ADHD comorbidity in Autism Spectrum Disorders

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ADHD, ASD and Autistic Traits

- ASD and ADHD comorbid presentation
- Autistic traits in ADHD
- Treatment implications

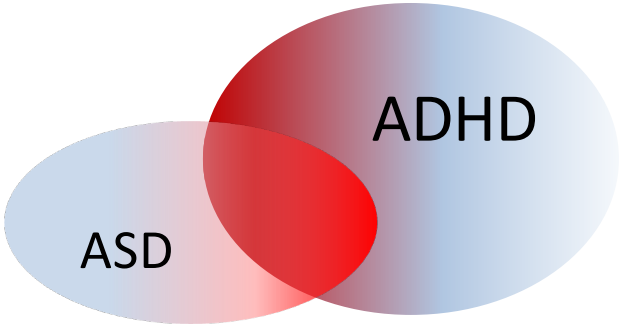
Neurodevelopmental Disorders (ASD and ADHD)

Shared Characteristics

	ADHD	ASD
Prevalence in Children	6-8%	2%
Heritability Estimates	75%	90%
Male:Female Ratio	2.5:1	4:1
Manifest early in life	Yes	Yes
Lifelong Disorders	Yes	Yes

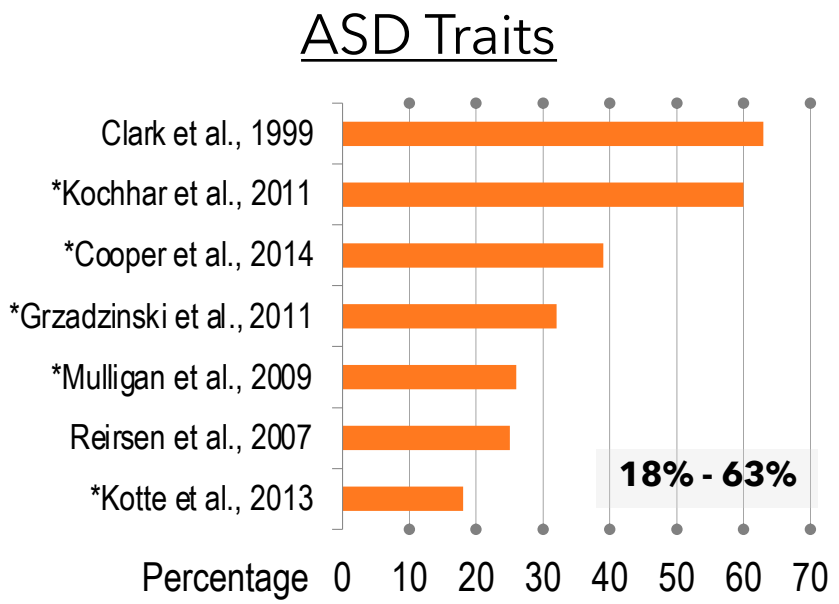
Distinct Symptom Triad

ASD	ADHD
- Impaired social interaction	- Inattention
- Impaired social communication	- Hyperactivity
- Restricted Repetitive Behaviors	- Impulsivity

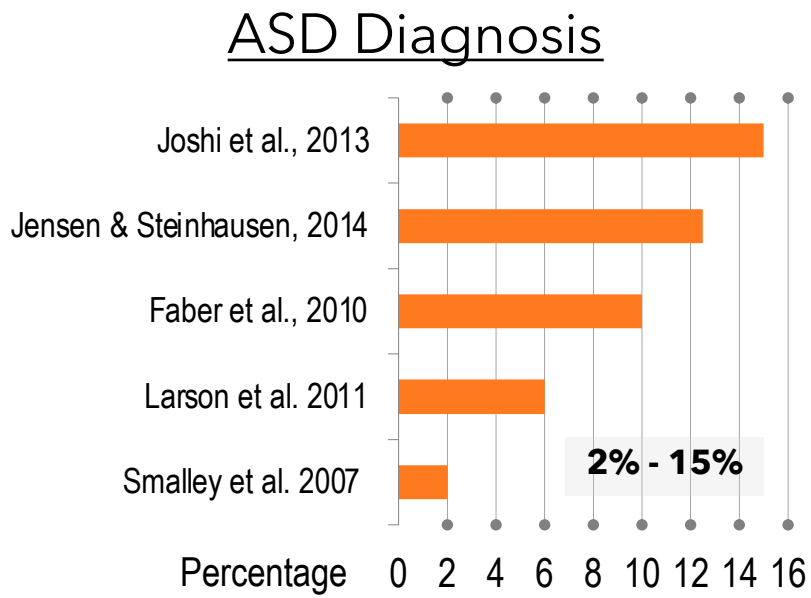


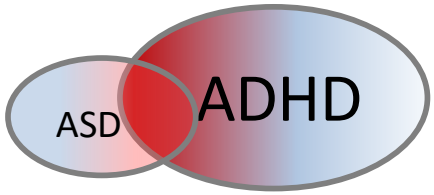
Bailey et al., 1995; Levy et al., 1997; Constantino & Todd, 2000, 2003; Ronald et al., 2005, 2006, 2008; Price et al., 2001; Fombonne, 2003; APA, 1994; MMWR, 2005; Kogan et al., 2009; ADDM Network, 2007, 2009; Bailey et al. 1996

ASD & ASD Traits in ADHD



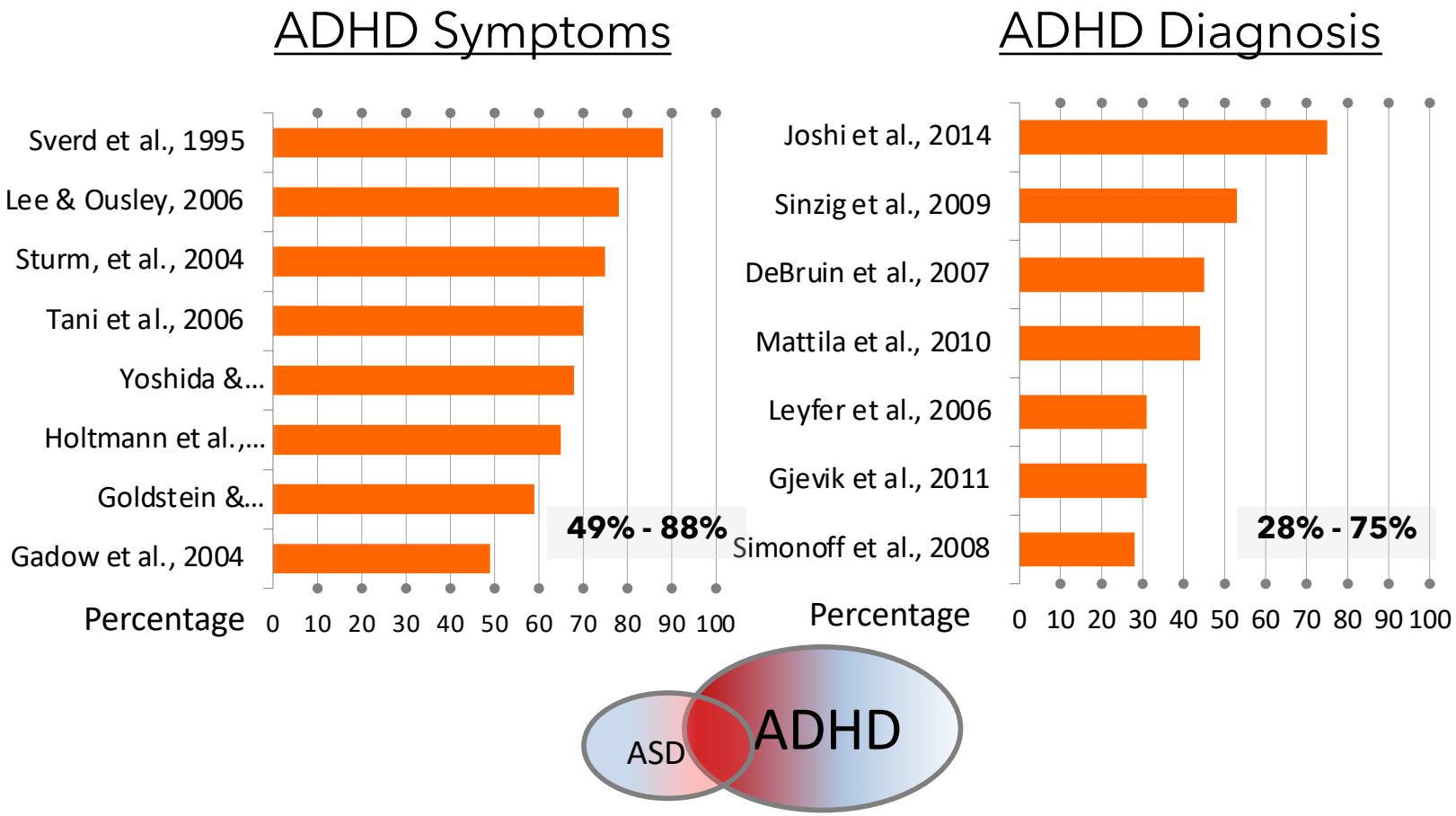
*ADHD Youth with no prior diagnosis of ASD





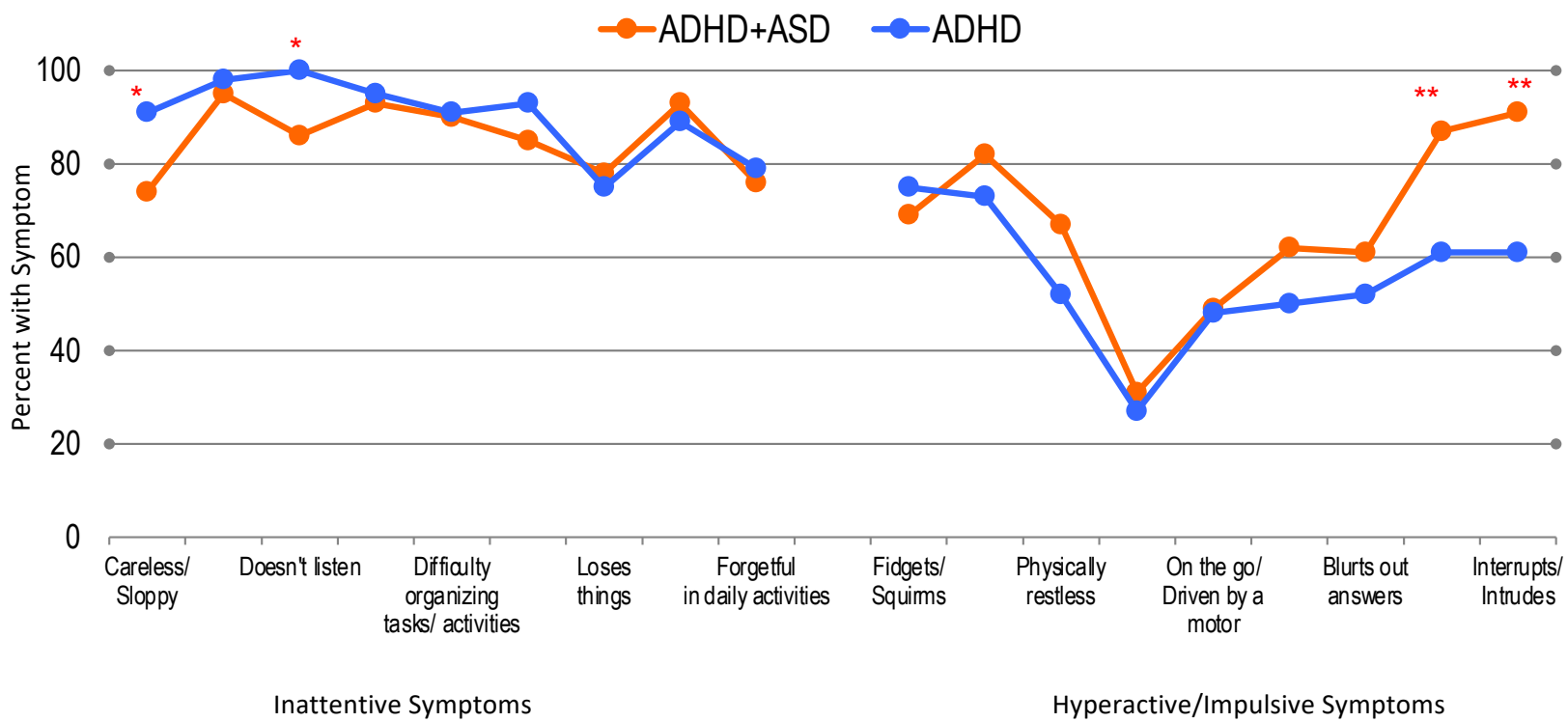
Comorbid ASD in up to 15% of the ADHD Populations

ADHD Symptoms & Diagnosis in ASD referrals



Comorbid ADHD in up to 75% of the ASD Populations

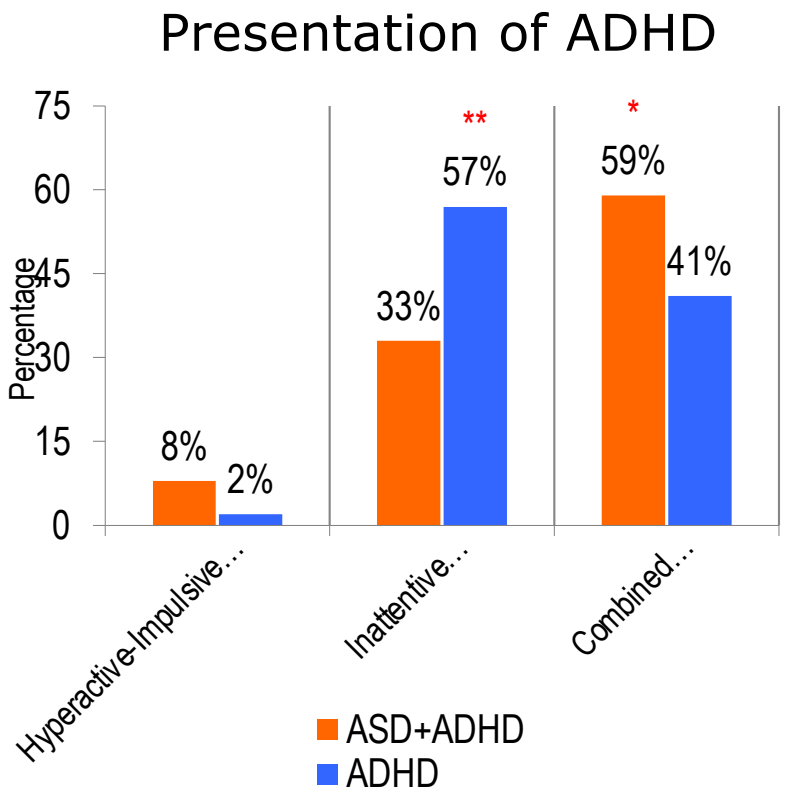
ADHD Symptom Profile in ASD

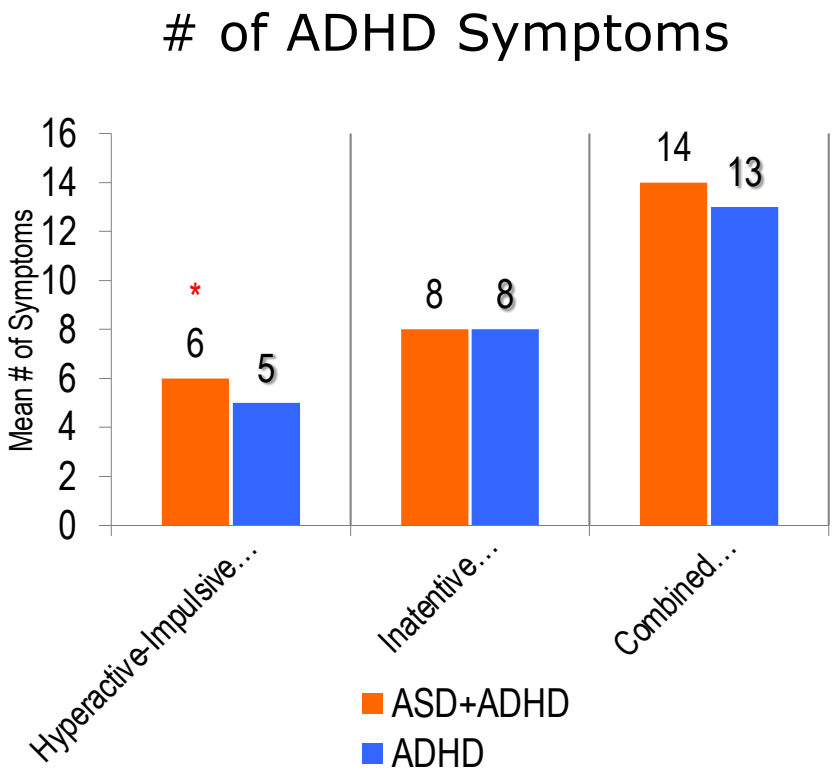


*p≤0.01, **p≤0.001

Joshi et al., 2014

Profile of ADHD in ASD

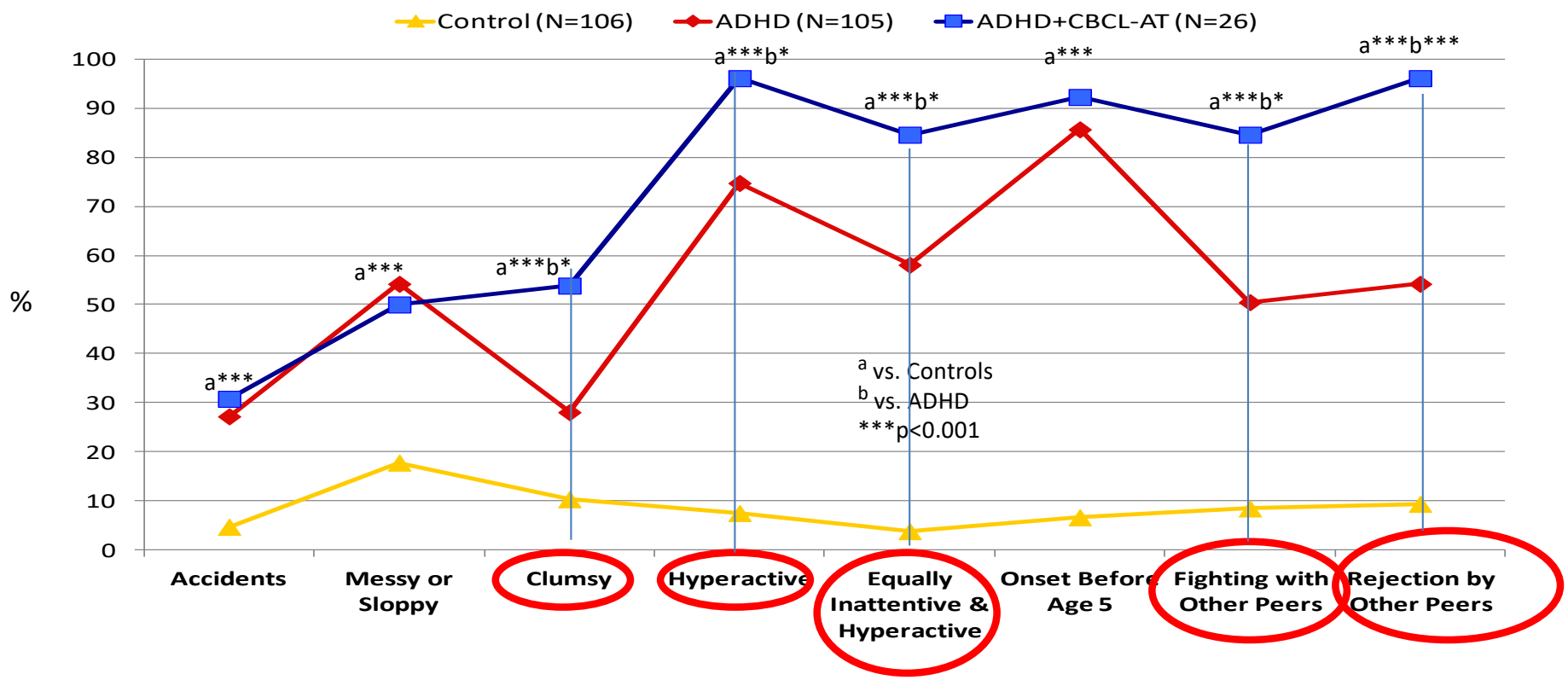




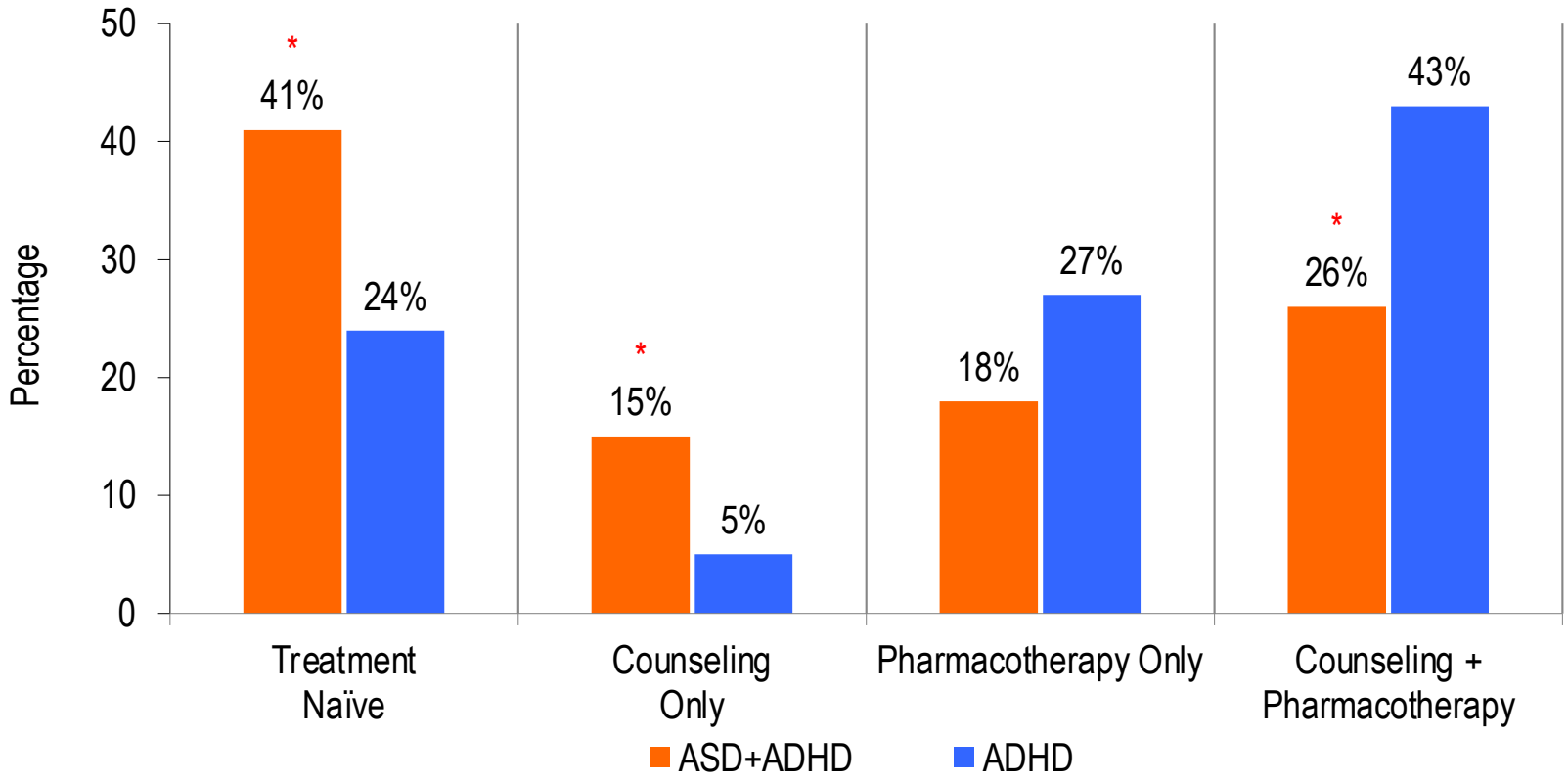
More robust form of ADHD (combined) presents more frequently in ASD

Joshi et al., 2014

Additional ADHD-Related Symptoms



ADHD Treatment History in ASD



Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

ADHD is undertreated in youth with ASD

Joshi et al., 2014

Implications of Unrecognized Comorbidity

ADHD

- Impairs intellectual/school performance
- Further compromises social functioning
- Interferes with ASD specific behavioral interventions
- Leads to attempts to treat ADHD with ASD specific interventions
- Failure to receive disorder specific treatment
- Increased risk for developing other psychiatric conditions
  - disruptive behaviors
  - substance abuse

ASD

- Receive inappropriately aggressive treatment for psychopathology
- Failure to recognize atypical precipitants that negatively affects psychopathology
- Failure to receive treatment specific for ASD
- Missed opportunity to implement early interventions for ASD

ADHD symptoms in ASD Youth

- ADHD symptoms are common in ASD (>50%)
- The clinical presentation of ADHD in ASD youth is typical of the disorder
- ASD youth with ADHD have significantly more impaired psychosocial functioning
- Significantly fewer ASD youth receive targeted treatment for ADHD

Treatment Trials in AUTISM

IQ: Low Versus High-functioning

Tx. Target: Symptoms Versus Syndromes

- Hyperactivity
- Irritability/Aggression
- Repetitive Behaviors/Anxiety
- Sleep dysregulation

Emerging Evidence: Pharmacotherapy for core features of Autism

ADHD Treatment Studies in ASD

ADHD Med Class	Controlled Trials		
	Total	N≥10	N<10
Stimulant Class			
Methylphenidate	5	5	-
Non-stimulant Class			
Atomoxetine	3	3	-
Guanfacine	2	1	1
Clonidine	2	-	2

- One trial in adults with ASD
- One trial exclusively in intellectually capable ASD (HF-ASD)
- No trials on Mixed Amphetamine Salts in ASD

CONTROLLED STUDIES for ADHD in AUTISM SPECTRUM DISORDER - *Methylphenidate*

RCT	Design [Duration]	Age [years]	Total (N)	HF	Dose [mg/day]	Efficacy	Tolerability	Comments
Ghuman et al., 2009	Crossover [4-Week]	Pre-school [3-5]	12	NR	15 ±5 [5 – 20]	Sign. ⇊ Hyperactivity -CPRS RR: 50%; ES: 0.97	TEAE: Buccal-lingual Movements Dose-LAE: 9 (64) Tx-LAE: 1 (6)	All participants with speech delay Response less than typically expected Improvement in social behaviors No worsening of ASD
Pearson et al., 2013 [MPH-ER]	Crossover [4-Week]	Children [7-12]	24	2/3rd	0.35 - 0.75 mg/kg	Sign. ⇊ ADHD -CTRS RR: 67% ES: NR	TEAE: Insomnia, ↓Appetite Dose-LAE: 5 (21) Tx-LAE: None	Typically expected response D/c of MPH-IR afternoon dose d/t AEs Improvement in social skills No worsening of ASD, Mood, or Anxiety
RUPP, 2005	Crossover [4-Week]	Children [5–13]	66	8%	7.5 – 50 mg	Sign. ⇊ Hyperactivity -ABC-H RR: 49% ES: 0.48	TEAE: Insomnia, ↓Appetite, Emotional outburst, Irritability Dose-LAE: 16 (24) Tx-LAE: 13 (18)	Majority of patients with ID & nonverbal Significant level of irritability at baseline Response less than typically expected ↑↑ fr. of emotional lability AE No worsening of ASD
Handen et al., 2000	Crossover [3-Week]	Children [5-11]	13	8%	NR	Sign. ⇊ Hyperactivity -CTRS-H RR: 61%; ES: NR	TEAE: P=NR Dose-LAE: 2 (15) Tx-LAE: 1 (1)	Significant level of irritability at baseline ↑↑ fr. of mood dysregulation AE No worsening of ASD
Quintana et al., 1995	Crossover [6-Week]	Children [7-11]	10	30%	0.4 - 0.7 mg/kg	Sign. ⇊ Hyperactivity -ABC-H/ CTRS-H ES: NR	TEAE: None Dose-LAE: None Tx-LAE: None	No mood dysregulation with Tx No difference in HD vs. LD response No worsening of ASD

NR=Not Reported; HF=High-Functioning; ID=Intellectual Disability; ES=Effect Size; RR=Response Rate; AE=Adverse Events; TEAE=Treatment Emergent AE; Dose-LAE=Dose-Limiting AE; Tx-LAE=Treatment-Limiting AE; CTRS=Conners' Teacher Rating Scale; CPRS=Conners' Parent Rating Scale; ABC-H=Aberrant Behavior Checklist-Hyperactivity subscale

Methylphenidate - RUPP Trial

Crossover RCT in ASD Youth with Hyperactivity

- Diagnoses: ASD + Hyperactivity (moderate-severe)
- Ages: 5-14 years (majority with Intellectual Disability)
- 3 Phases:

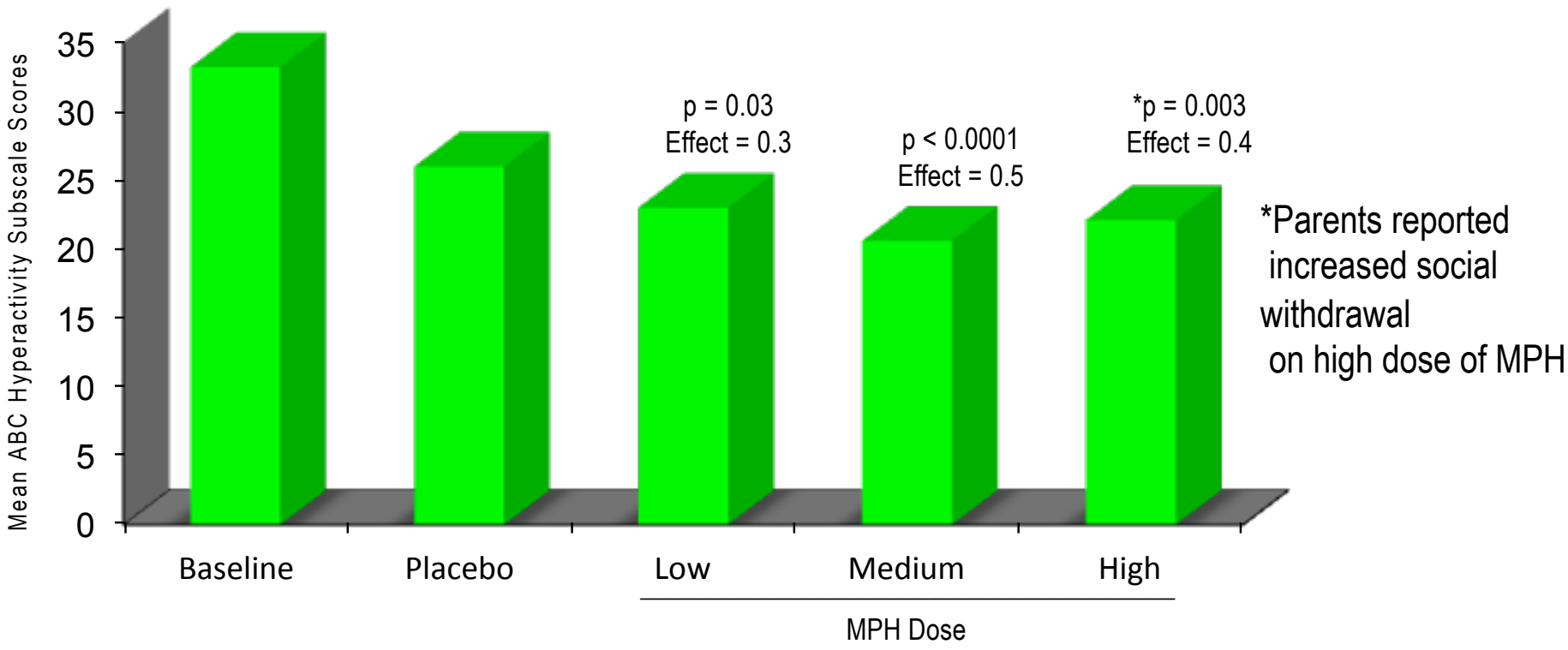
- MPH Dose (TID):
  - Low: 0.125mg/kg/day
  - Medium: 0.25 mg/kg/day
  - High 0.5 mg/kg/day

RUPP Autism Network, 2005

Methylphenidate – RUPP Trial

Efficacy

Crossover Phase Response: Parent-rated ABC-Hyperactivity Subscale

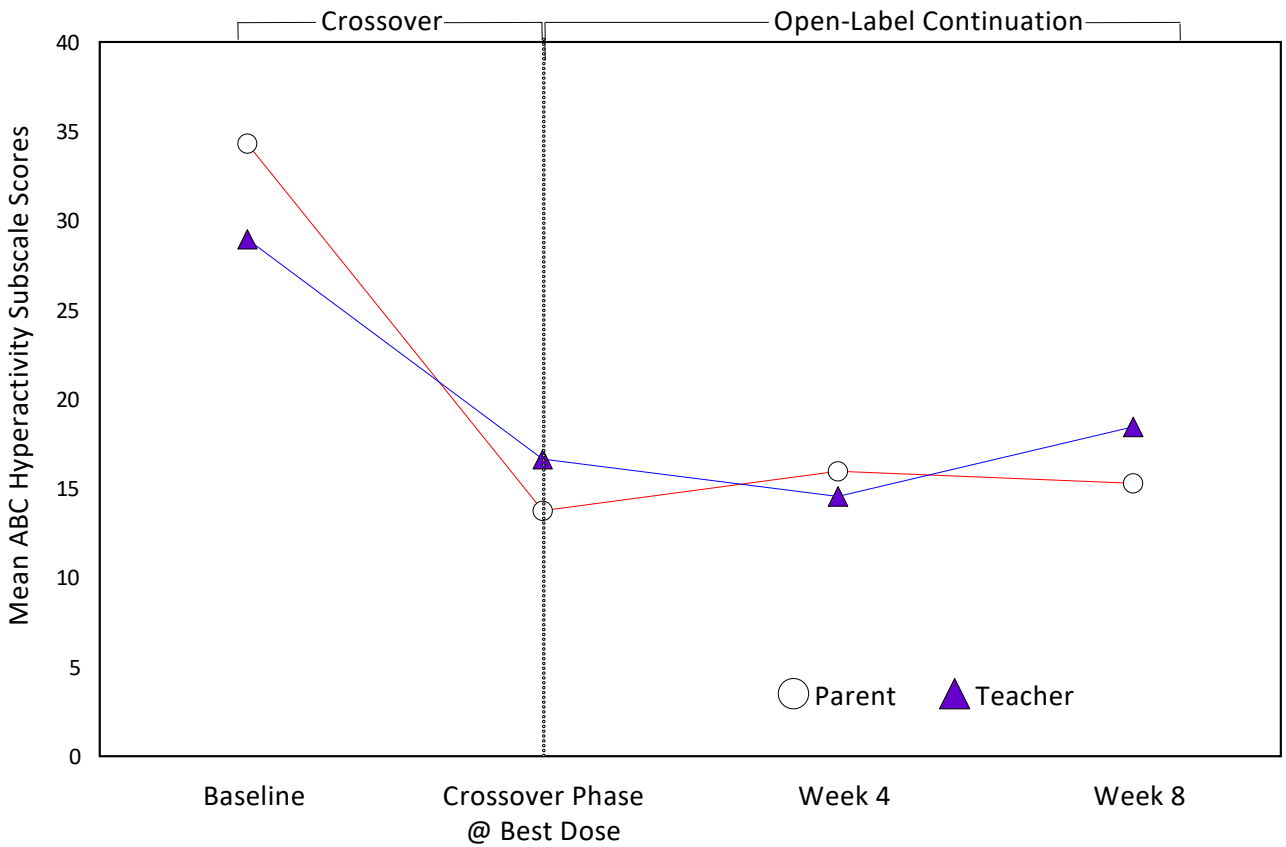


RUPP Autism Network, 2005

Methylphenidate – RUPP Trial

Efficacy

Continuation Phase Response: Informant-rated ABC-Hyperactivity Subscale



RUPP Autism Network, 2005

Methylphenidate – RUPP Trial

Efficacy

ADHD Response

Rate of Response: 50%

(≤2 CGI-I + ABC-H ⇊ >25-30%)

Effect Size: 0.20 – 0.54

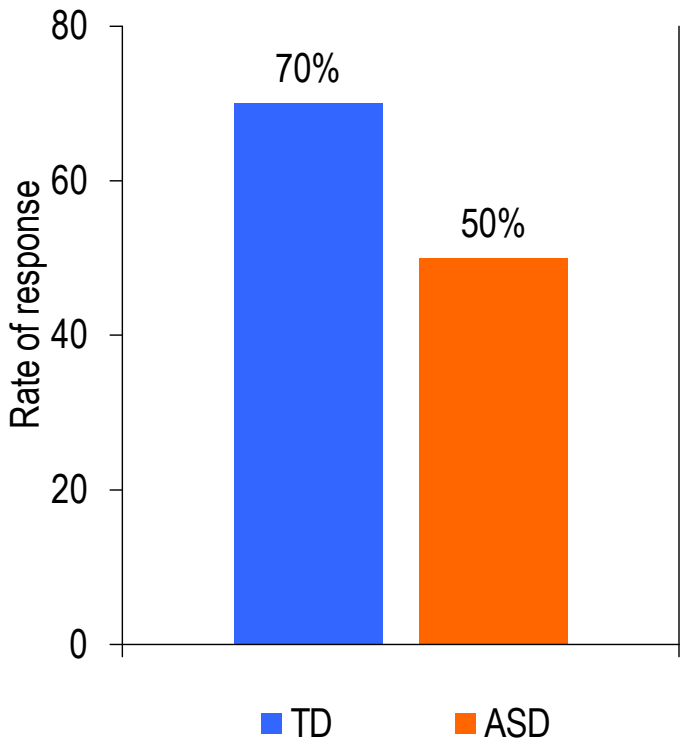
(vs. 0.35 – 1.31 in MTA trial)

ADHD response independent of:

- Level of IQ
- Subtypes of ASD

Additional Response*

Improvement in: - Joint Attention
- Self/Affect Regulation



MPH is less effective for ADHD in children with ASD than typically expected?

Comorbidity unknown in a patient population predominantly with low functioning autism

RUPP Autism Network, 2005; Jahromi et al., 2009*

Methylphenidate – RUPP Trial

Tolerability

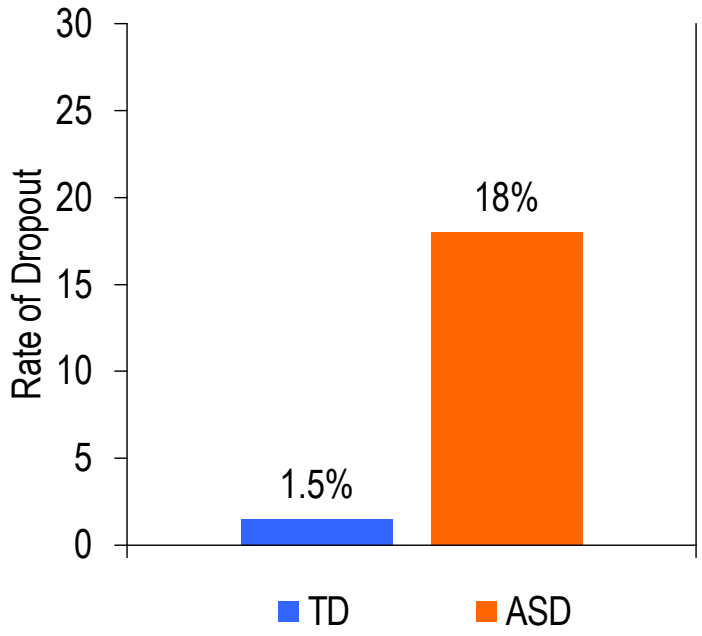
Common AEs:

- Decreased appetite
- Initial insomnia
- Irritability
- Emotional outbursts

No exacerbation of stereotypes or repetitive behaviors

Dropout: 18% (13/72)

- All dropout d/t treatment-limiting Aes
- 50% (6/13) dropout d/t inability to tolerate test dose
- 50% (6/13) dropout d/t irritability



MPH is associated with more frequent adverse effects in children with ASD than typically expected (**comorbidities??)**

RUPP Autism Network, 2005

Methylphenidate - Extended Release

Crossover RCT in ASD Children with ADHD

ASD + ADHD: N = 24
[Autistic Disorder=19/24; ADHD=19/24]
Male: 79%
Mean Age [Range]: 9 ±1.7 [7–12]
Mean IQ [Range]: 85 ±17 [46-112]

3 Trial Phases:

1. Placebo phase: 1 Week (N=24)
2. Tolerability phase: 2 day each on test doses of 3 different strengths of MPH (N=24)
3. Crossover Phase: 3 Week (N=24)

MPH-ER Dose Schedule

Duration [Week]	MPH Dosing (mg/Kg/day)	Morning MPH–ER dose	Afternoon MPH–IR dose
1	Low dose	0.2	0.15
1	Medium dose	0.35	0.25
1	High dose	0.5	0.3

Pearson et al., 2013

Methylphenidate - Extended Release

Dose comparison, RCT in children with ASD and ADHD

ASD + ADHD: N = 27

Male: 93%
Mean Age [Range]: 9 ±2.9 [5-14]

Study Design

- 6 weeks, flexible dosing schedule
- 3 different doses: Very Low (≤10mg/day) Low (≤20 mg/day) Moderate (≤ 40 mg/day)

Low dose	Medium dose
N=9	N=18
Mean dose 9.7mg/day	Mean dose 20.28 mg/day

Kim et al., 2017

Methylphenidate - Extended Release

Efficacy

Parent (ABC; *p<0.001*) and Clinician(ADHD RS-INV, *p<0.001*; CGI-I≤2=83%)-rated Measures:

- Significant dose-related improvement in ADHD symptoms
- Additional improvement in:
  - Irritability
  - Lethargy
  - Stereotypy
  - Hyperactivity
  - Inappropriate Speech

Tolerability

- No Serious or treatment limiting side effects
- Common side effects:
  - Insomnia [13.6% total]
  - Loss of appetite [10.5%]
  - Wear off [12.3%, less in medium dose group, *p=0.049*]

Pearson et al., 2013

OLT of MPH in Adults with HF-ASD

15 Adults aged 19-34 years (Mean age: 25 ±4.5 years)

- Intact intellectual ability (IQ Range: 99 – 144)
- Met the DSM-V criteria for ASD and ADHD
- At least moderate level of severity for ASD and ADHD (SRS=≥85; AISRS=≥24; & respective CGI-S ≥4)
- Not sign. symptoms of anxiety or mood dysregulation

Study Medication (MPH-ER Liquid Formulation: 25mg/5mL)

Flexible Dose Titration Schedule

Duration	QAM Dose
Initial dose:	5 mg/day
Titration phase (0-3 weeks):	5-60 mg/day
Maintenance phase (4-6 weeks):	Max. achieved dose

Dose at Endpoint

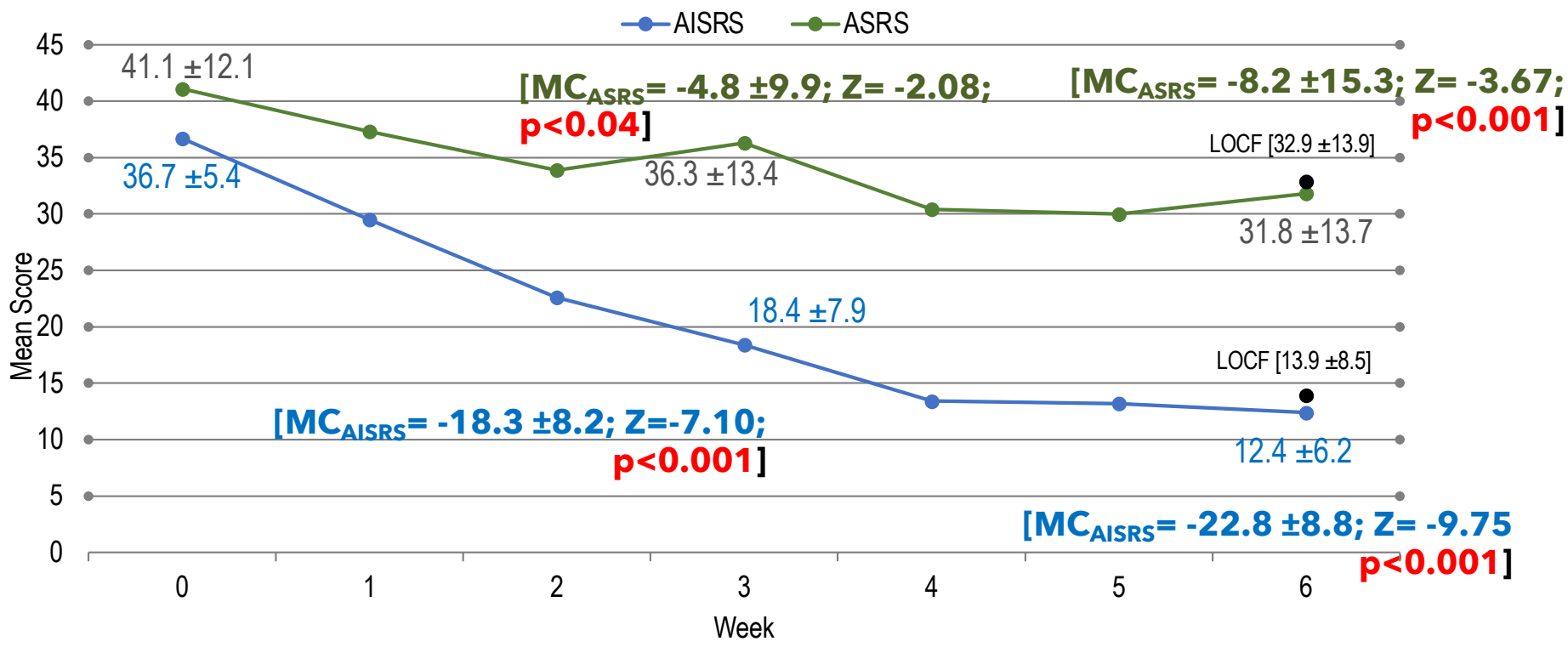
Mean dose:	49 ±15 mg/day	
Individual Doses:	60 mg/day	08 (53%)
	50 mg/day	02 (13%)
	20-40 mg/day	05 (33%)

Joshi et al., 2020

Treatment Response: ADHD Symptoms

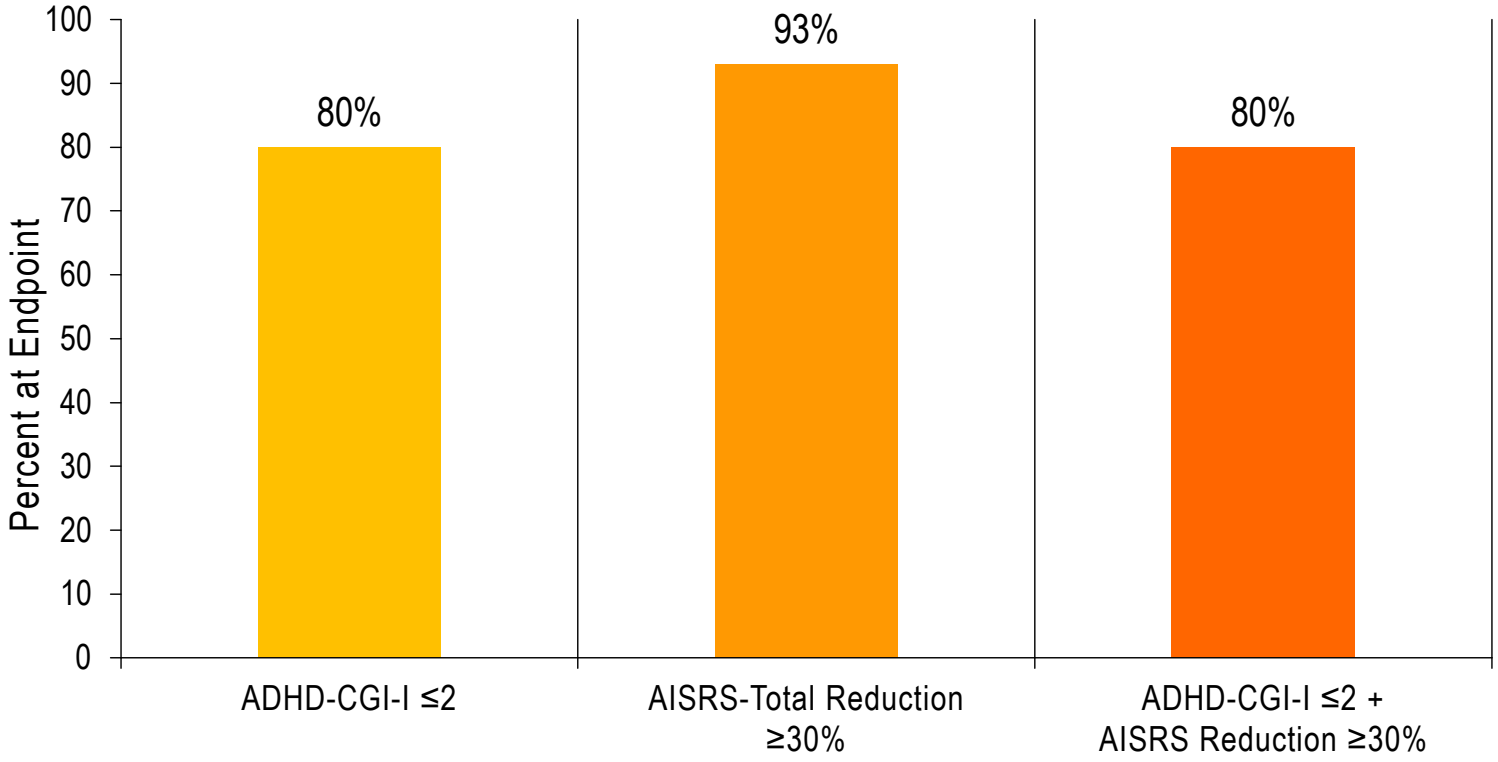
Clinician-Rated Adult Investigator Symptom Report Scale (AISRS)

Patient-Rated Adult Self-Report Scale (ASRS)



Joshi et al., 2020

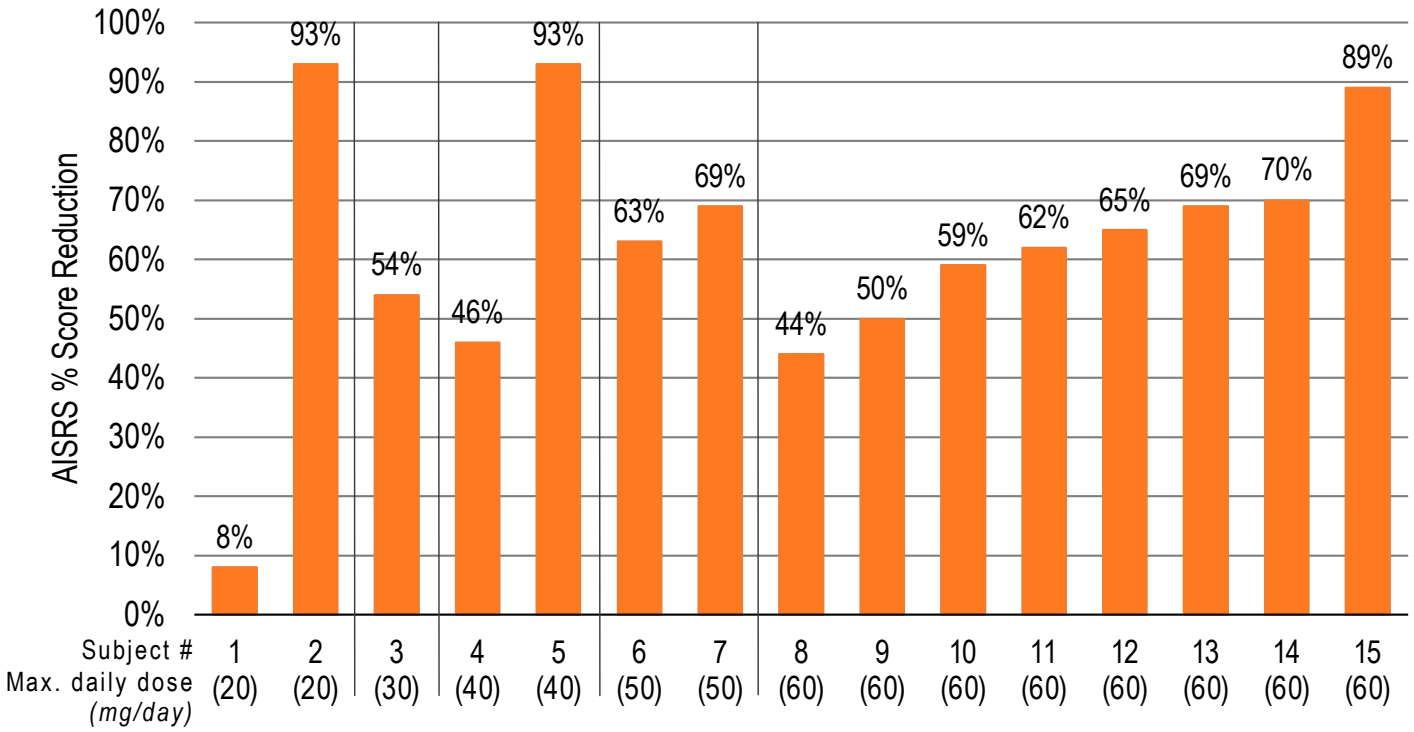
Treatment Response: Response Rate



Joshi et al., 2020

Treatment Response: ADHD Symptoms

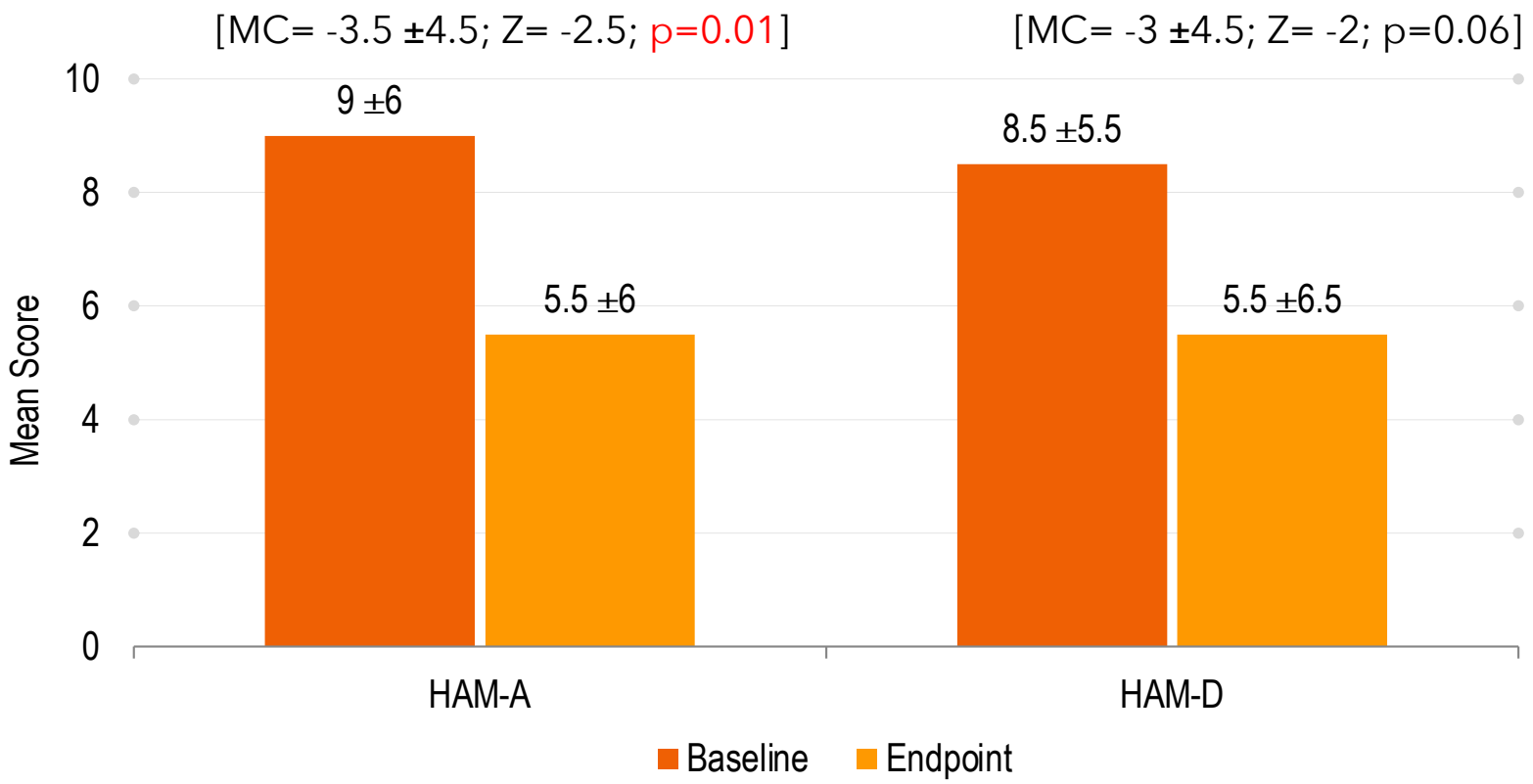
AISRS % Score Reduction at Trial Completion



Non-linear dose response

Joshi et al., 2020

Treatment Response: Associated Psychopathology

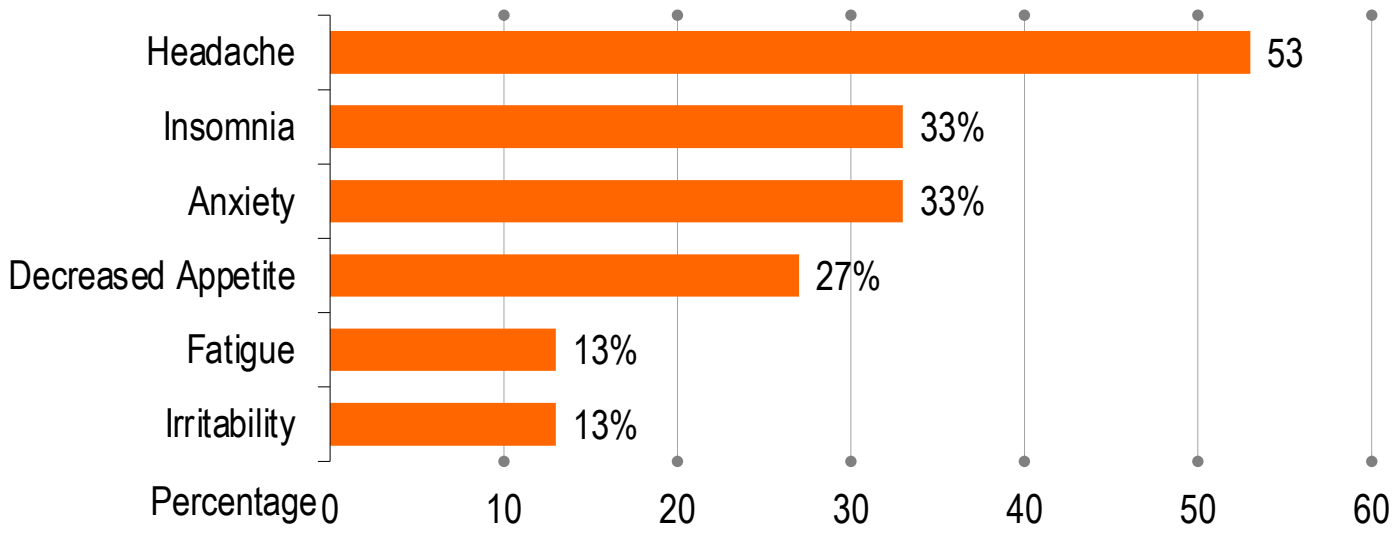


MC=Mean Change; HAM=A=Hamilton Anxiety Scale; HAM-D=Hamilton Depression Scale

Joshi et al., 2020

MPH ER – Adverse Events

Adverse Events (Mild-Moderate Severity)



Experienced any AEs: N=13 (87%)

Serious AEs: N=1 *(Report of OD on Benadryl [suicide attempt] at week-6. Prior h/o SI. [Upon completion continued tx. with study medication])*

Treatment Limiting AEs: N=1 *(Terminated at week-3 @ 20 mg/day d/t AEs: headaches, palpitations, jaw pain, & insomnia [resolved on d/c])*

Titration Limiting AEs: N=7 *(Headache[N=3], High Blood Pressure[N=2], Worsening of Anxiety[N=1], Nausea[N=1], Fatigue[N=1])*

Joshi et al., 2020

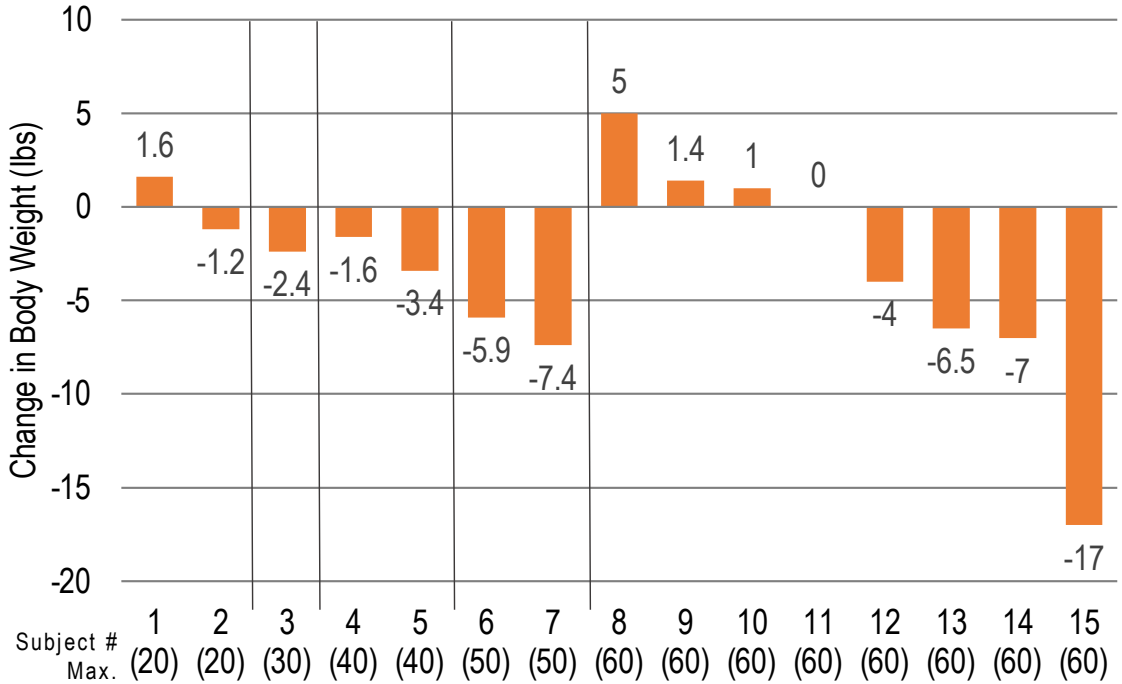
MPH ER – Adverse Events

	Baseline	Endpoint	Difference	p-value
Body weight *(kg)*	86 ±26.5	84.5 ±26.5	-1.45 ± 2.4	**0.01** [-2.59]
Pulse (bpm)	73 ±9.3	82 ±14.3	9 ±13.4	**0.007** [2.69]
Blood pressure *(mmHg)*				
Systolic	121.5 ±10.2	123 ±11.6	1 ±10.7	0.93 [0.08]
Diastolic	78.5 ±10.0	78.7 ±11.4	0.2 ±7.6	0.71 [0.37]

Pulse & Blood Pressure

Tachycardia *(heart rate >100 beats/min)*	N=3
High Blood Pressure *(systolic BP ≥140 mm/Hg &/or diastolic BP ≥90 mm/Hg)*	N=2

No QTc prolongation on ECG observed
(>460 or >60 ms increase from baseline)



Joshi et al., 2020

Methylphenidate response in ASD

- Modest response, less than observed in TD children
  - Less effective in treating hyperactivity symptoms
  - Although dose cannot be predicted, may respond to lower dose of MPH than expected (0.3mg/kg/day)
- May also improve Social Interaction (joint attention)
- Adverse effects are more prevalent and could be dose-dependent
- ADHD Response in a carefully chosen population, screened for comorbidities is same as that in typically developing children

RUPP Autism Network, 2005; DiMartino et al., 2004; Handen et al., 2000; MTA Trial, 2001

CONTROLLED STUDIES for ADHD in AUTISM SPECTRUM DISORDER – *Non-Stimulants*

ATOMOXETINE

RCT	Design [Duration]	Age (Yrs)	Total [N]	HF	Dose (mg/day)	Efficacy	Tolerability	Comments
Handen et al., 2015	Parallel [10-Week]	5-15	128	16%	1.4 ±0.5 mg/kg	⇊ ADHD (SNAP-IV) RR 47%; ES 0.8	↓Appetite Dose-LAE: None Tx-LAE: 5 (8) vs. 10 (16)	Significant level of baseline irritability Efficacy less than typically expected Typically expected tolerability No worsening of ASD, Mood, or SI
Harfterkamp et al., 2012	Parallel [8-Week]	6-16	97	6%	0.5-1.2 mg/kg	⇊ ADHD ADHD-RS [Mean↓ 8] RR 21% [P=NS]; ES NR	Nausea, ↓Appetite, Early waking, Fatigue Dose-LAE: None Tx-LAE: 1 (2) vs. 0	Significant level of baseline irritability Efficacy less than typically expected Typically expected tolerability No worsening of ASD
Arnold et al., 2006	Crossover [12-Week]	5-15	16	6%	44 ±22 20-100	⇊ Hyperactivity ABC-H [Mean↓= 5] RR 57%; ES 0.9	Upset stomach, N&V, Fatigue, Tachycardia Dose-LAE: None Tx-LAE: 1 (6) vs. 0	Significant level of baseline irritability All participants experienced GI AEs

GUANFACINE

RCT	Design [Duration]	Age (Yrs)	Total [N]	HF	Dose (mg/day)	Efficacy	Tolerability	Comments
Scahill et al., 2015 [GFC-ER]	Parallel [8-Week]	Children 5-14	62	37%	3 1 - 4	⇊ Hyperactivity ABC-H [%↓= 44] RR 50%; ES 1.67	Drowsiness, Fatigue, ↓Appetite, Dry mouth, Emotional/ tearful, Irritability, Anxiety Dose-LAE: 9 (30) vs. 5 (16) Tx-LAE: 4 (13) vs. 0	Significant level of baseline irritability Typically expected efficacy AEs at higher frequency than typically expected Mood & anxiety related AEs No worsening of ASD

NR=Not Reported; HF=High-Functioning; ES=Effect Size; RR=Response Rate; AE=Adverse Events; Dose-LAE=Dose-Limiting AE; Tx-LAE=Treatment-Limiting AE; SNAP-IV=Swanson, Nolan, & Pelham Rating Scale; ABC-H=Aberrant Behavior Checklist-Hyperactivity subscale; ADHD-RS=Attention Deficit Hyperactivity Disorder-Rating Scale

Atomoxetine

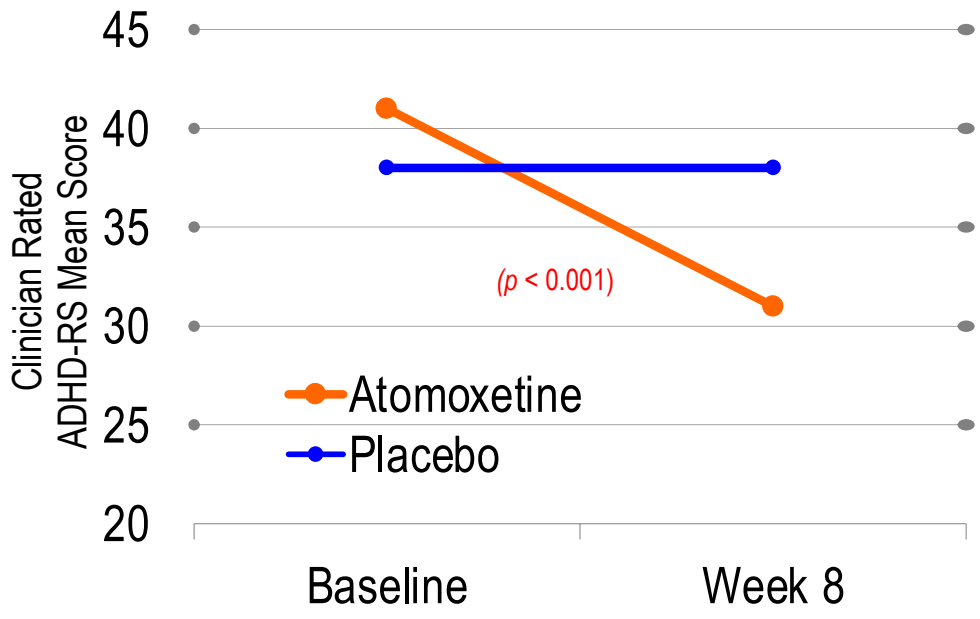
8-week RCT

- 97 children with ASD + ADHD diagnoses
  - 6-17 years (10 ±2.5)
  - 37% ADHD treatment naïve
  - IQ: 90 ±16 (61-138)
  - NO concomitant psychotropic medications
- Atomoxetine (BID) dosing:
  - Week-I: 0.5 mg/kg/day
  - Week-II: 0.8 mg/kg/day
  - Week-III: 1.2 mg/kg/day

Harfterkamp et al., 2012

Atomoxetine - Efficacy

Efficacy



ADHD-CGI-I ≤2

ATX[21%] ≯ PBO[9%] (p=0.14)

Less than expected magnitude of response to *atomoxetine*

(ADHD-RS mean reduction: ASD[8] vs. TYP[13-19])

Harfterkamp et al., 2012

Atomoxetine – Tolerability

- Rate of AEs: ATX 81% vs. PBO 65%
  - Nausea (29%^{ATX} vs. 8%^{PLO}; *p=0.009*)
  - Decreased appetite (27%^{ATX} vs. 6%^{PLO}; *p=0.006*)
  - Fatigue (22%^{ATX} vs. 8%^{PLO}; *p=0.05*)
  - Early Morning Awakening (10%^{ATX} vs. 0%^{PLO}; *p=0.03*)
- Treatment-limiting side effect: ATX 1/48 (fatigue) vs. PBO 0/49
- *No exacerbation of stereotypes or other repetitive behaviors*
- No serious side effects

***Atomoxetine* is associated with more frequent adverse effects in children with ASD compared to reported rates in children with typical development**

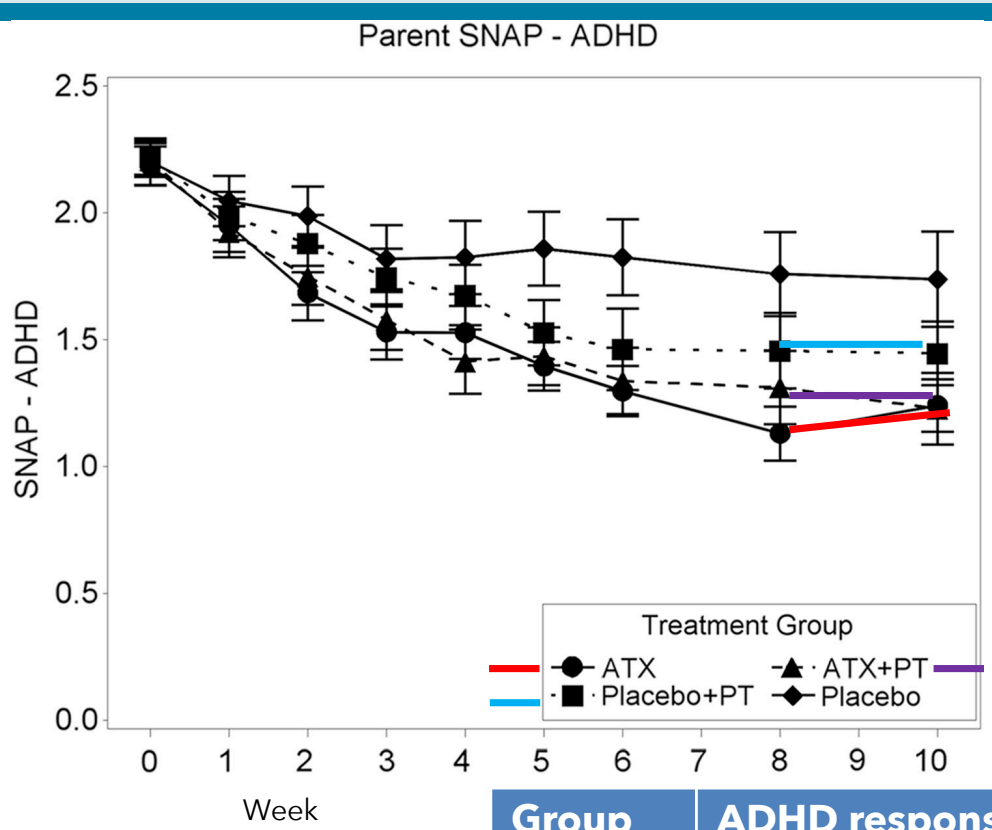
Harfterkamp et al., 2012

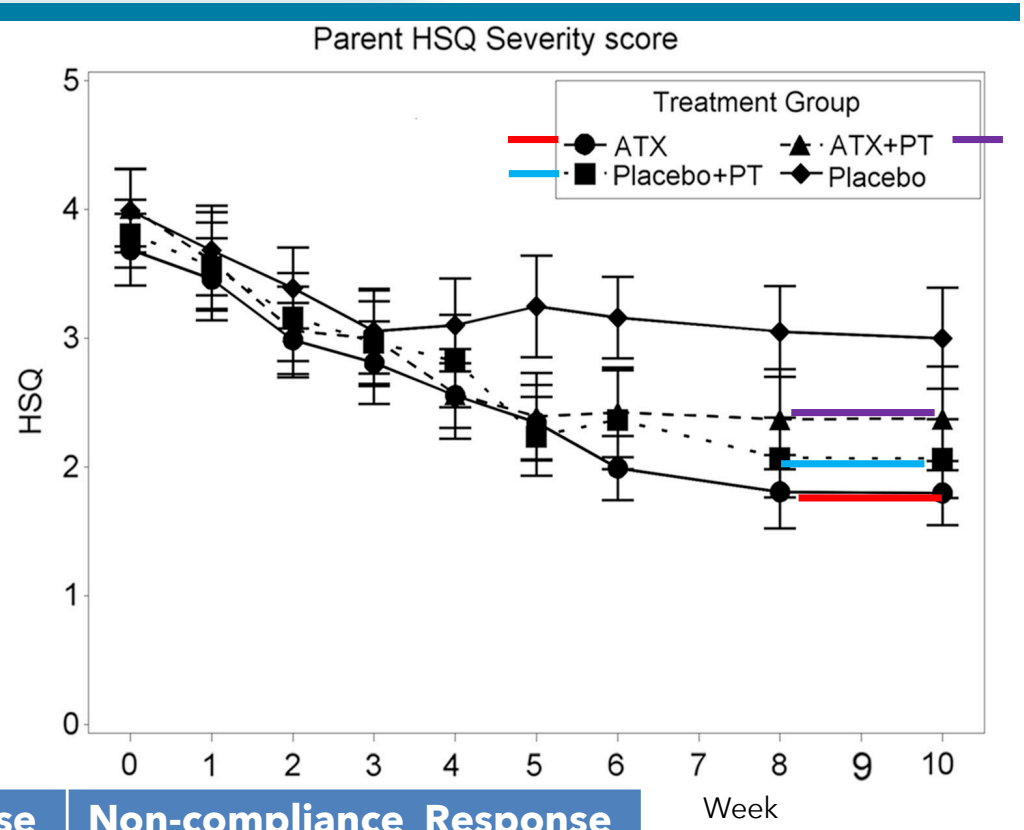
Atomoxetine & Parent Training

- 10-week RCT
- 128 children with ASD + ADHD
  - 5-14 yrs (8 ±2); 85% male
  - IQ 61-138 (82 ±24)
  - 55% with treatment-naive ADHD
- Dose:
  - 1.2-1.8 mg/kg/day
  - 45 ±21mg/day
  - Side effects: decreased appetite, abdominal pain
  - No treatment related serious adverse events

Handen et al., 2015

Atomoxetine & Parent Training





Group	ADHD response	Non-compliance Response	
ATX	47%	44%	0.003 [ES 0.64]
ATX+PT	45%	23%	0.03 [ES 0.47]
PT+PBO	29%	39%	0.06
PBO	19%	16%	

ADHD Response Rate:
ATX > PBO [p=0.015]
ATX+PT ≯ ATX [p=NS]

Handen et al., 2015

Atomoxetine & Parent Training

24-week extension phase

- 60% of RCT phase responders continued to meet criteria for ADHD

- Among ADHD responders:
  - ATX+PT 53% v ATX 23%
- Among noncompliance responders:
  - PT+ATX 58% v ATX 14%

Smith et al., 2016

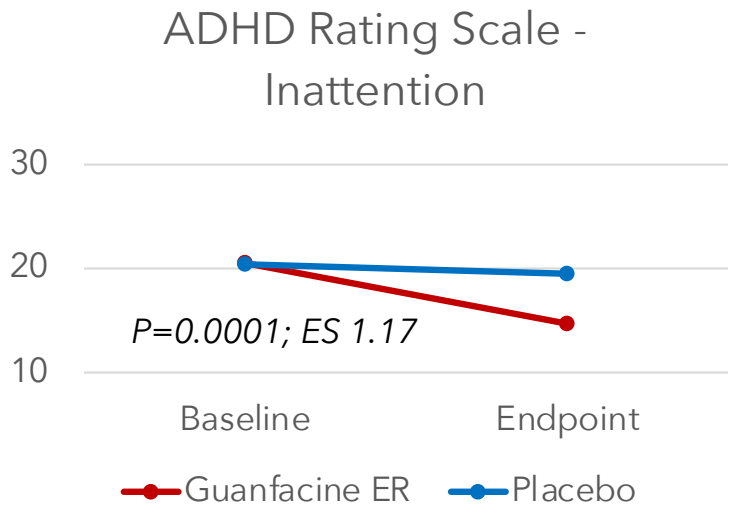
Guanfacine ER

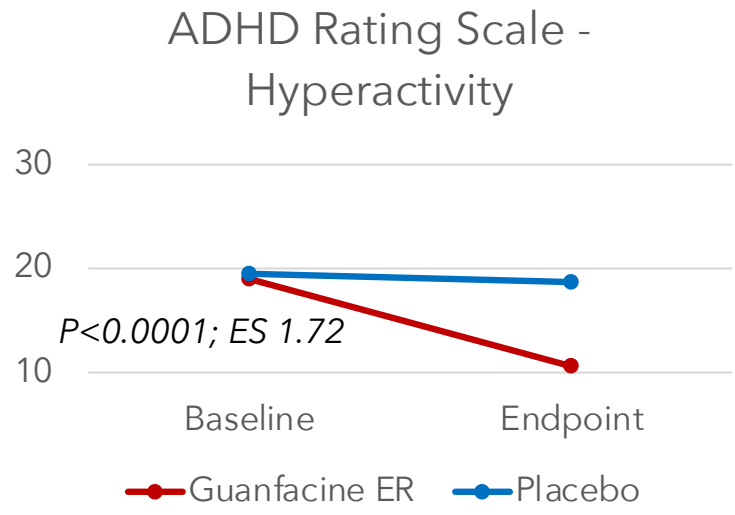
8-week RCT in ASD Youth with Hyperactivity

Autistic Disorder + Sign. Hyperactivity (ABC-Hyperactivity score ≥24 + CGI-S ≥4)	62
Mean Age [Range]	8.5 ±2.3 [5–14]
Male	86%
Drug-naive	55%
Dose	3 mg/day [1 - 4]

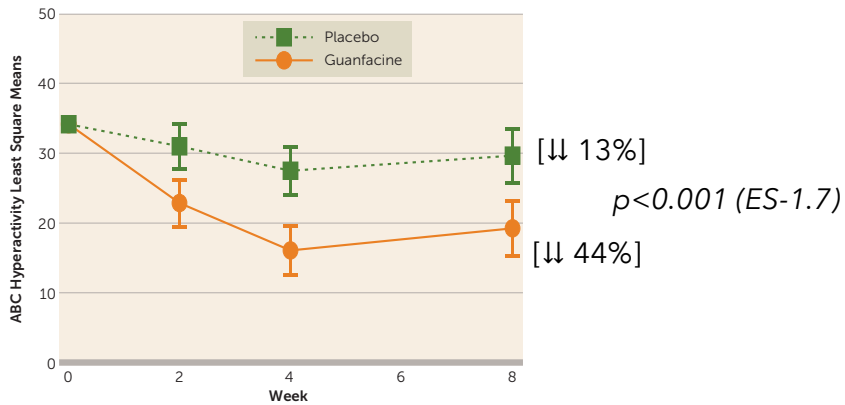
Scahill et al., 2015

Guanfacine ER - Efficacy





ABC-Hyperactivity Subscale



CGI-Improvement ≤2:

Guanfacine ER[50%] >PBO[9.4%]

Significant improvement in:

- Repetitive behaviors(ABC-Stereotypy)
- Communication(ABC-Inappropriate speech)

Response similar to Typicals

*(GXR[50-55%] > PBO[25%])**

Guanfacine ER – Efficacy

	PBO	GXR
• Dose-limiting AEs [d/t emotional lability/drowsiness]	5/32 [16%]	9/30 [30%]
• Treatment-limiting AEs	None	2 - Agitation[N=1] - Drowsiness[N=1]
• Serious AEs	None	1 (agitation @ 2mg/d)

Common AEs*	PBO	GXR	p-value
Drowsiness	9%	87%	<0.001
Fatigue	9%	63%	<0.001
Dec. appetite	6%	43%	<0.001
Dry mouth	3%	40%	<0.001
Emotional/tearful	9%	40%	0.01
Irritability	9%	37%	0.01
Anxiety	3%	30%	0.01
Mid-sleep awakening	6%	30%	0.02

*Reported in ≥5% & <0.05

Typically expected ADHD treatment response of GXR in children with ASD

Scahill et al., 2015

Alpha-2 Adrenergic Agonist: *Clonidine*

Delivery	Oral Clonidine (Jaselkis, et al. 1992)	Transdermal Clonidine (Frankhauser, et al. 1992)
Methods	6-week double-blind, cross-over *clonidine* PO 4-10 mcg/kg/d n=8 males, 5-13yo (8 ±3 yrs.) with ASD + hyperactivity (prior hx. of poor response)	4-week, double-blind, cross-over *clonidine* TTD 3.5 mcg/kg/d n=9 males (~13 yrs.) with ASD + hyperarousal symptoms (including hyperactivity)
Efficacy	Parent-teacher ratings: Superior to PBO in reducing Hyperactivity No significant separation from PBO on any of the clinician rated scales	No effect on ADHD symptoms per parent ratings
Tolerability	Drowsiness Hypotension	Sedation Fatigue

In Summary.....

ADHD Response in ASD Youth

- *Methylphenidate & Atomoxetine.*
  - Response in patients HF-ASD is similar to observed with ADHD
  - Adverse effects more frequent than typically expected may point to **missed comorbidities**
  - Improves affect regulation & joint attention
  - Response rate & magnitude **in patients with low IQ is less than expected**

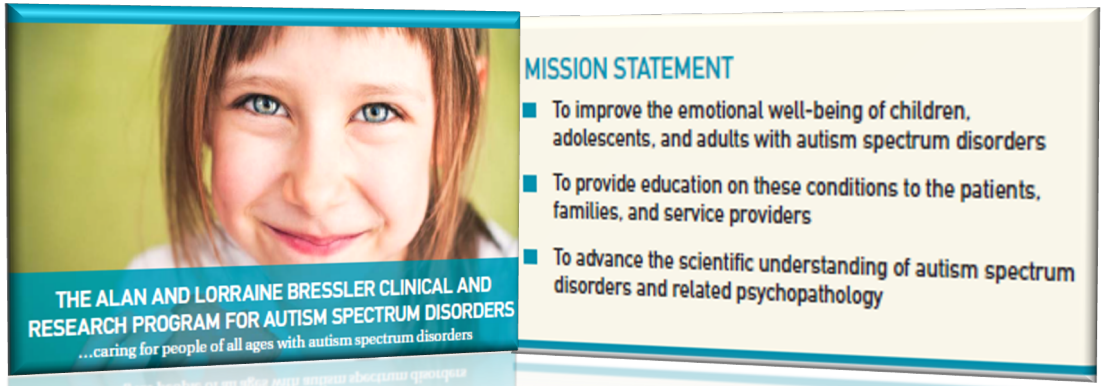
- *Guanfacine ER*. Response similar to observed in children with ADHD
- *Clonidine*. Poorly tolerated

Consider using clinical scales for monitoring treatment effect

ADHD checklists, ECG, labs, etc.

RUPP Autism Network, 2005; Pearson et al., 2013; Harfterkamp et al., 2012; Fankhauser et al., 1992; Jaselskis et al., 1992; Scahill et al., 2015

The Alan and Lorraine Bressler Clinical and Research Program for Autism Spectrum Disorders



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