

Measurement Issues for Clinical Trials in Autism

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Disclosures

- Consultant
 - Pfizer
 - 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	

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

- Early onset (before 30 months of age)
- 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*****

Reasons for Increasing Prevalence

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

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

Measurement Challenges in ASD

- Wide range of cognitive & verbal abilities
- Reliance on informants (observable behavior)
- Social Deficits, Anxiety, Repetitive Behavior, Restricted Interests: Overlap & Differences

Drug trials in ASD with sample size > 60 subjects

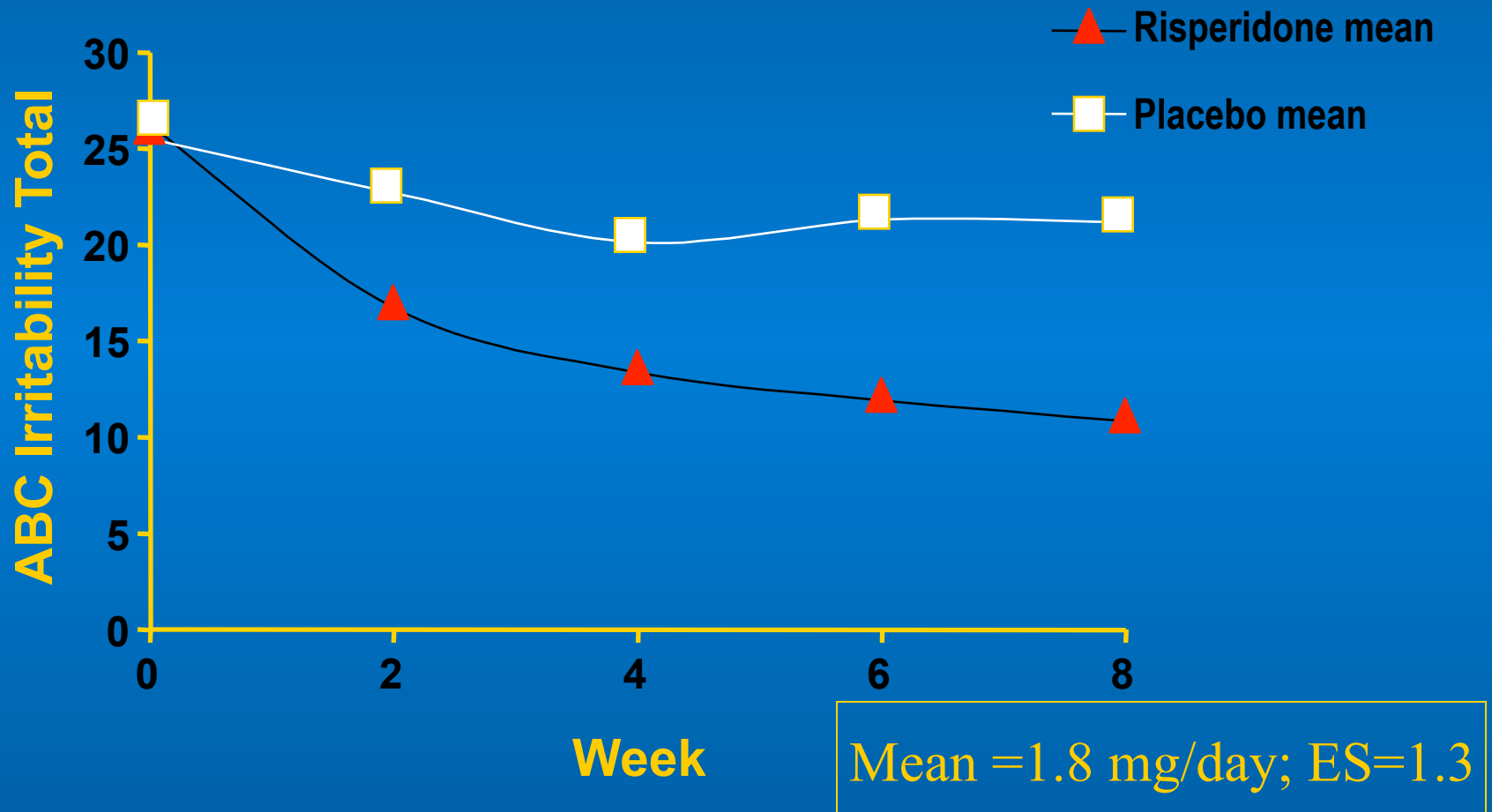
Drug	target	Results
fenfluramine	Social interaction	Act=Pla
secretin	Social Interaction	A=P
risperidone	Tantrums/aggression	A > P +++
aripiprazole	Tantrums/aggression	A > P ++
methylphenidate	Hyperactivity	A > P +
citalopram	Repetitive behavior	A=P
fluoxetine	Repetitive behavior	A=P

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

FDA Approved Drugs in Autism

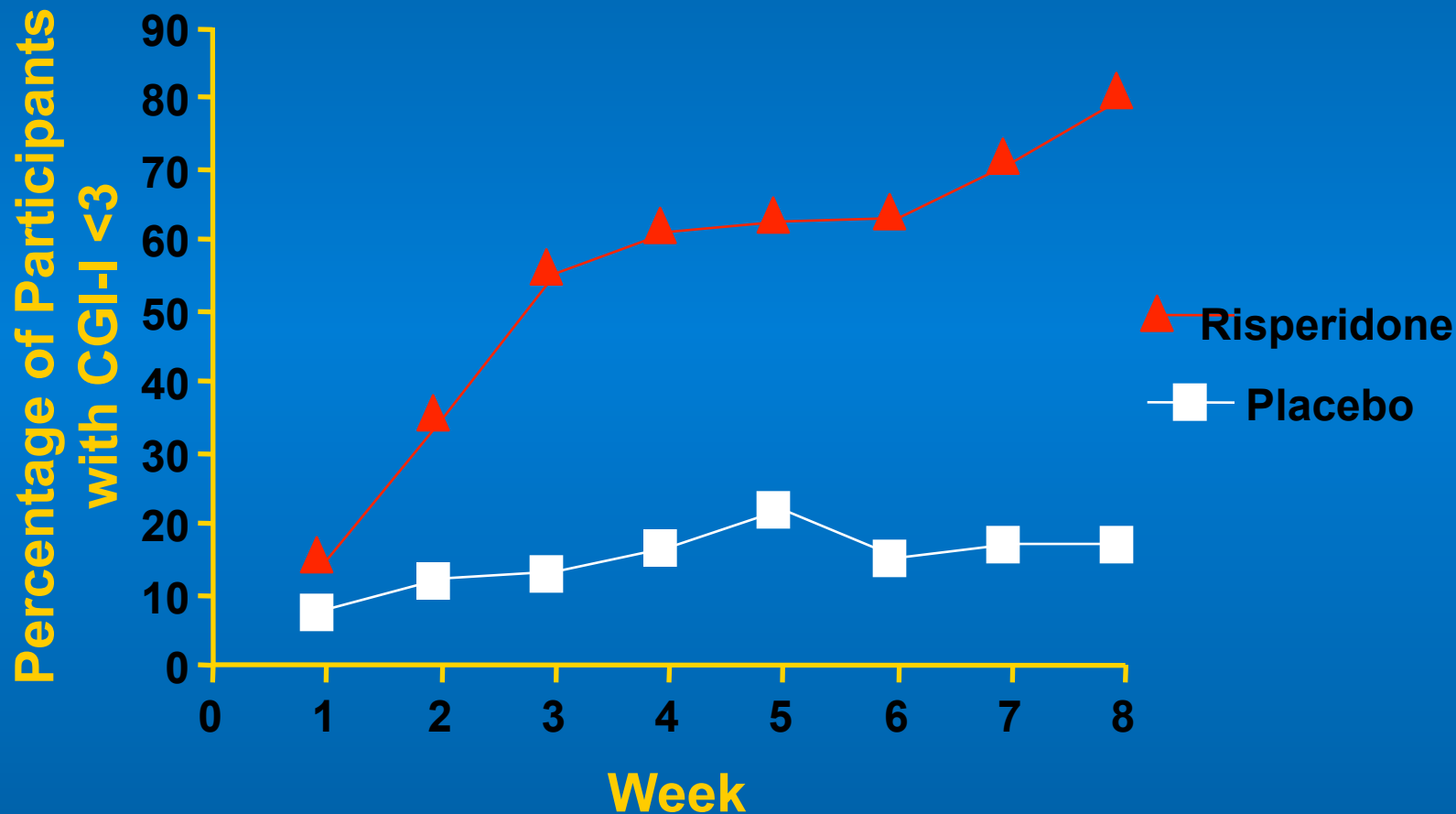
Drug	Year	Indication
Risperidone	2006	Irritability (Tantrums, aggression, self injury)
Aripiprazole	2009	

RUPP Autism Network: Irritability Scale



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

Clinical Global Impressions-Improvement



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

BMS Trial of Aripiprazole in Autism

- N=218 (195 males, 23 females)
- Aripiprazole 5 mg = 53
- Aripiprazole 10 mg = 59
- Aripiprazole 15 mg = 54
- Placebo: N=52
- Mean age \approx 9.5 years (range 5-17)

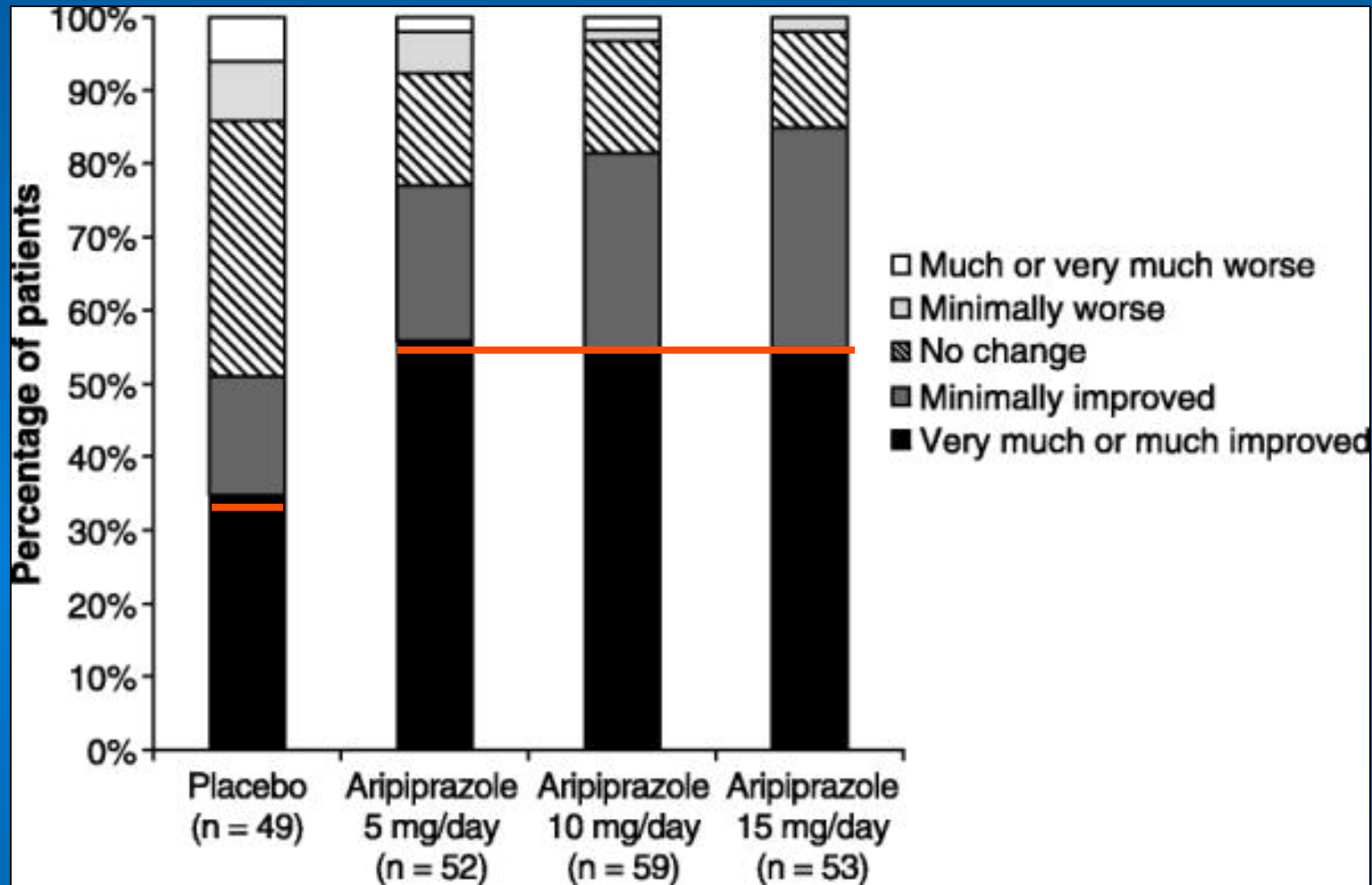
JAACAP 48(11):1110, 2009

Aripiprazole ABC Irritability scores

Dose	BL	EP (from graph)	ES
Placebo	28.0 (6.9)	18	
5 mg	28.6 (7.6)	16	.36
10 mg	28.2 (7.4)	14	.58
15 mg	28.9 (6.4)	14	.68

ES=change active – change in placebo ÷ 7.2 (SD)

Fig. 3 CGI-I by group at Week 8 (LOCF)



JAACAP 48(11):1110, 2009

Repetitive Behavior

Repetitive Behavior (RB)

DX	Behaviors	Impairment	Distress
ASD	Flapping, rocking flipping objects, watching the same video, lining up objects	Wastes time, interferes with daily living & social interaction, hinders constructive activities	If behavior is interrupted (drawn to it)
OCD	Washing, checking, repeating rituals, ordering & arranging	Wastes time, interferes with daily living & social interaction, avoidance	Unwanted behaviors ↓ anxiety/harm (has to do it)
TS	Tics (blinking, head jerking, shrugging, grunting, throat clearing)	Interferes with daily living & social interaction, social isolation	Unwanted urges & suppression (has to do it)

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Repetitive Behavior ASD, OCD, TS: Drug Response

DX	SSRIs	Risperidone
ASD	ACT = PLA	ACT > PLA (medium effect)
OCD	ACT > PLA Medium effect	ACT > PLA (medium effect as adjunctive Rx)
TS	ACT = PLA	ACT > PLA (large effect)

Obsessions, Preoccupations, Repetitive Behaviors

DX	Content	Impairment	Distress
OCD	Contamination, harm to self or others, need for symmetry	Wastes time, interferes with daily living & social interaction, → avoidance	Unwanted thoughts & behaviors; fear worries are real; compelled to perform behaviors ↓ anxiety/harm
	Washing, checking, repeating rituals, ordering & arranging		
ASD	Fans, air conditioners; Thomas TTE; need for routines (turn R at corner)	↓ social interaction; ↓ constructive activities; interferes with family life	If deterred from interest or behavior ; ↑ frustration – vigilant & over-reacts to change
	Flapping, flipping objects, watching the same video, echoing		

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 Global Improvement and a clinician measure of repetitive behavior (CYBOCS-PDD).

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

Clinical Global Impression-Improvement

1 = Very Much Improved

2 = Much Improved

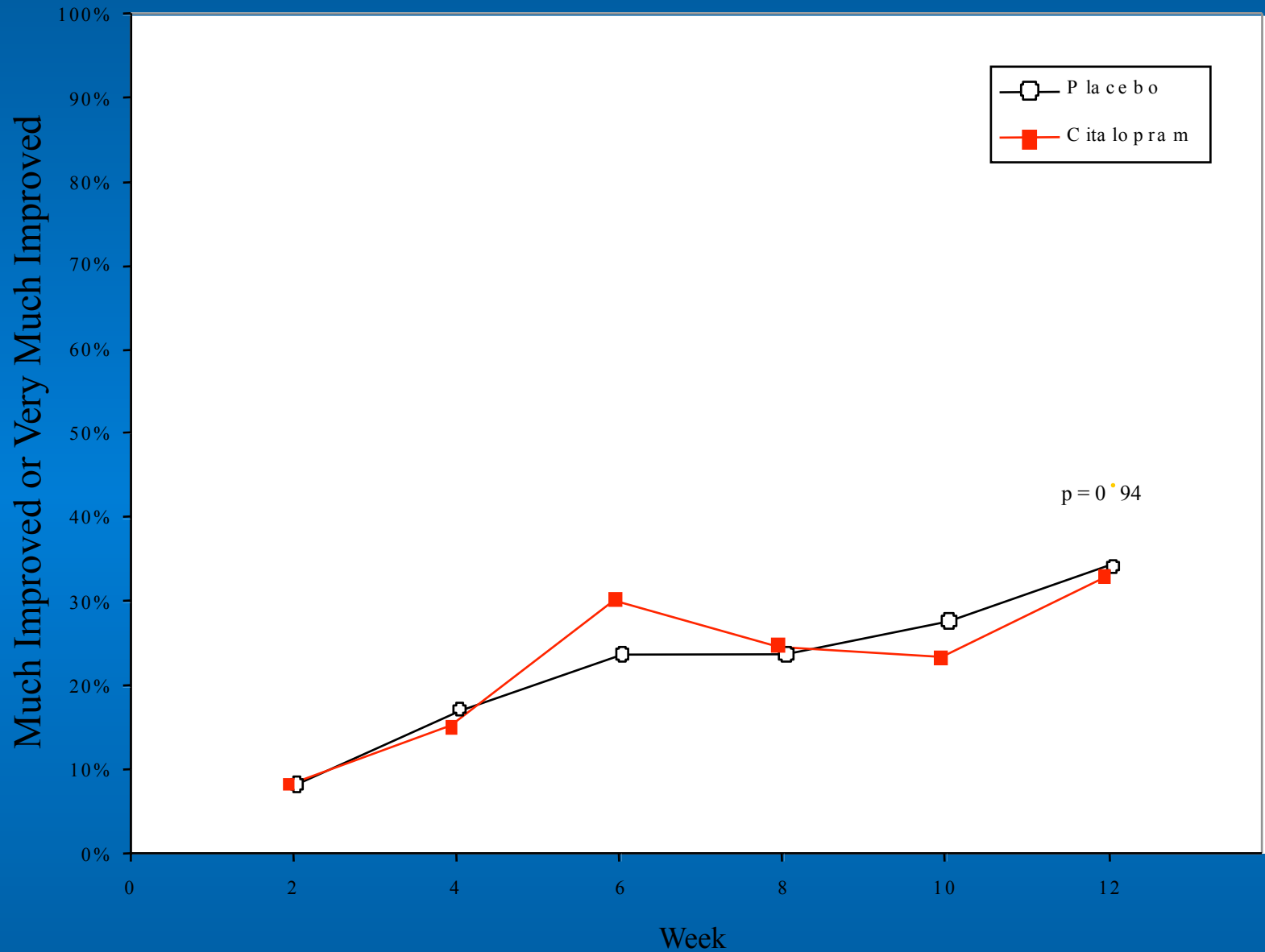
3 = Minimally Improved

4 = No Change

5 = Minimally Worse

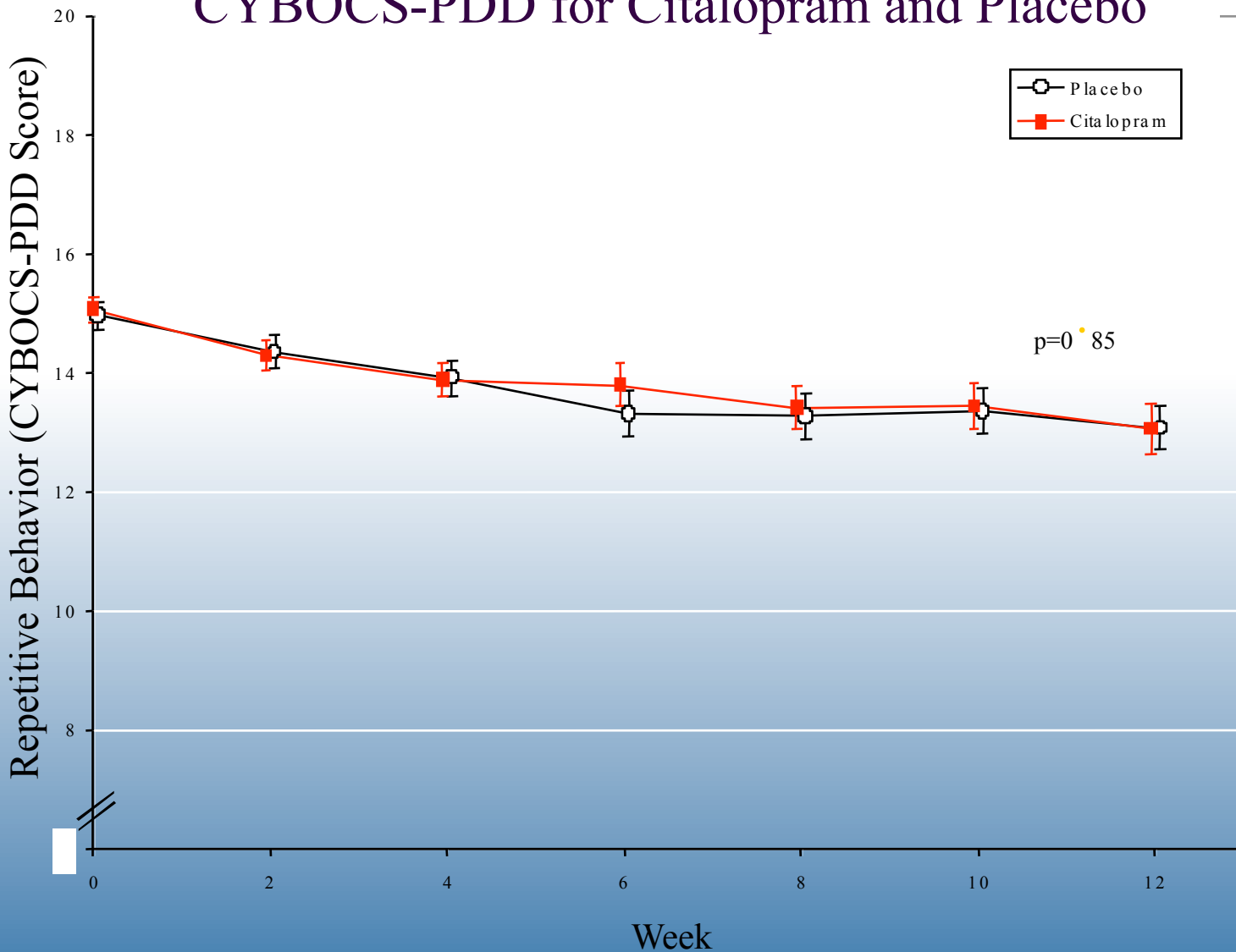
6 = Much Worse

7 = Very Much Worse



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

CYBOCS-PDD for Citalopram and Placebo



Children's Yale-Brown Obsessive-Compulsive Scale- modified for PDD

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.”

Restricted Interests, Preoccupations, Obsessions, Worries

DX	Content	Impairment	Distress
ASD	Fans, air conditioners; Thomas TTE. Insistence on routines (turn right at the corner)	↓ social interaction; ↓ constructive activities; interferes with family life	If deterred from interest (drawn to it); ↑ frustration - over-reacts to change
OCD	Contamination, harm to self or others, need for symmetry	Interferes with daily living & social interaction; promotes avoidance	Unwanted thoughts; conflict that worries are real
ANX	Upcoming events , peer acceptance, group situations, separation from parent(s)	Interferes with daily living, promotes avoidance, social isolation	Stuck on worry; frustration about worry; somatic responses

Anxiety

Anxiety ASD, Anxiety disorders: Drug Response

DX	SSRIs	Benzodiazepines	Alpha 2-delta
ASD	No evidence	No evidence	No evidence
GAD, SocP, SAD	ACT > PLA Medium effect	ACT > PLA (in adults)	pregabalin (in adults)

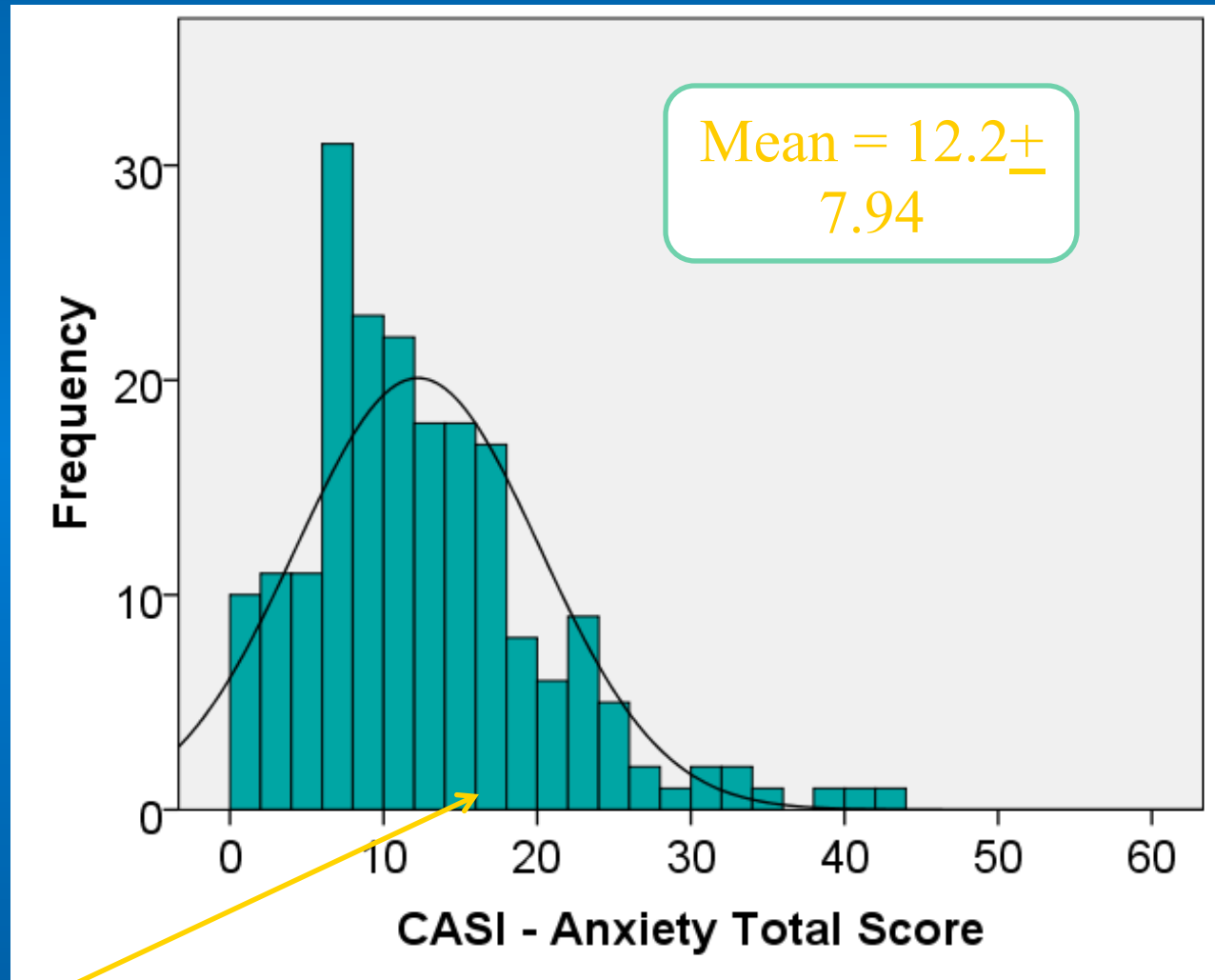
Demographic and Diagnostic Characteristics

N	415
Gender (% male)	353 (85%)
IQ < 70 (%)	200 (51%)
Non-verbal (%)	92 (23%) ^a
Autistic Disorder	336 (81%) ^b
Asperger's Disorder	20 (5%)
PDD-NOS	59 (14%)
Mean age (SD)	8.47 (2.87)
a= greater in < IQ 70; b=greater in < 70 IQ	

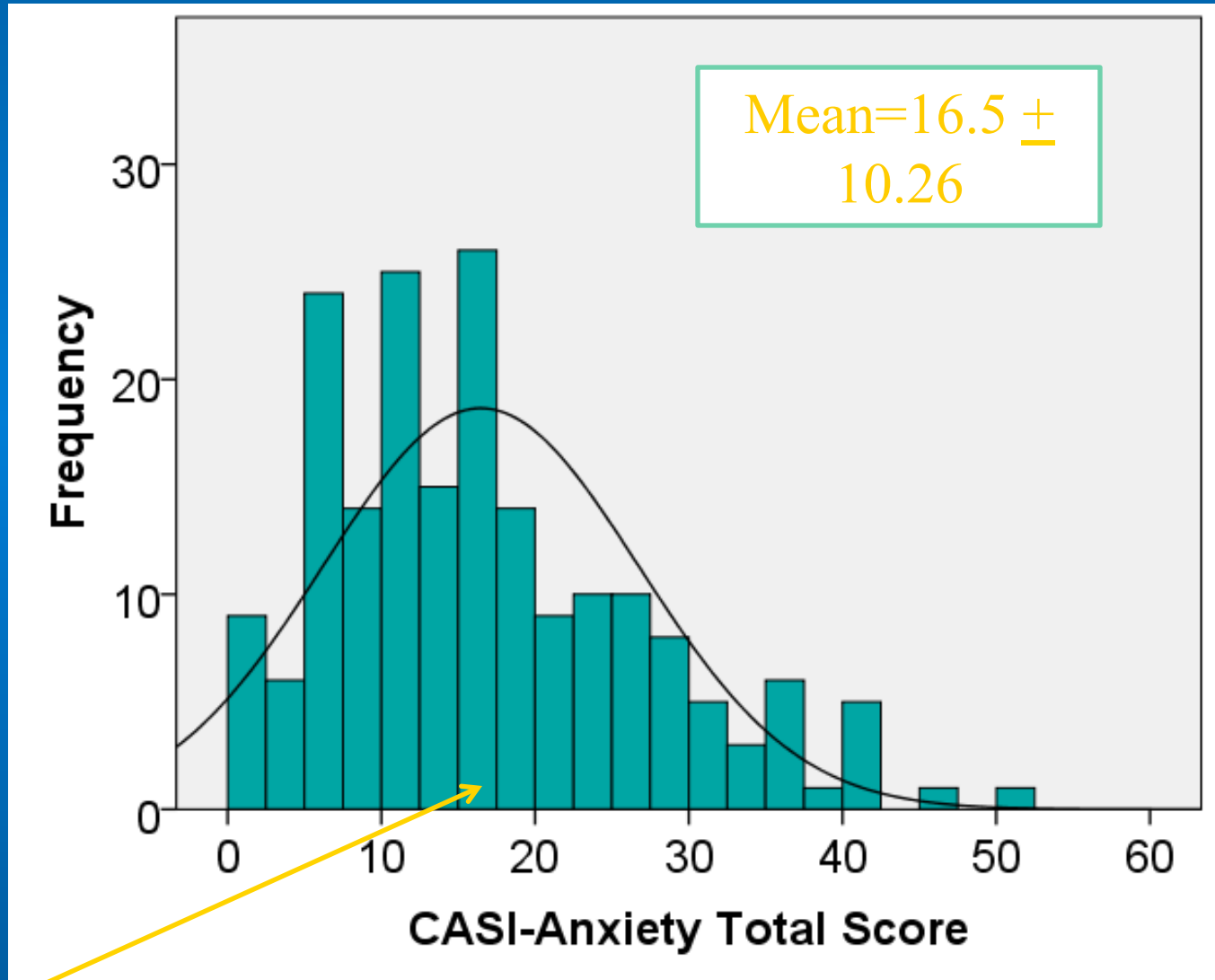
CASI Anx scale (N=415)

- 20-item, DSM-IV-based scale
- Parent-rated, scored 0 to 3
- Mean = 14.2 ± 9.4 (range 0 to 50)
 - IQ < 70: Mean = 12.24 ± 7.94
 - IQ \geq 70: Mean = 16.47 (10.26)

Distribution of 20-item CASI Anx in subjects < IQ 70



Distribution of 20-item CASI Anx in subjects \geq



CASI Anx items commonly endorsed (N=415)

item
More anxious in social situations
Acts restless or edgy
Has difficulty falling asleep

CASI Anx items rarely endorsed (N=415)

item
Complains about feeling sick when expects separation from parents
Worries about physical health
Nightmares about separation from parents

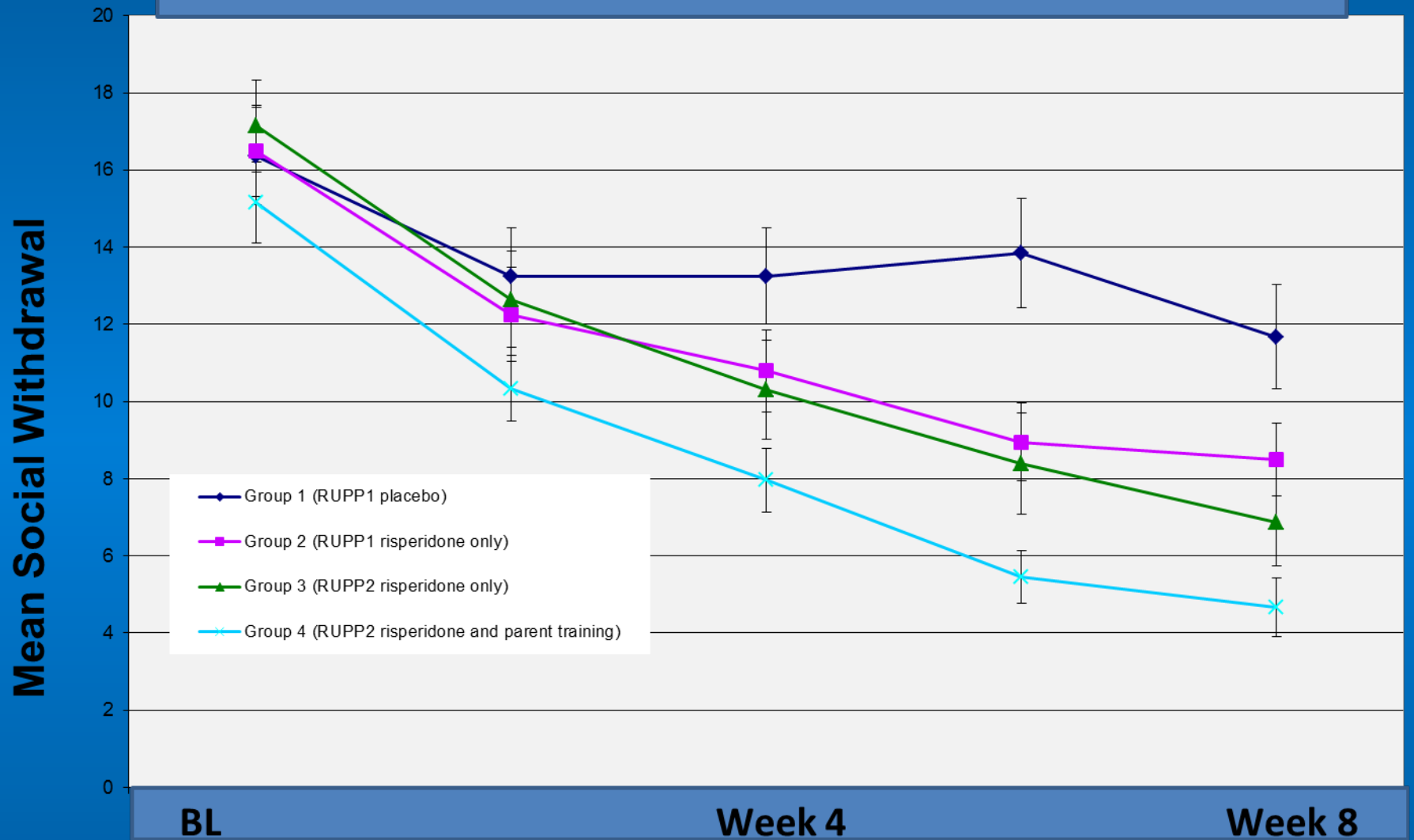
Social Anxiety

- May be of particular relevance to ASD
 - Even vague awareness of social disability may ↑ anxiety in social situations
 - ‘Failures’ in social interaction may ↑ social avoidance
 - Presence of social anxiety may amplify social avoidance and social disability

Social Disability

- ABC Social Withdrawal scale (16 items; 0-3)
 - “*is difficult to reach, contact or get through to*”
 - “*withdrawn; prefers solitary activities*”
 - “*shows few social reactions to others*”
 - “*does not try to communicate by words or gestures*”

Change in ABC-SW across four groups in RUPP RIS trials



Characteristics of a Good Primary Outcome Measure in Autism

- Relevant Target
- DD Population norms
- Not too long (but adequate coverage)
- Useable across range of age and IQ
- Reliable (unity of content, high test-retest)*
- Valid (Measures what it purports to measure)

*Inter-rater for clinician ratings

Drugs targeting social interaction in autism spectrum disorders

Drug	Double-blind trial	Sample size ≥ 40
Arbaclofen*	no	no
Memantine*	no	no
Oxytocin*	Yes?	no
D-cycloserine	yes	no
Secretin	yes	yes (A=P)
Fenfluramine	yes	yes (A=P)

* Trials underway

Future Directions

- 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