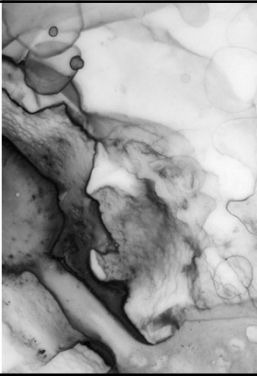


**MEDICATION MANAGEMENT IN PERSONS WITH AUTISM SPECTRUM DISORDERS**

Elizabeth Reeve MD



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**Medications**



- There is no "medication for autism"
- Only two medications, aripiprazole and risperidone, have FDA approval for the use in persons with autism to treat the associated symptoms of aggression

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**Preliminary Thoughts**

- Resources for persons with ASD, and other disabilities, have been significantly reduced post COVID
  - Closing of adult day programs
  - Lack of group home placement options
  - Lack of employees for group homes, schools, and to work as PCA's
- This lack of services has stressed families emotionally and financially
- Families/institutions increase their dependence on medications to manage behaviors when other resources are not available
- Expectations for what medications can do are often unrealistic

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**Disclosure**

I have no financial interests to disclose

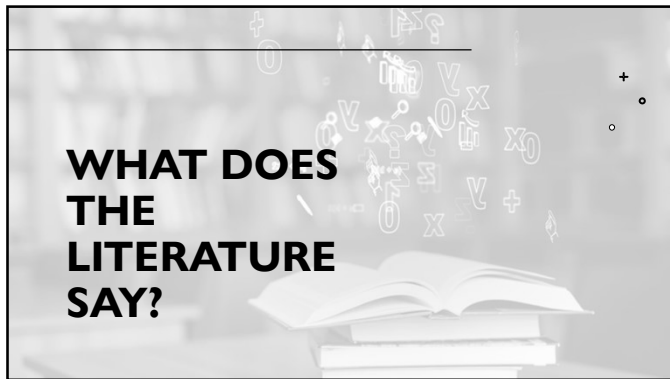
I *will* be discussing non-FDA approved uses of medications related to the treatment of symptoms in persons with autism

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**Epidemiology**

- Literature suggest comorbidity with mental health issues is the norm for persons with ASD, likely 70-75%
  - ADHD, mood and anxiety issues are the most common
  - More than 50% of persons with ASD are on at least one psychotropic medication and 20% are on three or more
- Medication choices to treat comorbidities are the same in the ASD population as they are in neurotypical persons

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## Fluoxetine

- SOFIA Study
- 158 children (5-17 years) with ASD randomized to fluoxetine or placebo for 14 weeks
- No significant between-group differences  
High rates of behavioral activation

Herscu et al, 2020, Journal of Autism and dev disorders

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## Sertraline

Low dose sertraline has improved language skills and passive eye tracking in young kids with Fragile X Syndrome who have comorbid ASD

These findings did not hold up in ASD kids without Fragile X


Hess et al, JDBP 2016;37(8)

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## Placebo Controlled Trail of Fluoxetine on the Repetitive Behaviors in ASD

- Hollander et al, Neuropsychopharmacology, 2005
  - 45 subjects, kids and adolescents
  - Two 8-week crossover periods
  - Low dose, 9.9 mg mean
  - Superior to placebo as measured on the CYBOCS
  - No differentiation using the CGI

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## Citalopram

- 159 children (5-17 years) with ASD randomized to citalopram (mean doses: 16.5 mg per day) or placebo for 12 weeks
- No differences on Clinical Global Impression, Improvement subscale or CY-BOCS-PDD Compulsion subscale
- Adverse events: high rates of increased energy (38%), anger/irritability (25%), aggression (23%) on citalopram

King et al, Archives of General Psychiatry, 2009

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## Buspirone

McDougle et al; Neuropsychopharmacology 2022

10-week placebo controlled double blind study, N=30, age 5-17, all had ASD diagnosis

Statistically significant decrease in anxiety

Dose range 7.5-45 mg



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## Mirtazapine for Anxiety with ASD

- 10-week randomized, double-blind, placebo-controlled trial 30 children with ASD (5-17 years)
- Treated with mirtazapine or placebo
- Primary outcome measures: Pediatric Anxiety Rating Scale (PARS) and CGI-I Mirtazapine resulted in significant within-group decrease
- No statistically significant differences in mean 10-week change between mirtazapine and placebo in anxiety

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## Non-stimulants

Small studies have shown benefit for both guanfacine and clonidine

- Improvement in hyperactivity and impulsiveness

Atomoxetine has been shown to be superior to placebo

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## Methylphenidate

- Four crossover trials with MPH in kids with ASD, total 113 subjects aged 5-13
- Low quality evidence that MPH may improve hyperactivity and inattention
  - In one of the studies 50% had improvement on hyperactivity scales

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## Memantine

NMDA receptor antagonist

- Blocks glutamate

Cochrane review August 2022

- 3 RTC's, 204 subjects, mean age of 9.4 years, 73%-87% male
- No clear evidence of difference between memantine and placebo

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## Stimulant Medication Treatment of Target Behaviors in Children with Autism

- J of Dev Behav Ped, April, 2008
  - 124 subjects 0-21 years old in Olmstead county MN 1976-1997
  - 52.4% had used stimulants, mean use 4 years
  - 398 episodes of use
    - 69.4 % had a favorable response

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## Baclofen/R-Baclofen

- GABA-B receptor agonist
- Mahdavinab et al; European Child/Adol Psych 2019, Dec
  - Baclofen as an adjuvant therapy for autism
    - 62 3-12 years old, all on Risperdal
    - Improvement on subscales of hyperactivity
- R-Baclofen
  - Evidence in autism mouse models of reversed social deficits and decreased repetitive behaviors
  - Human studies with 16p11.2 deletions have been positive

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## Oxytocin


- SOARS trial
  - Study of oxytocin in autism spectrum disorders
- Early studies with intranasal oxytocin showed promise in improving social skills
- Overall results are equivocal and mixed with no consistent findings



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## Inositol

- Mixed results in children with autism
  - Dose up to 200 mg/kg/day
- Better results for OCD
- Most common side effects are GI effects, usually diarrhea



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## Others

Bumetanide	Metformin	CBD	THC
<ul style="list-style-type: none"> <li>• Ambivalent and limited data, no consistent findings</li> </ul>	<ul style="list-style-type: none"> <li>• Potential language improvement in studies using metformin for overeating in Prader-Willi</li> <li>• More studies now happening</li> </ul>	<ul style="list-style-type: none"> <li>• Initial studies show benefit in social skills and communication</li> </ul>	<ul style="list-style-type: none"> <li>• Initial studies show benefit</li> </ul>

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## N-Acetyl cysteine

- Studies suggest a decrease in irritability, obsessiveness and repetitive behaviors
- 600 mg bid to 900 mg tid
- GI side effects, nausea, diarrhea, constipation

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## THC/CBD

- 12-week randomized double-blind, placebo-controlled trial
- 150 individuals (5-21 years) with ASD randomized to pure CBD, whole plant cannabis extract (including THC), or placebo followed by single-crossover
- Response criteria: “very much improved” or “much improved” on the Clinical Global Impression-Improvement score
  - 49% whole plant, 38% CBD, 21% placebo

Aran et al, Molecular Autism 2021

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## Beta Blockers

- May 2014 Meeting for Autism research in Atlanta Georgia
  - Double blind placebo-controlled trial with 20 patients
  - Scored higher than controls on a measure of social competence after a single dose of 40 mg propranolol
  - Ages 15-31, IQ above 85
  - No relationship between self reported anxiety and social benefit




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## Melatonin

- 125 youth (2-17.5 years) with ASD randomized to prolonged-release melatonin or placebo for 13 weeks
- 69% melatonin vs. 39% placebo responders (p=0.001)
  - (Gringas et al JAACAP 2017)
- 2-year open-label extension study demonstrated long-term safety and efficacy (Malow et al. JAACAP 2021)

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## Medications

	<b>Hyperactivity and impulsivity</b>	Stimulants Alpha adrenergic agents Atomoxetine
	<b>Obsessive/repetitive/anxious</b>	SSRIs/SNRI's Buspirone
	<b>Aggressive</b>	Antipsychotics, alpha adrenergic agents, mood stabilizers

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## Choosing a Medication

- There is no medication that is contraindicated based on the diagnosis of autism
- Common reasons for starting medications include difficulties with:
  - Sleep, hyperactivity and impulsivity, obsessiveness/rigidity and anxiety, aggression, self-injurious behaviors

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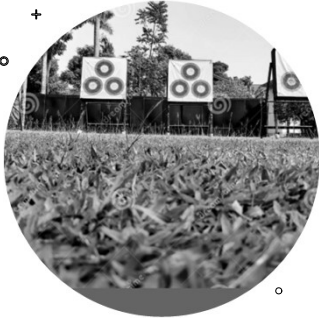
## ADHD and ASD

- Symptoms of ADHD affect 75% of persons with ASD
  - About 50% have inattention
  - About 50% have hyperactivity



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## Choose Your Target



- Hyperactivity/Impulsivity
- Anxiety/Obsessiveness
- Aggression
- Self injurious behavior
- Sleep

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## Hyperactivity/Impulsivity

- Do they need meds 24 hours a day?
  - Children with ASD may be more susceptible to the rebound irritability of stimulants
  - Appetite suppression with stimulants may be hard to manage in persons who are already picky eaters
- Is there comorbid anxiety?
  - Stimulants may worsen anxiety
- Can they swallow pills?
  - Are there oral texture issues

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Hyperactivity/Impulsivity

<b>Stimulants</b> <ul style="list-style-type: none"> <li>• Methylphenidate</li> <li>• Mixed amphetamine salts</li> <li>• Dexedrine</li> </ul>
<b>Nonstimulants</b> <ul style="list-style-type: none"> <li>• Alpha adrenergic             <ul style="list-style-type: none"> <li>• Clonidine and guanfacine</li> </ul> </li> <li>• Atomoxetine</li> </ul>

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## Antipsychotics

- Aripiprazole for ASD
  - Cochrane data base, May 2012
  - 2 studies, 316 children, 8 weeks
  - Less irritability, less hyperactivity, and decreased stereotypies
  - Side effects of weight gain, drooling, sedation and tremor



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## Anxiety/Obsessiveness

- SSRI's/SNRI's
- Buspar
- Remeron
- Benzodiazepines
  - Limited indications
- Inositol
- Atypical antipsychotics



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## BMI Change in ASD: Comparison of Risperidone and Aripiprazole

- 142 subjects age 2-20
- Started on meds for irritability
- Significant increase in BMI over one year's time for both groups
  - No difference between groups

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## Aggression/Agitation

- Atypical antipsychotics
  - Risperidone and Aripiprazole have FDA approval
- Anti-seizure medications
  - Divalproex, carbamazepine, topiramate
- Alpha adrenergics
- Beta blockers

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## Managing Increased Appetite

- Increased appetite may result in worsening behavior due to drive to eat that cannot be redirected
- Consider options for managing increased appetite
  - Anagnostou et al. JAMA psychiatry 2016
    - Metformin 500 mg bid was superior to placebo in reducing antipsychotic weight gain in kids/adolescents with ASD
  - Canitano; Brain and Dev, April 2005
    - Small open label trial with Topamax in ASD, 6 subjects, 3 dropped out due to agitation and irritability. Too small to assess benefit for weight loss
    - Studies in non ASD populations show benefit but side effects high


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# Sleep

- Antidepressants
  - Trazodone, mirtazapine, doxepin, tricyclics
- Alpha adrenergics
  - Clonidine, guanfacine
- Antipsychotics
  - Quetiapine
- Other
  - Melatonin

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# More Things to Consider

- How can you assess side effects in a nonverbal patient?
- Are the side effects making behavior worse?
  - Akathisia
  - Increased appetite
- How will you manage blood draws if needed?
- Is there a problem with administering the medication?

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# ?

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