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PSYCHIATRY ACADEMY

# Psychopharmacology of Autism Spectrum Disorder

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# Disclosures

I have the following relevant financial relationships with a commercial interest to disclose:

Sage Therapeutics – consultant

Acadia Pharmaceuticals – consultant

Oxford University Press – royalties

Springer Publishing – royalties



# 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 Objectives

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

# MEDICATIONS FOR HYPERACTIVITY AND INATTENTION IN ASD



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- Psychostimulants
- Atomoxetine
- Alpha-2 Agonists



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# Psychostimulants in ASD - *Methylphenidate (MPH)*

# RUPP Autism Network Study of Methylphenidate (MPH) for ADHD in Children with ASD



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## ***Test-Dose Phase***

72 children completed a 1-week single-blind test dose phase receiving 1 day of placebo and 2 days each of three ascending dosages of MPH; Six subjects dropped out due to irritability.

## ***Cross-Over Phase***

66 children (59 boys, 7 girls; mean age =  $7.5 \pm 2.2$  years) entered a randomized 4-week double-blind, placebo-controlled cross-over phase consisting of 1 week of placebo and 1 week each of two-three ascending dosages of MPH. Eight subjects dropped out, 7 due to adverse effects.

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.



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# Atomoxetine in ASD

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



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- 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



<b>Primary Outcome Measure</b>	<b>ATX = 48</b>	<b>PLA = 49</b>	<b>p Value</b>
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



<b>Adverse Events</b>	<b>ATX = 48</b>	<b>PLA = 49</b>	<b>p Value</b>
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.



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# Alpha-2 Agonists in ASD

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



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- 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.



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



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- 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



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- 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



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- 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
4. Sleep disturbance
5. Mood disorders
6. Anxiety disorders
7. Social/Language impairment



# MEDICATIONS FOR IRRITABILITY IN ASD

- Antipsychotics
- Mood Stabilizers



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# Antipsychotics in ASD



# 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



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## 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



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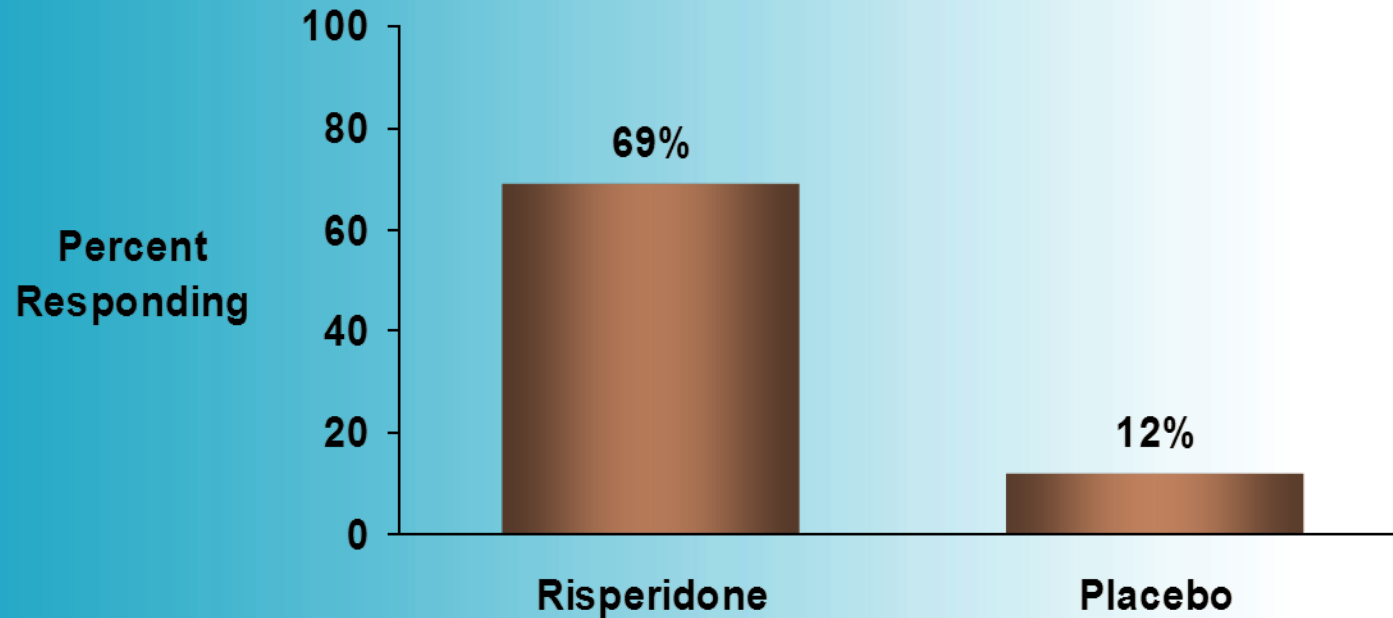
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- 101 subjects (82 boys, 19 girls)
- Diagnosis: autistic disorder
- Significant irritability (ABC Irritability subscale  $\geq 18$ )
- 8 weeks, double-blind, placebo-controlled, parallel groups
- Mean age =  $8.8 \pm 2.7$  y; range = 5–17 y
- Risperidone 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:  $\geq 25\%$  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.



# 8-WEEK RISPERIDONE TRIAL

- Adverse effects
- Mean increase in weight
  - Risperidone,  $2.7 \pm 2.9$  kg
  - Placebo,  $0.8 \pm 2.2$  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 – 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.



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# 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.



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# Medications for Repetitive Thoughts and Behaviors in ASD



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# 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.*



# CITALOPRAM IN ASD

- 149 children ( $9.4 \pm 3.1$  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 =  $16.5 \pm 6.5$  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



# TARGET SYMPTOM DOMAINS

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



# Medications for Sleep in ASD

# MEDICATIONS FOR SLEEP DISTURBANCE IN ASD



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



# 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 MOOD DISORDERS IN ASD



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- 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
4. Sleep disturbance
5. Mood disorders
6. **Anxiety disorders**
7. Social impairment



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# Medications for Anxiety in ASD



# MEDICATIONS FOR ANXIETY IN ASD

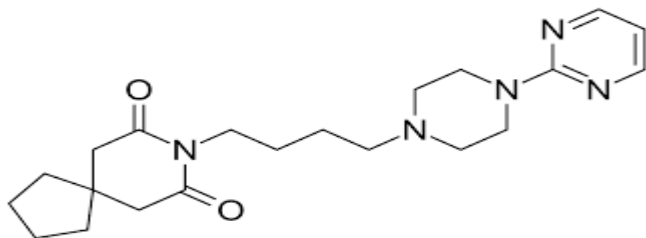
- Buspirone
- Mirtazapine
- Low-dose SSRIs

## Buspirone for anxiety

5-HT<sub>1A</sub> receptor partial agonist.

FDA approval for the treatment of generalized anxiety disorder in adults.

Favorable side effect profile



## 8-week open-label trial of buspirone for anxiety and irritability in PDD

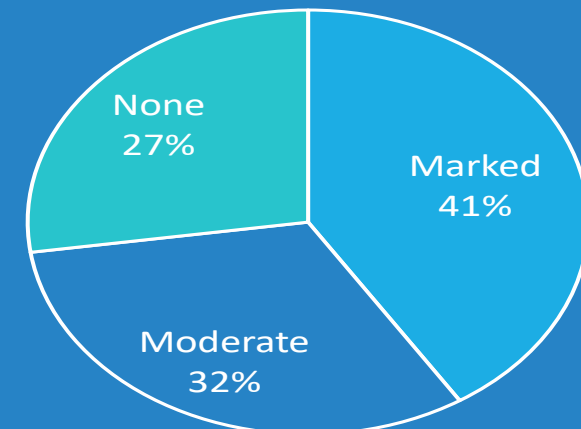
N = 22, (ages 6-16 years) with PDD-NOS or autistic disorder, majority inpatients

Starting dose = 5 mg tid, maximum dose = 45 mg/day, mean dose = 29.3 mg/day

Adverse effects:

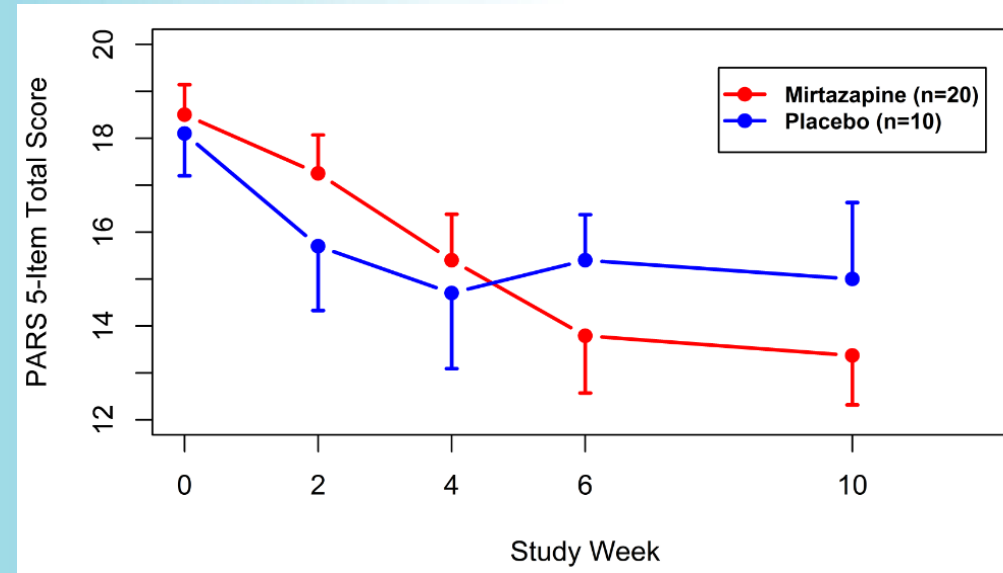
- Initial sedation = 2
- Slight agitation = 2
- Initial nausea = 1

### Improvement



# 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



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- 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



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

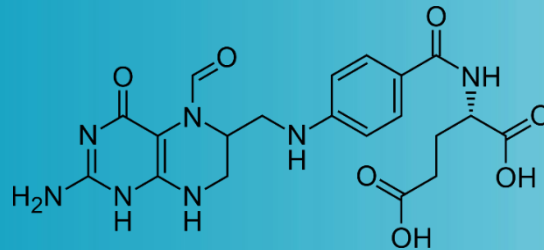
# Folinic Acid in ASD

## 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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