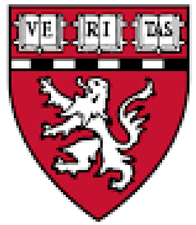
The Use of Psychiatric Medications in Autism and Related Disorders

Pilar Trelles, MD

Boston Children's Hospital

Until every child is well™



HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Learning Objectives

- To gain knowledge of evidence-based pharmacological therapies in ASD;
- To gain appreciation of treatment planning in ASD;
- To understand the benefits and limitations of medications for the treatment of behavioral symptoms in autism;
- To answer some of the most common concerns caregivers might have when deciding to start their child on a medications for behavioral symptoms.

Overview

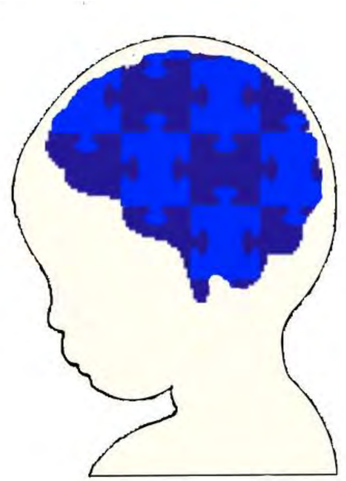
- Important Concepts
- Research Overview
- Deciding on Pharmacological Treatment
- Conclusions

Important Concepts

Terminology

- Autism and related disorders
- Typical development and atypical developmental trajectories
- Comorbidities

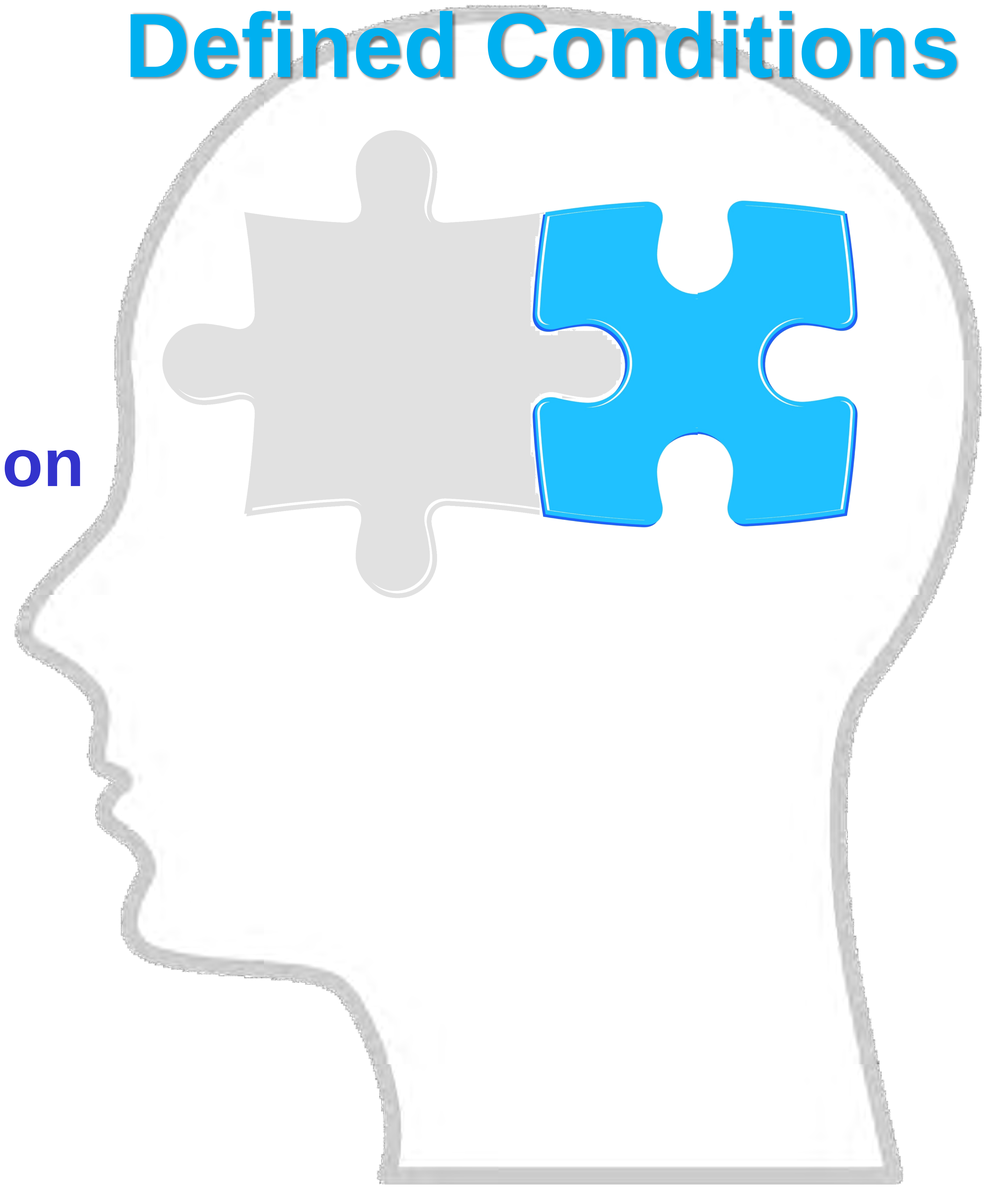
Overview of Treatments: What are the things my doctors consider?



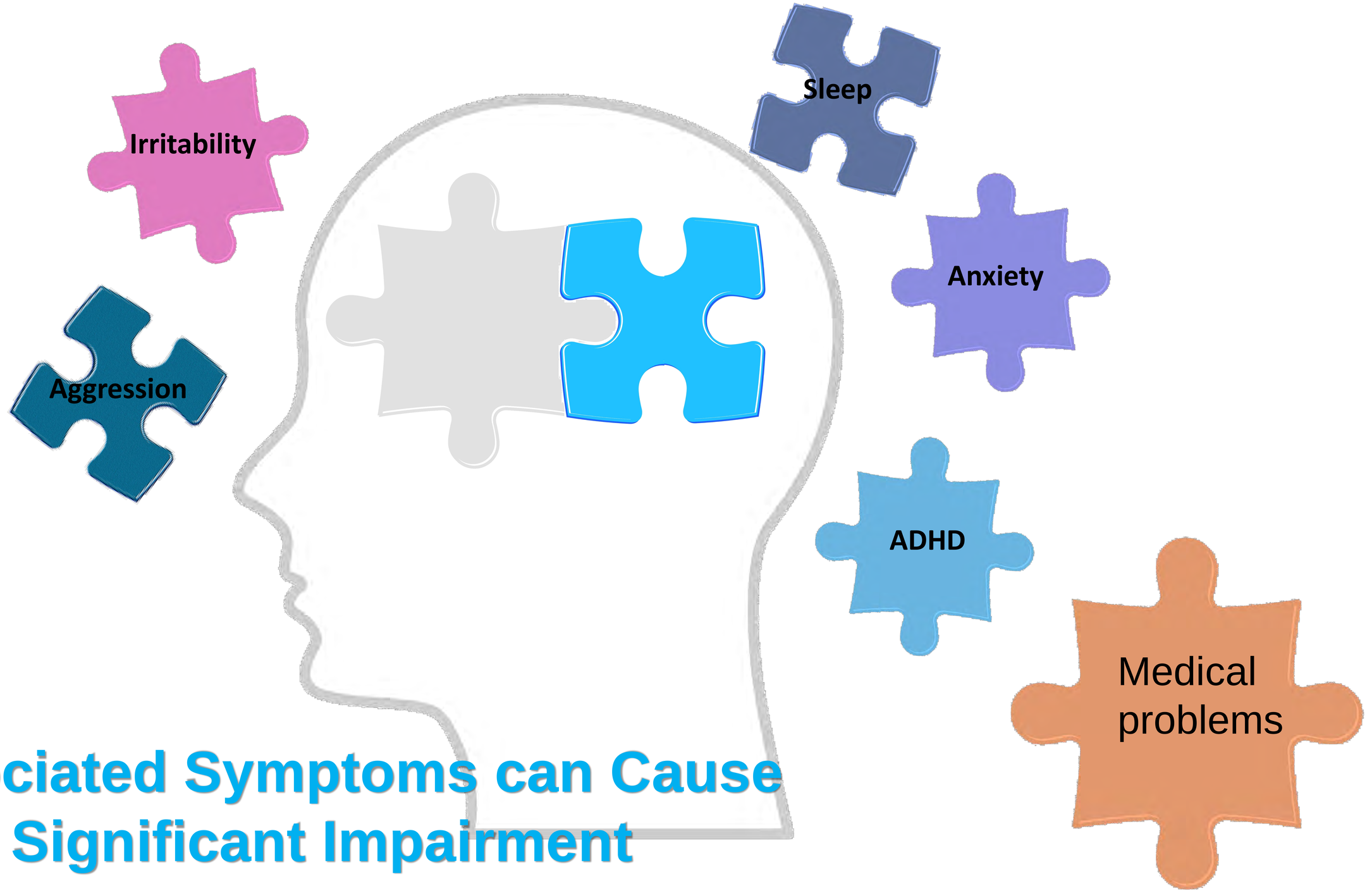
Behavioral Interventions	Pharmacological Interventions	Affiliated Disciplines
Comprehensive Programs Early behavioral interventions Educational interventions *Symptom Specific* Speech/Language Socialization Repetitive behaviors	*Symptom Specific Domain Approach* Irritability, aggression, disruptive behaviors, hyperactivity and inattention, repetitive behaviors	*Speech Therapy* *Occupational Therapy* *Physical Therapy*

Autism Spectrum Disorder: A Behaviorally Defined Conditions

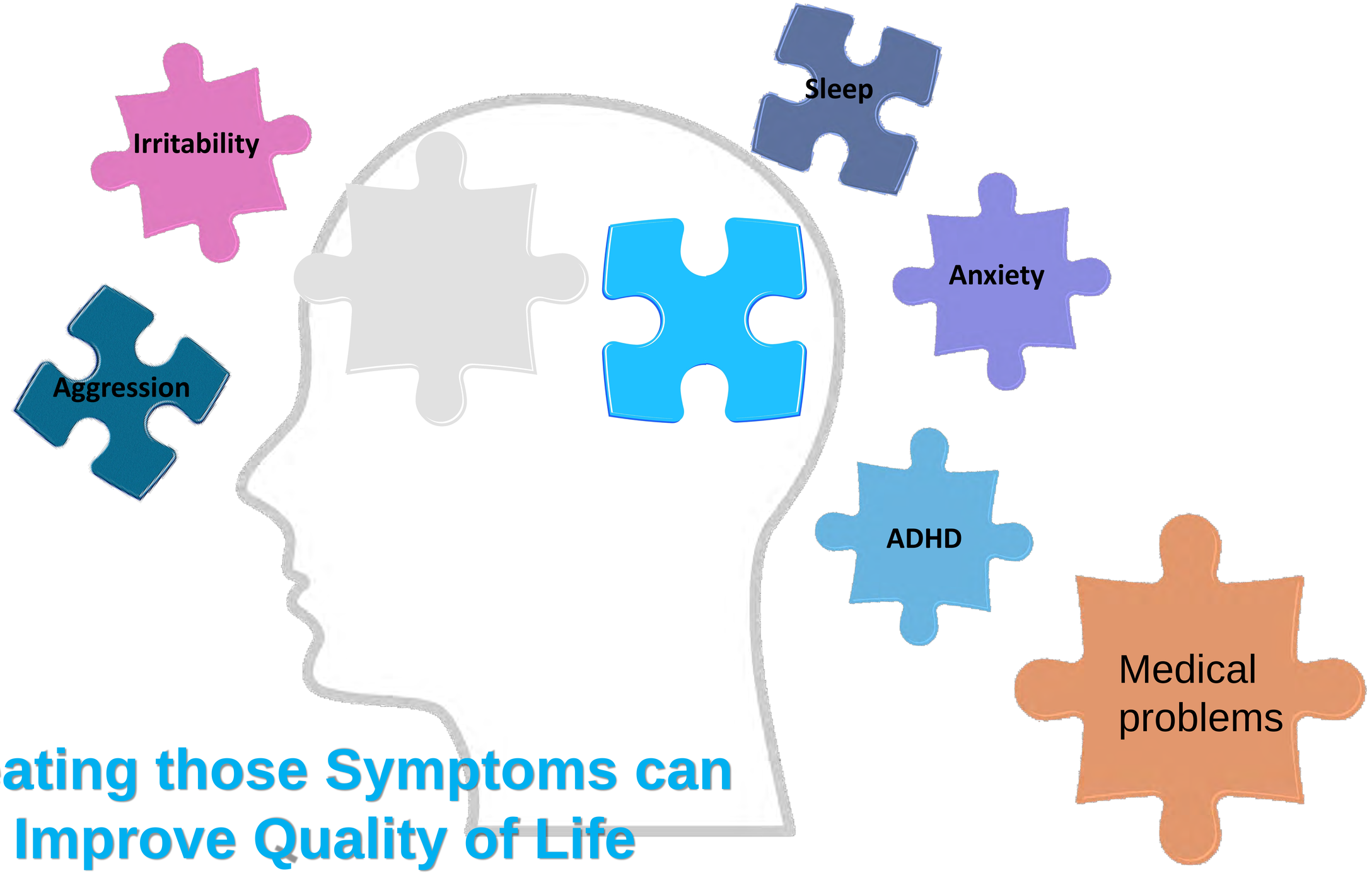
Deficits in social communication



Repetitive and restrictive behaviors



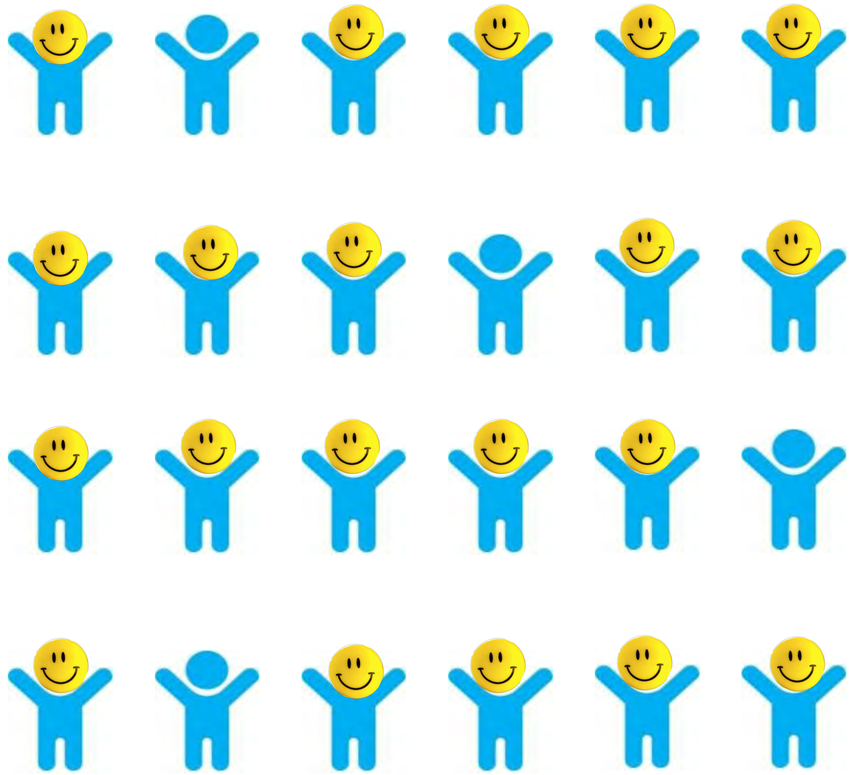
Associated Symptoms can Cause Significant Impairment



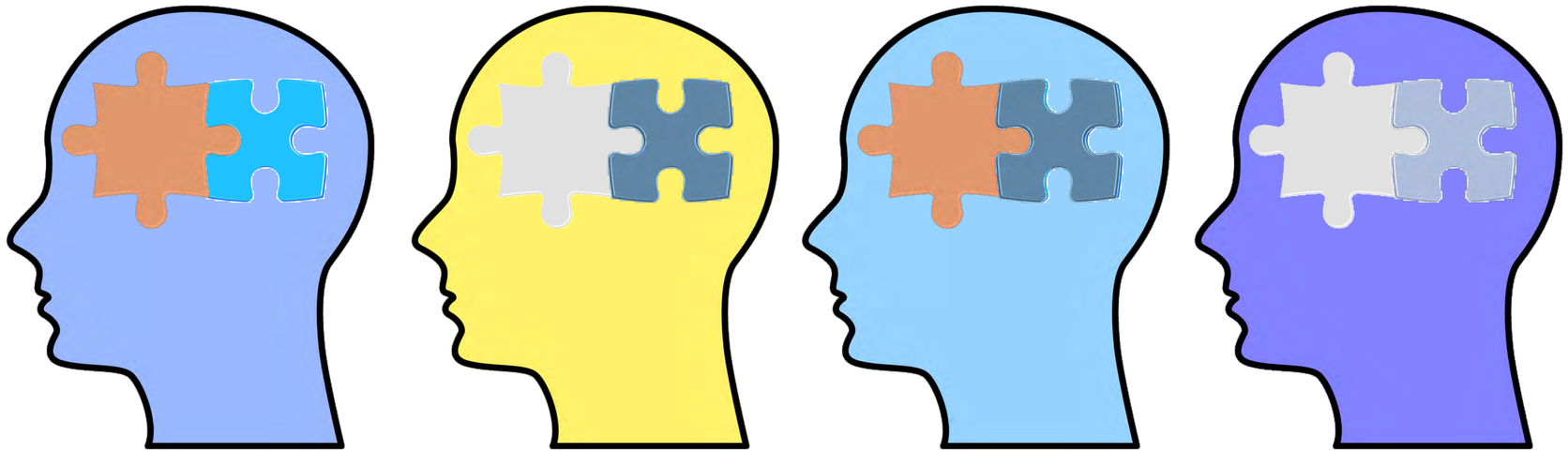
Treating those Symptoms can Improve Quality of Life

Research Overview

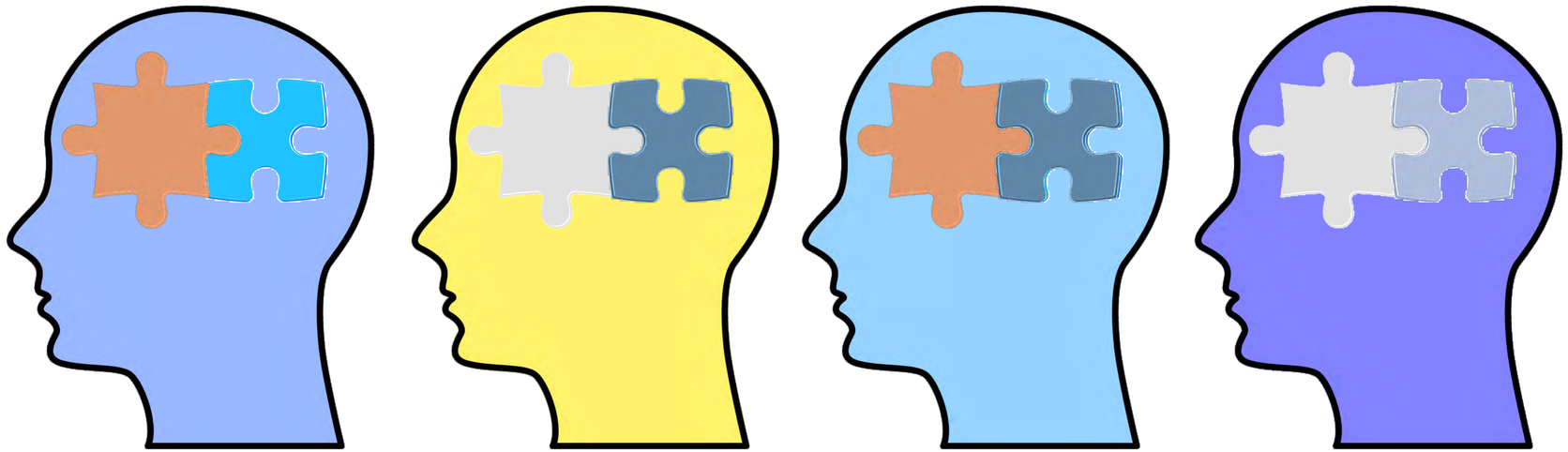
Clinical Trials



Autism is a Heterogenous Disorder



Autism and its Many Faces



Intellectual Disability

Intellectual Disability:

- Does *not* denote a single disease or entity with a single cause, mechanism, natural course, or prognosis;
- is a heterogeneous behavioral syndrome characterized by impairments in intellectual and adaptive skills;
- presents with a wide spectrum of abilities and disabilities, and clinical and behavioral patterns

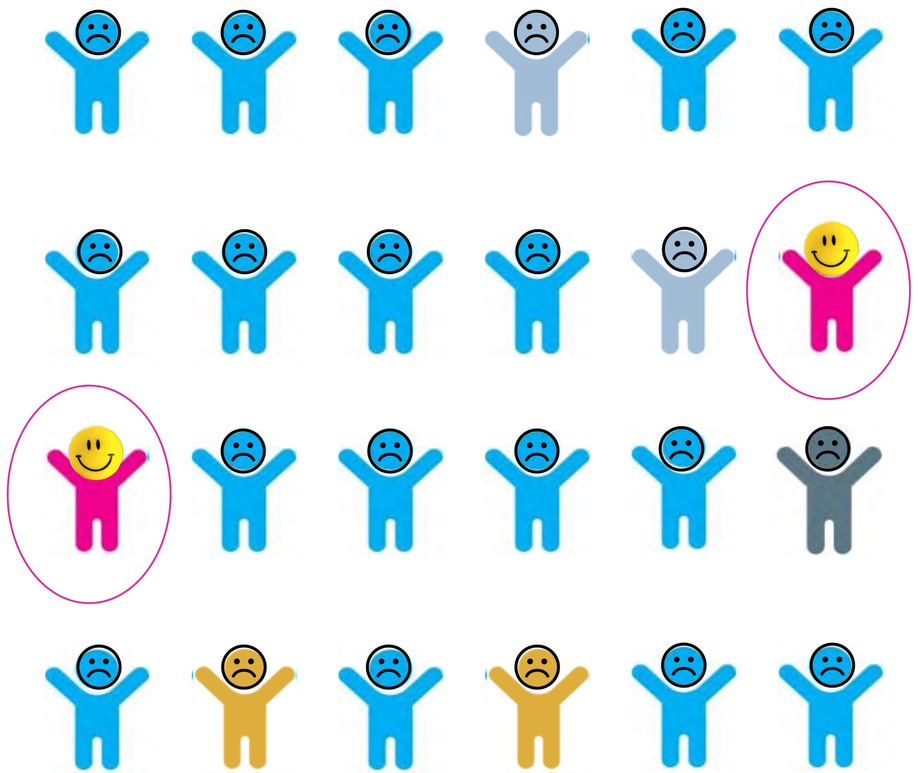
DSM5 Criteria:

- significantly sub-average intellectual functioning: an IQ of approximately 70 or below;
- concurrent deficits in adaptive functioning;
- onset is before age 18

APA, 2013

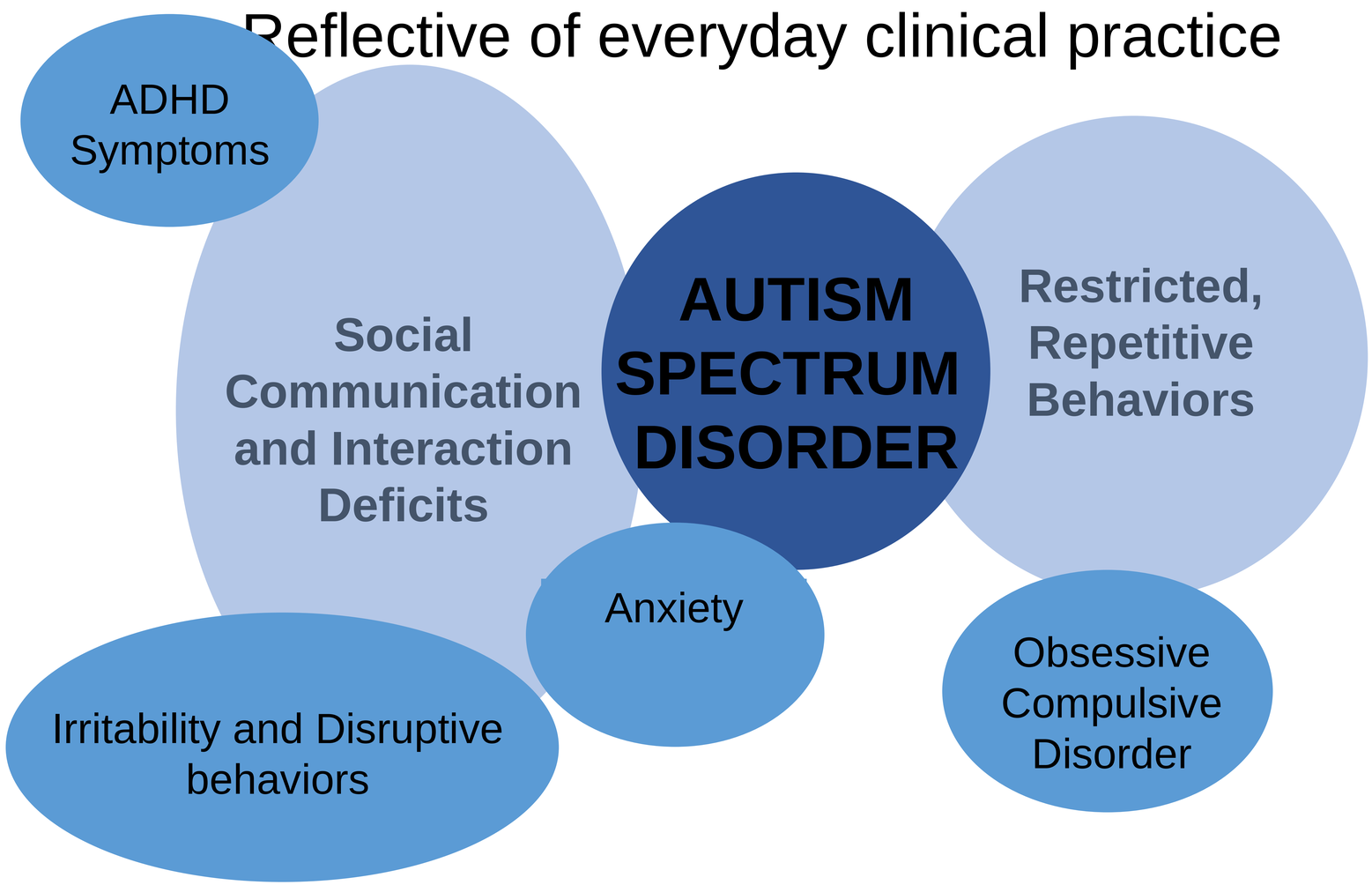
Clinical Trials in Autism and Related Conditions

Clinical Trials in Autism



Symptom Domain Approach

Reflective of everyday clinical practice



- Sleep Disturbance
- Feeding problems
- EEG Abnormalities
- Motor problems
- Immune Dysfunction

Deciding on Pharmacological Treatment

Symptom Domain Approach

- Irritability, aggression and disruptive behaviors.
- ADHD Symptoms: hyperactivity and inattention
- Repetitive and restrictive behaviors
- Anxiety and depression
- Sleep problems

Irritability, Aggression and Disruptive Behaviors

Atypical Antipsychotics

- Risperidone
- Clozapine
- Aripiprazole
- Quetiapine
- Ziprasidone
- Haloperidol
- Olanzapine

- Most studied medications in ASD in general
- Most studied medications in severely disruptive behaviors in ASD.
- Aripiprazole and Risperidone are the **only medications that are FDA approved** (large body of evidence) in the management of disruptive behaviors in ASD

Risperidone

- Most studied medication
- Efficacy established by two large RTC (2002, 2004), leading to FDA approval in 2006

The New England Journal of Medicine

Risperidone in the Treatment of Disruptive Behavioral Symptoms in Children With Autistic and Other Pervasive Developmental Disorders

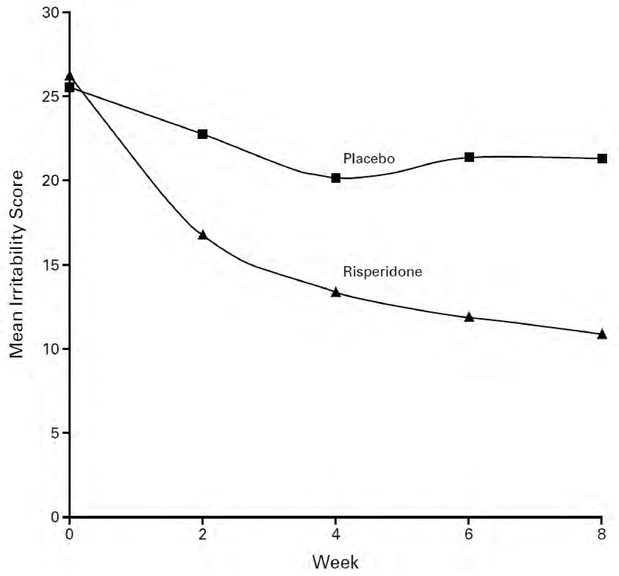
RISPERIDONE IN CHILDREN WITH AUTISM AND SERIOUS BEHAVIORAL PROBLEMS

Sarah Shea, MD*; Atilla Turgay, MD‡; Alan Carroll, MD§; Miklos Schulz, PhD‖; Herbert Orlik, MD*; Isabel Smith, PhD*; and Fiona Dunbar, MBBCh¶

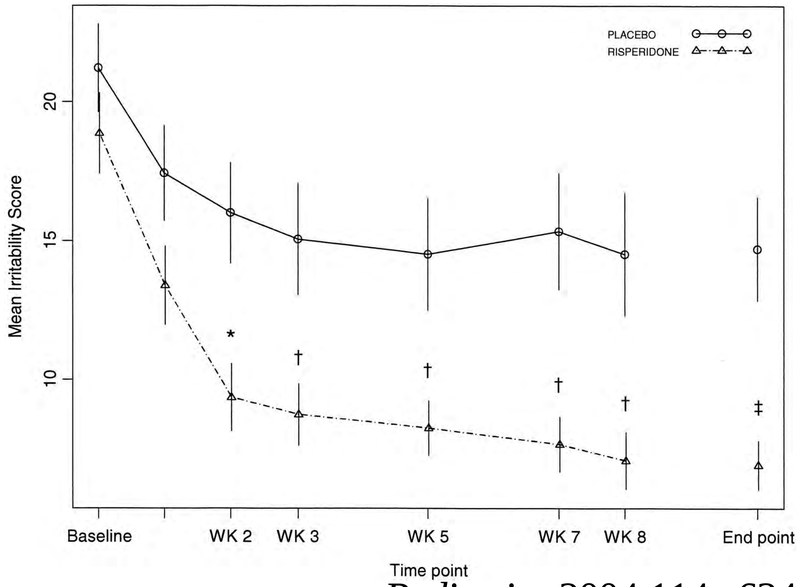
RESEARCH UNITS ON PEDIATRIC PSYCHOPHARMACOLOGY AUTISM NETWORK*

Risperidone

- Reductions of about 60% in Autism Behavior Checklist (ABC-I) compared to placebo.



N Engl J Med, Vol. 347, No. 5 · August 1, 2002

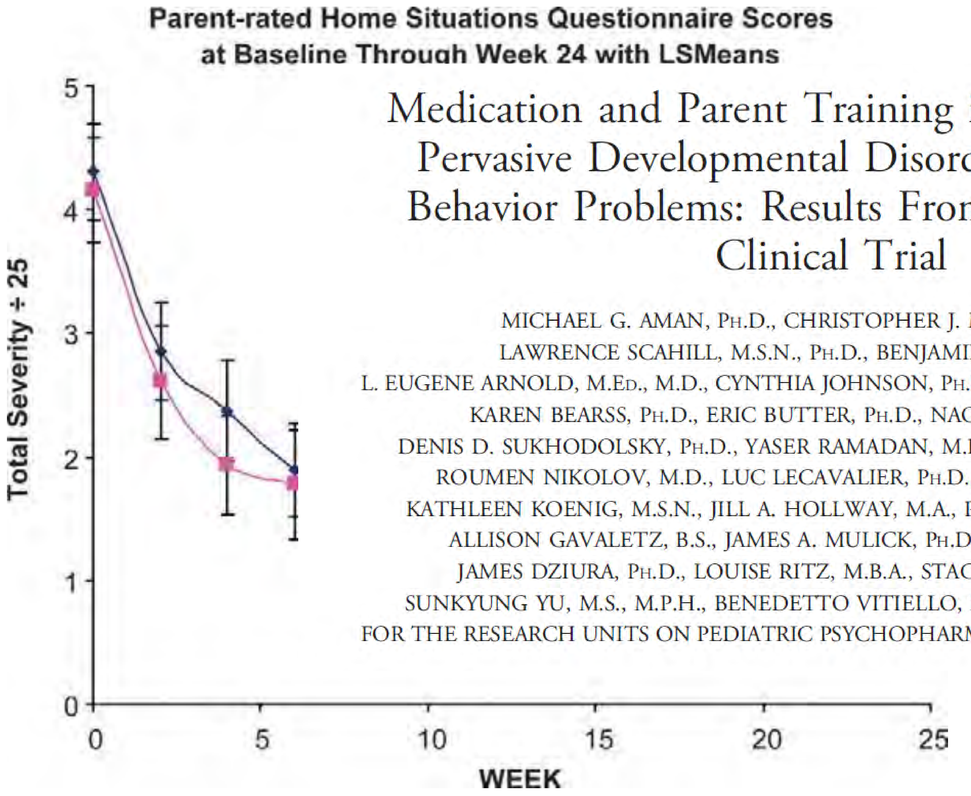


Pediatrics 2004;114;e634

Mean age: 7-8 years

Mean weight gain: +/- 2.5kg in 8 weeks

Risperidone & Parent Training



Medication and Parent Training in Children With Pervasive Developmental Disorders and Serious Behavior Problems: Results From a Randomized Clinical Trial

MICHAEL G. AMAN, PH.D., CHRISTOPHER J. MCDOUGLE, M.D., LAWRENCE SCAHILL, M.S.N., PH.D., BENJAMIN HANDEN, PH.D., L. EUGENE ARNOLD, M.ED., M.D., CYNTHIA JOHNSON, PH.D., KIMBERLY A. STIGLER, M.D., KAREN BEARSS, PH.D., ERIC BUTTER, PH.D., NAOMI B. SWIEZY, PH.D., DENIS D. SUKHODOLSKY, PH.D., YASER RAMADAN, M.D., STACIE L. POZDOL, M.S., ROUMEN NIKOLOV, M.D., LUC LECAVALIER, PH.D., ARLENE E. KOHN, B.A., KATHLEEN KOENIG, M.S.N., JILL A. HOLLWAY, M.A., PATRICIA KORZEKWA, M.S., ALLISON GAVALETZ, B.S., JAMES A. MULICK, PH.D., KRISTY L. HALL, B.A., JAMES DZIURA, PH.D., LOUISE RITZ, M.B.A., STACIE TROLLINGER, M.S., SUNKYUNG YU, M.S., M.P.H., BENEDETTO VITIELLO, M.D., ANN WAGNER, PH.D., FOR THE RESEARCH UNITS ON PEDIATRIC PSYCHOPHARMACOLOGY AUTISM NETWORK

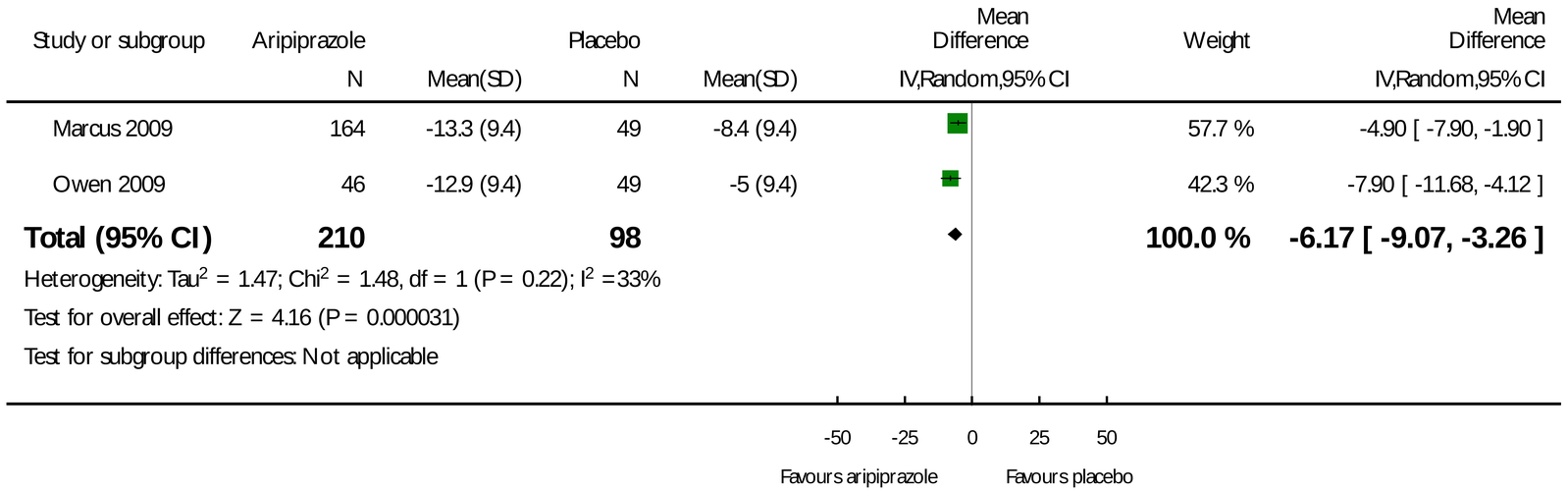
TABLE 2
n and Parent Training Treatments

Week 8	Week 16	Week 24
2.20	2.17	2.26
0.072	0.068	0.071
0.71	0.66	0.57
2.02	1.98	1.98
0.070	0.066	0.066
0.49	0.50	0.56
5.74	9.65	10.82
1.76	2.84	3.16
1.55	1.67	1.85
2.17	2.11	2.12
2.97	2.79	2.46

J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 48:12, DECEMBER 2009

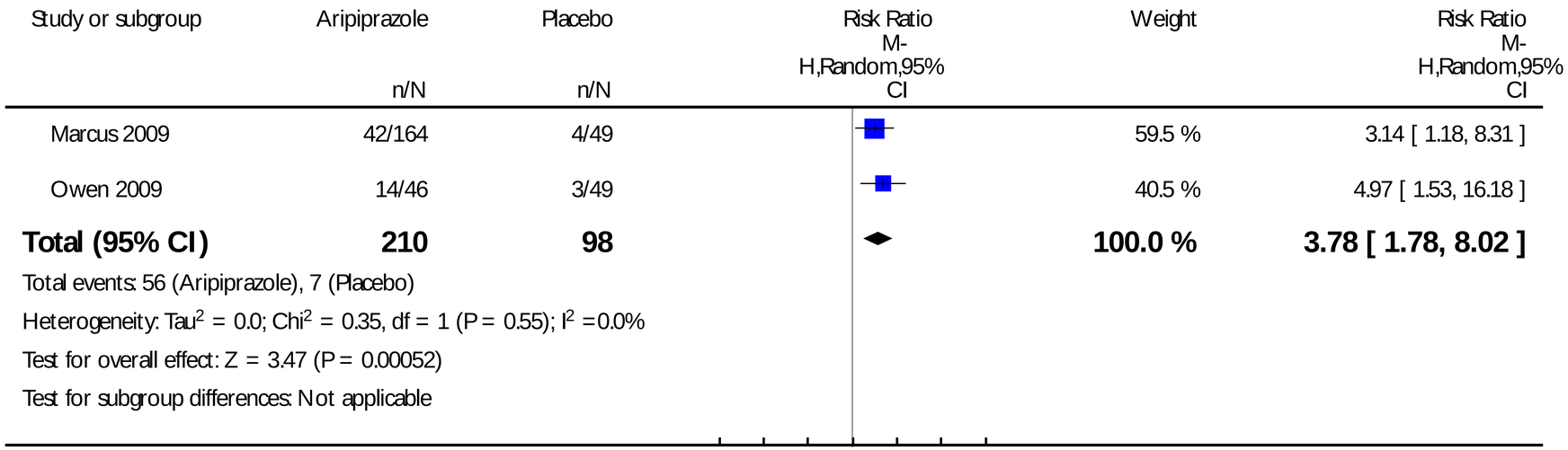
Aripiprazole

- FDA approval in 2009
- Reduction in ABC-I is dose dependent with about 50% reduction at 15mg



Cochrane Database of Systematic Reviews
26 JUN 2016 DOI: 10.1002/14651858.CD009043.pub3

Aripiprazole



Study or subgroup	Aripiprazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Marcus 2009	42/164	4/49		59.5 %	3.14 [1.18, 8.31]
Owen 2009	14/46	3/49		40.5 %	4.97 [1.53, 16.18]
Total (95% CI)	**210**	**98**		**100.0 %**	**3.78 [1.78, 8.02]**

Total events: 56 (Aripiprazole), 7 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.35$, df = 1 (P = 0.55); $I^2 = 0.0\%$

Test for overall effect: Z = 3.47 (P = 0.00052)

Test for subgroup differences: Not applicable

Cochrane Database of Systematic Reviews
26 JUN 2016 DOI: 10.1002/14651858.CD009043.pub3

Atypical Antipsychotics

- Risperidone
- Clozapine
- Aripiprazole
- Quetiapine
- Ziprasidone
- Haloperidol
- Olanzapine

- Most studied medications in ASD in general
- Most studied medications in severely disruptive behaviors in ASD.
- Aripiprazole and Risperidone are the **only medications that are FDA approved** (large body of evidence) in the management of disruptive behaviors in ASD

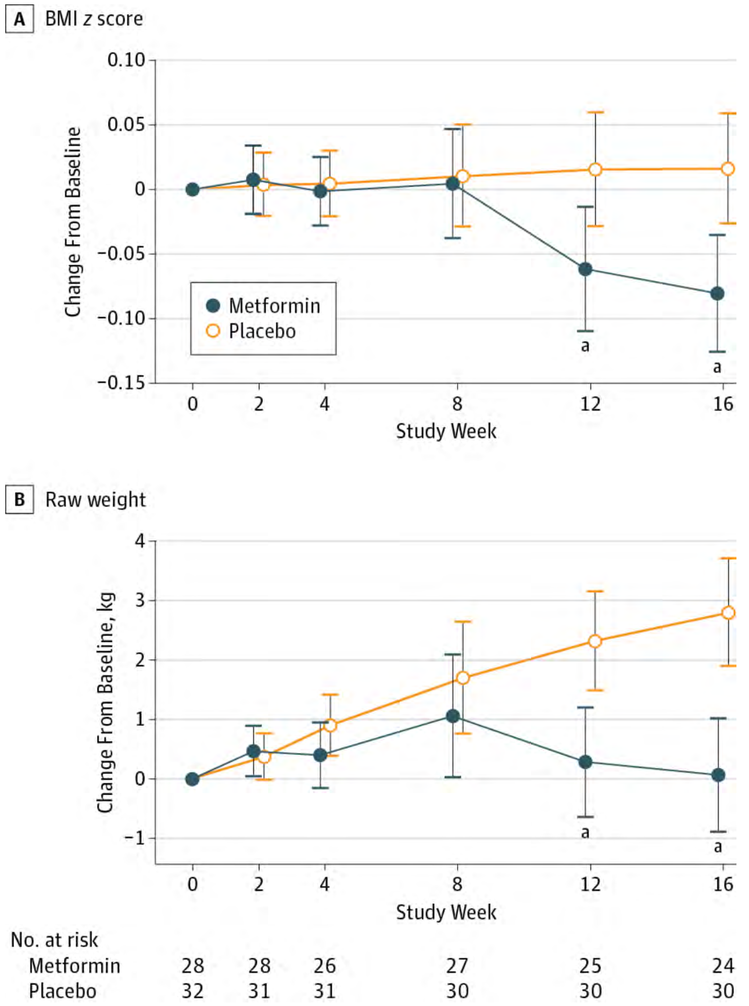
The Fine Print: Side Effects and Length of Trials

JAMA Psychiatry | Original Investigation

Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder

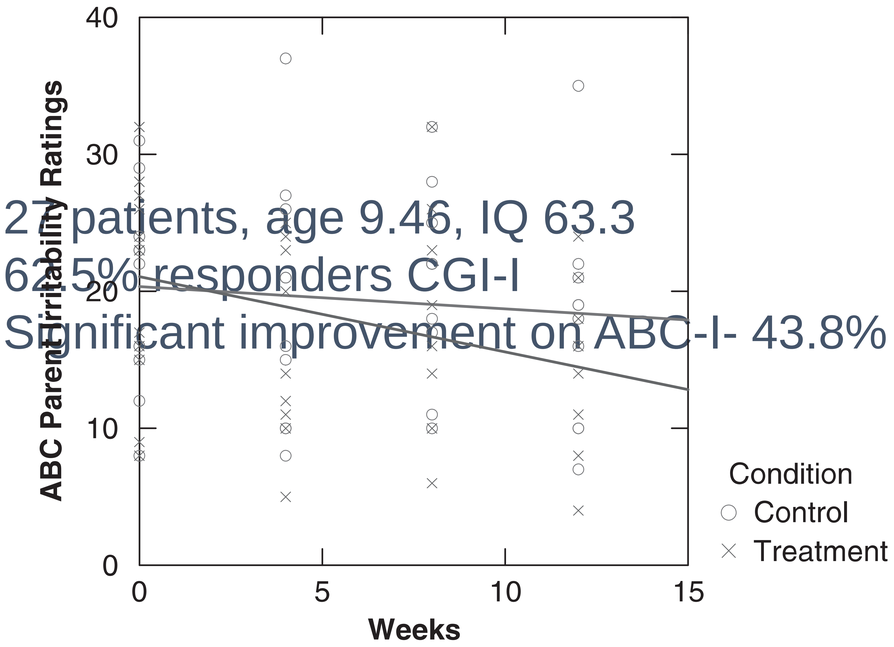
A Randomized Clinical Trial

Evdokia Anagnostou, MD; Michael G. Aman, PhD; Benjamin L. Handen, PhD; Kevin B. Sanders, MD; Amy Shui, MA; Jill A. Hollway, PhD; Jessica Brian, PhD; L. Eugene Arnold, MD; Lucia Capano, MD; Jessica A. Hellings, MD; Eric Butter, PhD; Deepali Mankad, MD; Rameshwari Tumuluru, MD; Jessica Kettel, MD; Cassandra R. Newsom, PsyD; Stasia Hadjiyannakis, MD; Naomi Peleg, MSc; Dina Odrobina, BMSc; Sarah McAuliffe-Bellin, MEd; Pearl Zakroysky, MPH; Sarah Marler, MA; Alexis Wagner, BS; Taylor Wong, BS; Eric A. Macklin, PhD; Jeremy Veenstra-VanderWeele, MD

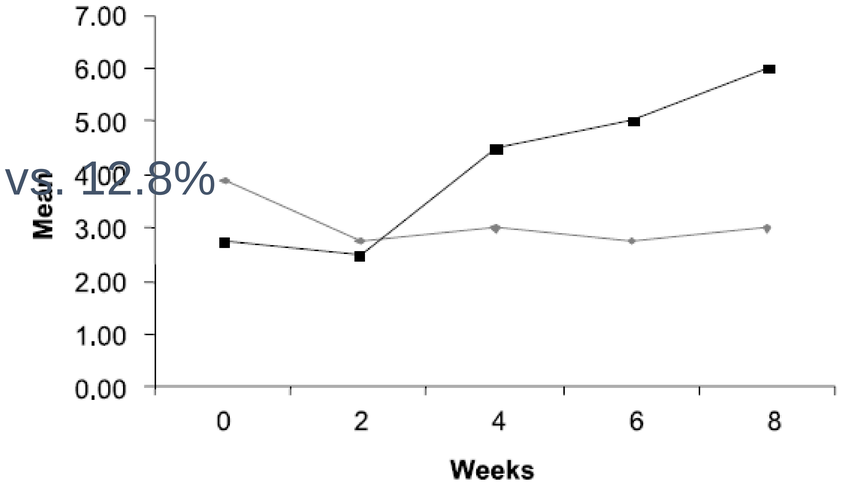


Mood Stabilizers: Valproate

- Found to be effective in reducing irritability (Clinical Global Impressions (CGI) scores or ABC-I)



Irritability associated with fluoxetine treatment



- 27 patients, age 9.46, IQ 63.3
- 62.5% responders CGI-I
- Significant improvement on ABC-I- 43.8% vs. 12.8%

Neuropsychopharmacology (2010) 35, 990–998

Eric Hollander*[,1,5], William Chaplin[2], Latha Soorya[3], Stacey Wasserman[3], Sherry Novotny[3], Jade Rusoff[3], Nicole Feirsen[3], Lauren Pepa[3] and Evdokia Anagnostou[4,5]

Journal of Clinical Psychopharmacology • Volume 26, Number 4, August 2006

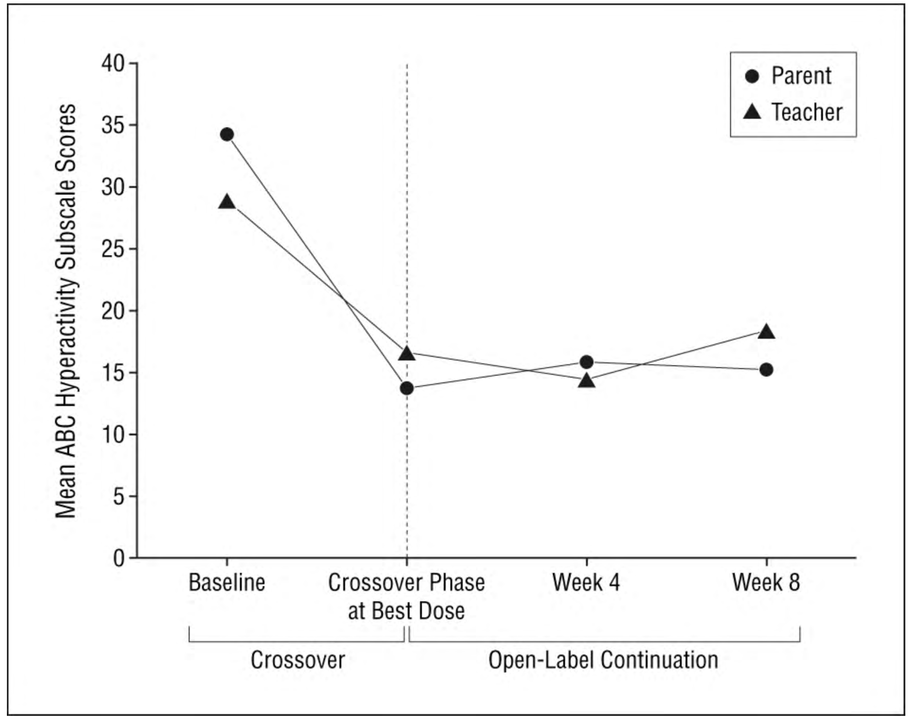
Anagnoustou, et. al.

ADHD symptoms: Hyperactivity and Inattention

Stimulants: Methylphenidate

Randomized, Controlled, Crossover Trial of Methylphenidate in Pervasive Developmental Disorders With Hyperactivity

Research Units on Pediatric Psychopharmacology (RUPP) Autism Network



Adverse Effects†

Appetite decrease
Difficulty falling asleep
Stomach or abdominal discomfort
Irritability
Emotional outburst
Anxiety
Depression
Repetitive behaviors and thoughts
Self-injury
Headache
Diarrhea
Social withdrawal
Increased motor activity
Bradycardia
Tiredness or fatigue

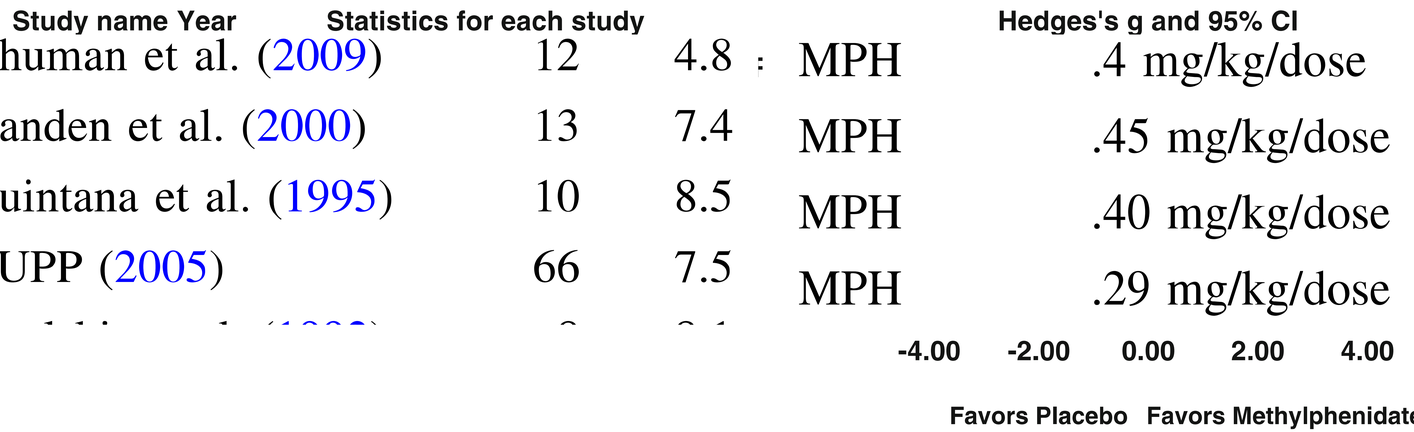
ARCH GEN PSYCHIATRY/VOL 62, NOV 2005

J Autism Dev Disord (2013) 43:2435–2441
DOI 10.1007/s10803-013-1793-z

ORIGINAL PAPER

Systematic Review and Meta-analysis of Pharmacological Treatment of the Symptoms of Attention-Deficit/Hyperactivity Disorder in Children with Pervasive Developmental Disorders

Brian Reichow · Fred R. Volkmar · Michael H. Bloch



Alpha$_2$- Agonists: Guanfacine

Extended-Release Guanfacine for Hyperactivity in Children With Autism Spectrum Disorder

Lawrence Scahill, M.S.N., Ph.D., James T. McCracken, M.D., Bryan H. King, M.D., Carol Rockhill, M.D., Bhavik Shah, M.D., Laura Politte, M.D., Roy Sanders, M.D., Mendy Minjarez, Ph.D., Jennifer Cowen, Ph.D., Jennifer Mullett, R.N., Chris Page, B.S., Denise Ward, M.A., Yanhong Deng, M.P.H., Sandra Loo, Ph.D., James Dziura, Ph.D., Christopher J. McDougle, M.D., Research Units on Pediatric Psychopharmacology Autism Network

TABLE 2. Scores on the Aberrant Behavior Checklist and ADHD Rating Scale at Baseline and Endpoint (Week 8)

	Guanfacine (N=30)				Placebo (N=32)					
	Raw Mean		Least-Squares Mean[a]		Raw Mean		Least-Squares Mean[a]			
Measure	Baseline	95% CI	Endpoint	95% CI	Baseline	95% CI	Endpoint	95% CI	p	Effect Size[b]
Aberrant Behavior Checklist Subscale										
Hyperactivity[c]	34.40	32.40–36.40	19.3	15.33–23.22	34.25	31.74–36.76	29.7	25.82–33.5	<0.0001	1.67
Irritability	20.30	16.79–23.81	13.5	10.01–17.06	18.06	14.54–21.58	16.1	12.68–19.5	0.20	0.27
Social withdrawal	13.60	10.08–17.12	9.8	7.26–12.27	12.06	8.71–15.41	8.6	6.10–11.0	0.41	0.13
Stereotypy	8.53	6.41–10.66	3.6	2.03–5.26	9.31	7.31–11.32	5.9	4.37–7.49	0.02	0.41
Inappropriate speech	6.33	5.02–7.65	4.2	3.24–5.26	6.84	5.63–8.06	5.99	4.50–6.97	0.004	0.50
ADHD Rating Scale										
Inattention	20.53	19.17–21.90	14.7	12.55–16.78	20.41	18.75–22.06	19.5	17.52–21.5	0.0001	1.17
Hyperactivity	19.00	17.38–20.62	10.6	8.50–12.75	19.50	17.71–21.29	18.7	16.6–20.6	<0.0001	1.72
Total	39.53	37.33–41.73	25.2	21.44–29.03	39.91	37.50–42.32	38.0	34.4–41.6	<0.0001	2.03

[a] Week

Atomoxetine

Atomoxetine for Hyperactivity in Autism Spectrum Disorders: Placebo-Controlled Crossover Pilot Trial

L. EUGENE ARNOLD, M.D., MICHAEL G. AMAN, PH.D., AMELIA M. COOK, B.A., ANDREA N. WITWER, M.A., KRISTY L. HALL, B.A., SUSAN THOMPSON, M.S.N., C.P.N.P., AND YASER RAMADAN, M.D.

J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 45:10, OCTOBER 2006

N=16, 6 wks

Significant improvement on ABC-H

Hyperactivity > Inattention

A Randomized Double-Blind Study of Atomoxetine Versus Placebo for Attention-Deficit/Hyperactivity Disorder Symptoms in Children With Autism Spectrum Disorder

Myriam Harfterkamp, M.D., Gigi van de Loo-Neus, M.D., Ruud B. Minderaa, M.D., Ph.D., Rutger-Jan van der Gaag, M.D., Ph.D., Rodrigo Escobar, M.D., Alexander Schacht, Ph.D., Sireesha Pamulapati, Ph.D., Jan K. Buitelaar, M.D., Ph.D., Pieter J. Hoekstra, M.D., Ph.D.

JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY
VOLUME 51 NUMBER 7 JULY 2012

N=97, 8 wks

1.2mg/kg/day

Significant improvement on ABC-H

Hyperactivity > Inattention

Atomoxetine in Autism Spectrum Disorder: No Effects on Social Functioning; Some Beneficial

Measure	*Atomoxetine (n = 48) Mean (SD) at baseline, LS mean after 8 weeks (95% CI)*[a]	*Placebo (n = 49) Mean (SD) at baseline, LS mean after 8 weeks (95% CI)*[a]	*Cohen's d effect size for difference between atomoxetine and placebo*[a]	*Difference in LS means between atomoxetine and placebo (95% CI)*[a]
ABC Irritability subscale	17.3 (9.1), 14.6 (12.7–16.4)	16.2 (9.5), 15.6 (13.8–17.3)	0.2	1.0 (−3.5–1.6) $p = 0.452$
ABC Lethargy/Social Withdrawal subscale	12.5 (8.4), 11.4 (9.9–13.0)	12.5 (8.0), 11.7 (10.1–13.2)	0.0	0.2 (−2.4–2.0) $p = 0.850$
ABC Stereotypic Behavior subscale	6.5 (5.1), 3.0 (2.1–3.9)	4.1 (4.5), 4.6 (3.7–5.4)	0.5	1.6 (−2.8–0.3) $p = 0.014$
ABC Hyperactivity subscale	28.4 (9.3), 21.2 (18.8–23.6)	25.4 (11.5), 25.6 (23.3–27.9)	0.6	4.4 (−7.8–1.1) $p = 0.010$
ABC Inappropriate Speech subscale	4.7 (3.2), 3.7 (3.3–4.3)	4.6 (3.4), 4.5 (4.0–5.1)	0.4	0.9 (−1.7–0.0) $p = 0.045$
CSBQ Total scale	53.6 (14.8), 46.2 (43.2–49.2)	53.1 (15.7), 50.1 (47.2–53.1)	0.4	3.9 (−8.1–0.3) $p = 0.069$
CSBQ Not Tuned subscale	14.8 (4.8), 13.0 (12.0–14.0)	14.9 (5.3), 14.1 (13.2–15.1)	0.3	1.2 (−2.6–0.3) $p = 0.106$
CSBQ Reduced Contact subscale	10.5 (5.5), 8.9 (8.0–9.8)	10.9 (4.4), 9.5 (8.6–10.4)	0.2	0.6 (−1.9–0.6) $p = 0.331$
CSBQ Orientation Problems subscale	9.8 (2.7), 8.9 (8.2–9.7)	9.9 (3.5), 9.0 (8.3–9.8)	0.0	0.1 (−1.2–1.0) $p = 0.889$
CSBQ Social Information subscale	9.4 (3.3), 8.7 (8.1–9.2)	9.6 (3.4), 9.3 (8.8–9.8)	0.3	0.6 (−1.4–0.1) $p = 0.110$
CSBQ Stereotyped subscale	5.8 (4.0), 4.2 (3.4–4.9)	4.8 (3.7), 5.0 (4.3–5.7)	0.3	0.8 (−1.8–0.2) $p = 0.123$
CSBQ Fear of Changes subscale	3.3 (1.9), 2.6 (2.3–3.0)	3.0 (1.9), 3.2 (2.8–3.5)	0.4	0.6 (−1.1–0.0) $p = 0.035$

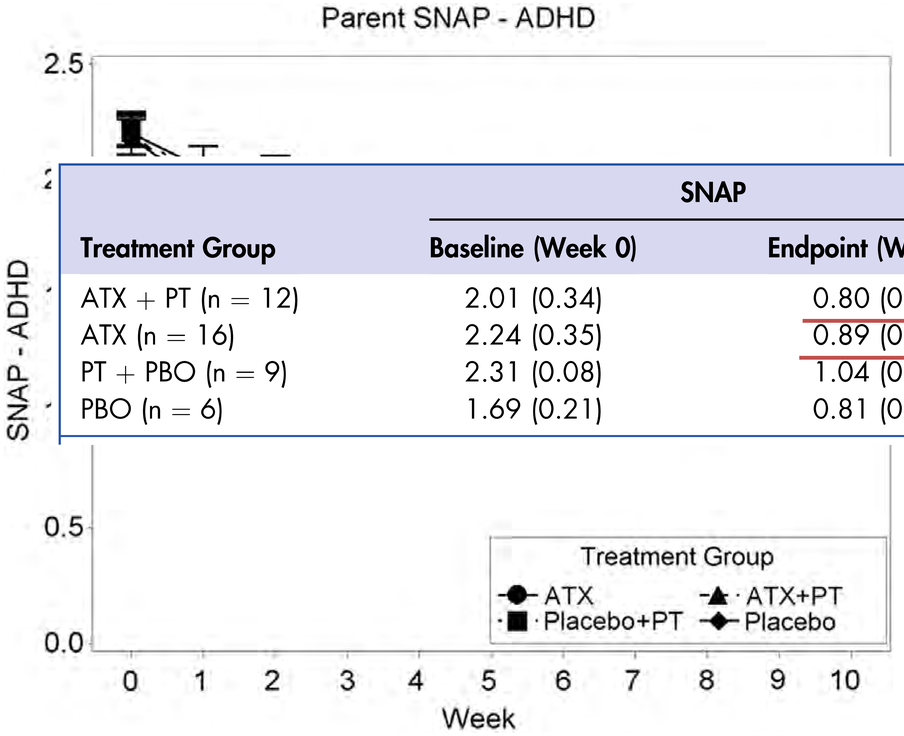
N=97

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 24, Number 9, 2014

Atomoxetine

Atomoxetine and Parent Training for Children With Autism and Attention-Deficit/Hyperactivity Disorder: A 24-Week Extension Study

Tristram Smith, PhD, Michael G. Aman, PhD, L. Eugene Arnold, MD, Laura B. Silverman, PhD, Luc Lecavalier, PhD, Jill Hollway, PhD, Rameshwari Tumuluru, MD, Susan L. Hyman, MD, Kristin A. Buchan-Page, BS, Jessica Hellings, MD, Robert R. Rice, Jr., PhD, Nicole V. Brown, MS, Xueliang Pan, PhD, Benjamin L. Handen, PhD



Treatment Group	SNAP		HSQ	
	Baseline (Week 0)	Endpoint (Week 34)	Baseline (Week 0)	Endpoint (Week 34)
ATX + PT (n = 12)	2.01 (0.34)	0.80 (0.49)	3.17 (1.77)	0.86 (1.05)
ATX (n = 16)	2.24 (0.35)	0.89 (0.44)	3.75 (1.34)	1.24 (1.08)
PT + PBO (n = 9)	2.31 (0.08)	1.04 (0.54)	4.08 (1.51)	1.07 (0.49)
PBO (n = 6)	1.69 (0.21)	0.81 (0.14)	2.31 (1.71)	1.07 (0.44)

Journal of the American Academy of Child & Adolescent Psychiatry
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Repetitive and Restrictive Behavior

Serotonergic Drugs: Repetitive and Restrictive Behaviors

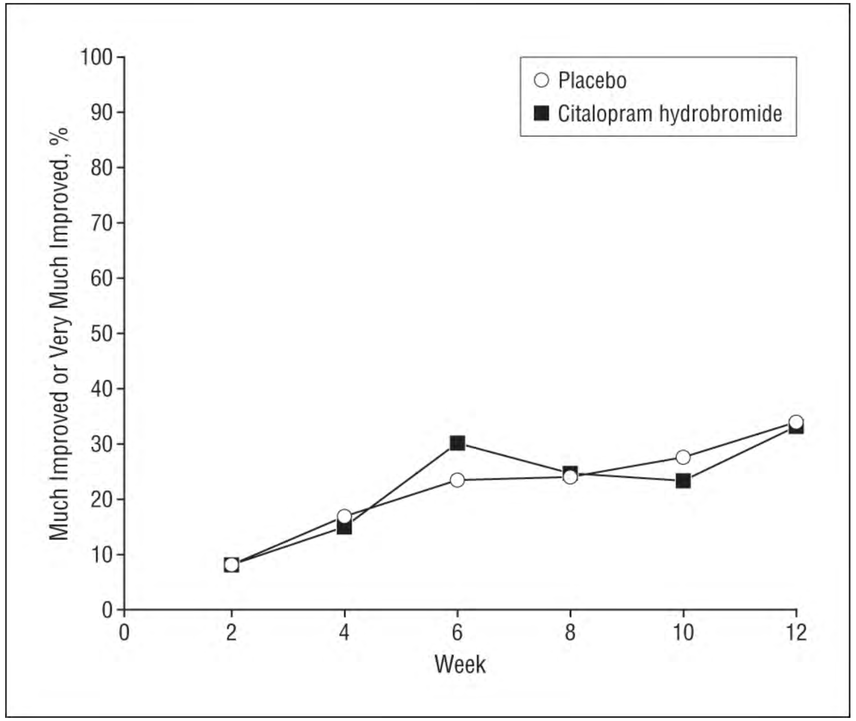
Medication	Open Label	Placebo Controlled
fluoxetine	+ + + +	+ + --
fluvoxamine	+	+ + --
sertraline	+ + +	
citalopram	+	--
escitalopram	+	
venlafaxine	+ +	
clomipramine		+
buspirone	+ +	

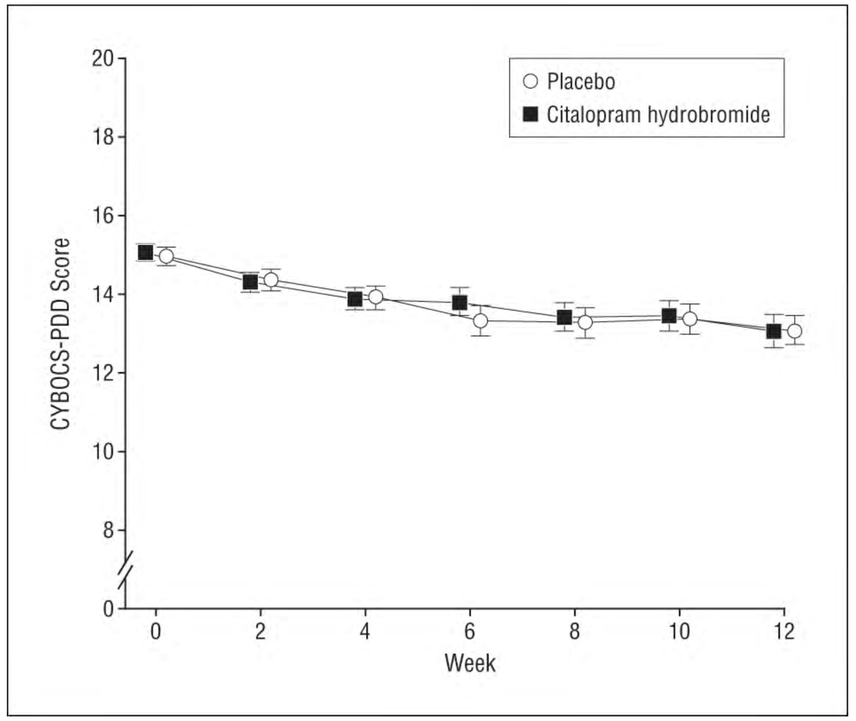
- Open-label in children and adults mostly positive
- RTC:
  - ❖ *Children: mixed results.*
  - ❖ *Adults: positive*
- Outcome measures:
  - ❖ *Y-BOCS > ABC- S*
  - ❖ *Compulsion vs. stereotopy*
- Activating side effect common in most samples

Lack of Efficacy of Citalopram in Children With Autism Spectrum Disorders and High Levels of Repetitive Behavior

Citalopram Ineffective in Children With Autism

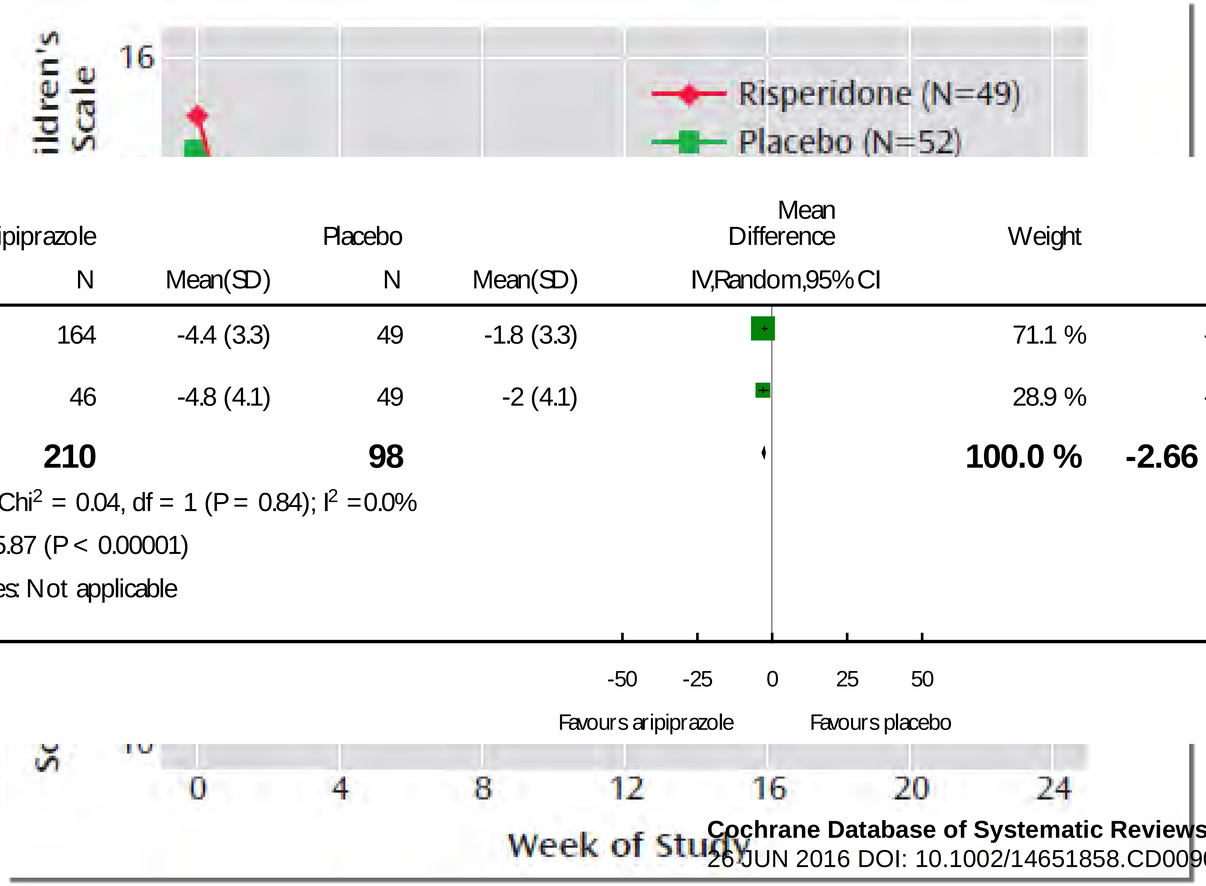
Bryan H. King, MD; Eric Hollander, MD; Linmarie Sikich, MD; James T. McCracken, MD; Lawrence Scahill, MSN, PhD; Joel D. Bregman, MD; Craig L. Donnelly, MD; Evdokia Anagnostou, MD; Kimberly Dukes, PhD; Lisa Sullivan, PhD; Deborah Hirtz, MD; Ann Wagner, PhD; Louise Ritz, MBA; for the STAART Psychopharmacology Network





N = 149

Risperidone and Abilify



Study or subgroup	Aripiprazole N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Marcus 2009	164	-4.4 (3.3)	49	-1.8 (3.3)		71.1 %	-2.60 [-3.65, -1.55]
Owen 2009	46	-4.8 (4.1)	49	-2 (4.1)		28.9 %	-2.80 [-4.45, -1.15]
Total (95% CI)	**210**		**98**			**100.0 %**	**-2.66 [-3.55, -1.77]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%

Test for overall effect: Z = 5.87 (P < 0.00001)

Test for subgroup differences: Not applicable

-50 -25 0 25 50

Favours aripiprazole Favours placebo

Cochrane Database of Systematic Reviews
26 JUN 2016 DOI: 10.1002/14651858.CD009043.pub3

McDougle et al, 2005, *Am J Psychiatry*

Sleep

Sleep Problems

- Sleep is a pervasive problem in autism
- Children with autism and related disorders can have atypical sleep patterns
- Poor sleep affects the family at large
- Significant association with family quality of life and caregiver stress

Using pharmacotherapy to address sleep disturbances in autism spectrum disorders

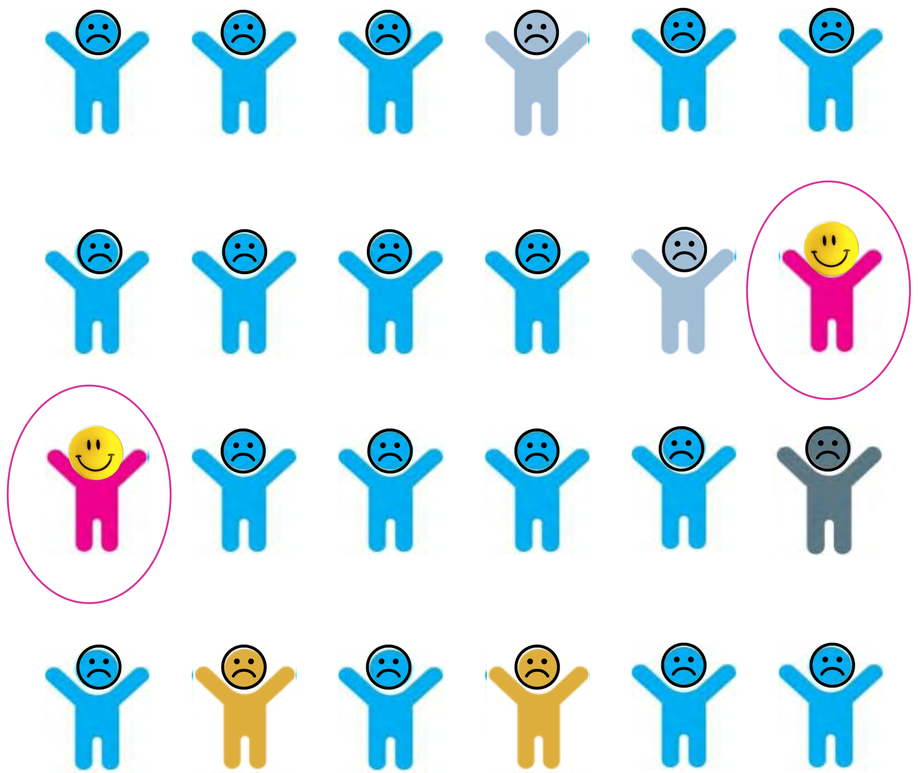
Valeria Mammarella[a], Silvia Orecchio[a], Noemi Cameli[a], Sara Occhipinti[a], Lavinia Marcucci[a], Giuliano De Meo[a], Alice Innocenti[a], Raffaele Ferri[b] and Oliviero Bruni [c]

Expert opinion: Currently, clinicians tend to select medications for the treatment of sleep disorders in ASD based on the first-hand experience of psychiatrists and pediatricians as well as expert opinion. Nevertheless, at the present time, the only compound for which there is sufficient evidence is melatonin, although antihistamines, trazodone, clonidine, ramelteon, gabapentin, or suvorexant can also be considered for selection.

EXPERT REVIEW OF NEUROTHERAPEUTICS
2023, VOL. 23, NO. 12, 1261–1276
https://doi.org/10.1080/14737175.2023.2267761

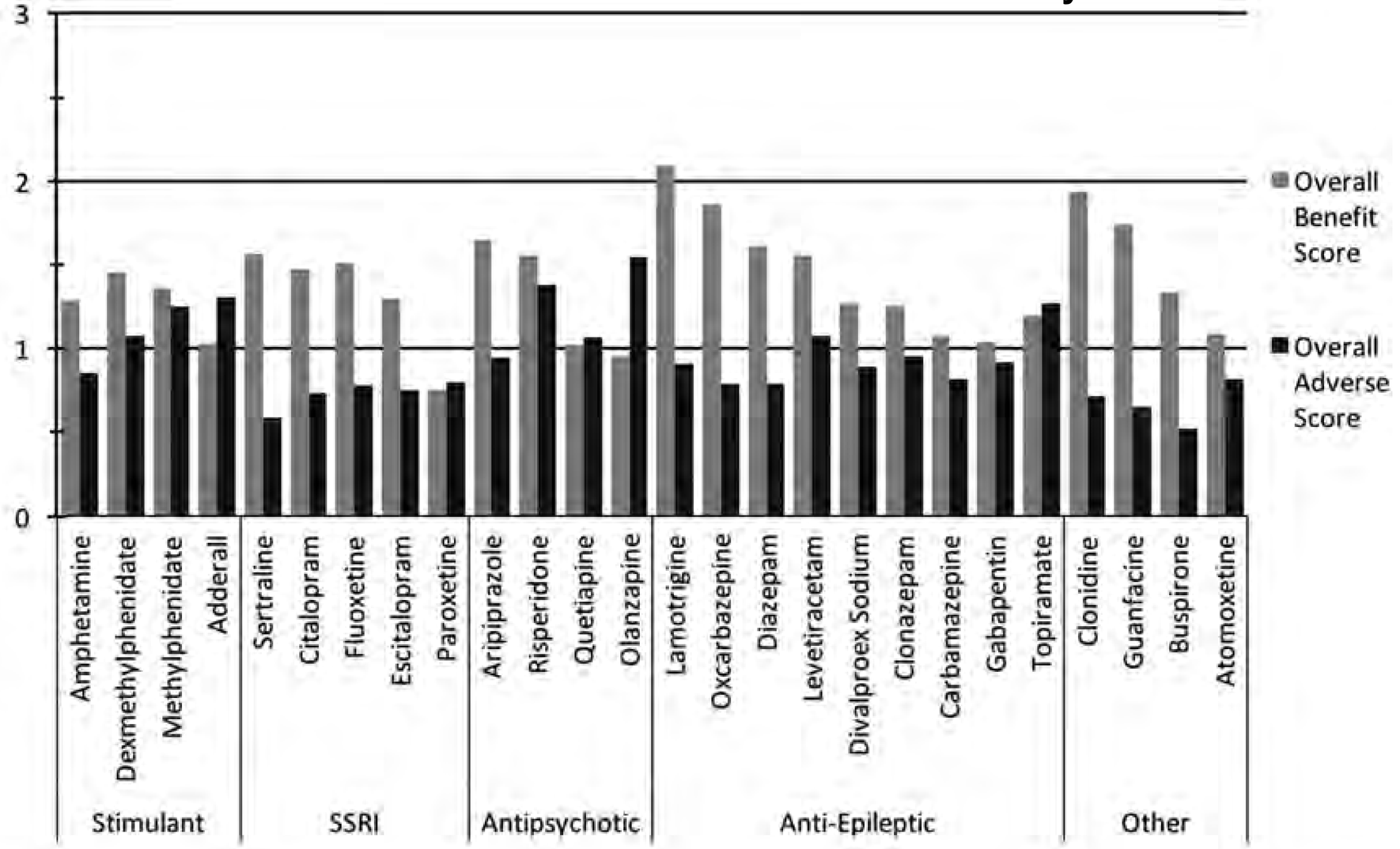
Clinical Trials in Autism and Related Conditions

Clinical Trials in Autism



Conclusions

Rating of the Effectiveness of 26 Psychiatric and Seizure Medications for Autism Spectrum Disorder: Results of a National Survey



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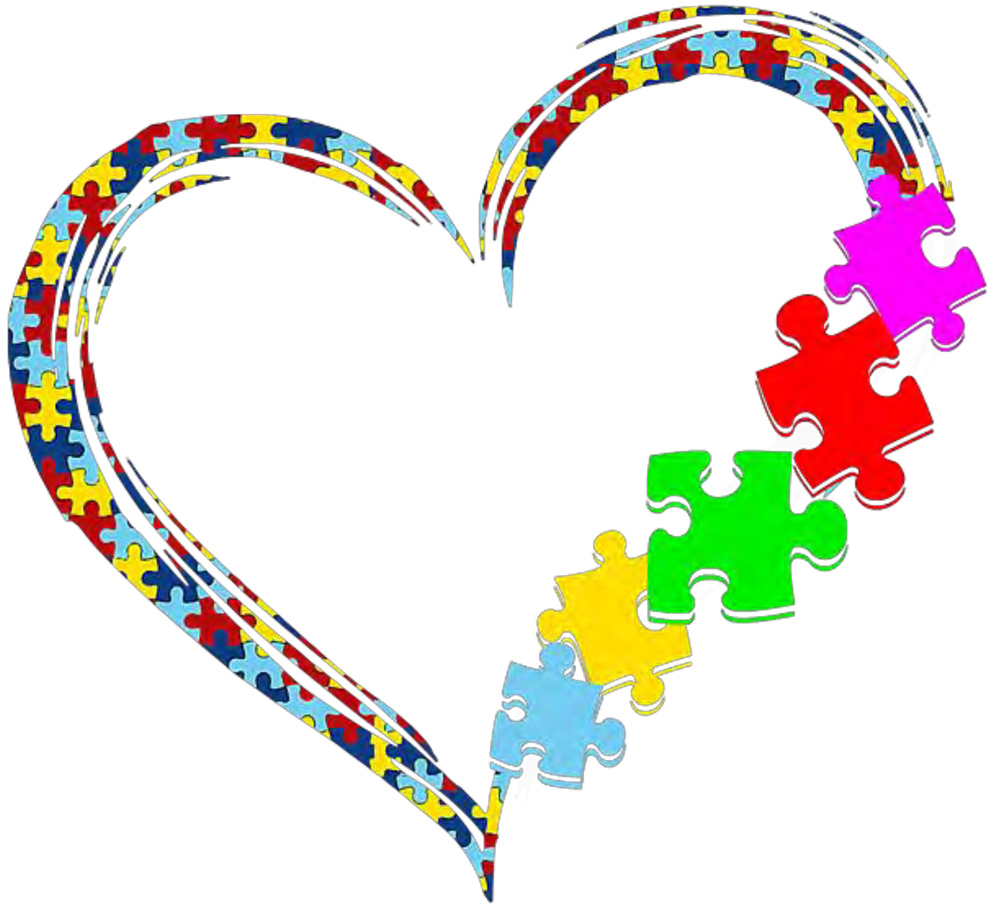
Volume 29, Number 2, 2019

Final Thoughts

- The foundation of treatment relies on behavioral and educational interventions;
- Pharmacological approaches in ASD use a symptom domain specific approach;
- The heterogeneity of autism and related conditions present major challenges in research;
- Treatment will be a dynamic and evolving process that responds to the needs of the child, family and demands of the environment;
- Strong alliance with your treatment team (school, therapy, medical providers, etc.) will be critical to identify the best treatment option.



Thank you!