When, why, and how to think about medicines for behavior in autism spectrum disorder

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What is Autism Spectrum Disorder?

“Autism is not a disease.” – Isabelle Rapin
It is certainly not a single disease.
Outline

• What do we know about medicines in ASD?
  – Needles of Evidence
  – Haystack of Uncertainty

• When, why, and how to consider medication?
  – Balancing benefit and risk

• Real world
  – A fictionalized example
Outline

• What do we know about medicines in ASD?
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• Real world
  – A couple of (fictionalized) examples
What treatments do we know work in ASD?
Behavioral Interventions
Behavioral Interventions

• Early Intensive Behavioral / Developmental Interventions
  • Approaches based on the UCLA/Lovaas Model or Early Start Denver Model improve cognitive, language, and adaptive outcomes in certain subgroups of children.

• Other behavioral interventions
  ▪ Cognitive behavioral therapy for anxiety
  ▪ Social skills training
Example: Early Start Denver Model (ESDM)

Results:

- Mean IQ increase 17.6 pts, to 7.0 for “control” (Assess and Monitor = A/M)
- Trend toward less decline in adaptive behavior (-.8 vs -11.2)

Dawson et al., *Pediatrics*, 2010
What do we know about medications in ASD?
What two medications have had the most independent randomized, controlled trials (RCTs) in autism spectrum disorder?

Oxytocin

Secretin
Secretin

- Seven placebo-controlled studies!
- High strength of evidence for lack of benefit
- Lesson to be learned:
  - Don’t draw conclusions from uncontrolled studies.

Disclaimer: Off-label use of medication

Secretin

Bodfish et al., NEJM, 1999
Secretin

“After they were told the results, 69 percent of the parents of the children in this study said they remained interested in secretin as a treatment for their children.”

- And plenty of physicians!

Bodfish et al., *NEJM*, 1999
Overall “Placebo” Response in ASD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
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<tbody>
<tr>
<td>Amantadine</td>
<td>King et al, 2001</td>
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<td>Aripiprazole</td>
<td>Owen et al, 2009</td>
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<td>Marcus et al, 2009</td>
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<td>Atomoxetine</td>
<td>Arnold et al, 2006</td>
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<td>Divalproex</td>
<td>Hollander et al, 2009</td>
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<td>Citalopram</td>
<td>King et al, 2009</td>
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<td>Fluvoxamine</td>
<td>McDougle et al, 1996</td>
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<td>Methylphenidate</td>
<td>RUPP, 2005</td>
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<td>Olanzapine</td>
<td>Hollander et al, 2006</td>
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<td>ORG 2766</td>
<td>Buitelaar et al, 1996</td>
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<td>Risperidone</td>
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<td>Chez et al, 2000</td>
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<td>Dunn-Geier et al, 2000</td>
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<td>Sandler et al, 1999</td>
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<td>Spondheim et al, 2002</td>
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<td>Valproate</td>
<td>Hellings et al, 2005</td>
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No. of Responders to Placebo

King et al., *JAMA Peds*, 2013
What medications have the most evidence for benefit in ASD?
Mixed dopamine and serotonin receptor blockers

- “Atypical Antipsychotic Medications”
  - Aripiprazole = high strength of evidence
  - Risperidone = high strength of evidence

- FDA approved based upon ‘Irritability’ subscale of Aberrant Behavior Checklist
  - Originally ‘irritability/agitation/crying’
  - Also show significant benefit on ‘hyperactivity/defiance’ and ‘stereotyped behavior’ subscales (in children who are highly agitated)

Example: Risperidone

![Graph showing improvement over weeks for Risperidone and Placebo.](image)

RUPP, *NEJM*, 2002
Example: Risperidone
Mixed receptor blockers

- Significant side effects
  - Weight gain
  - Sedation
  - Movement disorders
Metformin for weight gain due to mixed receptor blockers

- FDA approved for type 2 (obesity-related) diabetes
- Previously shown to stop weight gain in adults taking mixed receptor blockers for other conditions
- 16-week placebo-controlled study
- No significant difference in reported side effects
  - More days with gastrointestinal side effects with metformin

Disclosure: Off-label use of medication
Metformin

$\Delta = 2.7 \text{ kg}$
$P < 0.001$

$P = 0.003$

Anagnostou et al., JAMA Psychiatry, 2016

Disclosure: Off-label use of medication
What about medications that treat attention deficit hyperactivity disorder (ADHD) symptoms in ASD?

Law of 50%
Dopamine reuptake inhibitors (stimulants)

- FDA approved for ADHD
- Largest methylphenidate trial shows less benefit, more side effects than in ADHD without ASD (RUPP, 2005)
  - 49% “much” or “very much improved” + 30% symptom reduction
  - 18% could not tolerate lowest dose due to side effects
    - Irritability prominent
Norepinephrine reuptake inhibitor: Atomoxetine part 1

- FDA approved for ADHD
  - 97 youth (6-17 year olds) with ASD + ADHD
  - Atomoxetine 1.2mg/kg vs. placebo x 8 weeks
    - Only 21% of patients rated as “very much” or “much improved”
      - 9% on placebo
    - Only 1 patient stopped atomoxetine due to side effect (fatigue)
Norepinephrine reuptake inhibitor: Atomoxetine part 2

- FDA approved for ADHD
  - 128 children (5-14 year olds) with ASD + ADHD
  - Atomoxetine up to 1.8mg/kg (split) vs. placebo +/- parent training x 10 weeks
    - 47-48% “much improved” or “very much improved” on atomoxetine
      - 19% on placebo
    - Decreased appetite
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Beyond the evidence base…

• Haystack of Uncertainty
  – Medications with some rationale behind their use:
    • Insufficient evidence of benefit: Single large + study
    • Inadequate evidence of benefit: Small + pilot study
    • Mixed evidence: Large or Pilot trials +/-
    • Evidence of absence of benefit: Large - trial
    • Absence of evidence: No placebo-controlled trials
Insufficient evidence of benefit: Single medium to large positive trial
Alpha agonist: Guanfacine

- FDA approved for ADHD
  - 62 5-14 year olds with ASD + ADHD symptoms
  - Guanfacine extended-release (ER) 1-4mg (mode=3mg) x 8 weeks
    - 50% “much improved” on guanfacine ER
      - 9.4% on placebo
    - Sedation, decreased appetite, dry mouth
Prolonged-release melatonin

- Not FDA approved, not available in USA
- Gringas et al., JAACAP, 2017
  - 3 mm Pediatric formulation PedPRM
  - 125 children (2-17 years old) with ASD or Smith-Magenis Syndrome
  - 13 weeks of 2-5 mg of prolonged-release melatonin vs. placebo
  - 51 minutes of increased sleep in melatonin group vs. 19 in placebo
- Other positive trials of short-release melatonin
  - Shorter latency, earlier wake time
Insufficient evidence of benefit: Single positive pilot trial
Sulforaphane

- Singh et al., PNAS, 2014
  - Sulforaphane-rich broccoli sprout extract (freezer)
  - 40 adolescents & adults (13-30 years old)
    - 32/40 h/o fever improvement
    - 2:1 sulforaphane vs. placebo
  - 50-150 µmol daily
- Primary outcomes
  - ABC total $p < 0.001$
  - SRS total $p = 0.017$
- No placebo response!
Other examples of medications that suggest benefit in single studies

- Haloperidol (1/2 studies)
- Valproate (1/2 studies)
- Clonidine (1/1 studies)
- Folinic acid (1/1 studies)
- Vitamin D (1/2 studies)

Disclosure: Off-label use of medication
Mixed evidence: Pilot or large trials +/-
Serotonin Reuptake Inhibitors

- Insufficient Strength of Evidence
  - Citalopram study shows no benefit in overall ratings or repetitive behaviors, slight improvement in irritability/agitation
  - Differential response to placebo in less affected children
  - Activation very common (almost half)
  - Low-dose Fluoxetine also negative
  - No studies targeting anxiety or mood in children with ASD

Disclosure: Off-label use of medication
What is Meant By ‘Activation’?

• Increased energy
• Decreased need for sleep
• Impulsivity
• Mood changes
  – Lability
  – Irritability
  – Aggression

Disclosure: Off-label use of medication
Differences in Adults?

- Fluoxetine randomized controlled trial
  - Mean age = 34 years old
  - Mean IQ = 103
- Similar data with fluvoxamine
  - Broader benefit


Disclosure: Off-label use of medication
N-acetylcysteine

- Hardan et al., *Biol Psychiatry*, 2012
  - PharmaNAC preparation
    - 900 – 2700 mg daily x 12 wks
  - 29 children (3-11 years old) with ASD
  - ABC Irritability:
    - No placebo response
- Other trials negative
  - Different formulation
Evidence for Absence of Benefit
Not all mixed receptor blockers! Lurasidone RCT (n = 150)

Disclosure: Off-label use of medication Loebel et al., JADD, 2015
Intranasal Oxytocin
Can oxytocin impact social behavior in humans?

• Intranasal delivery

Andari et al., *PNAS*, 2010
One of several pilot studies...

- 35 participants, 4-week randomized treatment

Parker et al., *PNAS*, 2017
Definitive placebo-controlled study – 290 participants x 24 wks

Sikich et al., *NEJM*, 2021
Memantine

- Memantine
  - Largest randomized controlled study conducted in ASD to date showed no separation from placebo
  - Hardan et al., *Autism*, 2019

Disclosure: Off-label use of medication
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    • Mixed evidence: Large or Pilot trials +/-
    • Evidence of absence of benefit: Large - trial
    • Absence of evidence: No placebo-controlled trials
      – MANY EXAMPLES – NOT GOING TO REVIEW TODAY
Beyond reason...

• Pile of Misplaced Hope
  – Medications with no rationale behind their use and some accompanying risk / high cost:
    • Classic example = chelation
    • Current example = umbilical cord blood infusion
  – Not going to review this category
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Many Possible Targets for Treatment in ASD

- Medical comorbidity (start here)
- Core symptoms (behavioral treatment)
- Communication (behavioral and speech treatment)
- Psychosocial stress (structure and family treatment)
- Psychiatric comorbidity
  - Pay attention to family history
The Challenge of Managing Acute Changes in Behavior
Vignette 1 – Typical phone call

- 10-year-old boy with ASD and anxiety
  - Stable for more than 1 year on aripiprazole
- Phone message from pt's mother:
  - Last night: pt punched wall, threatened to kill anyone who came near, and said, "I want to die".
    - No move to actually hurt anyone.
    - Eventually settled down and went to sleep.
  - Today: pt told a teacher, “If you keep saying that, I will punch you in the face” while shaking his fist
    - Removed from the classroom, 1:1 the rest of the week

Disclosure: Off-label use of medication
Further Questions?

• 1) Is he safe right now?
• 2) Has anything happened that might have triggered this?
Vignette 1 – further questions

• Mother on the way home to meet him
  – School put him on the bus → mother hasn’t heard anything

• Trigger
  – Pt had sprained his ankle yesterday
  – Hobbling around, wearing an ACE bandage
  – Mother had not given pain medication for fear of interaction with his current medication
Vignette 1 - response

• Pain
  – Treat with acetaminophen or ibuprofen for next two days

• Call M.D. with update
Acute Behavioral Change

• Usually can find a trigger
• But child unlikely to make the connection
• Medical
  • Pain
  • Infection
  • Seizure
  • Pharmacology
• Environmental
  • Trauma, stress, staff change
  • Family stressors/expressed emotion
Common Medical Issues in ASD

• Seizures
  – Two peaks of incidence: early childhood, adolescence

• Gastrointestinal (GI) complaints
  – Constipation → common trigger
    • Often includes stool leakage
  – Heartburn/reflux

• Tooth decay

• Allergies
  – Food allergy ↑

• Minor injuries

• Ear infections

• Headaches

Managing Non-Acute Behavioral Concerns in ASD
Frequently, the Presenting Complaint is Non-Specific: Irritability/Agitation/Aggression
Irritability and Problem Behaviors (I/PB) in Autism Spectrum Disorder: A Practice Pathway for Pediatric Primary Care

1. ASSESS FOR I/PB
   - If I/PB
     - ASSESS SAFETY*
       - If UNSAFE
         - If SAFE
           - REVIEW THE PATIENT’S HISTORY AND LEVEL OF FUNCTIONING BEFORE AND AFTER THE ONSET OF I/PB

2. PRIORITIZE AND QUALIFY SPECIFIC BEHAVIORS FOR TREATMENT

3. CONSIDER ALL POTENTIAL CONTRIBUTORS TO I/PB
   - 5a. Assess and address any CURRENT MEDICAL PROBLEMS
   - 5b. Assess and address any DIFFICULTIES USING FUNCTIONAL COMMUNICATION Consider referral to SLP
   - 5c. Assess and address any PSYCHOSOCIAL STRESSORS
   - 5d. Assess and address any MALADAPTIVE REINFORCEMENT PATTERNS Consider referral for an FBA
   - 5e. Assess and address any CO-OCCURRING PSYCHIATRIC DISORDERS Consider referral to specialist

4. CONSIDER PSYCHOPHARMACOLOGICAL INTERVENTIONS FOR I/PB

5. CONSTRUCT THE INDIVIDUALIZED TREATMENT AND SAFETY PLAN

6. IMPLEMENT AND MONITOR THE TREATMENT PLAN

7. AT 3 MONTHS DO SYMPTOMS PERSIST?
   - Yes
   - No
     - RE-EVALUATE EVERY 3 MONTHS THEREAFTER

* If acute medical concerns or threat to safety consider transfer to a higher level of care. If suspicions of abuse or neglect contact protective services.

After assessing and addressing any contributing factors -or- In the interim in the case of severe irritability and problem behavior

McGuire et al., Pediatrics, 2016
Evaluating and Treating Agitation/Aggression in ASD

• Medical/sleep work-up

• Address psychosocial stressors

• Improve communication

• Improve maladaptive reinforcement
  – Differential reinforcement of other behavior (ABA)

• Treat co-occurring disorders first (make ADHD, anxiety, mood diagnosis)

• Return to non-specific irritability/agitation last
Teaching Communication to Replace a Problem Behavior

• Identify an **appropriate communication strategy** to replace the problem behavior

• Reinforce new appropriate communication with the desired consequence
Applied Behavior Analysis: Why Do Problem Behaviors Persist?

- Problem behaviors persist because they produce a desired consequence:
  
  - The delivery of a preferred item/activity (i.e., positive reinforcement)
  - The removal of a non-preferred or aversive item/activity (i.e., negative reinforcement)
  - Sensory stimulation
    » Pleasurable consequence
    » Attenuation of painful event
Behavioral Interventions

Behavioral treatments involve:

1. Continuing to reinforce existing appropriate behavior
2. Discontinuing the consequence found to maintain the problem behavior.
3. Teaching new and appropriate ways to access the consequence that maintained the inappropriate behavior.
Parent training for Problem Behavior

- Bearss et al., *JAMA*, 2015
- 180 children (3-7 years old) with ASD + disruptive behaviors
- 24 weeks of parent training vs. parent education
  - Medium effect size = 0.45
  - Similar to Parent-Child Interaction Therapy

Treatment of Co-Occurring Psychiatric Symptoms in ASD

Important to make a diagnosis!

Most common: ADHD, anxiety disorders, OCD, depression
Evaluation Pathway for ADHD in ASD

1. Sleep or medical problems
   - Insomnia
   - Seizure disorder

2. Co-occurring psychiatric symptoms
   - Mood
   - Anxiety

3. Evaluation of setting/structure
   - Communication tools
   - Schedule
   - Predictable reinforcement

If There Isn’t a Better Explanation or Treatment for Irritability/Agitation/Aggression…
Pathway for Medication for Irritability/Agitation/Aggression

1. Guanfacine/clonididine (consider only if impulsivity is a significant component)
2. Mixed receptor antagonists
   – Risperidone, aripiprazole
3. Dopamine receptor antagonist
   – Haloperidol
4. N-acetylcysteine (Pharma-NAC)
5. Propranolol?
   – Difficult to titrate in outpatient setting
6. Divalproex/lithium/carbamazepine/oxcarb?
7. Clonazepam (be wary of disinhibition)

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“Janna”

ADHD + Aggression
“Janna”

- Janna is a 7-year-old girl with a history of ASD, ADHD symptoms, and aggression, who presents for a consultation
  - Difficulty with hyperactivity, inattention at school
  - Anxiety around change, insistence on sameness vs. desire to have own way
  - Pinches mother, leaving marks
  - Pushes other children at school
  - In clinic, observed stereotyped/repetitive phrase speech only
“Janna”

• What has been the treatment to date?
  – Communication approach = verbal only
  – Discipline approach = threat of day-long loss of privileges
  – Previous medication trials:
    • Methylphenidate (concerta): dose-limiting irritability before benefit seen
    • Citalopram: dose-limiting lability at 5mg
    • Guanfacine (Intuniv): 1mg = improved, 2mg = fainted

Disclosure: Off-label use of medication
“Janna” Next Steps

• Communication
  – Move to mixed visual/verbal, particularly when upset
    • Visual schedule
    • Picture Exchange Communication System (PECS)

• Behavioral approach/discipline
  – Short-term rewards for compliance
“Janna” Medication Options

• Guanfacine ER?
  – Switched to bedtime
  – Over time, able to increase to 2 mg at night, while monitoring blood pressure carefully

• Atomoxetine?
  – May also benefit anxiety?
“Janna” Medication Options

• Mixed receptor blocker?
  – Why?
    • Likely to help with irritability/aggression/compliance/flexibility/hyperactivity
  – Why not?
    • Weight gain and metabolic risk
    • Risk of movement disorders, including tardive dyskinesia
    • Communication and behavioral supports not optimized
Core Questions for Mixed Receptor Blockers:

• Is someone getting hurt or likely to get hurt?
  – Aggression
  – Self-injury
  – Extreme impulsivity (elopement, car behavior, street behavior)

• Is child likely to lose access to educational or other setting without medication?

• Has everything else failed?
Summary

- Evidence supports mixed receptor blockers and parent training for irritability/agitation
- Evidence supports treatment of ADHD in ASD
- Think about medical, other triggers first
- Optimize communication, behavior supports second
- Real world medication management targets co-occurring disorders first, then non-specific irritability/agitation.
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