Piecing the Puzzle Together: Pharmacologic Approaches to Behavioral Management in Autism Spectrum Disorder

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Objectives

• Identify challenges associated with medication management in patients with autism spectrum disorder (ASD)

• Determine appropriate pharmacologic management of behavioral disorders in ASD

• Recognize the role for novel pharmacologic approaches to behavior management in ASD
Autism Spectrum Disorder (ASD)

High functioning autism, Asperger’s

Autism spectrum conditions

Severe or “classic” autism
Related Disorders

Associated Neurological Symptoms

Core Symptoms

Autism

Adapted from Autism Speaks®
Mayo Clinic Children's Center
Related Disorders
- OCD
- ADHD
- Immune dysfunction
- GI disorders
- Hormone dysregulation

Associated Symptoms
- Seizures
- Sleep deficits
- Mood and anxiety
- Hyperactivity and inattention

Core Symptoms
- Social deficits
- Repetitive behaviors

Autism

Mayo Clinic Children's Center
Behavioral Manifestations

1. Repetitive, stereotyped behaviors*
2. Irritability and aggression
3. Hyperactivity and inattention
4. Social impairment*

*Core Symptoms
Challenges in ASD

- **Limited Resources**
  - Training deficits
  - Limited data
  - Available services

- **Poly-pharmacy**
  - Psychotropic medications
  - Hesitation to discontinue

- **Drug Sensitivity**
  - Drug allergies
  - Dose-sensitive
  - Idiosyncratic adverse reactions

- **Patient Resistance**
  - Situational
  - Symptomatic

The “T” Word

• Services
  • Eligibility v. entitlement
  • Guardianship
• Continuity of care
• Adaptive functioning

Pharmacologic Options

- Repetitive, stereotyped behaviors
  - Selective serotonin reuptake inhibitors (SSRIs)

- Irritability and aggression
  - Antipsychotics
  - Valproic acid
  - Propranolol

- Hyperactivity and inattention
  - Methylphenidate
  - Clonidine

- Social impairment
Pharmacologic Options

- **Repetitive, stereotyped behaviors**
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  - Clonidine

- **Social impairment**
SSRIs

- Used for repetitive, stereotyped behaviors
- Co-morbid anxiety, depression, OCD
- Less efficacious and less tolerable in children than adults
- Primary agents
  - Sertraline
  - Fluoxetine

Pharmacologic Options

- Repetitive, stereotyped behaviors
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- Social impairment
Antipsychotics

• Risperidone*
  • Dose-response relationship
  • Target doses based on weight: 1-2.5 mg/day

• Aripiprazole*
  • No clear dose-response relationship
  • Less efficacious in some adults
  • Titrate to a maximum of 15 mg/day

*FDA-Approved in children

Antipsychotics

- Haloperidol
  - Inferior to risperidone in children and adolescents
  - Unclear efficacy in adults
- Olanzapine has “intermediate efficacy”
- None effective in preventing self-injury


*FDA-Approved in children*
• Valproic acid
  • Used as adjunctive treatment for irritability, aggression, and repetitive behaviors
  • Weak evidence

• Propranolol
  • Used for irritability in adults and children with developmental disability
  • Weak evidence

Pharmacologic Options

- Repetitive, stereotyped behaviors
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  - Propranolol

- Hyperactivity and inattention
  - Methylphenidate
  - Clonidine

- Social impairment
Stimulants

- Used for hyperactivity, inattention
- FDA-approved for co-morbid ADHD
- Controversial in patients with severe intellectual disability
- Methylphenidate
  - Typical doses poorly tolerated
  - ~50% response rate
  - Limited data in adults

• Clonidine
  • Used as second-line for hyperactivity or adjunctive treatment for irritability and aggression
  • Benefit in children with co-morbid sleep disturbances
  • Oral or transdermal

AB is a 8 year-old (25 kg) male with high-functioning ASD presenting with what mom reports as “more frequent and severe tantrums”. His irritability is currently maintained with appropriate behavioral intervention in addition to risperidone 1 mg daily. What is the most appropriate next step for AB?

A. Increase risperidone to the recommended maximum dose for his age (2.5 mg daily)

B. Up-titrate risperidone dose slowly every 2 weeks

C. Discontinue risperidone due to treatment failure and initiate aripiprazole

D. Initiate propranolol as adjunctive treatment
The Missing Pieces

Repetitive, stereotyped behaviors
- Selective serotonin reuptake inhibitors (SSRIs)

Irritability and aggression
- Antipsychotics
- Valproic acid
- Propranolol

Hyperactivity and inattention
- Methylphenidate
- Clonidine

Social impairment
The Missing Pieces

- **Repetitive, stereotyped behaviors**
  - Selective serotonin reuptake inhibitors (SSRIs)

- **Irritability and aggression**
  - Antipsychotics
  - Valproic acid
  - Propranolol

- **Hyperactivity and inattention**
  - Methylphenidate
  - Clonidine

- **Social impairment**
Augmentative Therapy

- Post-mortem analyses
- Animal studies
- Clinical trials
<table>
<thead>
<tr>
<th>Study design</th>
<th>Randomized, double-blind placebo-controlled trials</th>
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<tbody>
<tr>
<td>Population</td>
<td>Children with DSM-IV diagnosed autism</td>
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<tr>
<td>Inclusion Criteria</td>
<td>Age 4-12 years ABC-C score ≥12</td>
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<tr>
<td>Exclusion Criteria</td>
<td>Comorbid psychiatric conditions</td>
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<td></td>
<td>Severe mental disability</td>
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<tr>
<td></td>
<td>History of drug or alcohol abuse</td>
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<td></td>
<td>History of tardive dyskinesia</td>
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*Abberant Behavior Checklist-Community*
<table>
<thead>
<tr>
<th>Augmentative Research Series: Tehran University</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>10 weeks risperidone + intervention drug*</td>
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<tr>
<td>10 weeks risperidone + placebo</td>
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<tr>
<td><strong>Efficacy Outcomes</strong></td>
</tr>
<tr>
<td>Mean decrease in ABC-C scores:</td>
</tr>
<tr>
<td>1. Irritability#</td>
</tr>
<tr>
<td>2. Lethargy/social withdrawal</td>
</tr>
<tr>
<td>3. Stereotypical behavior</td>
</tr>
<tr>
<td>4. Hyperactivity</td>
</tr>
<tr>
<td>5. Inappropriate speech</td>
</tr>
<tr>
<td><strong>Safety Outcomes</strong></td>
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<tr>
<td>Rates of adverse effects</td>
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</tbody>
</table>

*Memantine, galantamine, or N-acetylcysteine
#Primary outcome
<table>
<thead>
<tr>
<th></th>
<th>Memantine (n=20)</th>
<th>Placebo (n=20)</th>
<th>F-Value</th>
<th>P-Value</th>
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<tbody>
<tr>
<td><strong>Irritability</strong></td>
<td>18.25</td>
<td>8.90</td>
<td>17.65</td>
<td>12.75</td>
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<tr>
<td><strong>Lethargy/social withdrawal</strong></td>
<td>16.55</td>
<td>11.65</td>
<td>16.85</td>
<td>13.85</td>
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<tr>
<td><strong>Stereotypical behavior</strong></td>
<td>8.83</td>
<td>3.30</td>
<td>8.26</td>
<td>6.99</td>
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<tr>
<td><strong>Hyperactivity</strong></td>
<td>23.0</td>
<td>8.25</td>
<td>22.45</td>
<td>13.85</td>
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<tr>
<td><strong>Inappropriate speech</strong></td>
<td>6.0</td>
<td>4.50</td>
<td>5.85</td>
<td>4.69</td>
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<table>
<thead>
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<th>Placebo (n=20)</th>
<th>Mean Difference</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>Irritability</td>
<td>15.59</td>
<td>5.3</td>
<td>14.95</td>
<td>8.8</td>
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<tr>
<td>Lethargy/social</td>
<td>11.1</td>
<td>5.6</td>
<td>10.4</td>
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<td>withdrawal</td>
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<td></td>
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<tr>
<td>Stereotypical</td>
<td>6.1</td>
<td>3.95</td>
<td>5.8</td>
<td>4.5</td>
</tr>
<tr>
<td>behavior</td>
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</tr>
<tr>
<td>Hyperactivity</td>
<td>20.85</td>
<td>10.85</td>
<td>22.3</td>
<td>16.05</td>
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<tr>
<td>Inappropriate</td>
<td>3.5</td>
<td>2.15</td>
<td>3.25</td>
<td>2.8</td>
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<tr>
<td>speech</td>
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<table>
<thead>
<tr>
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<th>N-acetylcysteine (n=20)</th>
<th>Placebo (n=20)</th>
<th>Mean Difference</th>
<th>P-Value</th>
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<tbody>
<tr>
<td><strong>Irritability</strong></td>
<td>21.2</td>
<td>11.95</td>
<td>19.7</td>
<td>14.35</td>
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<tr>
<td><strong>Lethargy/social withdrawal</strong></td>
<td>21.1</td>
<td>17.15</td>
<td>20.65</td>
<td>17.95</td>
</tr>
<tr>
<td><strong>Stereotypical behavior</strong></td>
<td>10.55</td>
<td>7.75</td>
<td>10.05</td>
<td>8.7</td>
</tr>
<tr>
<td><strong>Hyperactivity</strong></td>
<td>27.65</td>
<td>21.45</td>
<td>25.1</td>
<td>23.05</td>
</tr>
<tr>
<td><strong>Inappropriate speech</strong></td>
<td>5.7</td>
<td>4.95</td>
<td>4.75</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Augmentative Research Series: Tehran University

**Strengths**

- Doses of risperidone reflect clinical practice
- ABC-C rating scale

**Limitations**

- Wash-out period
- Exclusion of patients with co-morbid conditions
- Adverse effects
Memantine
- MOA: NMDA receptor antagonist
- Mean dose 16.8 mg/day
- Additional efficacy in:
  - Stereotypic behaviors
  - Hyperactivity
  - Variable response

Galantamine
- MOA: cholinesterase inhibitor
- Dosed 10 or 20 mg/day
- Additional efficacy in:
  - Social withdrawal

NAC
- MOA: restores glutathione, free radical scavenger
- Use in pediatrics
- Dosed 500 mg/day
- Additional efficacy in:
  - Hyperactivity
  - Conflicting results

The Missing Pieces

- Repetitive, stereotyped behaviors
  - Selective serotonin reuptake inhibitors (SSRIs)

- Irritability and aggression
  - Antipsychotics
  - Valproic acid
  - Propranolol

- Hyperactivity and inattention
  - Methylphenidate
  - Clonidine

- Social impairment
Based on the augmentative therapy studies presented, which of the following patients with ASD may benefit from treatment with memantine?

A. 6 year old male on appropriately dosed risperidone with continued disruptive behaviors

B. 20 year old male with increased outbursts in the setting of a group home transition

C. 3 year old female with significant tantrums resulting in self-injury

D. 9 year old male with co-morbid schizophrenia and ADHD with chief complaint of worsening irritability
Intranasal Oxytocin
Oxytocin

Fear reduction

Perceptual selectivity

Affiliative motivation

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<table>
<thead>
<tr>
<th>Study design</th>
<th>Randomized, double-blind, placebo-controlled, parallel trial</th>
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</thead>
<tbody>
<tr>
<td>Population</td>
<td>Children 6-12 years old with ASD</td>
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<td>Inclusion Criteria</td>
<td>4 weeks of stable medications</td>
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<td></td>
<td>Medically healthy</td>
</tr>
<tr>
<td></td>
<td>IQ &gt;40</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
<td>Psychiatric disorder</td>
</tr>
<tr>
<td></td>
<td>Nasal obstruction or regular nosebleeds</td>
</tr>
<tr>
<td></td>
<td>Hearing or vision impairment</td>
</tr>
<tr>
<td></td>
<td>Habitual consumption of large volumes of water</td>
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</tbody>
</table>

### Parker, et al., 2017

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Intranasal oxytocin 24 IU OR Placebo Administered twice daily for 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>1. Social abilities measured by the Social Responsiveness Scale (SRS)</td>
</tr>
</tbody>
</table>
| Secondary Outcomes | 1. Efficacy of oxytocin for core versus associated symptoms  
2. Tolerability |

Results

Results

Associated Symptoms

• Anxiety
  • Spence Score
  • Trend toward improvement
• Repetitive behaviors
  • RBS-R Score*
  • No difference

Tolerability

• Increased blood pressure in oxytocin group
• Nasal congestion
• No significant difference in adverse effects

*RBS-R=Repetitive Behaviors Scale-Revised

Interpretation

• Limitations
  • Gender: 84% male subjects
  • Parent reporting of symptoms

• Unanswered questions
  • Sub-populations
  • Confounding endogenous oxytocin

Oxytocin: The Bottom Line

• Several studies in last 2 years
  • Adults and children
  • Mixed results

“May be effective in improving social interactions in some patients.”

At the very least, “does not worsen symptoms”.
Pharmacologic Options

- **Repetitive, stereotyped behaviors**
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Augmentative therapy

- **Irritability and aggression**
  - Antipsychotics
  - Augmentative therapy
  - Valproic acid
  - Propranolol

- **Hyperactivity and inattention**
  - Methylphenidate
  - Clonidine

- **Social impairment**
  - Augmentative therapy
  - Oxytocin
The Pharmacist’s Approach

• Start low, go slow
• Limit multiple medication changes
• Review frequently
  • Assess for indications and adverse reactions
  • Identify complicating co-morbidities
  • Stop drugs that don’t work (taper)
• Anticipate challenges and facilitate continuity
LM is an 18 year old with ASD (non-verbal) and history of seizure presenting with new-onset repetitive chest tapping accompanied by increased irritability. His current medications include: risperidone 3 mg daily, Depakote 500 mg twice daily, sertraline 100 mg daily, methylphenidate 20 mg twice daily, and lorazepam 1 mg as needed for agitation. Which of the following should be on your differential when assessing LM’s new symptoms?

A. A new medical diagnosis presenting through behavioral symptoms
B. Medication side effects
C. Medication adherence
D. Recent changes in home or social environment
E. All of the above
Summary

• Patients with ASD face many challenges in their healthcare that warrant special attention from a pharmacist’s perspective

• A evidence-based approach should be taken when managing behaviors associated with ASD

• Studies of novel agents for ASD suggest that the approach to treatment in these patients should be highly individualized
Questions & Discussion