Psychopharmacology of Autism Spectrum Disorder

Christopher J. McDougle, MD
Director, Lurie Center for Autism
Professor of Psychiatry and Pediatrics
Massachusetts General Hospital and
MassGeneral Hospital for Children
Nancy Lurie Marks Professor
Harvard Medical School

LURIE CENTER FOR AUTISM

MASSACHUSETTS GENERAL HOSPITAL

MassGeneral Hospital *for* Children℠

Conflict of Interest Disclosure

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children

- I have no relevant financial relationships to report with a commercial interest.

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

Target symptom domains

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

Target symptom domains

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

Medications for hyperactivity and inattention in ASD

- Psychostimulants
- Atomoxetine
- Alpha-2 Agonists

PSYCHOSTIMULANTS IN ASD

RUPP Autism Network Study of MPH in Children With ASD + Hyperactivity

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children

- 72 Children (age, 5–14 y) with autism, Asperger's Disorder, or PDD NOS and significant "ADHD" symptoms
- Study design
  - 7-day test-dose period
  - 4-week double-blind trial of 3 dose levels (0.125, 0.25, 0.50 mg/kg/dose) of MPH TID and placebo in random order

MPH = Methylphenidate.
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.

Test-dose phase

- 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

- 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

- 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 autism

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

Categorical Response

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

Response to each dose of MPH was superior to placebo for autism 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

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children

- 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

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children

- 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

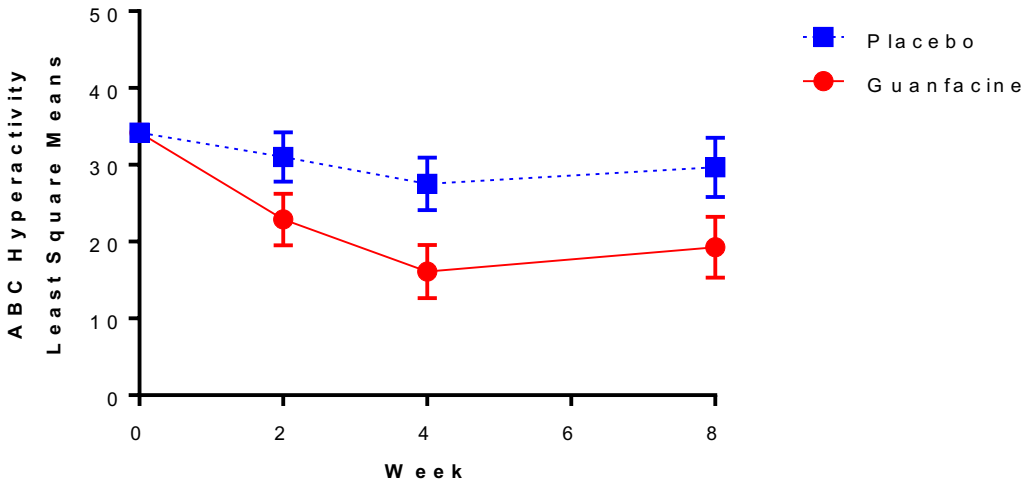
ASD = Autism Spectrum Disorder
ADHD = Attention-Deficit/Hyperactivity Disorder
Scahill et al. Am J Psychiatry 172(12):1197-1206, 2015.

Study of Extended-Release Guanfacine (XR-G) in Children with ASD + Hyperactivity

- 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
4. Mood disorders
5. Anxiety disorders
6. Social impairment

Medications for irritability in ASD

- Antipsychotics
- Mood Stabilizers

ANTIPSYCH0TICS 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 Autism and Serious Behavioral Problems

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children

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)

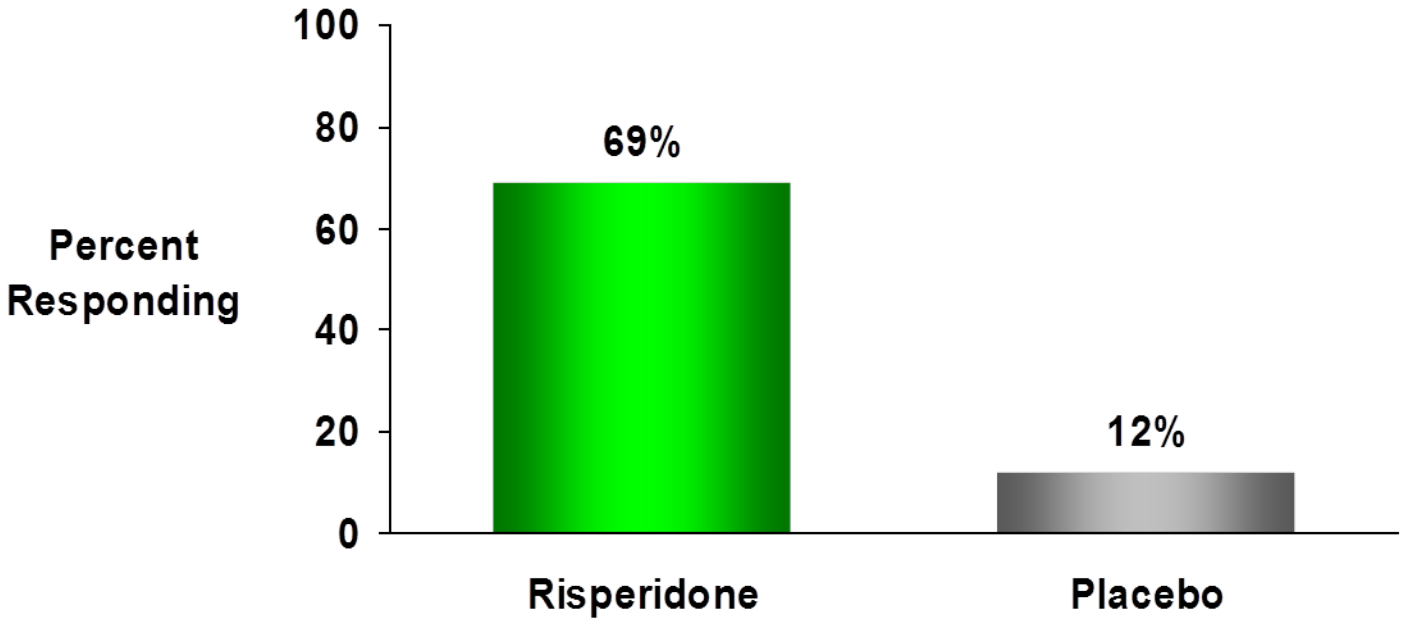
NIMH (Benedetto Vitiello, MD)

Risperidone in Children and Adolescents with autism

- 101 subjects (82 boys, 19 girls)
- Diagnosis: autistic disorder
- Significant irritability (ABC Irritability ≥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.
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.

RUPP Risperidone – Parent Management Training Trial

- 124 children (4 to 13 years) with PDDs and significant irritability
- 24-week, three-site, randomized, parallel groups trial
- Children randomized 3:2 to COMB (n=75) or MED (n=49)
- Parents in COMB received a mean of 10.9 PMT sessions

RUPP Autism Network. *J Am Acad Child Adolesc Psychiatry*. 2009;48(2):1143-1154.

RUPP Risperidone – Parent Management Training Trial

- Primary Outcome Measure (Home Situations Questionnaire [HSQ]); COMB > MED (P=.006)
- COMB > MED on ABC Irritability (P=.01), Stereotypic Behavior (P=.04), and Hyperactivity/Noncompliance (P=.04)
- Final Risperidone dose for MED (2.26 mg/day) vs. COMB (1.98 mg/day) (P=.04)

ABC = Aberrant Behavior Checklist.

RUPP Autism Network. *J Am Acad Child Adolesc Psychiatry*. 2009;48(2):1143-1154.

Aripiprazole in Autism – Flexible Dose Study

- 98 children and adolescents with autism (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 Aripiprazlole=2.1 kg

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

Aripiprazole in Autism – Fixed Dose Study

- 218 children and adolescents with autism (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.

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 autism.

Target symptom domains

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

Medications for Restricted, Repetitive Patterns of Behavior in ASD

- SSRIs

SSRIS IN CHILDREN AND ADOLESCENTS WITH ASD

DB, PC Trial of Fluvoxamine in Children and Adolescents with ASD

- 12-week DB, PC study: Fluvoxamine and 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 and Placebo
- 45 children and adolescents (8.18 ± 3.0 years) with ASD; IQ 63.65 ± 27.9
- Starting dose 2.5 mg/day, mean dose 9.9 ± 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 autism to date
- 158 subjects, ages 5-17 y
- Fluoxetine not effective for repetitive behaviors in youth with autism 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. **Mood disorders**
5. Anxiety disorders
6. Social impairment

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 autism.
- Challenges of diagnosing depression in autism.

Mood stabilizers in ASD

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

Target symptom domains

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

Medications for Anxiety in ASD

- Buspirone
- Mirtazapine
- Low-dose SSRIs

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

- 8-week study
- 22 subjects, age range = 6-16 yrs, majority inpatients
- 4 subjects on concomitant behavioral medications
- Target symptoms: Anxiety = 14, Irritability = 1, Anxiety and Irritability = 7

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

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

- Starting dose = 5 mg t.i.d.
- Maximum dose = 45 mg/day (reached within 3 weeks)
- Mean dose = 29.3 mg/day
- 9 subjects had a marked response; 7 subjects had a moderate response
- Adverse events: initial sedation = 2, slight agitation = 2, initial nausea = 1

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

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

- The 16 responders were followed up for 12-months (mean = 5.4 months)
- Therapeutic benefits were sustained in all subjects
- One subject (10 y.o. boy) developed an oro-facial-lingual dyskinesia (after 10 months) that resolved when drug was discontinued

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

Naturalistic Open-Label Trial of Mirtazapine in ASD

- Treatment duration ≥ 4 weeks (mean = 150 ± 103 days)
- 26 subjects; age range = 3.8 to 23.5 years, mean age = 10.1 ± 4.8 years; 20 had intellectual disability
- 17 subjects were taking concomitant behavioral medications; mean number of previous adequate medication trials equal 5.5 ± 5.4

Posey et al. *J Child Adolesc Psychopharmacol* 11:267-277, 2001.

Naturalistic Open-Label Trial of Mirtazapine in ASD

- Starting dose = 7.5 mg/day with weekly increases of 7.5 mg based on response and tolerability
- Final mean dose = 30.3 ± 12.6 mg/day
- Nine out of 26 (34.6%) subjects responded (Sleep Disturbance, Irritability, Hyperactivity)
- Most frequent adverse events = increased appetite, sedation, irritability

Posey et al. *J Child Adolesc Psychopharmacol* 11:267-277, 2001.

Low-dose SSRIs for anxiety in ASD

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

Target symptom domains

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

Medications Studied for Social Impairment in ASD

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

D-Cycloserine in Children with Autism

- 80 children (6.5 ± 2.8 years; range 3-12 years) with autistic disorder and significant social withdrawal
- 8-week, double-blind, placebo-controlled, parallel groups design
- D-cycloserine 1.7 mg/kg/day divided twice daily or placebo
- No drug-placebo difference on the CGI-I, ABC Social Withdrawal subscale, or Social Responsiveness Scale
- D-cycloserine generally well-tolerated
- Majority of responders maintained response during 16-week open-label extension

Posey DJ et al. *AACAP Poster 3.53,* 2008.

Lurie Center for Autism

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children

- Christopher J. McDougle, MD
- Ann Neumeyer, MD
- Nora Friedman, MD
- Yamini Howe, MD
- Sarah Kadzielski, MD
- Christopher Keary, MD
- Doug Maus, MD
- Michelle Palumbo, MD
- Ron Thibert, MD
- Diana Wasserman, MD
- Kirstin Birtwell, PhD
- Gillian Erhabor, PhD
- Alyssa Milot, PhD
- Lisa Nowinski, PhD
- Julia O'Rourke, PhD, MS, MMSc

http://www.massgeneral.org/children/services/treatmentprograms

(781)-860-1700

LURIE CENTER FOR AUTISM

LURIE CENTER FOR AUTISM
MASSACHUSETTS GENERAL HOSPITAL
MassGeneral Hospital for Children

Christopher J. McDougle, M.D.
CMCDOUGLE@PARTNERS.ORG
(781) 860-1783

Questions?