

Use of Medications in Children with Autism

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Psychopharmacology in PDD

Outline

- Goal of Intervention Research
- Trends in Clinical Practice
- Hyperactivity
- Repetitive Behavior
- Tantrums, Aggression, Self-injury
- Moving Forward

Disclosures

Consultant
Janssen
Bristol-Myers
Supernus
Neuropharm

Goal of Clinical Research

- Guide clinicians on the selection and staging of treatment interventions
- Identify the likelihood that this treatment will benefit this patient (with specific clinical characteristics)
- Identify the magnitude of change, the time to effect and the risk/benefit equation

Goal of Clinical Research: Guide Clinical Practice

The mother wants to know:

If I give this medicine to my child:

- What are chances that it will help?
- How much will it help?
- When will I start to see benefit?
- How much medicine does he (she) need?
- What are the side effects?

Questions to bear in mind

- What is the proper role of placebo for treatment trials with autism?
- Should medications used in autism have a basis in the underlying neurobiology?
- Should behavioral treatments always be tried first?
- Should medications used in autism be tested before they are used in clinical practice?

Target of Medication

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

Medications Used in Children with ASD

- Haloperidol
- Fenfluramine
- Clonidine
- Naltrexone
- Propranolol
- Stimulants¹
- Clomipramine
- SSRIs¹
- Secretin²
- Amantadine
- Anticonvulsants
- Atypical antipsychotics¹

1= Most commonly used

2= Best studied

Quiz Question #1: Sample size

- In a placebo controlled trial, children are randomly assigned to Active Drug or Placebo. So an N = 100 is 50 per group.
 - What TOTAL sample size would you consider MINIMUM to guide clinical practice for children with autism?
- a) 40 b) 20 c) 60 d) 100

Medication Patterns in Patients with Autism and PDD (Aman et al.)

	N. Carolina, 1993	N. Carolina, 2001
N (% response)	859 (53%)	1538(56%)
Any Medication	30.5%	45.2%
Antipsychotics	12.2%	16.5%
Antidepressants	6.1%	21.4%
Stimulants	6.6%	13.8%
Antihypertensives	4.4%	9.6%
Mood Stabilizers	3.9%	4.9%
Anticonvulsants	13.2%	12.5%

Hyperactivity in Children with PDD

Hyperactivity in PDD: Brief Background

- DSM-IV - don't diagnose ADHD in children with PDD
- Hyperactivity, disruptive behavior, and impulsiveness are common in children with PDD
- Community surveys show that hyperactivity is a common target symptom in children with PDD
- Limited evidence for the treatment of hyperactivity in PDD

Treatment of Hyperactivity in PDD

Drug	open	controlled	N > 40
Methylphenidate		X	X
Atomoxetine	X		
Clonidine	X	X	
Guanfacine	X		
Amantadine	X	X	
Naltrexone	X		

Hyperactivity in PDD

Drug	open	controlled	> PLA
Methylphenidate		X*	yes
Atomoxetine	X		
Clonidine	X	X	no
Guanfacine	X		
Amantadine	X	X	no
Naltrexone	X	X	no

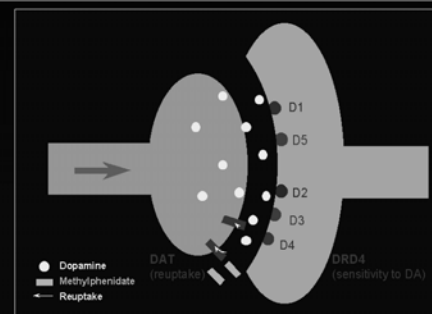
* drug with a trial in 40 or more subjects

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 Synapse



Courtesy of J. Swanson.

MPH in Children With PDD + Hyperactivity

- 7-day test dose period
 - 2 days on placebo & each dose level of MPH (N=72)
 - Daily phone contact to evaluate tolerability
 - 4-week double-blind trial (N=66)
 - 3 dose levels of MPH or placebo in random order
- RUPP Autism Network. Arch Gen Psych, 2005;62(11):1266-74
- 8-week open-label trial at best dose (N=34)

MPH in PDD + Hyperactivity: Dose Schedule

	16-24 kg			25-33 kg			≥34 kg		
	a.m.	noon	p.m.	a.m.	noon	p.m.	a.m.	noon	p.m.
Low Dose (0.125-0.18 mg/kg/dose)	2.5	2.5	2.5	5.0	5.0	2.5	5.0	5.0	2.5
Mid Dose (0.25-0.35 mg/kg/dose)	5.0	5.0	2.5	10.0	10.0	5.0	10.0	10.0	5.0
High Dose (0.5-0.6 mg/kg/dose)	10.0	10.0	5.0	15.0	15.0	10.0	20.0	20.0	10.0

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

MPH in PDD + Hyperactivity: Subject Characteristics

- 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
- Dose levels (morning dose)
 - Low = 0.15/mg/kg
 - Medium = 0.25 mg/kg
 - High = 0.5 mg/kg

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

MPH in Children With PDD + Hyperactivity: Parent Ratings

	N	Parent ABC Hyperactivity Mean (SD)	p	Effect Size*
Placebo	60	26.0 (9.90)		
Low dose	62	23.0 (11.29)	<0.05	0.3
Medium	58	20.8 (10.46)	<0.01	0.5
High dose	62	20.7 (10.24)	<0.01	0.5

*Placebo – active + average SD (10.47);

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

MPH Magnitude of Improvement on ADHD symptoms across various populations

	Dose Level	%	Change*
RUPP	Low	12%	
RUPP	Medium	13%	
RUPP	High	17%	
TS +ADHD	Medium	17%	
MTA (ADHD)	High +	≈ 40	

* Corrected for Placebo

MPH in PDD: Adverse Events → discontinuation in X-over

Adverse Event Point/Dose	Time
• Insomnia + aggression	Week 1/High
↓ Appetite + ↑self-injury	Week 2/High
↓ Appetite + Irritability +Insomnia	Week 2/Low
• Diarrhea	Week 2/Med.
↑ Repetitive behavior + irritability +insomnia	Week 2/High
↑ Stereotypy + insomnia + irritability	Week 3/High
• Tantrums + motor tics	Week 4/High

Tolerability of MPH in RUPP

- 6 of 72 (8%) could not tolerate even the medium dose during Test Dose period
- 7 of 66 (11%) dropped out of crossover due to adverse events
- Overall, 13/72 (18%) exposed to MPH dropped out due to adverse events
- Irritability (N=6) was the most common reason for discontinuation

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

MPH in PDD: Conclusions

- 1) At low doses (12.5-25 mg/day), MPH 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 probably won't bring about additional benefit and will cause more side effects

Guanfacine in PDD

Sample

N=25

Mean age = 9.0 ± 3.14

Gender: Boys=23, Girls=2

Diagnosis: Autism = 7, PDD-NOS = 18

Design - 8-week, open-label

Dose – 1.5 to 3.0 mg/day in 2 or 3 divided doses

Scahill et al., 2006

Guanfacine in PDD: ABC Hyperactivity

	BL (SD)	EP (SD)	change	ES
Parent	31.2 (8.8)	18.9 (10.4)	39%	
	1.4			
Teacher	29.9 (10.1)	21.9 (9.6)	27%	0.8

Guanfacine in Children with PDD: ABC

ABC Measure	---Parent---		---Teacher---	
	Baseline Mean (SD)	Endpoint Mean (SD)	Baseline Mean (SD)	Endpoint Mean(SD)
Hyperact.	31.2 (8.8)	18.9 (10.4) ^a	29.9 (10.1)	22.3 (9.4) ^a
Irritability	17.4 (13.2)	11.5 (8.3) ^a	16.8 (10.6)	15.1 (8.8) ^b
Stereotypy	8.8 (5.8)	5.4 (4.8) ^a	7.5 (5.4)	6.6 (5.5) ^b

Dose range .75 to 3.0 mg/d in three divided doses

a= p < .01

b= not significant

Guanfacine in PDD: SNAP IV

Subscale	BL (SD)	EP (SD)	change	ES
<u>Parent</u>				
Total	35.5 (8.2)	22.7 (10.0)	36%	1.5
Inattention	18.2 (5.1)	12.4 (5.6)	32%	1.2
Hyperactivity	17.3 (4.4)	10.2 (5.4)	41%	1.6
<u>Teacher</u>				
Total	33.1 (10.4)	27.2 (10.4)	18%	0.6
Inattention	16.9 (6.8)	14.2 (6.0)	16%	0.4
Hyperactivity	16.2 (5.3)	13.0 (5.9)	20%	0.6

Guanfacine in PDD: Adverse Events

Adverse Event	N
Irritability/tearfulness	10 (37%)
Sedation	8 (30%)
Sleep disturbance (mid-sleep awakening)	6 (24%)
↓Appetite	3 (12%)
Constipation	3 (12%)
Tiredness	2 (8%)
Perceptual Disturbance	2 (8%)

Guanfacine in PDD: Conclusions

- Guanfacine pilot data are encouraging
- Guanfacine does appear better tolerated than clonidine
- Children with PDD appear to be a higher risk for typical guanfacine adverse effects
- Dosing is not completely clear (sedation vs mid-sleep awakening)
- Start with 0.25 to 0.5 → 2.0 to 3.0 in divided doses (not clear that more is better)

SRI in Autism

Rationale

SRI are effective in OCD. Perhaps the preoccupations and repetitive behaviors in autism would improve as well.

Treatment of Repetitive Behavior in PDD

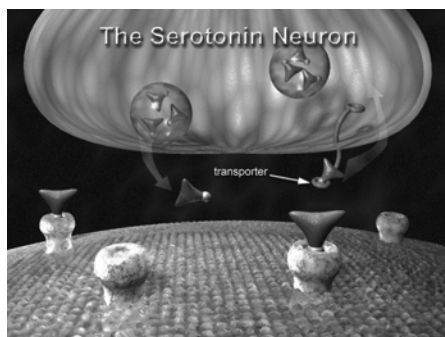
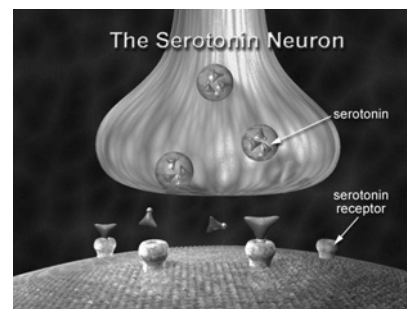
Drug	open	controlled	N > 40
Fluoxetine	X	X	
Fluvoxamine	X	X	
Citalopram	X	X ^a	X ^a
Sertraline	X		
Clomipramine	X	X	

a= results pending

Repetitive Behavior in PDD

Drug	open	controlled	> PLA
Fluoxetine	X	X	yes ^a
Fluvoxamine	X	X ^b	no
Citalopram	X	X ^c	
Sertraline	X		
Clomipramine	X	X	yes ^d

a=small effect; b=adults; c=pending; d= not commonly used



SSRI-Induced Activation

- Set of some or all behaviors
 - Insomnia
 - ↑ motor activity
 - ↑ impulsiveness
 - Talkativeness
 - Aggression

Fluoxetine vs. Placebo in Children and Adolescents With Autism

- Placebo controlled, randomized double-blind, crossover trial
- Primary outcome
 - CY-BOCS —clinician-rated instrument focused on repetitive behavior

Hollander et al. Neuropsychopharm, 2005;30(3):582-9

Sample Description

- N=39
- Mean age = 10
- 30 boys; 9 girls
- 90% autism; 10% Asperger's
- IQ range: 30-132 (59% in MR range)
- No significant differences in the groups at baseline
- CY-BOCS in range of 8-18
- Mean dose = 9.9 mg

Hollander E et al. Neuropsychopharm. 2005;30(3):582-9

Fluoxetine Dose

- Mean dose = 9.9 mg ± 4.35 (range = 2.5-20 mg)
- Dose schedule
 - Starting dose 2.5 mg for 1 week
 - Gradual increases each week as tolerated until week 4 to a maximum of 20 mg/day

Hollander et al. Neuropsychopharm. 2005;30(3):582-9

Results on Primary Outcome Measure

	Phase I			
	Fluoxetine		Placebo	
	BL	EP	BL	BL
EP				
CY-BOCS (3.2)	12.8 (2.6)	11.6 (3.8)	13.4 (2.9)	12.9
% Change	10%		4%	

ES = Δ active - Δ placebo + pooled SD at BL = 0.25
Starting Dose = 2.5; Mean Dosage \approx 10 mg (8 weeks)

Hollander et al. Neuropsychopharm. 2005;30(3):582-9

Adverse Effects by Treatment Group

Symptom	Fluoxetine (%)	Placebo (%)
Anxiety/Nervousne	15.9% (6/39)	33.3% (12/36)
Insomnia	35.9% (14/39)	47.2% (17/36)
Drowsiness	17.9% (7/39)	11.1% (4/36)
Agitation	46.2% (18/39)	44.4% (16/36)
Diarrhea	5.1% (2/39)	19.4% (7/36)
Anorexia	15.4% (6/39)	11.1% (4/36)
Weight Gain	0% (0/39)	2.8% (1/36)
URI	10.3% (4/39)	19.4% (7/36)

Hollander et al. Neuropsychopharm. 2005;30(3):582-9

Adverse Effects by Treatment Group

Symptom	Fluoxetine (%)	Placebo (%)
Anxiety/Nervousne	15.9% (6/39)	33.3% (12/36)
Insomnia	35.9% (14/39)	47.2% (17/36)
Drowsiness	17.9% (7/39)	11.1% (4/36)
Agitation	46.2% (18/39)	44.4% (16/36)

Hollander et al. Neuropsychopharm. 2005;30(3):582-9

SSRIs in PDD: Conclusions

- Little evidence for use in children with PDD
- Application of data from OCD is misleading
- SSRI-induced activation is common in children with PDD—dose related
- We can not answer mother's questions
- Large-scale studies are needed

SSRIs in PDD: Future Directions

- STAART Network study
- Citalopram vs placebo
- 149 subjects with PDD (Age 5 to 17) randomized to citalopram or placebo for 12 Weeks
- Primary outcomes Global Improvement and a measure of repetitive behavior (CYBOCS-PDD).

Atypical Antipsychotics

Tantrums, Aggression, Self-Injury in PDD

Drug	open	controlled	> PLA
Risperidone	X	X	yes ^{a,b}
Aripiprazole	X	X ^c	
Olanzapine	X		
Quetiapine		X	
Ziprasidone	X		

a= FDA approved; b=replicated; c=underway

Research Units on Pediatric Psychopharmacology Autism Network Risperidone Trial

Risperidone in Children with Autism and Tantrums, Aggression, Self-injury

- 8-week, randomized, double-blind, placebo-controlled, parallel groups (N=101)
- 8-week, open-label trial, for placebo non-responders
- 4-month, open-label for all responders (N=63)
- 2-month, randomized, double-blind discontinuation study (N=32)

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

RUPP Risperidone: Sample

- N=101 (82 males, 19 females)
 - Risperidone: N=49
 - Placebo: N=52
- Mean age = 8.8 years (range 5-17)

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

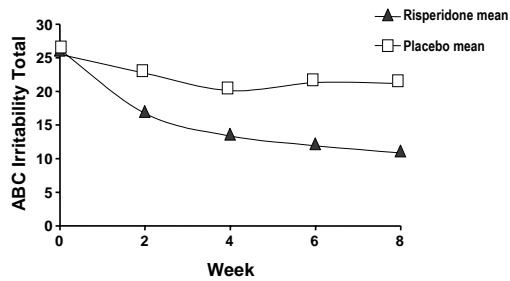
ABC Irritability Scores at Baseline and End Point by Treatment Group

ABC Scale	Risperidone		Placebo	
	Baseline Mean (SD)	End Point Mean (SD)	Baseline Mean (SD)	End Point Mean (SD)
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



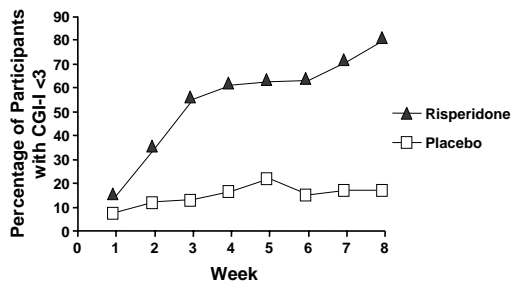
RUPP Autism Network. NEJM, 347(5): 314-321.

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

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

Clinical Global Impressions-Improvement



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

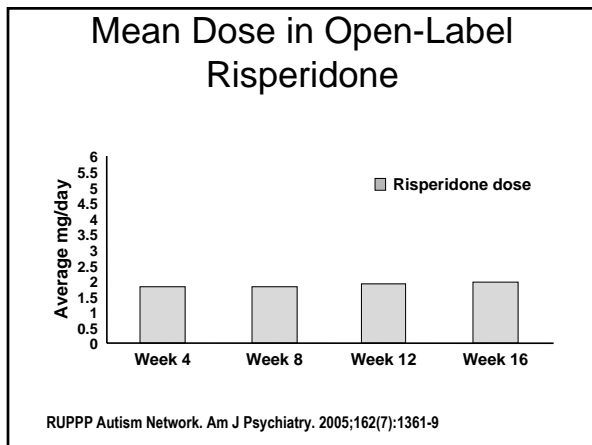
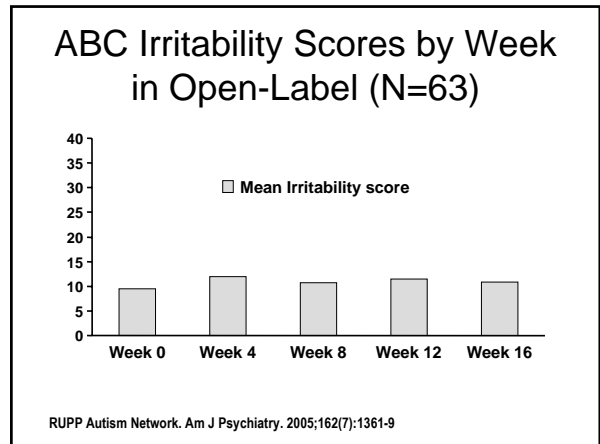
RUPP Risperidone Study: Adverse Effects

Adverse Effect	RISP (N=49) N (%)	PLA (N=52) N (%)	p-Value
↑ Appetite (Mild) 0.05	24 (49.0)	15 (28.8)	
↑ 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
Drizzling	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

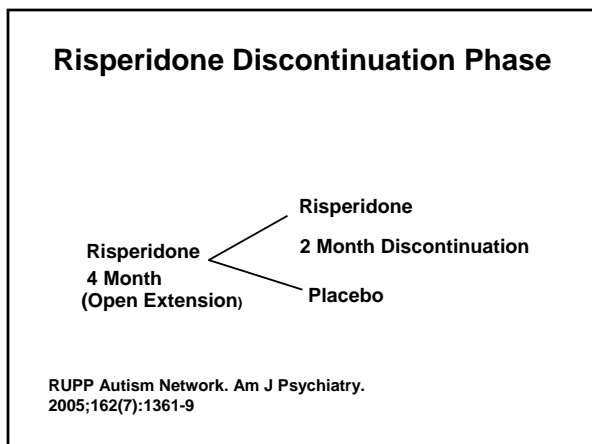
RUPP Autism Network. NEJM, 347(5): 314-321.

Four Month Open label

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

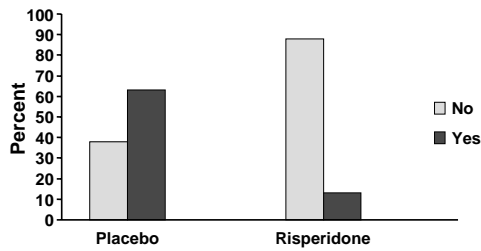


- ### Risperidone Extension: Weight Gain
- N=63 followed for 6 months of treatment
 - Mean weight gain = 5.6 ± 3.9 kg
 - No clear predictors of weight gain
 - Weight gain greatest in first 2 months
 - 1.4 kg/month vs. average of 0.88 kg/month
 - Monitoring and counseling about diet and weight at the start of treatment
- Martin A et al. Am J Psychiatry. 2004;161(6):1125-7



- ### RUPP Risperidone Discontinuation Phase
- Definition of relapse
 - $\geq 25\%$ increase on Irritability subscale
 - and
 - CGI-Improvement score of much worse or very much worse
- RUPP Autism Network. Am J Psychiatry. 2005;162(7):1361-9

Relapse Rate by Group (N=32)



Yates $\chi^2 = 6.53$, $p = 0.01$; Placebo 10/16 vs. risperidone 2/16;

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

Risperidone in PDD: Conclusions

- 1) At low to medium doses (1.25 to 2.0 mg/day), helps about 70% of children.
- 2) At low to medium doses, it will produce about 50% improvement in tantrums, aggression, self-injury
- 3) At low to medium doses, it will be well-tolerated and benefits endure over time
- 4) Weight gain is a concern that requires monitoring throughout treatment

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

Risperidone only vs Risperidone + PMT

Design

6-month study

124 subjects: randomly assigned to risperidone only (N=49) or risperidone + PMT (N=75)

Risperidone only vs Risperidone + PMT

Study Model:

The medication ↓ tantrums, aggression and self-injury, setting the stage for PMT improve every day living skills.

The two treatments are directed at related but separate outcomes.

Thank You