

Psychopharmacology in autism: Fifteen Years of Progress, Long Way to Go

Lawrence Scahill, MSN, PhD

Professor of Nursing & Child Psychiatry

Director of the Research Unit on
Pediatric Psychopharmacology

Yale Child Study Center

Disclosures

- Consultant
 - Biomarin
 - Roche
 - Bracket
- Research Funding
 - NIMH, NICHD
 - Shire Pharmaceuticals
 - Roche Pharmaceuticals
 - Pfizer
 - Tourette Syndrome Association

NIH Multisite Trials in Children with ASDs past 14 years

Study	N	Target	Ages	Date	Published
Risperidone vs placebo	101	Irritability	5-17	2002	NEJM
Methylphenidate vs placebo	66	Hyperactivity	5-14	2005	Arch Gen Psych
Citalopram vs placebo	149	Repetitive Behavior	5-17	2009	Arch Gen Psych
Risperidone vs RIS + Parent Training	124	Irritability & Adaptive Behavior	4.5-13	2009, 2012	J Am Acad Child Psych
Parent Training vs Parent Education	180	Irritability & Adaptive Behavior	3-7	In process	
Guanfacine vs placebo	112	Hyperactivity	5-14	In process	

Psychopharmacology in ASDs

Outline

- Goal of Clinical Research
- Definition of ASD
- Modern sociology of autism
- Psychopharm Scorecards
- Two Risperidone Trials
- Future Directions

Goal of Clinical Research

- Provide guidance to clinicians on the selection and staging of treatment interventions
- Identify the probability that a given treatment will benefit patients with specific characteristics
- Identify the magnitude of change, the time to effect and the risk/benefit ratio

What Every Mother Wants to Know

If my child starts this medicine:

- What are the chances that it will work?
- If it works, how much will it help?
- How long will it take to ‘kick in?’
- How long will my child have to stay on the medicine?
- What are the short- and long-term side effects?

Autism Spectrum Disorders (ASDs)

- Autism
- Asperger's Disorder
- Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS)

Autism Spectrum Disorders (ASD)

- Early onset (before 30 months of age)
- Delayed social interaction
- Delayed & deviant communication
(not in Asperger's)
- Repetitive behaviors & restricted interests
(stereotypy, fans and air conditioners, British royalty)

DSM-IV Differential diagnosis: Plain & Simple

<u>ASD Type</u>	<u>Social Delay</u>	<u>Language Delay</u>	<u>Repetitive Behavior*</u>
Autism	Yes	Yes	Yes
Asperger's	Yes	No	Yes
PDD-NOS	Yes	Maybe	Maybe

* or Restrictive Interests (preoccupied with train schedules, fans, air conditioners, horses)

ASDs: Other Essential Features

- 4:1 male to female
- 30% to 70% Mentally Retarded
- Impaired daily living skills (not explained by MR)
- 25% have seizures
- High rates of serious behavioral problems, hyperactivity and anxiety

Prevalence: How Common are ASDs?

- Historically
 - Autism 2 to 5 cases per 10,000
- Current
 - Autism: 20 per 10,000
 - ASDs: 110 per 10,000

≈ 550,000 school-age children

- Is there a true rise in the frequency of ASDs?

Center for Disease Control, 2012*****

Prevalence is all about counting cases

- Counting all cases (rarely achieved)
- Clinically-referred cases
 - subset of all cases (invariably underestimates prevalence)
- Community surveys
 - Necessary, but costly and not easy

prevalence is always an estimate!

Reasons for Increasing Prevalence

- Broadening of diagnostic rules
- Better population sampling
- Better diagnostic methods (especially among lower IQ and higher IQ children)

Sociology of Autism

- Refrigerator mothers
- Rising Prevalence
- Secretin
- Vaccines
- Andrew Wakefield
- Doug Flutie



INSIDE THE WORLD OF AUTISM

More than one million Americans may have it, and the number of new cases is exploding. What **scientists** have discovered. What **families** should know.



Lancet retracts 'utterly false' MMR paper

guardian.co.uk 2/2/2010



Andrew Wakefield, 1998
paper in Lancet – retracted
due to misconduct



Reduced stigma
(Doug Flutie factor)

www.dougflutiejrfoundation.com

The ABCDs of DSM-V

- **A:** Deficits in social communication and social interaction (blends social with communication)
- **B:** Restricted, repetitive patterns of behavior (includes insistence on sameness)
- **C:** Symptoms are present in early childhood
- **D:** Symptoms impair everyday functioning

www.dsm5.org/ProposedRevisions

Target of Medication

- Core Features of Autism
 - Social Interaction
 - Repetitive Behavior/Restricted Interests
 - Impaired Communication
- Specific Behavioral Problems
 - Hyperactivity
 - Tantrums, Aggression, Self-injury
 - Anxiety

Drugs Used in ASD

- Haloperidol
- Fenfluramine
- Clonidine
- Guanfacine
- Naltrexone
- Propranolol
- Stimulants
- Clomipramine, SSRIs
- Atomoxetine
- Secretin
- Amantadine, memantine
- Oxytocin
- Anticonvulsants
- Atypical antipsychotics

Drugs targeting social interaction in autism spectrum disorders

Drug	Double-blind trial	Sample size \geq 40	Answer mother's questions
Amantadine	yes	no	no
Memantine	no	no	no
Oxytocin	yes	no	no
D-cycloserine	yes	no	no
Secretin	yes	yes	yes
Fenfluramine	yes	yes	yes

Drug trials in ASD with sample size > 60 subjects

Drug	target	Results
fenfluramine	Social interaction	Act=Pla
secretin	Social Interaction	A=P
risperidone	Tantrums/aggression	A > P +++
aripiprazole	Tantrums/aggression	A > P ++
methylphenidate	Hyperactivity	A > P +
citalopram	Repetitive behavior	A=P
fluoxetine	Repetitive behavior	A=P

+ = small effect; ++ = medium; +++ = large

Most Common Drug Classes in ASD

- SSRIs
- Atypical Antipsychotics*
- Stimulants

* risperidone & aripiprazole are FDA-approved for children with autism and irritability

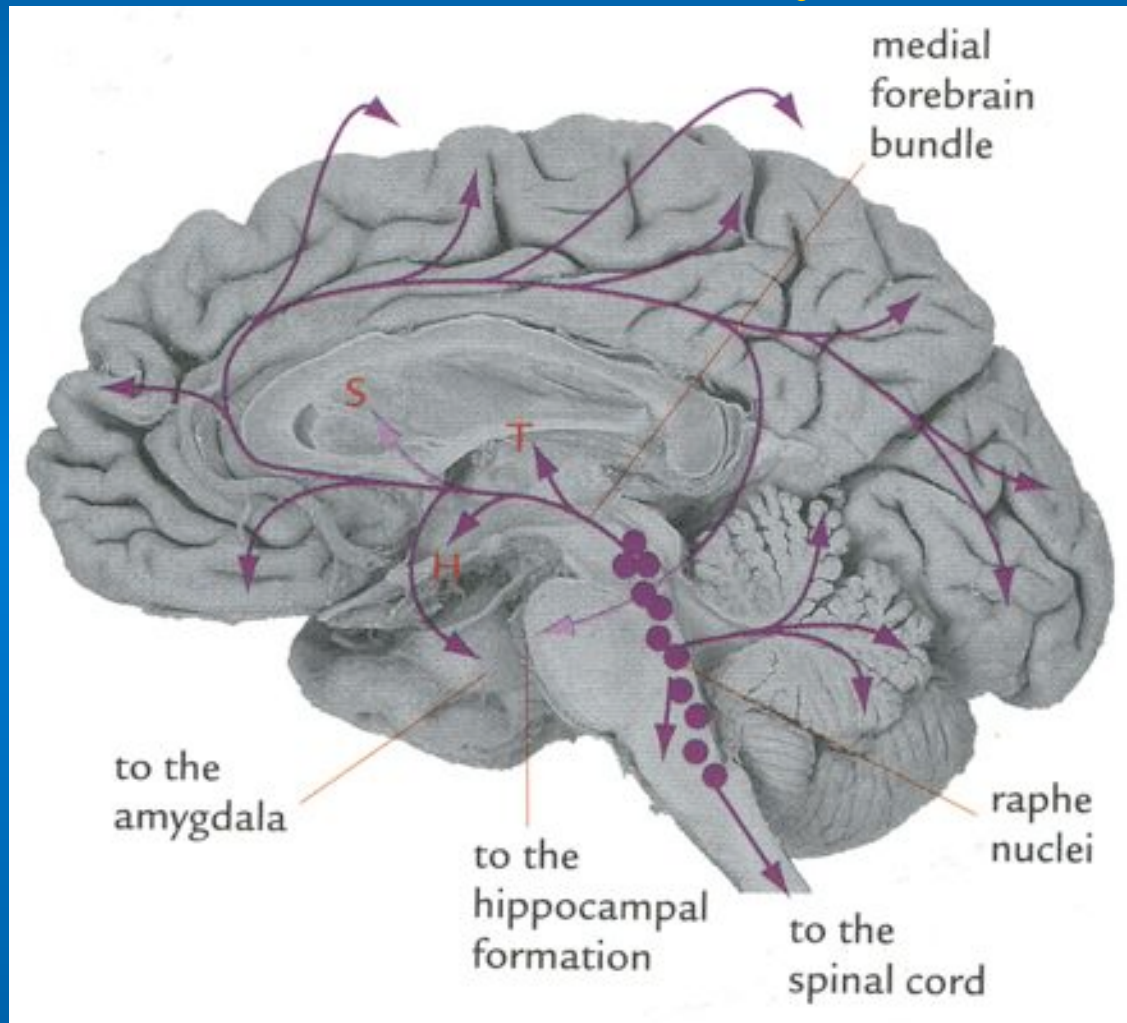
SSRIs in Children with ASDs

Target	Repetitive Behavior	Rigidity (Trouble with Transitions)	Anxiety	Irritability
Rationale	Effective for OCD (repetitive behavior)	Need for sameness (? obsessional or anxiety)	Effective in anxiety disorders	? Mood/ Anxiety → over-reaction in everyday living situations

Treatment of Repetitive Behavior in ASDs

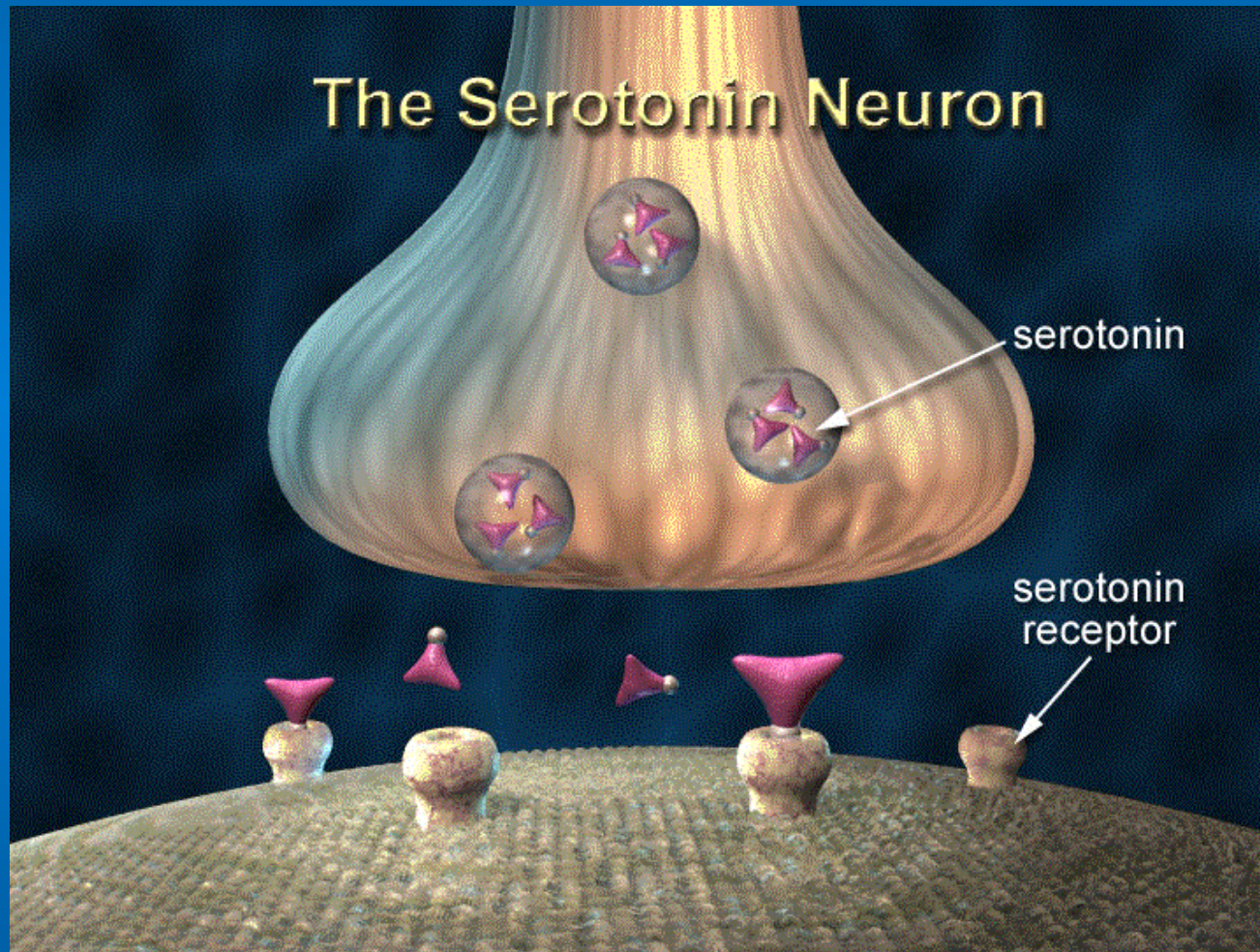
<u>Drug</u>	<u>open</u>	<u>Placebo</u> <u>controlled</u>	<u>N > 60</u>
Fluoxetine	X	X	X
Fluvoxamine	X	X	
Citalopram		X	X
Sertraline	X		
Escitalopram	X		
Clomipramine*	X	X	Not commonly used in ASDs

Serotonin System

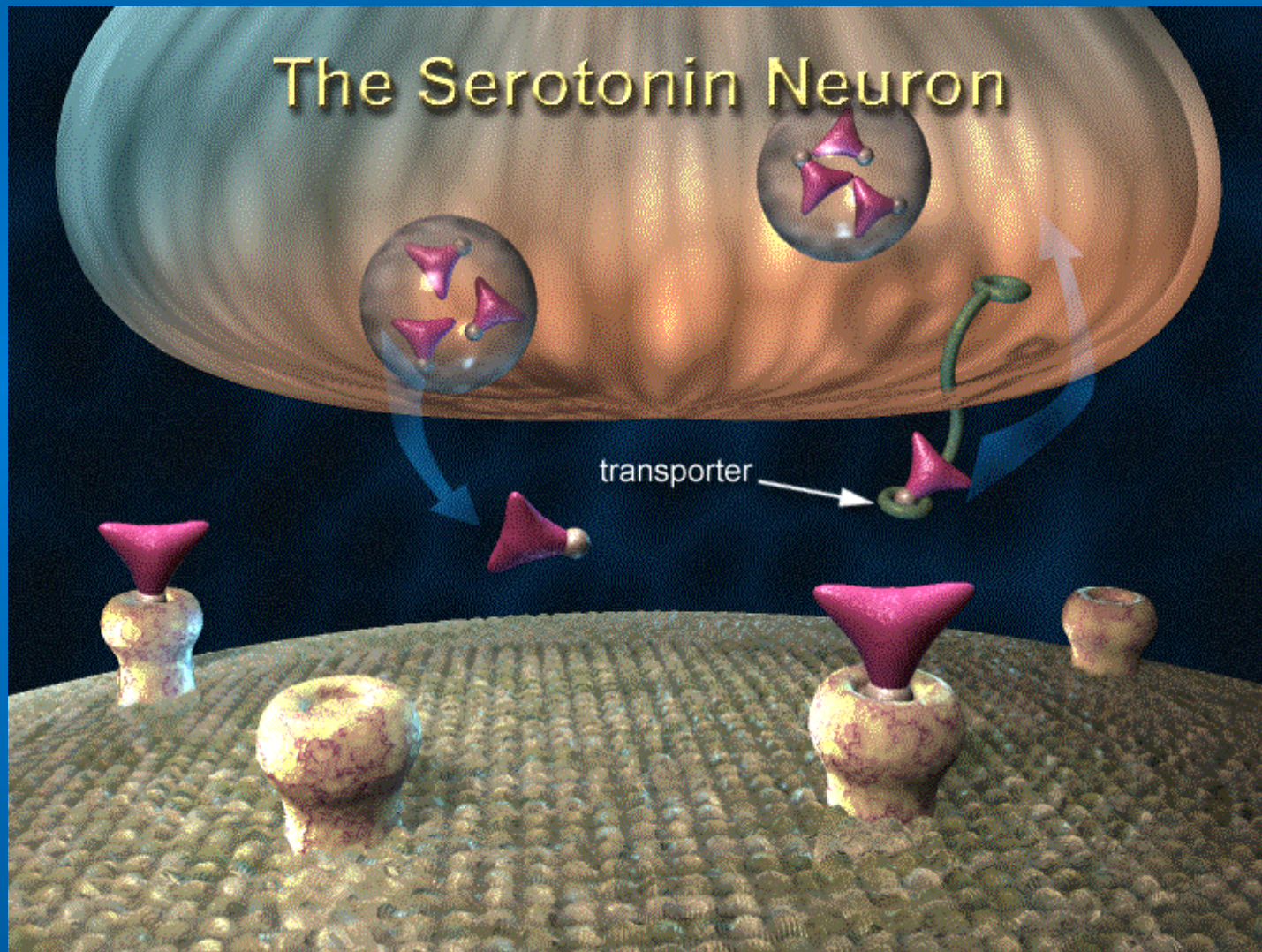


Nolte & Angevine, 1995

The Serotonin Neuron



The Serotonin Neuron



Neuropharm

“a specialty pharmaceutical group focused on the development of drugs for the treatment and management of selected developmental and degenerative disorders.”

www.stockopedia.co.uk/share-prices/neuropharm-LON:NPH/

www.fiercebiotech.com/story/neuropharm-shares-tank-phase-iii-failure/2009-02-18

“NPL-2008 failed to demonstrate a significant reduction in repetitive behavior in autistic patients when compared to placebo. A total of 158 patients, aged between 5 and 17, were enrolled into the SOFIA study in which patient received either NPL-2008 or placebo during a 14-week treatment period.”

STAART Consortium: Citalopram in PDD

- RCT in 149 subjects with PDD (Age 5 to 17)
- Citalopram (n=73) or placebo (n=76) → 12 Weeks
- Primary outcomes Clinical Global Impression - Improvement and a clinician measure of repetitive behavior (CYBOCS-PDD).

King et al., STAART Group (2009) Arch Gen Psych

Citalopram vs Placebo (N=149)

Clinical Global Impression-Improvement

1 = Very Much Improved

2 = Much Improved

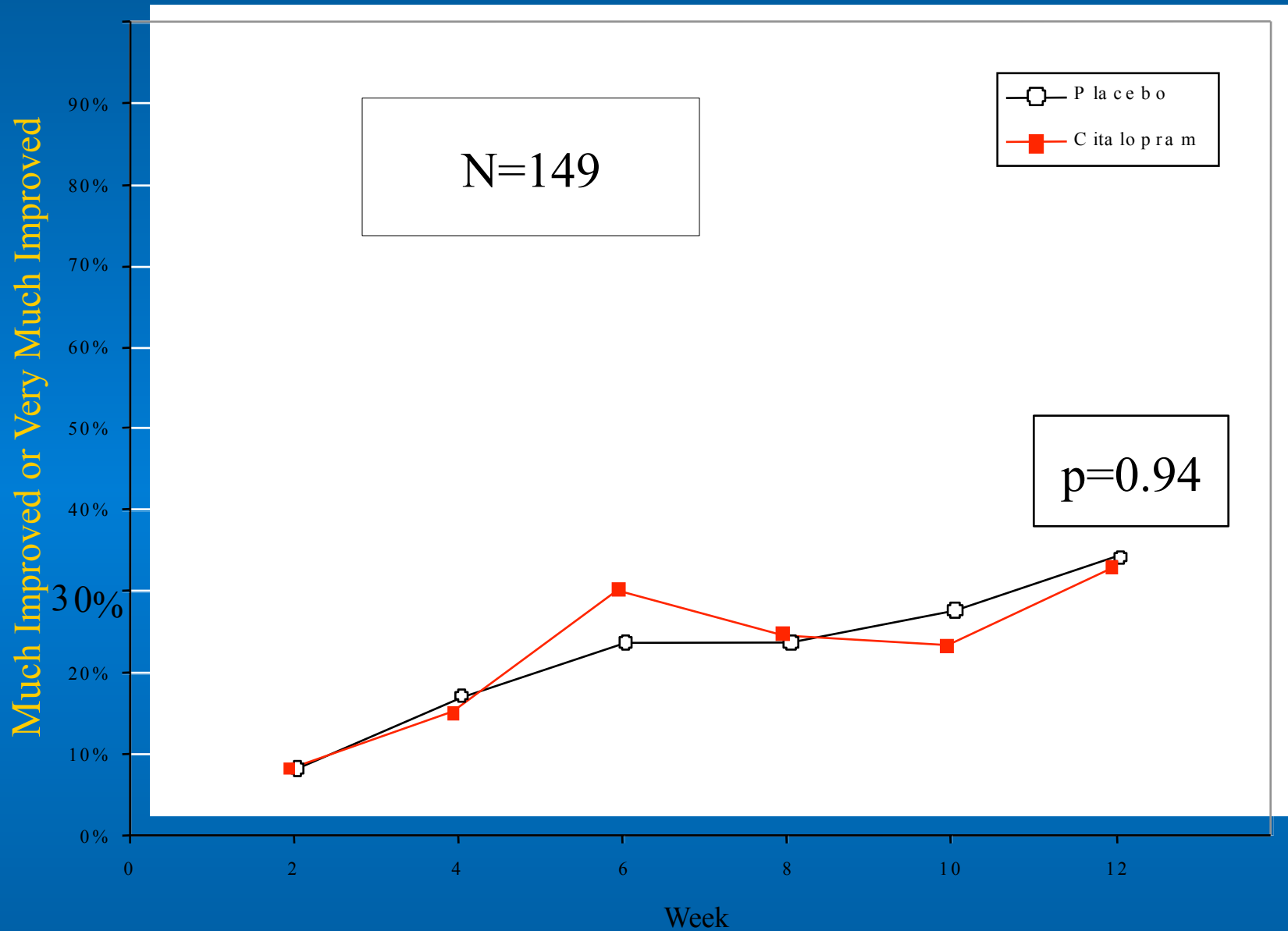
3 = Minimally Improved

4 = No Change

5 = Minimally Worse

6 = Much Worse

7 = Very Much Worse



Much Improved or Very Much Improved on (CGI-I) over 12-Week

Citalopram vs Placebo: Adverse Events*

<u>Adverse Event</u>	<u>CITAL</u>	<u>PLA</u>
	<u>N (%)</u>	<u>N (%)</u>
↑ energy	28 (38.4%)	15 (19.7%)
- initial insomnia	17 (23.3%)	7 (9.2%)
↑ impulsiveness	14 (19.2%)	5 (6.6%)
↓ concentration	9 (12.3%)	2 (2.6%)
↑ Hyperactivity	9 (12.3%)	2 (2.6%)
↑ Stereotypy	8 (11.0%)	1 (1.3%)
↑ Diarrhea	19 (26.0%)	9 (11.8%)
↑ initial insomnia	17 (23.3%)	7 (9.2%)

* < .05; King et al., STAART Group (2009) Arch Gen Psych

Conclusions: SSRIs in Children with ASDs

Evidence	Repetitive Behavior	Anxiety	Rigidity (trouble with Transitions)	Irritability
Placebo-controlled	yes	no	no	no ?
open	yes	yes	yes	yes

Treatment of Hyperactivity in Children with ASDs

Hyperactivity in ASD: Brief Background

- DSM-IV - don't diagnose ADHD in children with ASD
- Hyperactivity, disruptive behavior, and impulsiveness are common in children with ASD
- Community surveys show that stimulants are commonly used in children with ASD
- Evidence was limited

Treatment of Hyperactivity in PDD

<u>Drug</u>	<u>open</u>	<u>controlled</u>	<u>N > 60</u>
Methylphenidate		X	X
Atomoxetine	X	X	
Clonidine	X	X	
Guanfacine	X	X	
Amantadine	X	X	
Naltrexone	X	X	

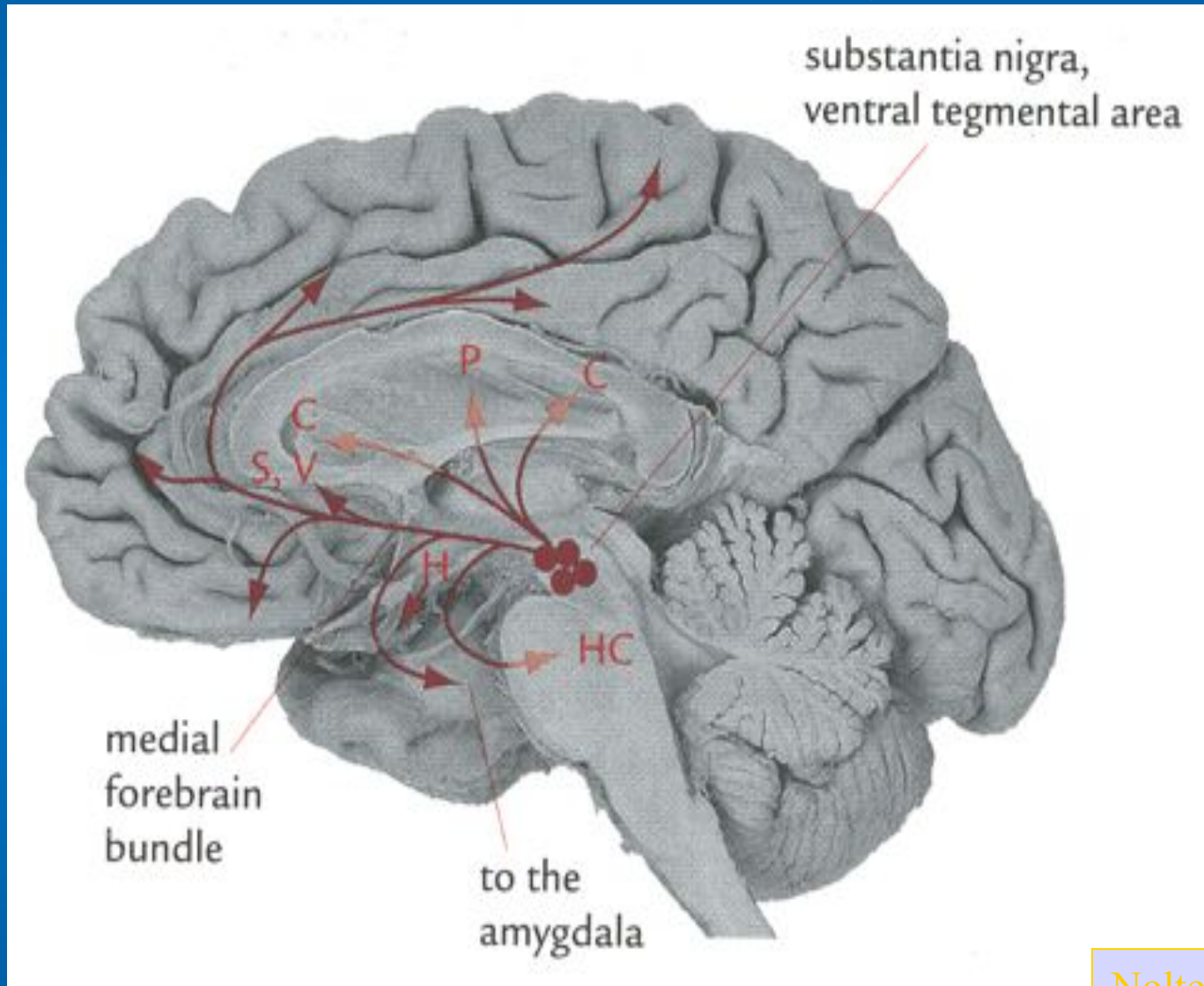
RUPP Trial
MPH > PLA
Effect size: small
to medium

RUPP Autism Network: Methylphenidate in Children With PDD + Hyperactivity

RUPP = Research Unit on Pediatric
Psychopharmacology

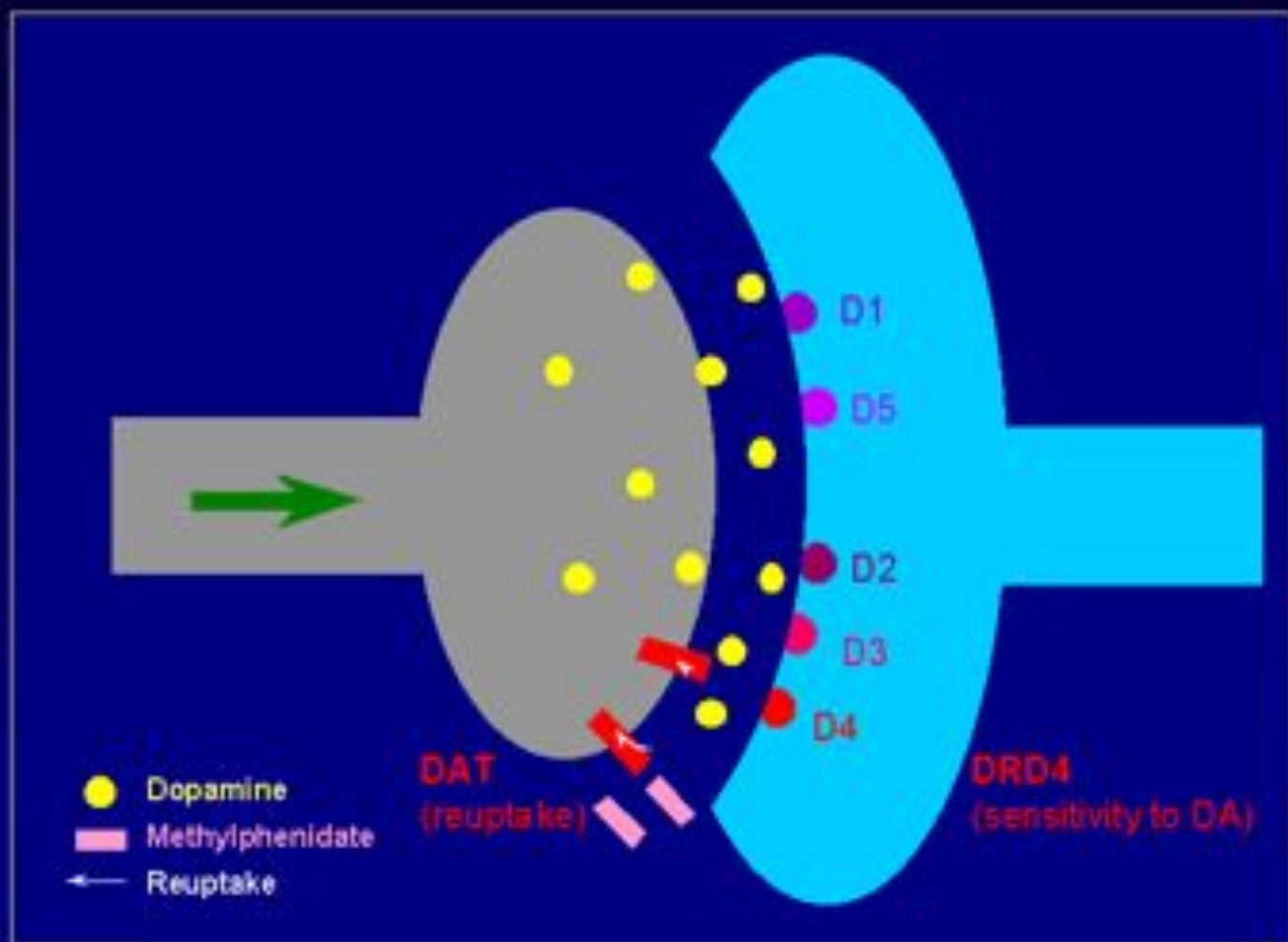
RUPP Autism Network. Arch Gen Psych 2005;62(11):1266-74

Dopamine System



Nolte & Angevine, 1995

Dopamine Synapse



Courtesy of J. Swanson.

MPH in Children With PDD + Hyperactivity: Subject Characteristics in Crossover

- Sample N=66 (59 boys, 7 girls)
- Mean age = 7.5 ± 2.2 years (range 5.0-13.7)
- Mean IQ = 63 ± 33
- Autism = 56
- Three doses of MPH and placebo in random order

RUPP Autism Network. Arch Gen Psych. 2005;62(11):1266-74

MPH Improvement on Teacher Rating of ADHD symptoms

	Dose Level	% Change*
RUPP	Low	12%
RUPP	Medium	13%
RUPP	High	17%

* Corrected for Placebo

In ADHD \approx 40% over placebo

MPH in PDD: Conclusions

- 1) At low doses (12.5-25 mg/day), the medicine helps about 50-60% of children.
- 2) At low doses, it will produce about 20% improvement
- 3) At low doses, it will be well-tolerated
- 4) Higher doses are unlikely to bring about additional benefit and may ↑ risk of adverse effects

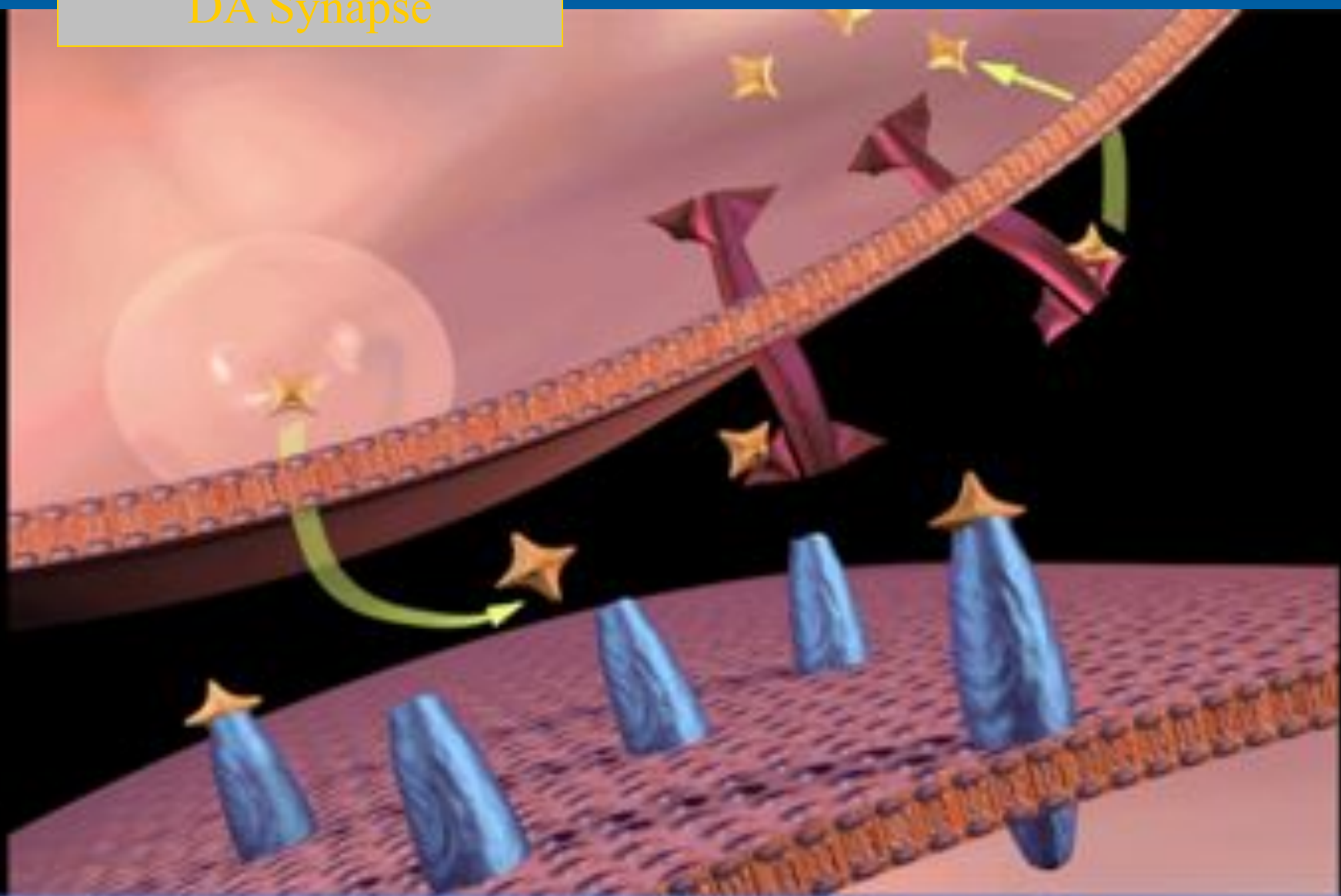
Treatment of Serious Behavioral Problems in Children with ASDs

Atypical Antipsychotics in ASD

<u>Drug</u>	<u>open</u>	<u>Placebo</u> <u>controlled</u>	<u>N > 60</u>
Risperidone*	X	X	X
Olanzapine	X		
Ziprasidone	X		
Quetiapine	X		
Aripiprazole*	X	X	X

* FDA Approved for Rx of 'irritability' in autism

DA Synapse



Research Units on Pediatric
Psychopharmacology Autism
Network
Risperidone Trials

RUPP Risperidone: Sample

- N=101 (82 males, 19 females)
 - Risperidone: N=49
 - Placebo: N=52
- 8-week, randomized, double-blind, placebo-controlled, parallel groups
- Mean age = 8.8 years (range 5-17)

RUPP Autism Network. NEJM, 347(5): 314-321.

ABC Irritability Scores at Baseline and End Point by Treatment Group

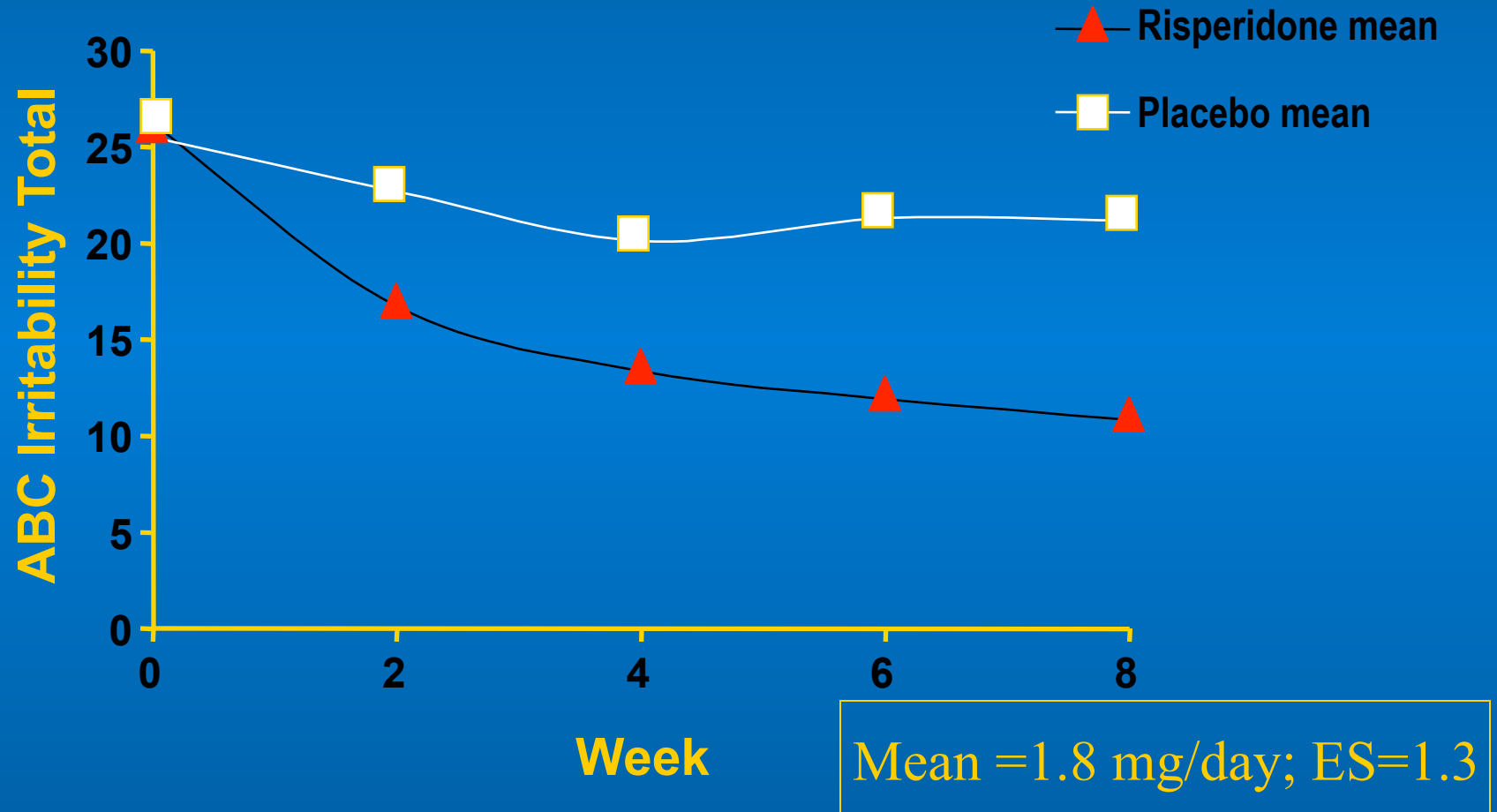
ABC Scale	Risperidone		Placebo	
	Baseline Mean (SD)	End Point Mean (SD)	Baseline Mean (SD)	End Point Mean (SD)
Irritability	26.2 (7.9)	11.3 (7.4)	25.5 (6.6)	21.9 (9.5)

Mean Dose=1.8 mg/day

p<0.0001; Effect Size = 1.3;

RUPP Autism Network. NEJM, 347(5): 314-321.

RUPP Autism Network: Irritability Scale



RUPP Autism Network. NEJM, 347(5): 314-321.

Clinical Global Impression-Improvement

1 = Very Much Improved

2 = Much Improved

3 = Minimally Improved

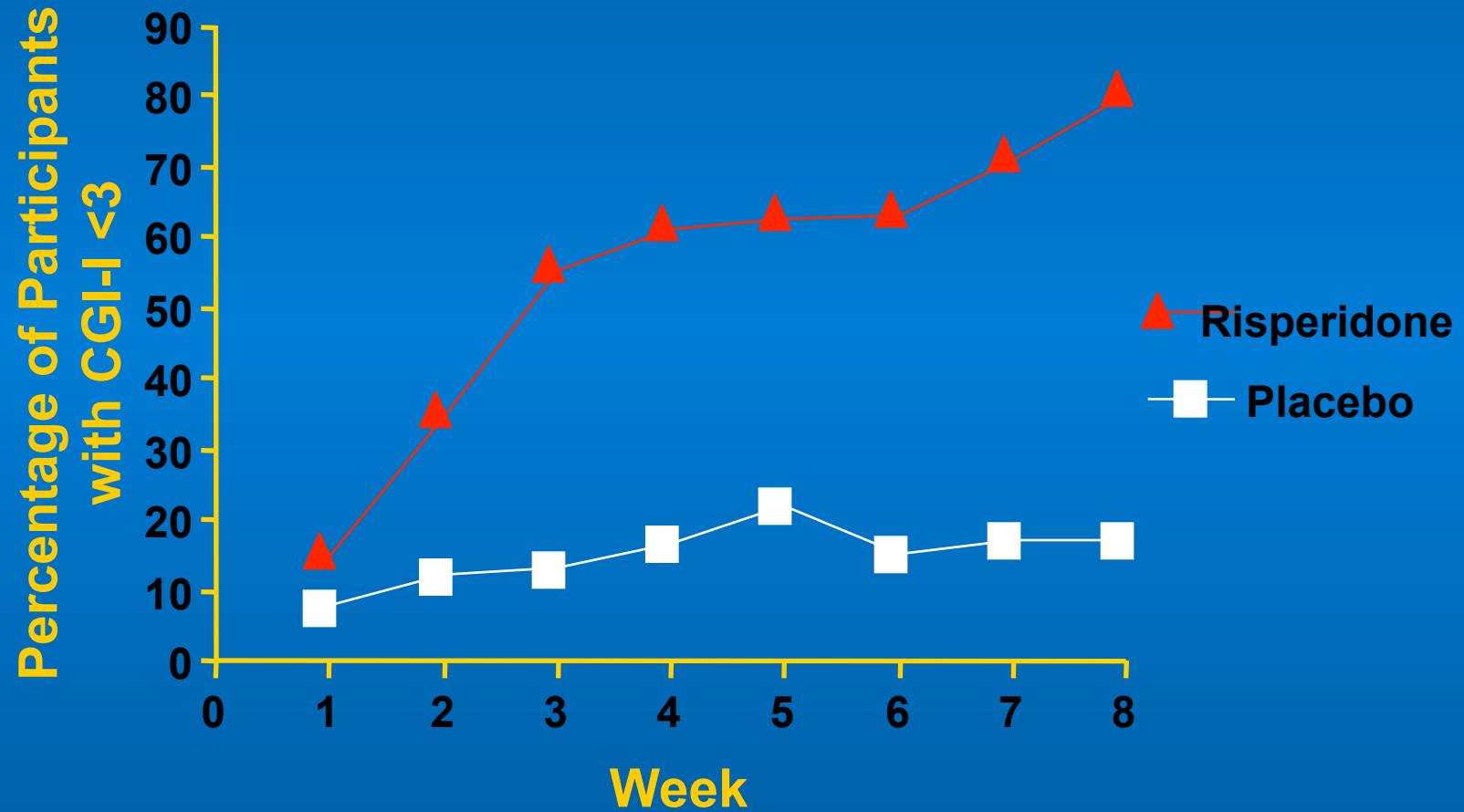
4 = No Change

5 = Minimally Worse

6 = Much Worse

7 = Very Much Worse

Clinical Global Impressions-Improvement



RUPP Autism Network. NEJM, 347(5): 314-321.

RUPP Risperidone Study: Adverse Effects

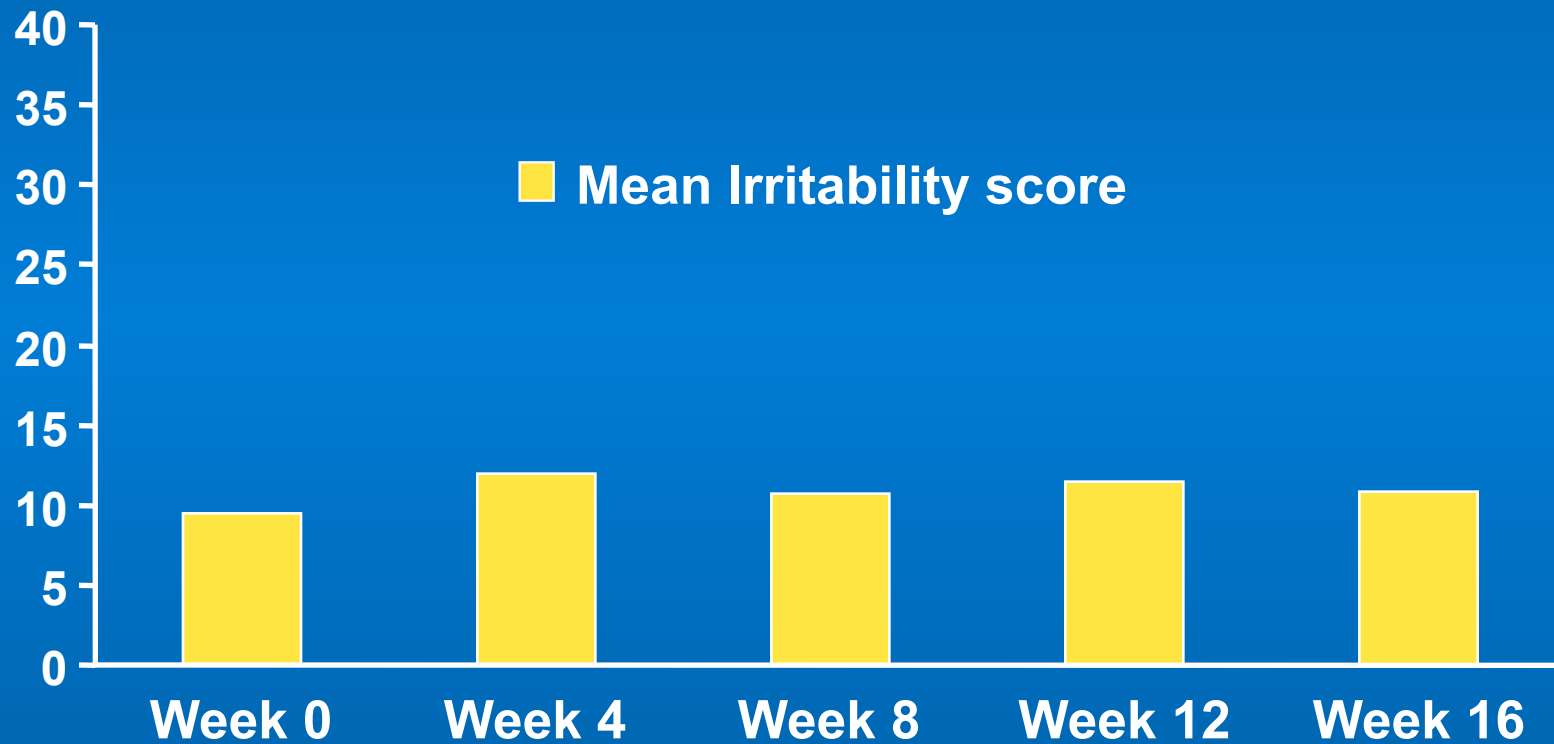
Adverse Effect	RISP (N=49) N (%)	PLA (N=52) N (%)	p-Value
↑ Appetite (Mild)	24 (49.0)	15 (28.8)	0.05
↑ Appetite (Mod)	12 (24.5)	2 (3.8)	0.01
Tiredness	29 (59.2)	14 (26.9)	0.002
Drowsiness	24 (49.0)	6 (11.8)	<0.001
Drooling	13 (26.5)	3 (5.8)	0.01
Tremor	7 (14.3)	1 (1.9)	0.05
Mean Weight Gain (kg)	2.7 ± 2.9	0.8 ± 2.2	<0.01

RUPP Autism Network. NEJM, 347(5): 314-321.

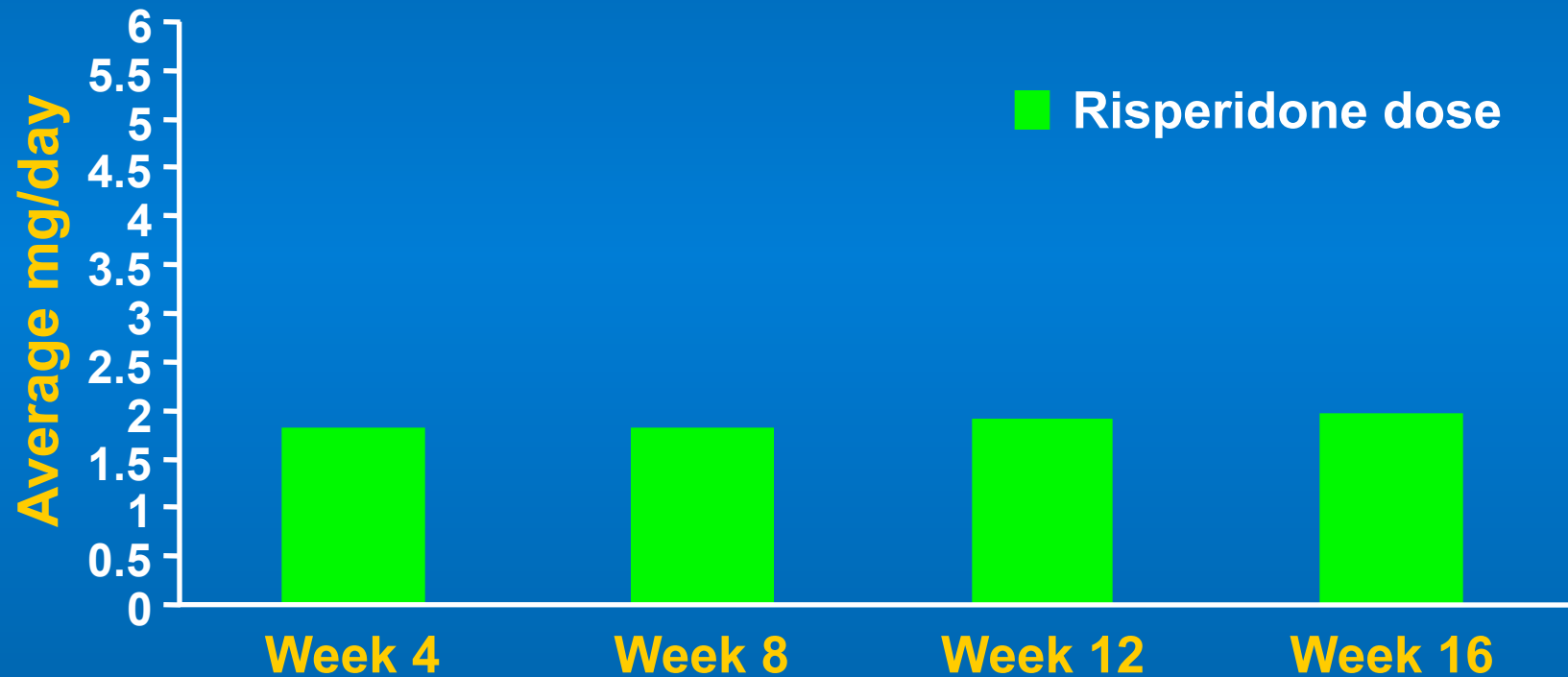
Four Month Open label

RUPP Autism Network. Am J Psychiatry. 2005;162(7):1361-9

ABC Irritability Scores by Week in Open-Label (N=63)



Mean Dose in Open-Label Risperidone



Risperidone Extension: Weight Gain

- N=63 followed for 6 months of treatment
- Mean weight gain = 5.6 ± 3.9 kg
 - No clear predictors of weight gain
- Weight gain greatest in first 2 months
 - 1.4 kg/month vs. average of 0.88 kg/month
- Monitoring and counseling about diet and weight at the start of treatment

Risperidone in Autism: Conclusions

- 1) At low to medium doses (1.25 to 1.75 mg/day), 70% of children with autism + tantrums, aggression, self-injury will show positive response.
- 2) Magnitude of improvement $\geq 50\%$
- 3) At low to medium doses, drug is well-tolerated and benefits endure over time
- 4) Discontinuation at 6 months \rightarrow relapse
- 5) Weight gain requires monitoring throughout treatment

RUPP Autism Network:
Risperidone only vs.
Risperidone + Parent Training

RUPP Autism Network, JAm Acad Child Adoles Psychiatry, 11/09

Risperidone only vs Risperidone + Parent Training

Design

- 6-month study
- 124 subjects (age 4 to 13 years)
- Random assignment
 - risperidone only (N=49) or
 - risperidone + Parent training (N=75)

Risperidone only vs Risperidone + PT

Study Model:

The medication ↓ tantrums, aggression and self-injury, setting the stage for PT improve adaptive skills.

↓ noncompliance → ↑ adaptive skills (can't do vs won't do)

Behavior Therapy: Basics

- Antecedents & consequences (function of the behavior)
- Environmental manipulation (↓ triggering situation)
- ↑ functional communication (teach child to request a *break* vs acting out to escape demands)
- Extinction (selective ignoring)
- Positive reinforcement (go for incremental success)

Sample Characteristics

Variable	MED	COMB
Age	7.5	7.4
Irritability	29.7 (6.10)	29.3 (6.97)
Autism	32 (65.3)	49 (65.3)
PDD-NOS	13 (26.5)	22 (29.3)
Asperger's	4 (8.2)	4 (5.3)
Average IQ	11 (22.5)	28 (38.4)*

*P < .05

Maladaptive Behavior Outcomes

Measure	COMB (75)		MED (N=49)		ES
	BL	EP	BL	EP	
HSQ	4.3 (1.67)	1.23 (1.36)	4.16 (1.47)	1.68 (1.36)	0.34*
ABC-Irritability	29.3 (6.97)	11.0 (6.64)	29.7 (6.10)	14.5 (9.90)	0.48*

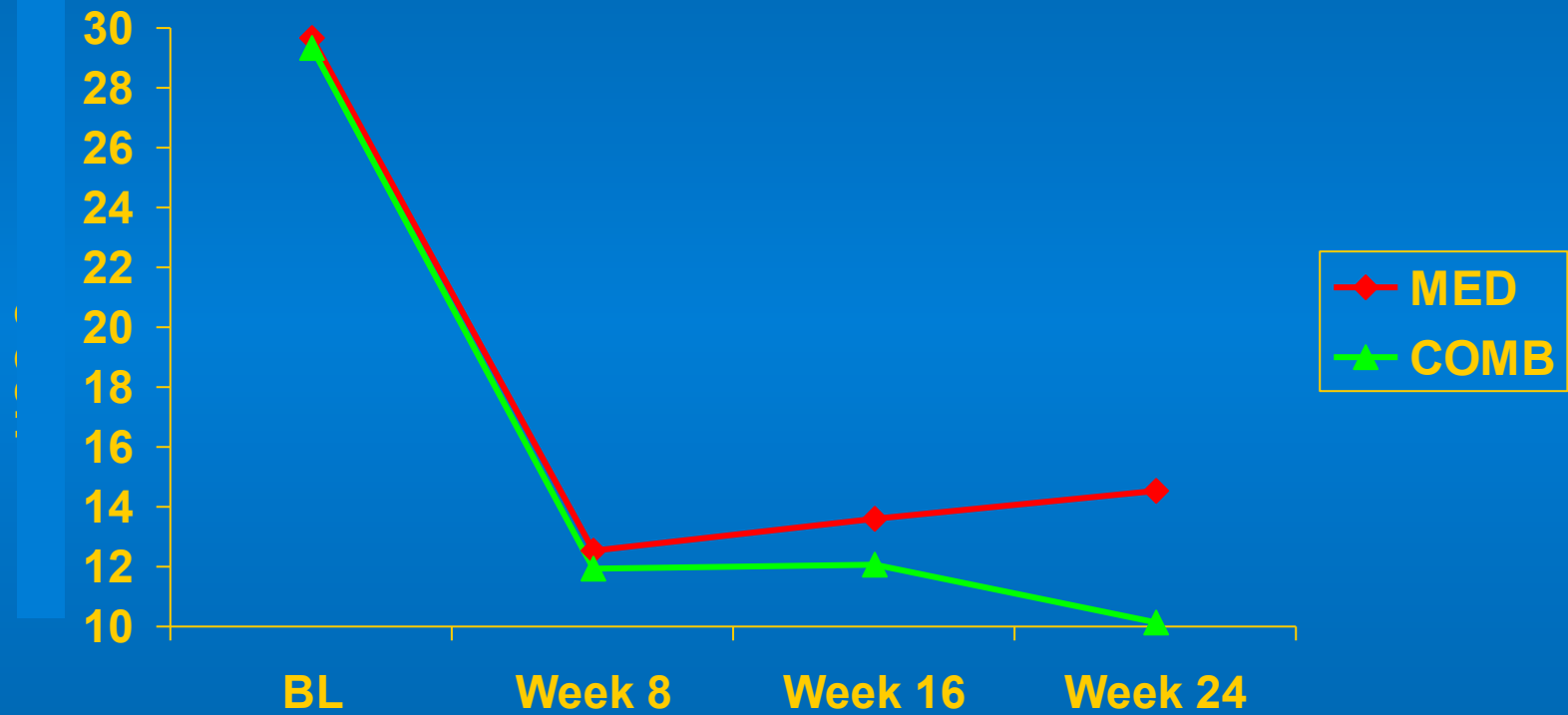
* $p < .05$

Maladaptive Behavior Outcomes

Measure	COMB (75)		MED (N=49)		ES
	-- BL--	-- EP--	-- BL--	-- EP--	
ABC-Irritability	29.3 (6.97)	11.0 (6.64)	29.7 (6.10)	14.5 (9.90)	0.48*

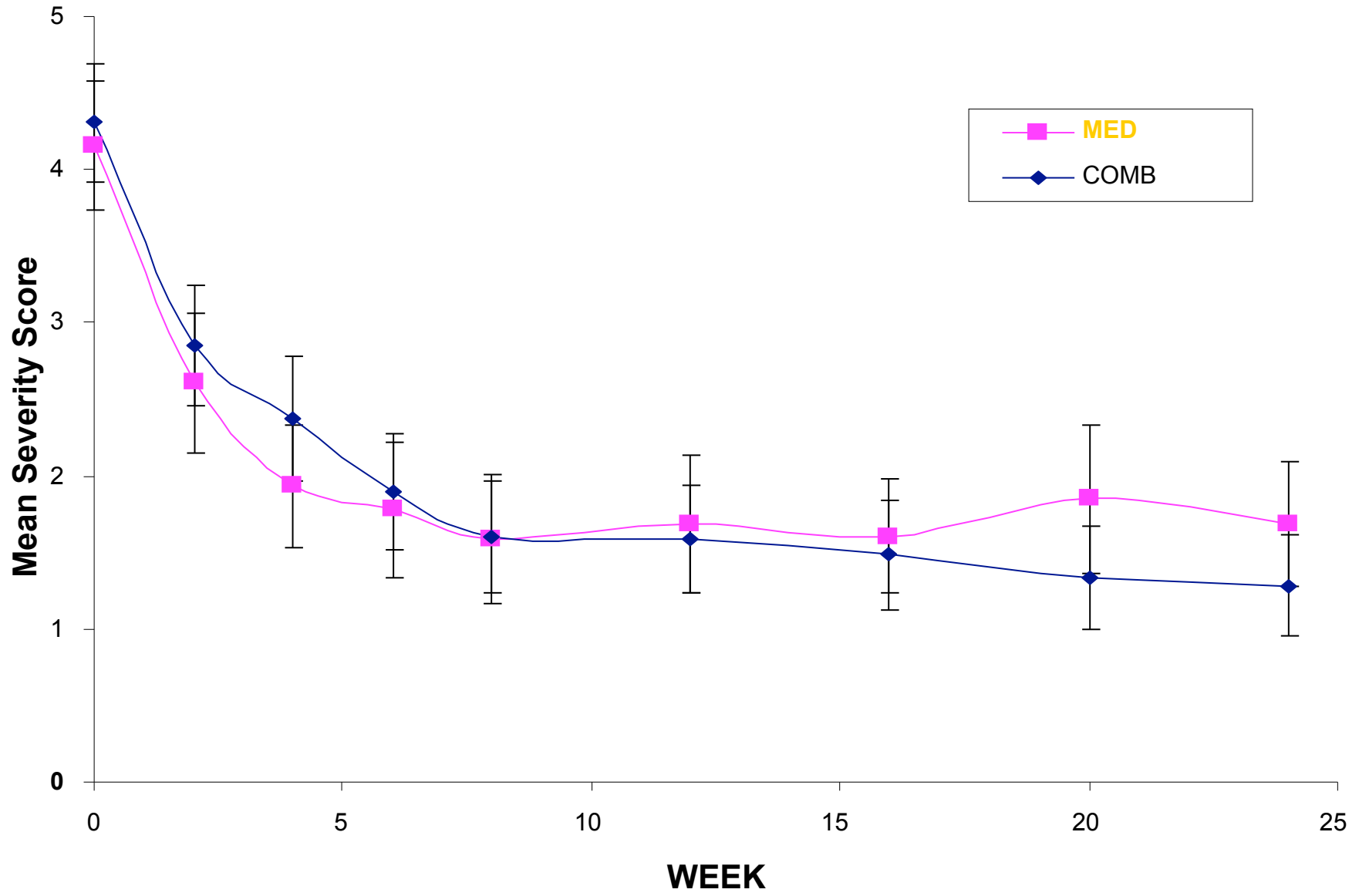
* $p < .05$

ABC Irritability



ES = .48

Parent-rated Home Situations Questionnaire Scores at Baseline Through Week 24 with LSMeans



Adaptive Behavior Outcomes

* $p < .05$

Vineland Domain	COMB (65)		MED (N=42)		ES
	-- BL--	-- EP--	-- BL--	-- EP--	
Daily Living	50.8 (18.49)	55.6 (21.86)	41.1 (19.81)	45.3 (20.48)	.13
Socialization	59.5 (15.01)	67.4 (18.48)	53.5 (14.41)	56.6 (17.38)	.35*
Communication	61.2 (20.95)	63.9 (22.65)	53.2 (19.94)	53.6 (20.23)	.15
Adaptive Composite	53.1 (15.66)	57.9 (19.03)	45.8 (15.50)	47.8 (15.81)	.22*

RUPP Autism Network, JAm Acad Child Adoles Psychiatry, 02/12

Adaptive Behavior Outcomes

* $p < .05$

Vineland Domain	COMB (65)		MED (N=42)		ES
	-- BL--	-- EP--	-- BL--	-- EP--	
Daily Living	50.8	55.6	41.1	45.3	.13
Socialization	59.5	67.4	53.5	56.6	.35*
Communication	61.2	63.9	53.2	53.6	.15
Adaptive Composite	53.1	57.9	45.8	47.8	.22*

RUPP Autism Network, JAm Acad Child Adoles Psychiatry, 02/12

RIS + PT vs RIS only on Vineland Adaptive Behavior scales

	Daily Living	Socialization	Communication
COMB > MED	No	yes	No

Scahill et al., JAm Acad Child Adoles Psychiatry, 02/12

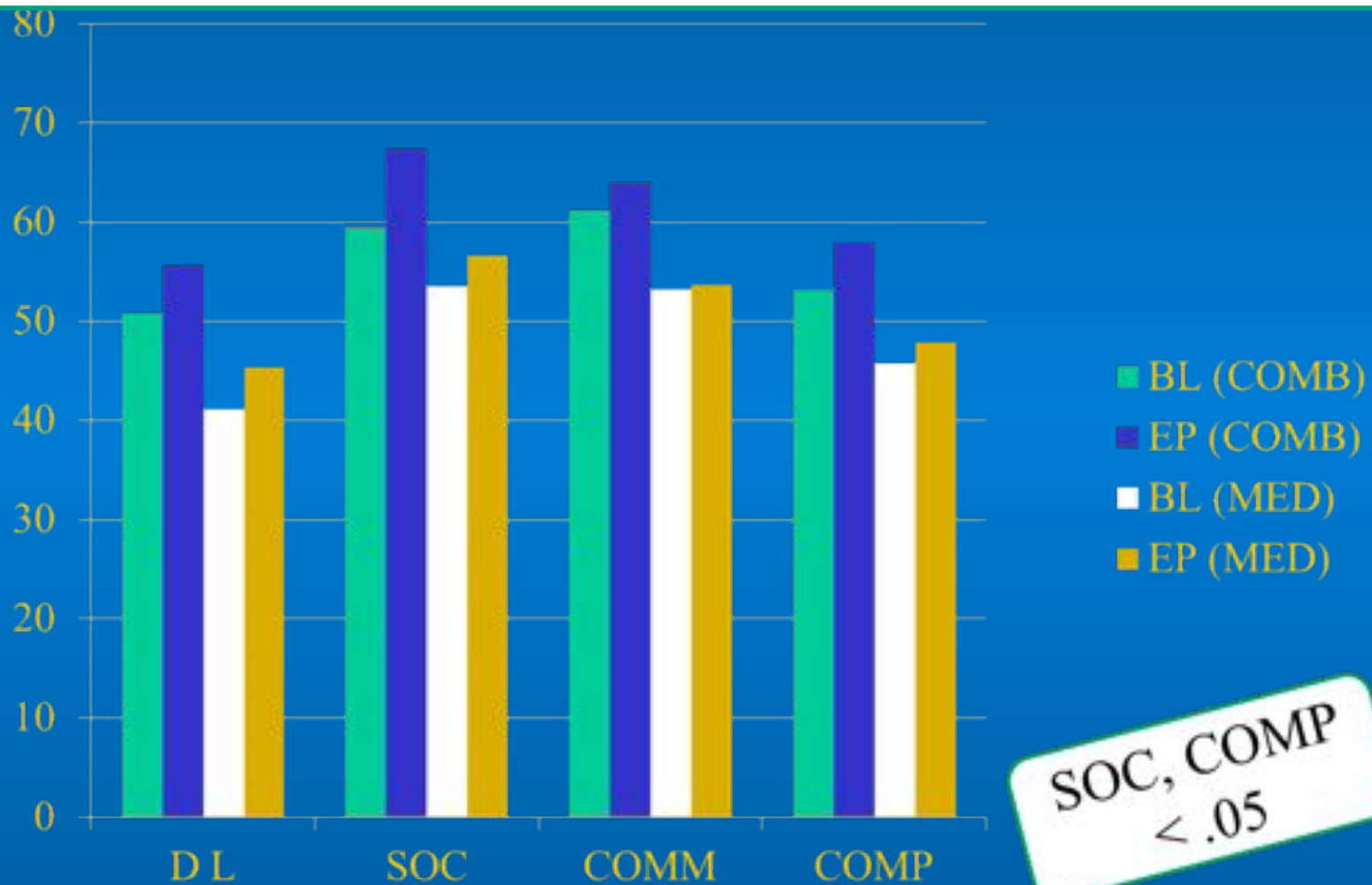
Adaptive Behavior Outcomes

Vineland Domain	COMB (65)		MED (N=42)		ES
	-- BL--	-- EP--	-- BL--	-- EP--	
Daily Living	50.8	55.6	41.1	45.3	.13
Socialization	59.5	67.4	53.5	56.6	.35*
Communication	61.2	63.9	53.2	53.6	.15
Adaptive Composite	53.1	57.9	45.8	47.8	.22*

RUPP Autism Network, JAm Acad Child Adoles Psychiatry, 02/12

* $p < .05$

Vineland (Scahill et al., 2012; JAACAP)



SOC, COMP
< .05

NIH Multisite Trials in Children with ASDs past 15 years

Study	N	Target	Ages	Results
Risperidone vs placebo (2002)	101	Irritability	5-17	RIS > PLA (large effect)
Methylphenidate vs placebo (2005)	66	Hyperactivity	5-14	MPH > PLA (small to medium effect)
Citalopram vs placebo (2009)	149	Repetitive Behavior	5-17	CITALO = PLA
RIS vs RIS + Parent Training (2009, 2012)	124	Irritability & Adaptive Behavior	4.5-13	RIS + PT > RIS alone (small to medium effect)*

* Small to medium effect over large effect of drug alone

Future Directions

- Parent Training as a ‘stand alone’ treatment
- Drug selection
 - Based on ↑ understanding of neurobiology
 - Drugs not on the market (industry partnership)
 - Begin with adults (establish safety)
 - Needed
 - Better outcome measures (e.g., social disability, anxiety)

Compounds worthy of study in ASD

Ready?
y?

Compound	On market	Target	Available measure
SSRI	Yes	Anxiety	Not Quite
Pregabalin			
D1 Antagonist	No	SIB	OK
Oxytocin	Yes	Social interaction	} Yes, but
mGluR antagonist	No		
mGluR agonist	No		
Vasopressin R antagonist	No		

Thank you