

The Role of Psychopharmacology in Autism Spectrum Disorder

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Disclosures of Potential Conflict – 5 Years

I have received research funding from Astellas Therapeutics

I have received consultation compensation from Ionis Therapeutics, Sage Therapeutics and the Angelman foundation

No medication will be discussed today that has relation to my sources of conflict

Off-Label Use Of Medication



In this presentation, all discussion of use of medication refers to **“off-label”** use other than risperidone and aripiprazole for irritability in children and adolescents with autistic disorder.



COMMON TREATMENT TARGETS IN ASD

1. Motor hyperactivity and inattention
2. Repetitive behavior
3. Depression and Anxiety
4. Irritability (aggression, self-injury, severe tantrums)



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Methylphenidate for ADHD in ASD

- 72 subjects (age, 5–14 y)
 - Full range of ASD with co-occurring ADHD
- Study design
 - 7-day test-dose period
 - 4-week double-blind trial of 3 dose levels (0.125, 0.25, 0.50 mg/kg/day) of MPH TID and placebo in random order
- Outcome Measures
 - Aberrant Behavioral Checklist (ABC) – Hyperactivity

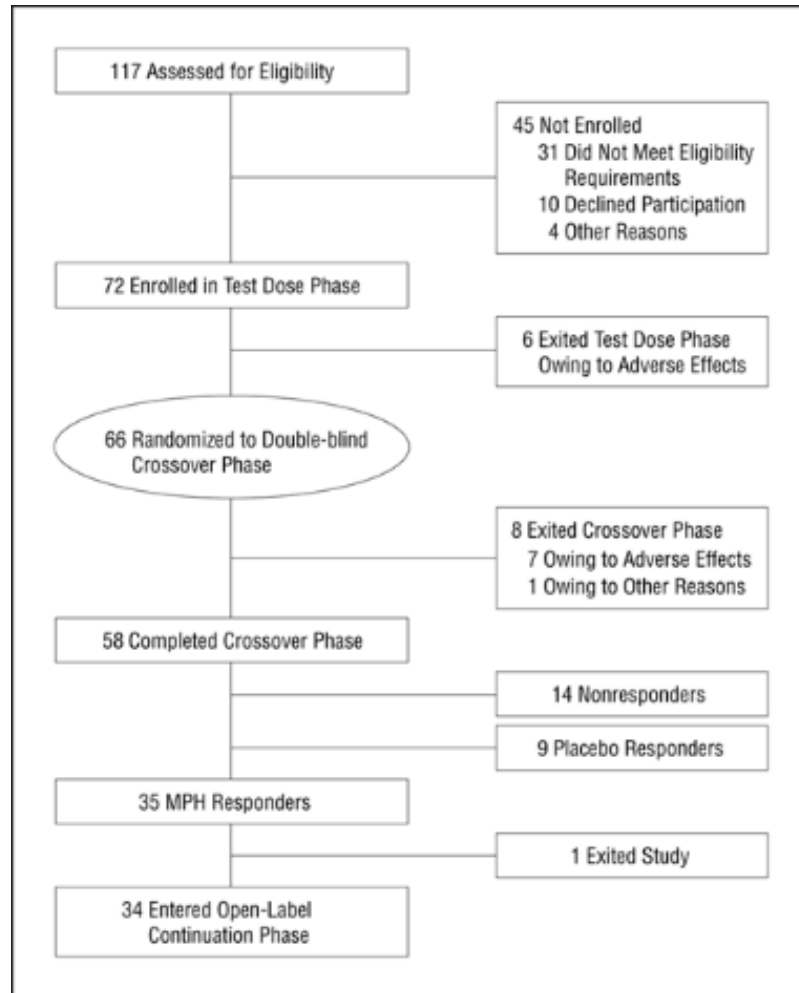
ASD = autism spectrum disorder.

PDD NOS = pervasive developmental disorder not otherwise specified.

ADHD = attention deficit/hyperactivity disorder.

RUPP Autism Network. *Arch Gen Psychiatry* 2005; 62:1266-1274.

Methylphenidate for ADHD in ASD



- MPH > placebo
 - Teachers (P=.009)
 - Parents (P<.001)
- 44 Subjects were responders
 - MPH (n=35)
 - Placebo (n=9)
- Tolerability
 - 18% dropped out
 - Dose dependent risk of social withdrawal
 - Better tolerability with long-acting MPH (Kim et al., 2017)

Atomoxetine for ADHD in ASD



- 8-week study – Double blind, placebo
- 97 subjects (age range: 6-17 yrs; mean 9 -10 yrs) ($IQ \geq 60$)
- 3-week titration (0.5 mg/kg/day; 0.8 mg/kg/day; 1.2 mg/kg/day)
- Outcome measures
 - ADHD-Rating Scale
 - Clinician Global Impression - Improvement

ATX = Atomoxetine.

Harfterkamp et al. *J Am Acad Child Adolesc Psychiatry* 51:733-741, 2012.

Atomoxetine for ADHD in ASD

Primary Outcome Measure	ATX = 48	PLA = 49	p Value
ADHD-RS (Total)	40.7 31.6	38.6 38.3	< .001
ADHD-RS (Inattention)	20.7 17.2	20.6 19.9	.003
ADHD-RS (Hyperactivity)	20.0 14.5	17.9 18.4	< .001

Magnitude of effect (ADHD-RS) in ASD (8.2), in ADHD (13 to 19)
Nausea, decreased appetite and fatigue

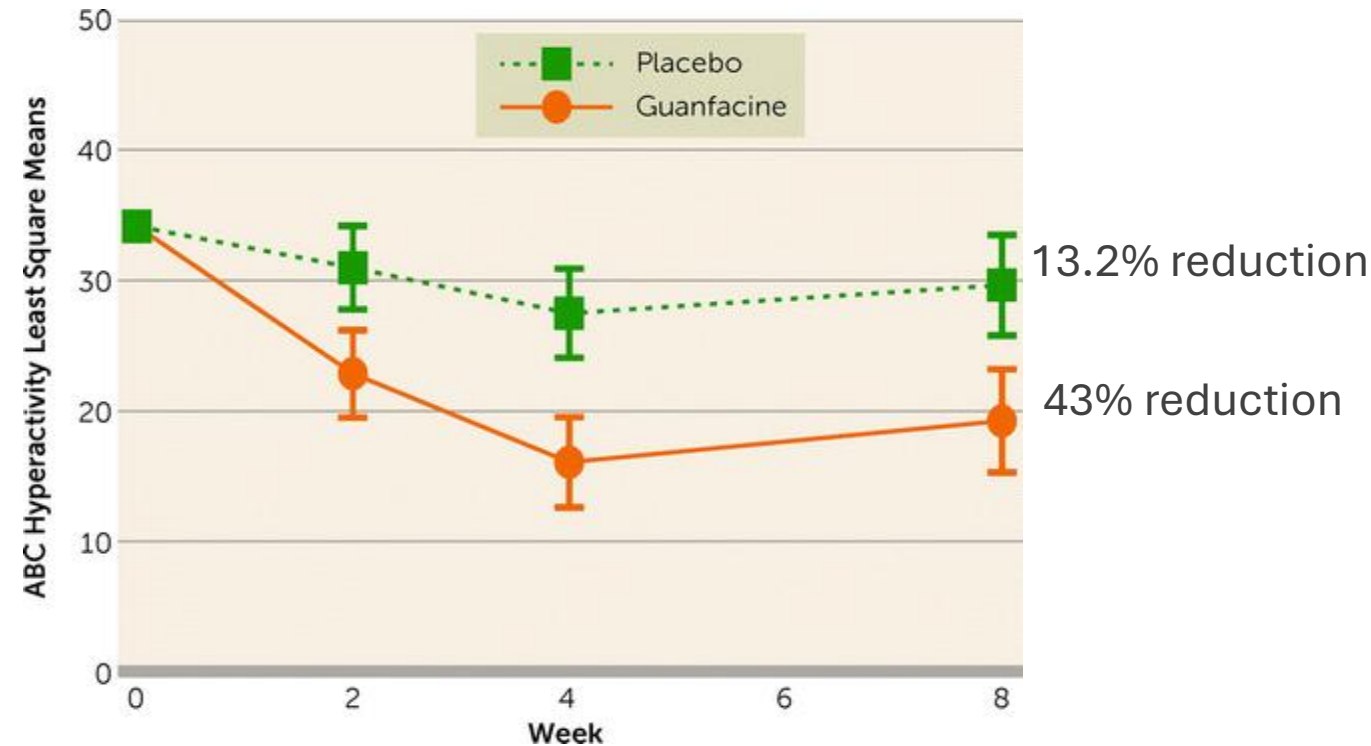


Extended Release Guanfacine for ADHD in ASD

- 8-week study – Double Blind, Placebo
- 62 subjects, age range 5-14 years, 21 subjects with IQ >70
- Modal dose of ER Guanfacine was 3 mg/day (range 1-4 mg/day)
- Outcome Measures
 - ABC – hyperactivity
 - CGI – improvement

Scahill et al. *American Journal of Psychiatry* May, 2015.

ER Guanfacine for ADHD in ASD



- 50% positive response on CGI-I as compared to 9.4% for placebo
- Drowsiness, fatigue, emotional fragility, irritability
- Blood pressure and pulse rates decreased with BP returning to pretreatment



Motor Hyperactivity and Inattention

CLINICAL APPROACH

- Guanfacine, Clonidine (regular or ER)
- Methylphenidate, Amphetamine
 - Jornay PM – methylphenidate 8-10 hour delay in onset, then 8-10 extended release
- Atomoxetine
- “New” non-stimulants
 - Viloxazine – Norepinephrine reuptake inhibitor
 - Clonidine Extended Release – oral suspension (Onyda XR)



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Repetitive Behaviors are Common in ASD

Stereotyped play

Stereotyped movements

Restricted interests

Insistence on sameness



Serotonergic Drugs in ASD

Children

- Fluoxetine¹ (158 kids)
 - No better than placebo
- Citalopram² (149 kids)
 - No better than placebo
- Fluoxetine³ (146 kids)
 - Equivocal results with no improvement on CGI-I

16.7-23.5 % Discontinuation
rates in trials

¹Herscu et al. 2020

²King et al. 2009

³Reddihough et al. 2019

Adults

- Fluvoxamine⁴
 - Better than placebo
- Fluoxetine⁵
 - Better than placebo
- Sertraline⁶
 - Open label - improvement
- Clomipramine⁷
 - Better than placebo

⁴McDougle et al. 1996

⁵Hollander et al. 2012

⁶McDougle et al. 1998.

⁷Gordon et al. 1993

Zhou et al., 2021 for review



Repetitive Behavior

CLINICAL APPROACH

- Maximize Behavioral Therapies
- Assessment of treatment of psychiatric comorbidities
 - Hyperactivity, irritability, insomnia
- In adults: SSRI vs clomipramine

SSRI: Selective Serotonin Reuptake Inhibitor

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Mood Disorders - Depression



There are no published double blind placebo controlled trials of medication for treating depression in autism.

SSRI's and Side Effects in ASD

- SSRI's:
 - Watch for increased energy level/ impulsiveness, hyperactivity, insomnia, and irritability¹
 - Black Box Warning in Children and Young Adults
- Bupropion/Clomipramine
 - Use with caution in patients with seizure disorders
- Mirtazapine
 - Recent small pilot trial of treatment of anxiety in children with autism²
 - Good tolerability but 50% rates of weight gain
 - Failure to separate from placebo in a small trial

¹King BH et al. *Arch Gen Psychiatry*. 2009; 66(6):583-590.

²McDougle et al. *Neuropsychopharmacology*. 2022 47(6):1263-1270.

Prospective, Open-Label Trial of Buspirone in Children and Adolescents with ASD



- 8-week study
- 22 subjects, age range = 6-16 yrs, majority inpatients, majority with PDD
- Mean dose 29.3 mg/day (range 15-45 mg/day)
- Marked response (9 subj), Moderate response (7 subj)
- Adverse event: initial sedation = 2, slight agitation = 2, initial nausea = 1, mouth movements (reversible) = 1

Buitelaar et al. *J Clin Psychiatry* 59:56-59, 1998.

Mood/Anxiety Disorders



CLINICAL APPROACH

DEPRESSION

- Psychopharmacological treatment as usual

ANXIETY

- Mirtazapine and buspirone may carry lower risk for behavioral side effects than SSRI's but efficacy evidence remains preliminary
- Guanfacine or Clonidine commonly tried in practice though minimal research



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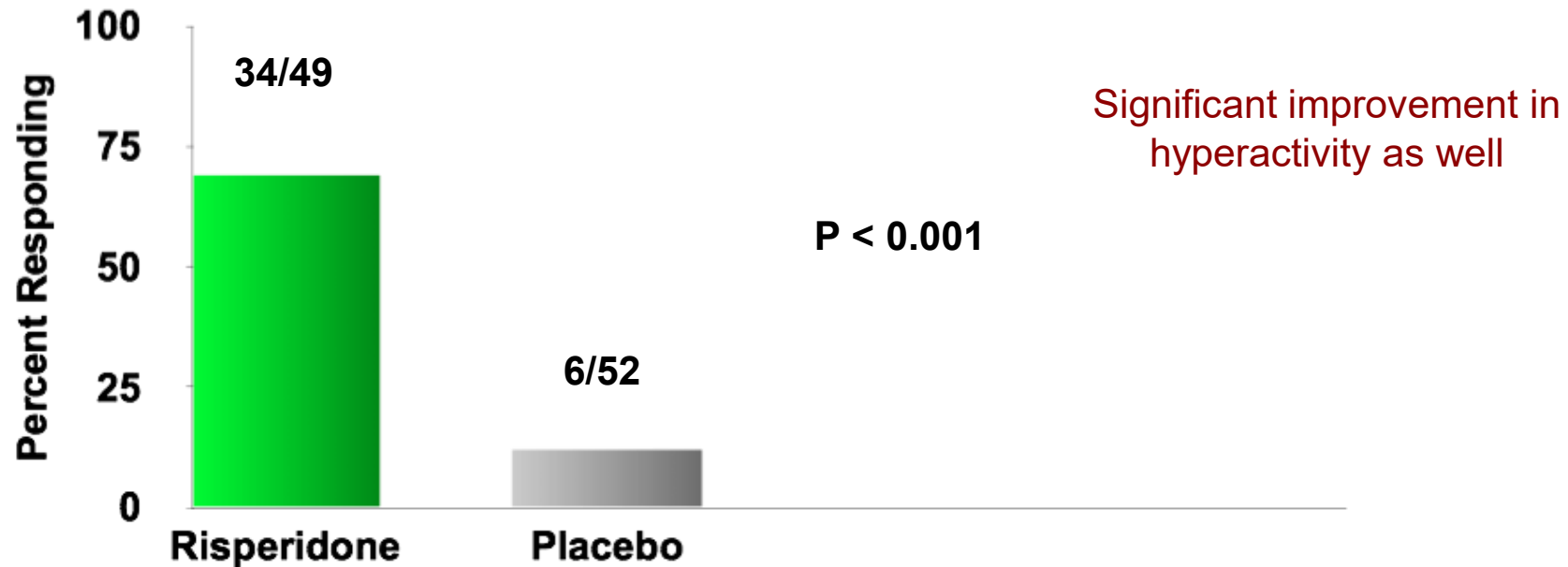
Risperidone for Irritability in ASD

- 82 boys/19 girls, mean age 8.8 ± 2.7 y
- Autistic disorder with significant irritability
- 8 weeks, double-blind, placebo
- Mean dose = 1.8 ± 0.7 mg/day; range = 0.5–3.5 mg/day
- Outcome Measures (“responder” criteria)
 - ABC – irritability (≥ 25 % reduction score)
 - CGI – improvement (1 or 2 on CGI-I)

ABC = Aberrant Behavior Checklist.

RUPP Autism Network. *N Engl J Med*. 2002;347:314-321.

Risperidone for Irritability in ASD



Mean increase in weight

- Risperidone, 2.7 ± 2.9 kg
- Placebo, 0.8 ± 2.2 kg; $P < 0.001$

Side effects more common in risperidone group:

- Increased appetite, Fatigue/drowsiness, Dizziness, Drooling

Other Mood Stabilizers

- Aripiprazole¹: 98 subject, double blind, placebo 8 week, 6-17 y/o
 - Mean dose (8.5 mg) better than placebo (ABC- irritability, P <0.001)
 - Side effects: Fatigue, somnolence and weight gain (mean: 2.1 kg)
 - BAART Trial²: Head to head risperidone vs aripiprazole
 - Risperidone > aripiprazole on ABC – irritability
 - By 3 months no meaningful difference in weight gain (aripiprazole: 4.36 vs risperidone: 5.55 kg)
- Haloperidol^{3,4}: Several double blind, placebo-controlled trials
 - Strong evidence for efficacy in irritability and aggression
 - High rates of dystonia and dyskinesia
- Divalproex sodium (Valproate): Mixed results on placebo trials
 - 30 subjects (mean age 11 y/o) showed no difference in aggression⁵
 - 55 subjects (mean age 9.5 y/o) showed improvement in irritability⁶

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¹Owen et al. Pediatrics. 2009;124:1533-1540.

²DeVane et al. Pharmacotherapy 2019 Jun;39(6):626-635.

³Anderson LT et al. *Am J Psychiatry*. 1984;141:1195-1202.

⁴Campbell M et al. *J Am Acad Child Adolesc Psychiatry*. 1997;36:835-843.

⁵Hellings et al. J Child Adolescent Psychopharmacology. 2005; 15(4) 682-692.

⁶Hollander et al. Neuropsychopharmacology. 2010; 35(4):990-998.

Metformin for Overweight

- 16 week DB/PC multi-site, 60 subjects (6-17 y/o) with weight gain from atypicals
- Subjects: Stable on atypical 1 month w $>7\%$ increase in BMI
- Dosing: 500 mg BID (6-9y), 850 BID (10-17y)
- Primary outcome:
 - 1) safety/tolerability
 - 2) Change in BMI from baseline (z scores)

Anagnostou et al. JAMA Psychiatry 2016;73(9):928-937



Results: Metformin for Overweight

- BMI z score reduced by 0.10 compared to placebo
 - Placebo: Mean weight(kg)/BMI gain: 2.8/0.52
 - Metformin: Mean weight(kg)/BMI gain: 0.07/-0.43
 - 11% had 8-9% BMI decrease
 - Change not apparent until after 8 weeks
- Tolerability: Good
 - Metformin group: more days of GI complaints
 - One severe AE in metformin group: agitation

Alternative Weight Modulation Options

- Topiramate:
 - Case reports of reduced appetite when added to antipsychotic medications^{1,2}
- Samidorphan + olanzapine:
 - Found to mitigate odds of clinically significant weight gain as compared to olanzapine alone in populations with schizophrenia³
- Semaglutide (GLP-1 Receptor agonist):
 - Large double blinded placebo controlled trials in patients on antipsychotics with schizophrenia showed reversal of evolving metabolic syndrome⁴
 - Studies in autism likely to come in the future

¹Crowley et al. J Child Adolesc Psychopharmacol. 2015; 25(2):183-5.

²Mazzone & Ruta Brain Dev. 2006; 28(10):668.

³Jawad et al. J Affect Disorder. 2022; 301:99-106. for review

⁴Gasneshalingam et al. JAMA Psychiatry. 2025; 82(11):1065-1074.

Other Mood Stabilizers

- Ziprasidone¹: 12 subject, open label, 6 week, 8-20 y/o
 - 75% response, range 20-160 mg, no weight gain
- Olanzapine²: 11 subject, DB/PC, 8 week, 9 y/o
 - Response: 3/6 (1/5 for placebo), 7.5 ± 4.8 lbs gain, 10 mg mean dose
- Quetiapine³: 4 open label studies with mixed results
- Paliperidone⁴: 25 subject, open label, 8 week, 12-21 y/o
 - 83% response, mean dose 7.1, mean weight gain 5 lbs, sedation
- Negative Trials: Lurasidone⁵ and brexpiprazole⁶ and pimavanserin⁷
- Clozapine⁸: Multiple case reports and case series showing improvement in “disruptive behavior”

¹Malone et al. J Child Adolesc Psychopharmacol. 2007;17:779-790

²Hollander E et al. J Child Adolesc Psychopharmacol. 2006;16(5):541-548.

³Hardan & Handen 2005 for review

⁴Stigler et al. Psychopharmacology. 2012; 223(2):237-245.

⁵Loebel et al. J Autism Dev Disord. 2016;46(4):1153-63.

⁶Ward et al. J Child Adolesc Psychopharmacol. 2025;35(4):194-201.

⁷Bugarski-Kirola et al. JACAP 2026

⁸Teixeria da Rosa et al. J Psychopharmacol. 2024;38(4):324-343 for review

Clozapine in Catatonia



- Retrospective case series:
 - 12 subjects (7-37 years, mean 19.6 years) with ASD + catatonia (11 failed lorazepam taper)
 - 11 “responders:” CGI-I of “much improved” or “very much improved”
 - Mean dose of 381.3 mg/day (mean clozapine level of 406.5 ng/mL)
 - Most common side effects:
 - Sedation (11/12)
 - Weight gain (6/12)
 - Constipation (4/12)
 - Enuresis (4/12)
 - Sialorrhea (4/12)

Thom et al. Expert Review of Clinical Pharmacology. 2023

Irritability

CLINICAL APPROACH

- Ziprasidone, Risperidone, Aripiprazole
- Depakote, Carbamazepine, Oxcarbazepine, Topiramate, Lithium
- Quetiapine, Olanzapine, Paliperidone, Haloperidol
- Adjunctive:
 - Beta-blocker (London et al. 2020)
 - Benzodiazepine, Alpha-agonist

Medications Studied for Social Impairment in Autism (2026)

- Negative Studies

- Secretin
- Naltrexone
- Lamotrigine
- Amantadine
- Risperidone
- Fluoxetine
- Citalopram
- D-Cycloserine
- Oxytocin¹
- Cannabidiol²
- Zolmitriptan

- Under Investigation

- Vasopressin
- Balovaptan
- Leucovorin (Folic Acid)
- Fecal Microbiota Transplant (FMT)
- Sulphoraphane
- Bumetanide (repetitive behaviors specifically)

¹Yamasue et al. Mol Psychiatry. 2020 Aug;25(8):1849-1858

²<https://clinicaltrials.gov/study/NCT04745026?cond=autism&intr=Cannabidiol&rank=5>

The Lurie Center

Mission

Our goal is to advance knowledge of autism spectrum and related disorders and to rapidly translate discovery into exceptional care over a lifetime.

Multidisciplinary clinic for children and adults with autism and developmental disabilities

What disciplines?

Where?

