MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Module Topic 9

Psychopathology Associated with Autism

An Overview

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DSM Criteria for Autism

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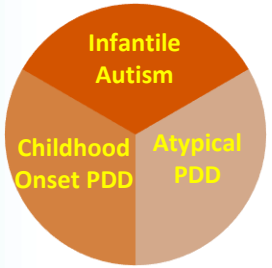
Schizophrenic Reaction - Childhood Type

DSM-I
(1952)

Schizophrenia - Childhood Type

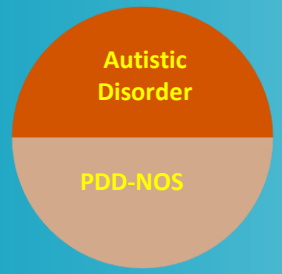
DSM-II
(1968)

Pervasive Developmental Disorders



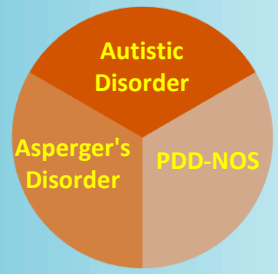
DSM-III
(1980)

Pervasive Developmental Disorders



DSM-III-R
(1987)

Pervasive Developmental Disorders



DSM-IV/-TR
(1994/2000)

Autism Spectrum Disorder

DSM-5/-TR
(2013/2022)

Implications of Unrecognized Reciprocal Comorbidity of ASD & Psychopathology

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Failure to Recognize Psychopathology

- Further worsens compromised psycho-social functioning
- Interferes with ASD specific behavioral interventions
- Fails to receive disorder specific treatment
- Increases risk for developing other psychiatric conditions
- (disruptive behaviors, mood dysregulation, & substance abuse)

Prevalence of Psychopathology in General Population

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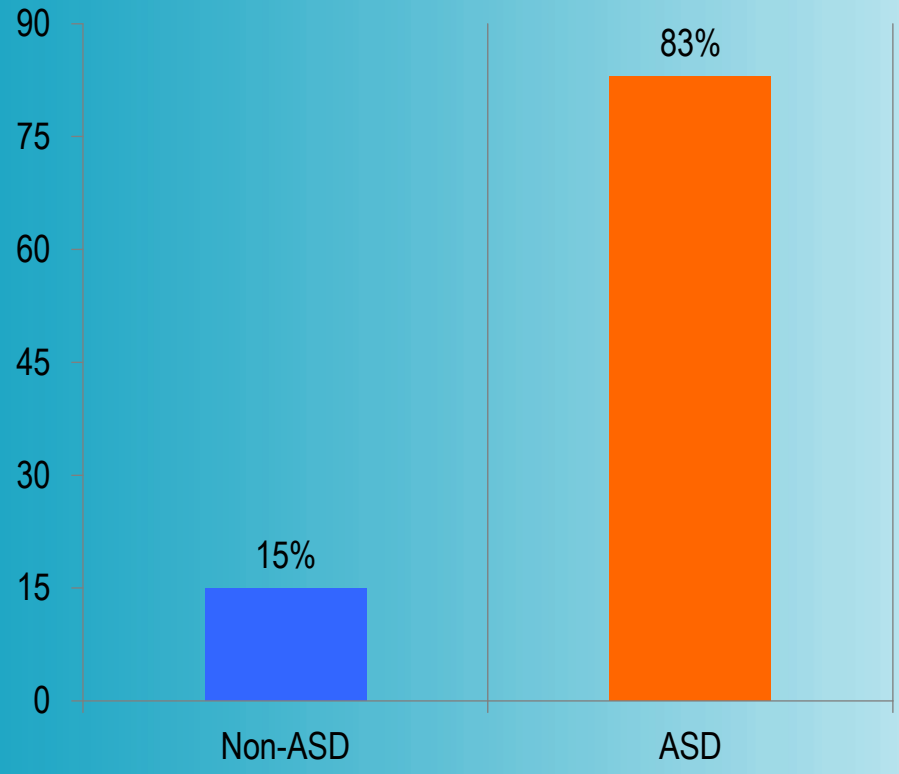
Emotional & Behavioral Difficulties in Children with Autism



A parent-reported survey
(2003-04)
in
School-aged Children
(4-17 years)

CDC Surveys (NHIS & NSCH).

Comorbidity Associated with ASD

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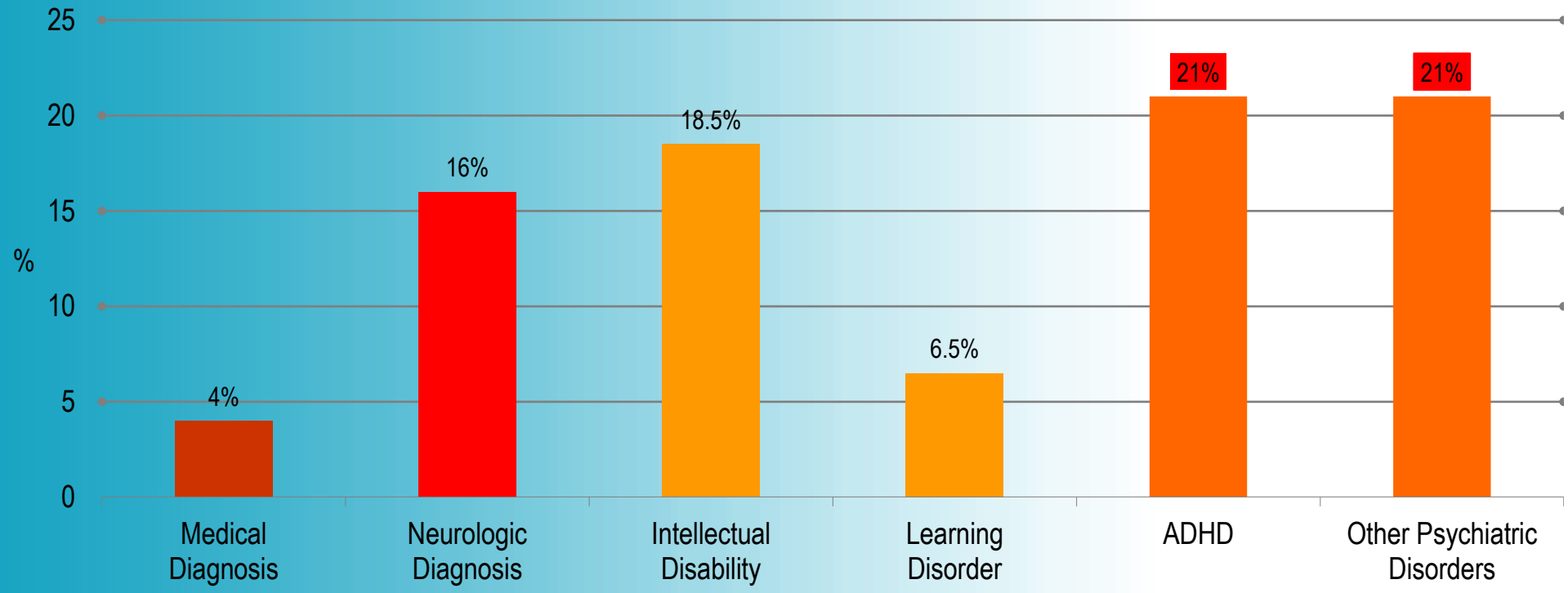
Comorbidity in US population-based sample of ASD

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



Autism & Developmental Disabilities Monitoring Network Surveillance Year 2002. Levy et al. 2010.

Psychiatric Disorders Associated with AUTISM

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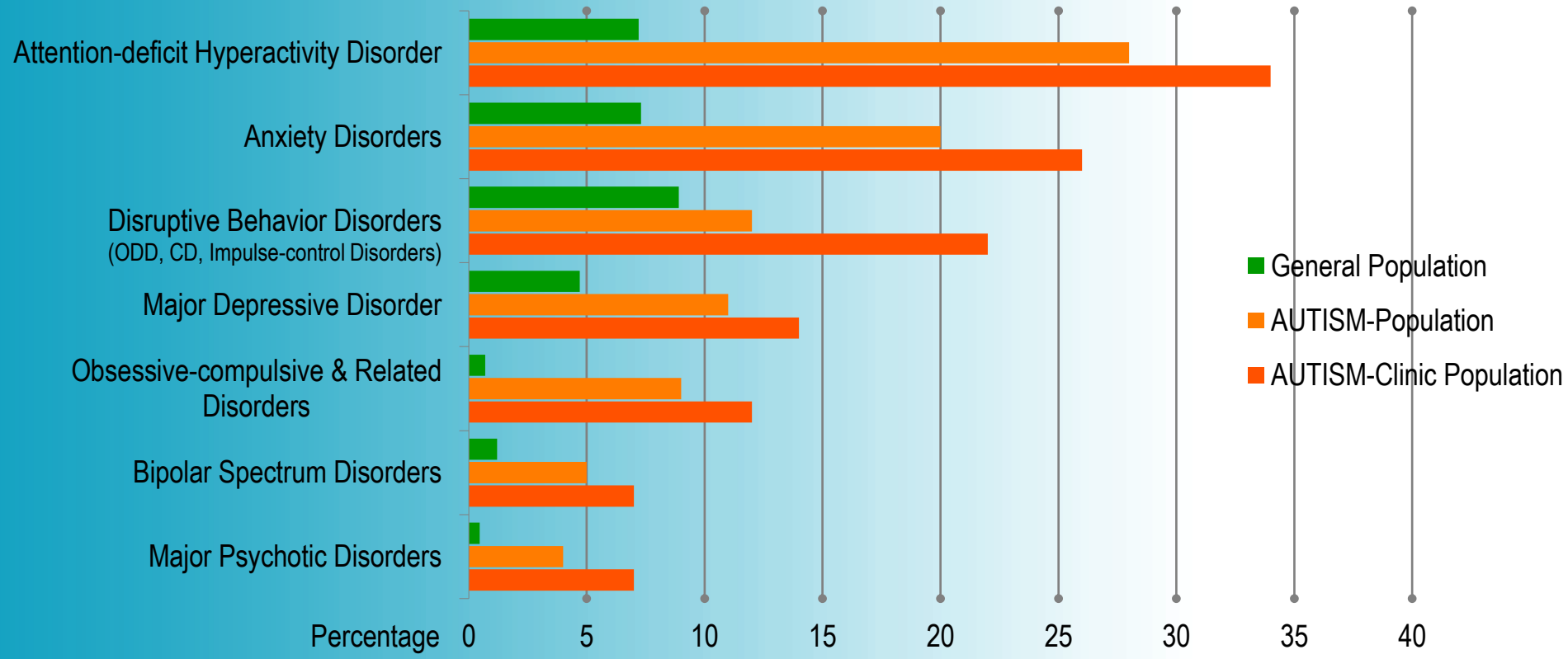
Prevalence (Pooled Point Estimates)



Lai et al. 2019

J Autism Dev Disord (2010) 40:1361–1370
DOI 10.1007/s10803-010-0996-9

ORIGINAL PAPER

The Heavy Burden of Psychiatric Comorbidity in Youth with Autism Spectrum Disorders: A Large Comparative Study of a Psychiatrically Referred Population

Gagan Joshi · Carter Petty · Janet Wozniak · Aude Henin · Ronna Fried · Maribel Galdo · Meghan Kotarski · Sarah Walls · Joseph Biederman

Published online: 23 March 2010

Abstract The objective of the study was to systematically examine patterns of psychiatric comorbidity in referred youth with autism spectrum disorders (ASD) including autistic disorder and pervasive developmental disorder not otherwise specified. Consecutively referred children and adolescents to a pediatric psychopharmacology program were assessed with structured diagnostic interview and measures of psychosocial functioning. high levels of psychiatric comorbidity and dysfunction comparable to the referred population of youth without ASD. These findings emphasize the heavy burden of psychiatric comorbidity afflicting youth with ASD and may be important targets for intervention.

Keywords Autism spectrum disorders · Psychiatric comorbidity · Children and adolescents

Prevalence of ASD in Psychiatrically Referred Youth

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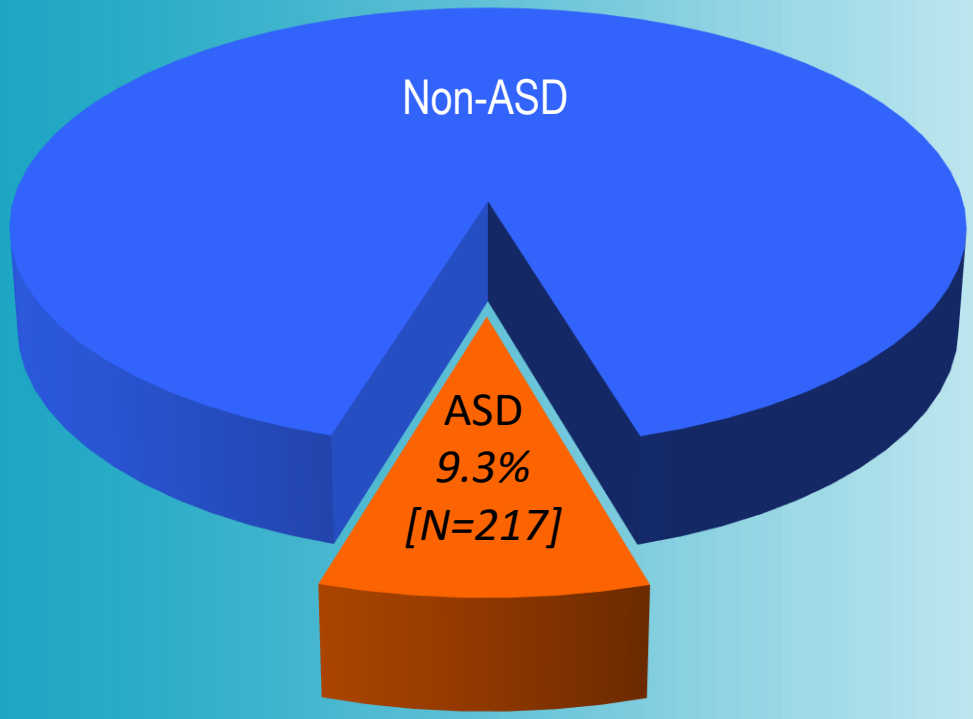

Total N:	2323
Total Duration:	15 years (1991-2006)
Male:	87%
Age *(yrs)*:	9.7 ±3.6 (3-17)
Intellectual Ability & Language Skills:	Clinically not impaired in majority of the referred youth

Autism Prevalence 4 x Higher than General Population

Joshi et al. 2010.

Psychiatrically Referred Youth with ASD

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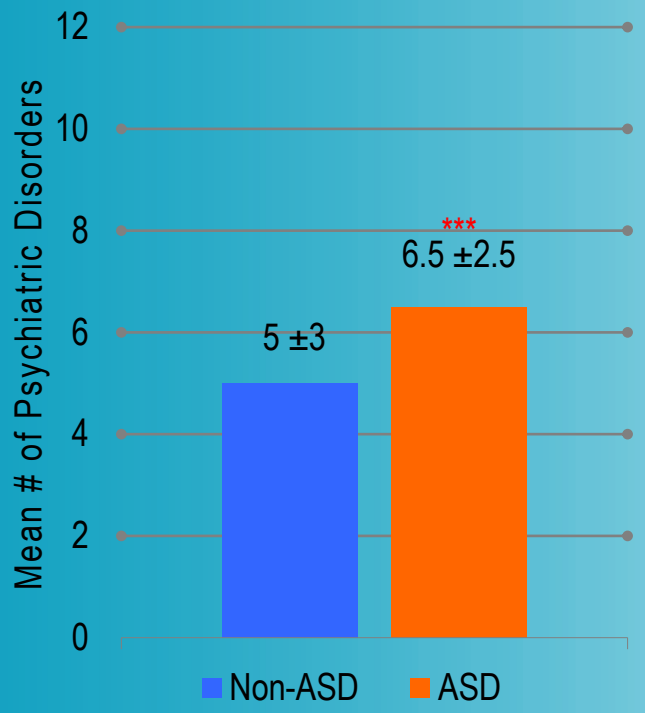
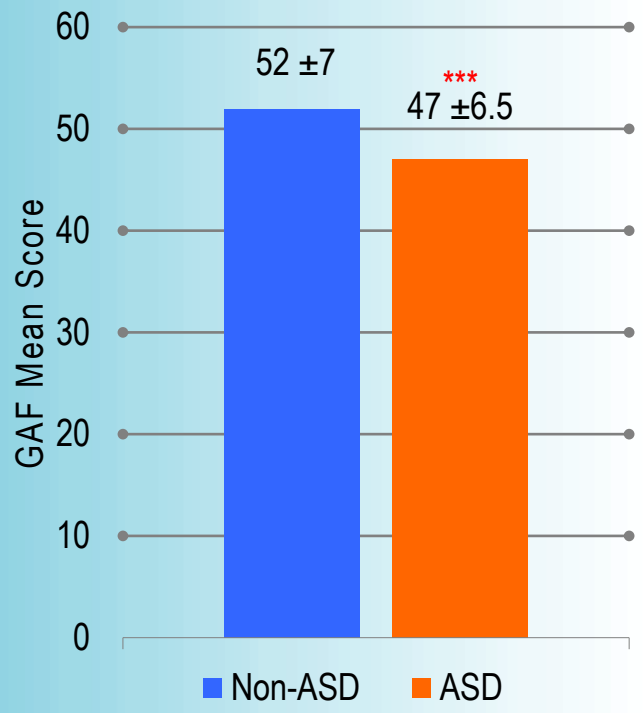
Burden of Psychopathology



Global Functioning



Statistical Significance: ***p≤0.001

Greater Burden of Psychopathology & Poorer Level of Functioning

Joshi et al. 2010.

Psychopathology Associated with ASD

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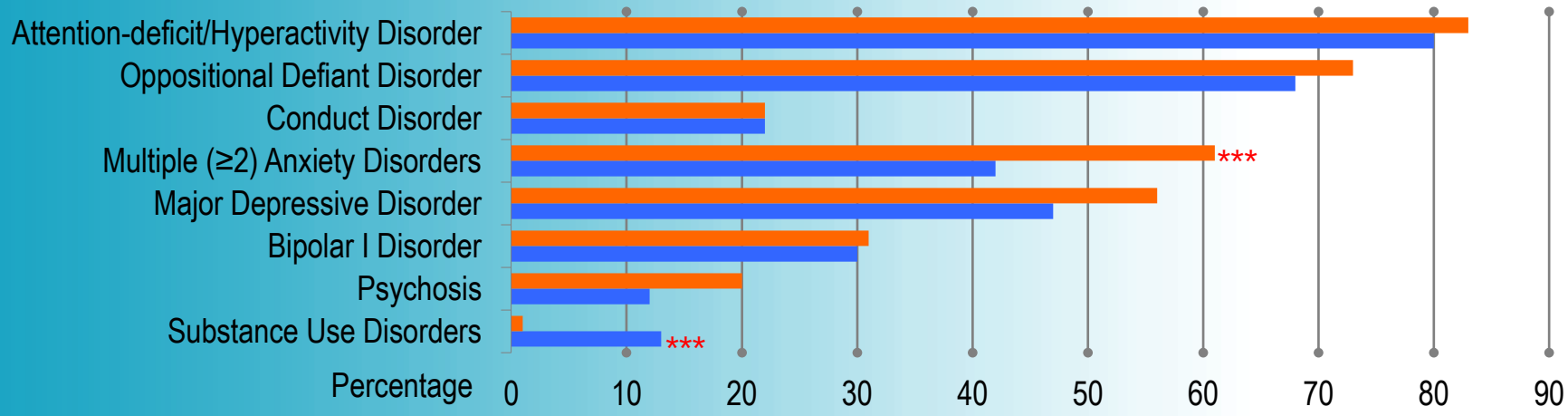
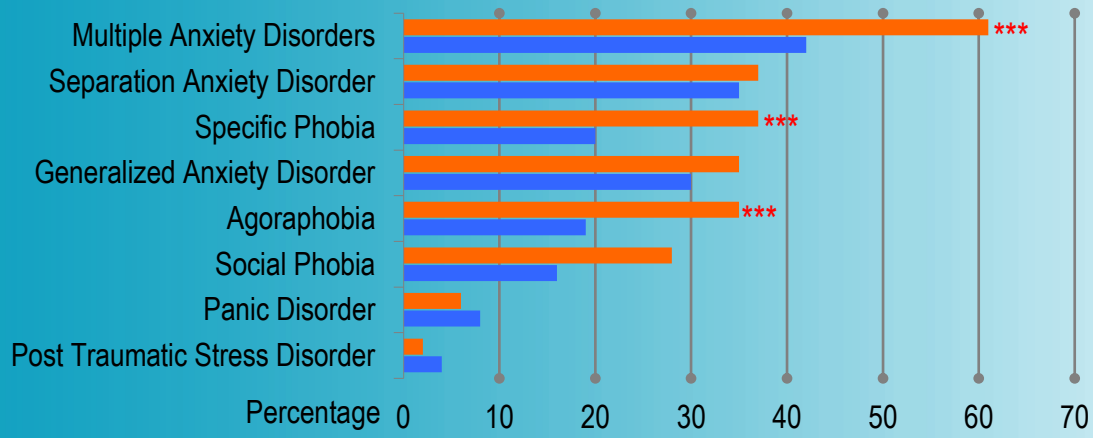
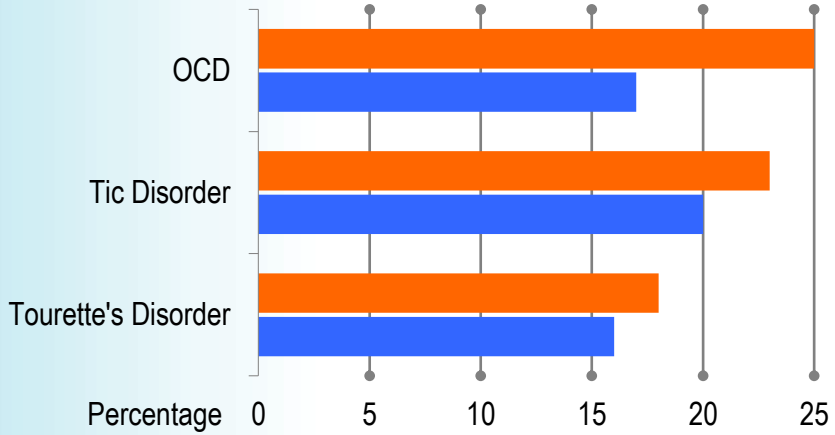
Lifetime Psychiatric Comorbidity



Anxiety Disorders



Repetitive Behavior Disorders



ASD NON-ASD Statistical Significance: ***p≤0.001

Joshi et al. 2010.

Treatment History

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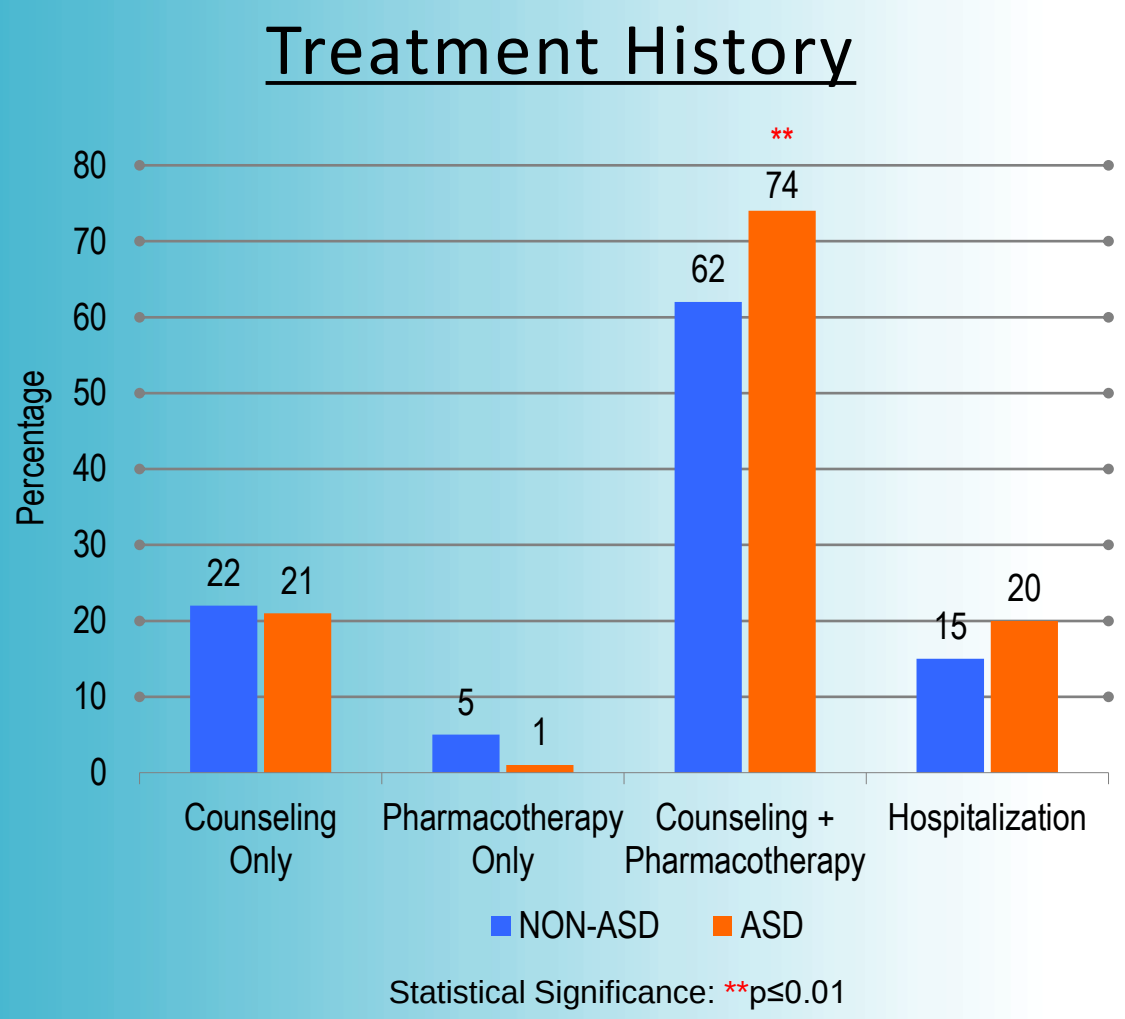

Joshi et al. 2010.

Risk for Psychiatric Disorders in ASD

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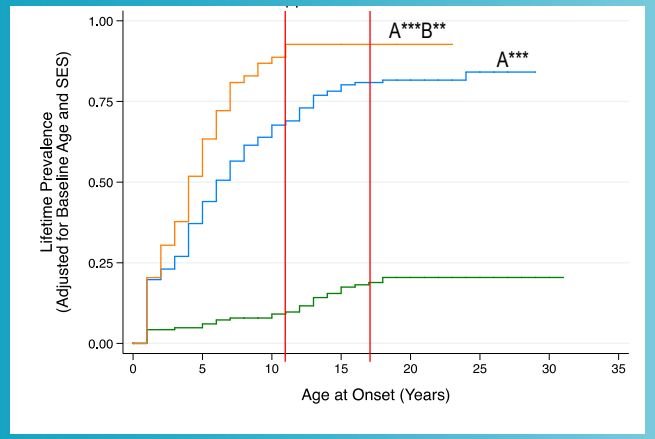
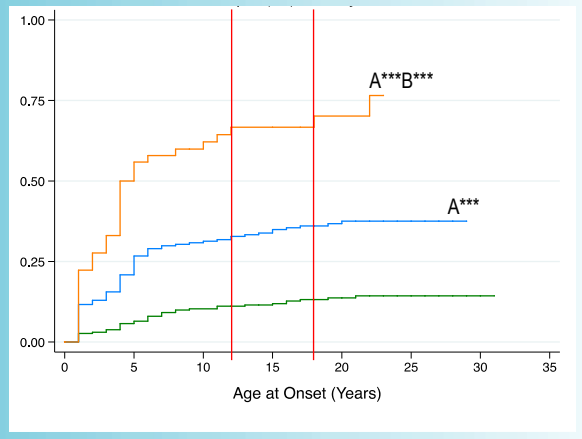
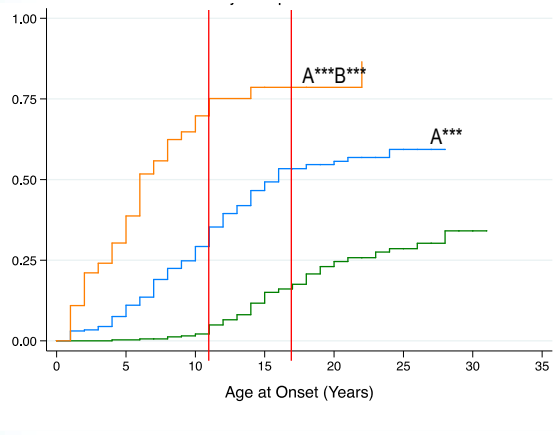
Oppositional Defiant Disorder



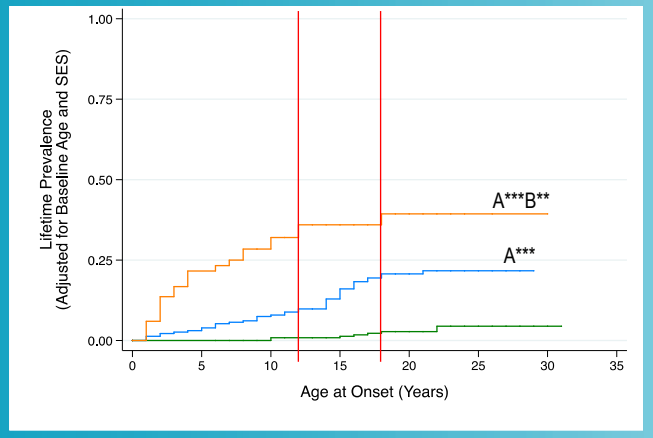
Multiple (≥2) Anxiety Disorders



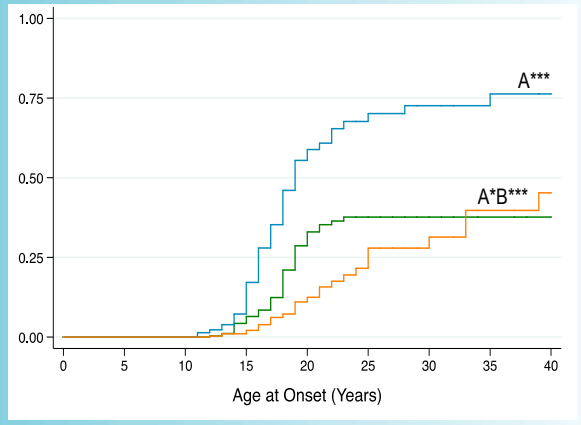
Major Depressive Disorder



Bipolar Disorder



Substance Use Disorders



Controls ADHD-AT ADHD+AT

*P<.05, **P<.005, ***P<.001

[A] Versus Controls. [B] Versus ADHD-AT

Joshi et al. 2019.

Ages at Onset of Psychiatric Disorders

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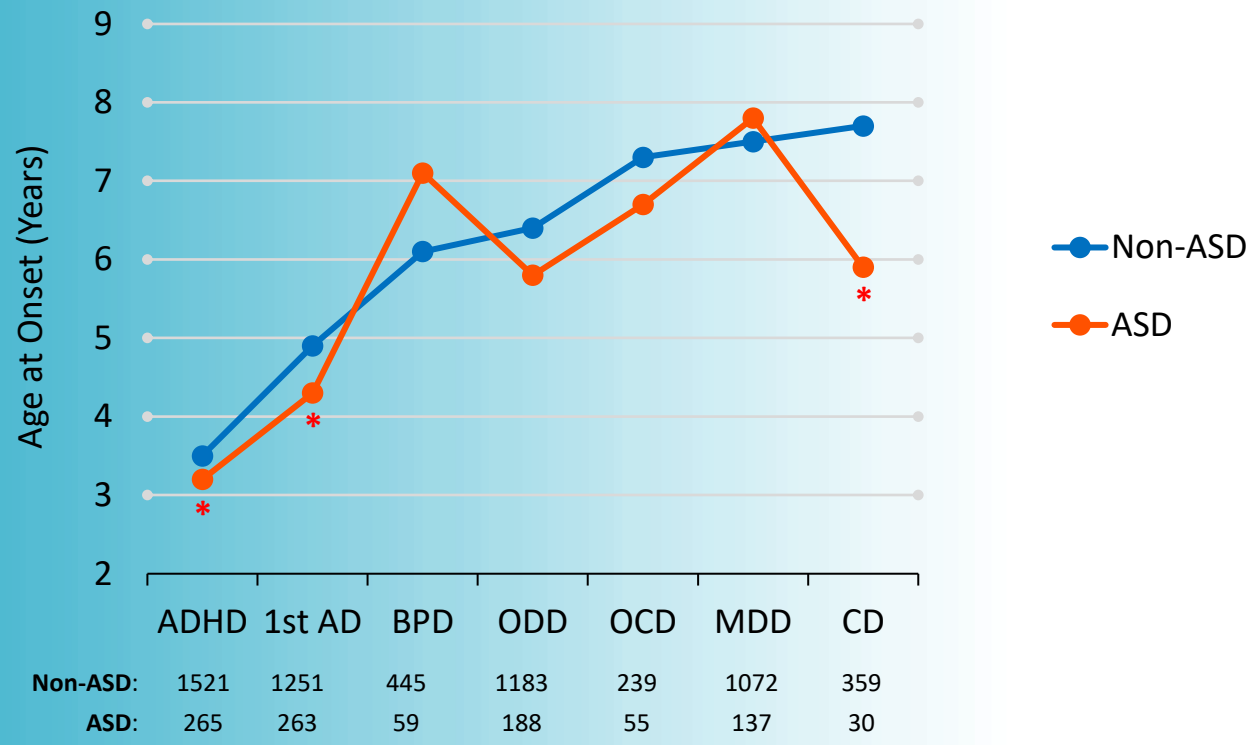
Sex Effect in Non-ASD versus ASD Referred Populations



	ADHD	1st AD	BPD	ODD	OCD	MDD	CD
Non-ASD:	1521	1251	445	1183	239	1072	359
ASD:	265	263	59	188	55	137	30

Statistical Significance: **P* ≤.05

Ages at Onset of Psychiatric Disorders

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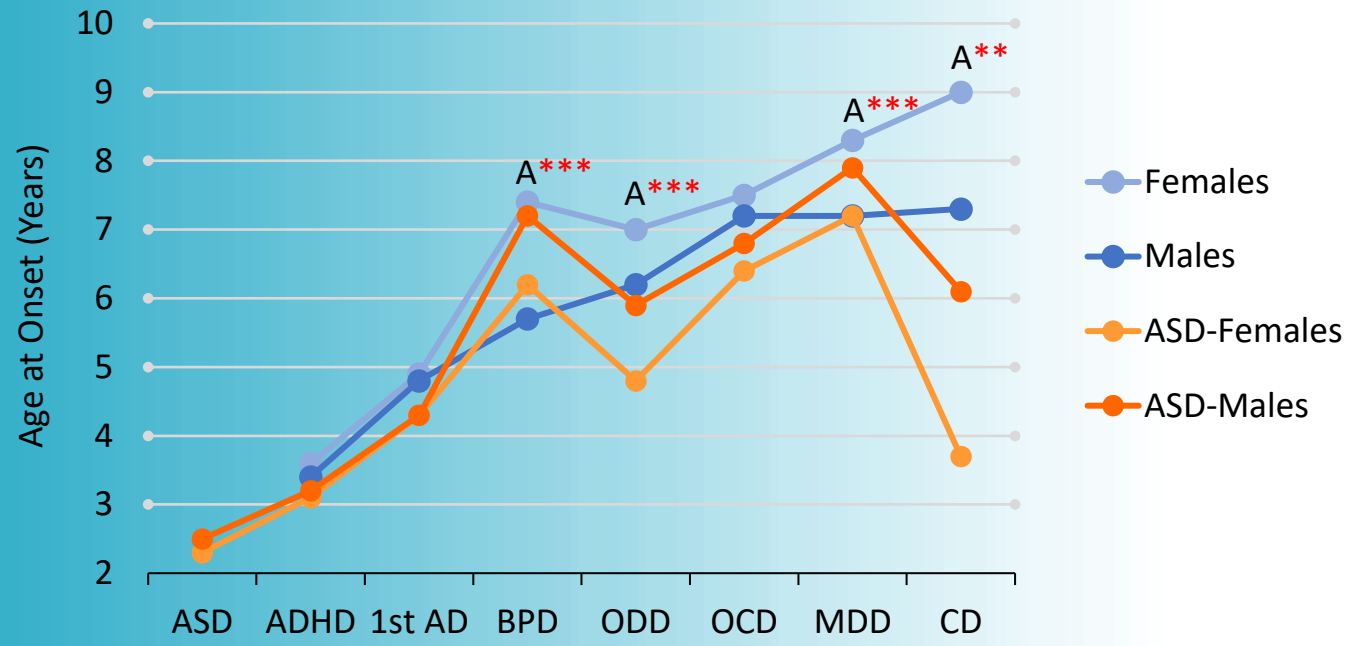
Sex Effect in ASD and Non-ASD Referred Populations



Females:		359	399	119	313	77	336	74
Males:		1162	852	326	870	162	736	285
ASD-Females:	37	31	35	9	23	7	21	3
ASD-Males:	273	234	228	50	165	48	116	27

Statistical Significance: *$P \leq .05$, **$P \leq .01$, ***$P \leq .001$; A= versus Males

Longitudinal Presentation of Autism and Psychopathology

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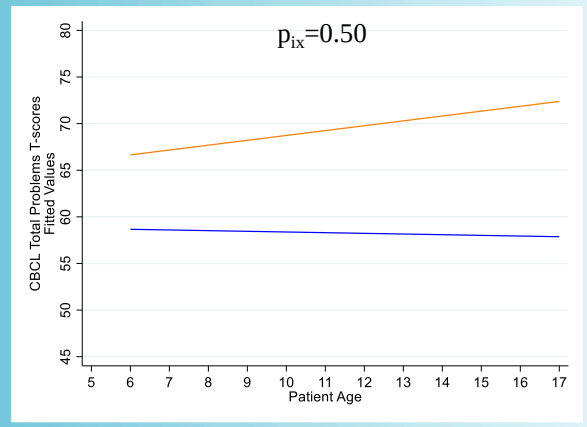
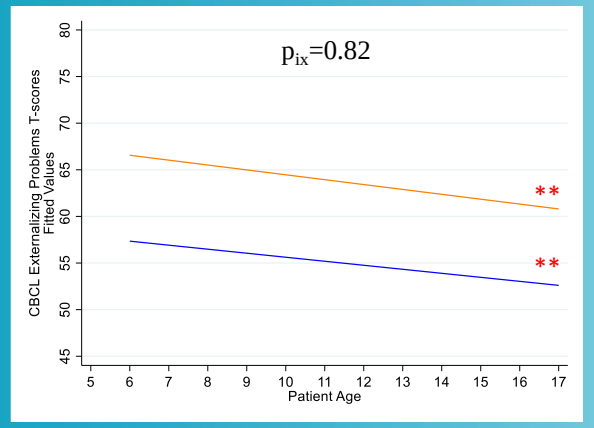
Severity of Psychopathology (CBCL-Composite Scales)

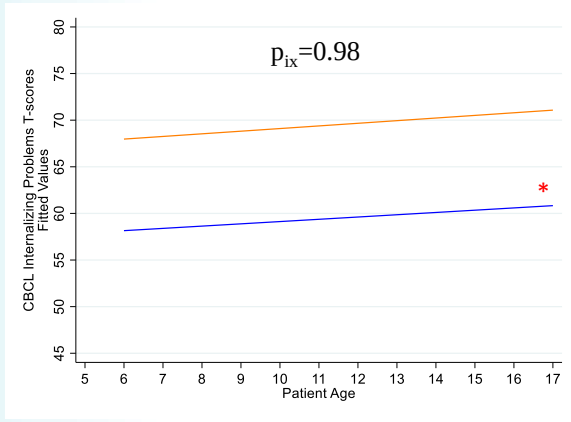
Total Problems



Externalizing Problems

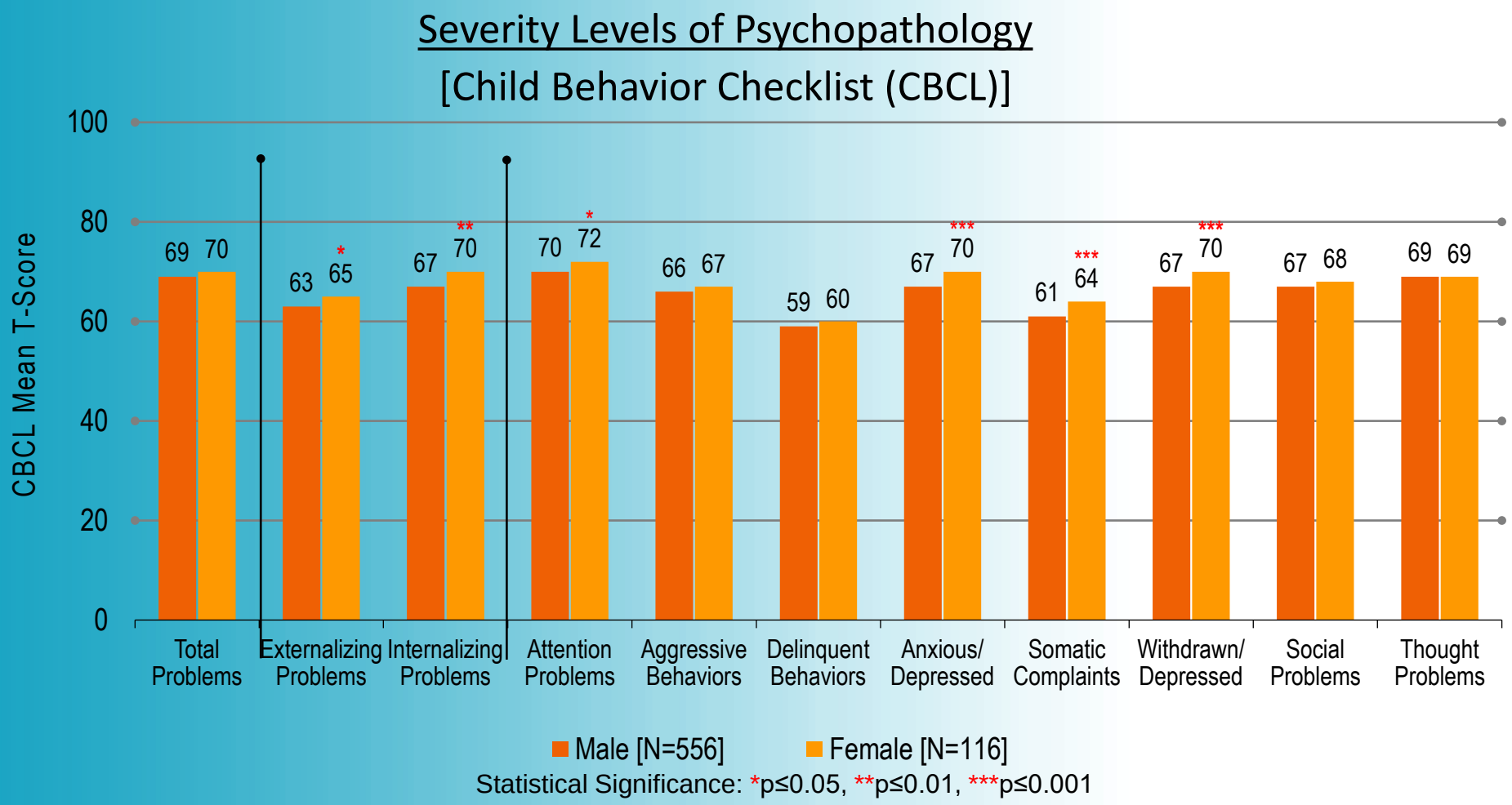


Internalizing Problems



Within Group Age Effect Statistical Significance: *p<.05; **p<.01

Sex Effects on Pattern of Psychopathology



Sex Effects on Pattern of Psychiatric Disorders

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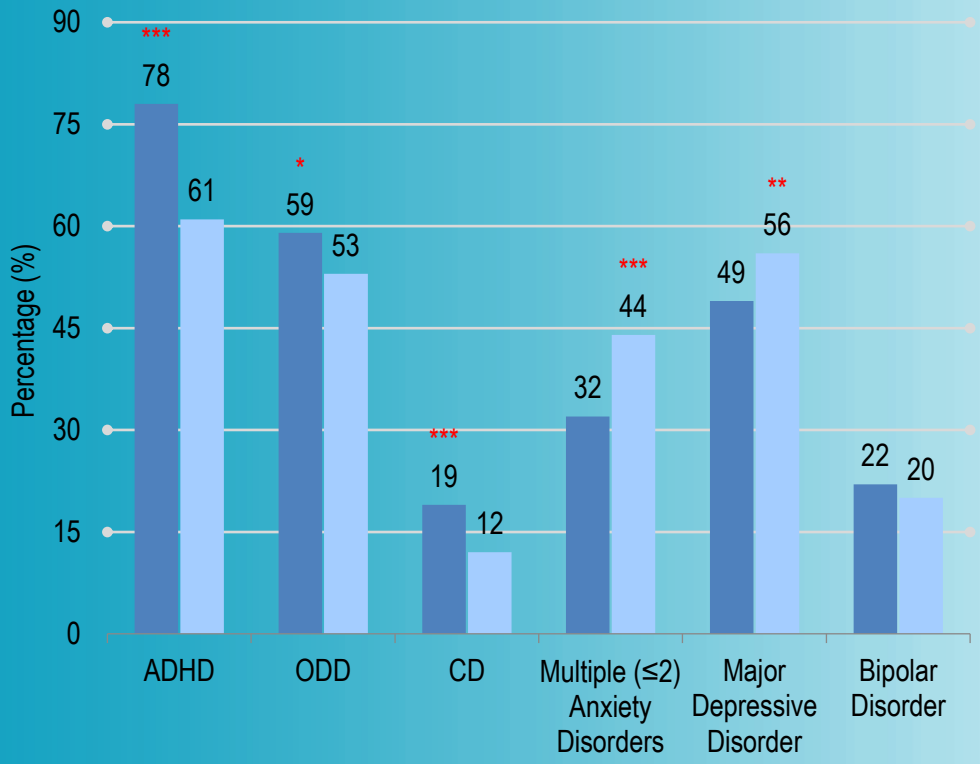
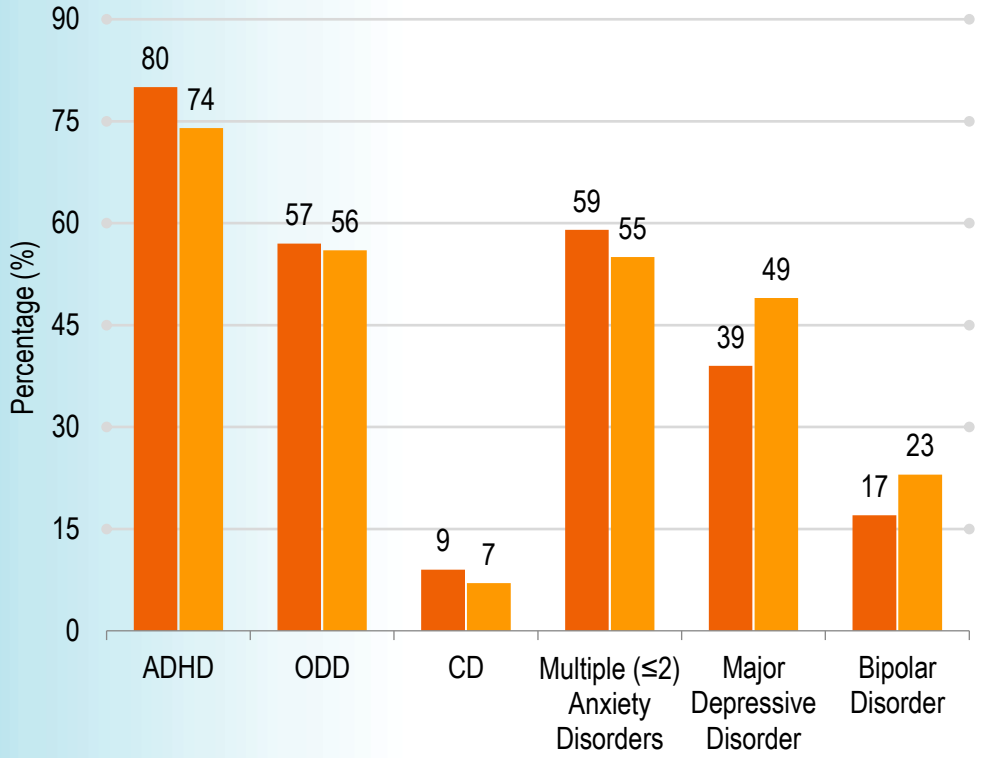
Non-ASD Population



ASD Population



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

Emotional Dysregulation

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Child Behavior Checklist (CBCL) Profile of Emotional Dysregulation (ED)

- ED profile based on the composite T-scores of CBCL subscales:
  - Inattention
  - Aggression
  - Anxious/Depressed

CBCL-AAA Subscales Composite T-Score	**Level of Emotional Dysregulation (ED)**
<180	Low/No ED
≥180	Presence of ED
≥ 180 and <210 (≥1SD & <2SD) (t-score of ≥60 on each CBCL-AAA subscales)	Deficient Emotional Self Regulation (DESR)
≥210 (≥2SDs)	Severe Emotional Dysregulation (SED)

Joshi et al. 2018.

Emotional Dysregulation in ASD

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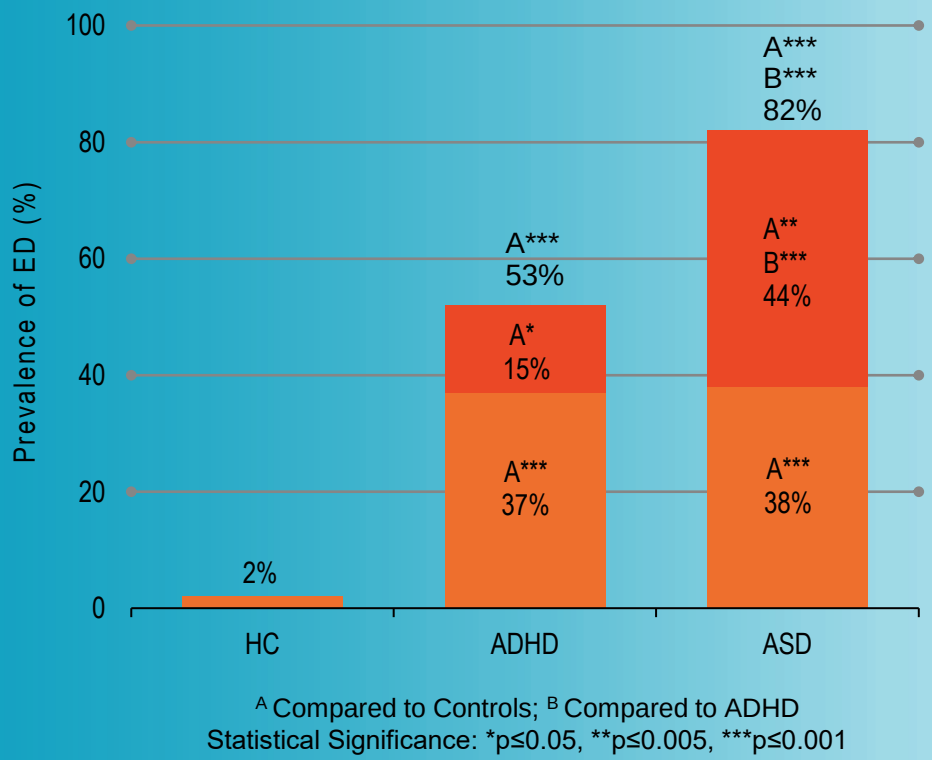
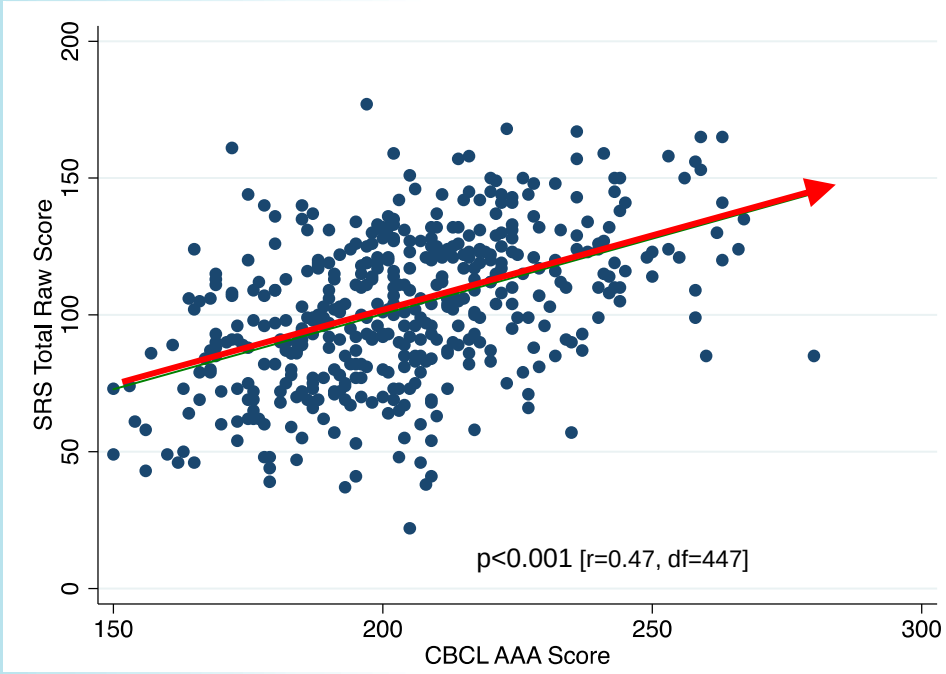
Child Behavior Checklist – Emotional Dysregulation Profile (CBCL-ED)



High Prevalence of ED in Youth with ASD



Positive correlation between severity of ED & autistic traits

Joshi et al. 2018.

Prescribing Patterns: Clinical Profile

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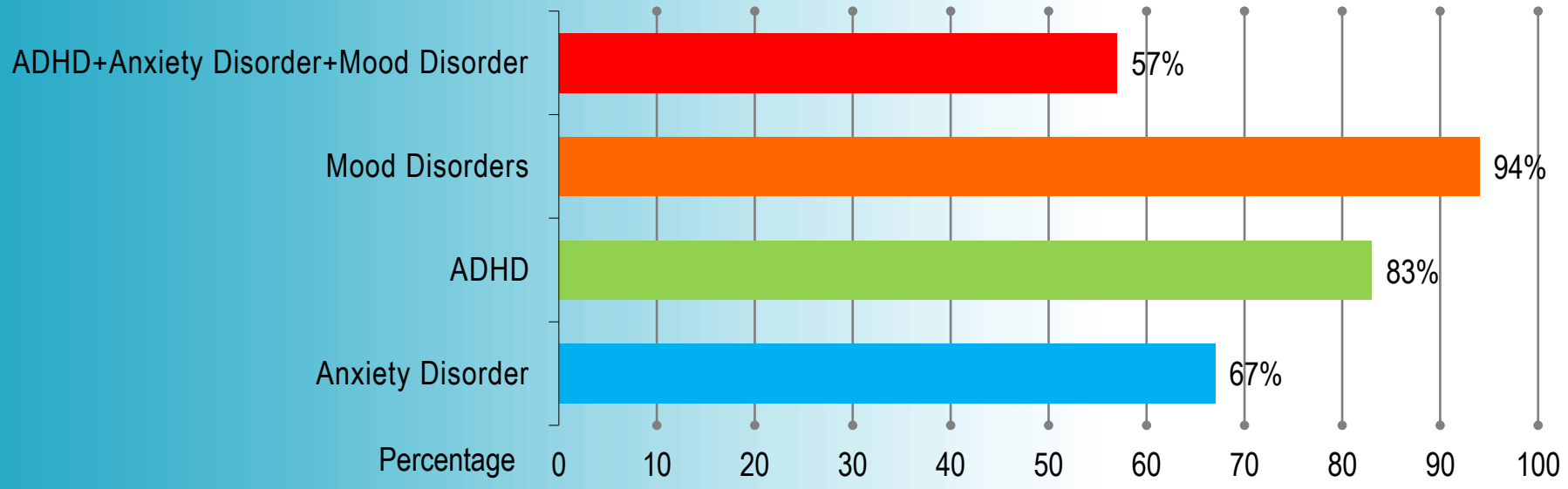
Total N	54
Age *(yrs)*	13 ±3 (7-19)
Male	76%
Autistic Disorder	61%
Asperger's Disorder/PDD-NOS	39%

Associated Psychopathology



Shekunov, Wozniak, Joshi et al. 2017.

Prescribing Patterns: Treatment Profile

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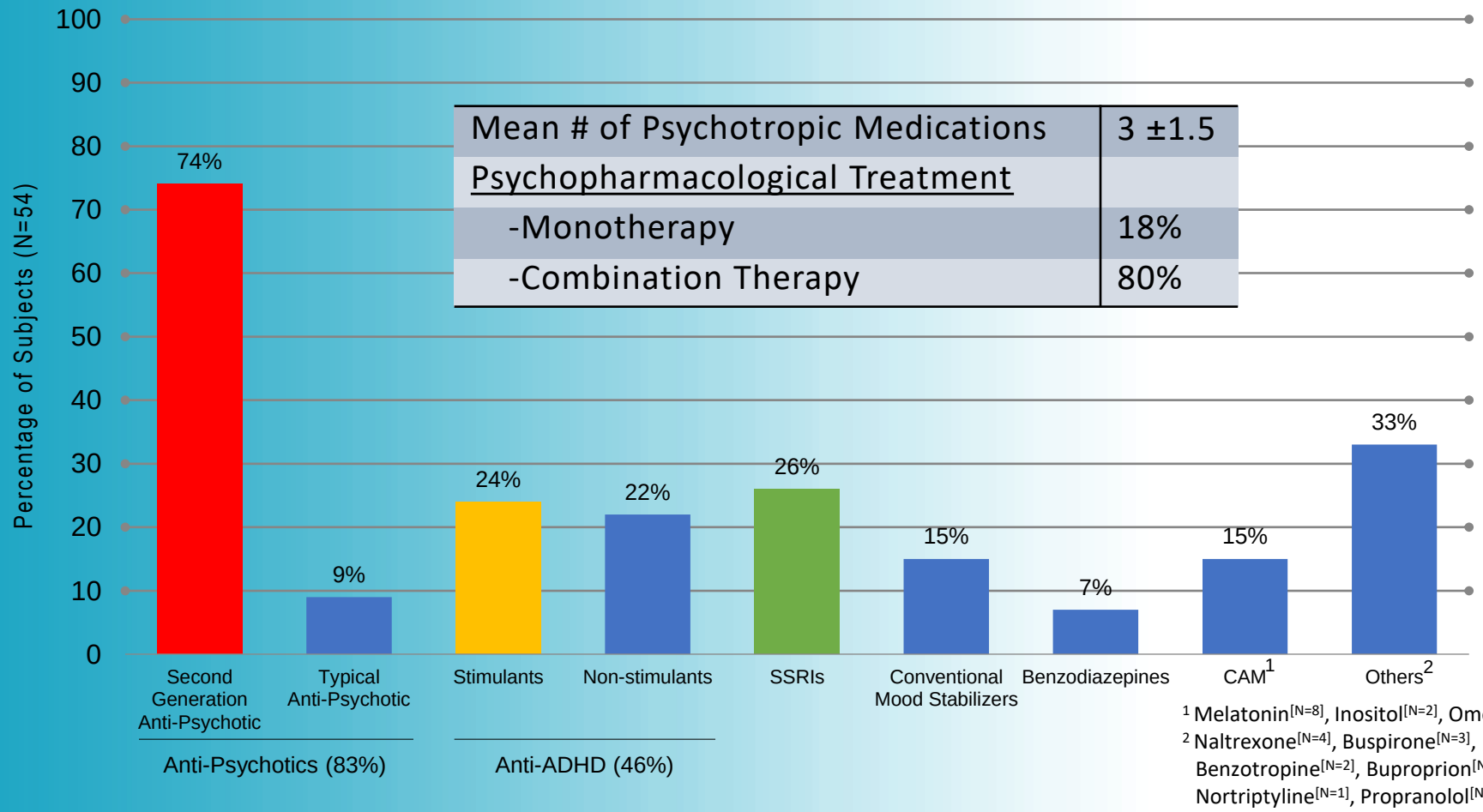

Mean # of Psychotropic Medications	3 ±1.5
Psychopharmacological Treatment	
-Monotherapy	18%
-Combination Therapy	80%

[1] Melatonin[N=8], Inositol[N=2], Omega-3 FA[N=1]
[2] Naltrexone[N=4], Buspirone[N=3], Metformin[N=3], Benzotropine[N=2], Buproprion[N=2], Duloxetine[N=2], Nortriptyline[N=1], Propranolol[N=1]

93% of ASD youth were prescribed NON-FDA approved medication

Shekunov, Wozniak, Joshi et al. 2017.

Clinical Assessment of Psychopathology in ASD

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Assessing Psychopathology in ASD: Challenges & Limitations

- Atypical/impaired non-verbal responses
- Impaired psychological mindedness
- Inability to describe emotions (Alexithymia)
- Concrete thinking (inability to deal with abstract concepts)

Autistic Traits Related Triggers/Stresses

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Atypical Triggers/Stressors

- Sensory Dysregulation (sensory overload)
- Change in structure/routine
- Limiting preferred activity
- Managing unstructured time
- Situations demanding cognitive flexibility
- Socially-emotionally demanding situations

Age Related Stressors

- Pre/Teen stage (increasing social demands)
- Transition stage (middle school, moving to college)

Phenocopy/Misattribution of ATs

- Repetitive Behaviors vs. Pediatric OCD/Tics
- Autistic traits vs. Negative features of Schizophrenia
- Autistic Traits vs. Cluster A Personality Disorder
- Social disinterest vs. Social phobia
- Mis-reading Non-verbal vs. Paranoid referential thinking
- Poor Executive Control vs. Bipolar Disorder

Parsing Psychopathology from ASD

- Differences in onset and course of psychopathology
- Qualitative differences in symptom presentation
- Family history of psychopathology
- Assess psychopathology by taking a non-hierarchical approach in applying DSM-based diagnostic criteria for psychiatric disorders.

In Summary

- Historically, psychopathology was under recognized in AUTISM populations
- Psychiatrically referred youth and adults with ASD suffer from greater burden of psychopathology than typically observed.
- Youth and adults with ASD suffer from similar range of psychiatric disorders as observed in typically developing individuals.
- Absence of typically expected sex differences in the clinical presentation of Autism in psychiatrically referred youth.
- Emotional Dysregulation is the most frequent and higher than expected profile of psychopathological presentation observed in AUTISM populations.

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Module Topic 9
Psychopathology Associated with Autism

AUTISM and ADHD

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Historical Perspective: Co-occurrence of ADHD and ASD

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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 in Referred Populations with ADHD

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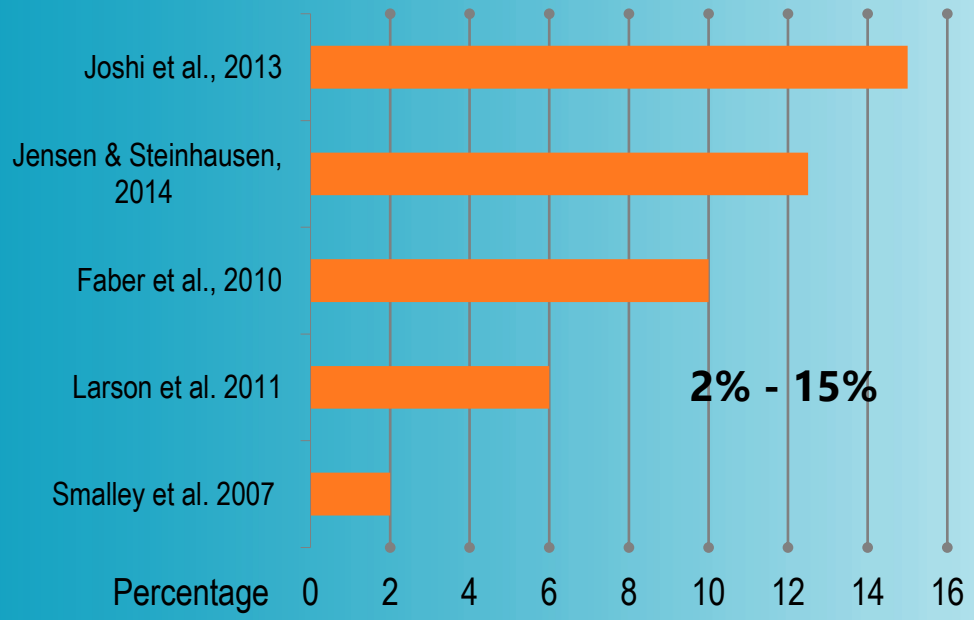
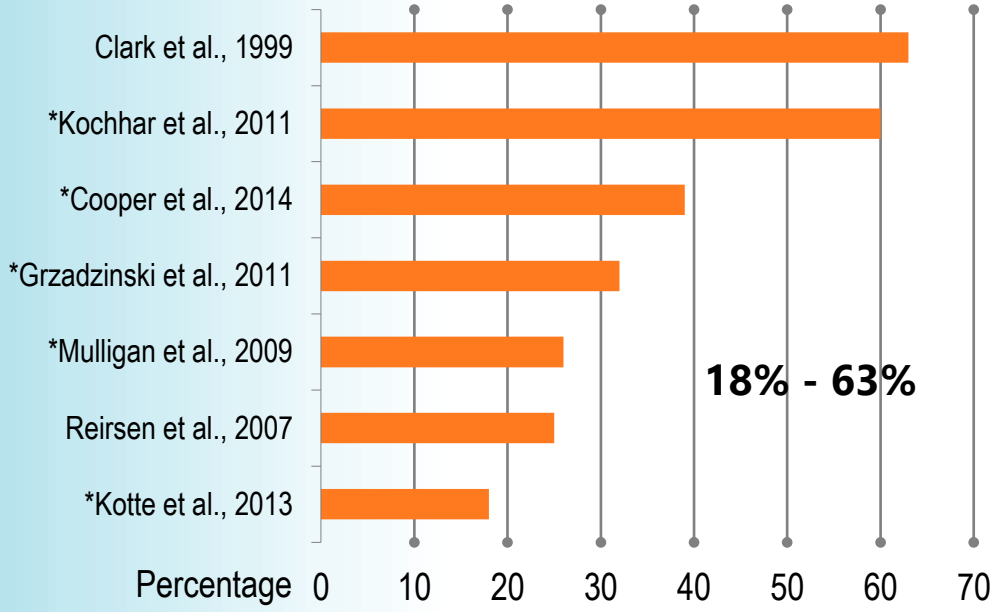
Autism Spectrum Disorder



Significant Autistic Traits



*ADHD Youth with no prior diagnosis of ASD

Comorbid ASD in up to 15% of the ADHD Populations

Burden of Autistic Traits in ADHD Populations without ASD

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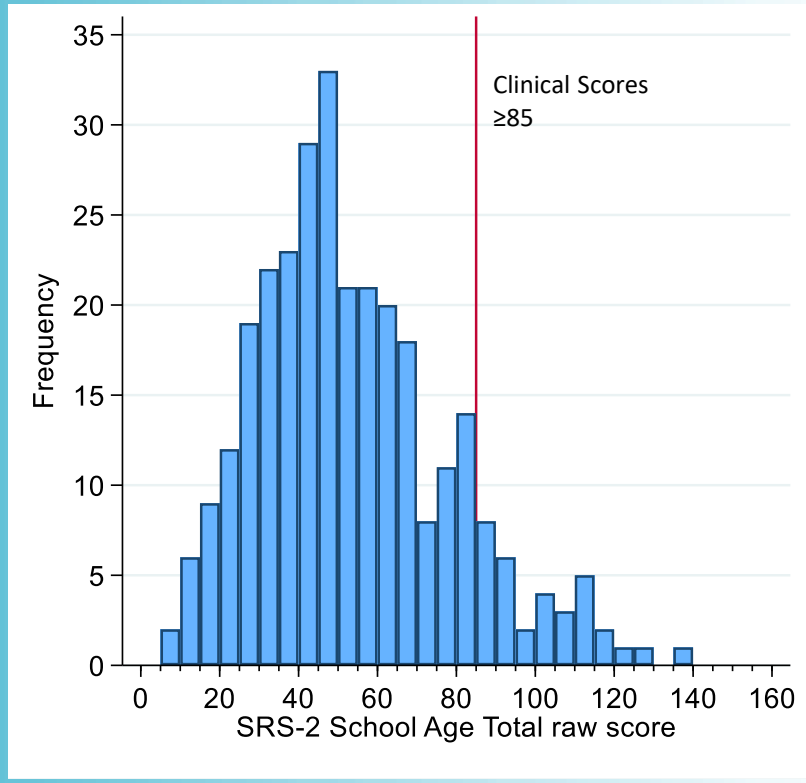
Distribution of SRS-2 Total Raw Scores



Presence of Significant ATs in ADHD Populations without ASD

Prevalence of ADHD in Populations with AUTISM

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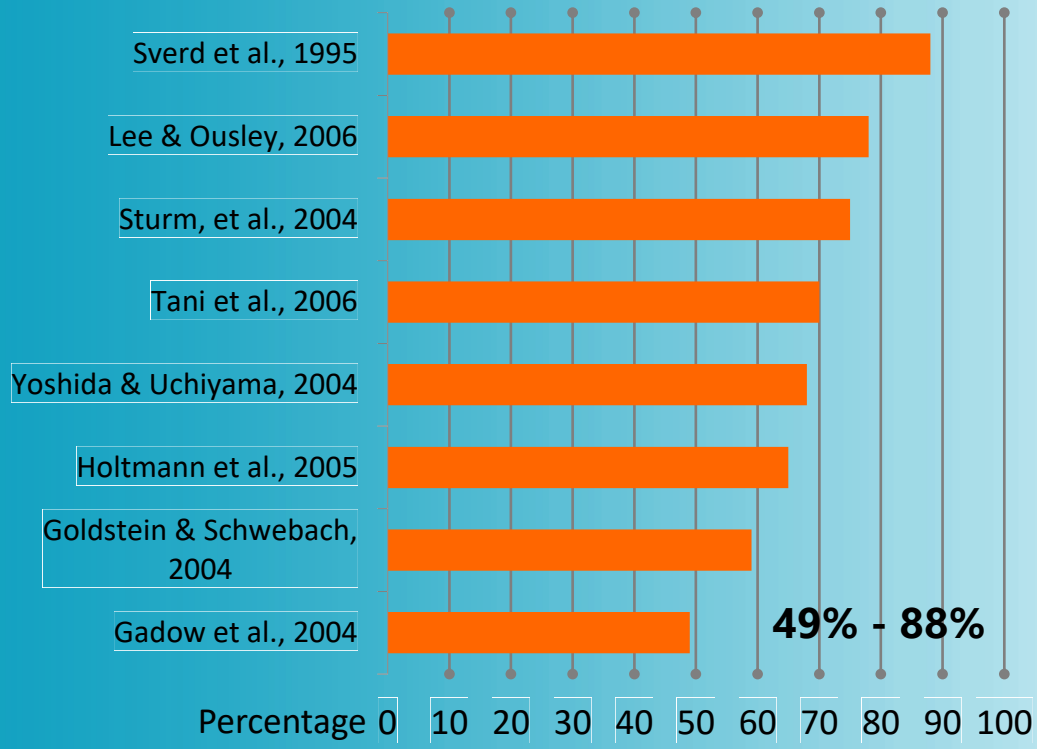
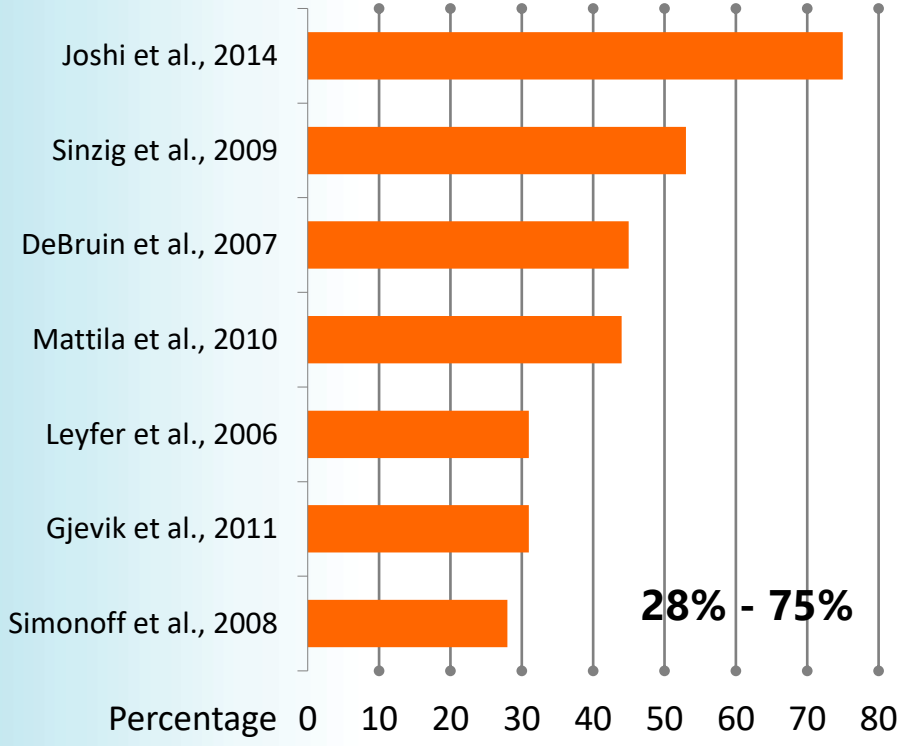
ADHD Symptoms

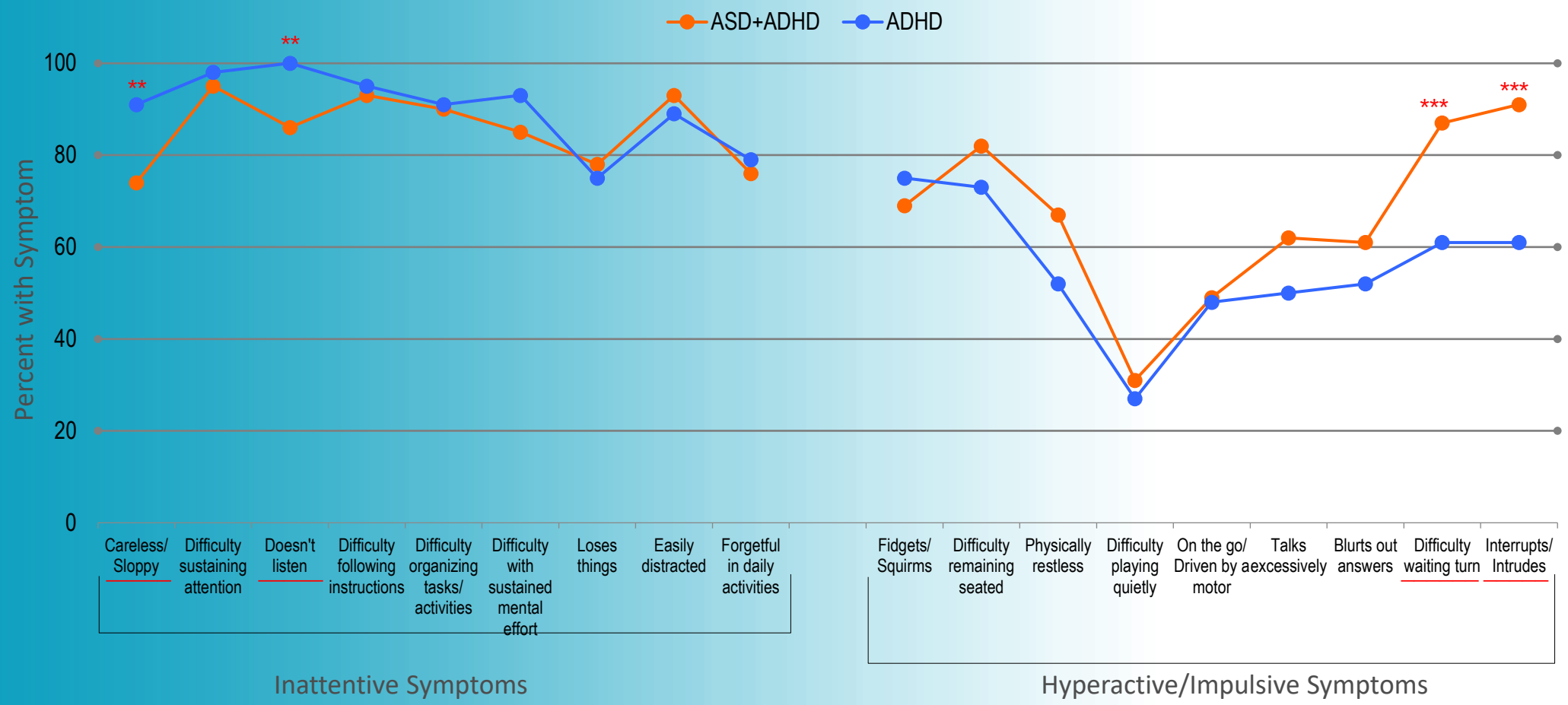


ADHD Diagnosis



Comorbid ADHD in up to 75% of the ASD Populations

ADHD Symptom Profile in ASD



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

Joshi et al. 2014.

Profile of ADHD in ASD

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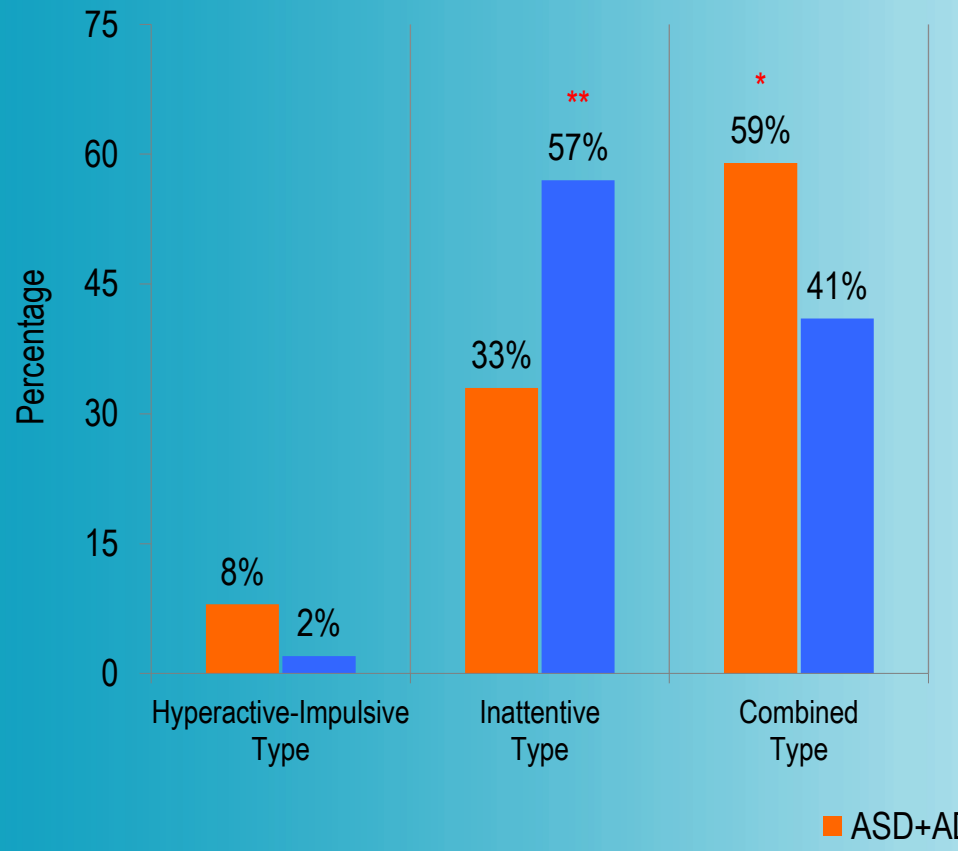
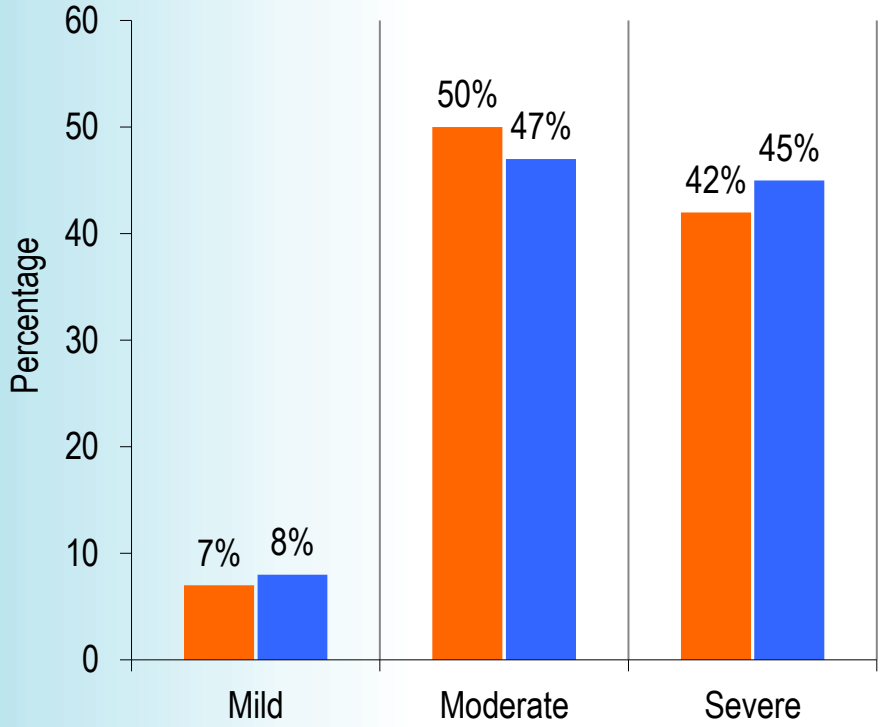
Subtypes of ADHD



Severity of ADHD



Joshi et al. 2014.

Severity Profile of Comorbid ADHD & ASD

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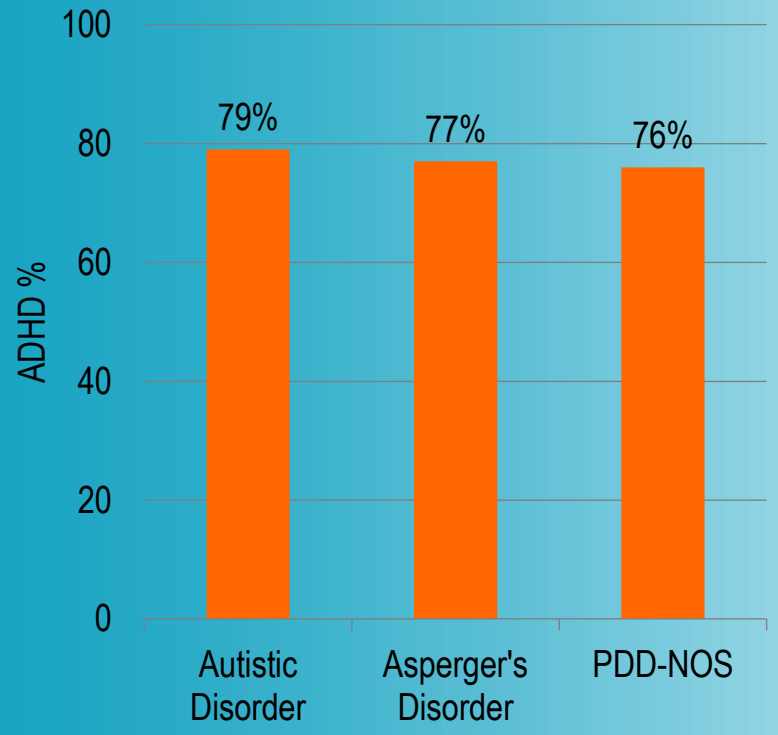
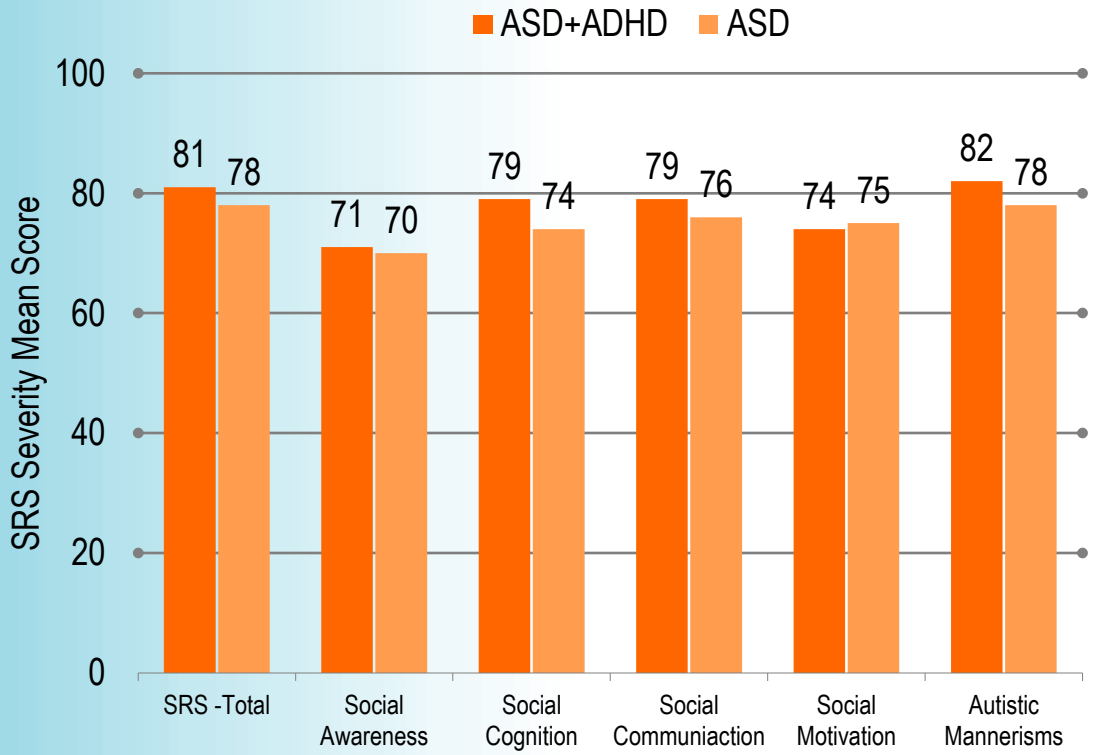
Distribution of ADHD



Severity of ASD



Joshi et al. 2014.

Diffusion Tensor Imaging Findings in ADHD ± ASD

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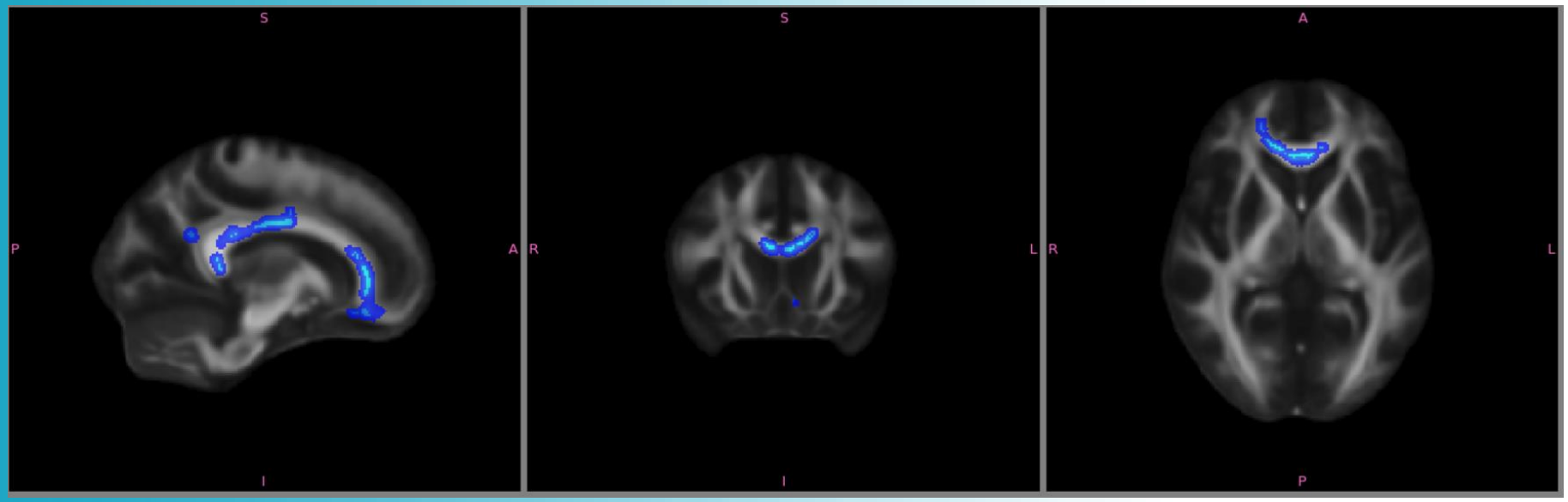
Similar ADHD Profile of DTI Underconnectivity in ASD Youth with ADHD



Cingulum-Corpus Callosal tracts DTI underconnectivity

Treatment of ADHD in ASD

- 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 ASD

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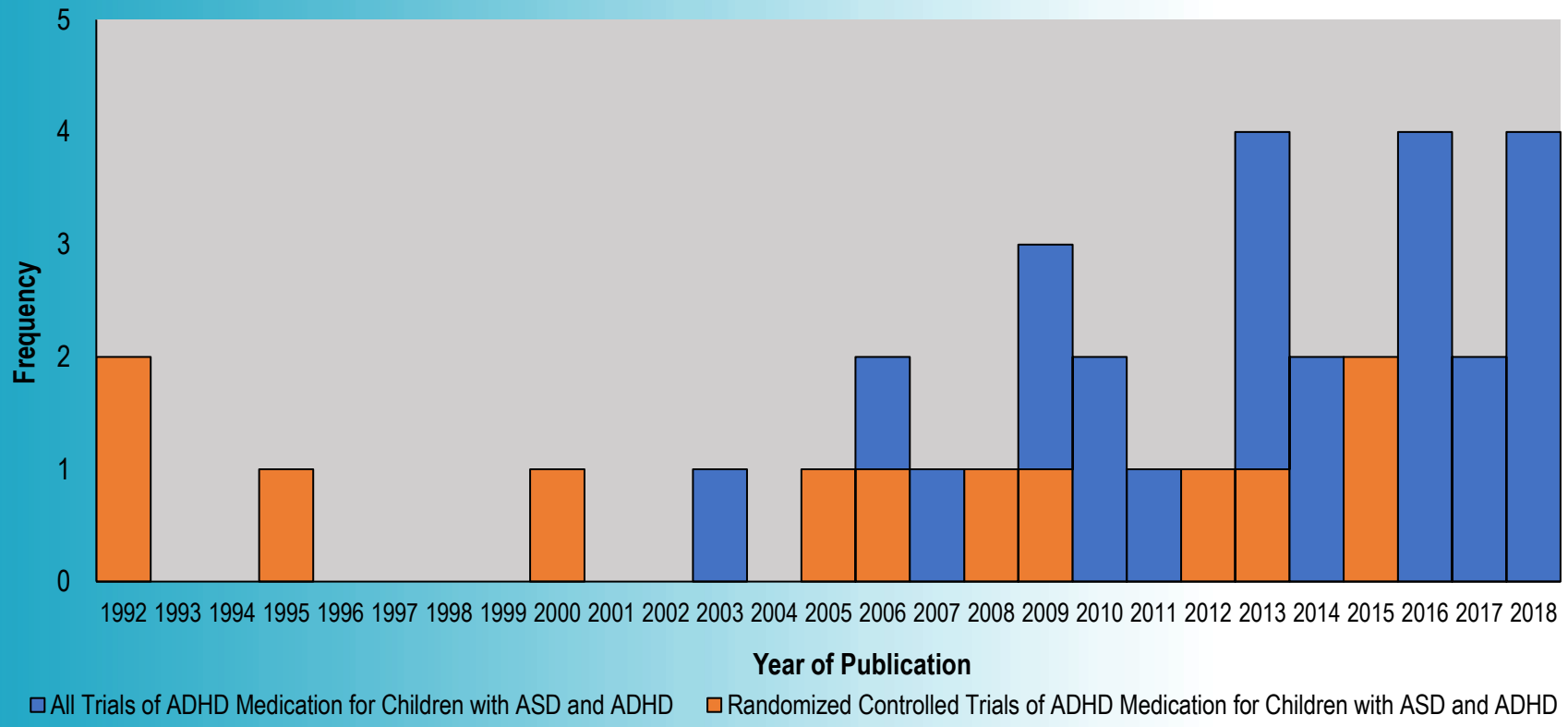
Frequency of Published Anti-ADHD Treatment Trials in ASD



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

Joshi et al. 2021, 2022.

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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 -Improvement with Tx 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/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 -D/c of MPH-IR afternoon dose d/t AEs -Improvement with Tx in social skills -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 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

Joshi et al. 2021, 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% 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: 57% ES: 0.90	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, 2022.

Effect Size of Anti-ADHD Response in ASD versus Typicals

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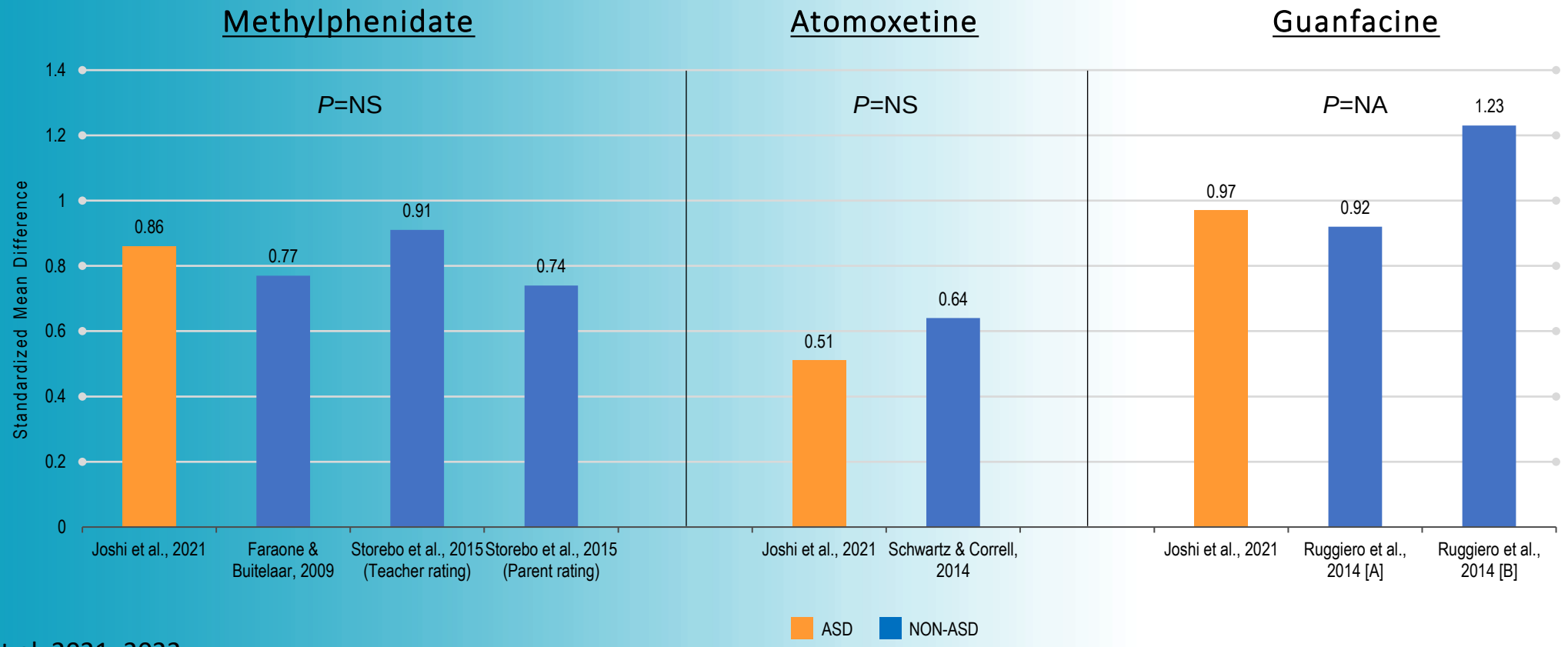
Standardized mean differences (SMD) for efficacy of Anti-ADHD Tx.



Joshi et al. 2021, 2022.

Limitations of Previous Controlled Trials of ADHD in ASD

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- 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.

Joshi et al. 2020.

OLT of MPH in Adults with ASD

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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)

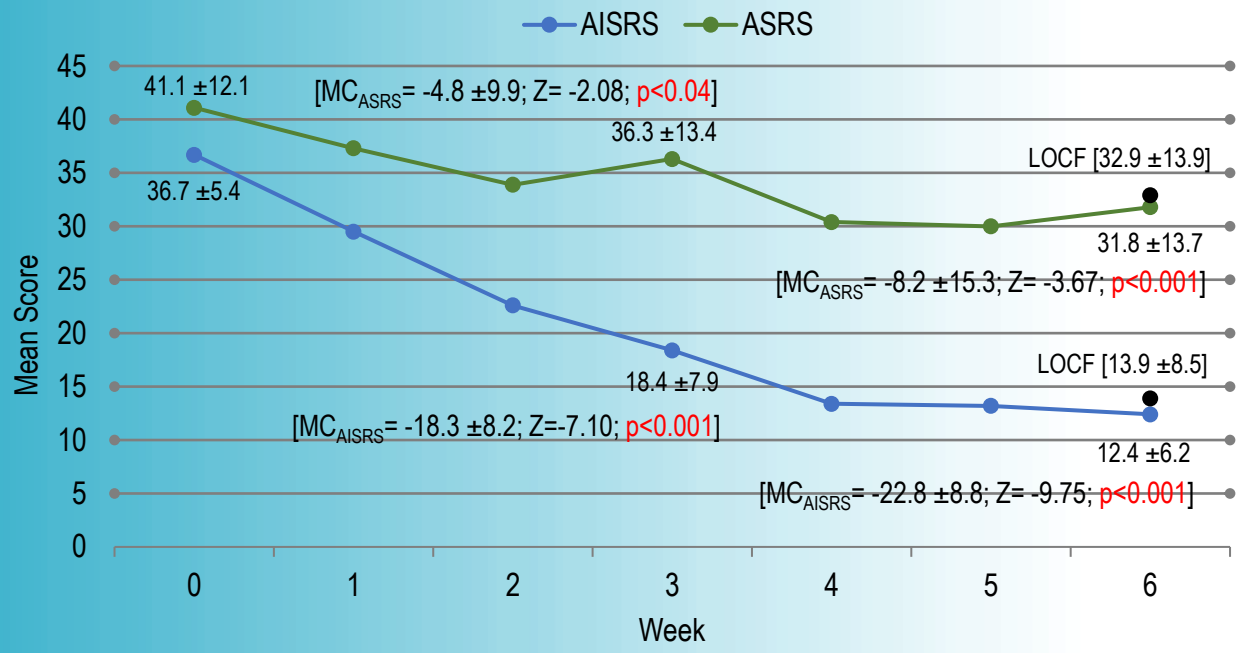
Mean dose:	49 ±15 mg/day	
At Dose:	60 mg/day	08 (53%)
	50 mg/day	02 (13%)
	20-40 mg/day	05 (33%)

Joshi et al. 2020.

Treatment Response: ADHD Symptoms

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

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



MC=Mean Change

Joshi et al. 2020.

Treatment Response: Autism Traits

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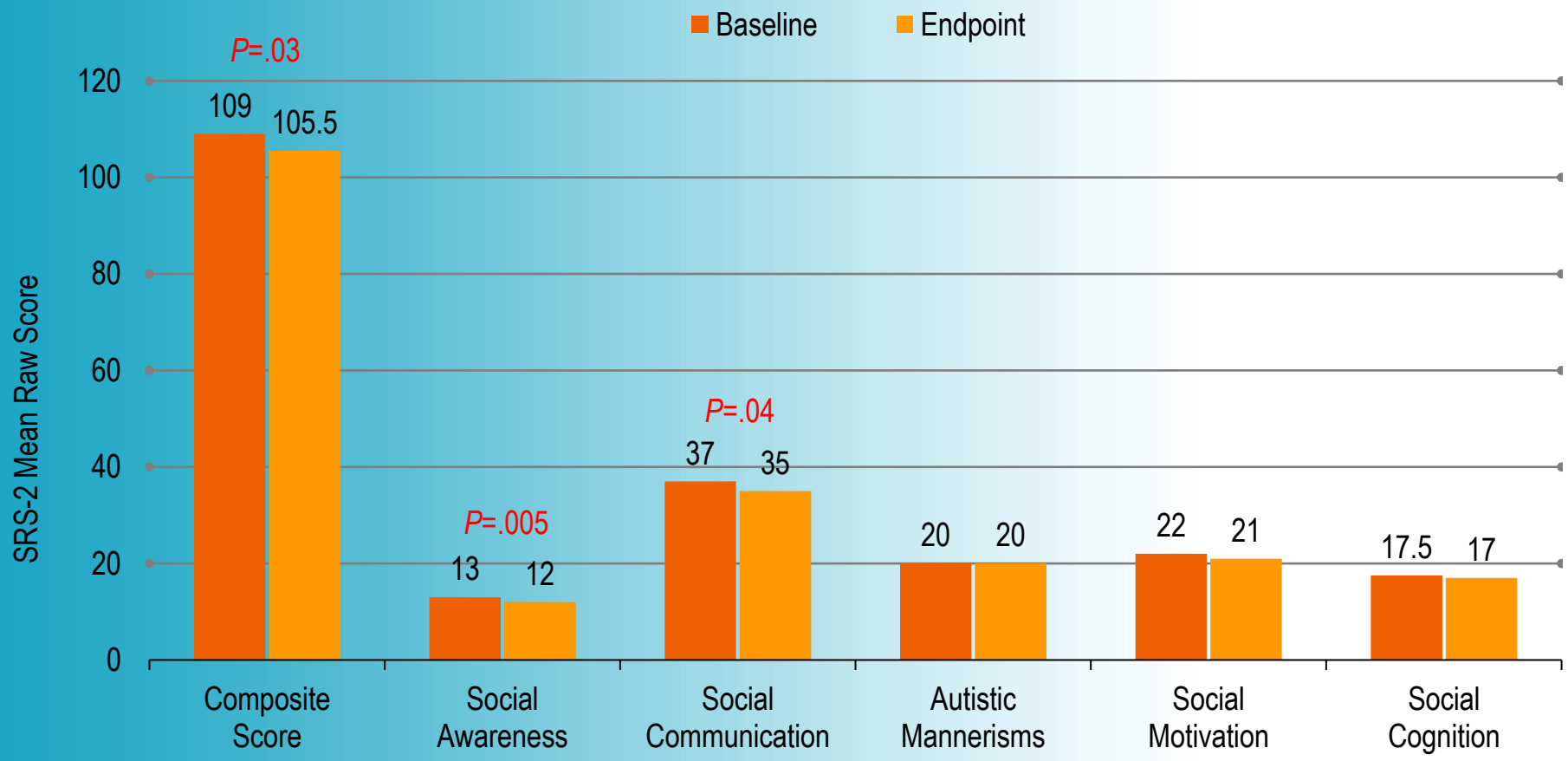
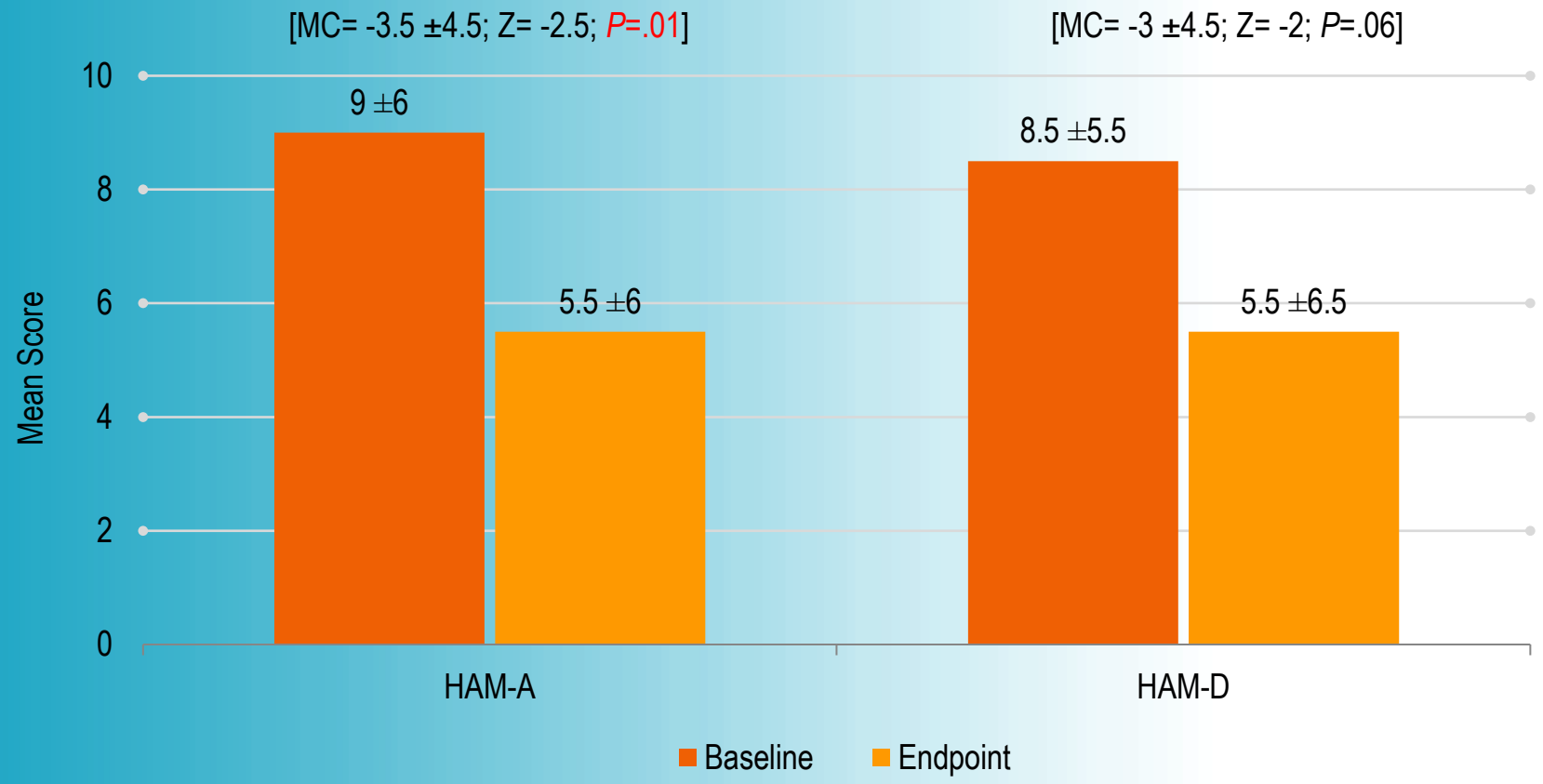
Social Responsiveness Scale (SRS-2)



Joshi et al. 2020.

Treatment Response: Associated Psychopathology

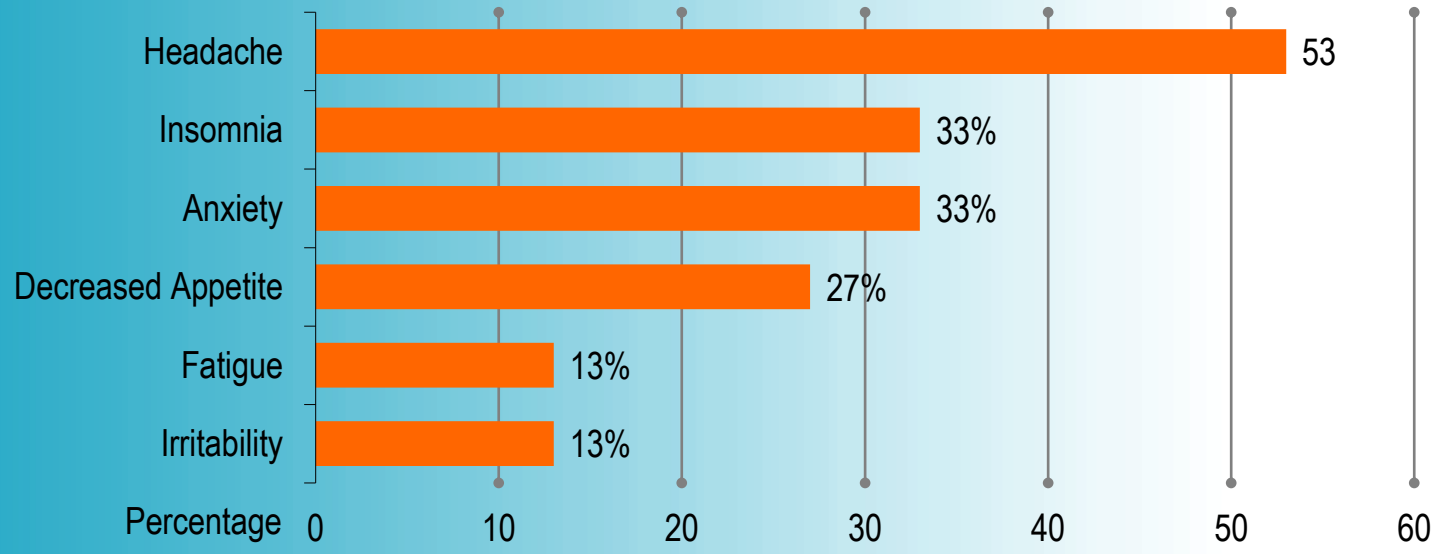


MC=Mean Change; HAM=A=Hamilton Anxiety Scale; HAM-D=Hamilton Depression Scale

Joshi et al. 2020.

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.

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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