# Treating Hyperactivity: Other Medications

- Clonidine efficacious in 2 small placebo-controlled trials[1,2]
- Open-label guanfacine in RUPP MPH nonresponders is positive, suggesting that guanfacine may be an alternative[3]

[1]Jaselskis CA et al. *J Clin Psychopharmacol*. 1992;12:322-327.
[2]Fankhauser MP et al. *J Clin Psychiatry*. 1992;53:77-82.
[3]Scahill L et al. *J Child Adolesc Psychopharmacol*. 2006;16(5):589-598.

# Atomoxetine in Higher-Functioning PDD

- Prospective open-label study in 16 drug-free children (age, 6–14 y) with PDDs and nonverbal IQ of ≥70
- Significant ADHD symptoms
- Atomoxetine dosing: 0.5 mg/kg/d x 1 wk, then 0.8 mg/kg/d x 1 wk, then 1.2 mg/kg/d. Dose increased to 1.4 mg/kg/d at Week 4 for nonresponders
- Mean dose: 1.2 ± 0.3 mg/kg/d

Posey DJ et al. *J Child Adolesc Psychopharmacol,* 2006; 16(5):599-610.

# Atomoxetine in PDD With ADHD Symptoms

- 12/16 (75%) *much* or *very much improved* on the CGI scale
- 2/16 (13%) *much worse* due to irritability
- Conclusions
  - Encouraging results
  - Possible alternative to stimulants and $\alpha_2$-adrenergic agonists
  - Placebo-controlled studies needed

CGI = Clinical Global Impressions.

Posey DJ et al. *J Child Adolesc Psychopharmacol*, 2006; 16(5):599-610.

# Potential Targets of Pharmacotherapy

1. Motor hyperactivity, inattention
2. **Repetitive behavior**
3. Aggression, self-injury, property destruction
4. Impaired social relatedness

# Serotonin Reuptake Inhibitors (SRIs)

- Rationale for studying SRIs in autism
  - Similarities to obsessive-compulsive disorder
  - Serotonin abnormalities in autism

# SRIs in Autism

- Clomipramine better than placebo and desipramine in children and young adults with autism[1]
- Fluvoxamine better than placebo in **ADULTS** with autism[2]
- Fluvoxamine no better than placebo and poorly tolerated in **CHILDREN** with PDDs[3]
- Fluoxetine better than placebo and well tolerated in children with PDDs[4]

[1]Gordon CT et al. *Arch Gen Psychiatry.* 1993;50:441-447.
[2]McDougle CJ et al. *Arch Gen Psychiatry.* 1996;53:1001-1008.
[3]McDougle CJ. Unpublished data.
[4]Hollander E et al. *Neuropsychopharmacology*. 2005; 30:582-589.

# Citalopram in PDDs

- 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.

# Potential Targets of Pharmacotherapy

1. Motor hyperactivity, inattention
2. Repetitive behavior
3. **Aggression, self-injury, property destruction**
4. Impaired social relatedness

# 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
  - Clozapine
  - Risperidone
  - Olanzapine
  - Quetiapine
  - Ziprasidone
  - Aripiprazole
  - Paliperidone

# Clozapine

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

# Risperidone in Children With Autism 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)

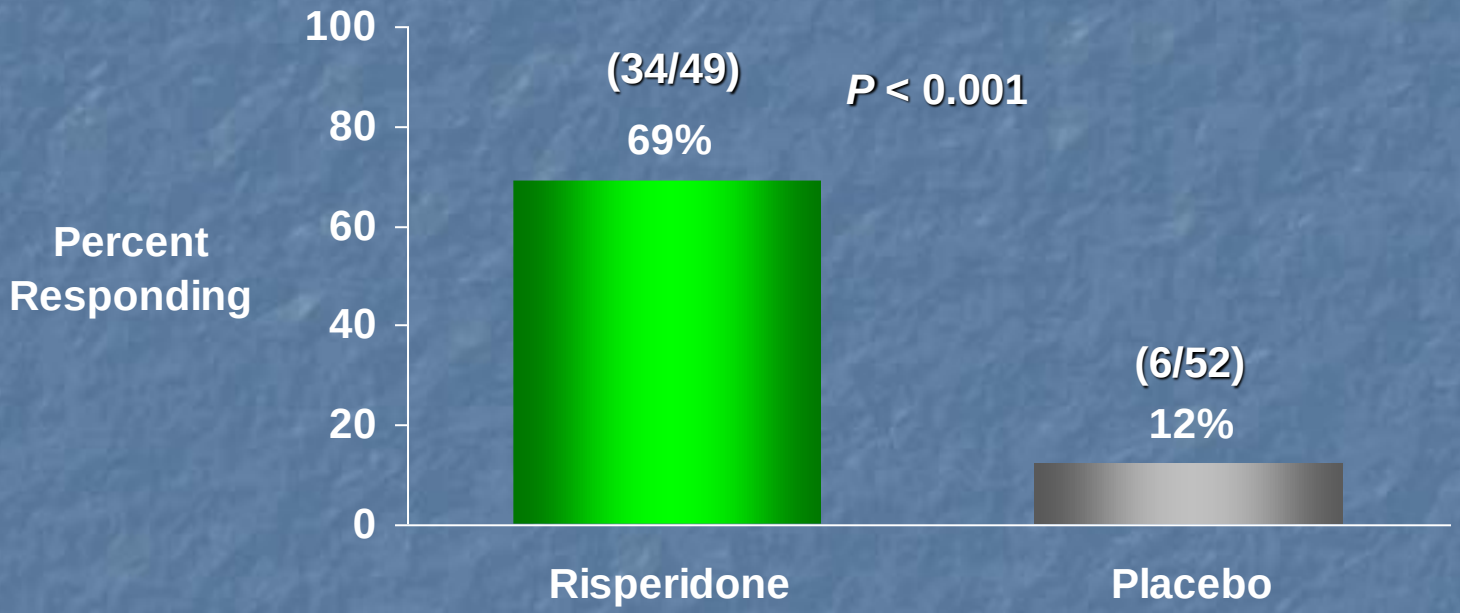
NIMH (Benedetto Vitiello, MD)

# Acute Risperidone Trial: RUPP in Children and Adolescents

- 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.

# Acute Risperidone Trial: RUPP




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.

# Acute Risperidone Trial: RUPP

- 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.

# Baseline and Endpoint ABC Scores by Group

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

# 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, unpublished data.

# 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, unpublished data.

# Olanzapine vs. Haloperidol

- 12 children with autism (7.8 ± 2.1 y)
- 6-week open-label, parallel groups
- Olanzapine 7.9 ± 2.5 mg/d

  Haloperidol 1.4 ± 0.7 mg/d
- Response: Olanzapine 5/6 Haloperidol 3/6
- Weight Gain:

  Olanzapine 9.0 ± 3.5 lbs; range 5.9 – 15.8 lbs

  Haloperidol 3.2 ± 4.9 lbs; range - 5.5 – 8.8 lbs

Malone RP et al. *J Am Acad Child Adolesc Psychiatry*. 2001;40:887-894.

# Olanzapine – Double-Blind, Placebo Controlled Study

- 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

- **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

- Retrospective case series, 14.15 ± 8.29 wk
- 12 subjects
- Mean age = 11.62 ± 4.38 y; range = 8 to 20 y
- Mean dose = 59.23 ± 34.76 mg/d; range = 20-120 mg/d
- Response: 6/12 (50%) on CGI-I
- No significant weight gain

McDougle CJ et al. *J Am Acad Child Adolesc Psychiatry*. 2002;41:921-927.

# Ziprasidone

- 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.

# Aripiprazole in Asperger's Disorder and PDD NOS

- 14-week prospective, open-label study
- 25 subjects (6 female, 19 male; age = 8.6 y, range = 5-17 y)
- IQ = 82, range = 50-132
- Target Symptoms = Irritability, aggression, self-injury (ABC Irritability subscale score ≥ 18)
- Dose 7.8 mg/d, range 2.5 – 15 mg/d

Stigler et al. *J Child Adolesc Psychopharmacol*. 2009; 19(3):265-274.

# Aripiprazole in Asperger's Disorder and PDD NOS

**Response:** CGI-I = "Much Improved" or "Very Much Improved" and a ≥ 25% improvement in ABC Irritability subscale score 21/25 (84%)

**ABC Irritability Subscale Score:**

Baseline = 28, Endpoint = 8.8

**Adverse Effects:**

Mild tiredness = 16, Moderate tiredness = 1

Mild EPS = 6

Weight gain = 19, Mean = 2.3 lbs, range = -3.3 – 7.7 lbs

Stigler et al. *J Child Adolesc Psychopharmacol*. 2009; 19(3):265-274.

# Aripiprazole in Autism – Flexible Dose Study (CN138-178)

- 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.  AACAP Poster 3.60, 2008

# Aripiprazole in Autism – Fixed Dose Study (CN138-179)

- 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

Owen et al. AACAP Poster 3.59, 2008

# Potential Targets of Pharmacotherapy

1. Motor hyperactivity, inattention
2. Repetitive behavior
3. Aggression, self-injury, property destruction
4. **Impaired social relatedness**

# Medications Studied for Social Impairment in Autism

- 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

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

# Prognosis For Autistic Disorder

- Three consistent outcome factors:
  - IQ
  - The presence or absence of speech
  - The severity of the disorder
- Up to 28% of children with no neurologic disorder in early childhood develop a seizures in adolescence or later. Peak age of onset is 11-14 years old
- A small number of children with autism show intellectual and language decline in adolescence
- While a significant number of children with autism may have coexisting psychiatric disorders there is no increased risk for schizophrenia

# Future Directions

- **Motor Hyperactivity/Inattention**
  - Double-blind, placebo-controlled trial of atomoxetine
  - Double-blind, placebo-controlled trial of guanfacine
- **Repetitive Behavior**
  - Pilot studies of riluzole
- **Aggression, Self-Injury, Property Destruction**
  - Pilot studies of paliperidone
- **Impaired social Relatedness**
  - Controlled trial of D-cycloserine + Social Skills Training
  - Double-blind, placebo-controlled trial of memantine
  - Pilot studies of intranasal oxytocin

# Christian Sarkine Autism Treatment Center

- Christopher J. McDougle, MD
- David J. Posey, MD
- Naomi B. Swiezy, PhD
- Kimberly A. Stigler, MD
- Craig Erickson, MD
- Noha Minshawi, PhD
- Patricia Korzekwa, MS
- Stacie Pozdol, MS
- Doug Gaebler, MSW
- Heather Coates, BS
- Arlene Kohn, BA
- Elizabeth Kiefer, MA
- Lauren Mathieu-Frasier, MS
- Jennifer Mullett, RN, BC CCRP
- Jon Diener, BS
- Amy Tennant, BS
- Iryna Ashby, BS
- Melodie Rose, BA

www.iupui.edu/~psycdept/autism/index.htm

(317) 274-8162

# Question 1

- A 3 year old girl presents with impaired receptive and expressive language. She has stereotyped hand movements although her parents say that up to the age of 18 months she seemed to be have purposeful hand skills. Her height and weight are age appropriate but her head growth has decelerated after she passed her second birthday. The most appropriate diagnosis is:
  - A Autistic disorder
  - B Rett's disorder
  - C Asperger's disorder
  - D Childhood disintegrative disorder
  - E Pervasive developmental disorder NOS

# Question 2

- The RUPP study on the treatment of aggression in Autism presents evidence on the use of which atypical antipsychotic for this presentation?
  - A Haloperidol
  - B Quetiapine
  - C Olanzapine
  - D Risperidone
  - E Aripiprazole

# Question 3

- Which of the following is a semi-structured interactive assessment that can be conducted with a during an evaluation for an autism spectrum disorder?
  - A. Autism Diagnostic Observation Schedule (ADOS)
  - B. Autism Diagnostic Interview Revised (ADI-R)
  - C. Childhood Autism Rating Schedule (CARS)
  - D. Pervasive Developmental Disorders Screening Test (PDDST)
  - E. Checklist for Autism in Toddlers (CHAT)

# Answers

- 1) B
- 2) D
- 3) A