MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Psychopharmacology of Autism Spectrum Disorder

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Disclosures

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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.

Lecture Objective

1. Describe the target symptoms associated with autism spectrum disorder (ASD) that may be responsive to pharmacotherapy.

2. Identify which medications are most effective at treating which type of target symptoms associated with ASD.

3. Define the potential side effects associated with medications used to treat target symptoms associated with ASD.

TARGET SYMPTOM DOMAINS

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Sleep disturbance
5. Mood disorders
6. Anxiety disorders
7. Social/language impairment

TARGET SYMPTOM DOMAINS

1. **Motor hyperactivity and inattention**
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Sleep disturbance
5. Mood disorders
6. Anxiety disorders
7. Social/language impairment

MEDICATIONS FOR HYPERACTIVITY AND INATTENTION IN ASD

- Psychostimulants
- Atomoxetine
- Alpha-2 Agonists

PSYCHOSTIMULANTS IN ASD
- *METHYLPHENIDATE*

TEST-DOSE PHASE - MPH

- 6 out of 72 subjects were unable to tolerate ≥ 2 dose levels of MPH and were dropped from the study
- 16 out of the remaining 66 subjects had intolerable adverse events at the highest dose of MPH; entered modified crossover phase
- Irritability was the most common reason for intolerability

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

CROSS-OVER PHASE – MPH

- 58/66 subjects completed the crossover phase
- 7 subjects dropped out due to intolerable adverse events
- There was a statistically significant main effect of dose of MPH on the ABC Hyperactivity subscale score as rated by both teacher (Primary Outcome Measure; P =.009) and parent (P <.001)

ABC = Aberrant Behavior Checklist.

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

CATEGORICAL RESPONSE - MPH

- 44 subjects were rated as responders to at least 1 week of treatment (MPH or placebo)
- MPH (n = 35), Placebo (n=9)
- Subject age, IQ, *diagnosis (trend, P =.07), and weight did not moderate treatment response
- *Subjects diagnosed with Asperger's disorder and PDD NOS were more likely to be classified as responders to both placebo and MPH than those with autistic disorder

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

CATEGORICAL RESPONSE MPH

	Placebo	Low	Medium	High
Asperger's disorder/ PDD NOS (n=19)	6 (32%)	7 (37%)	7 (37%)	6 (32%)
Autistic disorder (n=47)	6 (13%)	13 (28%)	15 (32%)	12 (26%)

Response to each dose of MPH was superior to placebo for autistic disorder subgroup ($P < .001$), but not for the Asperger's disorder/PDD NOS subgroup ($P > .05$)

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

MPH Summary

- 35/72 subjects (49%) responded to MPH
- 13/72 (18%) exposed to MPH dropped out due to adverse events

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

Atomoxetine in ASD

DB, PC TRIAL OF ATX FOR ADHD SYMPTOMS IN CHILDREN WITH ASD

- 8-week study
- 97 subjects (age range: 6-17 yrs; mean 9 -10 yrs) (IQ > 60)
- 3-week titration (0.5 mg/kg/day; 0.8 mg/kg/day; 1.2 mg/kg/day)
- Primary outcome measure – ADHD-RS

ATX = Atomoxetine.

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

DB, PC TRIAL OF ATX FOR ADHD SYMPTOMS IN CHILDREN WITH 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

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

DB, PC TRIAL OF ATX FOR ADHD SYMPTOMS IN CHILDREN WITH ASD

CGI-I (ADHD) p Value 0.14	ATX = 48	PLA = 49
Very Much Improved	0	1
Much Improved	9	3
Minimally Improved	12	6
No Change	16	30
Minimally Worse	4	3
Much Worse	2	3
Very Much Worse	0	0

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

DB, PC TRIAL OF ATX FOR ADHD SYMPTOMS IN CHILDREN WITH ASD

Adverse Events	ATX = 48	PLA = 49	p Value
Nausea	14	4	.009
Decreased Appetite	13	3	.006
Early Morning Awakening	5	0	.027

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

DB, PC TRIAL OF ATX FOR ADHD SYMPTOMS IN CHILDREN WITH ASD

- Summary
- Effects on Hyperactivity > Inattention in ASD
- Effects on Hyperactivity = Inattention in ADHD
- Magnitude of effect (ADHD-RS) in ASD (8.2), in ADHD (13 to 19)
- Concerns
- Duration of Study
- Starting dose (0.5 mg/kg/day) and rate of upward titration

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

Alpha-2 Agonists in ASD

STUDY OF EXTENDED-RELEASE GUANFACINE (XR-G) IN CHILDREN WITH ASD + HYPERACTIVITY

- 62 Children (age, 5-14 y) with ASD and significant ADHD symptoms (ABC Hyperactivity subscale score > 24)
- Study design
  - 8-week, randomized, db, pc, fixed-flexible dose, clinical trial

ASD = Autism Spectrum Disorder
ADHD = Attention-Deficit/Hyperactivity Disorder
Scahill et al. Am J Psychiatry 172(12):1197-1206, 2015.

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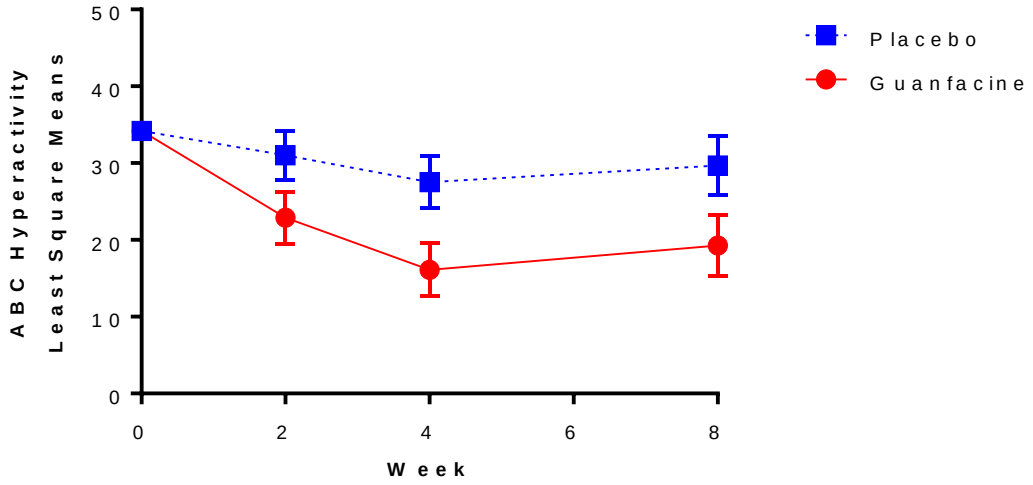
STUDY OF EXTENDED-RELEASE GUANFACINE (XR-G) IN CHILDREN WITH ASD + HYPERACTIVITY

- XR-G Group (n = 30):
  - 43.6% decline in ABC-H subscale score – 34.2 to 19.3
- Placebo Group (n = 32):
  - 13.2% decline in ABC-H subscale score – 34.2 to 29.7 ($P < 0.0001$; effect size = 1.67)

Scahill et al. Am J Psychiatry 172(12):1197-1206, 2015.

STUDY OF EXTENDED-RELEASE GUANFACINE (XR-G) IN CHILDREN WITH ASD + HYPERACTIVITY



Least squares means on Aberrant Behavior Checklist-Hyperactivity subscale scores for XR-guanfacine and placebo groups during the eight-week trial. Higher scores reflect greater hyperactivity.

Scahill et al. Am J Psychiatry 172(12):1197-1206, 2015.

STUDY OF EXTENDED-RELEASE GUANFACINE (XR-G) IN CHILDREN WITH ASD + HYPERACTIVITY

- Rate of Positive Response
  - XR-G Group: 15/30 = 50%
  - Placebo Group: 3/32 = 9.4%
  - (P = 0.001)
- Modal dose for XR-G = 3 mg/day for drug and placebo groups.

Scahill et al. Am J Psychiatry 172(12):1197-1206, 2015.

STUDY OF EXTENDED-RELEASE GUANFACINE (XR-G) IN CHILDREN WITH ASD + HYPERACTIVITY

- Most common adverse events
  - drowsiness
  - fatigue
  - emotional fragility
  - tearfulness
  - irritability
- B/P readings returned to baseline measures by Week 8
- HR remained 10 points below baseline measures at Week 8
- No clinically significant changes on electrocardiogram

Scahill et al. Am J Psychiatry 172(12):1197-1206, 2015.

TARGET SYMPTOM DOMAINS

1. Motor hyperactivity and inattention
2. **Irritability** (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
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MEDICATIONS FOR IRRITABILITY IN ASD

- Antipsychotics
- Mood Stabilizers

Antipsychotics in ASD

TYPICAL ANTIPSYCHOTICS

- Several RCTs of haloperidol associated with improvement in a variety of symptoms including aggression and irritability
- Adverse effects: dystonia, dyskinesias

RCT = randomized clinical trial.

Anderson LT et al. *Am J Psychiatry.* 1984;141:1195-1202.
Campbell M et al. *J Am Acad Child Adolesc Psychiatry.* 1997;36:835-843.

ATYPICAL ANTIPSYCHOTICS

- Serotonin antagonism in addition to dopamine antagonism
- Lower risk of dyskinesias
- Individual drugs include
  - Risperidone
  - Aripiprazole
  - Paliperidone
  - Olanzapine
  - Quetiapine
  - Ziprasidone
  - Clozapine

RISPERIDONE IN CHILDREN WITH AUTISTIC DISORDER AND SERIOUS BEHAVIORAL PROBLEMS

RUPP Autism Network

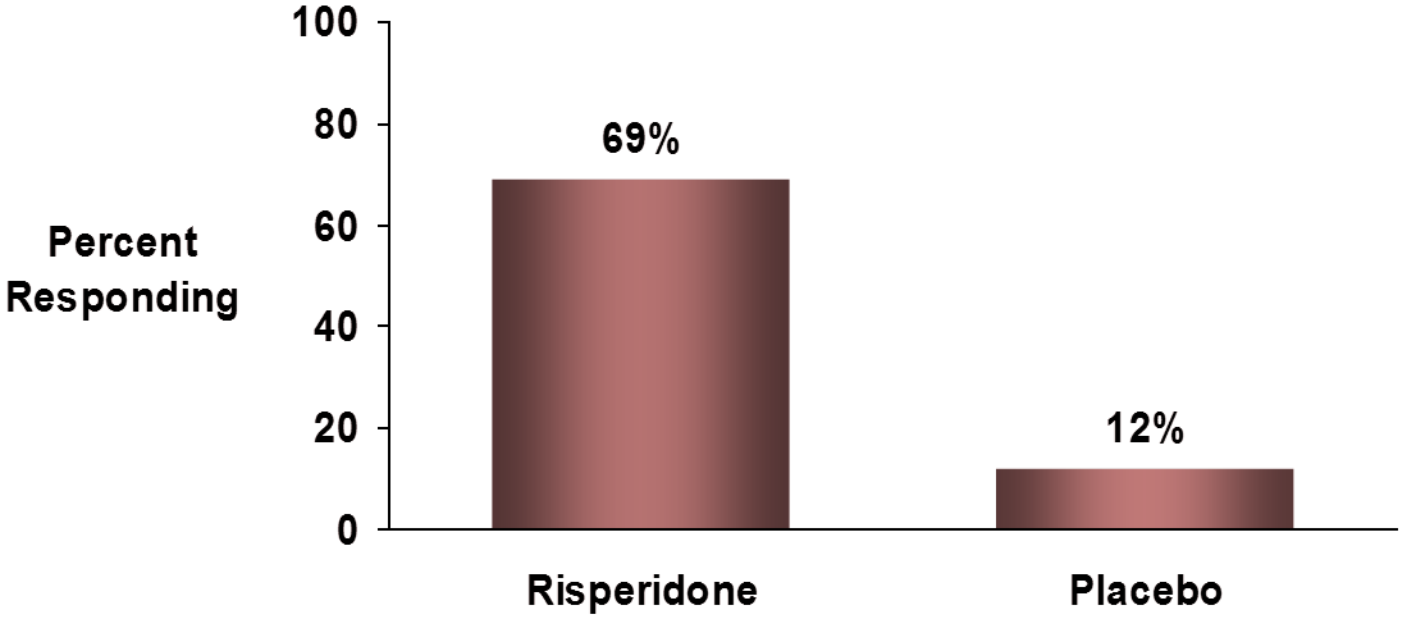
- Indiana University (Christopher J. McDougle, MD)
- Kennedy-Kreiger, Johns Hopkins (Elaine Tierney, MD)
- Ohio State University (Michael G. Aman, PhD; L. Eugene Arnold, MD)
- Yale Child Study Center (Larry Scahill, MSN, PhD)
- UCLA (James T. McCracken, MD)
- NIMH (Benedetto Vitiello, MD)

RISPERIDONE IN CHILDREN AND ADOLESCENTS WITH AUTISTIC DISORDER

- 101 subjects (82 boys, 19 girls)
- Diagnosis: autistic disorder
- Significant irritability (ABC Irritability subscale ≥18)
- 8 weeks, double-blind, placebo-controlled, parallel groups
- Mean age = 8.8 ± 2.7 y; range = 5–17 y
- Risperidone 1.8 mg/d; range = 0.5–3.5 mg/d

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

8-WEEK RISPERIDONE TRIAL



Response criteria: ≥25% improvement in the ABC-I score, and a rating of "much improved" or "very much improved" on the CGI-I

ABC-I = Aberrant Behavior Checklist–Irritability subscale.
CGI-I = Clinical Global Impressions–Improvement.
RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

BASELINE AND ENDPOINT ABC SCORES BY GROUP

	Risperidone			Placebo	
ABC	**Baseline**	**Endpoint**		**Baseline**	**Endpoint**
Irritability *P* < 0.001	26.2 (7.9)	11.3 (7.4)		25.5 (6.6)	21.9 (9.5)
Social Withdrawal *P* = 0.03/NS	16.4 (8.2)	8.9 (6.4)		16.1 (8.7)	12.0 (8.3)
Stereotypy *P* < 0.001	10.6 (4.9)	5.8 (4.6)		9.0 (4.4)	7.3 (4.8)
Hyperactivity *P* < 0.001	31.8 (9.6)	17.0 (9.7)		32.3 (8.5)	27.6 (10.6)
Inappropriate Speech *P* = 0.03/NS	4.8 (4.1)	3.0 (3.1)		6.5 (3.6)	5.9 (3.8)

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

8-WEEK RISPERIDONE TRIAL

- Adverse effects
- Mean increase in weight
  - Risperidone, 2.7 ± 2.9 kg
  - Placebo, 0.8 ± 2.2 kg; $P < 0.001$
- Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group; all $P < 0.05$
- AIMS and Simpson-Angus: no EPS

AIMS = Abnormal Involuntary Movement Scale.
EPS = extrapyramidal symptoms.
RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

ARIPIPRAZOLE IN AUTISTIC DISORDER - FLEXIBLE DOSE STUDY

- 98 children and adolescents with autistic disorder (age 6-17 years) with significant irritability
- 8-week, double-blind, placebo-controlled, parallel groups, flexibly-dosed (2-15 mg/day) trial
- Aripiprazole (8.5 mg/day) more efficacious than placebo on Aberrant Behavior Checklist Irritability subscale (P<.001)
- Discontinuation rates: PLA=5.9% Aripiprazole=10.6%
- Most common AEs with aripiprazole were fatigue and somnolence
- Weight gain PLA=1.0 kg Aripiprazole=2.1 kg

Owen et al. *Pediatrics*. 2009;124(6):1533-1540.

ARIPIPRAZOLE IN AUTISTIC DISORDER – FIXED DOSE STUDY

- 218 children and adolescents with autistic disorder (age 6-17 years) with significant irritability
- 8-week, double-blind, placebo-controlled, parallel groups, fixed-dose (5 mg, 10 mg, 15 mg) trial
- Aripiprazole (5 mg, 10 mg, 15 mg) more efficacious than placebo on Aberrant Behavior Checklist Irritability subscale ($P<.05$ for all)
- Discontinuation rates: PLA=7.7%, 5 mg=9.4%, 10 mg=13.6%, 15 mg=7.4 %
- Common AEs leading to discontinuation: sedation, drooling, tremor, akathisia, EPS
- Weight gain PLA=0.3 kg, 5+10 mg=1.3 kg, 15 mg=1.4 kg

Marcus et al. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1110-1119.

OLANZAPINE – DOUBLE-BLIND, PLACEBO CONTROLLED STUDY IN ASD

- 11 children with pervasive developmental disorders (9 y)
- 8-week, double-blind, placebo-controlled
- Olanzapine 10 ± 2.04 mg/d
- Response: Olanzapine 3/6 Placebo 1/5
- Weight Gain: Olanzapine 7.5 ± 4.8 lbs
  Placebo 1.5 ± 1.5 lbs

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

QUETIAPINE IN ASD

Four open-label studies:

1. Age range 6-15 y, Dosage range 100-350 mg/d, Response 2/6 (Martin et al. 1999)
2. Age range 10-17 y, Dosage range 100-450 mg/d, Response 2/9 (Findling et al. 2004)
3. Age range 5-28 y, Dosage range 25-600 mg/d, Response 8/20 (Corson et al. 2004)
4. Age range 7-17 y, Dosage range 265-689 mg/d, Response 6/10 (Hardan & Handen 2005)

ZIPRASIDONE IN ASD

- 6-week prospective, open-label study
- 12 subjects
- Mean age = 14.5 ± 1.8 y; range = 12 to 18 y
- Mean dose = 98.3 ± 40.4 mg/d; range = 20 to 160 mg/d
- Response: 9/12 (75%) on Clinician CGI-I
- No significant weight gain
- QT_c increased a mean of 14.7 msec; none > 448 msec

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

CLOZAPINE IN ASD

- Case reports only
- Can lower the seizure threshold
- Risk of agranulocytosis
- Frequent blood draws necessary
- Possible use in Catatonia

Mood Stabilizers in ASD

MOOD STABILIZERS IN ASD

- There are no large-scale DB, PC trials of any mood stabilizer demonstrating efficacy for irritability in ASD.

Medicaitons for Repetitive Thoughts and Behaviors in ASD

SSRIs in Children and Adolescents with ASD

DB, PC TRIAL OF FLUVOXAMINE IN CHILDREN AND ADOLESCENTS WITH ASD

- 12-week DB, PC study: Fluvoxamine vs. Placebo
- 34 children and adolescents (mean age 9.5 years) with ASD
- Fluvoxamine started at 25 mg/day every other day, mean dose = 106.9 mg/day
- Responders: Fluvoxamine 1/18, Placebo 0/16
- Prominent adverse events: insomnia, motor hyperactivity, agitation and aggression

McDougle CJ et al. *Unpublished data.*

DB, PC CROSSOVER TRIAL OF LIQUID FLUOXETINE IN CHILDREN AND ADOLESCENTS WITH ASD

- Crossover study: 8 weeks of Fluoxetine vs. Placebo
- 45 children and adolescents (8.18 $\pm$ 3.0 years) with ASD; IQ 63.65 $\pm$ 27.9
- Starting dose 2.5 mg/day, mean dose 9.9 $\pm$ 4.35 mg/day
- Fluoxetine > Placebo on CY-BOCS Compulsion scale; No difference on global autism measure
- No difference between Fluoxetine and Placebo in reported adverse events

Hollander E et al. *Neuropsychopharmacology*. 2005; 30:582-589.

CITALOPRAM IN ASD

- 149 children (9.4 ± 3.1 years) with PDDs and significant repetitive behavior
- 12-week, double-blind, placebo-controlled, parallel groups design
- Citalopram started at 2.5 mg/day; max dose = 20 mg/day; (mean dose = 16.5 ± 6.5 mg/day)
- No drug-placebo difference in response on CGI-I or in score reduction on CY-BOCS-PDD
- Significantly more adverse events with citalopram than placebo: increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, and dry skin or pruritus

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

ACTN STUDY OF FLUOXETINE IN ASD: S O F I A

- 14-week, double-blind, placebo-controlled
- Largest trial of SSRI in ASD to date
- 158 subjects, ages 5-17 y
- Fluoxetine not effective for repetitive behaviors in youth with ASD vs. placebo

ACTN = Autism Clinical Trials Network
Autism Speaks, press release 2009

SSRIs IN ADULTS WITH ASD FOR REPETITIVE BEHAVIOR

- Fluvoxamine better than placebo in ADULTS with autistic disorder[1]
- Fluoxetine better than placebo in ADULTS with PDDs[2]

[1]McDougle CJ et al. *Arch Gen Psychiatry*. 1996;53:1001-1008.
[2]Hollander E et al. *Am J Psychiatry.* 2012;169:292-299.

TARGET SYMPTOM DOMAINS

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. **Sleep disturbance**
5. Mood disorders
6. Anxiety disorders
7. Social/Language impairment

Medications for Sleep in ASD

MEDICATIONS FOR SLEEP DISTURBANCE IN ASD

- Melatonin
- Trazodone
- Clonidine
- Mirtazapine
- Amitriptyline
- Diphenhydramine and Benzodiazepines

MELATONIN

- 13 controlled studies of melatonin for sleep disturbance in children with neurodevelopmental disorders (n = 424)
- Parallel groups and crossover designs
- Dose 1-10 mg
- Melatonin > placebo in all 13 studies
- Adverse events = mild and similar to placebo

Hollway and Aman *Res Dev Disabil* 32: 939-962, 2011.

TRAZODONE

- No controlled studies in children with sleep disturbance
- Begin (50 mg) ½ to 1 tab at bedtime; increase by this amount weekly to 25 to 300 mg at bedtime
- Discuss potential adverse event of priapism

CLONIDINE

- No controlled studies in children with sleep disturbance
- Begin (0.1 mg) ½ to 1 tab at bedtime; increase by that amount weekly to 0.2 to 0.3 mg at bedtime
- May develop tolerance and develop mid-nocturnal awakening

MIRTAZAPINE

- No controlled studies in children with sleep disturbance
- Begin (15 mg) ¼ tab at bedtime; increase by this amount weekly to 3.75 to 45 mg at bedtime
- Prominent adverse events are increased appetite, weight gain and sedation
- Available in a soluble tablet

AMITRIPTYLINE

- No controlled studies in children with sleep disturbance
- Begin (50 mg) ½ to 1 tab at bedtime; increase by this amount weekly to 25 to 300 mg at bedtime
- Can lower the seizure threshold
- Consider baseline electrocardiogram
- Blood level available

DIPHENHYDRAMINE AND BENZODIAZEPINES

- 3 controlled studies of diphenhydramine (DPH) in children with sleep disturbance; results were mixed
- No controlled studies of benzodiazepines in children with ASD with sleep disturbance
- Both can cause paradoxical worsening of sleep and behavior. Benzos can contribute to cognitive impairment and cause physical dependence
- DPH and Benzos not recommended for routine use

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MEDICATIONS FOR MOOD DISORDERS IN ASD

- Antidepressants
- Mood Stabilizers

ANTIDEPRESSANTS IN ASD

- There are no published DB, PC trials of medication for treating depression in ASD.
- Challenges of diagnosing depression in ASD.

MOOD STABILIZERS IN ASD

- There are no published DB, PC trials of medication for treating bipolar disorder in ASD.

TARGET SYMPTOM DOMAINS

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
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5. Mood disorders
6. **Anxiety disorders**
7. Social impairment

Medications for Anxiety in ASD

MEDICATIONS FOR ANXIETY IN ASD

- Buspirone
- Mirtazapine
- Low-dose SSRIs

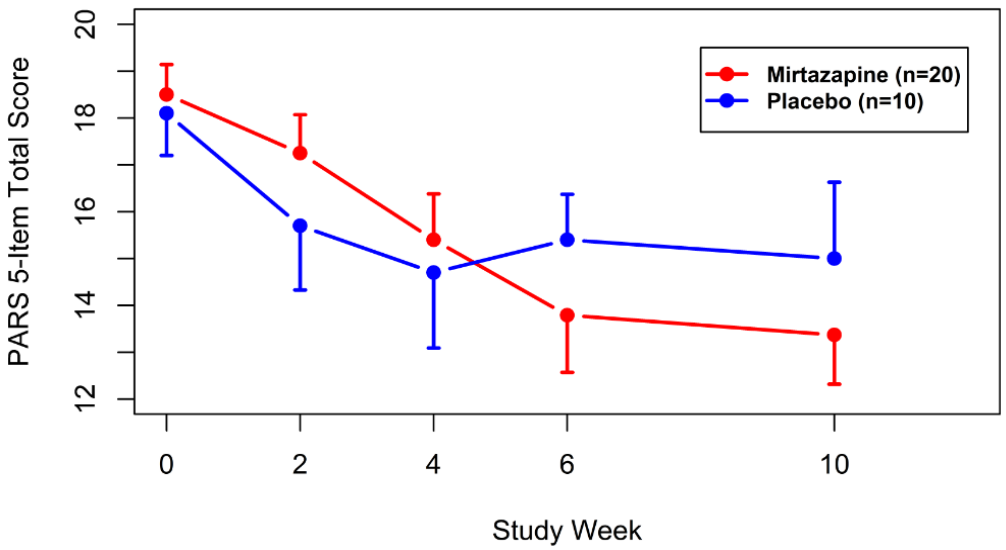
DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF BUSPIRONE FOR RESTRICTED AND REPETITIVE BEHAVIOR IN YOUNG CHILDREN WITH ASD

- 24-week study
- 166 subjects, age range 2-6 years
- Randomly assigned to placebo, 2.5 mg or 5.0 mg of buspirone twice a day
- No significant difference between groups on the ADOS Composite Total Score (overall symptoms of autism)
- There was evidence of improvement on the ADOS Restricted and Repetitive Behavior score and the Repetitive Behaviors Scale-Revised score but only for the buspirone 2.5 mg twice a day group
- No significant difference in adverse events between groups

Chugani et al. *J Pediatr*, 170:45-53, 2016.

Pilot Data on Mirtazapine for Anxiety in 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 in anxiety (ES 1.76, $p<0.001$)
- No statistically significant differences in mean 10-week change between mirtazapine and placebo
- Adverse events: no severe adverse events or suicidality. Most common adverse events included sedation, appetite increase, and irritability. No significant differences in adverse event frequency between mirtazapine and placebo.

LOW-DOSE SSRIs FOR ANXIETY IN ASD

- There are no published DB, PC trials of low-dose SSRIs for treating anxiety in ASD.

TARGET SYMPTOM DOMAINS

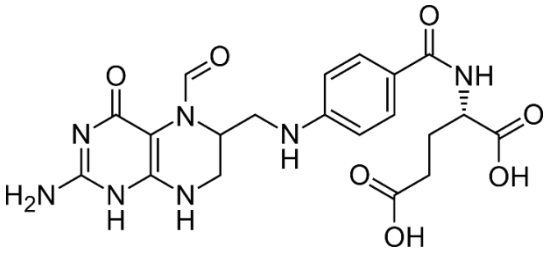
1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Sleep disturbance
5. Mood disorders
6. Anxiety disorders
7. **Social/Language impairment**

MEDICATIONS STUDIED FOR SOCIAL IMPAIRMENT IN ASD

- Not effective
  - Fenfluramine
  - Naltrexone
  - Lamotrigine
  - Amantadine
  - Risperidone
  - Fluoxetine
  - Citalopram
  - Memantine

Folinic Acid in ASD

Folinic acid for language impairment in ASD



- Central folate disturbances have been associated with ASD

Folate receptor autoantibodies (FRAAs) interfere with folate transport across the blood-brain barrier and cause cerebral folate deficiency

Frye et al. 2018

- 38 children (3-15 years) with ASD randomized to 12 weeks of folinic acid (2 mg/kg per day, maximum dose 50 mg) or placebo
- Folinic acid associated with improvement in verbal communication compared to placebo (0.02)
- FRAA status predictive of response to treatment
- No serious side effects

A multi-site trial of folinic acid for the treatment of language impairment in children (5-12 years) with ASD is underway.

Frye, R. E., Slattery, J., Delhey, L. et al. (2018). Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. *Molecular psychiatry*, *23*(2), 247–256.

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