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Diagnosis and Treatment of ADHD in Autism

Gagan Joshi, MD
Associate Professor of Psychiatry

Director, The Bressler Program for Autism Spectrum Disorder
Massachusetts General Hospital, Harvard Medical School

Disclosures

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Disclosures 2023-2026

Source	Research/ Grant Support	Honorarium (for this/other Meetings)	Unpaid Consultant	Royalties/ Licensing
National Institute of Mental Health (Award # K23MH100450)	✓			
Demarest Lloyd Jr Foundation	✓			
Genentech, Inc.	✓			
American Academy of Child & Adolescent Psychiatry		✓		
American Physician Institute		✓		
Hackensack Meridian Health		✓		
Neuroimmune Institute		✓		
New York University (Grand Rounds)		✓		
Optum Health Education		✓		
Regional Council of Child and Adolescent Psychiatry of Eastern Pennsylvania and Southern New Jersey		✓		
EuMentis Therapeutics			✓	
Mass General Brigham Innovation				✓

Comorbidity Associated with Autism

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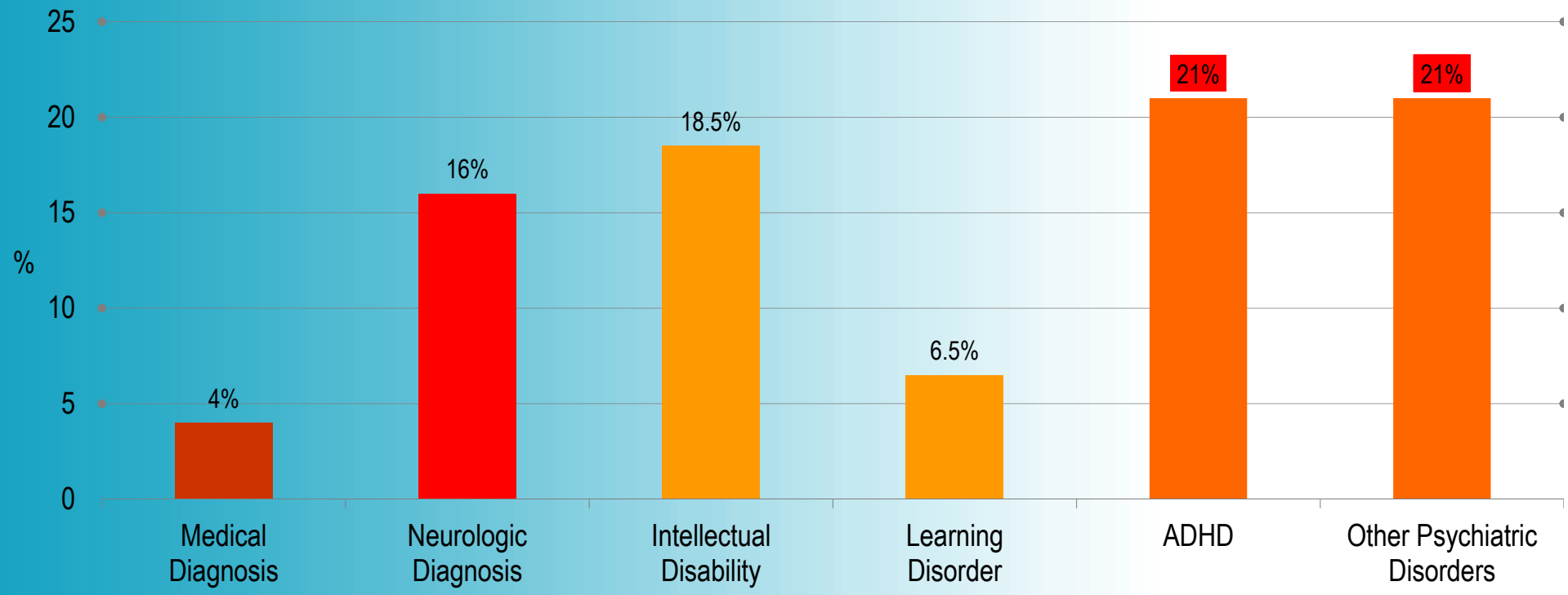
Comorbidity in US population-based sample of ASD

(Medical records of children 8 years old reviewed by trained clinicians)



CDC-ADDM Network Surveillance Year 2002-Levy et al. 2010

Psychiatric Comorbidity in Autism

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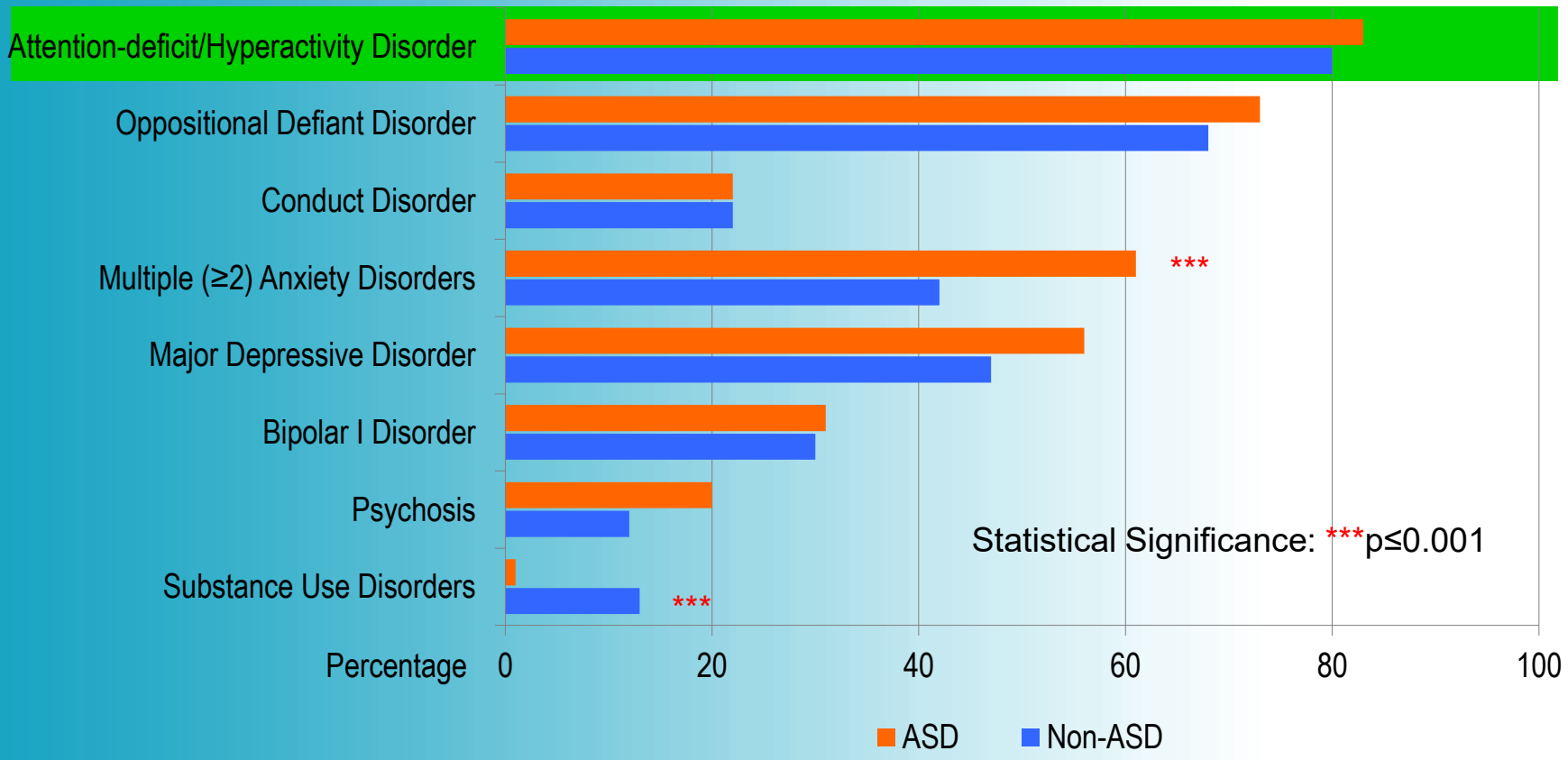
Lifetime Psychiatric Comorbidity



ADHD is the most frequent disorder associated with Autism

Joshi et al., 2010

Historical Perspective: Co-occurrence of ADHD and Autism

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- Majority of ASD with Intellectual Disability
- ADHD symptoms considered as an associated feature of ASD and not a distinct co-occurring disorder
- Ability to (hyper) focus on preferred activities precluded recognition of ADHD comorbidity with ASD
- Trials in ASD populations with ID suggested poor response to anti-ADHD medications

Prevalence of Autism and ADHD Comorbidity

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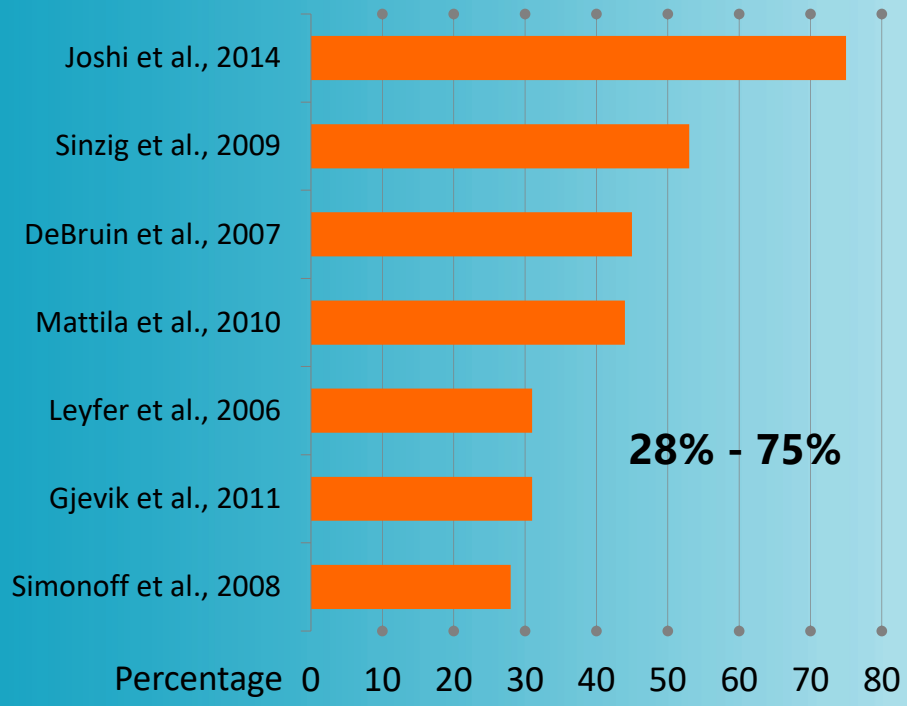
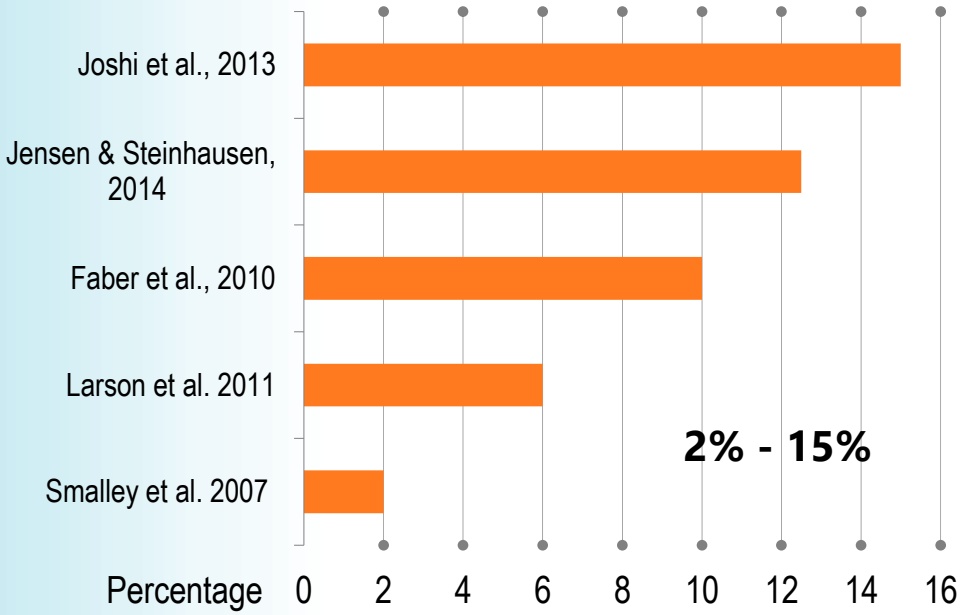
ADHD in ASD Populations



ASD in ADHD Populations



Asymmetrical Bidirectional Overlap

Burden of Autistic Traits in ADHD Populations without Autism

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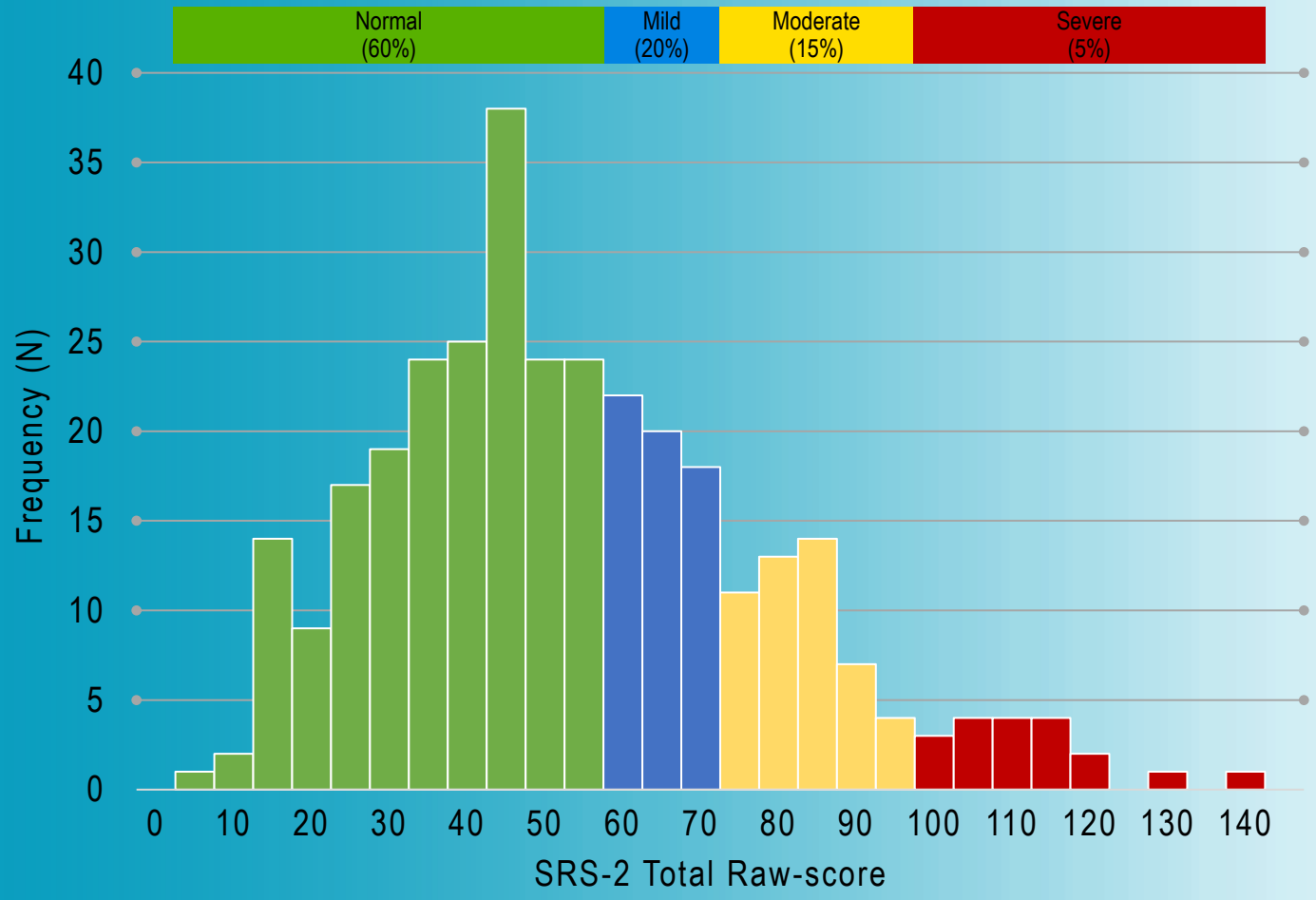
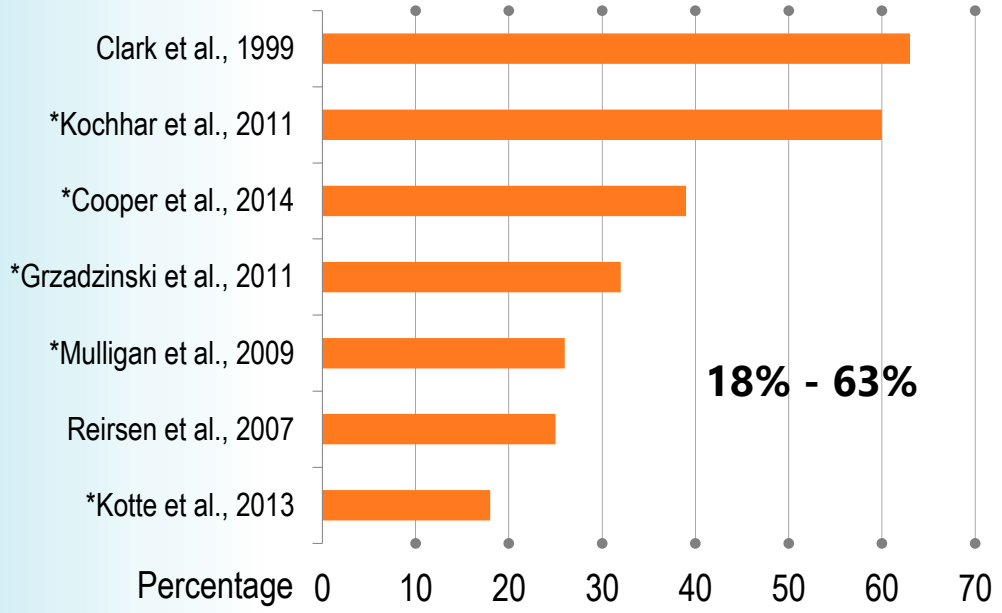
Autistic Traits Severity Distribution on SRS-2



Significant Autistic Traits



*ADHD Youth with no prior diagnosis of ASD

ADHD Symptom Profile in Autism

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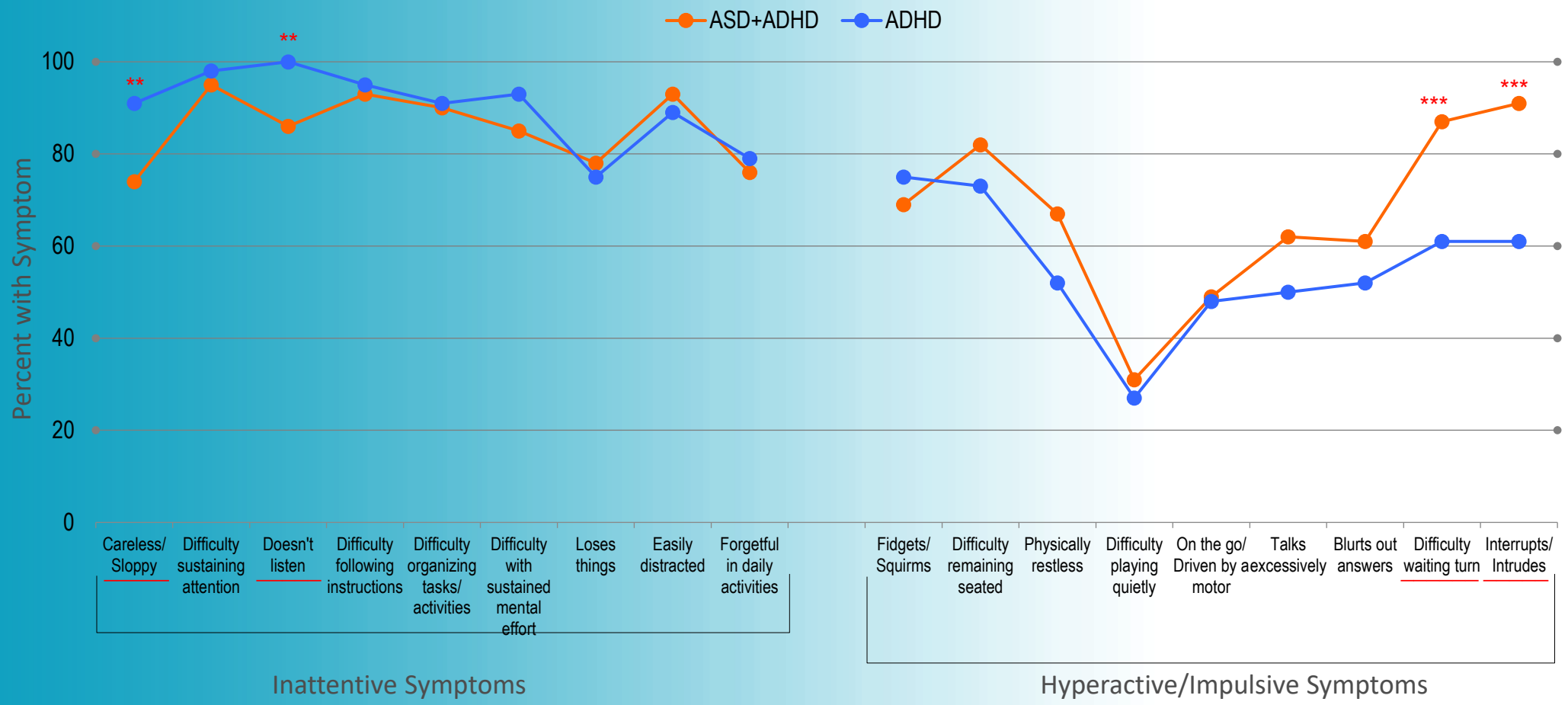

Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

Joshi et al. 2014

Profile of ADHD in Autism

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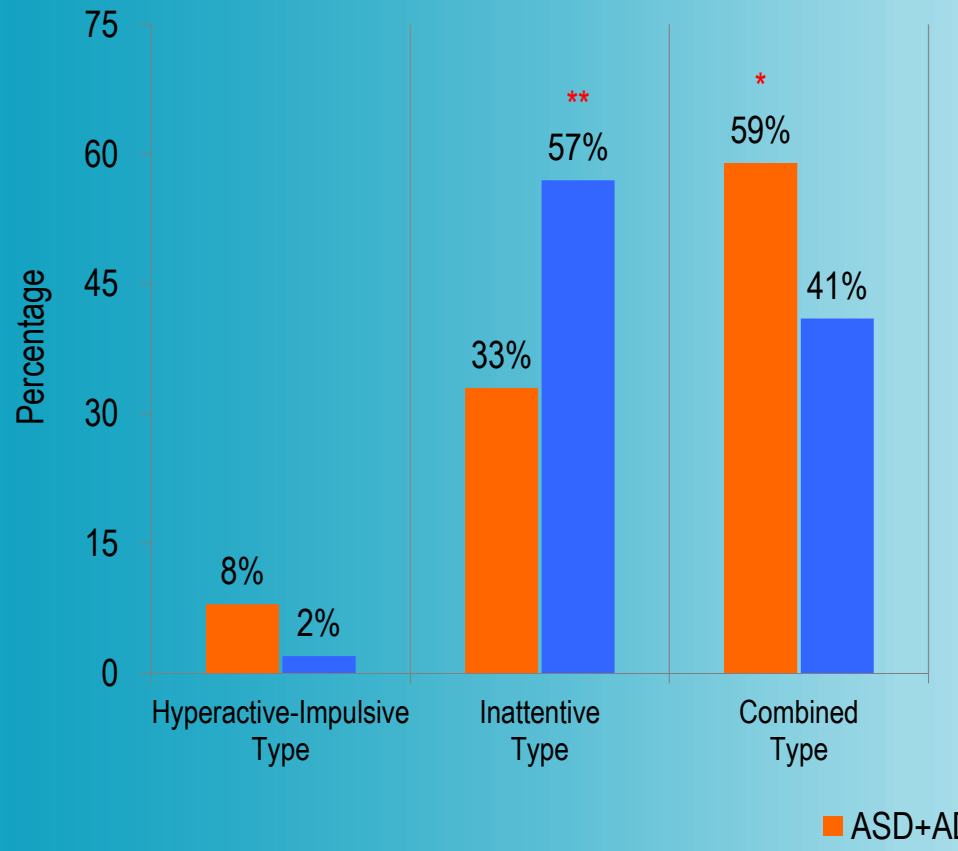
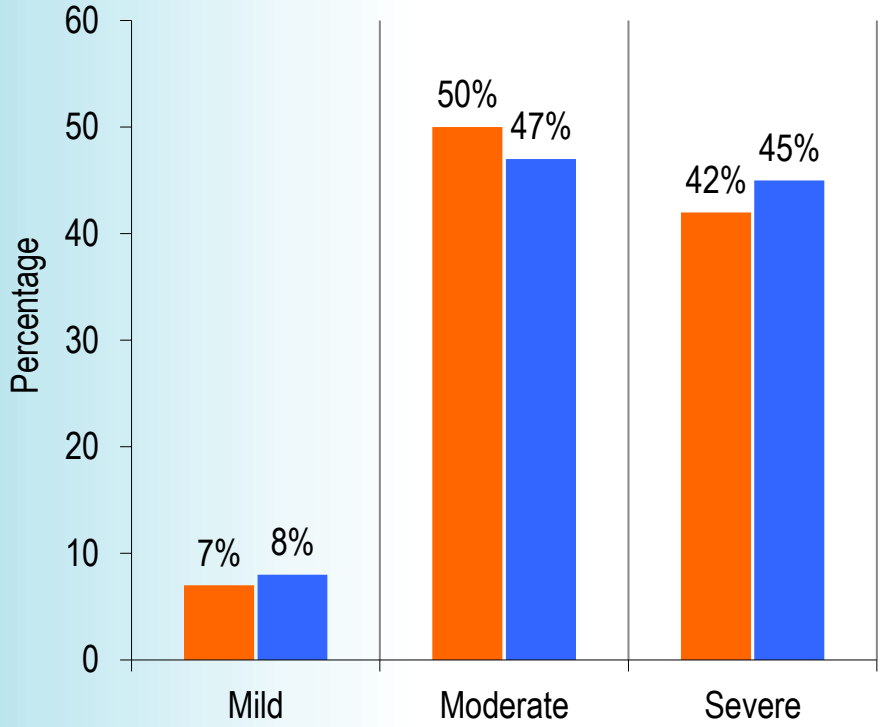
Subtypes of ADHD



Severity of ADHD



Joshi et al. 2014

Severity Profile of Comorbid ADHD and Autism

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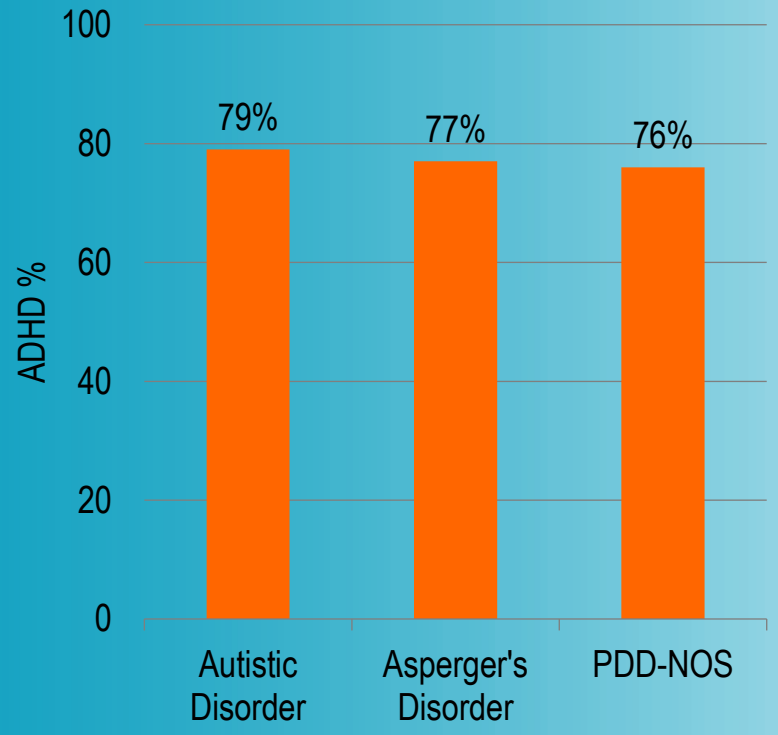
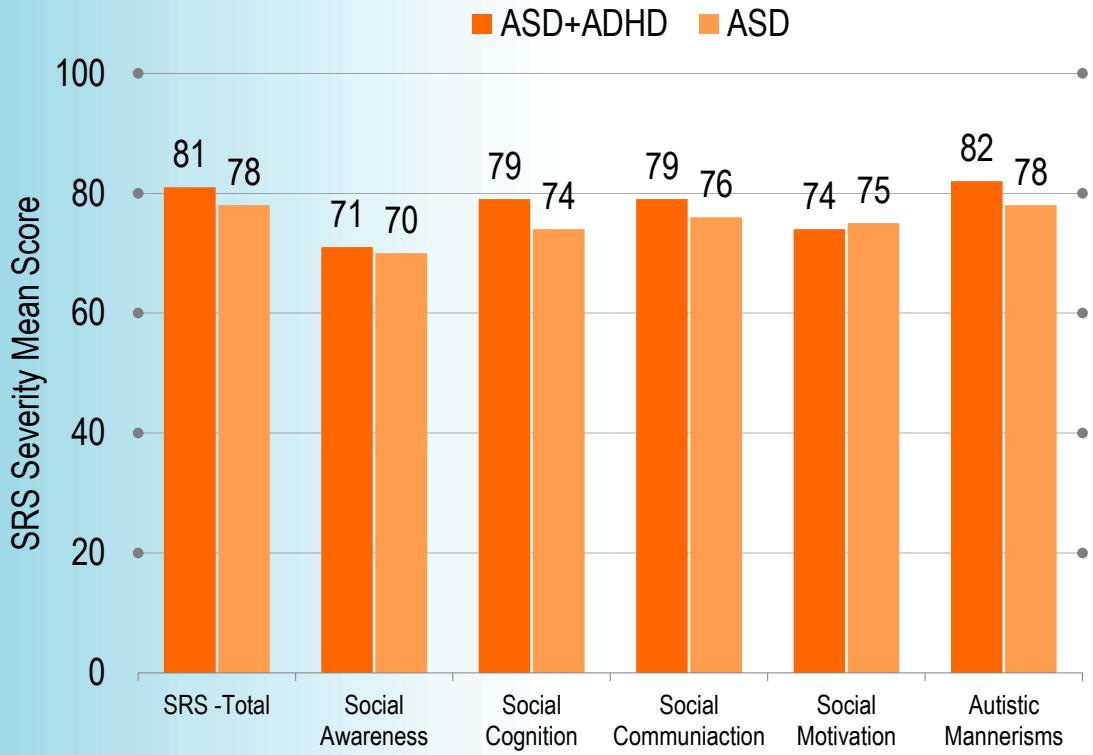
Distribution of ADHD



Severity of ASD



Joshi et al. 2014

Diffusion Tensor Imaging Findings in ADHD ± Autism

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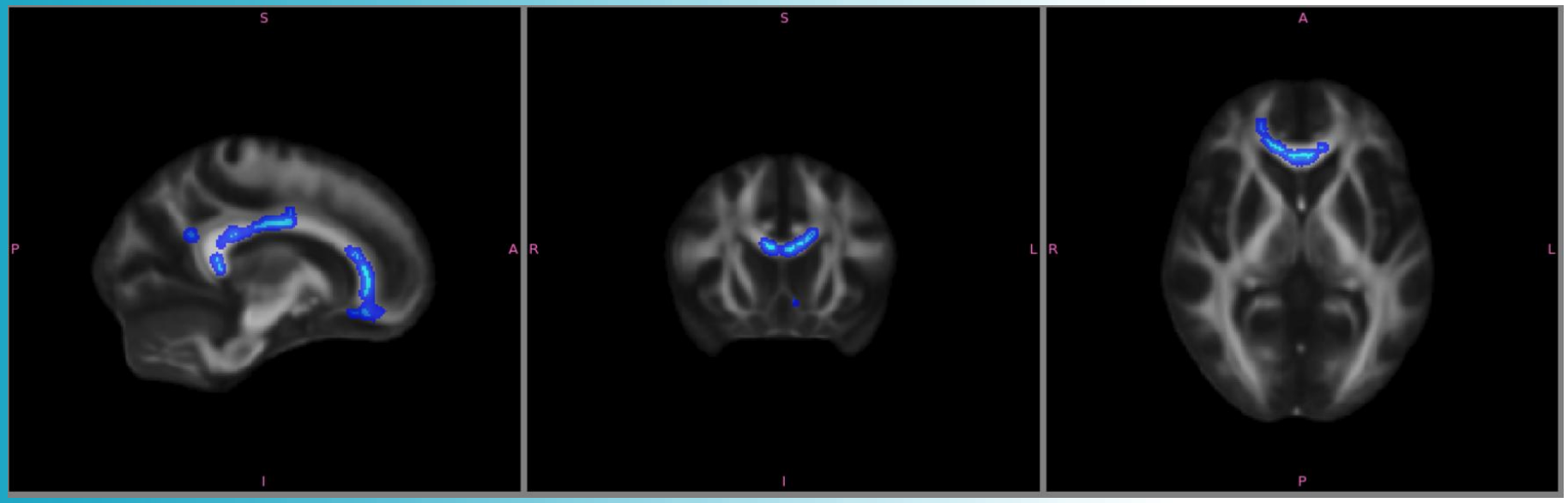
Similar ADHD Profile of DTI Underconnectivity in ASD Youth with ADHD



Cingulum-Corpus Callosal tracts DTI underconnectivity

Yuwen, Joshi et al. 2023

Treatment of ADHD in Autism

- ADHD is the most common psychopathology associated with HF-ASD
- Anti-ADHD medication is the most widely prescribed treatment in individuals with ASD
- Stimulants are the most widely prescribed psychotropic agent in youth with ASD (12% of the ASD population)
- Methylphenidate is the most commonly prescribed stimulant in youth with ASD

Campbell et al. 1972 & 1976. Handen et al. 2000
Stigler et al. 2004.

Anti-ADHD Controlled Trials in Autism

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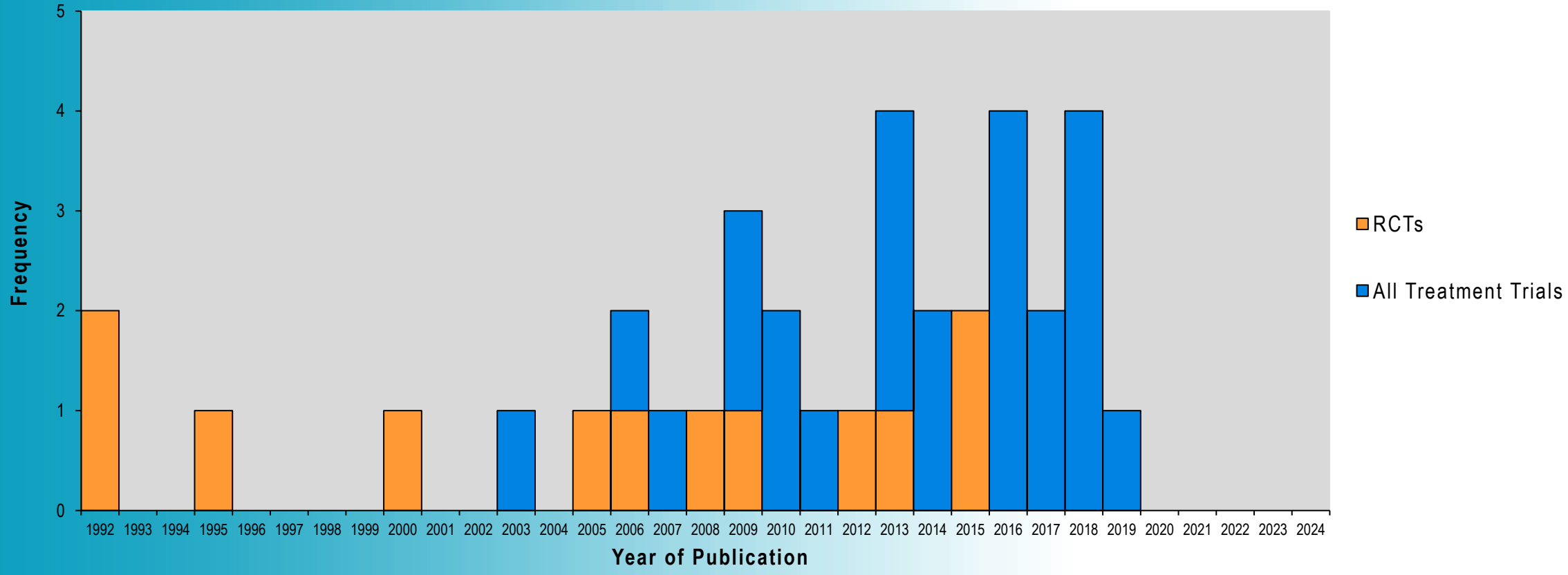
Frequency of Published Anti-ADHD Treatment Trials in ASD



Total Controlled Trials: N=12
(In last >30 years)

Joshi et al., 2021; Joshi & Wilens, 2022

STIMULANT CLASS OF ANTI-ADHD CONTROLLED TRIALS 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 worse than typically expected -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/day	Sign. ↓↓ ADHD -CTRS RR: 67% ES: NR	TEAE: Insomnia, ↓Appetite Dose-LAE: 5 (21) Tx-LAE: None	-2/3rd intellectually intact & 1/3rd with mild ID -Typically expected response -No worsening of ASD, Mood, or Anxiety
RUPP, 2005	Crossover [4-Week]	Children 5–13	66	8%	7.5 - 50	Sign. ↓ Hyperactivity -ABC-H RR: 49% ES: 0.48	TEAE: Insomnia, ↓Appetite, Emotional outburst, Irritability Dose-LAE: 16 (24) Tx-LAE: 13 (18)	-Majority participants with ID & nonverbal -Significant level of irritability at baseline -Response worse 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)	-Participants with ID -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/day	Sign. ↓↓ Hyperactivity -ABC-H/ CTRS-H ES: NR	TEAE: None Dose-LAE: None Tx-LAE: None	-Majority participants with ID (70%) -No mood dysregulation with Tx -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

Joshi et al., 2021; Joshi & Wilens, 2022

NON-STIMULANT CLASS OF ANTI-ADHD CONTROLLED TRIALS IN AUTISM SPECTRUM DISORDER

ATOMOXETINE

RCT	Design [Duration]	Age [years]	Total [N]	HF	Dose [mg/day]	Efficacy	Tolerability	Comments
Harden et al., 2015	Parallel [10-Week]	Youth 5-15	128	16%	1.4 ±0.5 mg/kg/day	Sign. ↓ ADHD -SNAP-IV RR: 47% (vs. 60% in typicals) ES: 0.80	TEAE: ↓Appetite Dose-LAE: None Tx-LAE: 5 (8) vs. 10 (16)	-Majority with ID (83.5%) -Significant level of irritability at baseline -Efficacy less than typically expected -Typically expected tolerability -No worsening of ASD, Mood, or SI
Harfterkamp et al., 2012	Parallel [8-Week]	Youth 6-16	97	6%	0.5 - 1.2 mg/kg/day	Sign. ↓ ADHD -ADHD-RS [Mean↓= 8] RR: 21% [P=NS] ES: NR	TEAE: Nausea, ↓Appetite, Early waking, Fatigue Dose-LAE: None Tx-LAE: 1 (2) vs. 0	-Majority without ID -Significant level of irritability at baseline -Efficacy less than typically expected -Typically expected tolerability -No worsening of ASD
Arnold et al., 2006	Crossover [12-Week]	Youth 5-15	16	6%	44 ±22 20 - 100	Sign. ↓ Hyperactivity -ABC-H [Mean↓= 5] RR: 43% ES: 0.73	TEAE: Upset stomach, N&V, Fatigue, Tachycardia Dose-LAE: None Tx-LAE: 1 (6) vs. 0	-Majority with ID -Significant level of irritability at baseline -Efficacy less than typically expected -Typically expected tolerability

GUANFACINE

RCT	Design [Duration]	Age [years]	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	Sign. ↓↓ Hyperactivity -ABC-H [%↓= 44] RR: 50% ES: 1.67	TEAE: Drowsiness, Fatigue, ↓Appetite, Dry mouth, Emotional/ tearful, Irritability, Anxiety Dose-LAE: 9 (30) vs. 5 (16) Tx-LAE: 4 (13) vs. 0	-Majority with ID (66%) -Significant level of irritability at baseline -Typically expected efficacy -AEs at higher frequency than typically expected -No worsening of ASD

NR=Not Reported; HF=High-Functioning; ES=Effect Size; RR=Response Rate; AE=Adverse Events; TEAE=Treatment Emergent AE; 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

Joshi et al., 2021; Joshi & Wilens, 2022

Secondary Response of Hyperactivity to Non-ADHD Trials in Autism

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Controlled-Trials

Agent	Study	Age	Total [N]	HF	Target Symptom	Measure	Hyperactivity
Selective Serotonin Reuptake Inhibitors							
Citalopram	King et al., 2009	Youth	149	-	RRB	ABC-H	-
Fluoxetine	Reddihough et al., 2019	Youth	146	±	RRB	ABC-H	-
Tricyclic Antidepressants							
Clomipramine	Remington et al., 2001	Youth	36	NA	Autism	ABC-H	-
Anti-Anxiety Medication							
Buspirone	Chugani et al., 2016	Pre-Schooler	166	NA	Autism	ABC-H	-
Glutamate Modulating Agents							
Lamotrigine	Belsito et al. 2001	Children	28	-	Autism	ABC-H	-
Amantadine	King et al. 2001	Youth	39	-	Irritability/Hyperactivity	ABC-H	-
N-Acetylcysteine	Hardan et al., 2012	Children	29	-	Irritability	ABC-H	-
	Wink et al., 2016	Children	31	±	Autism	ABC-H	-
Memantine	Ghaleiha et al., 2012	Children	40	NA	Irritability	ABC-H	+
	Aman et al., 2015	Children	121	-	Autism	ABC-H	-
Atypical Antipsychotics							
Risperidone	RUPP, 2002	Youth	101 63	±	Irritability	ABC-H	+
Aripiprazole	Owen et al., 2009 Marcus et al., 2009	Youth	98 218	NA	Irritability	ABC-H	+

NA=Not Assessed; HF-High Functioning; RRB=Restricted Repetitive Behaviors; ABC-H=Aberrant Behavior Checklist-Hyperactivity subscale

Promising efficacy of atypical antipsychotics for treating Hyperactivity in the context of irritability in youth with Autism

Limitations of Previous Controlled Trials of ADHD in Autism

- No trials on *Mixed Amphetamine Salts* in ASD
- No trials in *Adults* with ASD
- Trials predominantly conducted in *Intellectually Impaired* populations with ASD
- Recruited ASD participants with significantly elevated levels of *Irritability*
- Majority of trials assessed for *Hyperactivity* response

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Six-Week Open-Label Trial of Methylphenidate Extended-Release Liquid Formulation (Quillivant XR) for the Treatment of ADHD in Intellectually-intact Adults with ASD

Clinical Trials Registration @ ClinicalTrials.gov
Registration Number: NCT02096952
URL: https://clinicaltrials.gov/ct2/show/NCT02096952?term=NCT02096952

Study Approved by: Partners Human Research Committee Institutional Review Board

Study Funded by: Pfizer, Inc.

OLT of MPH in Adults with Autism

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Participant Characteristics (N=15)

- Adults aged 19-34 years (Mean age: 25 ±4.5 years)
- Intact intellectual ability (IQ Range: 99 – 144)
- Met the DSM-5 criteria for ASD and ADHD
- At least moderate level of severity for ASD and ADHD (SRS=≥85; AISRS=≥24; & respective CGI-S ≥4)
- Not experiencing 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

Study Medication (MPH-ER)

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

Joshi et al. 2020

Treatment Response: ADHD Symptoms

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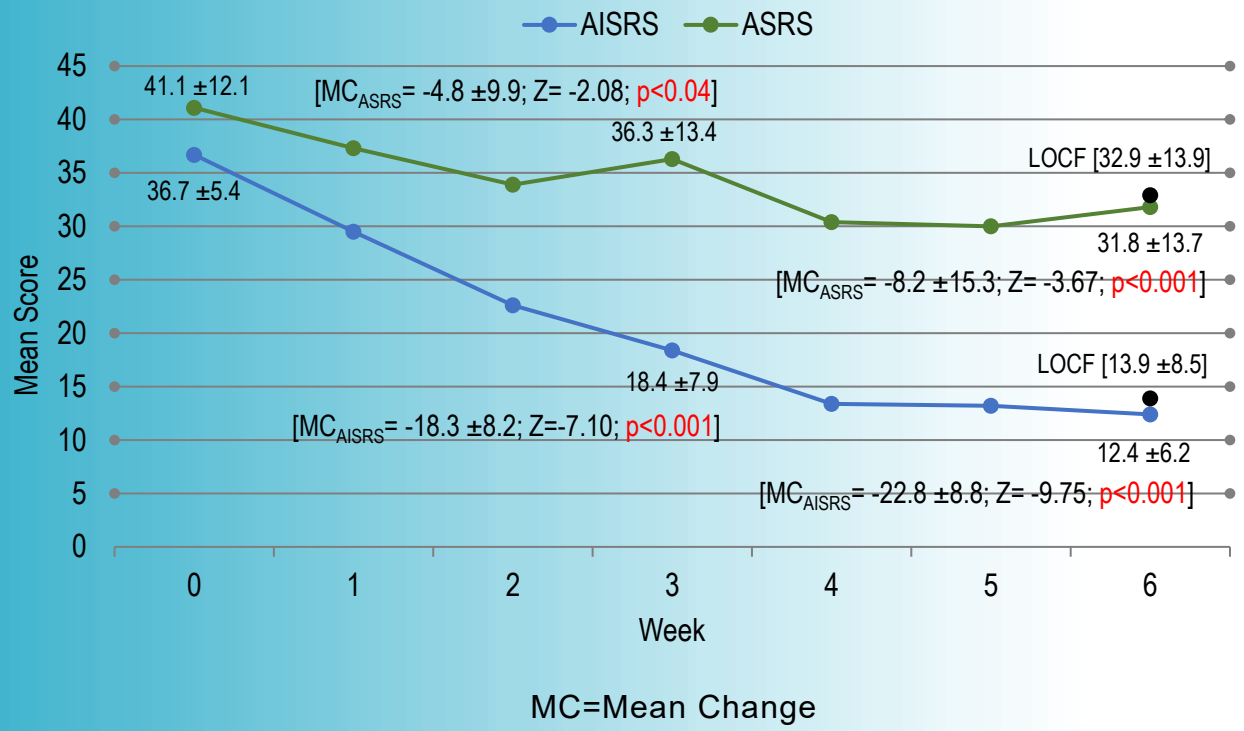
Clinician-Rated: Adult Investigator Symptom Report Scale (AISRS)

Patient-Rated: Adult Self-Report Scale (ASRS)



MC=Mean Change

Joshi et al. 2020.

Joshi et al. 2020

Adverse Events

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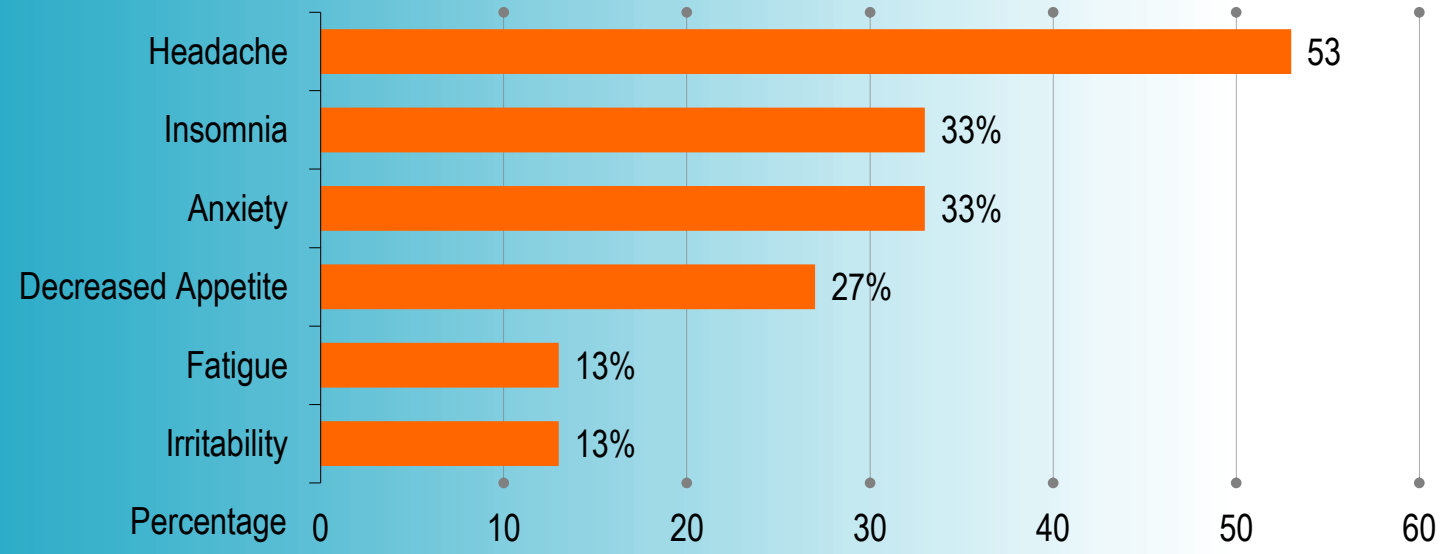
Adverse Events (Mild-Moderate Severity)



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

Treatment Response: Autism Traits

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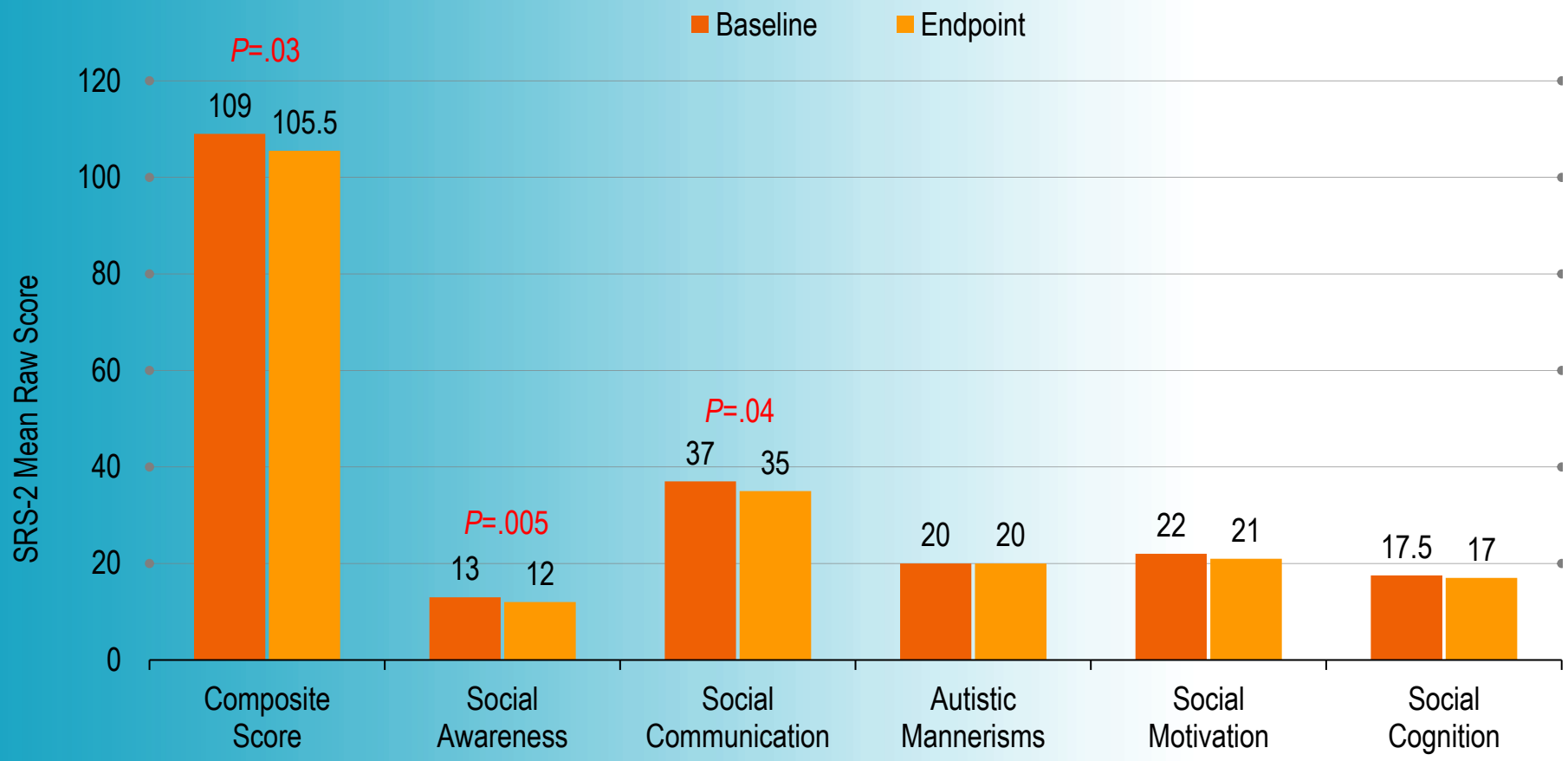
Social Responsiveness Scale (SRS-2)



Joshi et al. 2020.

Joshi et al. 2020

Treatment Response: Associated Psychopathology

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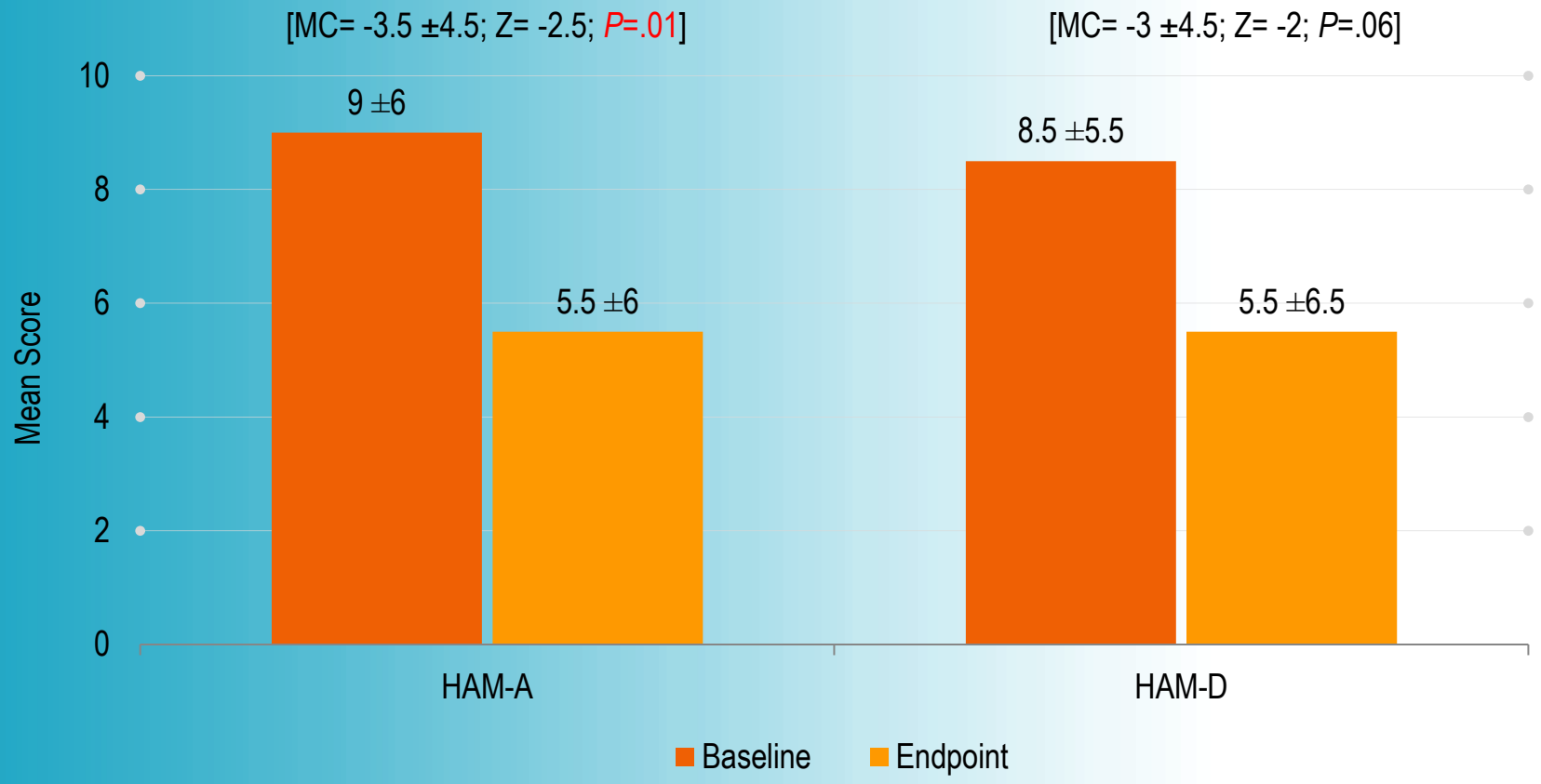

MC=Mean Change; HAM=A=Hamilton Anxiety Scale; HAM-D=Hamilton Depression Scale

Joshi et al. 2020.

Joshi et al. 2020

In Summary

- High prevalence of ADHD in individuals with ASD
- Typical clinical presentation of ADHD in youth with autism
- Paucity of anti-ADHD controlled trials in autism populations
- Anti-ADHD response worse than typically expected in autism youth with ID and with high levels of irritability
- Treatment for ADHD was not associated with worsening of ASD features
- Typically expected response of MPH in adults with autism

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

Massachusetts General Hospital
Boston MA

Gagan Joshi, MD
Janet Wozniak, MD
Atilla Ceranoglu, MD
Craig Surman, MD
Mai Uchida, MD
Usman Ghumman, MD
James Luccarelli, MD, DPHIL
Hagar Kandel, MBBCh, MSc
Maura DiSalvo, MPH
Atilla Gonenc, PhD
Ronna Fried, EdD
Brittney Jurgen, PMHNP-BC
Carly Ramos, PMHNP-BC
Rachel Veenbaas, PMHNP-BC

Stephen Faraone, PhD
John D.E. Gabrieli, PhD
Nichole Zurcher, PhD
Elise Robinson, ScD
Sheeba A. Anteraper, PhD
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Leena Phan
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Milla Zabib