ≥9 years: 27%

Two-thirds of Broader Phenotype identified after age 5 years

\*80% more likely to have psychiatric comorbidity compared to cases identified at earlier ages (<9 years)

Referral by Age (N=863)

Half of the referrals between ages 8 & 17 years.
Areas of Social-emotional Development
- Non-verbal communication skills
- Social skills
- Empathy
- Abstracting ability
- Cognitive Flexibility
- Executive Control
- Introspective ability

Social-emotion Competence Across the Lifespan

Young Adult (19–35 years)
- ± Intellectual success
- Challenges:
  - Social & relationship
  - Transition to adulthood
- At risk for drug abuse
- At risk for depression, anxiety, psychosis

Adult (≥36 years)
- Delayed social milestones (marriage, children)
- Social-emotional isolation
- Suffer from anxiety & mood dysregulation

Preschool (0–5 years)
- Minimal social-emotion demands
- ± Superior intellectual capacity
- Sensory Dysregulation

Latency (6–12 years)
- Socially isolated
- Bullied
- Impaired intellectual functioning
- Present with ADHD

Teensage (13–18 years)
- Social difficulties (friends, prom, dating)
- Impaired intellectual performance
- At risk for depression, anxiety, psychosis

Social phase

Professional Phase
Factors Associated with Delay in Identification of ASD

- Broader phenotype*
- High-functioning* (intact language skills)
- Intact eye contact
- Socially curious (intact social orientation & initiation)***
- Presence of comorbidity (psychiatric/medical)*
- Female gender
- Intact intense non-verbal communication
- Absence of idiosyncratic speech (echolalia, scripting)
- ASD features more cognitive than motor (repetitive behaviors [rocking/flapping])
- Developmental masking of social deficits (until demands exceeds capacity)

*Shattuck et al., 2009; **Levy et al., 2010; ***Maenner et al., 2013
Lack awareness of social challenges

Diagnosed early in life

Diagnosis of ASD requires:
  - Diagnostic tools: ADIR/ADOS
  - Neuropsychological assessment
  - Genetic work-up

Psychiatric disorders are uncommon with AUTISM

ASD Training related Issues
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>33. Is socially awkward, even when he or she is trying to be polite.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>34. Avoids people who want to be emotionally close to him or her.</td>
<td>1</td>
<td>2</td>
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<td>35. Has trouble keeping up with the flow of a normal conversation.</td>
<td>1</td>
<td>2</td>
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<td>36. Has difficulty relating to adults.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>37. Has difficulty relating to peers.</td>
<td>1</td>
<td>2</td>
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<tr>
<td>38. Responds appropriately to mood changes in others (e.g., when a friend's or playmate's mood changes from happy to sad).</td>
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<td>2</td>
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<td>39. Has an unusually narrow range of interests.</td>
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<td>2</td>
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<td>40. Is imaginative, good at pretending (without losing touch with reality).</td>
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<td>2</td>
<td>3</td>
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<td>41. Wonders aimlessly from one activity to another.</td>
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<td>2</td>
<td>3</td>
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<tr>
<td>42. Seems overly sensitive to sounds, textures, or smells.</td>
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<td>2</td>
<td>3</td>
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<td>43. Separates easily from caregivers.</td>
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<td>2</td>
<td>3</td>
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<td>44. Doesn't understand how events relate to one another (cause and effect) the way other children his or her age do.</td>
<td>1</td>
<td>2</td>
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<td>45. Focuses his or her attention to where others are looking or listening.</td>
<td>1</td>
<td>2</td>
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<td>46. Has overly serious facial expressions.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>47. Is too silly or laughs inappropriately.</td>
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<td>2</td>
<td>3</td>
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<td>48. Has a sense of humor, understands jokes.</td>
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<td>2</td>
<td>3</td>
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<td>49. Does extremely well at a few tasks, but does not do as well at most other tasks.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>50. Has repetitive, odd behaviors such as hand flapping or rocking.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>51. Has difficulty answering questions directly and ends up talking around the subject.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>52. Knows when he or she is talking too loud or making too much noise.</td>
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<td>2</td>
<td>3</td>
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<tr>
<td>53. Talks to people with an unusual tone of voice (e.g., talks like a robot or like he or she is giving a lecture).</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>54. Seems to react to people as if they are objects.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>55. Knows when he or she is too close to someone or is invading someone's space.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>56. Walks in between two people who are talking.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>57. Gets teased a lot.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>58. Concentrates too much on parts of things rather than seeing the whole picture.</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>For example, if asked to describe what happened in a story, he or she may talk only about the kind of clothes the characters were wearing.</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>59. Is overly suspicious.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>60. Is emotionally distant, doesn't show his or her feelings.</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>61. Is inflexible, has a hard time changing his or her mind.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>62. Gives unusual or illogical reasons for doing things.</td>
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<td>2</td>
<td>3</td>
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<tr>
<td>63. Touches others in an unusual way (e.g., he or she may touch someone just to make contact and then walk away without saying anything).</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>64. Is too tense in social settings.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>65. Stares or gazes off into space.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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</tbody>
</table>
More than one-third of youth screened positive for ASD

Total N: 396
Age Range: 4-18 years
IQ: Predominantly Intact

SRS Screen+ for ASD: 40% (N=157) (T-Score >65)
Child Behavior Checklist–ASD Profile

Level of Dysfunction on Child Behavior Checklist in Psychiatrically Referred Youth

CBCL T-score

ASD Youth
- Age range: 6-18 years
- Mean IQ: 99 ±14
- IQ>70: 100%

ASD Subtypes
- Autistic Disorder = 52%
- Asperger’s Disorder = 25%
- PDD-NOS = 23%

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

CBCL-ASD Subscales (Withdrawn behavior, Social, & Thought Problems)
aggregate cutoff T-score of ≥195 is suggestive of ASD

Non-ASD Psychiatric Controls (N=62)
ASD (N=65)
### MGH Autism Spectrum Disorder DSM-5 Diagnostic Symptom Checklist

**Name: ___________________________**  
**Age: _______ years**  
**Gender: Male / Female**

**Assessment Guidelines:**  
1. Incorporate information from clinical observation and all available sources.
2. Offer suggested prompts to elicit features of concern.

#### Diagnostic Features

<table>
<thead>
<tr>
<th>A</th>
<th>Deficits in Social Communication and Interaction (as manifested by lifetime history of at least three of the following):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
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<tr>
<td></td>
<td>Not1</td>
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<tr>
<td>1</td>
<td>Deficits in social-emotional reciprocity</td>
</tr>
<tr>
<td></td>
<td>• Does not share or request appropriately in social settings</td>
</tr>
<tr>
<td></td>
<td>• Seems unaware of others' feelings or is unable to express his/her feelings</td>
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<tr>
<td></td>
<td>• Does not offer or seek comfort or make comfort a real need</td>
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<tr>
<td></td>
<td>• Socially inappropriate reciprocal behavior</td>
</tr>
<tr>
<td></td>
<td>• Inability to spontaneously share attending, enjoyments, achievements, or interests</td>
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<td></td>
<td>• Inability to engage in a cooperative joint and joint activity with others</td>
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<td></td>
<td>• Difficulties with arising or maintaining a conversation</td>
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<td></td>
<td>• Limited ability to engage in back-and-forth reciprocal conversation (especially on other person's topic of interest)</td>
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<td></td>
<td>• Does not talk to some friends or social clubs to make small talk</td>
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</tbody>
</table>

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<thead>
<tr>
<th>B</th>
<th>Restricted, Repetitive Patterns of Behavior, Interests, or Activities (as manifested by lifetime history of at least two of the following):</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
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<tr>
<td></td>
<td>Not1</td>
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<tr>
<td>1</td>
<td>Stereotyped or repetitive motor movements, speech, or use of objects (Stimming)</td>
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<tr>
<td></td>
<td>• Clay modeling, hand flapping, finger flapping</td>
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<tr>
<td></td>
<td>• Whole body movement (e.g., cradling, rocking)</td>
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<tr>
<td></td>
<td>• Repetitive use of objects (e.g., lining up, flipping, or moving objects)</td>
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<tr>
<td></td>
<td>• Stereotyped, repetitive, or stereotypic speech (when spoken)</td>
</tr>
<tr>
<td></td>
<td>• Other uses of repetitive objects (not including chewing)</td>
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<td></td>
<td>• Pleading words, echolalia, or秧式 speech (in the basic sense) (not including delayed echolalia)</td>
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<td></td>
<td>• Pacing or moving in a stereotyped manner (when standing)</td>
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<tr>
<td></td>
<td>• Pacing or moving in a stereotyped manner (when standing)</td>
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<thead>
<tr>
<th>C</th>
<th>Symptoms Present in the Early Developmental Period</th>
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<td>Absent</td>
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<td></td>
<td>Not1</td>
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<tr>
<td>1</td>
<td>Socially significant impairments in social communication (Dyspraxia)</td>
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<tr>
<td></td>
<td>• Without support, some significant deficits in social communication</td>
</tr>
<tr>
<td></td>
<td>• Marked deficits in initiating and maintaining conversations (Dyspraxia)</td>
</tr>
<tr>
<td></td>
<td>• Marked deficits in initiating and maintaining conversations (Dyspraxia)</td>
</tr>
<tr>
<td></td>
<td>• Sensory and perceptual abnormalities and stereotyped patterns of behavior</td>
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<tr>
<td></td>
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<td></td>
<td>• Sensory and perceptual abnormalities and stereotyped patterns of behavior</td>
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<tr>
<th>D</th>
<th>Clinically Significant Impairment in Social, Occupational, or Other Important Areas of Functioning</th>
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<tbody>
<tr>
<td></td>
<td>Absent</td>
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<tr>
<td></td>
<td>Not1</td>
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<tr>
<td>1</td>
<td>Associated with Intellectual Disability (IQ: &lt; 70)</td>
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<tr>
<td></td>
<td>• Associated with a structure language impairment:</td>
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<td></td>
<td>• Associated with a structure language impairment:</td>
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<td></td>
<td>• Associated with known factors:</td>
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<td></td>
<td>• Associated with known factors:</td>
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<td></td>
<td>• Associated with known factors:</td>
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<thead>
<tr>
<th>E</th>
<th>Associated Features</th>
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<tr>
<td></td>
<td>Absent</td>
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<td></td>
<td>Not1</td>
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<tr>
<td>1</td>
<td>Fine or motor coordination impairment</td>
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<td></td>
<td>• Sensory axes behaviors (hunching)</td>
</tr>
<tr>
<td></td>
<td>• Sensory axes behaviors (hunching)</td>
</tr>
<tr>
<td></td>
<td>• History of developmental regression (loss of acquired social or language skills)</td>
</tr>
</tbody>
</table>

**Clinician: ___________________________**  
**Date: ___________________________**
Comorbidity associated with ASD

Comorbidity in US population-based sample of ASD
(Medical records of children 8 years old reviewed by trained clinicians)

- Medical Diagnosis: 4%
- Neurologic Diagnosis: 16%
- Intellectual Disability: 18.5%
- Learning Disorder: 6.5%
- ADHD: 21%
- Other Psychiatric Disorders: 21%

Autism & Developmental Disabilities Monitoring Network Surveillance Year 2002;
Levy et al., 2010
Prevalence of ASD in Psychiatrically Referred Youth

Total N: 2323
Total Duration: 15 years (1991-2006)
Male: 87%
Age (yrs): 9.7 ±3.6 (3-17)

Intellectual Ability & Language Skills: Clinically not impaired in majority of the referred youth

Joshi et al., 2010
Psychopathology Associated with ASD

Lifetime Psychiatric Comorbidity

- Attention-deficit/Hyperactivity Disorder
- Oppositional Defiant Disorder
- Conduct Disorder
- Multiple (≥2) Anxiety Disorders
- Major Depressive Disorder
- Bipolar I Disorder
- Psychosis
- Substance Use Disorders

Statistical Significance: ***p≤0.001

Joshi et al., 2010
Psychopathology Associated with Psychiatrically Referred ASD Populations

Lifetime Psychiatric Comorbidity

**YOUTH**

- Attention-deficit/Hyperactivity Disorder
- Oppositional Defiant Disorder
- Conduct Disorder
- Multiple (≥2) Anxiety Disorders
- Major Depression
- Bipolar I Disorder
- Psychosis
- Substance Use Disorders

**ADULTS**

- Attention-deficit/Hyperactivity Disorder
- Oppositional Defiant Disorder
- Conduct Disorder
- Multiple (≥2) Anxiety Disorders
- Major Depression
- Bipolar I Disorder
- Psychosis
- Substance Use Disorders

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

Joshi et al., 2013, 2014
# 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>
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</table>

### Distinct Symptom Triad

<table>
<thead>
<tr>
<th>ASD</th>
<th>ADHD</th>
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<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>
Implications of Unrecognized Reciprocal Comorbidity

**ADHD**
- Impairs intellectual/school performance
- Further worsens already compromised social functioning
- Interferes with ASD specific behavioral interventions
- Leads to attempts to treat ADHD with ASD specific interventions
- Failure to receive disorder specific treatment
- Increases risk for developing other psychiatric conditions (disruptive behaviors & substance abuse)

**ASD**
- Risk of receiving inappropriately aggressive treatment for psychopathology
- Failure to recognize atypical precipitants negatively affecting psychopathology
- Failure to receive treatment specific for ASD
- Miss opportunity to implement early interventions for ASD
Prevalence of Significant ASD Traits/Dx 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, 10, 20, 30, 40, 50, 60, 70

**ASD Diagnosis**

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

Percentage: 2, 4, 6, 8, 10, 12, 14, 16

*ADHD Youth with no prior diagnosis of ASD

Comorbid ASD in up to 15% of the ADHD Populations
Autistic Traits in Referred Youth

ADHD Research Participants

Total N: 242
Age Range: 6-18 years
IQ: >70

CBCL-ASD Profile* for ASD: 18% (N=44)

Kotte, Joshi, Biederman et al., 2013
ADHD Symptom Profile in the Presence of Autistic Traits

**DSM-III-R Symptoms**

- ADHD (N=198) vs. ADHD+CBCL-AT (N=44)

% Endorsed

Difficulty remaining seated, Fidgety, Difficulty playing quietly, Talks excessively, Shifts activities, Difficulty sustaining attention, Difficulty following instruction, Easily distracted, Interrupts or intrudes, Blurs out answers, Difficulty waiting turn, Acts before thinking, Loses things, Doesn’t listen

**Additional Symptoms**

- ADHD (N=105) vs. ADHD+CBCL-AT (N=26)

% Endorsed

Accidents, Messy or Sloppy, Clumsy, Hyperactive, Equally Inattentive & Hyperactive, Onset Before Age 5, Fighting with Other Peers, Rejection by Other Peers

* vs. ADHD; Statistical Significance: *p≤0.05, **p≤0.005

Kotte, Joshi, Biederman et al., 2013
Social Disability Associated with ADHD+AT

Social Disability in Youth with ADHD±AT per Social Adjustment Inventory for Children & Adolescents [SAICA]

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

Kotte, Joshi, Biederman et al., 2013
Emotional Dysregulation Associated with ADHD+AT

Emotional Dysregulation [ED] in Youth with ADHD±AT per CBCL-ED Profile*
* [composite T-scores of the Attention, Aggression, & Anxious/Depressed subscales]

Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001
Psychiatric Disorders Associated with ADHD+AT

Lifetime Psychiatric Comorbidity

- Disruptive Behavior Disorders
- Mood Disorders
- Multiple Anxiety Disorders
- Substance Use Disorders

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

Kotte, Joshi, Biederman et al., 2013
Prevalence of Significant ADHD Symptoms/Dx in Populations with ASD

ADHD Symptoms

Gadow et al., 2004
Goldstein & Schwebach, 2004
Holtmann et al., 2005
Yoshida & Uchiyama, 2004
Tani et al., 2006
Sverd et al., 1995
Lee & Ousley, 2006
Sturm, et al., 2004

Percentage
10 20 30 40 50 60 70 80 90 100

49% - 88%

ADHD Diagnosis

Simonoff et al., 2008
Gjevik et al., 2011
Leyfer et al., 2006
Mattila et al., 2010
DeBruin et al., 2007
Sinzig et al., 2009
Joshi et al., 2014

Percentage
0 10 20 30 40 50 60 70 80

28% - 75%

Comorbid ADHD in up to 75% of the ASD Populations
Clinical Correlates of ADHD in Youth with ASD

### Demographic Characterization

<table>
<thead>
<tr>
<th>Demographics</th>
<th>ASD+ADHD</th>
<th>ADHD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N)</td>
<td>107</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>11 ±3.4</td>
<td>11.5 ±3.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>94 (88%)</td>
<td>57 (77%)</td>
<td><strong>0.05</strong></td>
</tr>
<tr>
<td>Race (Caucasian)</td>
<td>88 (83%)</td>
<td>67 (91%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>2 ±0.97</td>
<td>1.38 ±0.62</td>
<td>&lt;<strong>0.001</strong></td>
</tr>
<tr>
<td>Full scale IQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>97 ±14</td>
<td>102 ±16</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>IQ range</td>
<td>70 - 133</td>
<td>71 - 132</td>
<td></td>
</tr>
<tr>
<td>&gt;85</td>
<td>85 (79%)</td>
<td>62 (84%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Values expressed as N (%) or Mean ±Standard Deviation; IQ=Intelligence Quotient

Subtypes of ASD (N = 107)

- **62%** Autistic Disorder
- **24%** Asperger's Disorder
- **14%** PDD-NOS

Joshi et al., 2014
ADHD Symptom Profile in ASD

ADHD+ASD

ADHD

Percent with Symptom

Careless/ Sloppy sustaining attention
Doesn't listen
Difficulty following instructions
Difficulty organizing tasks/activities
Difficulty with sustained mental effort
Loses things
Easily distracted
Forgetful in daily activities

Inattentive Symptoms

Fidgets/ Squirms
Difficulty remaining seated
Physically restless
Difficulty playing quietly
On the go/ Driven by a excessively
Talks
Blurt out answers
Difficulty waiting turn
Interrupts/ Intrudes

Hyperactive/Impulsive Symptoms

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

Joshi et al., 2014
Profile of ADHD in ASD

Subtypes of ADHD

<table>
<thead>
<tr>
<th>Subtype</th>
<th>ASD+ADHD</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactive-Impulsive</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Inattentive</td>
<td>33%</td>
<td>57%</td>
</tr>
<tr>
<td>Combined Type</td>
<td>59%</td>
<td>41%</td>
</tr>
</tbody>
</table>

Mean # of Symptoms

<table>
<thead>
<tr>
<th>Subtype</th>
<th>ASD+ADHD</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactive-Impulsive</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Inattentive</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Combined Type</td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

Joshi et al., 2014
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
Severity Profile of Comorbid ADHD & ASD

**ADHD**
- Mild: 7% ASD+ADHD, 8% ADHD
- Moderate: 50% ASD+ADHD, 47% ADHD
- Severe: 42% ASD+ADHD, 45% ADHD

**ASD**
- SRS - Total: 81 ASD+ADHD, 78 ASD
- Social Awareness: 78 ASD+ADHD, 71 ASD
- Social Cognition: 79 ASD+ADHD, 79 ASD
- Social Communication: 79 ASD+ADHD, 74 ASD
- Social Motivation: 76 ASD+ADHD, 74 ASD
- Autistic Mannerisms: 82 ASD+ADHD, 78 ASD

Joshi et al., 2014
**Level of Functioning**

### School Functioning

- **Repeated Grades**
  - ASD+ADHD: 19%
  - ADHD: 11%

- **Extra Tutoring**
  - ASD+ADHD: 77%
  - ADHD: 80%

- **Special Classes**
  - ASD+ADHD: 51%
  - ADHD: 23%

### Global Functioning

- **GAF-Lifetime**
  - ASD+ADHD: 46±5
  - ADHD: 51±5

- **GAF-Current**
  - ASD+ADHD: 48±8
  - ADHD: 53±6

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

*Joshi et al., 2014*
ADHD Treatment History in ASD

ADHD undertreated in youth with ASD

Joshi et al., 2014

Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001
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</td>
</tr>
<tr>
<td>ASD [N=26]</td>
<td><strong>AB 89</strong></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</td>
<td>11</td>
</tr>
<tr>
<td>Trail Making Subtest</td>
<td><strong>AB 10</strong></td>
</tr>
<tr>
<td>Inhibition Colour-Word</td>
<td>12</td>
</tr>
<tr>
<td>Interference Subtest</td>
<td><strong>AB 10</strong></td>
</tr>
<tr>
<td>Switching Colour-Word</td>
<td>11</td>
</tr>
<tr>
<td>Interference Subtest</td>
<td><strong>AB 10</strong></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
In Summary.....

ASD+ADHD: Prevalence & Presentation

• 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
Controlled Treatment Trials of ADHD in ASD

**Stimulants**
- Methylphenidate preparations:  
  - IR (for Hyperactivity)
  - ER (for ADHD symptoms)

**SNRI**
- Atomoxetine (for ADHD symptoms)

**Alpha-2 Adrenergic Agonists**
- Gunafacine (for ADHD symptoms)
- Clonidmine (for Hyperactivity)

**Second Generation Antipsychotics**
- Risperidone (for Irritability + Hyperactivity)
- Aripiprazole (for Irritability + Hyperactivity)
Methylphenidate – RUPP Trial

Crossover RCT in ASD Youth with Hyperactivity

- Diagnoses: ASD + Hyperactivity (moderate-severe)
- Ages: 5-14 years (majority with Intellectual Disability)
- 3 Phases:
  - **Tolerability Phase**: 1-week test dose (N=72)
    - One day of PBO & 2 days each of 3 MPH doses
    - MPH Dose (TID):
      - Low: 0.125 (mg/kg/day)
      - Medium: 0.25
      - High: 0.5
  - **Double-blind Crossover Phase**: 4-week (N=66)
    - One week each of PBO & 3 doses of MPH
  - **Open-label Phase**: 8-week (N=35)
MPH-RUPP Trial: Efficacy

Crossover Phase Response:
Parent-rated ABC-Hyperactivity Subscale

8-week Open-label Continuation Phase Response:
ABC-H Subscale

*Parents reported increased social withdrawal on high dose of MPH

Mean ABC Hyperactivity Subscale Scores

<table>
<thead>
<tr>
<th>MPH Dose</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>p=0.03</td>
<td>p&lt;0.001</td>
<td>*p=0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td>ES=0.3</td>
<td>ES=0.5</td>
<td>ES=0.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Crossover Phase Response:
Parent-rated ABC-Hyperactivity Subscale

8-week Open-label Continuation Phase Response:
ABC-H Subscale

Parent and Teacher Crossover Open-label Continuation Phase Response:
ABC-H Subscale

RUPP Autism Network, 2005

www.mghcme.org
Efficacy

Anti-ADHD Response

Anti-ADHD response independent of:
- Level of IQ
- Subtypes of ASD

Additional Response*

Improvement in:
- Joint Attention
- Self/Affect Regulation

MPH is less effective than typically expected for the treatment of ADHD in children with ASD

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

Tolerability

Common AEs:
- Decreased appetite
- Initial insomnia
- Irritability
- Emotional outbursts

No exacerbation of stereotypes/repetitive behaviors

Dropout: 18% (13/72)
- All dropout d/t treatment-limiting AEs
  - 50% (6/13) dropout d/t inability to tolerate test dose
  - 50% (6/13) dropout d/t irritability

More than typically expected adverse effects associated with MPH in children with ASD
Methylphenidate - Extended Release

Crossover RCT in ASD Children with ADHD

ASD + ADHD: N = 24
[Autistic Disorder=19/24; ADHD=19/24]

Male: 79%
Mean Age [Range]: 9 ±1.7 [7–12]
Mean IQ [Range]: 85 ±17 [46-112]

**Trial Phases**
- Placebo phase: 1 Week (N=24)
- Tolerability phase: 2 day each on test doses of 3 different strengths of MPH (N=24)
- Crossover Phase: 3 Week (N=24)

<table>
<thead>
<tr>
<th>Duration [Week]</th>
<th>MPH Dosing (mg/Kg/day)</th>
<th>Morning MPH-ER dose</th>
<th>Afternoon MPH-IR dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low dose</td>
<td>0.2</td>
<td>0.15</td>
</tr>
<tr>
<td>1</td>
<td>Medium dose</td>
<td>0.35</td>
<td>0.25</td>
</tr>
<tr>
<td>1</td>
<td>High dose</td>
<td>0.5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Pearson et al., 2013
Methylphenidate - Extended Release

**Efficacy**

Parent-Teacher$^{(SNAP-IV; p<0.001)}$/ Clinician$^{(CGI-I\leq2=67\%)}$-rated Measures:

- Significant dose-related improvement in ADHD symptoms  
  (Linear dose response)
- Additional improvement in:  
  - Irritability  
  - Oppositional behaviors  
  - Social Skills

**Tolerability**

- Serious/Treatment Limiting AEs: None
- Dose-limiting AEs: 5/24 d/c MPH-IR dose d/o AE (late afternoon irritability)
- Common AEs:  
  - Insomnia $^{[9/24^{(High Dose MPH)} \text{ vs. } 5/24^{(PBO)}]}$  
  - Loss of appetite $^{[9/24^{(High Dose MPH)} \text{ vs. } 1/24^{(PBO)}]}$
Atomoxetine

8-week RCT in Youth with ASD

ASD + ADHD symptoms: N = 97
[ABC-Hyperactivity score ≥24 + CGI-S ≥4]

Male: 86%
Mean Age [Range]: 10 ±2.5 [6–17]
IQ: 90 ±16 [61–138]

ADHD Treatment-naïve: 37%
NO concomitant psychotropic medication: 100%

ATX Fixed Once-daily Dose
Titration Schedule

<table>
<thead>
<tr>
<th>Duration</th>
<th>ATX Dosing (mg/Kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week-I</td>
<td>0.5</td>
</tr>
<tr>
<td>Week-II</td>
<td>0.8</td>
</tr>
<tr>
<td>Week-III</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Hafterkamp et al., 2012
**Atomoxetine**

### Efficacy

#### Clinician-Rated Scales

<table>
<thead>
<tr>
<th>Clinician Rated ADHD-RS Mean Score</th>
<th>Atomoxetine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>

**ADHD-CGI-I ≤2:**

ATX[^21%] ≠ PBO[^9%] (p=0.14)

Less than expected magnitude of response

(ADHD-RS mean reduction: ASD[^8] vs. TYP[^13-19])

### Tolerability

- **Rate of TEAEs:** ATX[^81%] vs. PBO[^65%]
- **Common AE:**
  - Nausea (ATX=29% > PBO=8%; p=0.009)
  - Decreased appetite (ATX=27% > PBO=6%; p=0.006)
  - Fatigue (ATX=22% > PBO=8%; p=0.05)
  - Early Morning Awakening (ATX=10% > PBO=0%; p=0.03)
- **Serious AEs:** None
- **Treatment Limiting AEs:** ATX[^1/48] vs. PBO[^0/49]

No exacerbation of stereotypes/repetitive behaviors

ATX is associated with more frequent AEs in youth with ASD than typically expected

_Harterkamp et al., 2012_
Atomoxetine + Parent Training*
(*for ADHD & noncompliance)

10-week RCT in Youth with ASD

ASD + ADHD symptoms: N=128 [ATX=64]
[SNAP-ADHD mean item score ≥1.5 + CGI-S ≥4]

Male: 85%
Mean Age [Range]: 8 ±2 [5–14] years
IQ [±70]: 82 ±24 [61–138]
Mean Dose [Range]: 45 ±21 [1.2–1.8 mg/kg/day]

RATE OF RESPONSE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Responders (SNAP ↓ ≥30% +CGI-I ≤2)</th>
<th>Non-compliance Responders (HSQ ↓ ≥30% +CGI-I ≤2)</th>
<th>% ↓ HSQ p=value (vs.PBO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATX</td>
<td>47%</td>
<td>44%</td>
<td>51%</td>
</tr>
<tr>
<td>ATX + PT</td>
<td>45%</td>
<td>23%</td>
<td>41%</td>
</tr>
<tr>
<td>PT + PBO</td>
<td>29%</td>
<td>39%</td>
<td>46%</td>
</tr>
<tr>
<td>PBO</td>
<td>19%</td>
<td>16%</td>
<td>25%</td>
</tr>
</tbody>
</table>

SNAP=Swanson, Nolan, & Pelham; HSQ=Home Situations Questionnaire; ES=Effect Size

ADHD Response Rate: - ATX > PBO [p=0.015]
- ATX+PT ≠ ATX [p=NS]

Handen et al., 2015
Atomoxetine + Parent Training

24-week Extension Phase Trial in Youth with ASD

ASD + ADHD: N=84 [PT=40]
(RCT Responder[N=43] + PBO Non-responder[N=41])

Male: 85%
Mean Age [Range]: 8 ± 2 [5–14] years
IQ: 82 ± 24 [61–138] (Majority IQ > 70)
Mean Dose [mg/day]: 38 ± 17

Responders

Controlled Extension Phase (week-34):
60% of the acute phase responders continued to meet response criteria for ADHD (SNAP ↓ ≥ 30% + CGI-I ≤ 2)

Open-label Extension Phase (week-34):
- ADHD Responder (SNAP ↓ ≥ 30% + CGI-I ≤ 2): PT+ATX Superior to ATX
  PT+ATX[53%] > ATX[23%]
- Noncompliance Responder (HSQ ↓ ≥ 30% + CGI-I ≤ 2): PT+ATX[58%] > ATX[14%]

Common AEs in OLT

GI
- Dec. appetite: 54%
- Nausea: 32%
- Vomiting: 32%
- Constipation: 20%
- Abdominal pain: 17%
- Diarrhea: 15%

Headache: 39%
Labile mood: 32%
Fatigue: 27%
Sleep disturbance: 24%

Smith et al., 2016
Guanfacine-ER

8-week RCT in ASD Children with Hyperactivity

Autistic Disorder + Hyperactivity: N = 62
[ABC-Hyperactivity score ≥24 + CGI-S ≥4]

Male: 86%
Mean Age [Range]: 8.5 ±2.3 [5–14]
IQ ≥70: 37%
Drug-naïve: 55%
Dose [Range]: 3 mg/day [1–4]

<table>
<thead>
<tr>
<th>Duration [Week]</th>
<th>Dose [mg/day]</th>
<th>&lt;25 Kg</th>
<th>≥25 Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Scahill et al., 2015
Guanfacine-ER

**Efficacy - ADHD**

**Parent-Rated ABC-Hyperactivity Subscale**

![Graph showing comparison between Placebo and Guanfacine-ER over 8 weeks.](image)

- **Clinicin-Rated Scales**
  - **ADHD-RS**: GFX-ER > PBO
    - Inattention+Hyperactivity <0.0001; ES=2
    - Inattention 0.0001; ES=1.2
    - Hyperactivity <0.0001; ES=1.7
  - **CGI-Improvement ≤2:**
    - GXR [50%] > PBO [9.4%]

**Efficacy – Other Features**

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

Scahill et al., 2015; *Biederman et al., 2008*
Guanfacine-ER

Tolerability

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>GXR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-limiting AEs</td>
<td>5/32</td>
<td>9/30</td>
<td></td>
</tr>
<tr>
<td>[d/t emotional lability/drowsiness]</td>
<td>[16%]</td>
<td>[30%]</td>
<td></td>
</tr>
<tr>
<td>Treatment-limiting AEs</td>
<td>None</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Agitation[N=1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Drowsiness[N=1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>None</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(agitation @ 2mg/d)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Common AEs*

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>GXR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>9%</td>
<td>87%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9%</td>
<td>63%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dec. appetite</td>
<td>6%</td>
<td>43%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3%</td>
<td>40%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emotional/tearful</td>
<td>9%</td>
<td>40%</td>
<td>0.01</td>
</tr>
<tr>
<td>Irritability</td>
<td>9%</td>
<td>37%</td>
<td>0.01</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3%</td>
<td>30%</td>
<td>0.01</td>
</tr>
<tr>
<td>Mid-sleep awakening</td>
<td>6%</td>
<td>30%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Reported in ≥5% & <0.05

Cardiovascular AEs

- BP & pulse declined during the study GXR titration phase
- BP returned to baseline values at week-8
- Pulse [mean] 10 points below baseline at week-8
- Drop in diastolic BP [≥10-point]: GXR[N=5] vs. PBO[N=3] (p=NS)

Typically expected anti-ADHD treatment response of GXR in children with ASD

Scahill et al., 2015
Alpha-2 Adrenergic Agonist - Clonidine

Two Crossover RCTs in Male Children with Autistic Disorder

**Oral Clonidine**
- 6-week trial with oral clonidine 4-10 micro gms/kg/day
- 8 males (mean age: 8 ±3 yrs.) with autistic disorder + hyperactivity (prior hx. of poor response)

**Transdermal Clonidine**
- 4-week trial with transdermal clonidine 3.5 micro gms/kg/day
- 9 males (mean age: 13 yrs.) with autistic disorder + hyperarousal symptoms (including hyperactivity)

**Efficacy**
- Oral Clonidine: Superior to placebo in reducing Hyperactivity *(Informant rating; NOT clinician rating)*
- Transdermal Clonidine: No effect on ADHD symptoms *(per parent rating)*

**Tolerability**
- Major adverse-effect: Drowsiness
- Fatigue

*Jaselskis et al., 1992; **Fankhauser et al., 1992*
Emotional Dysregulation in ASD

Child Behavior Checklist - Emotional Dysregulation Profile (CBCL-ED)

CBCL-ED profile based on the composite T-scores of CBCL subscales:

- Attention
- Aggression
- Anxious/Depressed

<table>
<thead>
<tr>
<th>CBCL-AAA Subscales Composite T-Score</th>
<th>Level of Emotional Dysregulation (ED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;180</td>
<td>Low/No ED</td>
</tr>
<tr>
<td>≥180</td>
<td>Presence of ED</td>
</tr>
<tr>
<td>≥180 &amp; &lt;210 (≥1SD &amp; &lt;2SD) (t-score of ≥60 on each CBCL-AAA subscales)</td>
<td>Deficient Emotional Self Regulation (DESR)</td>
</tr>
<tr>
<td>≥210 (≥2SDs)</td>
<td>Severe Emotional Dysregulation (SED)</td>
</tr>
</tbody>
</table>

High Prevalence of ED in Youth with ASD

Positive correlation between severity of ED & autistic traits

Prevalence of ED

- HC: 2%
- ADHD: 54%
- ASD: 83%

p<0.001 [r=0.47, df=447]
Risperidone: RUPP - Trial

8-week RCT in Autistic Disorder Youth with Irritability

Autistic Disorder + Sign. Irritability: N = 101
[ABC-Irritability score ≥18 + CGI-S ≥4] [RISP=49]

Mean Age [Range]: 9 ±3 [5–17]
Pre-pubertal [Children]: 87%
Male: 81%

Intellectually-capable (IQ ≥70): 17%

Mean Dose [Range]: 1.8 ±0.7 [0.5–3.5] mg/day

RISP Flexible Dose Titration Schedule

<table>
<thead>
<tr>
<th>AM</th>
<th>PM</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 Kg</td>
<td>-</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>≥20 Kg</td>
<td>-</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Maximum Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤45 Kg</td>
<td>1 mg</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>&gt;45 Kg</td>
<td>1.5 mg</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

RUPP Autism Network, 2002
**Risperidone-Trial: Efficacy**

**Efficacy-Irritability**

**Parent-Rated ABC-Irritability Subscale**

- **Clinician-Rated CGI-Impovement Subscale**

**Efficacy-Associated Features**

- Sign. improvement in:
  - Repetitive behaviors (CY-BOCS & ABC)
  - Hyperactivity (ABC)

- No change in other core features of ASD

Response criteria: ≥25% ↓ ABC- Irritability score + CGI-I ≥2

---

RUPP Autism Network, 2002
Risperidone-Trial: Tolerability

- Most AE were mild and self-limited
- No EPS observed
- No treatment limiting AE
- No serious AEs

Weight Gain

24-week Exposure to Risperidone (1.65 mg/day)

<table>
<thead>
<tr>
<th>Week</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week-8</td>
<td>2.5 ± 1.6</td>
</tr>
<tr>
<td>Week-16</td>
<td>4.2 ± 2.8</td>
</tr>
<tr>
<td>Week-24</td>
<td>5.4 ± 3.4</td>
</tr>
</tbody>
</table>

Common AEs

<table>
<thead>
<tr>
<th>Inc. Appetite</th>
<th>PBO</th>
<th>RISP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29%</td>
<td>74%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27%</td>
<td>59%</td>
<td>0.003</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>12%</td>
<td>49%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4%</td>
<td>16%</td>
<td>0.05</td>
</tr>
<tr>
<td>Drooling</td>
<td>6%</td>
<td>27%</td>
<td>0.02</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>0.8 ± 2.2 kg</td>
<td>2.7 ± 3 kg</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- 2-4 fold ↑ in prolactin in 0→8 week
- Longitudinal downward trend in serum prolactin level
- Asymptomatic hyperprolactinemia

Asymptomatic Hyperprolactinemia

<table>
<thead>
<tr>
<th>Serum Prolactin</th>
<th>Baseline</th>
<th>8 Weeks</th>
<th>6 Months</th>
<th>22 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11.8±12.1</td>
<td>37.2±16.4</td>
<td>32.2±18.2</td>
<td>22.9±12.0</td>
</tr>
</tbody>
</table>

Scahill et al., 2016; Anderson et al., 2007; RUPP Autism Network, 2002
Aripiprazole

8-week RCT in Autistic Disorder Youth with Irritability

Autistic Disorder + Sign. Irritability: N = 98
[ABC-Irritability score ≥18 + CGI-S ≥4] [ARIP=47]
Mean Age [Range]: 9 years [6–17]
Pre-pubertal [Children]: 85%
Male: 88%
Mean Dose [Range]: 8.5 [2–15] mg/day

ARIP Flexible Dose Titration Schedule

<table>
<thead>
<tr>
<th>Duration</th>
<th>Daily Dose</th>
<th>N [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week-I</td>
<td>2 mg/day</td>
<td>02 [05]</td>
</tr>
<tr>
<td>Week-II-VI</td>
<td>5 mg/day</td>
<td>13 [33]</td>
</tr>
<tr>
<td>Week-II-VI</td>
<td>10 mg/day</td>
<td>16 [41]</td>
</tr>
<tr>
<td>Week-II-VI</td>
<td>15 mg/day</td>
<td>08 [21]</td>
</tr>
</tbody>
</table>

Owen et al., 2009
Aripiprazole

Efficacy - Irritability

Sign. improvement on ABC-I & CGI-I from week-1 onwards

Efficacy – Other Features

Significant improvement in:
- Hyperactivity\(^{(ABC-H)}\)
- Repetitive behaviors\(^{(ABC-Stereotypy \& CY-BOCS)}\)
- Communication\(^{(ABC-Inappropriate speech)}\)
Aripiprazole

**Tolerability**

- 77% of the participants completed the trial
- Adverse Events:  - ARIP[^92%] vs. PBO[^72%]
  - Severity: Mild-moderate
  - Serious AEs: None
  - Tx-Limiting AEs: ARIP[^N=5] vs. PBO[^N=3]
  - Common AEs: - Fatigue[^21%]
    - Somnolence[^17%]
- EPS: ARIP[^17% [N=8]] > PBO[^8% [N=4]]
- Weight gain:  - Mean: ARIP > PBO (2kg vs. 0.8kg; p<0.005)
  - Clinically sign: ARIP > PBO (29% vs. 6%; p<0.01)
    (≥7% inc. from baseline)
- Metabolic Parameters & EKG:
  - No clinically significant change with treatment

*[^N=1 x Fatigue, Vomiting, Wt gain, SIB, Aggression]*
Anti-ADHD Response in Youth with ASD

- **MPH & ATX**: Less than expected rate & magnitude of response
  - Adverse effects more frequent than typically expected
  - Additionally improves affect regulation & joint attention
  - MPH tolerated at lower than expected dose

- **Guanfacine-ER**: Response similar to observed in children with ADHD

- **Clonidine**: Poorly tolerated

- **Risperidone & Aripiprazole**: Improves Irritability + Hyperactivity

MPH=Methylphenidate; ATX=Atomoxetine
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.
## Demographic Characteristics

### Participants
- Total participants: 11
- Gender *(male)*: 09 (82%)
- Ethnicity *(Caucasian)*: 10 (91%)

### Age *(years)*
- Mean: 24 ±3
- Range: 19-28

### Full Scale IQ
- Mean: 117 ±16
- Range: 99 - 144

### 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/SNRI/DNA: 06 (55%)
  - Atypical Antipsychotic: 01 (09%)
Study Medication

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

### Flexible Dose Titration Schedule

<table>
<thead>
<tr>
<th>Duration Weeks [Days]</th>
<th>Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.5 [0-3]</td>
<td>5</td>
</tr>
<tr>
<td>0.5-1 [4-7]</td>
<td>10</td>
</tr>
<tr>
<td>1-1.5 [8-10]</td>
<td>20</td>
</tr>
<tr>
<td>1.5-2 [11-14]</td>
<td>30</td>
</tr>
<tr>
<td>2-2.5 [15-17]</td>
<td>50</td>
</tr>
<tr>
<td>2.5-3 [18-21]</td>
<td>60</td>
</tr>
<tr>
<td>3-6 [22-42]</td>
<td>Max. achieved dose</td>
</tr>
</tbody>
</table>

### Study Medication (MPH-ER)

- Mean dose: 49 ±16 mg/day
- Dose range: 20-60 mg/day

**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
Treatment Response: ADHD Symptoms

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

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Mean AISRS Score ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>35.5 ± 3.5</td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>12 ± 6</td>
</tr>
<tr>
<td>6</td>
<td>14 ± 9.2</td>
</tr>
</tbody>
</table>

MC = Mean Change

[MC = -21.4 ± 8; Z = -3; p = 0.003]
Treatment Response: ADHD Symptoms

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

Mean ASRS Score

Weeks

MC = Mean Change

LOCF [34 ± 10.6]

33 ± 10

[MC = -9 ± 11; Z = -2; p = 0.03]
Treatment Response: Outcome Measures

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

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

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

[MC= -8 ±17; Z=1; p=0.33]

[LOCF [97 ±28]

MC=Mean Change

Bressler Clinical & Research Program For Autism Spectrum Disorder

www.mghcme.org
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])
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