Center for Autism and Related Disorders
at Kennedy Krieger Institute

JOHNS HOPKINS
MEDICINE

An Update on Diagnosis and Treatment of Autism Spectrum Disorder

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Disclosures

COI: Receiving part of the KKI salary from a study project funded by PCORI

"Off-label" or non-FDA approved uses of some medications are mentioned to reflect common clinical practice.

Will not discuss complementary and alternative treatments

Use generic names of the medications mentioned.

No confidential patient information will be mentioned

Objectives

- Improve skills in identification of neurodevelopmental, language and social emotional delays.
- Promote optimal development through developmental screening and surveillance.
- Gain a greater understanding of strategies/medications that can help with common challenges associated with autism.

Structure of the Talk

1. Introduction and background information
2. Diagnostic criteria
3. Screening and surveillance
4. Evaluating ASD and co-occurring conditions
5. Concept of and prevalence of comorbidity in ASD
6. Overview of treatments
7. Treatment of selected co-occurring conditions
8. Selected medication and other biological treatments.
9. Mental health crisis
10. Inpatient hospitalization

The mysteries remain,
I keep the same
cycle of seed-time
and of sun and rain..

Hilda Dolittle

Definition of Autism Spectrum Disorder

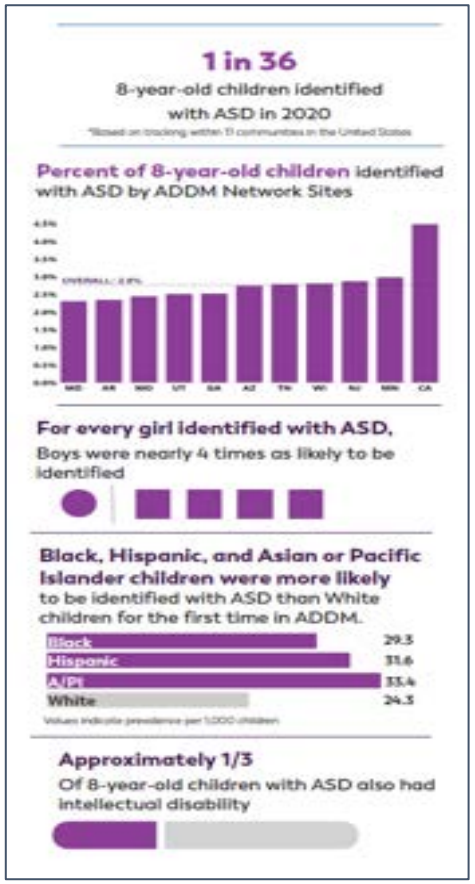
Autism spectrum disorder ("ASD" or "autism") is a **complex neurodevelopmental disorder** (with marked **heterogeneity**) characterized by **2 core features**:

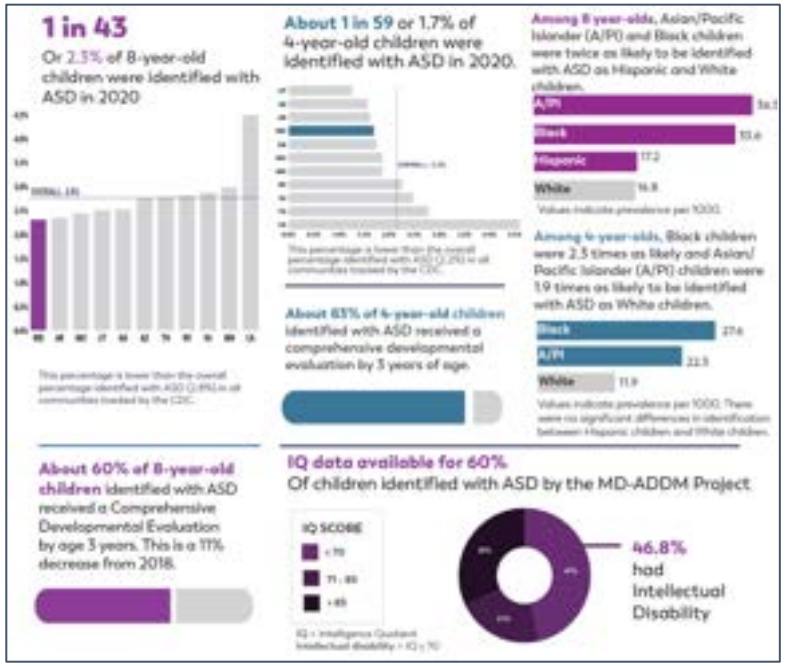
- Persistent deficits in **social communication** across multiple contexts.
- **Restricted and repetitive** patterns of behaviors, interests and activities.

Adapted from DSM-5, APA 2013

Prevalence

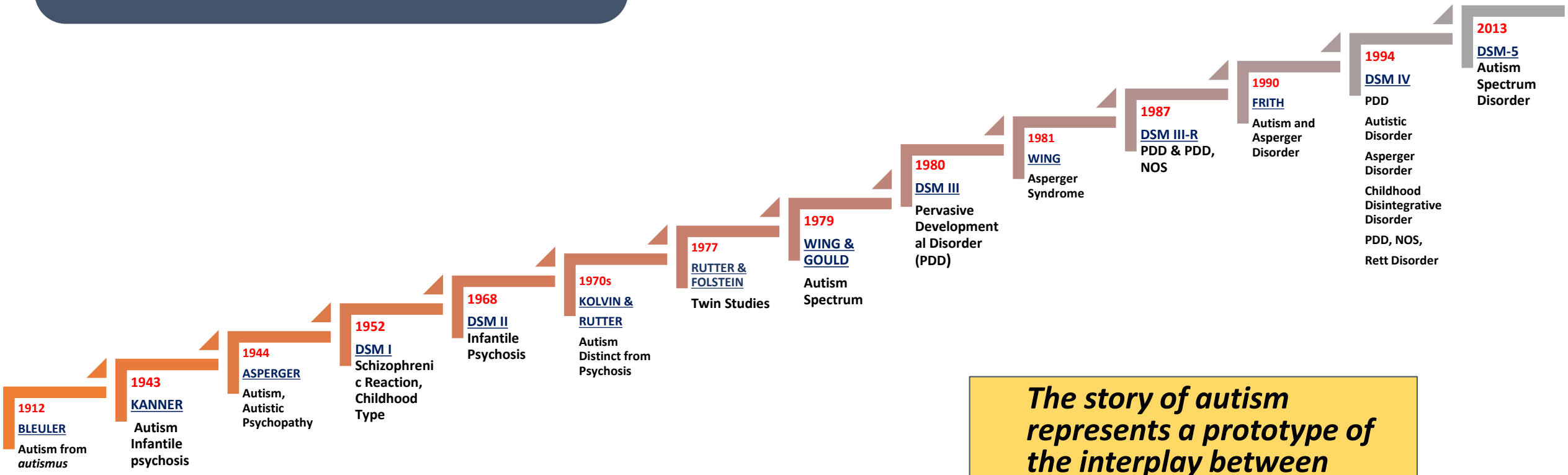
- Worldwide prevalence is **1 in 100** (WHO; Zeidan et al, 2020)
- About **1 in 36** children has been identified with autism spectrum disorder (ASD) according to estimates from CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network.
- ASD is reported to occur in all racial, ethnic, and socioeconomic groups.
- ASD is nearly 4 times more common among boys than among girls.
- About 1 in 6 (17%) children aged 3–17 years were diagnosed with a developmental disability, as reported by parents, during a study period of 2009-2017.





CDC, 2020

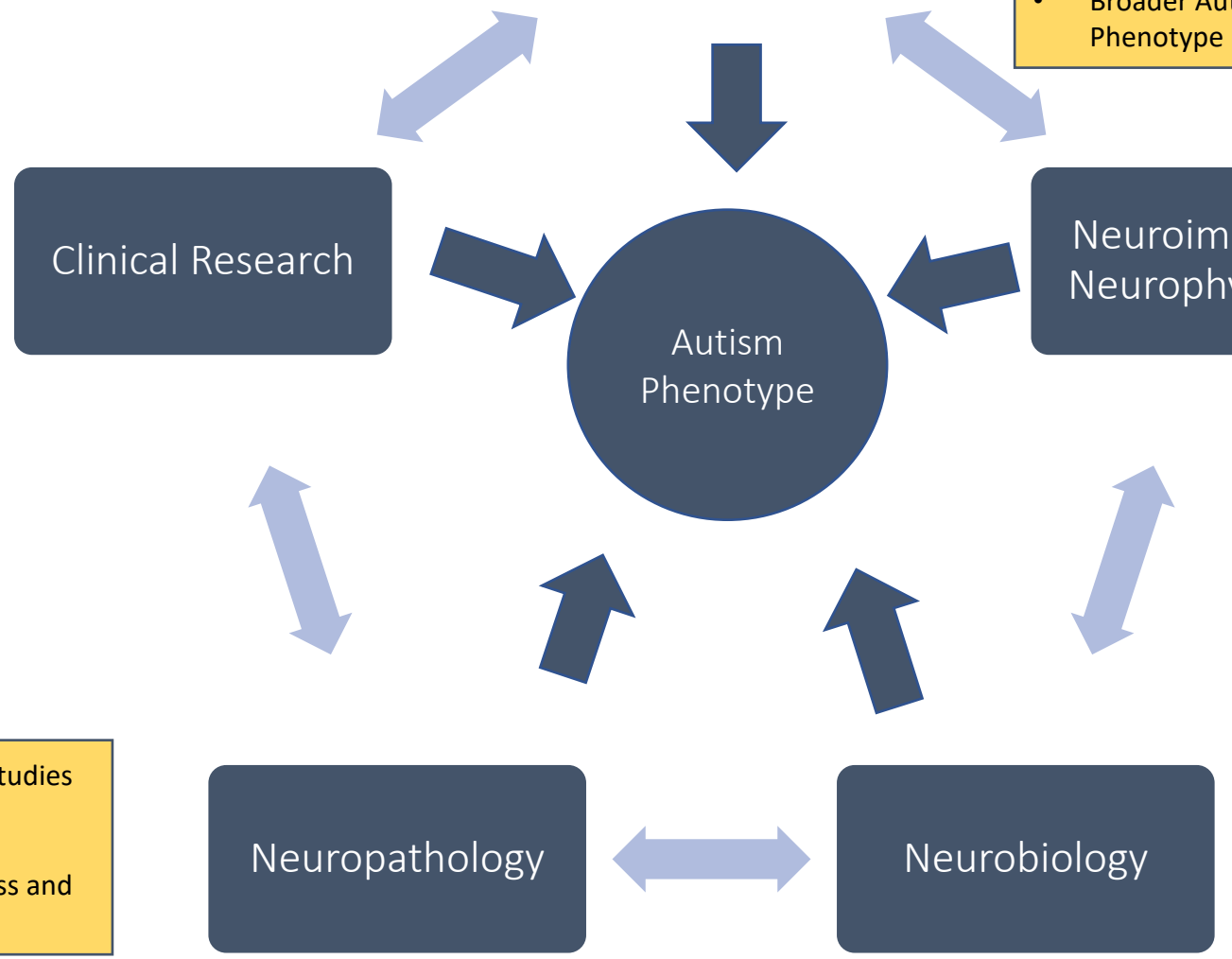
Conceptual Evolution of Autism



The story of autism represents a prototype of the interplay between clinical and scientific progress in the field of child psychiatry in the 20th century.

Sir Michael Rutter

Converging Evidence has Informed the Current Understanding of ASD



- Twin Studies
- Familial recurrence
- Neurogenetic Syndromes with autistic features
- Chromosomal hotspots
- Broader Autism Phenotype

- Nosology
- Delineation of co-occurring conditions from core features
- Early Intervention research
- Treatment research

- Overgrowth and other structural abnormalities.
- Dissociation of cortical and subcortical GM growth
- Altered functional connectivity
- Structural alterations in white matter pathways.
- EEG abnormalities

- Post-mortem studies
- Minicolumnar abnormalities
- Purkinje cell loss and dysfunction

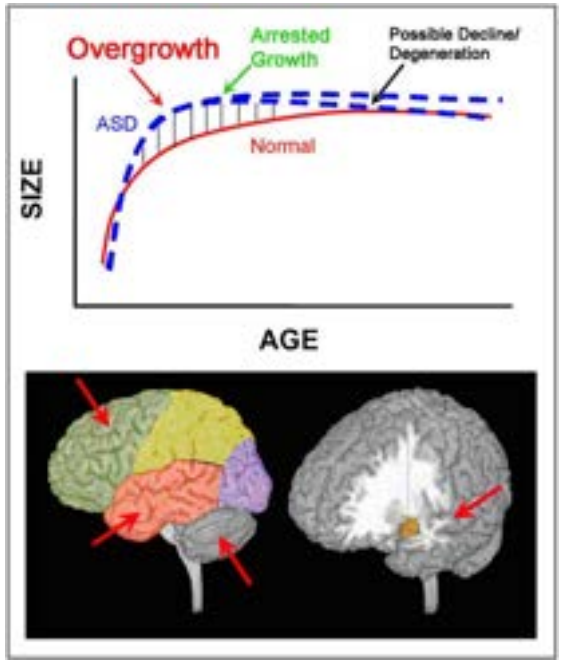
- Altered cytostructure
- Synaptogenesis and pruning
- Signaling pathways
- Neuronal migration
- Neurotransmitter research
- Excitatory Inhibitory imbalance

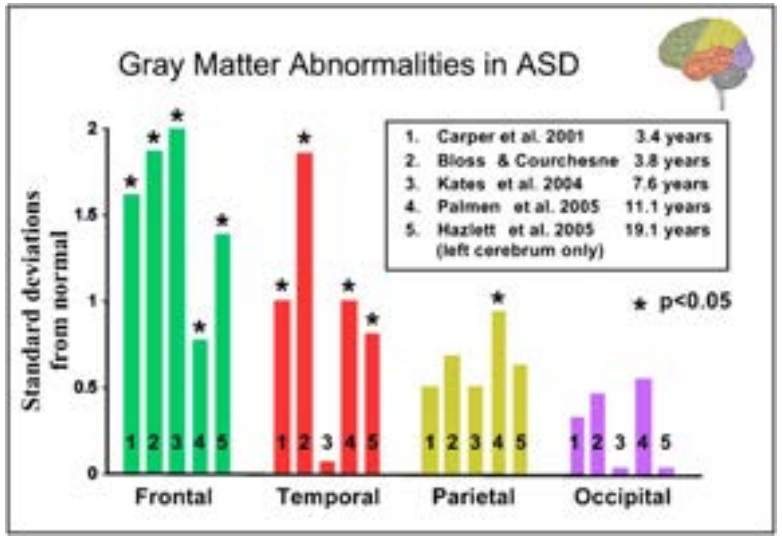
Trajectory of Brain Growth in ASD

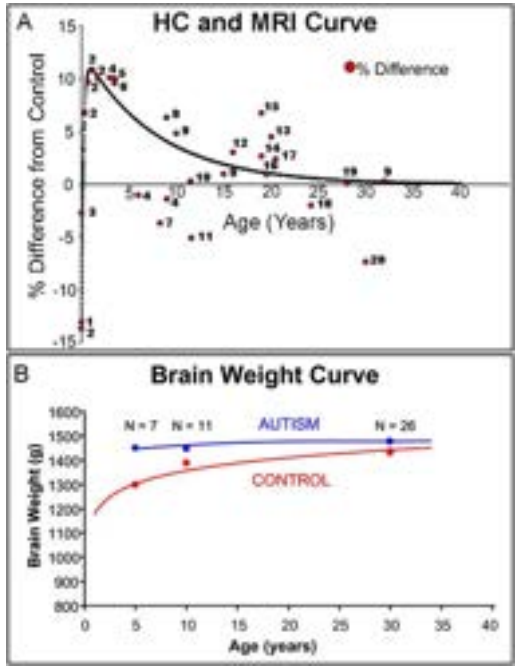
Brain growth across the life span in autism: Age-specific changes in anatomical pathology

Eric Courchesne, Kathleen Campbell, Stephanie Solso*

BRAIN RESEARCH 1380 (2011) 138–145







- Frontotemporal enlargement
- Disorder of association cortices
- TBV, SA, CT have dissociable inheritance

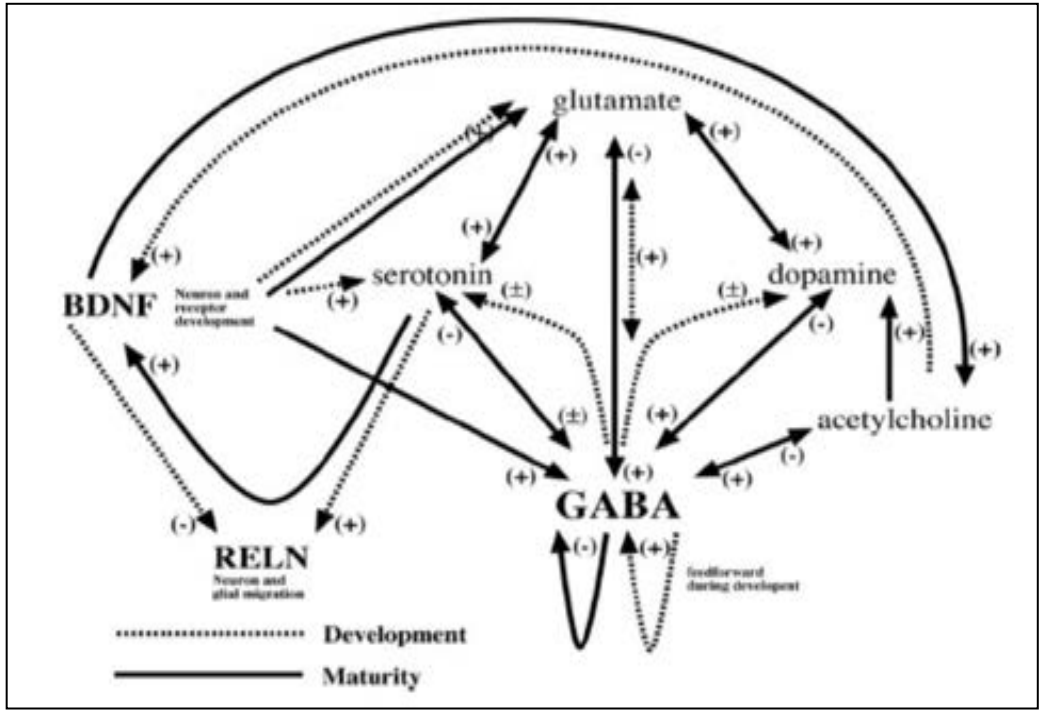
Courchesne, 2011

Neurotransmitters and Neuromodulators

- **Serotonin (most evidence)**
- Dopamine
- Noradrenaline
- Acetylcholine
- Glutamate & GABA (E:I imbalance)
- Endogenous Opioids

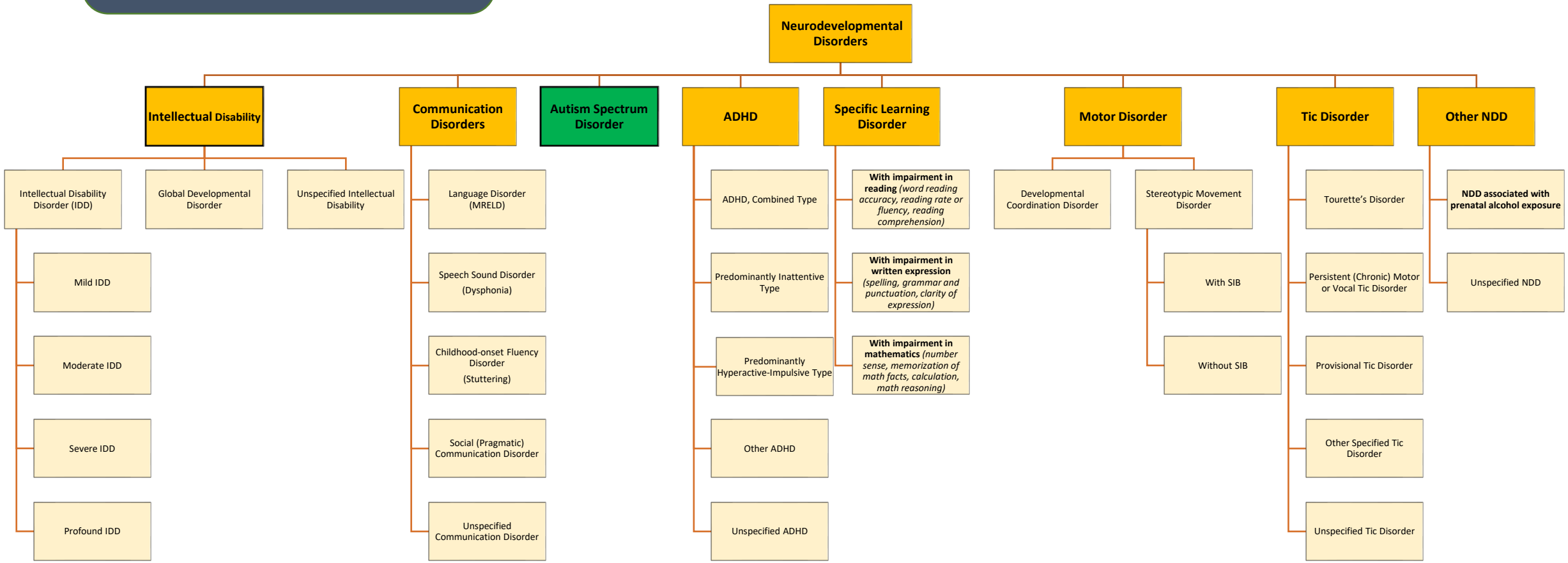
Lam et al, 2006

- Complex interplay between **genes and the environment** with various genes activated at different ages.
- Various processes (for example synaptogenesis, pruning, neural migration and signaling and other neural pathways) **may be affected**
- **Neurotransmitters in the developing brain** themselves that facilitate or block communication in these pathways can interact in complex ways.
- **Psychotropic medications enhance or reduce** this communication**.**



Bethea and Sikich, 2007

DSM-5 Neurodevelopmental Disorders



DSM-5, APA, 2013

DSM-5 Autism Spectrum Disorder (Criterion A): All Present

Persistent deficits in social communication and social interaction across multiple contexts

Deficits in social-emotional reciprocity

- **Abnormal social approach**
- **Failure of normal back-and-forth conversation**
- **Reduced sharing of interests, emotions, or affect**
- **Failure to initiate or respond to social interactions.**

Deficits in nonverbal communicative behaviors used for social interaction

- **Poorly integrated verbal and nonverbal communication**
- **Abnormalities in eye contact and body language or deficits in understanding and use of gestures**
- **A total lack of facial expressions and nonverbal communication**

Deficits in developing, maintaining, and understanding relationships.

- **Difficulties adjusting behavior to suit various social contexts**
- **Difficulties in sharing imaginative play or in making friends**
- **Absence of interest in peers.**

DSM-5, APA, 2013

DSM-5 Autism Spectrum Disorder (Criterion B): 2 out of 4 Present

Restricted, repetitive patterns of behavior, interests, or activities

Stereotyped or repetitive motor movements, use of objects, or speech	Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior	Highly restricted, fixated interests that are abnormal in intensity or focus	Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment
Simple motor stereotypies Lining up toys Flipping objects Echolalia Idiosyncratic phrases	Extreme distress at small changes Difficulties with transitions Rigid thinking patterns Greeting rituals Need to take same route or eat same food every day	Strong attachment to or preoccupation with unusual objects Excessively circumscribed or perseverative interests	Apparent indifference to pain/temperature, Adverse response to specific sounds or textures, Excessive smelling or touching of objects, Visual fascination with lights or movement (“Stimming”)

DSM-5, APA, 2013

DSM-5 Autism Spectrum Disorder: Diagnostic Specifiers

Severity

- **Level 1** (mild, support needed), **level 2** (moderate, substantial support) and **level 3** (severe, very substantial support).
- Based on social communication impairments and restricted, repetitive patterns of behavior

Onset

- Symptoms **must be present in the early developmental period** (but **may not become fully manifest until social demands exceed limited capacities** or may be **masked by learned strategies** in later life).

Impairment

- Symptoms cause **clinically significant impairment** in social, occupational, or other important areas of current functioning.

Exclusions

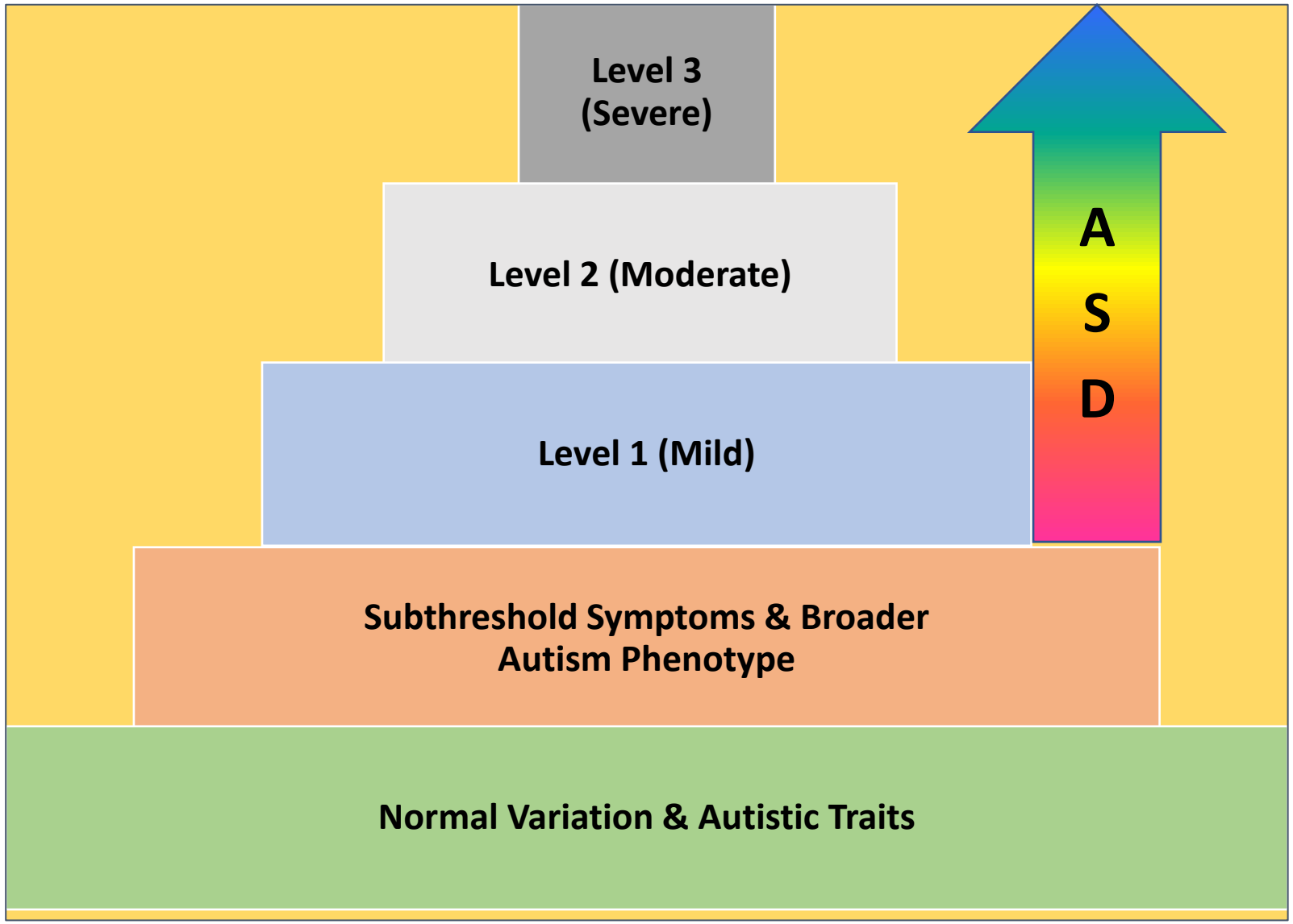
- These disturbances are not better explained by **intellectual disability** or **global developmental delay**

Associations

- With or without accompanying ***intellectual impairment***
- With or without accompanying ***language impairment***
- Associated with a known ***medical or genetic condition or environmental factor***
- Associated with another ***neurodevelopmental, mental, or behavioral disorder***
- With ***catatonia***

DSM-5, APA, 2013

Continuum of Autism Spectrum



Patterns of "Onset" in Autism

MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS 10:139-143 (2004)

DEVELOPMENTAL REGRESSION IN AUTISM SPECTRUM DISORDERS

Sally J. Rogers*
University of California, Davis Medical Center, M.I.N.D. Institute, Davis, California

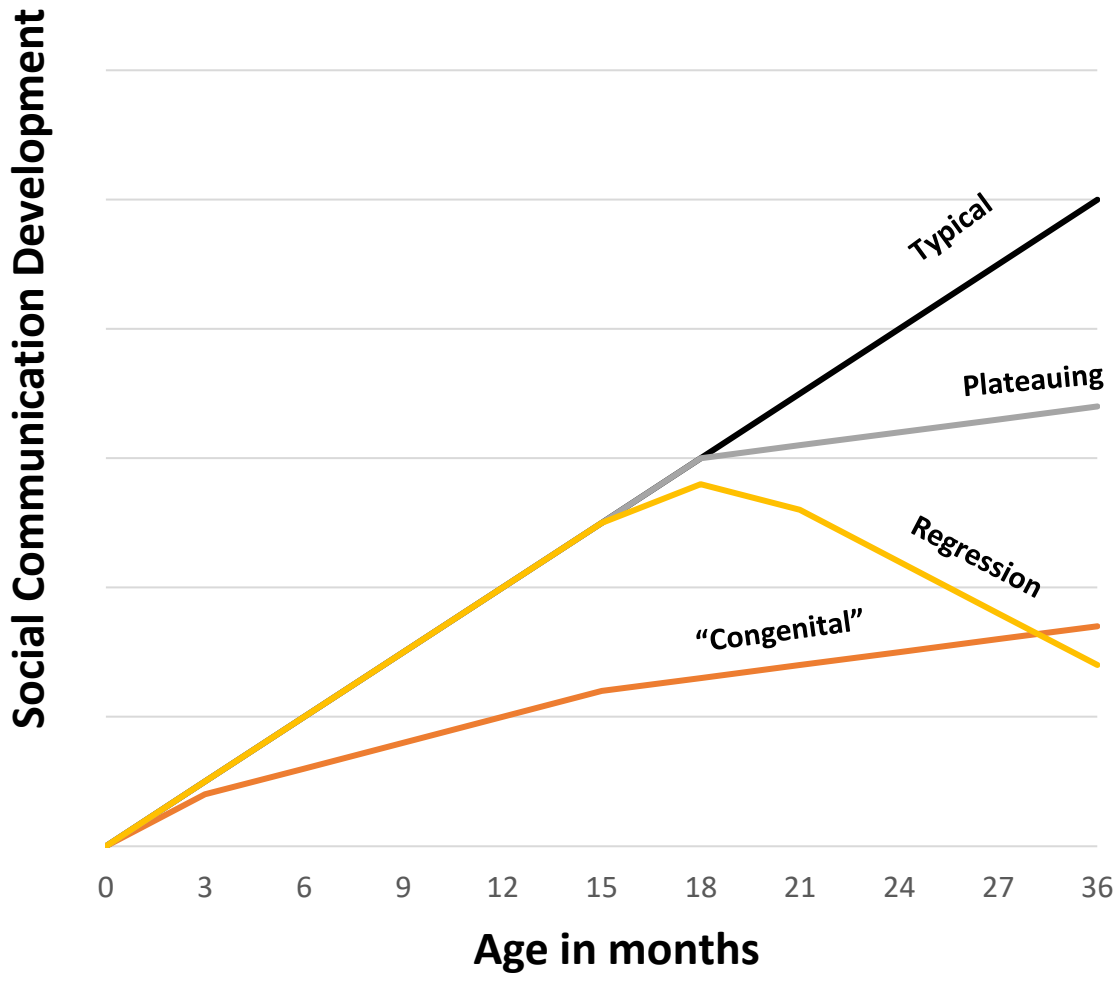


Figure Based upon Rogers' 2004 review.

Symptoms present from birth ("Congenital")

- **May reflect differences in temperament/regulation**

Early milestone achievement followed by a developmental plateau (Plateauing)

- **Babbling not progressing to speech,**
- **Social interests not developing into social interactions, social games or imitation.**

Clear loss of previously acquired skills (True regression)

- **Occurs after a period of typical development.**
- **Should get an EEG**

ASD Screening and Surveillance

American Academy of Pediatrics

Identification, Evaluation, and Management of Children With Autism Spectrum Disorder

Developmental and behavioral screening for all children

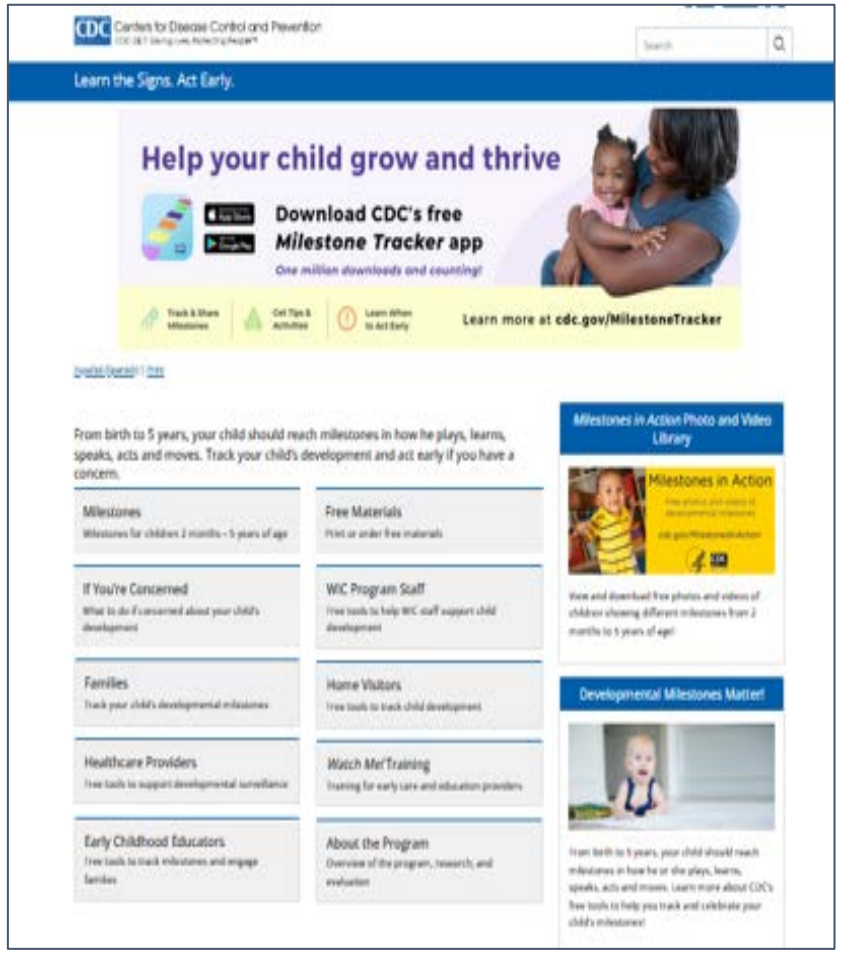
- During regular **well-child visits** at **9 months, 18 months and 30 months**
- May identify delays in motor, language and cognitive delays, not social

Monitor all children for ASD

- **Developmental surveillance at all visits**
- Standardized **parent reported autism specific screening** tests at **18 and 24 months** of age in their primary care visits.
- Red flags
- Asking caregivers for any concerns about development or behavior.
- "**Learn the Signs. Act Early**" (CDC Website)

Diagnostic Evaluation

- At risk children
- Early intervention services
- Cognitive and language testing.
- Usually, diagnosis made by a specialist but can be made by primary care providers if they are comfortable with it.



Hyman, Levy et al, AAP, 2020

Red Flags for ASD

TABLE 4 Red Flags: Early Symptoms of ASD

	Symptom
By 12 months	• Does not respond to name
By 14 months	• Does not point at objects to show interest
By 18 months	• Does not pretend play
General	• Avoids eye contact and may want to be alone
	• Has trouble understanding other people's feelings or talking about their own feelings
	• Has delayed speech and language skills
	• Repeats words or phrases over and over (echolalia)
	• Gives unrelated answers to questions
	• Gets upset by minor changes
	• Has obsessive interests
	• Makes repetitive movements like flapping hands, rocking, or spinning in circles
	• Has unusual reactions to the way things sound, smell, taste, look, or feel

Information from this table is adapted from http://www.cdc.gov/ncbddd/autism/signs.html.

Hyman, Levy, Myers, et al, AAP 2020

6-12 Month-Olds

- **Infrequent or no babbling**
- **Lack of eye contact or smile**
- **No interest in looking at faces**
- **Unusual, high-pitched squeals**

9-24 Month-Olds

- **ANY signs of regression**
- **Infrequent response to social interactions**
- **Decreased eye contact**
- **Limited facial expressions**
- **Inconsistent response to name (in absence of hearing loss)**
- **No words by 16 months or no 2-word phrases by 24 months**
- **Uses other person's hand as a tool**
- **Limited use of gestures (especially pointing)**
- **Doesn't easily learn simple new interactive routines**
- **Echoing what others say without regular spontaneous speech**
- **Overly attached to unusual objects**
- **Repetitive or odd play or other behavior**
- **Odd sensory interests (fans, lights, spinning)**
- **Insistence on sameness; resistance to change**

Rebecca Landa, Ph.D.
https://pathfindersforautism.org/articles/treatments-therapies/red-flags-early-signs-of-autism-spectrum-disorders/

AACAP Practice Parameter Recommends ASD Screening, Diagnosis and Treatment

Practice Parameter for the Assessment and Treatment of Children and Adolescents With Autism Spectrum Disorder

Fred Volkmar, MD, Matthew Siegel, MD, Marc Woodbury-Smith, MD, Bryan King, MD, James McCracken, MD, Matthew State, MD, PhD, and the American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI)

Journal of the American Academy of Child & Adolescent Psychiatry
VOLUME 53 NUMBER 2 FEBRUARY 2014

Recommendation 1. The developmental assessment of young children and the psychiatric assessment of all children should routinely include questions about ASD symptomatology [CS].

Recommendation 2. If the screening indicates significant ASD symptomatology, a thorough diagnostic evaluation should be performed to determine the presence of ASD [CS].

Recommendation 3. Clinicians should coordinate an appropriate multidisciplinary assessment of children with ASD [CS].

Recommendation 4. The clinician should help the family obtain appropriate, evidence-based, and structured educational and behavioral interventions for children with ASD [CS].

Recommendation 5. Pharmacotherapy may be offered to children with ASD when there is a specific target symptom or comorbid condition [CG]

Recommendation 6. The clinician should maintain an active role in long-term treatment planning and family support and support of the individual [CG].

Recommendation 7. Clinicians should specifically inquire about the use of alternative/complementary treatments and be prepared to discuss their risk and potential benefits [CS].

CS: Clinical Standard
CG: Clinical Guidance

Screening and Diagnostic Scales

Practice Parameter for the Assessment and Treatment of Children and Adolescents With Autism Spectrum Disorder

Fred Volkmar, MD, Matthew Siegel, MD, Marc Woodbury-Smith, MD, Bryan King, MD, James McCracken, MD, Matthew State, MD, PhD, and the American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI)

Journal of the American Academy of Child & Adolescent Psychiatry
VOLUME 53 NUMBER 2 FEBRUARY 2014

TABLE 1 Summary of Selected Assessment Instruments for Autism Spectrum Disorder[a]

Scale (see legend)	Uses	Age Range	Method of Administration	Population Studied	Scale characteristics	Reference
ABC	screening	children	parent rated	AD	57 items, scale 1-4	Krug *et al.*, 1980[43]
CARS	screening	children	clinician rated	AD	15 items, scale 1-4	Schopler *et al.*, 1980[44]
M-CHAT-2	screening	toddlers	parent rated	AD	23 items, yes/no	Robins *et al.*, 2001[45]
CSBS-DP-IT-Checklist	screening	toddlers	parent rated	AD	24 items	Wetherby *et al.*, 2008[46]
ASQ	screening	child/adult	parent rated	AD/AspD	40 items, yes/no	Berument *et al.*, 1999[47]
AQ	screening	child/adult	self or parent rated	AspD	50 items, scale 0-3	Baron-Cohen *et al.*, 2001[48]
CAST	screening	4-11 years	parent rated	AspD	37 items, yes/no	Scott *et al.*, 2002[49]
ASDS	screening	5-18 years	parent or teacher rated	AspD	50 items, yes/no	Myles *et al.*, 2000[50]
GADS	screening	3-22 years	parent or teacher rated	AspD	32 items, scale 0-3	Gilliam, 2001[51]
ASDI	screening	child/adult	interview + clinician rated	AspD	50 items, yes/no	Gillberg *et al.*, 2001[52]
SRS	screening	4-18 years	parent or teacher rated	AspD	65 items, scale 1-4	Constantino *et al.*, 2003[53]
ADI-R	diagnostic	child/adult	interview + clinician rated	AD/AspD	see text	Lord *et al.*, 2003[54]
DISCO	diagnostic	child/adult	interview + clinician rated	AD/AspD	see text	Wing *et al.*, 2002[55]
ADOS-2	diagnostic	child/adult	semi-structured interactive session	AD/AspD	see text	Lord *et al.*, ~~1994~~[56] 2012

Note: ABC = Autism Behavior Checklist; AD = autism disorder; ADI = Autism Diagnostic Interview—Revised; ADOS = Autism Diagnostic Observation Schedule; AQ = Autism Quotient; ASDI = Asperger Syndrome Diagnostic Interview; ASDS = Asperger Syndrome Diagnostic Scale; AspD = Asperger's disorder; ASQ = Autism Screening Questionnaire; CARS = Childhood Autism Rating Scale; CAST = Childhood Autism Screening Test; M-CHAT = Checklist for Autism in Toddlers; CSBS-DP-ITChecklist = Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist; DISCO = Diagnostic Interview for Social and Communication Disorders; GADS = Gilliam Asperger's Disorder Scale; Parent = primary caregiver; SRS = Social Responsiveness Scales.

[a]Note that these instruments may need to be revised to provide evidence of validity for DSM-5 ASD and supplement but DO NOT REPLACE clinical diagnosis.

JAACAP Practice Parameters for ASD, 2014

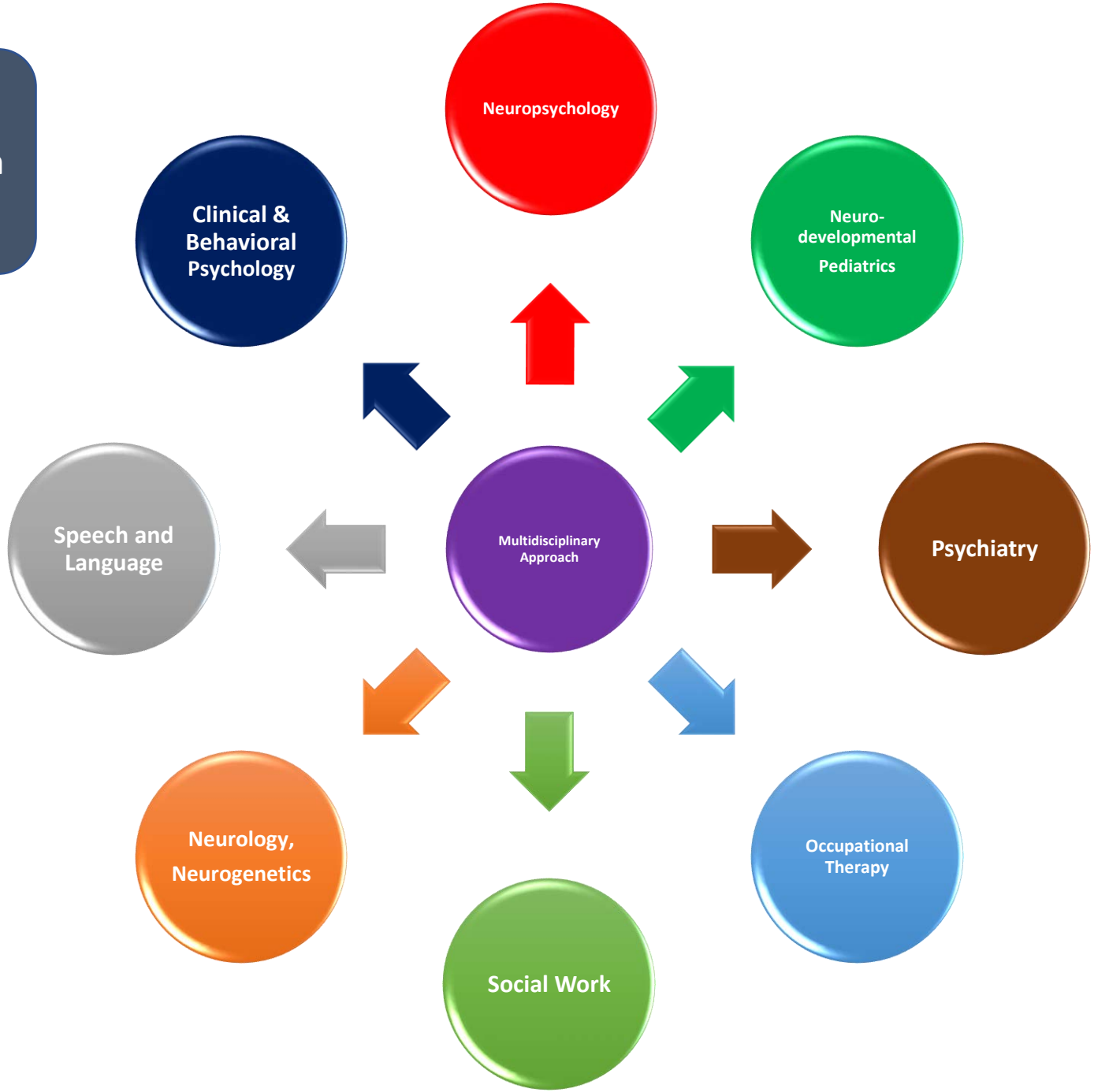
Autism Diagnostic Interview-Revised
(Michael Rutter, Ann LeCouteur, and Catherine Lord), 2003

- Parent report of developmental history of autistic features
- Useful for **diagnosing autism**, **planning treatment**, and **distinguishing autism from other developmental disorders**
- Provides categorical results for three domains**:** **Language/Communication**, **Reciprocal Social Interactions, and Repetitive Behaviors/Interests**
- Standardized interview and response coding
- 90–150 minutes to administer, including scoring
- Children and adults with a **mental age above 2 years, 0 months**

Autism Diagnostic Observation Schedule-2
(Catherine Lord, Michael Rutter, et al.), 2012

- To assess and diagnose autism spectrum disorders (ASDs**) across age, developmental level, and language skills**
- Standardized **behavior observation (play based)** and coding
- 40–60 minutes to administer
- **12 months–adulthood**
- **5 modules** – chosen based on the developmental level and communication ability
  - Module 1 – Preverbal
  - Module 2 –Some beginning speech
  - Module 3 – Able to communicate in sentences
  - Module 4 – Older teens and adults with fluent speech
  - Toddler Module
- Modules 1-4 provide cutoff scores for autism and autism spectrum classifications
- Modules 1 through 3 also provide a Comparison Score indicating level of autism spectrum—related symptoms compared to children with ASD who are the same age and have similar language skills.
- Toddler Module provides ranges of concern reflecting the extent to which a child demonstrates behaviors associated with ASD.

Multidisciplinary Approach to Evaluation is Necessary



Types of Evaluation & Assessment

Team Evaluations

Toddler/Preschool

- Developmental Pediatrician/Neurologist/Psychiatrist + Speech-Language Pathologist (ADOS)
- + Occupational Therapist
- + Social Work

- **School Age**
  - Neurodevelopmental Pediatrician/Neurologist + ADOS (SLP)
  - Psychiatrist + ADOS (SLP)
  - Neuropsychologist + Speech-Language Pathologist (ADOS) + Neurologist

- **Transition Age**
  - Psychiatrist/Neurodevelopmental Pediatrician
  - + Speech-Language
    - + Occupational Therapy
    - + Neuropsychology

Independent Evaluations

- ADOS (SLP or Psychologist)
- Speech and language w/wo ADOS
- Occupational Therapy
- Neuropsychological Evaluation/Testing
- Clinical/Behavioral Psychology
- Social work evaluation
- Care Coordination
- Neurodevelopmental pediatrics
- Neurology/neurogenetics
- Psychiatry

Essential Elements of History for an ASD Focused Evaluation

Developmental History

- Start *with "when did you first have any concerns…?"* and then use it as a reference point.
- Prenatal, perinatal, postnatal, infancy, preschool and so on.
- Elicit history of early milestones (motor, speech/language, social, early play skills, any unusual behaviors or preoccupations, "red flags").
- Determine trajectory of development (evolution of speech/language, social skills and interest, play skills.
- Determine if there are delays.

Autism Specific Questions

- Ask questions about "red flags".
- Current communication abilities
- Echophenomena
- Scripting
- Misreading emotions/social situations
- Misinterpreting others' intentions
- Interest in peers
- Understanding of relationships including concept of "friend".
- Age-appropriate play skills
- Preoccupations ("obsessions")
- Ritualistic behaviors ("compulsions")
- Routine driven and challenges with adapting to changes/transitions
- Stereotypies
- Sensory Sensitivities (General sensory, special senses) – under or over-reactivity

Medical History

- Head trauma/seizures
- Pain
- Prior genetic or other testing
- Vision and hearing
- Menstrual history
- Other health concerns especially GI (constipation)
- Previous biomedical treatments (GCCF Diet, other CAMs, OTC, Herbal)

Sleep

- Any early sleep problems
- Determine routine
- Any snoring/apnea – Family history of sleep apnea, any T & A removal.
- Other sleep disorder
- Previous sleep disorders evaluation/study

Feeding and Appetite

- Any oromotor problems or other swallowing concerns
- Any food selectivity/restriction
- Food preferences based on texture of foods
- Overeating/"obsession" with food.
- Rumination
- Pica
- Weight loss or weight gain
- Any symptoms suggestive of Eating Disorders (ARFID, AN, BN)

Educational History

- Current placement (mainstream, special education, autism focused, non-public, virtual learning, home schooling)
- IEP/504 Plan – accommodations and related services.
- Academic functioning
- Any suspensions or behavioral concerns
- Psychoeducational testing

Social and Family History

- Parental occupations and educational level,
- Family support system
- Siblings
- Parental stress
- Family history of ASD, BAP features, other genetic disorders, psychiatric, medical

"Traditional" Psychiatric History

- Previous treatments (psychiatric, psychology, behavioral, in home)
- Any ER visits or inpatient or partial hospitalization
- Other as indicated – legal, substance abuse

Psychiatric Co-occurring Conditions (Presenting Concerns and Psychiatric ROS)

- ADHD,
- Disruptive behaviors
- Anxiety Disorders and OCD
- Mood disorders and emotional dysregulation
- Psychosis (reality testing, erroneous thinking, perceptual abnormalities)
- Tic Disorders
- Catatonia
- Gender Dysphoria/Identity

Problem behavior

- Aggressive behavior (type, context, directed towards, frequency, antecedents, predictability, gains, safety)
- Self-injurious behaviors (type, frequency, context, antecedents, predictability, gains, safety)
- Disruptive behaviors (Type, context, frequency, predictability, gains, safety)
- Property destruction

Safety Assessment

- Suicidality
- Homicidal ideation
- Access to weapons

ASD Focused Psychiatric Exam

Observation

- Dysmorphic features (facial, head, others if indicated)
- Macules/café-au-lait and other birth marks
- Abnormal movements (stereotypies and others)
- Perseverative behaviors
- Activity level
- Response to name
- Joint attention
- Use of nonverbal communication (gestures, pointing)
- Other aspects of pragmatics
- Sensory arousal/sensitivities
- Play
- Parent child interaction
- Self-talk and preoccupations

Social Interaction

- Initiation of and reciprocal socialization
- Eye contact
- Verbal communication (speech and language)
- Use of nonverbal communication (gestures, pointing)
- Socially engaged and rapport/Disengaged and preoccupied
- Distractibility (internal versus external)
- Social immaturity

Others

- Usual elements of a psychiatric MSE
- Mood, thought
- Perceptual abnormalities
- Older adolescents – reality testing
- Cognitive exam.
- Use of a wordless picture book.

Laboratory and Other Investigations

- Need for laboratory testing and neuroimaging should be balanced with practical considerations including anxiety surrounding blood draws or being in a scanner.
- There is no blood test for ASD.
- Goal is to rule out treatable conditions (such as mitochondrial disorders and other genetic and metabolic disorders, including inborn errors of metabolism).
- Genetic testing should be done if there are any dysmorphic features (also refer for clinical genetics evaluation)

- Fragile X Syndrome should be ruled out in any child with a developmental disorder
- Genetic testing – Karyotyping is becoming redundant.
- Chromosomal microarrays have become standard of care.
- Whole exome sequencing is being done frequently.
- Neuroimaging is only done if there are any neurological comorbidities or if there are dysmorphic features.
- EEG – only if there is a concern about seizures.

Considering Psychiatric Comorbidity in ASD

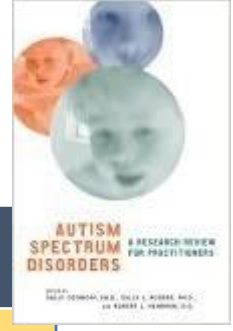
- Identifying comorbidity in ASD can be **challenging**.
- Co-occurring conditions can be
  - A. True co-occuring condition (**heterotypic comorbidity**)
  - B. Symptoms are similar to the co-occurring condition, but **ASD is a better explanation.**
  - C. **Epiphenomenon** of the ASD phenotype.
- **Diagnostic Overshadowing**
- Assessment complicated by **heterogeneous presentations** including
  - Variability in language abilities,
  - Varying intellectual abilities,
  - Limited availability of measures adapted to measure

the condition

Co-occurring psychiatric conditions in autism spectrum disorder

Tamara E. Rosen, Carla A. Mazefsky, Roma A. Vasa and Matthew D. Lerner

INTERNATIONAL REVIEW OF PSYCHIATRY, 2018
https://doi.org/10.1080/09540261.2018.1450229



When signs of problems outside the autism spectrum are apparent

- **Hyperactivity, distractible attention**
- **Sad or irritable mood, decreased pleasure in activities, increased withdrawal, vegetative signs**
- **Increased anxiety**
- **Affective instability (Emotional Dysregulation)**
- **Cognitive disorganization**

When there is an abrupt change in behavior from "baseline"

- **First rule out a medical problem (seizures, migraines, pain, medication SE)**

When there is a severe and incapacitating problem behavior

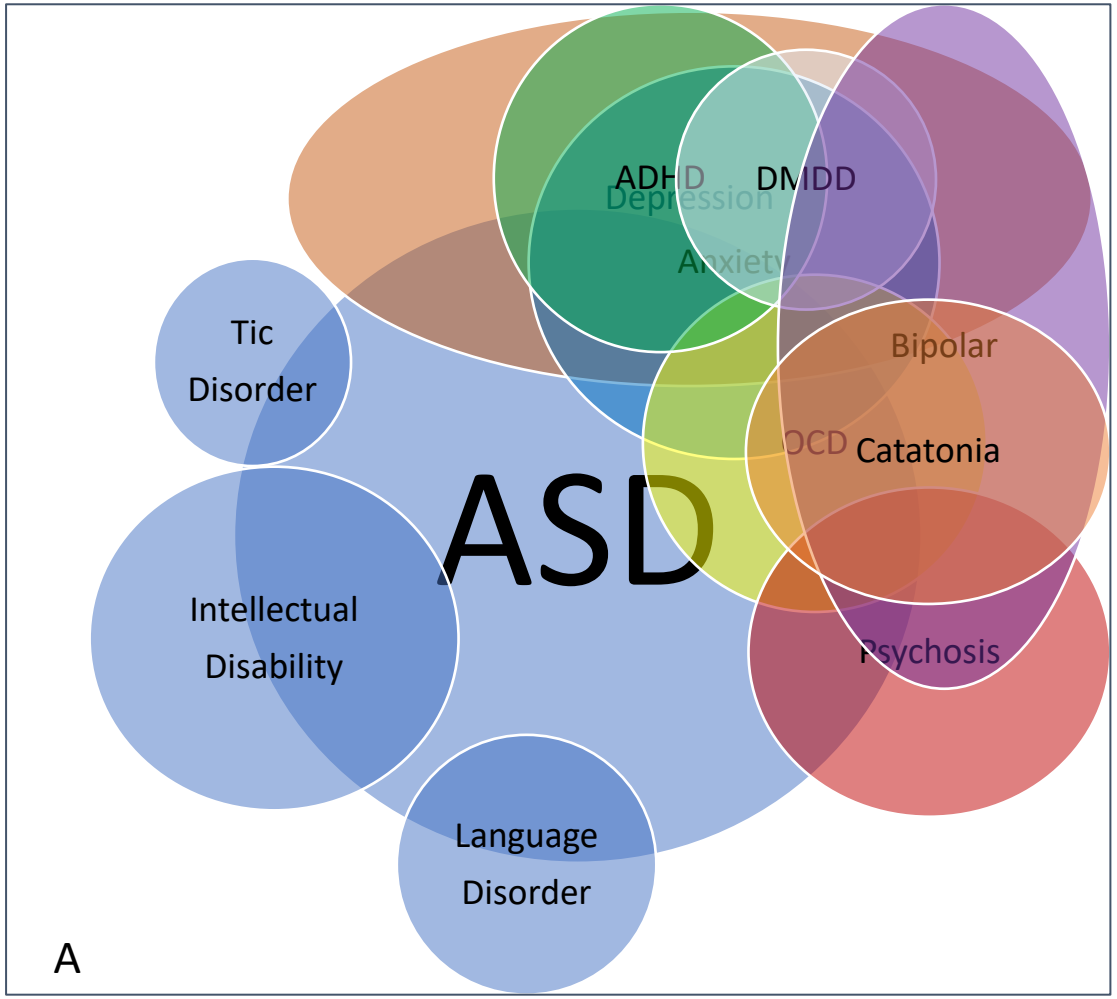
- **Aggression, SIBs, Disruptive behaviors, Sleep disturbance**

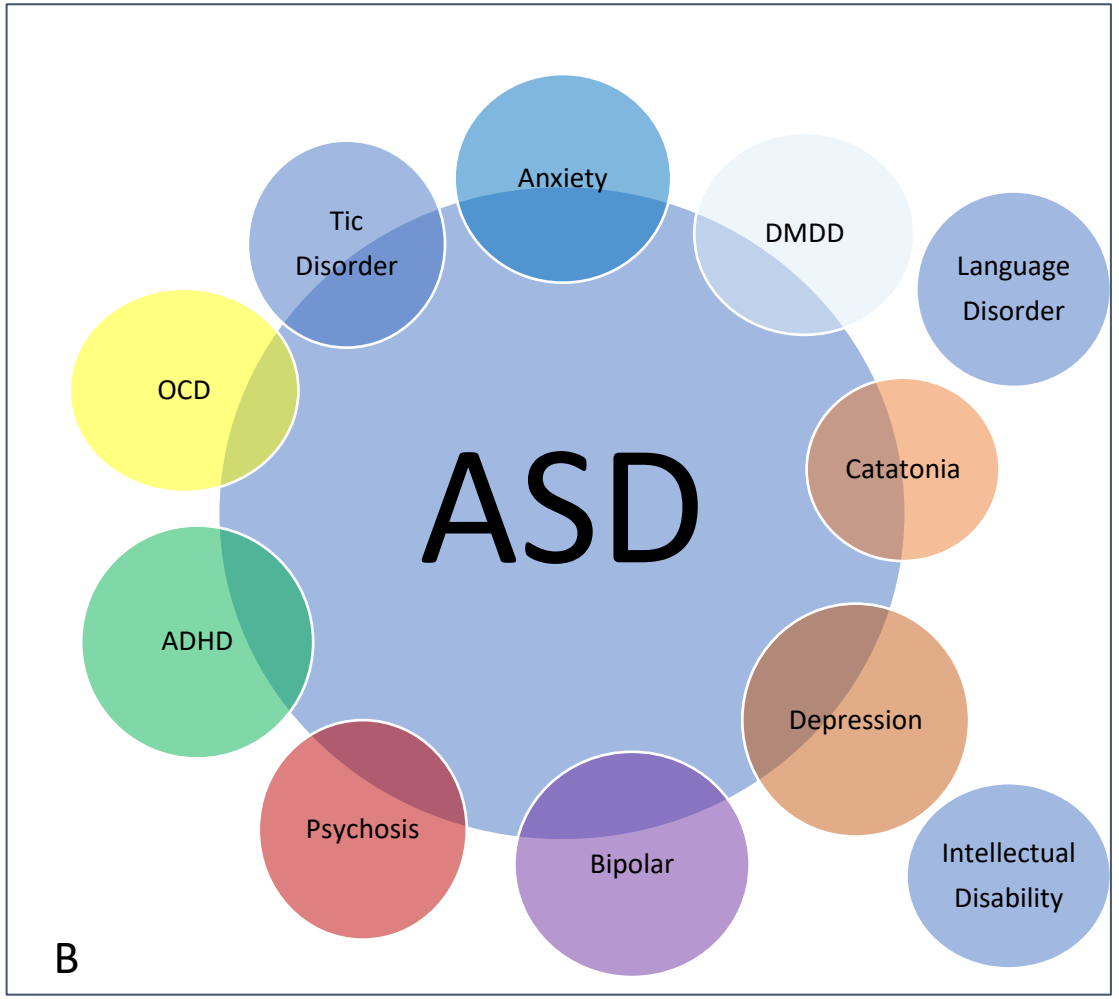
When there is worsening of behavior already present

- **Decreased communication**
- **Increased hand flapping or motor stereotypies**
- **Decreased adaptive behaviors and daily living skills**

When patient does not respond to treatment as expected.

Disentangling Phenomenological Overlaps and (Moving) Targets
Lumping vs Splitting





Psychiatric Disorders in Children With Autism Spectrum Disorders: Prevalence, Comorbidity, and Associated Factors in a Population-Derived Sample

EMILY SIMONOFF, M.D., F.R.C.Psych., ANDREW PICKLES, Ph.D., TONY CHARMAN, Ph.D., SUSIE CHANDLER, Ph.D., TOM LOUCAS, Ph.D., AND GILLIAN BAIRD, F.R.C.P.C.H.

ABSTRACT

Objective: Autism spectrum disorders are now recognized to occur in up to 1% of the population and to be a major public health concern because of their early onset, lifelong persistence, and high levels of associated impairment. Little is known about the associated psychiatric disorders that may contribute to impairment. We identify the rates and type of psychiatric comorbidity associated with ASDs and explore the associations with variables identified as risk factors for child psychiatric disorders. **Method:** A subgroup of 112 ten- to 14-year old children from a population-derived cohort was assessed for other child psychiatric disorders (3 months' prevalence) through parent interview using the Child and Adolescent Psychiatric Assessment. *DSM-IV* diagnoses for childhood anxiety disorders, depressive disorders, oppositional defiant and conduct disorders, attention-deficit/hyperactivity disorder, tic disorders, trichotillomania, enuresis, and encopresis were identified. **Results:** Seventy percent of participants had at least one comorbid disorder and 41% had two or more. The most common diagnoses were social anxiety disorder (29.2%, 95% confidence interval [CI]) 13.2–45.1), attention-deficit/hyperactivity disorder (28.2%, 95% CI 13.3–43.0), and oppositional defiant disorder (28.1%, 95% CI 13.9–42.2). Of those with attention-deficit/hyperactivity disorder, 84% received a second comorbid diagnosis. There were few associations between putative risk factors and psychiatric disorder. **Conclusions:** Psychiatric disorders are common and frequently multiple in children with autism spectrum disorders. They may provide targets for intervention and should be routinely evaluated in the clinical assessment of this group. *J. Am. Acad. Child Adolesc. Psychiatry*, 2008;47(8):921–929. **Key Words:** autism, child psychiatric disorders, prevalence, Special Needs and Autism Project.

Earlier comorbidity studies were based on clinician diagnosis, were not systematic.

Most studies have been of clinically referred populations – risk of referral bias.

Mental health difficulties persist into older age and did not improve over time in autistic adults (Roestorf et al, 2022)

TABLE 1

Prevalence of *DSM-IV* Disorders

Disorder	3-Mo Point Prevalence/100	95% CI
Any disorder	70.8	58.2–83.4
Any main disorder[a]	62.8	49.8–75.9
Any emotional disorder[b]	44.4	30.2–58.7
Any anxiety or phobic disorders[c]	41.9	26.8–57.0
Generalized anxiety disorder	13.4	0–27.4
Separation anxiety disorder	0.5	0–1.6
Panic disorder	10.1	0–24.8
Agoraphobia	7.9	3.0–12.9
Social anxiety disorder	29.2	13.2–45.1
Simple phobia	8.5	2.8–14.1
Obsessive-compulsive disorder	8.2	3.2–13.1
Any depressive disorder	1.4	0–3.0
Major depressive disorder	0.9	0–2.3
Dysthymic disorder	0.5	0–1.4
Oppositional or conduct disorder	30.0	14.9–45.0
Oppositional defiant disorder	28.1	13.9–42.2
Conduct disorder	3.2	0–7.1
Attention-deficit/hyperactivity disorder	28.2	13.3–43.0
Other disorders[d]	24.7	14.1–35.3
Enuresis	11.0	4.1–17.7
Encopresis	6.6	1.8–11.4
Tourette syndrome	4.8	0.1–9.5
Chronic tic disorder	9.0	3.3–14.6
Trichotillomania	3.9	0–10.3

Note: CIs = confidence intervals.

[a] Includes attention-deficit/hyperactivity disorder, oppositional and conduct disorders, and any emotional disorder.

[b] Includes all anxiety disorders, phobias, and mood disorders.

[c] Includes anxiety disorders, panic disorder, phobias, and obsessive-compulsive disorder.

[d] Includes Tourette syndrome, chronic tics, trichotillomania, enuresis, and encopresis.

3 Recent Studies of Co-occurring Psychiatric Disorders in ASD

Front. Psychiatry 13:856208.doi: 10.3389/fpsyt.2022

J Autism Dev Disord. 2019 September ; 49(9): 3819–3832.

Rates of Co-occurring Psychiatric Disorders in Autism Spectrum Disorder using the Mini International Neuropsychiatric Interview

Maya G. Mosner[1], Jessica L. Kinard[2], Jasmine S. Shah[1], Sean McWeeny[1], Rachel K. Greene[1], Sarah C. Lowery[1], Carla A. Mazefsky[3], Gabriel S. Dichter[1,2,4,5]

- UNC-Chapel Hill Study used Mini International Neuropsychiatric Interview (MINI) in assessing co-occurring psychiatric disorders in children, adolescents and young adults with ASD.
- 67 individuals with ASD ranging from 8 to 25 years of age (M=16.97, SD=3.75)
- **35** were C/A and 32 participants were young adults (>18y) older than 18 years of age).
- All were fluent, and did not have ID.
- **91% of C/A** and **31% of YA** had 1 or more co-occurring disorder.
- MINI diagnostic rates were comparable to previous studies on C/A.
- MINI rates were lower relative to rates for YA

Mosner et al, 2019

Population-Based Psychiatric Comorbidity in Children and Adolescents With Autism Spectrum Disorder: A Meta-Analysis

Tuba Mutluer[1,2], Herdem Aslan Genç[3], Aslıhan Özcan Morey[3], Hale Yapici Eser[1,2], Beliz Ertinmaz[4], Merve Can[5] and Kerim Munir[6]

- A systematic literature search was performed using PubMed and Web of Science databases restricted to population-based study publications in the English **between May 1, 2015, and May 31, 2020.**
- **39 studies** were analyzed
- Prevalence estimates of **22.9% (95% CI: 17.7-29.2) for intellectual disability**; **26.2% (22-31) for attention-deficit hyperactivity disorder**; **11.1%(8.6-14.1) for anxiety disorders; 19.7% (11.9-30.7) for sleep disorders; 7% (5.2- 9.3) for disruptive disorders; 2% (1.3- 3.1) for bipolar disorders; 2.7% (1.8- 4.2) for depression; 1.8% (0.4–8.7) for obsessive-compulsive disorder**; and **0.6% (0.3–1.1) for psychosis.**
- Psychiatric comorbidity in population-based studies is lower than in clinical and referred samples.

Mutluer et al, 2022

Translational Psychiatry (2023)13:71

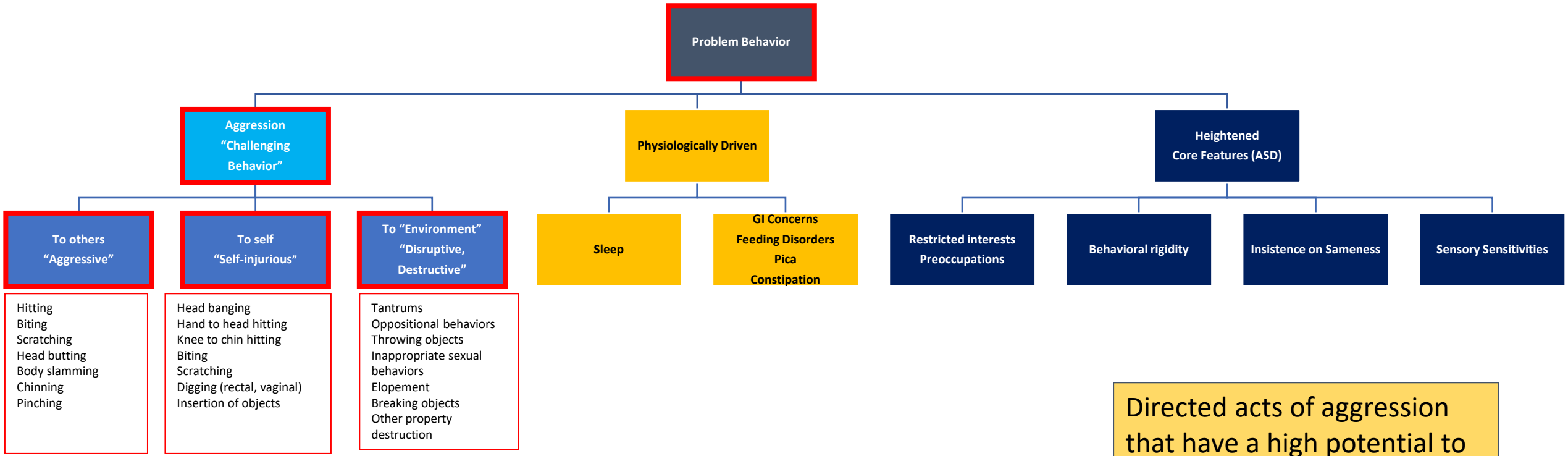
Comorbidities in autism spectrum disorder and their etiologies

Vahe Khachadourian[1,2,3], Behrang Mahjani[1,2], Sven Sandin[1,2], Alexander Kolevzon[1,2], Joseph D. Buxbaum[1,2,3,4], Abraham Reichenberg[1,2,3,5] and Magdalena Janecka[1,2,3,4,5]

- SPARK Study cohort
- **42,569 ASD** and **11,389 non-ASD** siblings.
- **74%** had at least 1 comorbid psychiatric disorder.
- More average number of disorders than the non-ASD siblings.
- **Preterm birth** and **hypoxia** at birth were most common associations.
- These exposures were associated with several distinct comorbidities in ASD cases, including attention and behavior problems, psychiatric and neurological disorders, and growth conditions.

Khachadourian et al, 2023

Problem Behavior



Directed acts of aggression that have a high potential to or do result in ***harm to other people, self or property***.

Problem Behavior

- **20%** with ASD have irritability and aggression at moderate to severe levels (Fung et al, 2016)
- **>50%** exhibit severe emotional dysregulation (Fung et al, 2016).
- **Increased Risk:**

1. **Biological, psychological and environmental** factors (Machalichek, 2016)
2. **Severity of core features** of ASD (Matson & Rivet, 2008)

3**. Severity of intellectual disability** (Dunlap, 2006; Murphy , 2009; Esteves, 2021)

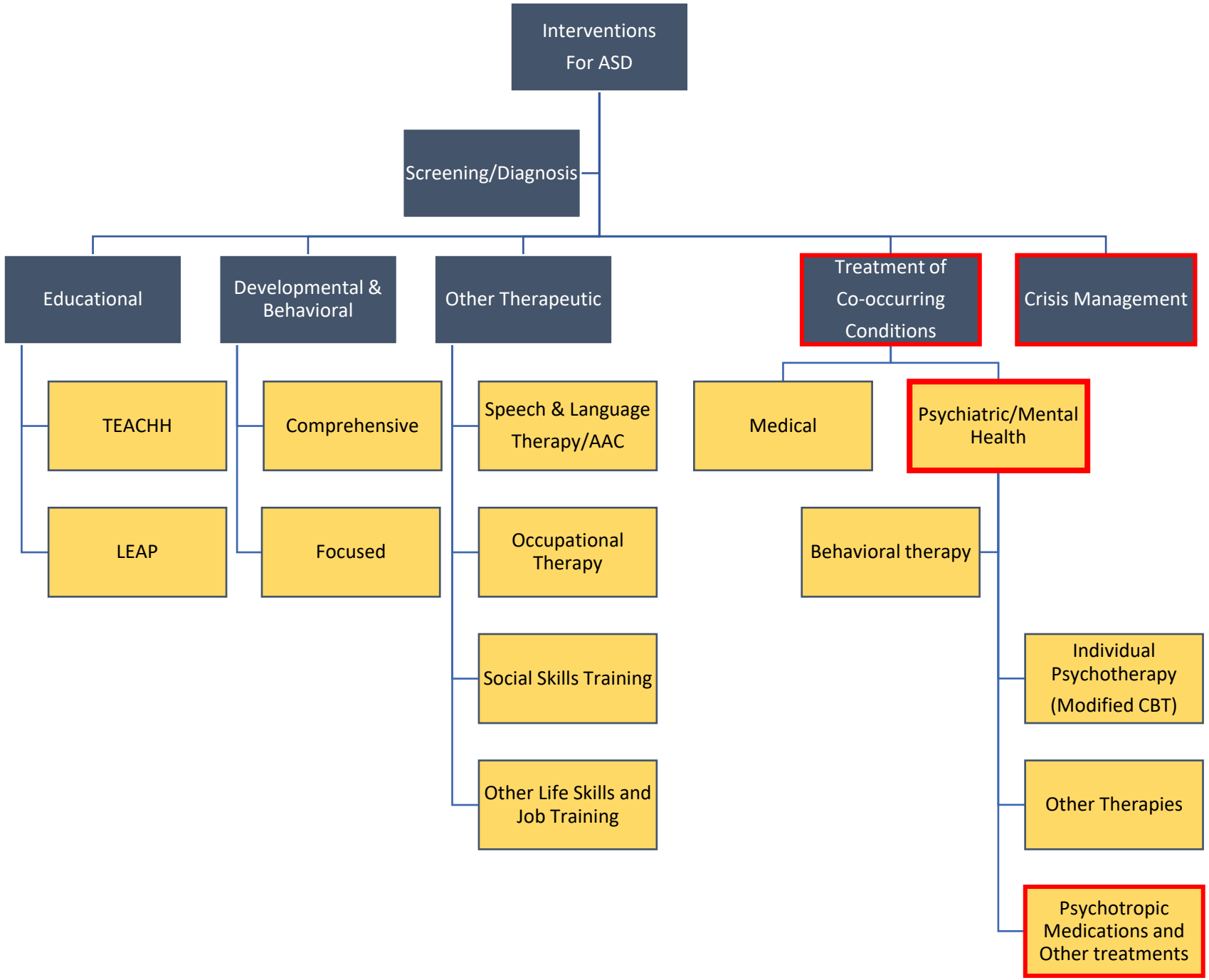
Gender **may not be a factor** especially in ASD alone, ASD+ID – M>F (Esteves, 2021)

- May cause severe disruption of functioning of the child, caregiver stress and burnout.

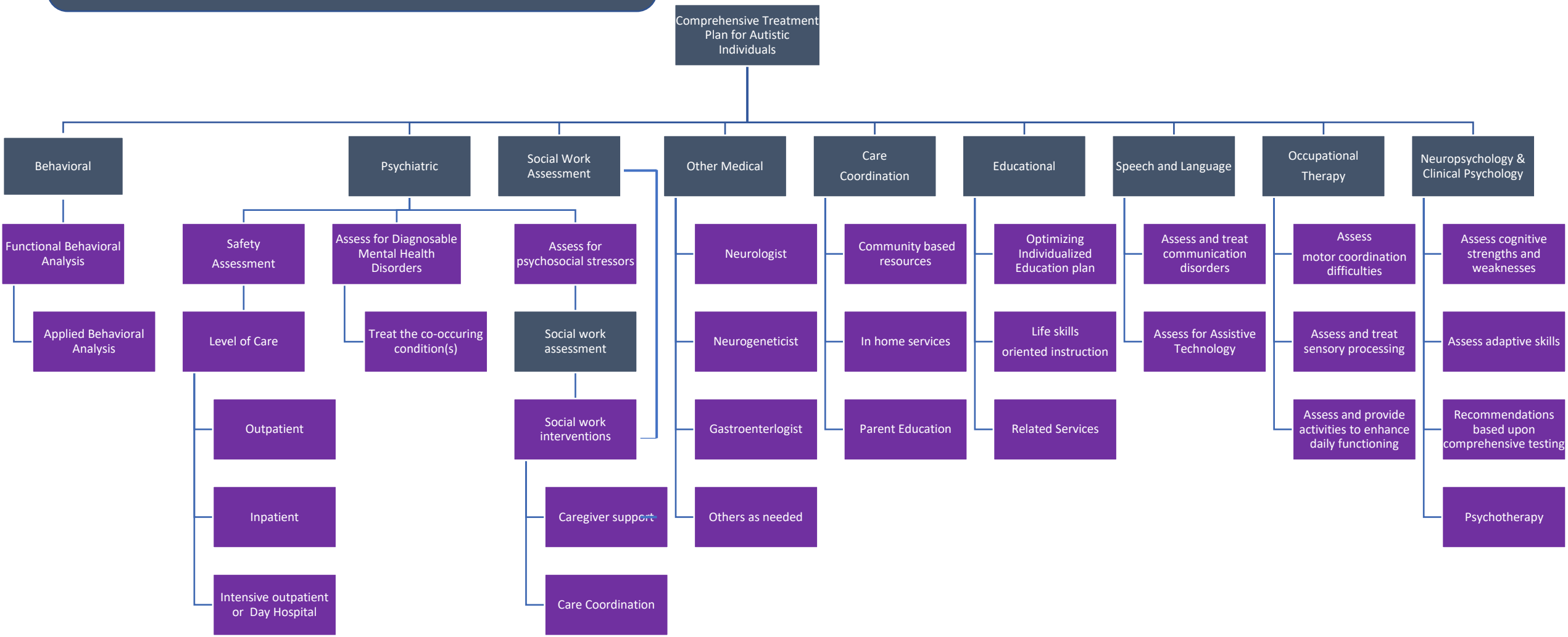
- Caregivers are frequent targets (56% toward caregivers, 32% toward non-caregivers; 68% had history of targeting caregivers, 49% toward non-caregivers, ***Kanne & Mazurek, 2011***)

- **Consequences**

Reduced QOL for the child and parents.
Financial hardship for the parents.
Interfere with learning of the child.
Require *non-public* school settings.
ER boarding
Inpatient hospitalization
Out of home placements


Interventions For ASD
Screening/Diagnosis
Educational
Developmental & Behavioral
Other Therapeutic
Treatment of Co-occurring Conditions
Crisis Management
TEACHH
LEAP
Comprehensive
Focused
Speech & Language Therapy/AAC
Occupational Therapy
Social Skills Training
Other Life Skills and Job Training
Medical
Psychiatric/Mental Health
Behavioral therapy
Individual Psychotherapy (Modified CBT)
Other Therapies
Psychotropic Medications and Other treatments

Treatment Plan: Complex, Multidisciplinary, Takes Time



ABA Therapy

- Based on behavioral principles **(Antecedent -Behavior-Consequence)**.
- Functional behavioral assessment (FBA) is conducted to identify the antecedent stimulus and understand the function of the behavior.
- In children with ID and ASD, PB can help with - escape/avoidance/access to tangibles.
- Behavioral interventions attempt to **replace these dysfunctional behavioral patterns** with more appropriate behaviors.
- Can start with ABA therapy or in combination with medications.
- Several clinical trials in ASD looking at combination treatments (med+ABA).
- **Challenges**: Generalization may be difficult for the child across settings

  Takes time to replace behaviors

  Shortage of providers

  Caregivers may not be able to consistently implement complex plans

Recent metaanalysis studies of effectiveness of 4 ABA based modalities (Yu et al, 2020) indicated no significant effects in outcomes of ASD features, living skills and other measures

Other Psychosocial Interventions

Modified CBT

- One of the most widely used approaches in those with higher intellectual capability and verbal abilities.
- May be moderately effective in treating mood disorders and anxiety (Weston et al, 2016)
- Limited research in adults.

Mindfulness Based Therapy

Social Skills training

Life Skills Training

Face Your Fears

General Considerations When Prescribing Medications for ASD

- We do not have medications to treat the core features
- Directed to target behaviors or MH symptoms.

- Goal is to **reduce the intensity of (manage) interfering behaviors or symptoms**

- **Indications:**
  1. **Diagnosed MH condition**(s) impacting learning or interfering with functioning
  2. **Safety concerns**
  3. Behavioral and other non-pharmacological approaches not successful

- Before starting medications baseline bloodwork, EKG (if needed)

- If comorbidity, start with targeting one -> Optimize treatment to an effective dose, then treat another.

- **1/3 of patients** with ASD (3 yrs-65 yrs) – on a psychotropic **medication without a MH Dx** *(Houghton, 2017).*

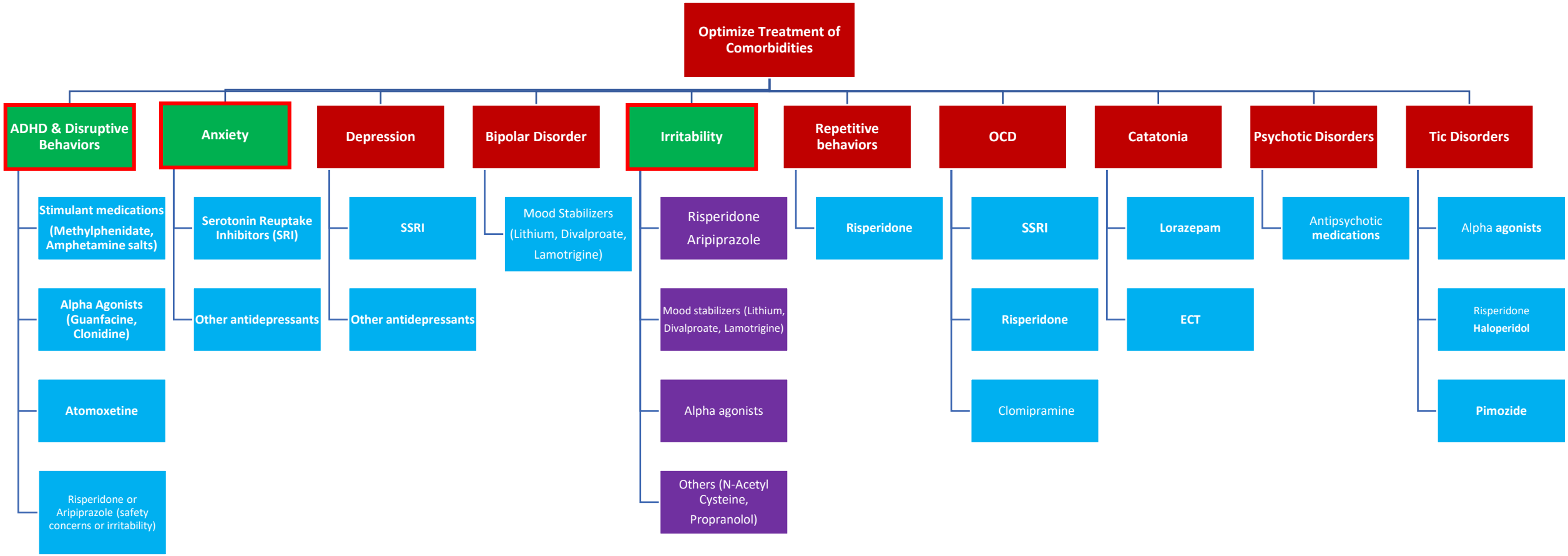
- **50%** of children with ASD are treated with psychotropic medications in N. America & Europe (*Jobski, 2017*)

- **Polypharmacy: 6.8 to 87%** of youth with ASD are prescribed > 1 medication (Ritter et al, 2021)
  - Psychiatric comorbidity
  - Physical aggression
  - SIBs
  - Males
  - Older

STOMP: Stopping Over-Medication of Psychotropic Medications in pts with ASD (2016, UK)

STOMP-STAMP: Supporting Treatment and Appropriate Medication in Paediatrics (2018, UK)

Medications To Treat Co-occurring Disorders in ASD



Recent RCTs in ASD (Medications & Neuromodulation)

Table 1. Randomized controlled trials of medications or neurostimulation in autism spectrum disorder published in 2019, 2020, or 2021, grouped by mechanism of action

Agent (category)	Year	Sample size	Age range (years)	Primary outcome	Primary outcome
Existing psychotropic agents in ASD					
Fluoxetine (SSRI) [21▪]	2020	168	5–17	Repetitive behaviour (CY-BOCS, CGI)	No difference
Fluoxetine (SSRI) [17]	2019	146	7.5–18	Obsessive–compulsive behaviour (CYBOCS-PDD)	Ambiguous
Sertraline (SSRI) [19]	2019	58	2–6	Language (MSEL)	No difference
Gene expression or transcriptional regulation					
Folinic acid [50]	2020	19	3–10	Core symptoms (ADOS)	Improved
E:I signalling					
Intranasal ketamine (2 doses) [63]	2020	21	14–29	Social withdrawal (ABC)	No difference
Bumetanide [69▪]	2020	83	3–6	Core symptoms (CARS and CGI)	Improved
Bumetanide [70▪]	2021	120	3–6	Core symptoms (CARS)	Improved
Bumetanide [71▪]	2020	92	7–15	Core symptoms (SRS-2)	No difference
Donepezil and choline [140]	2019	60	5–16	Language (PLS-4)	Ambiguous
Immune					
Sulforaphane [91]	2021	57	3–12	Core symptoms (OACIS)	No difference
Prednisolone [141]	2021	40	3–7	Language (ADL and ABFW)	Ambiguous
Neuropeptide					
Oxytocin [94▪▪]	2021	290	3–17	Social withdrawal (ABC)	No difference
Oxytocin [142]	2020	40	18–35	Core symptoms (SRS)	No difference
Other					
Cannabinoid [99▪]	2021	150	5–21	Disruptive behaviours (HSQ-ASD and CGI)	Improved
Dextromethorphan/quinine [143]	2020	14	18–60	Irritability (ABC)	Improved
Neurostimulation					
rTMS [117▪]	2021	78	8–17	Core symptoms (SRS)	No difference
rTMS [116▪]	2020	40	16–35	Executive Function (CANTAB)	No difference

Ambiguous: Multiple primary endpoints with conflicting results; primary endpoint not specified; primary endpoint borderline significant with moderate or greater effect sizes; or significant primary endpoints do not persist across prespecified sensitivity analyses. ABC, Aberrant Behaviour Checklist; ABFW, Assessment Child Language Test in Phonology, Vocabulary, Fluency, and Pragmatics; ADL, Language Development; ADOS, Autism Diagnostic Observation Schedule; CANTAB, Cambridge Neuropsychological Test Automated Battery; CARS, Childhood Autism Rating Scale; CGI, Clinical Global Impression; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Inventory; HSQ, Home Situations Questionnaire; MSEL, Mullen Scales of Early Learning; OACIS, Ohio Autism Clinical Impressions Scale; PDD, pervasive developmental disorder; PLS-4, Preschool Language Scale-4; SRS, Social Responsiveness Scale.

Novel treatments in autism spectrum disorder

Danielle Baribeau[a,b,c], Jacob Vorstman[a,b], and Evdokia Anagnostou[a,b,c]

Curr Opin Psychiatry 2022, 35:101–110

FIGURE 1. Potential novel treatments and treatment targets under investigation in autism. ASD, autism spectrum disorder; E:I, excitatory:inhibitory; RNAi, RNA interference.

Baribeau et al, 2022

ADHD in ASD

- **ADHD is a neurodevelopmental disorder with a developmental trajectory.**
- **Stimulants tried first** - although may not be as effective in ASD as in ADHD (only 49% response rate in RUPP MPH study); higher risk of adverse effects (18% d/cd due to adverse effects in RUPP MPH study).
- **Start with methylphenidate** or amphetamine salts.
- **Atomoxetine** tried next – or first, if there is comorbid anxiety
- **Alpha-2 agonists** added if symptoms not controlled by stimulants alone; can start with alpha agonists if severe hyperactivity –impulsivity predominate.
- **Atypical antipsychotics** - severe aggression, impulsive behaviors leading to safety concerns elopement/running/other unsafe behaviors.

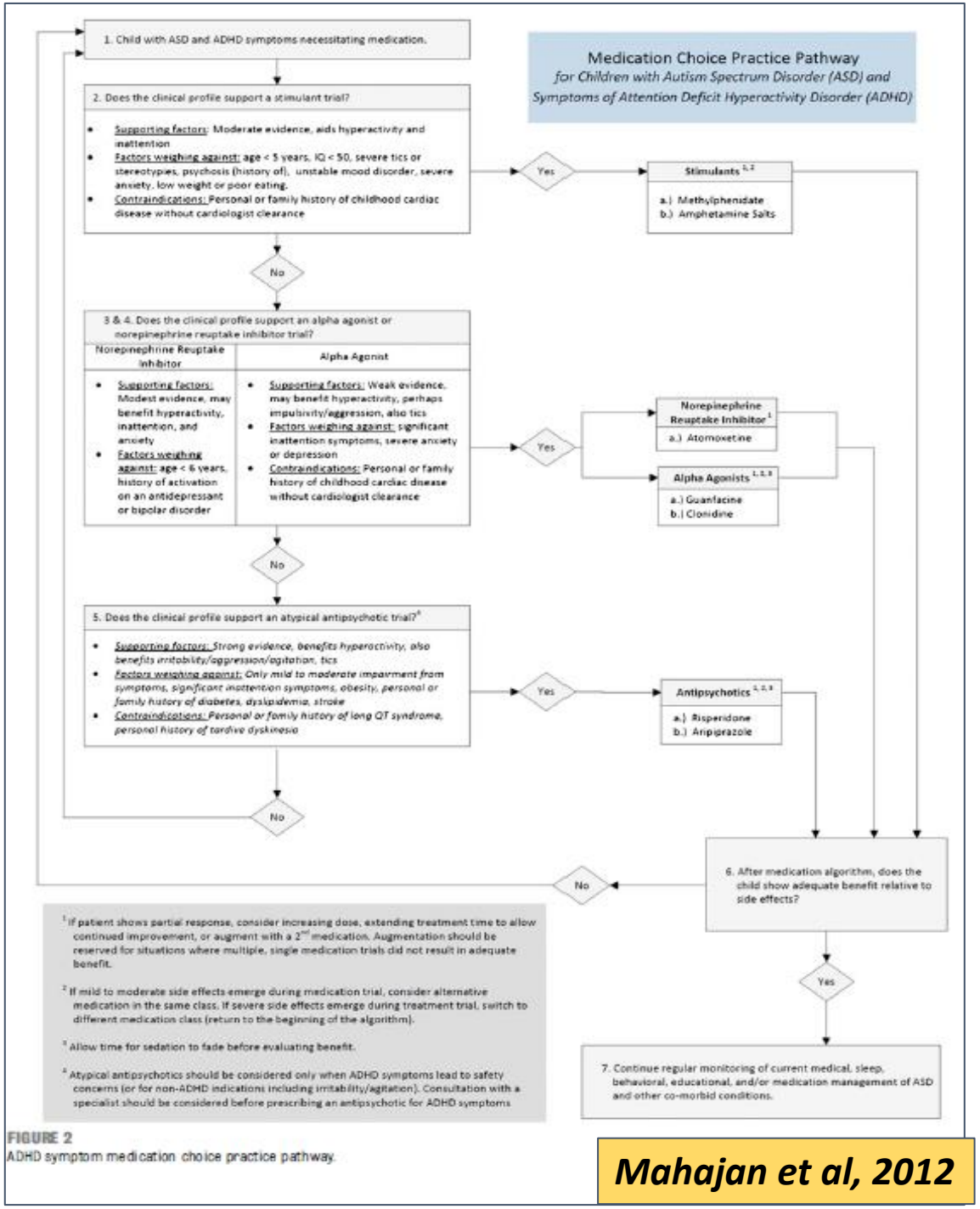


FIGURE 2
ADHD symptom medication choice practice pathway.

Mahajan et al, 2012

Anxiety in ASD

- Anxiety can be difficult to diagnose and treat in nonverbal patients.
- Look for signs of typical anxiety disorders.
- Use standardized scales to supplement clinical impression.
- Limited evidence base for psychopharmacological interventions for core anxiety symptoms for children and adolescents, and adults.
- **21-32%** prescribed SSRI medications (Reddidough et al, 2019).
- **Vasa et al (2014)** – systematic review of treatments in children and adolescents.
- **Menezes et al (2022)** – systematic review of treatments in adults
- Evidence base is somewhat **better for non-psychopharmacological interventions** (Modified CBT, Modified Mindfulness Based Therapy, and others), but participant numbers are low.
- Clinically, **start with SSRI medications** as in typically developing population with usual precautions. Monitor with a scale.
- **Treat associated/comorbid conditions** (ADHD, OCD, Mood Disorders)

TABLE 1 Summary of Medications for the Treatment of Anxiety in Youth With ASD

Symptoms[a]	Medication[b]	Dose Range[b]		References
		Starting Dose	Maximum Dose	
Core anxiety symptoms	Sertraline[c]	12.5 mg daily	200 mg daily	Reviews in typically developing youth: Mohatt et al (2013), Strawn et al (2014)
	Fluoxetine[c]	2.5–5 mg daily	60 mg daily	
	Citalopram[c]	2.5–5 mg daily	40 mg daily	
	Escitalopram[c]	1.25–2.5 mg daily	20 mg daily	
Specific anxiety symptoms[d]				
Sleep disturbance	Melatonin	2 mg hs	10 mg hs	Guenoe et al (2011)
	Clonidine	0.05 mg hs	0.2 mg hs	Nguyen et al (2014)
	Trazodone[e]	12.5–25 mg hs	100 mg hs	
Physiologic symptoms[f]	Clonidine[f]	0.05 mg hs for 1 week then bid-qid	0.1 mg tid-qid	No data in TD or ASD youth; recommendations based on clinical consensus
	Guanfacine[f]	0.05 mg hs for 1 week then bid-qid	1 mg tid	
	Clonidine ER[f]	0.1 mg hs or qam	0.2 mg hs or qam[g]	
	Guanfacine ER[f]	1 mg hs or qam	4 mg hs or qam[g]	
	Propanolol	10 mg bid-tid or prn	30 mg tid	
Behavioral dysregulation[f]	Clonidine	0.05 mg hs for 1 week then bid-qid	0.1 mg tid-qid	Reviews by: Mahajan et al (2012), Ji and Findling (2014)
	Clonidine ER	0.1 mg daily	0.2–0.3 mg daily	
	Guanfacine	0.5 mg hs for 1 week then bid tid	1 mg tid	
	Guanfacine ER	1 mg hs[g]	4 mg hs or qam	
Situational anxiety[g]	Lorazepam	0.25–0.5 mg prn	2 mg prn	No data in TD or ASD youth; recommendation based on clinical consensus
	Propanolol	5–10 mg prn	20 mg prn	

bid, twice daily; ER, extended-release; hs, bedtime; prn, as needed; qam, each morning; qid, 4 times per day; tid, 3 times per day.

[a] Specific anxiety symptoms refer to individual or limited symptoms of anxiety, whereas core anxiety symptoms refer to the entire syndrome of cognitive, affective, and physiologic changes associated with anxiety.

[b] Maximum doses are based on data in TD children and adolescents. Higher doses in this table should only be used in consultation with a specialist versed in their use, such as a child psychiatrist or developmental-behavioral pediatrician

[c] Discuss side effects including risk of behavioral activation. Higher doses may be needed for fast metabolizers. Slow metabolizers may need lower doses.

[d] Behavioral dysregulation refers to symptoms of irritability, aggression, property destruction, and self-injury. For severe behavioral dysregulation, refer to a mental health specialist or follow the ATN pathway for treatment of irritability and problem behaviors.

[e] There are no data to support the use of trazodone. It is only recommended in children aged >8 years. The risk of priapism should be discussed with the family.

[f] For short and ER clonidine and guanfacine preparations, monitor blood pressure and heart rate at each visit. Check for orthostatic hypotension if dizziness, light-headedness, or falls are reported. Guanfacine ER can be started in the evening initially due to the possibility of sedation and then switched to morning, if needed. Alternatively, it can be started directly in the morning if tolerated by the patient. Guanfacine is preferred over clonidine during daytime hours because of its longer half-life and lower potential for sedation.

[g] Lorazepam is a short-acting benzodiazepine (6–8 hours). For situational anxiety, it should be given 30 min before the event. There are no data on the use of propranolol in children and adolescents, but it is u
treatment of situational anxiety.

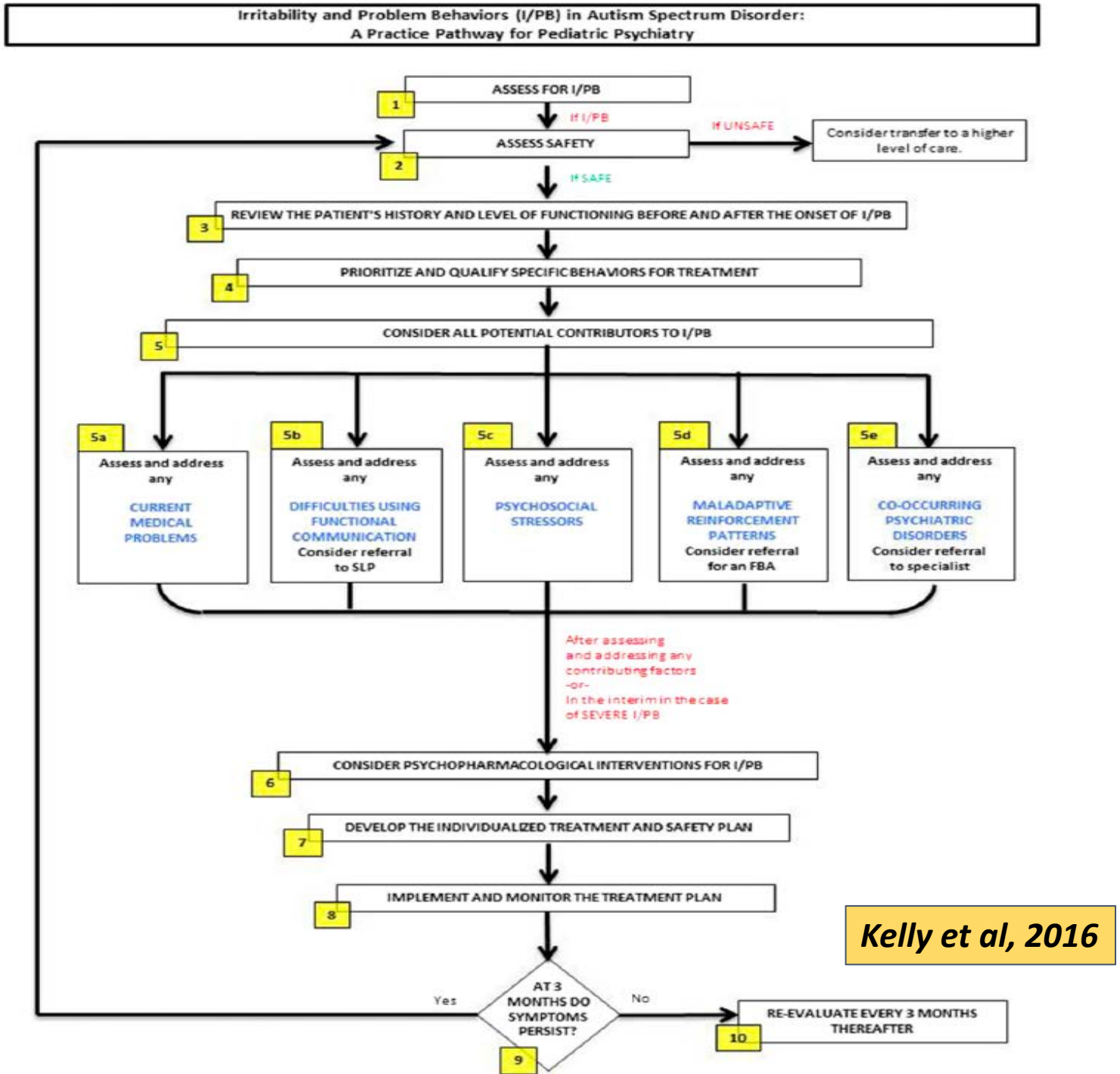
Vasa et al, 2016

Irritability and Problem Behavior in Autism Spectrum Disorder: A Practice Pathway for Pediatric Primary Care

Irritability and Problem Behavior (and possibly DMDD, Mood Disorders and Aggression)

Irritability

- Vocal and motoric outbursts
- Expressive of anger, frustration and distress
- Referred to as “meltdowns”, “temper tantrums” and “rages”
- Can lead to problem behavior (aggression)
- Is a transdiagnostic presentation especially in children may be indicative of emotional dysregulation, depression, or anxiety.
- Treatment requires careful parsing out of the symptoms and appropriate treatment.



Kelly et al, 2016

Other Selected DSM Diagnoses (Mood Disorders, OCD, Schizophrenia, Feeding and Eating Disorders)

- OCD, mood and psychotic disorders may have considerable phenomenological overlap with autistic features and may thus be more challenging to recognize or treat.

- Overall prevalence rates are low

- Muluer et al (2022) – metanalysis of population based studies 2015-2020

Bipolar disorders - 2% (1.3- 3.1)
Depression - 2.7% (1.8- 4.2)
OCD - 1.8% (0.4–8.7) ; and
Psychosis - 0.6% (0.3–1.1)

2nd opinion should be sought if there are any concerns about the diagnosis or if no response to usual treatments.

- There are no specific guidelines for management of these conditions, so treated as in typically developing population with the usual medication options.

Feeding and Eating Disorders

- Phenomenological overlaps with AN
- Some consider AN to be the “female version” of ASD.
- ARFID vs food selectivity of ASD
- Treatment requires specialized team approach as per ED guidelines. No specific guideline for ASD.

Table 1 Pharmacologic management of aggression in ASD, selected controlled trials

Medication	Author	Study design	N	Age (years)	Details	AEs
Antipsychotics/selected controlled trials						
Haloperidol	Campbell et al[85]	12-week, RPCT	42	2.6–7.8	Haloperidol superior to placebo on stereotypy and social withdraw subscales of CPRS	Sedation, acute dystonic reaction in two subjects
	Anderson et al[84]	14-week, RPCT	45	2.3–7.9	Haloperidol superior to placebo on all subscales of CPRS	Sedation, increased irritability
Risperidone	McDougle et al[90]	12-week, RPCT	31	18–43	Risperidone superior to placebo on CGI-I and SIB-Q	Abnormal gait (n=1), sedation
	McCracken et al[86]	8-week, RPCT	101	5–17	Risperidone superior to placebo on ABC-I and CGI-I	Weight gain, increased appetite, fatigue
	Shea et al[91]	8-week, RPCT	79	5–12	Risperidone superior to placebo on ABC-I	Somnolence, weight gain
	RUPP[92]	Part 1: 16-week open-label extension of 2002 trial	Part 1: 63	5–17	Sustained improvement on ABC-I	Weight gain
		Part 2: 8-week DB placebo-substitution study	Part 2: 32	5–17	62.5% relapse rate in placebo group	Increased aggression in placebo group
	Aman et al[93]	Naturalistic 21-month follow-up	84	5–17	Improved scores on ABC-I; significant rate of continued use	Weight gain, excessive appetite, enuresis
Aripiprazole	Marcus et al[88]	8-week, RPCT (fixed dose)	218	6–17	Aripiprazole superior to placebo on ABC-I	Weight gain, sedation, EPS
	Owen et al[87]	8-week, RPCT (flexible dose)	98	6–17	Aripiprazole superior to placebo on ABC-I and CGI-I	Weight gain
	Marcus et al[89]	52-week open-label extension of 2009 trial	330	6–17	Aripiprazole superior to placebo on ABC-I and CGI-I	Weight gain, increased appetite, vomiting, insomnia
Olanzapine	Hollander et al[73]	8-week RPCT	11	6–14	Olazapine superior to placebo on CGI-I, but not on CY-BOCS or OAS-M	Weight gain, sedation
Lurasidone	Loebel et al[94]	6-week RPCT (fixed dose)	150	6–17	Lurasidone not superior to placebo at either dose	Vomiting, somnolence
Antiepileptic medications/selected controlled trials						
Valproic acid	Hellings et al[95]	8-week RPCT	30	6–20	Valproic acid not superior to placebo on ABC-I	Skin rash, weight gain, elevated ammonia
Other medications/selected controlled trials						
N-acetylcysteine (NAC)	Hardan et al[109]	12-week RPCT	29	3.2–10.7	NAC superior to placebo on ABC-I	Minimal gastrointestinal symptoms
Naltrexone	Campbell et al[114]	6-week RPCT	41	2.9–7.8	Improved hyperactivity on CPRS but no improvement in self-injury	Well tolerated

Abbreviations: AEs, adverse events; ASD, Autism spectrum disorder; RPCT, randomized placebo-controlled trial; CPRS, Children's Psychiatric Rating Scale; CGI-I, Clinical Global Impression-Improvement scale; SIB-Q, Self-Injurious Behavior Questionnaire; ABC-I, Aberrant Behavior Checklist Irritability subscale; RUPP, Research Units on Pediatric Psychopharmacology; DB, double-blind; EPS, extrapyramidal symptoms; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; OAS-M, Overt Aggression Scale modified.

Aggression in autism spectrum disorder: presentation and treatment options

Fitzpatrick et al, 2021

Aggression

- Recent summary of some of the clinical trials conducted for aggression.
- Antipsychotics form the bulk of the medications studied.
- There are several case reports, case series, retrospective chart reviews and open label trials of various psychotropic medications.
- In clinical practice, frequently use is based upon practice in non-NDD populations

Antipsychotic Medications

Risperidone (2006) and aripiprazole (2009) have been FDA approved for treatment of irritability in children and adolescents with ASD.

Risperidone –

- Approved in **5-17** year olds.
- **RUPP trial** showed reduced ABC-I scores, tantrums, aggression and SIBs.
- Rapid weight gain, increased appetite, fatigue, and anxiety are common
- Hyperprolactinemia, sexual side effects, and gynecomastia.

Aripiprazole

- Approved **in 6-17** year olds.
- Improvements in the ABC irritability, hyperactivity, and stereotypy subscales
- Weight gain, sedation, increased appetite, and extrapyramidal symptoms

Other medications have shown some promise in studies, but do not have the FDA approval.

Quetiapine, Olanzapine, ziprasidone, paliperidone, quetiapine – limited evidence but may respond clinically in individual cases.

Lurasidone not found to be effective in 1 study in 6-17 yr olds, fixed dose (20, 60, placebo) (Loebel, et al, 2016).

Clozapine – for refractory cases.

Long acting injectables – small case reports/case series – aripiprazole, risperidone (*Fortea, 2018*), paliperidone (Kowalski, 2011)

Haloperidol – efficacious in some studies, for agitation/aggression. EPS limits use.

Other FGAs – limited to no studies, but used if SGAs are not effective (moderate potency, low potency).

Other approaches

Electroconvulsive Therapy

- ***Refractory SIB*** that are not responding to medications and behavioral interventions and there is a severe risk of severe self harm.
- ***Catatonia*** not responsive to lorazepam.

Non-Invasive Brain Stimulation

Transcranial Magnetic Stimulation (TMS)
Transcranial Direct Current Stimulation (t-DCS)
Preliminary studies only. (London, 2018)
Recent systematic review (Khalegi et al, 2020)
Could be useful for some core features (repetitive behaviors); need for more studies

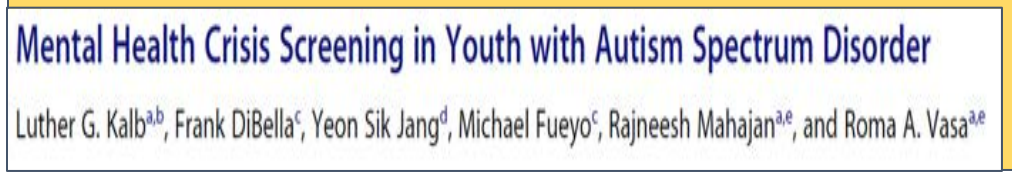
Ketamine – no evidence base for its use in ASD.

Cannabidiol (CBD)

- CB1 (mostly brain) and CB2 (rest of the body) receptors
- **CBD** - neuroprotective effects and may improve the functioning of the endocannabinoid system.
- Not FDA approved for ASD.
- Preliminary studies that show some improvements in ASD features, hyperactivity, anxiety features (Agarwal et al, 2019).
- Case series examined use of cannabis preparations in **Fragile X syndrome** (Tartaglia et al, 2019) noticeable reductions in social avoidance and anxiety, as well as improvements in sleep, feeding, motor coordination, language skills, anxiety, and sensory processing..

Mental Health Crisis

- Patients with ASD (and other neurodevelopmental conditions) are vulnerable to mental health crisis.
- May be multifactorial
- Several consequences (as in problem behavior)
- Mental Health Crisis Assessment Scale-Revised- MCAS-R (*Kalb and Vasa)*
- 23 item, parent report


Mental Health Crisis Screening in Youth with Autism Spectrum Disorder

Luther G. Kalb[a,b], Frank DiBella[c], Yeon Sik Jang[d], Michael Fueyo[c], Rajneesh Mahajan[a,e], and Roma A. Vasa[a,e]

2022

Safety Assessment

- Is there a ***risk of significant harm*** to self, to others or property destruction?
- Is there an ***imminent risk*** of physical harm to self or others?
- Is it a ***crisis situation***?
- Ultimately, level requires clinical judgement
- How can the patient be managed in the least restrictive setting?
- Outpatient (least restrictive) -> Intensive outpatient -> Partial hospitalization -> Inpatient (most restrictive).
- Psychiatric boarding of patients with DD in the emergency rooms for prolonged durations due to limited to no appropriate inpatient beds.

Inpatient Treatment

- **Very few inpatient units** are available for autistic individuals.
- **2 in Maryland** – The neuropsychiatry units at Sheppard Pratt and NBU at KKI.
- A **multidisciplinary team** approach is essential.
- Team members should be **comfortable and trained** in working with autistic individuals with challenging behaviors.
- Team members should have **a general understanding/knowledge** about various aspects of care children with ASD, as well as their own specific disciplines.
- There are **no guidelines** for inpatient treatment.
- Several studies through the Simon's Foundation sponsored **Autism Inpatient Collection**.
- Awareness of empirical data/studies – rational approach to treatment, so that that there is no random cocktail of multiple medications. If going out of the purview of empirically based treatment approaches, should be able to justify the approach.

Take Home Points

- Converging evidence has delineated ASD to be a genetically based complex neurodevelopmental disorder with marked heterogeneity in its etiology and clinical presentations.
- Screening and surveillance should be done at every age by primary care providers and specialists with a comprehensive evaluation and testing if indicated.
- Patients diagnosed with ASD are vulnerable to develop both medical and mental health comorbidities which may require specialist treatments.
- Psychiatric co-occurring disorders in ASD should spur further and ongoing assessment for other co-occurring disorders.
- There is a limited evidence base for efficacy of psychotropic medications in ASD, yet they are commonly used by themselves or in combination with other modalities.
- Use of psychotropic medications and the level of care is driven by safety concerns and interfering comorbid conditions or behaviors.

Thanks for your attention!