Autism: Overview, Treatment, and Communication

MALAURA CREAGER, PHARMD
NMPHA SPRING 2019
Learning Objectives

Pharmacists and technicians:
- Describe the criteria used to diagnose autism
- Identify common comorbidities for autism
- Evaluate the effectiveness of their communication with a person with autism

Pharmacists:
- Recommend and monitor pharmacological treatment for autism and its comorbidities

No financial or institutional conflicts of interest to disclose
Why this matters

Pharmacy school may not cover the disorder
  ◦ Educating providers is guideline-directed

Not enough specialists—psychiatrists

Primary care managing patients

Higher frequency of adverse effects

Patients’ and caregivers’ frustrations with their providers
Outline

Background
- Diagnosis criteria
- Epidemiology
- Etiology
- Pathophysiology

Treatment

Communicating with autism patients and their families
Diagnosis
Diagnosing

No laboratory tests

Evaluate behavior and history

Trained professionals can diagnose by age 2

Symptoms often noticed younger

Understanding the definition is important for the healthcare team

Diagnosis includes 4 required sections
Deficits in Social Communication Interactions

3 out of 3 required deficits

- Social-emotional reciprocity
- Non-verbal communication
- Developing, maintaining, and understanding relationships

What this looks like: #nofilter

- Taking turns in conversations
- Not understanding unspoken messages
- Not understanding layered levels of relationships
- Perspective-taking
- Not understanding peer pressure
Diagnosis part 2: Restricted, repetitive behavior, interests, or activities

2 out of 4 required for diagnosis

- Stereotyped or repetitive motor movements, use of objects, speech
- Insistence on sameness/ritualized behavior
- Restricted, fixated interests
- Hypo-hyperreactive to sensory input

What this looks like: #nofilter

- Difficulty with transitions
- Stimming
- Lining up toys
- Single topic of conversation
- Great with routines, and patterns
- Sensory overload & meltdowns

Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. APA, 2013
Diagnosis parts 3 and 4

Present in early development, but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life

- Gender
- Young adults

Cause clinically significant impairment in functioning
Diagnosis:
Severity for parts 1 and 2

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Requiring support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 2</td>
<td>Requiring substantial support</td>
</tr>
<tr>
<td>Level 3</td>
<td>Requiring very substantial support</td>
</tr>
</tbody>
</table>

Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. APA, 2013
Severity vs Spectrum

**MEASURED INTELLIGENCE**

- Intellectual disability — Gifted

**SOCIAL INTERACTION**

- Not interested in others — A variety of friendships

**COMMUNICATION**

- Nonverbal — Verbal

**BEHAVIORS**

- Intense — Mild

**SENSORY**

- Not very sensitive — Very sensitive

**MOTOR**

- Uncoordinated — Coordinated

(Repetitive behaviors, unusual behaviors such as hand flapping, etc.)

(Response to touch, smell, sound, taste, and feel)

(Gross motor, such as walking)

(Fine motor, such as using fingers to grasp a small item)

www.cdc.gov/ncbddd/autism/signs.html
Severity vs Spectrum: The patient’s perspective

Sometimes when people think of this word, they think of the autism spectrum as being like this:

A very linear looking ‘spectrum’, which gives the impression that people range from being ‘a little autistic’ to ‘very autistic’.

Hm. How can you be ‘a little autistic’?

It’s that vague language that I always find confusing.

https://the-art-of-autism.com/understanding-the-spectrum-a-comic-strip-explanation/
Severity vs Spectrum: The patient’s perspective

The spectrum consists of many different ‘traits’, or ways in which the brain processes information.

Some traits create difficulties in every day life. (hence being diagnosed)

But also many traits are useful in every day life.

https://the-art-of-autism.com/understanding-the-spectrum-a-comic-strip-explanation/
Epidemiology

WHO IS MOST AFFECTED
Child Prevalence 2014
Autism and Developmental Disabilities Monitoring (ADDM)

8-year-old children
16 states
N=325,483 (2014)

1.7% is the average percentage identified with ASD
1 in 59 8-year-old children were identified with ASD by ADDM in 2014

www.cdc.gov/ncbddd/autism/addm-community-report/key-findings.html
ADDM
Prevalence over time

Baio J et al. MMWR Surveill Summ. 2018; 67(SS-6): 1-23
ADDM Prevalence over time

Baio J et al. MMWR Surveill Summ. 2018; 67(SS-6): 1-23
ADDM key findings

Gender Ratio

Intellectual Ability

IQ greater than 70: 69%
IQ less than or equal to 70: 31%
...and 30% had not been able to access a provider for a formal diagnosis by age 8
Adult prevalence

- Fewer studies
- Estimated similar to children
- Adults more likely to have severe disabilities
- For those no longer autistic, high rates of comorbidities
Adult prevalence

Fewer studies

Estimated similar to children

Adults more likely to have severe disabilities

For those no longer autistic, high rates of comorbidities
Comorbidities*

Medical
- Seizures
- Gastrointestinal issues
  - Malnutrition
  - Obesity
  - Constipation
- Asthma
- Allergies
- Bone fractures
- Pneumonia
- Down’s syndrome

Psychiatric
- *But are they really
- Sleep disorders
- Irritability (communication)
- Hyperactivity
- Anxiety
- Depression
- Obsessive-compulsive disorder
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---

Lord C et al. *Lancet*. 2018 published online


Clinical issues

- Gender identity/dysphoria
- Transition to adulthood
- Suicide risk
- Patient vs caregiver goals
- Blood draws for anything
- Time burden/commitment
- Access to services
Etiology
## Risk factors

<table>
<thead>
<tr>
<th>Maternal environment</th>
<th>Birth circumstances</th>
<th>MMR vaccine</th>
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<tbody>
<tr>
<td>Nutrition</td>
<td>Low birthweight</td>
<td>No</td>
</tr>
<tr>
<td>• Vitamin D</td>
<td>Preterm birth</td>
<td></td>
</tr>
<tr>
<td>• Folic acid</td>
<td>Hypoxia</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Valproic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Opioids prior to conception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
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<tr>
<td>Parental age</td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th>Identified genetic causes</th>
<th>Not clearly identified Fragile X</th>
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<tr>
<td>Heritability</td>
<td>70-93%</td>
</tr>
<tr>
<td>Older sibling with autism</td>
<td>7%-20% of subsequent siblings</td>
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Genetics

Howes OD. *J Psychopharmacol*. 2017; 32:3-29
Pathophysiology

#NOFILTER
Neurobiology

Brain volume
- Overgrowth early in development
- Altered connectivity
  - Overall under-connectivity
  - Over-connectivity in frontal and occipital lobes
- Reduced/impaired growth later in development

GABA signaling/switch

Elevated serotonin

Ben-Ari Y. Trends in Neurosciences. 2017;40(9), 536-554
Courchesne E et al. Brain Res. 2010;1380:138-45
Zielinski BA et al. Brain. 2014; 137 (6); 1799-812.
Treatment
Screening

US Preventative Services Task Force: insufficient evidence

Recommended by most other authorities

American Academy of Pediatrics: 18 and 24 months

American Academy of Neurology:
- Surveillance at all visits until school age
- Screening with CHAT or Autism Screening Questionnaire if
  - Fail surveillance
  - Autism sibling
  - Language delayed
  - Autism-related symptoms or concerns

Modified Checklist for Autism in Toddlers (M-CHAT) for primary care
Guideline treatment overview

First line: therapy

◦ Coaching parents and caregivers on how to interact with children with autism
◦ School-based interventions
◦ Social skills training

Insufficient evidence to recommend any medication for core symptoms

May use medications for comorbidities
Choosing medication treatment

Know what the actual diagnosis is

Define the goals of therapy

Use a validated tool to measure the progress toward goal
  - Core symptoms: CARS, CGI, ADOS, SRS, ABC, etc

Use evidence, but be aware of the limitations of evidence in this population
  - Low sample size
  - Often not studied at all
  - Seizure disorders excluded

Be suspicious of adverse reactions
  - Paradoxical
  - Gastrointestinal
Choosing medication treatment: Good resources

**John Hopkins Review for Children and Adolescents**


**British Guidelines for Children and Adults**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Children</th>
<th>Adults</th>
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<tbody>
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<td>Case-by case. Follow other guidelines. (S)</td>
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<td>Cautious trial with SSRIs, followed by risperidone if poor response. Monitor for worsening. (B)</td>
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<td>Melatonin in combination with behavioral interventions, based on findings in children (S)</td>
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| **Irritability**          | Risperidone or aripiprazole but only when behavioral interventions have failed (A) | • Case by case. (S)  
• Aripiprazole, risperidone, or SSRI should only be considered cautiously and after considering alternatives (S) |
| **ADHD**                  | • First line: methylphenidate (A)  
• Second line: atomoxetine or α2A receptor agonist (A)  
• May experience more side effects and less response than non-ASD patients (A) | Case by case. Follow other guidelines. (S)                              |
| **Tic disorders & Tourette’s** | Case by case. Follow other guidelines (S)                              | Case by case. Follow other guidelines. (S)                              |

A=Directly based on category I evidence, B=Directly based on category II evidence or extrapolated from category I evidence, S=Standard of good clinical care

Adapted from Howes OD. *J Psychopharmacol*. 2018; 32:3-29
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**Evidence is for risperidone, NOT SSRIs**  
SSRIs=poorly studied, poor outcomes

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Adapted from Howes OD. J Psychopharmacol. 2018; 32:3-29
What we will discuss

Risperidone and aripiprazole pearls

Bumetanide
- Has not been recommended by any guideline
- Newer studies
- Mechanism unusual

Most other mechanisms of action are similar to neurotypical patients

Brief pearls

First line guideline recommendation: learning how to communicate
Treatment:
Irritability and aggression

RISPERIDONE

ARIPIPRAZOLE

Treatment: Irritability and aggression

Risperidone and aripiprazole
- FDA approval: irritability associated with autistic disorder in pediatric patients
- For tantrums, self-injurious or violent behavior
- Reserve for those who are at risk for serious adverse events
- Best for stabilization—label indicates to increase dose to therapeutic effect, then titrate downward to reduce adverse events
- Head to head trial: neither superior to the other

Goel R et al. *Int Rev Psychiatry*. 2018; 30(1):78-95
# Dosing

<table>
<thead>
<tr>
<th>Ages</th>
<th>Aripiprazole</th>
<th>Risperidone &lt;20kg</th>
<th>Risperidone ≥20kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages</td>
<td>6-17</td>
<td>5-16</td>
<td></td>
</tr>
<tr>
<td>Initial Dose</td>
<td>2 mg/day</td>
<td>0.25 mg/day</td>
<td>0.5 mg/day</td>
</tr>
<tr>
<td>Recommended Dose</td>
<td>5-10 mg/day</td>
<td>0.5 mg/day</td>
<td>1 mg/day</td>
</tr>
<tr>
<td>Maximum Dose</td>
<td>15 mg/day</td>
<td>3 mg/day</td>
<td>3 mg/day</td>
</tr>
<tr>
<td>Dose</td>
<td>≤5 mg/day</td>
<td>0.25 mg/day</td>
<td>0.5 mg/day</td>
</tr>
<tr>
<td>Schedule</td>
<td>≥1 week</td>
<td>Initial: 4 days</td>
<td>Subsequent: ≥2 weeks</td>
</tr>
</tbody>
</table>

**Aripiprazole [package insert]. Otsuka Pharmaceutical; 2017.**

**Risperidone [package insert]. Janssen Pharmaceuticals; 2018.**
Aripiprazole & Risperidone Pearls

Prolactin levels
- Risperidone increased
- Aripiprazole decreased

May dose either once daily, but twice daily may decrease somnolence

Side effects: weight gain, somnolence, anticholinergic, vomiting, constipation, EPS (not akathisia)

Lowers seizure threshold

Check for dose adjustments for CYP3A4 and CYP2D6 drug interactions and genetic tests
- Fluoxetine, paroxetine, carbamazepine

Possible Risk of TdP
These drugs can cause QT prolongation **BUT** currently lack evidence for a risk of TdP when taken as recommended.
Bumetanide for core symptoms

3 recent trials

Review article:

Gamma aminobutyric acid (GABA)

Normal action
- Chief inhibitory neurotransmitter
- Normally chloride level within cell is low
- Allows chloride to enter cell
- Hyperpolarizes cell = inhibits action potential

Fetal neurons
- Chloride levels high
- GABA is a stimulatory neurotransmitter
Gamma aminobutyric acid (GABA)

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Fetal neurons
- Chloride levels high
- GABA is a stimulatory neurotransmitter
Paradoxical effects: Benzodiazepines and barbiturates in some epilepsy

Paradoxical effects: Benzos and barbiturates in some epilepsy
Immature

Adult

Pathological conditions

GABA excites

GABA inhibits

NKCC1

Na+

K+

Cl−

KCC2

High intracellular chloride

Low intracellular chloride

High intracellular chloride

ORIGINAl ARTICLE

Effects of bumetanide on neurobehavioral function in children and adolescents with autism spectrum disorders

E Lemonnier, N Villeneuve, S Sonle, S Serret, A Rosler, M Roue, P Brosset, M Viellard, D Bernoux, S Rondeau, S Thummler, D Ravel and Y Ben-Ari
Bumetanide in autism 2017

Prospective, randomized, controlled

N=88; 2-18 years

Duration: 3 months

Intervention:

◦ Bumetanide 2 mg BID (0.08 mg/kg BID if under 25kg)
◦ Bumetanide 1 mg BID (0.04 mg/kg BID if under 25kg)
◦ Bumetanide 0.5 mg BID (0.02 mg/kg BID if under 25kg)
◦ Placebo

Outcomes:

◦ Childhood Autism Rating Scale (CARS), Clinical Global Impressions Scale (CGI), Social Responsiveness Scale (SRS)

<table>
<thead>
<tr>
<th>CARS change</th>
<th>0.5 mg BID N=20</th>
<th>1 mg BID N=23</th>
<th>2 mg BID N=22</th>
<th>Placebo N=23</th>
<th>P-value Fisher’s exact</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4</td>
<td>11 (55%)</td>
<td>10 (43.5%)</td>
<td>11 (50%)</td>
<td>4 (17.4)</td>
<td>0.0125</td>
</tr>
<tr>
<td>≥6</td>
<td>10 (50%)</td>
<td>5 (21.7%)</td>
<td>8 (36.4%)</td>
<td>1 (4.3%)</td>
<td>0.0029</td>
</tr>
<tr>
<td>≥8</td>
<td>7 (35%)</td>
<td>2 (8.7%)</td>
<td>3 (13.6%)</td>
<td>1 (4.3%)</td>
<td>0.1701</td>
</tr>
</tbody>
</table>
Bumetanide 2017 results

Change in CARS scores versus baseline

Blue = treatment group
Orange = placebo group


**Bumetanide 2017 Potassium**

- ▼ = Placebo
- ▲ = 0.5 mg BID
- 🔴 = 1 mg BID
- ▲ = 2 mg BID

![Graph showing changes in potassium levels over study days for different dosages of Bumetanide.](image)
Bumetanide summary

Might improve core symptoms
Lowest dose of 0.5 mg BID was effective
Potassium levels were monitored
No seizure disorders included
Not mentioned in any guideline
Other treatment pearls

Depression/anxiety
- SSRIs have not been studied in children for depression, but poorly tolerated
- Adults: SSRIs better tolerated
- Dose slowly

Sleep disturbances
- Melatonin

ADHD/hyperactivity
- Methylphenidate
- Atomoxetine

Overall:
- Use other guideline recommendations
- Monitor closely for adverse effects, especially GI/activation

Goel R et al. Int Rev Psychiatry. 2018; 30(1);78-95.
## Treatments: Mixed, poor, or lacking evidence

<table>
<thead>
<tr>
<th>Drugs</th>
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<tbody>
<tr>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Memantine</td>
</tr>
<tr>
<td>Donepezil</td>
</tr>
<tr>
<td>SSRIs for core symptoms</td>
</tr>
<tr>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Clomipramine</td>
</tr>
<tr>
<td>Arbaclofen</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Topiramate</td>
</tr>
<tr>
<td>Oxytocin</td>
</tr>
<tr>
<td>Digestive enzymes</td>
</tr>
<tr>
<td>Sulforaphane</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
</tr>
</tbody>
</table>

Communication
Communication

Pharmacist-autism communication struggles
- Body language = rudeness
- Professional pride over communication mishaps
- Lack of training on autism
- Lack of time

Pharmacists are vital in autism
- Need medication, but higher rate of adverse effects
- Bridge the gap for primary care
- Non-psychiatric medications
- Be willing to be the expert
“Respect the way I need to communicate with you”: Healthcare experiences of adults on the autism spectrum

Christina Nicolaidis¹,²,³, Dora M Raymaker¹,³, Elesia Ashkenazy³, Katherine E McDonald³,⁴, Sebastian Dern³, Amelia EV Baggs³, Steven K Kapp³, Michael Weiner³,⁵,⁶ and W Cody Boisclair³
Factors affecting experiences with healthcare

**Autism-related**
- Verbal communication skills
  - Literalness
- Sensory sensitivities
- Body awareness

**Provider-level**
- Lack of knowledge about autism
- Attributing all symptoms/behaviors to autism
- Equating communication to IQ
- Unwillingness to communicate in writing
- Skill in incorporating supporters

**System-level**
- Organization trouble in navigating system
- Stigma about autism
- Societal issues with employment/insurance

Recommendations from study participants to healthcare providers

“Respect the way I need to communicate with you”

Dim lights

Don’t use open-ended or vague questions

Find out how your patient’s needs are unique

Advocate for your patients

Provide information
  ◦ Navigating healthcare
  ◦ Aids to help prepare for interacting with providers
  ◦ Where to find good information
  ◦ Rights in healthcare
Tools for communication

Time

Remember the diagnosis
Review: Autism Spectrum Disorder Diagnosis

Deficits in social communication interactions (3/3)

- Social-emotional reciprocity
- Non-verbal communication
- Developing, maintaining, and understanding relationships

Restricted, repetitive behavior, interests, or activities (2/4)

- Stereotyped or repetitive motor movements, use of objects, speech
- Insistence on sameness/ritualized behavior
- Restricted, fixated interests
- Hypo-hyperreactive to sensory input

Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. APA, 2013
### Tips for communication in autism

- **“Give me some space”**
- **Turn down the noise and the lights**
- **Listen for the message behind the behavior**
- **Communicate your message clearly**
- **Write or use pictures**
- **Change your approach**
- **Don’t use open-ended questions**
- **Give choices to give control**
- **Be patient**
- **Honor special interests**
Tips for communication in autism

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Tip: "Give me some space"
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- Don’t use open-ended questions
- Give choices to give control
- Be patient
- Honor special interests
Conclusion
Take home points

01
Autism diagnosis:
- Impaired social communication
- Restrictive, repetitive behavior or interests

02
Prevalence is increasing, but services are struggling to keep pace

03
Medications are effective for comorbidities, but more likely to cause side effects

04
Communication requires time and keeping the diagnosis in mind
Autism

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NMPHA SPRING 2019

https://the-art-of-autism.com/understanding-the-spectrum-a-comic-strip-explanation/