

Reduction of severe and challenging behaviors in children, teens, and adults with severe autism

SIG leader:

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Statement of Purpose

- **Jill Escher**, MA, JD, President, National Council on Severe Autism (NCSA) and Founder, Escher Fund for Autism. Research and programs philanthropist, advocate, expert on stakeholder priorities, parent
- **Amy SF Lutz**, Vice President, National Council on Severe Autism. Author of books on severe autism, founder of nonprofit aimed at treatment for individuals suffering from aggression and self-injury, parent.

Showing of video: A Voice for Severe Autism

Please watch it at actnowforsevereautism.com

CHALLENGING BEHAVIORS IN PROFOUND AUTISM

INTERNATIONAL SOCIETY FOR AUTISM RESEARCH
INAUGURAL SPECIAL INTEREST GROUP

AUSTIN, TEXAS
MAY 13, 2022

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Kennedy Krieger Institute



Prevalence of Problem Behaviors in ASD/ID

- **27~50%** of individuals with ASD (Richards, Oliver, Nelson, Moss, 2012; Soke et al., 2016).
- **10~15%** of individuals with intellectual and developmental disabilities (IDD) (Emerson et al., 2001).
- NB ~ **~40%** of individuals with ASD have ID

Profound Autism

- A proposed term that captures the following:
 - 1) Need for 24 h access to an adult when problems arise
 - 2) inability to be alone in a residence
 - 3) inability to manage basic ADLs

As proposed by Lord et al. in the Lancet Commission on the future of care and clinical research in autism, 2022.

Profound Autism

- Emphasizes not the core autism symptoms, but
 - 1) comorbid significant ID
 - 2) highly limited language capacity
- Proposed by Lord et al. only as an administrative term
 - Is that enough??

Prevalence and Risk Factors for Challenging Behavior

- Risk factors:
 - Level of intellectual disability (ID)
 - Language and communication deficits
 - Adaptive skills deficits
 - Concomitant psychopathology
 - Concomitant genetic conditions
 - Concomitant medical conditions
 - Sensory impairment
 - Social circumstances
 - Family circumstances
 - Genetic loading
 - Resources – or lack thereof

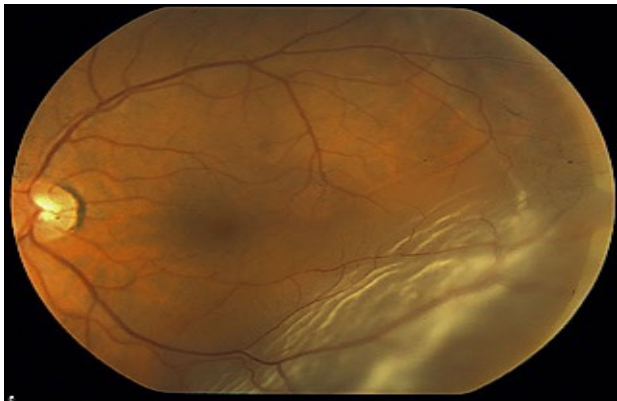
Forms of Problem Behavior

SIB	<ul style="list-style-type: none">• head banging, head hitting• self biting• pulling out own hair• skin picking• face slapping	<ul style="list-style-type: none">• eye poking• self scratching• lip/tongue/gum biting• knee to face, chin• tooth self-extraction
Aggression	<ul style="list-style-type: none">• hitting• kicking• scratching	<ul style="list-style-type: none">• biting• pinching• choking
Disruption	<ul style="list-style-type: none">• throwing objects• breaking/ripping items• knocking over furniture	<ul style="list-style-type: none">• screaming• spitting• breaking windows, doors
Pica	<ul style="list-style-type: none">• ingestion of: rocks• dirt, miracle grow• feces, painted wood	<ul style="list-style-type: none">• glass, clothes• oil, pens, toothbrush• metal, metal spiral from notebook
Other PB	<ul style="list-style-type: none">• elopement• fecal smearing• disrobing	<ul style="list-style-type: none">• inserting objects into electrical outlets• jumping out of a window• excessive stereotypic behavior

Injuries Observed Over 20 Years

- Loss of vision/hearing
- Cerebral hemorrhage
- Skull fractures
- Broken bones
- Detached lens/retina
- Bruising, swelling
- Bleeding
- Bacterial infections
- Mutilation of tongue/lips
- Trauma-induced nasal/facial deformity
- Cauliflower ears
- Ruptured rectum
- Calluses
- Scarring
- Hyperpigmentation
- Surgery to remove ingested items from pica

Pictures are worth a thousand words



Measures Taken to Manage Problem Behavior Prior to Admission

- Helmets
- Bandages
- Mouth guards
- Face masks
- Arm pads
- Medication
- 24-hour home aides
- 2:1 school staffing
- Behavioral services
- Hospitalization
- Isolation/seclusion
- Rigid arm restraints
- Restraint
- Tied to chairs

Welcome to a war zone

- Severe behaviors in ASDs are:
 - Highly unpredictable
 - Highly limiting for the child and family
 - Don't get better on their own
 - Dangerous with real risk of severe injury
 - Emotionally draining
 - Physically exhausting



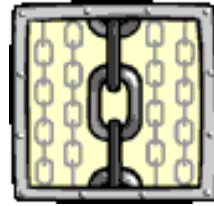
KKI Neurobehavioral Unit Waitlist

- 209 children, adolescents and adults currently waiting
- 57 have been waiting from before COVID-19
- ~15% require more than 1:1 staffing
- ~10% have high medical acuity
- ~10% are already in restrictive equipment
- *Waiting time for admission 6-24+ months*

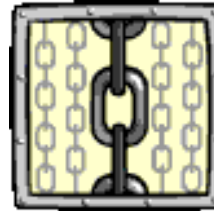
Relevance

- Challenging behavior in profound ASD is an immense problem
 - Truly a national crisis
 - Affects individuals with ASD *across the lifespan*
- It will likely become more dire with ongoing increase in prevalence of ASD
- We are in desperate need of:
 - Enhancing understanding of challenging behaviors
 - Improved treatment options
 - RESEARCH
 - ADVOCACY

ASD/ID



Psychiatric disorders



Challenging Behaviors



Frequency of Psychiatric Illness in ASD

- Anxiety disorders – ~30%
- ADHD – 14~70%
- Affective disorders – 5~10%
- Psychotic disorders – 4~11%
- Catatonia – 12~20%

This really should NOT come as a surprise given shared genetic susceptibility loci between ASD and other psychiatric illnesses.

Psychiatric Illness in ID

- Increased risk in ID –3-5x greater than general population
 - First demonstrated in the Isle of Wight studies
 - Borwick-Duffy et al. 1990. “Who are the dually diagnosed?” Am J MR
 - Repeatedly demonstrated in multiple international studies
- *Current* best treatment practices:
 - Follow the research-supported paradigms for typically-developing individuals with the same dx

Multiple disorders as the rule of thumb

- Mosner, MG et al. Rates of co-occurring psychiatric disorders in ASD using the mini international neuropsychiatric interview. Journal of Autism and Developmental Disabilities, 2019.
- 91% children and 31% adults received at least 1 DSM DX

Associated literature overview:

70~95% of youth with ASD have at least one DSM DX

41~60% have two or more

24% have three or more

Open questions

- Best diagnostic paradigms for individuals with ASD +/- ID
- Psychiatric diagnostic challenges with profound ID
- Best treatment paradigms
 - Psychotropic interventions in ASD/ID often spin out of general child psychiatry, which often spin out of adult psychiatry. . .
 - Is that enough?
- Access to treatment
- Acceptance of treatment

Research

- Science advances through quality research
- Profound autism is often overlooked or frankly excluded from clinical research
 - Barriers appear great at first glance given the potential research subjects
 - Consent
 - Reliable participation
 - Cooperation with laboratory and imaging measures
 - The neurodiversity movement and our PC/cancel culture discourages it
 - It's not “pretty.”

THIS IS AN UNTAPPED GOLD MINE WITH VAST POTENTIAL TO MAKE A DIFFERENCE

Can we fathom a medical community without research in brittle diabetes, severe hypertension or Grade 4 cancers?



Unmet Research Needs for Severe Behavior Challenges in ASD

Matthew Siegel, MD, Director of the Developmental Disorders Program, Maine Behavioral Health, Associate Professor of Psychiatry and Pediatrics of Tufts University and Faculty Scientist, MMC Research Institute. Inpatient and outpatient treatment for severe autism.

UNMET RESEARCH NEEDS FOR SEVERE BEHAVIOR CHALLENGES IN ASD

There are significant gaps in our understanding of etiology, longitudinal course, and the efficacy and effectiveness of assessment and treatment approaches for severe behavior challenges. Specifically, there is a dearth of research on:

- Longitudinal studies of aggression and self-injury across the lifespan
- Validated, clinically practicable diagnostic tools for psychiatric co-morbidity
- Novel approaches to aggression and self injury grounded in biological mechanisms and objective measures
- Rigorous controlled group studies of ABA-based treatment for challenging behavior, and of multi-disciplinary treatment packages (e.g.ABA+FCT+Meds+Family Training)
- Effectiveness and key elements of complex, real-world treatment packages (residential treatment and in-home behavioral services)
- In general, those with severe behavior or profound autism are excluded from much of current ASD research. (Stedman A, et al., 2018)

Distress in Autistic Individuals Co-occurs with Treatable Psychiatric Conditions



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HEALTH
UNIVERSITY OF UTAH

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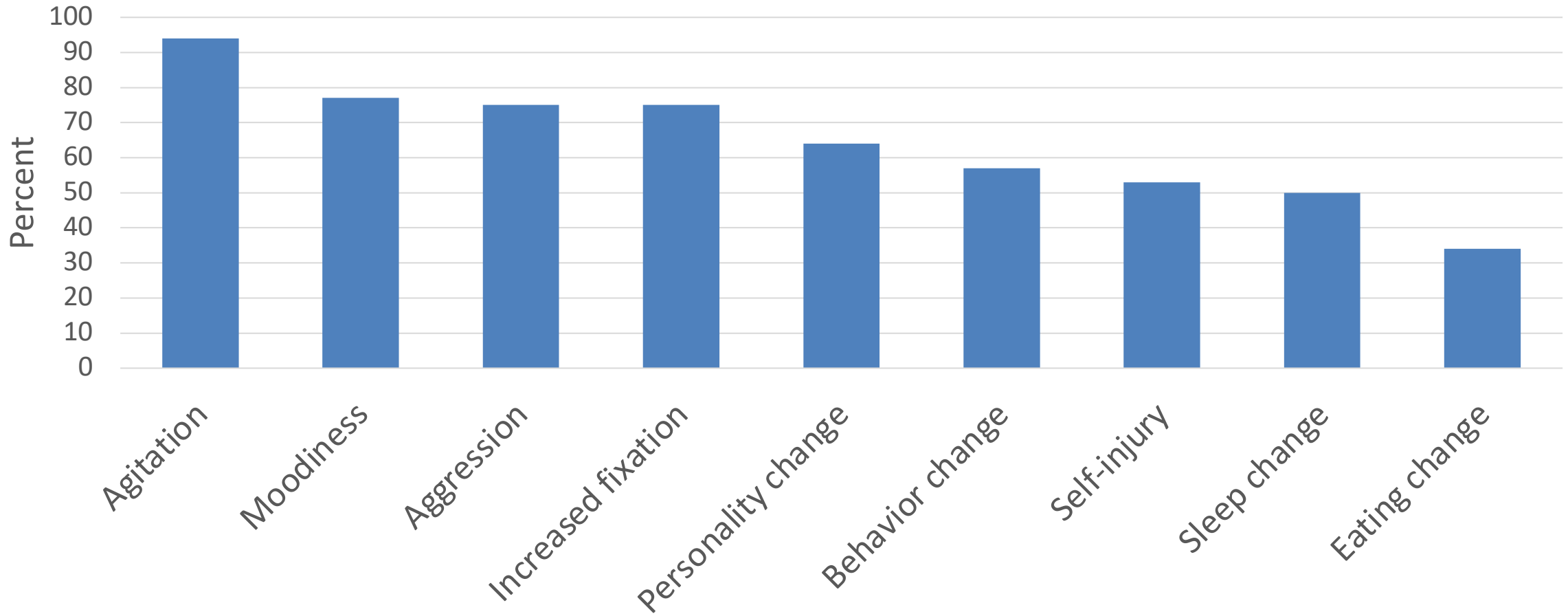
DISCLOSURES

- Consultant, Advisory Board and Steering Committee member for BioMarin Pharmaceuticals
- Consultant and Scientific Advisory Board member for Taysha Gene Therapies
- Consultant for Encoded Therapeutics
- Consultant for Synlogic Therapeutics
- University of Utah has copyrighted the Sources of Distress

CRISIS CARE AND PSYCHIATRIC CO-MORBIDITIES IN AUTISM

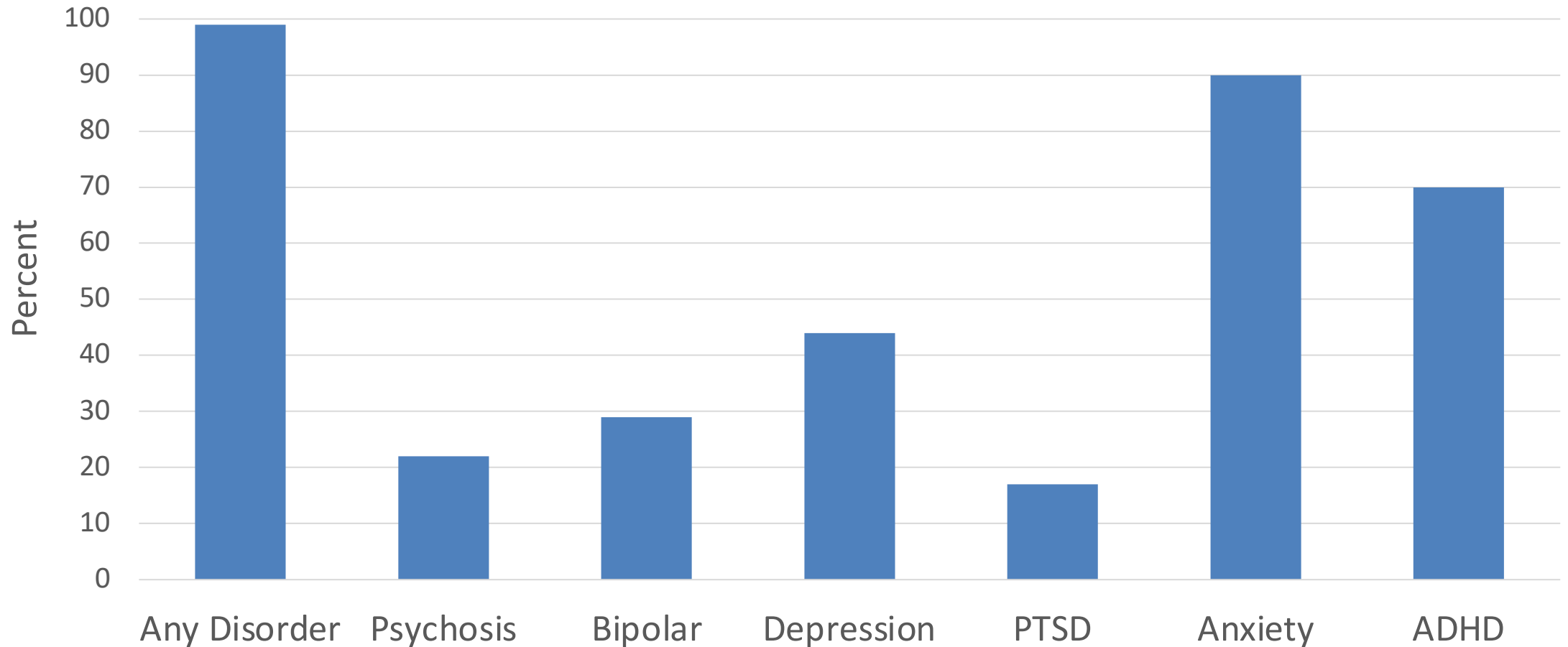
- Acute behavioral crises in ASD associated with psychiatric comorbidities, environmental stressors, and medical concerns (Perisse et al, 2010)
- Mental health co-morbidities in ASD are associated with challenging behaviors, such as self injury or aggression, and often lead to crisis intervention (Carroll et al, 2014, Kanne and Mazurek, 2011)

DISTRESS MANIFESTATIONS IN N=115 AUTISTIC INDIVIDUALS PRESENTING IN CRISIS



Roxanne Bartel, unpublished data

SCREEN POSITIVE PSYCHIATRIC CONDITIONS ACCOMPANYING DISTRESS



Roxanne Bartel, unpublished data

TREATMENT RESISTANCE VS. UNRECOGNIZED OPPORTUNITIES

- 67% taking an antipsychotic medication, yet still in crisis
- 82% of those with SIB were taking an antipsychotic medication
- 82% of those with bipolar disorder were taking an antipsychotic medication
- 91% of those presenting with SIB screened in for either depression or bipolar disorder
- 48% of those with bipolar disorder and SIB were also taking an antidepressant
- In bipolar disorder and SIB, low use of non-antipsychotic mood stabilizers: 30.4% anticonvulsants, 9% lithium

Psychotropic use - Clinical patterns, challenges and future directions

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Child Psychiatry Fellow - Kennedy Krieger
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INSAR 2022



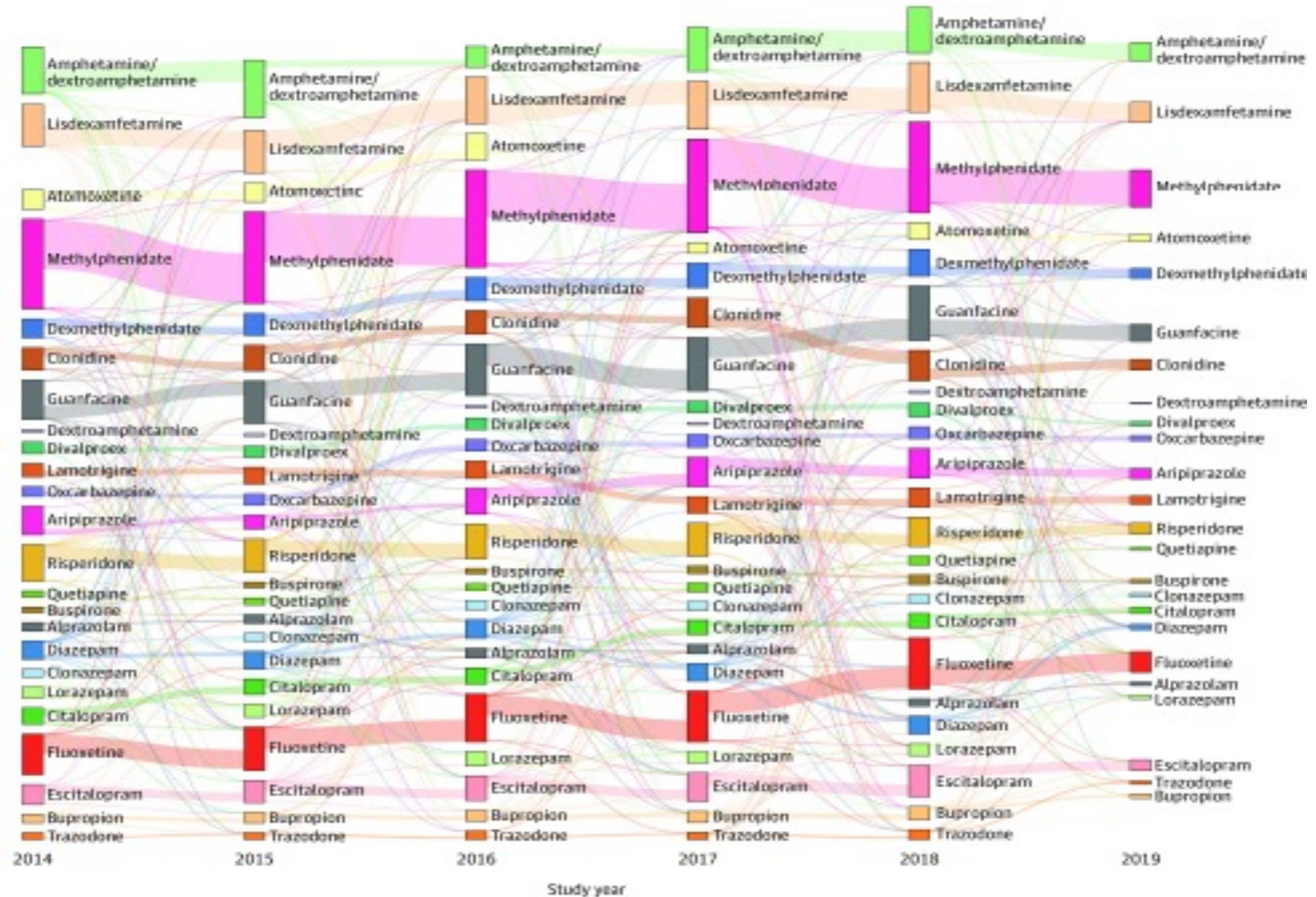
Current Patterns

- **Polypharmacy** common, ranging from 28.6% to 31.5%.
- Single-drug regimens showed **frequent shifts** annually
- Antipsychotics - common comorbidities included combined type ADHD and anxiety disorder
- Did not always **cluster per clinical guidelines**
- Some medications (eg, diazepam, dextroamphetamine, and lamotrigine) weakly associated with specific comorbidity diagnoses



Sankey Diagram

- Depicts frequency patterns by drug and transiency of prescribing patterns
- Monotherapy groups only in this diagram



Comorbidity Correlation Heat Map



Current Patterns

- Psychotropic use more than **9-fold** that of children w/o ASD dx
- Differences greatest for antipsychotics - **22-fold** those of the general population
- Cohort level differences in ADHD medication use smallest but still nearly **6-fold**
- Polypharmacy
- Prescribing intensity factors – **more frequent medical care, behavioral concerns, desperation** among families and providers
- Divergent care patterns driven by **therapeutic uncertainty** "Physician prescribing fingerprints"



Prescription Use among Children with Autism Spectrum Disorders in Northern New England: Intensity and Small Area Variation

Samantha A. House, DO, MPH^{1,2}, David C. Goodman, MD, MS^{1,2,3}, Shelsey J. Weinstein, BA², Chiang-Hua Chang, PhD³, Jared R. Wasserman, MS³, and Nancy E. Morden, MD, MPH^{2,3,4}

Objective To measure prescription use intensity and regional variation of psychotropic and 2 important nonpsychotropic drug groups among children with autism spectrum disorders (ASDs) compared with children in the general population.

Study design Cross-sectional study of ambulatory prescription fills from Maine, Vermont, and New Hampshire all-payer administrative data, 2007-2010.

Results Overall there were 13 100 children diagnosed with ASD (34 584 person years [PYs]) and 936 721 (1.7 million PYs) without ASD diagnosis. The overall prescription fill rate was 16.6 per PY in children with ASD and 4.1 per PY in the general population. Psychotropic use among children with ASDs was 9-fold the general population rate (7.80 vs 0.85 fills per PY); these children comprised 2.0% of the pediatric population but received 15.6% of psychotropics. Nonpsychotropic drug use was also higher in the population with ASD, particularly the youngest: among those under age 3 years, antibiotic use was 2-fold and antacid use nearly 5-fold the general population rate (3.2 vs 1.4 and 1.0 vs 0.2 per PY, respectively). Among children with ASDs, prescription use varied substantially across hospital service areas, as much as 3-fold for antacids and alpha agonists, more than 4-fold for benzodiazepines (5th to 95th percentile).

Conclusions The overall psychotropic and nonpsychotropic prescription intensity among children with ASDs is characterized by broad regional variation, suggesting diverse provider responses to pharmacotherapeutic uncertainty. This variation highlights a need for more research, practice-based learning, and shared decision making with caregivers surrounding therapy for children with ASDs. (*J Pediatr* 2016;169:277-83).

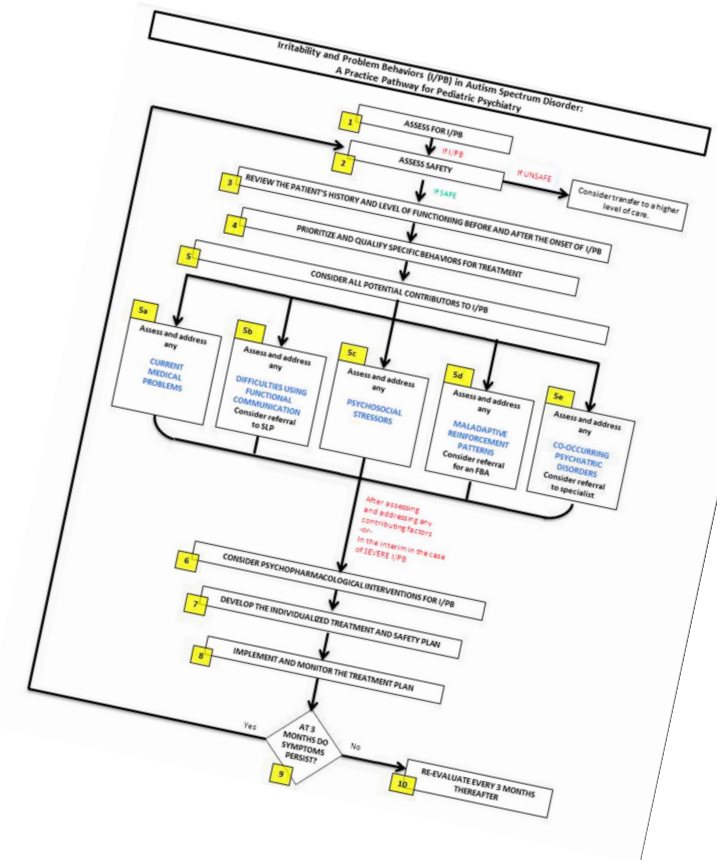
Table IV. Age- and sex-standardized mean annual prevalence of prescription medication use by cohort and by payer type, 2007-2010

	Children with ASDs				General pediatric population				Ratio overall prevalence: children with ASD/general population
	Overall	Medicaid	Commercial	Ratio of Medicaid to commercial	Overall	Medicaid	Commercial	Ratio of Medicaid to commercial	
Observation time weighted annual percent of population with any use	78%	78%	76%	1.03	58%	62%	54%	1.14	1.26
Drug group specific fill rates									
Psychotropics									
ADHD medications	26%	26%	25%	1.03	5%	7%	4%	1.81	3.63
Antidepressants	19%	18%	21%	0.85	3%	3%	2%	1.38	5.24
Antipsychotics	22%	24%	16%	1.54	1%	2%	1%	3.79	12.25
Benzodiazepines	6%	6%	5%	1.13	1%	1%	1%	1.28	5.74
Alpha agonists	6%	6%	5%	1.28	0%	1%	0%	3.81	10.13
Nonpsychotropics									
Oral antibiotics	40%	40%	38%	1.05	36%	38%	33%	1.14	1.06
Prescription antacids	5%	5%	4%	1.40	2%	3%	2%	1.68	1.91
Annual observation weighted proportion of the cohort filling prescriptions for									
No psychotropics	54%	54%	57%	96%					
Medications from 1 or more psychotropic drug group(s)	46%	46%	43%	106%	8%	11%	6%		
Medications from 2 or more psychotropic drug group(s)	23%	24%	21%	118%					
Medications from 3 or more psychotropic drug group(s)	8%	8%	7%	125%					

Psychotropics include all of the medication groups above. [Table II](#) lists the medications included in each group.

Applying Efficacy/Effectiveness research in clinical settings

- Results from subsequent studies for FDA approved agents (Risperidone/Aripiprazole) – **continue demonstrating efficacy for short term improvement**; maintenance efficacy Risperidone > Aripiprazole; **moderating factors** viz side effect profiles
- Prescribing patterns far wider than FDA approved drugs
- Difficulties developing guidelines for use of off label medication use
- Dissemination of existing guidelines (ATN etc)
- Efficacy data/trials (RCTs) vs Effectiveness (Real world, qualitative data)
- **Best Practices: Evidence based Practice vs Practice based Evidence**



Searching for Best Practices - Needle in a haystack

- **Moderate to large effect sizes:** Risperidone and Aripiprazole (atypical antipsychotics) and NAC (antioxidant/glutamatergic modulator)
- **Moderate effect sizes:** Clonidine (α_2 adrenergic agonist), Methylphenidate (psychostimulant) and Tianeptine (Tricyclic Antidepressant)
- **Small effect sizes:** Citalopram (SSRI), Venlafaxine (SNRI) and Naltrexone (opioid competitive antagonist)
- **Negative compounds:** Valproate, Amantadine, Dextromethorphan, Levetiracetam, Mecamylamine, Omega 3 fatty acids, Secretin, Haloperidol, Clomipramine



Searching for Best Practices - Needle in a haystack

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Mary Ann Liebert, Inc.
Pp. 107-123
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Rating of the Effectiveness of 26 Psychiatric and Seizure Medications for Autism Spectrum Disorder: Results of a National Survey

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Abstract
Objective: The objective of this study was to provide an evaluation of the benefits and adverse effects (AEs) of psychiatric and seizure medications commonly used for individuals with autism spectrum disorder (ASD).
Methods: As part of the National Survey on Treatment Effectiveness for Autism, we report ratings of 26 psychiatric and seizure medications by 505 participants. Each medication was rated with a standardized scale for overall benefits, overall AEs, and specific symptoms affected. The frequency of use and net perceived benefit (overall benefit minus overall AE) are reported.
Results: Most medications were rated as having a slightly greater benefit than AE. Six medications (lamotrigine, oxcarbazepine, clonidine, guanfacine, buspirone, and sertraline) had benefit ratings that were more than twice their adverse rating. Conversely, some medications had slightly negative net benefit ratings (worse AEs than benefits on average), including Adderall, Paroxetine, Quetiapine, Olanzapine, and Topiramate. However, there were wide variations in individual ratings of benefits and AEs, suggesting that clinical response to medications was highly variable, so these scores simply represent averages. A ranking of the top medications as to which net perceived benefit for each of 18 different symptoms is provided, which may provide some clinical guidance as to which medications may be most worth considering for a given symptom. A comparison of the survey results with the results of clinical trials shows generally good agreement in terms of medication benefits with some differences; in some cases the differences are because the clinical trials did not assess all of the symptoms assessed by this survey.
Conclusions: It is hoped that physicians and their patients will find the survey results useful in selecting the most promising medications for a given symptom, and also for monitoring for likely benefits and AEs, especially for medications for which few or no studies have been carried out in ASD populations.

- Most commonly used : stimulants, antipsychotics, seizure medications, and SSRIs
- Polypharmacy increased with age
- Six medications (Lamotrigine, Oxcarbazepine, Clonidine, Guanfacine, Buspirone, and Sertraline) benefit ratings **more than twice** their adverse rating
- Some medications **slightly negative net benefit** ratings including **Adderall, Paroxetine, Quetiapine, Olanzapine, and Topiramate**
- Antipsychotics: Risperidone and aripiprazole most commonly used; Aripiprazole highest net benefit followed by risperidone, quetiapine, and finally olanzapine
- **Quetiapine and Olanzapine** had **negative net benefit** scores

TABLE 7. TOP MEDICATIONS FOR SYMPTOMS

<i>Symptoms</i>	<i>Medication (benefit rating)</i>
Aggression/agitation	Oxcarbazepine (0.33), Lamotrigine (0.28), Guanfacine (0.21), Aripiprazole (0.16), Clonidine (0.16), Sertraline (0.14), Fluoxetine (0.13), Buspirone (0.12)
Anxiety	Sertraline (0.55), Buspirone (0.38), Citalopram (0.33), Fluoxetine (0.32), Diazepam (0.29), Oxcarbazepine (0.26), Clonidine (0.21), Escitalopram (0.19), Guanfacine (0.18), Lamotrigine (0.14)
Attention	Guanfacine (0.42), Amphetamine (0.20), Dexmethylphenidate (0.16), Clonidine (0.11)
Cognition (ability to think)	Guanfacine (0.21), Dexmethylphenidate (0.09), Sertraline (0.07)
Depression	Sertraline (0.23), Citalopram (0.21), Escitalopram (0.18), Fluoxetine (0.16)
General benefit, no one particular symptom	Clonidine (0.09), Lamotrigine (0.07), Escitalopram (0.07)
Hyperactivity	Guanfacine (0.27), Clonidine (0.20), Amphetamine (0.18), Oxcarbazepine (0.11), Dexmethylphenidate (0.10), Sertraline (0.10)
Irritability	Oxcarbazepine (0.18), Lamotrigine (0.14), Sertraline (0.14), Guanfacine (0.12), Clonidine (0.12), Fluoxetine (0.10), Buspirone (0.10)
Language/communication	Sertraline (0.04), Guanfacine (0.03), Divalproex Sodium (0.02)
Lethargy (easily tired)	Diazepam (0.06), Clonidine (0.02), Buspirone (0.02)
OCD	Sertraline (0.12), Fluoxetine (0.08), Citalopram (0.08)
Seizures	Lamotrigine (0.38), Levetiracetam (0.33), Oxcarbazepine (0.29), Diazepam (0.12)
Self-injury	Lamotrigine (0.07), Buspirone (0.04), Citalopram (0.04)
Sensory sensitivity	Oxcarbazepine (0.11), Guanfacine (0.07), Amphetamine (0.05)
Sleep (falling asleep)	Clonidine (0.59), Guanfacine (0.11), Clonazepam (0.06)
Sleep (staying asleep)	Clonidine (0.39), Guanfacine (0.08), Lamotrigine (0.07)
Social interaction and understanding	Guanfacine (0.10), Sertraline (0.10), Amphetamine (0.05)
Stimming/perseveration/desire for sameness	Escitalopram (0.04), Oxcarbazepine (0.04), Diazepam (0.03)
Tics/abnormal movements	Guanfacine (0.10), Amphetamine (0.02), Clonazepam (0.02)

Benefit to Harm Ratios

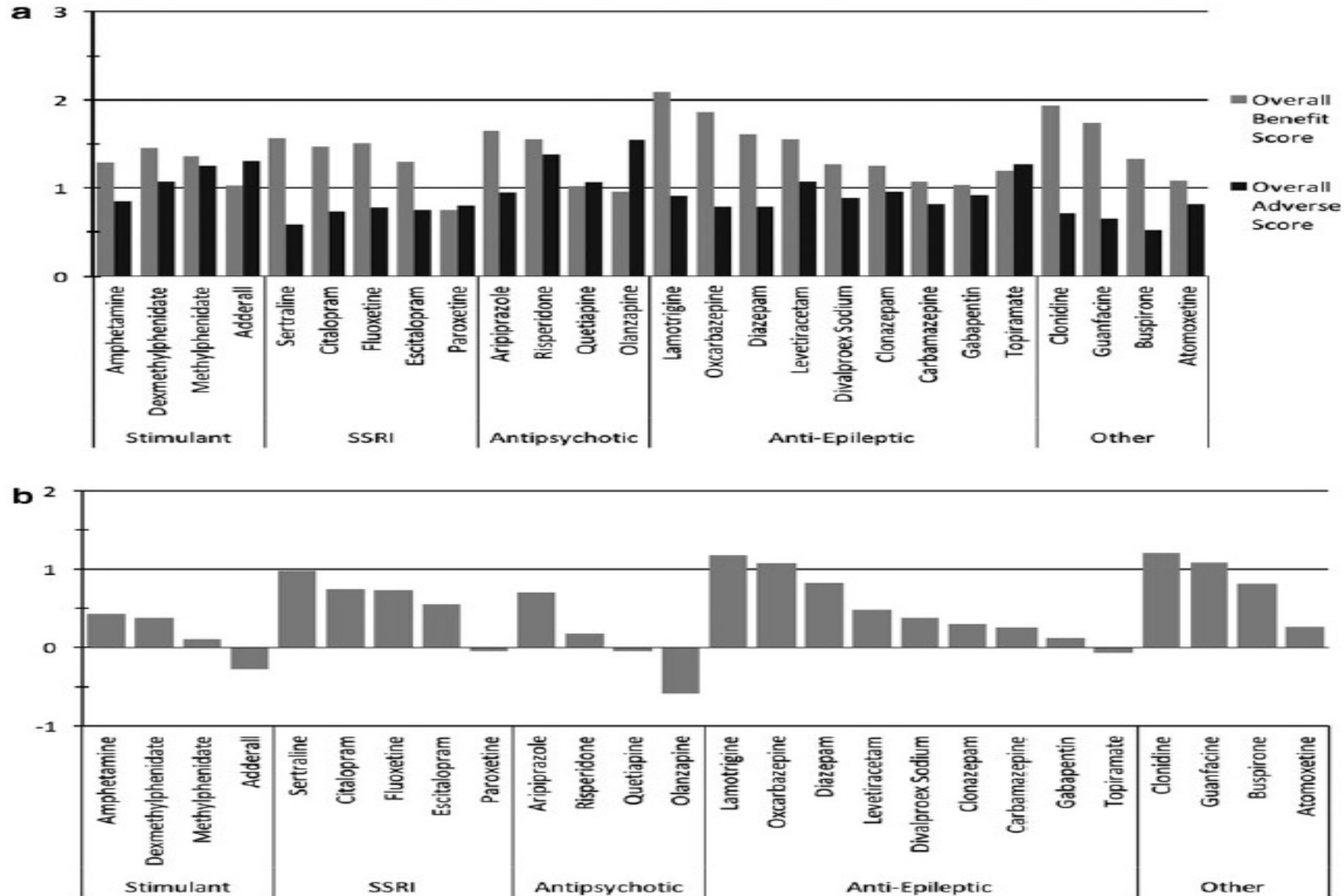


FIG. 8. Overall benefit score and adverse score for all psychiatric and seizure medications. (a) Overall benefit and adverse scores. (b) Net benefit scores.

Benefit to Harm Ratios

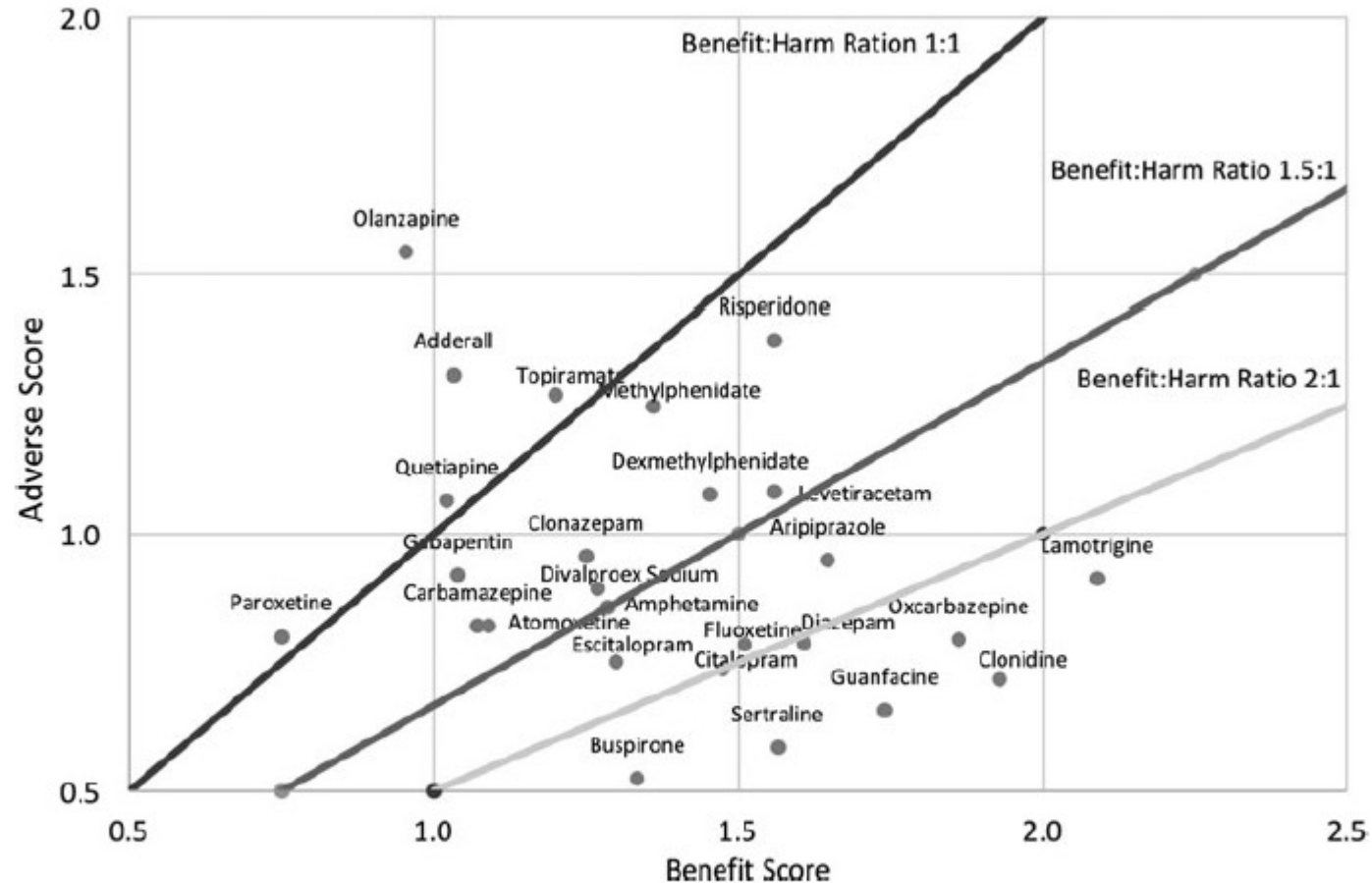


FIG. 9. Benefit:harm ratio of all psychiatric medications. Plot of overall AE versus overall benefit for all medications. There are three lines indicating the ratio of overall benefit to overall AE for ratios of 1:1, 1.5:1, and 2:1. Medications on the *lower right* have the highest ratio of overall benefit to overall AE.

Failed trials and pipeline molecules

- Balovaptan: small molecule antagonist of the vasopressin V1A receptor
- Bumetanide: loop diuretic
- Arbaclofen: selective GABA-B receptor agonist
- Mavoglurant: antagonist of the metabotropic glutamate receptor 5 (mGluR₅)
- Memantine: voltage-dependent uncompetitive antagonist at glutamatergic NMDA receptors
- Fenfluramine: serotonergic, sympathomimetic
- Naltrexone: competitive opioid antagonist
- Intranasal Oxytocin: neuropeptide hormone
 - Cannabinoid receptor agonist
 - Vasopressin 1A antagonist
 - Tyrosine hydroxylase inhibitor

Study Design

Limitations and Obstacles

- Phenotypic heterogeneity but **lack of sub phenotyping/separable phenotypic dimensions**
- Lack of **severity subtyping**
- Effect of **diagnostic consolidation, study exclusion criteria**
- **Functional characterization** of "problem behaviors", "irritability", "aggression"
- Differences between aims of early phase **proof of concept or mechanism trials** (Phase I and II) versus later stage **efficacy** studies (Phase III)
- Risk/Benefit analysis and **guidelines** for short term stabilization vs maintenance treatment recommendations

Drug development for Autism Spectrum Disorder (ASD): Progress, challenges, and future directions



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Table 3 Biomarkers in ASD Under Examination.

Biomarker	Potential type
Eye Tracking	
multiple paradigms	S,D,M
Resting state electroencephalogram (EEG)	D
alpha power/ coherence/ suppression	D
gamma power	D
beta power	PG
Event Related Potentials (ERPs)	
visual, auditory, multisensory	D
Pupillometry (emotional faces)	D
Facial emotion labeling (pictures)	D
Whole Blood Serotonin (WBS)	
WBS+ N- Acetylserotonin + melatonin	D
Cerebrospinal fluid arginine vasopressin	D,M

Legend:

S: suspectibility/ risk

D: diagnostic

M: monitoring

PG: prognostic

PR: predictive

PD: pharmacodynamic response

SF: safety

(see BEST-<https://www.ncbi.nlm.nih.gov/books/NBK326791/>)

Table 1 Current Challenges in ASD Clinical Trials.

Managing ASD heterogeneity
 Failures of preclinical to clinical translation of targeted treatments
 Lack of validated, objective biomarkers for diagnosis, stratification, treatment prediction, early change detection, target mechanism engagement, and relevant neural circuit modulation
 Need for improved clinical endpoints
 Prioritization of molecular targets
 Creating more robust trial designs
 Navigating regulatory requirements for new therapeutic indications
 Defining priorities for therapeutics directed towards comorbidities
 Incorporating participant/caregiver perspectives
 Addressing anticipated research ethical issues

Study Design

Limitations and Obstacles

- Negative trials of targeted compounds blamed on:
 - **Clinical endpoint** insensitivity to change
 - Vulnerability to **placebo** effects (Masi et al., 2015)
 - Impact of **non-ASD** behaviors (Hus et al., 2013 ; Sturm et al., 2017)
 - Possible **age and IQ effects** (Jeste and Geschwind, 2016 ; Anagnostou, 2018)
- Recommend operationally defining **ASD severity, separable phenotypic dimensions, cognition,** and **co- morbidities** serve as **grouping definitions** and/or **refined treatment endpoints** - link to **differential treatment response**

Challenges across the globe: Perspective from Pakistan



- Child Psychiatry and multi-disciplinary care in infancy
- Lack of epidemiological studies assessing prevalence and impact
- Delays in recognition and early interventions
- Dearth of specialist services, concentration in urban areas, barriers to access
- Unique cultural strengths and weaknesses – social support group and caregiver centered interventions vs stigma and caregiver burden
- Polypharmacy, restrictive settings treatment without oversight
- Efforts spearheaded by advocates, parents and non-profit groups – Autism Society of Pakistan and others



ASD and Comorbid ID

Click to add text
Click to add text

Audrey Thurm, PhD, Director, Neurodevelopmental and Behavioral Phenotyping Service, Office of the Clinical Director, NIMH. Author of a recent paper on improving research on severe autism.

Alycia Halladay, PhD, Chief Science Officer, Autism Science Foundation. Advocate, research expert.

Why focus on Intellectual Disability here?

Challenging behaviours at early adulthood in autism spectrum disorders: topography, risk factors and evolution

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Table 2 Relationship between challenging behaviours and clinical variables at T4

	Irritability		Lethargy		Stereotypy		Hyperactivity	
	Median (IntQ) [*]	P value	Median (IntQ)	P value	Median (IntQ)	P value	Median (IntQ)	P value
Best estimate DQ								
1. Severe intellectual disability (DQ < 40)	24.4 (11.1; 42.2)	.0001	31.25 (14.6; 47.9)	0.3	38.1 (14.3; 57.1)	0.002	29.2 (12.5; 45.8)	.0001
2. Moderate intellectual disability (40 ≤ DQ < 55)	12.2 (8.9; 17.8)		29.2 (22.9; 35.4)		16.7 (9.5; 38.1)		12.5 (8.3; 16.7)	
3. Mild intellectual disability (55 ≤ DQ < 70)	4.4 (1.1; 18.9)		17.7 (6.25; 31.25)		23.8 (9.5; 38.1)		13.5 (3.1; 29.2)	
4. Without intellectual disability (DQ ≥ 70)	4.4 (0.0; 13.3)		25.0 (8.3; 41.7)		14.3 (0.0; 23.8)		8.3 (4.2; 14.6)	
Expressive language								
Speech	13.3 (4.4; 28.9)	0.009	27.1 (12.5; 45.8)	0.4	19.05 (9.5; 38.1)	0.005	14.6 (6.25; 31.25)	0.001
No speech	26.7 (12.2; 42.2)		33.3 (14.6; 45.8)		47.6 (11.9; 57.1)		33.3 (15.6; 51.0)	
Gender								
Man	17.8 (4.4; 33.3)	0.7	27.1 (12.5; 45.8)	0.8	23.8 (9.5; 47.6)	0.5	18.75 (8.3; 37.5)	0.6
Woman	22.2 (2.2; 44.4)		27.1 (10.4; 45.8)		38.1 (0.0; 52.4)		14.6 (8.3; 33.3)	
Gastrointestinal disorders								
Absence	15.6 (4.4; 31.1)	0.1	25.0 (12.5; 41.7)	0.2	19.1 (9.5; 38.1)	0.002	16.7 (6.25; 37.5)	0.2
Presence	20.0 (11.1; 35.6)		33.3 (12.5; 47.9)		42.9 (19.1; 57.1)		21.9 (12.5; 43.75)	
Sleeping disorders								
Absence	11.1 (2.2; 31.1)	0.005	25.0 (14.6; 41.7)	0.4	14.3 (9.5; 38.1)	0.002	14.6 (6.3; 31.3)	0.02
Presence	24.4 (13.3; 40.0)		33.3 (10.4; 47.9)		38.1 (19.1; 57.1)		22.9 (12.5; 47.9)	
Epilepsy								
Absence	15.6 (4.4; 33.3)	0.4	29.2 (16.7; 45.8)	0.3	23.8 (9.5; 47.6)	0.8	16.7 (8.3; 37.5)	0.3
Presence	22.2 (6.7; 40.0)		12.5 (8.3; 35.4)		23.8 (4.8; 57.1)		33.3 (8.3; 47.9)	
	<i>r</i> (Spearman) [†]	P value	<i>r</i> (Spearman)	P value	<i>r</i> (Spearman)	P value	<i>r</i> (Spearman)	P value
Symptom severity	0.52	.0001	0.32	0.001	0.50	.0001	0.54	.0001

Significant associations (P value < .05) are presented in bold.

^{*}IntQ = (Q25; Q75).

[†]*r* = Spearman's rank correlation.

Because challenging behavior and intellectual disability travel together

People with ID also tend to have more severe ASD symptoms and more health care needs

Table 1. Sample characteristics.

	Total sample	ASD with ID	ASD without ID	Group differences
	M (SD)/frequency	M (SD)/frequency	M (SD)/frequency	<i>p</i>
<i>n</i>	2177	394	1783	
Age	12.23 (3.31)	12.60 (3.35)	12.15 (3.30)	0.015
Gender				0.090
Male	79.51%	76.40%	80.20%	
Female	20.49%	23.60%	19.80%	
Race				0.228
White	77.45%	75.89%	77.79%	
Black	6.84%	8.38%	6.51%	
American Indian/Alaska Native	1.10%	1.78%	0.95%	
Asian	4.27%	5.08%	4.09%	
Native Hawaiian/Other Pacific Islander	0.23%	0%	0.28%	
Some other race	2.25%	2.79%	2.13%	
Two or more races	7.85%	6.09%	8.24%	
Family poverty ratio ^a	267.42 (128.42)	269.72 (127.99)	256.99 (129.96)	0.075
Single parent	16.99%	20.32%	16.26%	0.057
Autism symptom severity				<0.001
Mild	52.55%	21.34%	59.41%	
Moderate/severe	47.45%	78.66%	40.59%	
Past-year health care visit	89.06%	94.42%	87.88%	<0.001

ASD: autism spectrum disorder; ID: intellectual disability.

^aIncome of household as percentage of federal poverty level; variable imputed six times.

Table 1. Sample characteristics.

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Rates of ID in ASD range and vary by factors such as age

Supplemental Table 2. Percentage of children with co-occurring intellectual disability* among children aged 4 and 8 years with autism spectrum disorder, Early Autism and Developmental Disabilities Monitoring Network, 4 sites†, United States, 2010, 2012, and 2014

	2010		2012		2014		2010-2014 p-value for trend in % with ID
	Total No. with cognitive test scores (% of all children with ASD)	No. (%) with co-occurring ID	Total No. with cognitive test scores (% of all children with ASD)	No. (%) with co-occurring ID	Total No. with cognitive test scores (% of all children with ASD)	No. (%) with co-occurring ID	
Site							
Arizona							
Age 4	105 (85.4)	43 (41.0)	80 (62.5)	33 (41.3)	90 (69.2)	45 (50.0)	P=0.21
Age 8	145 (93.5)	47 (32.4)	150 (92.0)	32 (21.3)§	138 (86.2)	36 (26.1)§	P=0.22
New Jersey							
Age 4	291 (82.7)	143 (49.1)	337 (83.6)	149 (44.2)	418 (81.3)	189 (45.2)	P=0.34
Age 8	314 (77.7)	91 (29.0)§	329 (71.7)	96 (29.2)§	371 (72.3)	108 (29.1)§	P=0.97
North Carolina							
Age 4	¶	¶	¶	¶	142 (61.5)	64 (45.1)	**
Age 8	¶	¶	¶	¶	214 (87.3)	62 (29.0)§	**
Utah							
Age 4	97 (73.5)	40 (41.2)	¶	¶	¶	¶	**
Age 8	160 (84.2)	36 (22.5)§	¶	¶	¶	¶	**

Abbreviations: ASD = autism spectrum disorder; ID = intellectual disability

*defined as a score ≤ 70 on the most recent standardized intellectual ability test

†including sites for which at least 60% of children with autism spectrum disorder had intellectual ability test score data for at least one surveillance year

§Pearson chi-square $p < 0.01$ for comparison with children aged 4 years

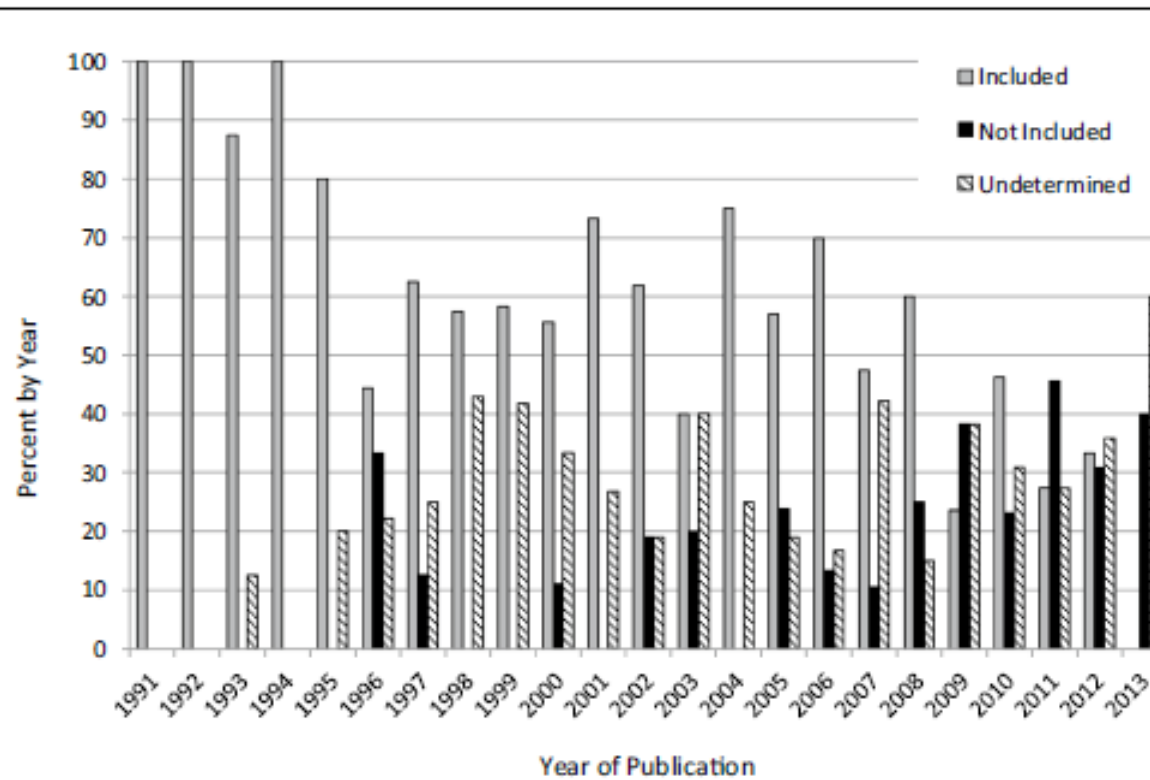
¶No or insufficient (<60% with intellectual ability test scores) data for site and surveillance year

** Trend not estimated for sites with less than three years of data

Christensen, et al. (2019). Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 4 Years - Early Autism and Developmental Disabilities Monitoring Network, Seven Sites, United States, 2010, 2012, and 2014. *MMWR Surveill Summ*, 68(2), 1-19. doi:10.15585/mmwr.ss6802a1

Trends in Autism treatment research: increasing exclusion of severely affected over time

Fig. 2 Inclusion of the severely affected ASD population in treatment studies over time

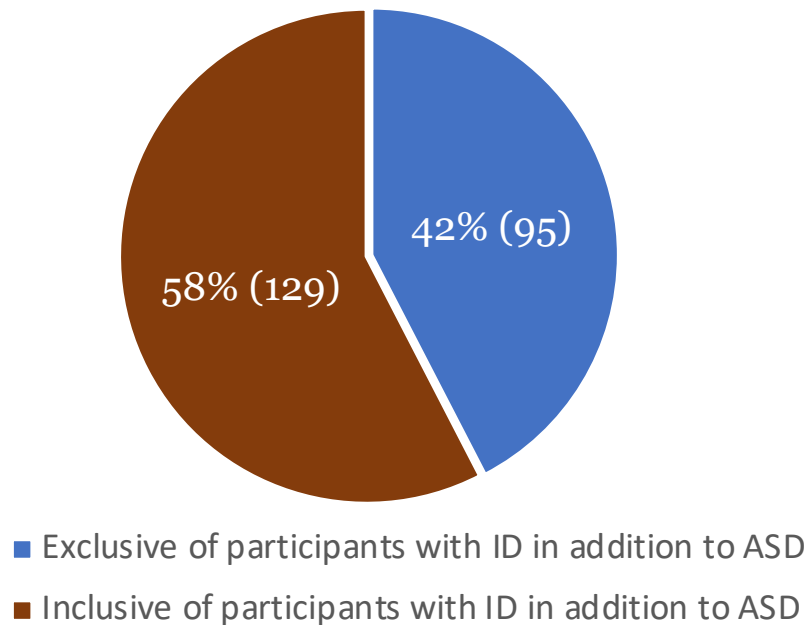


Stedman et al. 2019 (shown here) show trends for ASD treatment research; Jack & Pelphrey (2017) for neuroimaging research; Russell et al. (2019) for all ASD research

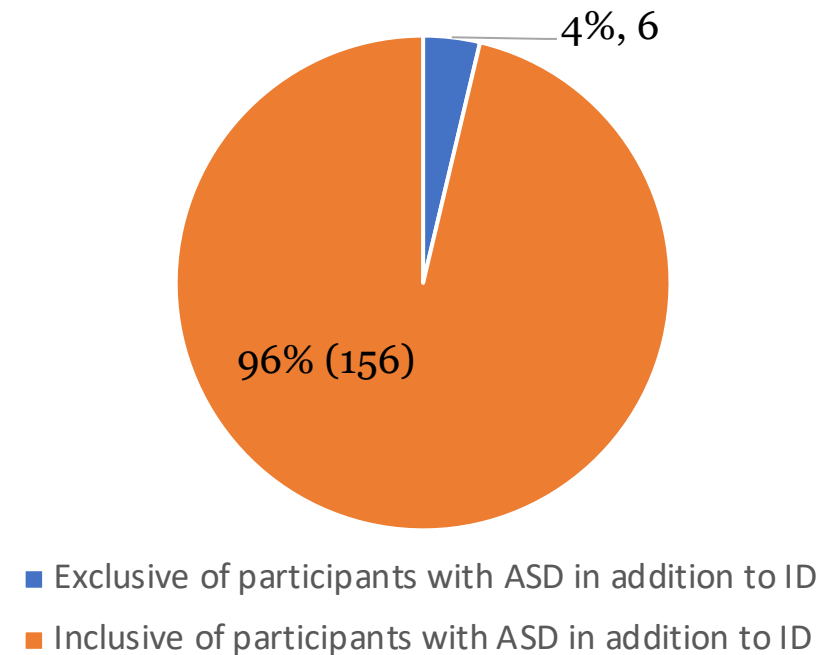
Current (2021) Representation of ID in Autism Spectrum Disorder (ASD) Research

- Up to 50% of individuals with ASD also have ID, but individuals with ID are routinely excluded from ASD research (Charman et al., 2011; Christensen et al., 2019; Loomes et al., 2017)

Recruitment Bias in ASD Studies



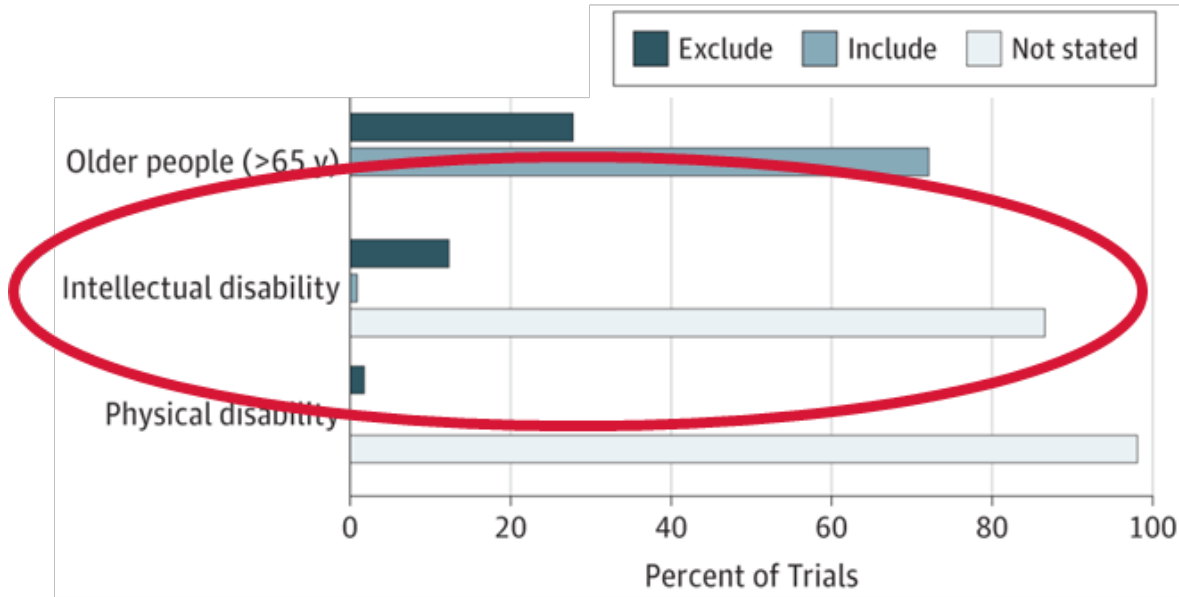
Recruitment Bias in ID Studies



This issue of excluding people with ID is not specific to autism research

From: **Improving Public Health Requires Inclusion of Underrepresented Populations in Research**

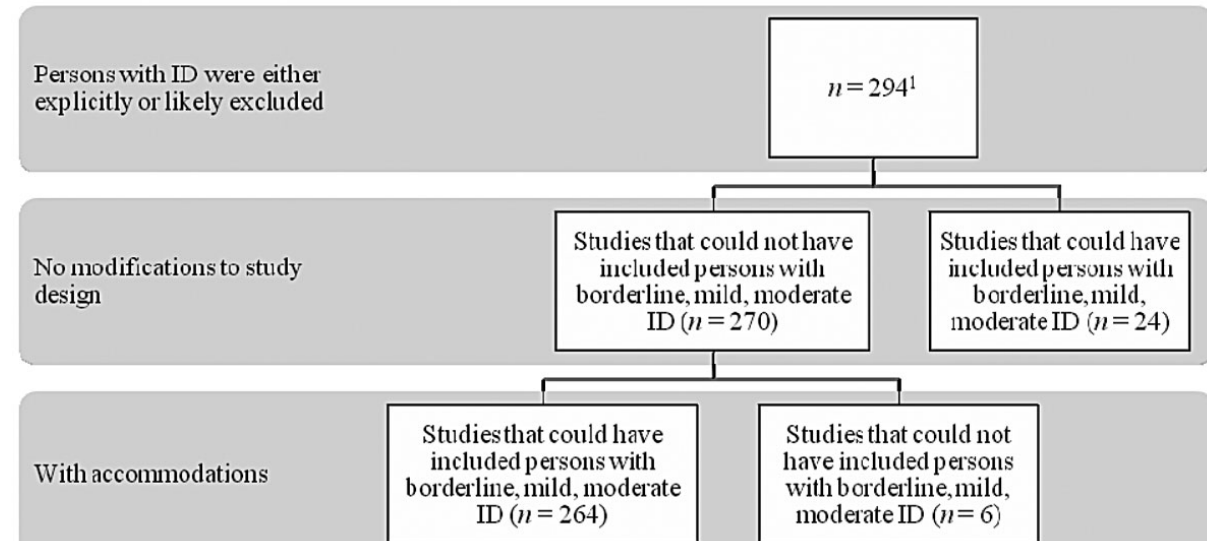
JAMA. 2018;319(4):337-338. doi:10.1001/jama.2017.19138



Open NIH-Funded Phase 3 and 4 Studies as of October 19, 2017. Clinicaltrials.gov records (N=338) were reviewed. Majority of trials did not address whether ID included.

From: **Where are persons with intellectual disabilities in medical research?**

JIDR. 2014;58(9):800-809. doi:10.1111/jir.12091



From $n = 300$ studies in top-tier medical journals between 2007-2011, only 2% explicitly included persons with ID. With minor accommodations, people with ID could have participated in 70% of the studies.

Scientific consequences of exclusion from mental health research

- Parallel exclusion of people with very high IQ not common
- Lack of generalizability to population with low IQ
- May limit understanding of psychiatric and medical comorbidities within conditions under study, if the subset with high rate of comorbidity excluded
- Difficult to accurately assess role of IQ (or adaptive behavior) in disorder under study, given restricted range of IQ

Psychological Medicine

[cambridge.org/psm](https://www.cambridge.org/psm)

Original Article

Neurocognition and adaptive functioning in a genetic high risk model of schizophrenia

A. M. Fiksinski^{1,2,3}, E. J. Breetvelt^{2,3}, Y. J. Lee², E. Boot^{2,3}, N. Butcher^{2,3}, L. Palmer³,
E. W. C. Chow^{2,4}, R. S. Kahn^{1,5}, J. A. S. Vorstman^{1,4,6,7} and A. S. Bassett^{2,3,4,8,9}

Inclusion criteria were (1) molecularly confirmed 22q11.2 deletion using standard methods ... (2) completion of a comprehensive battery of neurocognitive tests ... and (3) the absence of moderate or more severe intellectual disability (i.e. FSIQ <54)

Stigma and ID: From Exclusionary to Inclusionary Research

- Variety of reasons cited for excluding individuals with ID from developmental disabilities research:

Theoretical

- Heterogeneity in study sample → limited understanding of pathophysiology (Farmer & Thurm, 2021)

Methodological

- Current outcome measures have limited reliability, validity, and sensitivity to change for individuals with ID (Farmer & Thurm, 2021; Farmer et al., 2020; Kelleher & Wheeler, 2020)

Practical

- Feasibility
- Behavioral, linguistic, cognitive, and attentional demands (Farmer & Thurm, 2021)

Other reasons people with ID excluded from mental health research?

- Concern about consent process
- Not available for convenience sampling (e.g., school-based sample doesn't include children living in residential facility)
- Study methodology not appropriate or available for people with ID – this trend seems to be increasing specifically for ASD research as well

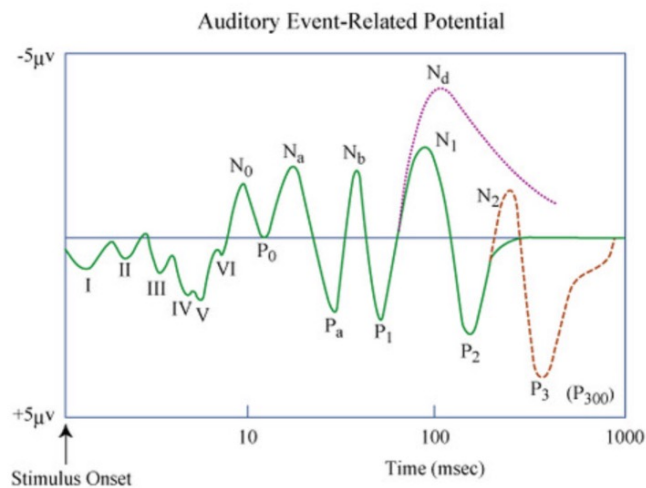
Future Directions: Inclusive Research Design



- Participatory action research strategies can facilitate the involvement of individuals with ID in biomedical research to ensure it is relevant and beneficial (Werner & Roth, 2014)
- Together, stakeholders in the community and biomedical researchers can work to ensure:
 - Current research endeavors are relevant to individuals with ID
 - Research acts in the interests of individuals with ID
 - Research is collaborative

Future Directions: Measurement Development and improvements in scoring/psychometrics

- Future research warranted to develop objective biomarkers, such as event-related potentials (Ethridge et al., 2020; Key et al., 2020), and targeted instruments, such as the Communication Complexity Scale (Brady et al., 2020), for IDD populations



Development of the Communication Complexity Scale

Nancy C. Brady ✉, Kandace Fleming, Kathy Thiemann-Bourque, Lesley Olswang, Patricia Dowden,

Muriel D. Saunders and Janet Marquis

[https://doi.org/10.1044/1058-0360\(2011/10-0099\)](https://doi.org/10.1044/1058-0360(2011/10-0099))

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Barriers to Inclusion of Individuals with Destructive Behavior in Research

Nathan Call, PhD, BCBA-D

Professor of Pediatrics, Emory University School of Medicine

Clinical Director, Marcus Autism Center



Barriers to Inclusion of Individuals with Destructive Behavior in Research

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Professor of Pediatrics, Emory University School of Medicine
Clinical Director, Marcus Autism Center



Destructive Behavior and ASD Research

- Presence of destructive behavior (e.g., aggression, self-injury) has typically been an exclusionary criterion in research on ASD
 - **Scientific rationale:** considered to represent outliers
 - **Practical rationale:** few sites possess the expertise or resources to work with individuals who engage in extreme forms of destructive behavior



Important but unaccounted for sources of variability

- Many studies that have specifically targeted destructive behavior have treated autistic individuals with destructive behavior as a homogenous group.
- There are reasons to believe that distinct subtypes exist, particularly around the function the destructive behavior serves for the individual
- Likely different mechanisms and outcomes for each subtype



Barriers to Inclusion of Individuals with Destructive Behavior in Research

Nathan Call, PhD, BCBA-D
Professor of Pediatrics, Emory University School of Medicine
Clinical Director, Marcus Autism Center



Click to add notes

Henry Roane, PhD, Upstate Medical University Professor of Pediatrics, Division Chief of Center for Behavior, Development, and Genetics. Co-author of more than 100 research articles and chapters as well as several academic texts on the assessment and treatment of behavior disorders in children with autism and related disorders.

Mental Health Parity

- **Judith Ursitti**, Vice President of Community Affairs, Council of Autism Service Providers



Thought Leadership Summit Challenging Behaviors: Objectives and Outcomes

Donna S Murray PhD CCC-SLP

VP Clinical Programs, Autism Speaks

Adjunct Professor Clinical Pediatrics, Cincinnati Children's Hospital Medical Center

University of Cincinnati, School of Medicine



Thought Leadership Summit Challenging Behaviors: Objectives and Outcomes

The Leadership Thought Summit was held on Dec. 3 & 4th 2020 with approximately 65 invited attendees representing various stakeholders and experts in the field

Outcome workgroups met during 2021 and summation document will be available 2022

Co-Chairs: Matt Seigel MD and Henry Roane PhD

Objective: Characterize the landscape of services and supports for people with autism with severe behavior challenges. Using the landscape as a starting point, the summit aimed to catalyze innovations in programs and policies to improve systems of care.

Output: The summit participants helped structure information regarding

- (a) what we know and what we need to know;
- (b) challenges and barriers to creating systems of care and specialized programs, and
- (c) what needs to happen to improve the systems of care for people across the autism spectrum with challenging behaviors.



Thought Leadership Summit Challenging Behaviors: Objectives and Outcomes

Follow-up groups of national experts worked to produce four primary documents

1. A prioritized needs assessment for advocacy to guide the development of a strategic plan for policy change.
2. A prioritized needs assessment for science to guide the development of a strategic plan for future research.
3. A roadmap, that include resources for families/caregivers to assist in navigating the system of care (family and provider co-led).
4. A summative document that provides guidance for administrators and clinicians, on how to develop, improve, and replicate programs and services that form comprehensive systems of care for people with ASD impacted by challenging behaviors.



Identified Research and Advocacy Priorities

Research

- Systematic Framework/Model for Screening and Assessment
- More Extensive Research into Evidence Based Practices
- Training Modalities
- Restrictive Interventions/safety
- Outcome Measures
- Person-Centered vs. FA Approach to Care
- Multi-site randomized controlled group trial of a protocolized assessment and treatment intervention
- Comparative effectiveness research on complex real world treatment packages
- Research on the physiologic and other potential biological underpinnings (mechanisms)

Advocacy

- Reimbursement from Third Party Payors
- Trained and Qualified Professionals
- Educational Services
- Environmental Supports
- Interagency/Interprofessional Communication Strategies
- Requirement and funding for community homes staffed to support individuals with high behavioral needs
- Licensure for behavior analysts in all 50 states, to allow Medicaid reimbursement.
- Funding needs across agencies
- Crisis Management

Research Planning Grant Awards-Behavior Challenges



Wayne Fisher,
Ph.D., BCBA-D,
Robert Wood
Johnson Medical
School



Matthew Siegel,
MD, Maine
Behavioral
Healthcare

Rutgers University

Project: *Developing a randomized controlled trial (RCT) for assessing and treating significant challenging behavior in persons with autism.*

This research project aims to make behavioral interventions more accessible by creating a new framework for the assessment and treatment of challenging behaviors. This new model will be flexible enough to address individual needs while being standardized enough to fit a range of treatment settings. With this funding, researchers will collect preliminary data about the model and use it to develop a plan for a full RCT that tests its effectiveness.



Henry Roane,
Ph.D., Upstate
Medical
University



Eric M. Butter,
Ph.D., Nationwide
Children's
Hospital

University of Nebraska Medical Center

Project: *Developing a Decision-Making Clinical Manual for Assessment and Treatment of Challenging Behavior*

This project aims to fill a need by developing a decision-making manual that guides clinicians and service providers through the best practices they need to effectively assess and treat severe challenging behaviors. This manual will be in the form of both a written and video database and will decrease barriers to access while giving people with autism more choice over their treatment options. Once the manual is built, researchers will gather preliminary data on its feasibility, efficacy and user experience. They will then pilot the manual with families served in the Severe Behavior Department at the Munroe-Meyer Institute and will modify the manual based on the data. Finally, researchers will design a plan for a multi-site RCT in severe behavior programs nationwide.



Amanda N. Zangrillo, PsyD, BCBA-D, University of Nebraska
Medical Center



Tara A. Fahmie, PhD, BCBA-D, University of Nebraska
Medical Center

DISCUSSION

- OUTCOMES AND NEXT STEPS
- JOIN THE CONVERSATION