Autism Spectrum Disorder: Treating Target Symptoms

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Learning Objectives

1st

Neurodiversity

Review the concept of neurodiversity

OVERVIEW

2nd

Case Studies

Review a case of a patient with Autism Spectrum Disorder

CASES

3rd

Causes and Presentation

Introduce the concept of Target Symptoms in the context of A.S.D.

BEHAVIORS

4th

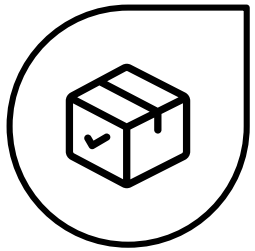
Approach

Develop an approach to choose interventions that will match to the Target Symptom

MANAGE

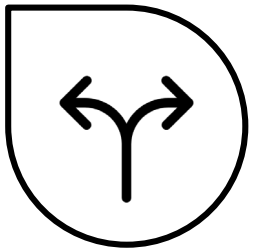
OVERVIEW 01

Developmental Disability vs. Neurodiversity



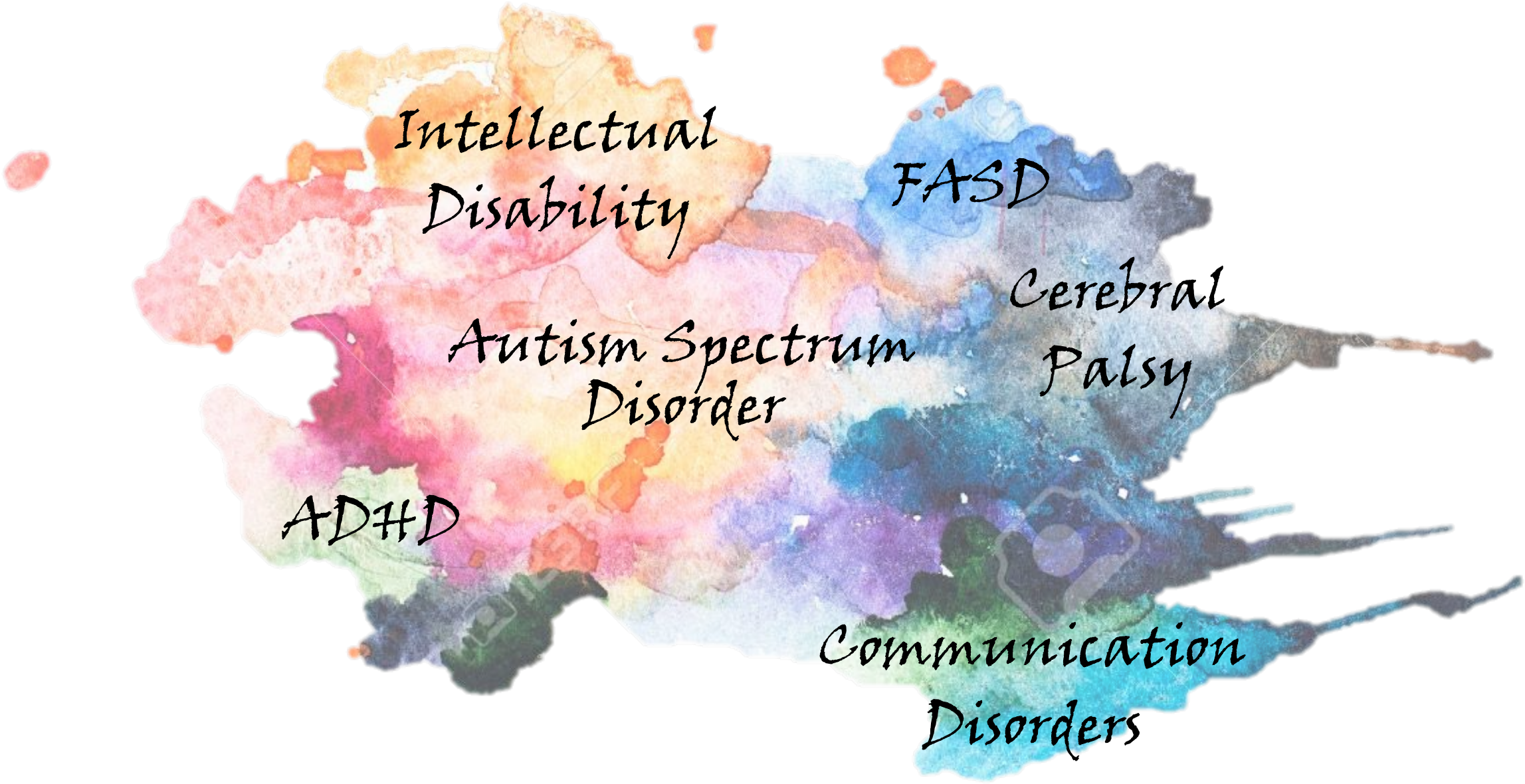
Developmental Disability

- Individuals with neurodevelopmental differences who are necessarily functionally impaired due to their difference



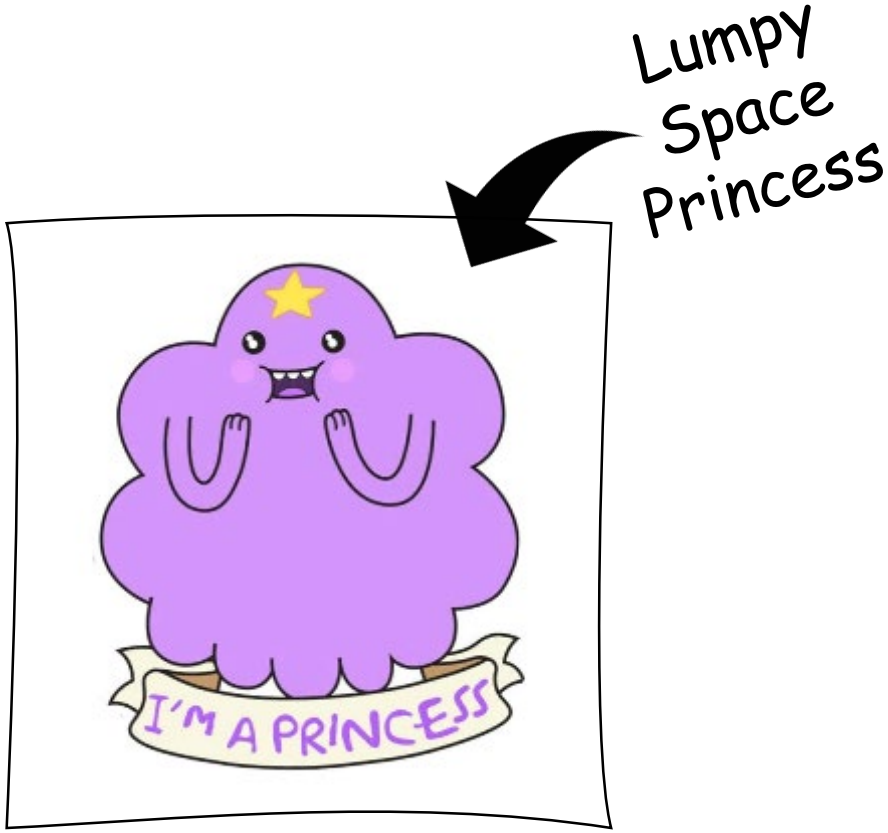
Neurodiversity

- Spectrum of neurodevelopmental differences
- Brain differences do not necessarily indicate disability or dissatisfaction
- Recognition of strengths and abilities


Intellectual Disability
FASD
Cerebral Palsy
Autism Spectrum Disorder
ADHD
Communication Disorders

Lumpers or Splitters?

Researchers



Me

Overlaps in Behavior Problems

In this study of 179 caregivers (83% mothers) of children 4 to 13 years old with CP (n=77), ASD (n=58), and GDD/ID (n=44):

- Substantial overlap within subscales (especially between ASD and GDD/ID)
- ASD received higher ratings than CP on all subscales
- Hyperactivity-inattention subscale ratings highest for all conditions

Conclusion: Behavioral problems are not unique or specific to any condition. Clinicians must be attuned to commonalities of behavior problems across diagnoses, irrespective of syndrome-specific expectations

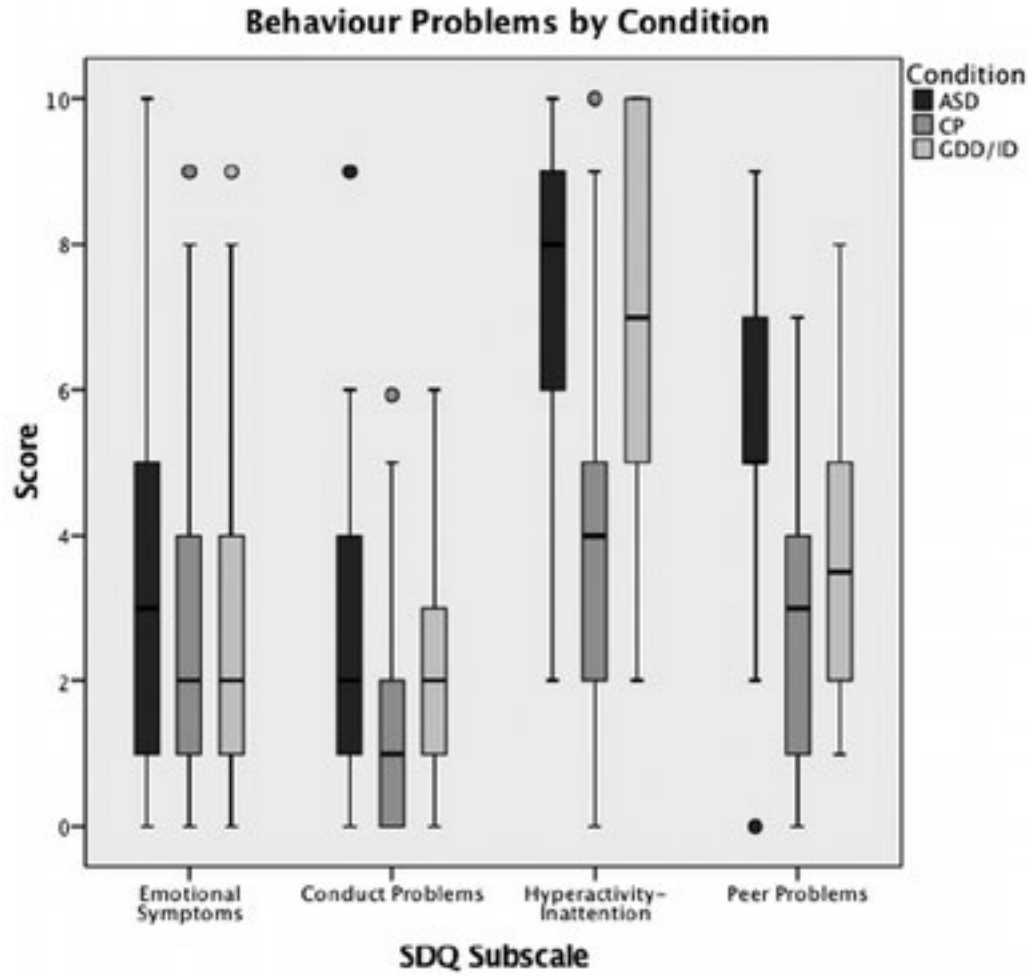


FIGURE 2 Box plots for Strengths and Difficulties Questionnaire (SDQ) subscales across conditions. ASD, autism spectrum disorder; CP, cerebral palsy; GDD/ID, global developmental delay/intellectual disability

Gardiner et al, 2020

CASES 02

Case Study 1

Demographics

8 year old female, adopted, attending grade 2

Past Medical History

Autism Spectrum Disorder

Medications

Melatonin
Restoralax
Vitamin D, fish oil

Presenting Behavior

Worsening behavior since last year: Temper tantrums, crying with separation, unfamiliar faces, when dad leaves for work

Previous Management

Behavioural Therapy
Risperidone 0.25mg

Case Study 2

Demographics

14 year old male living with bio parents and younger brother

Past Medical History

Autism Spectrum Disorder
ADHD

Medications

Aripiprazole 30mg
Quetiapine 300mg
Guanfacine XR 6mg

Presenting Behavior

Aggression towards family
Responding to limits being set.
Sleep disturbance (<5h per night for 1 week)

Previous Management

Quetiapine 25-50mg PRNs
Risperidone
Adderall XR
Fluoxetine

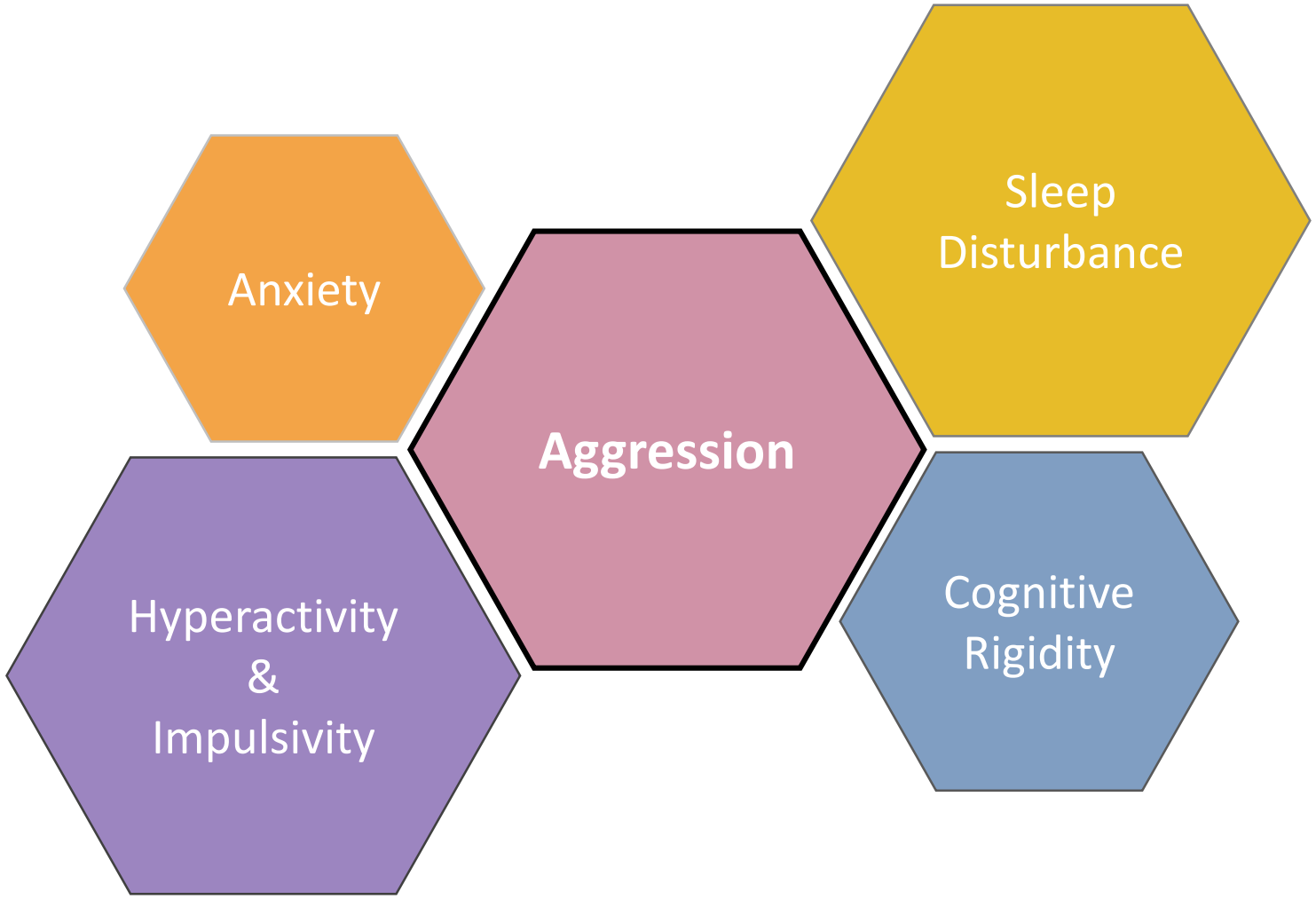
BEHAVIORS | 03

Burden of Behavioral Problems

- point prevalence: 22.5% (any behavioral problem in individuals with ID/NDD, across all levels of function)
- 12-month prevalence: 51.8% (any aggressive behavior)
  - 37.6% verbal aggression
  - 24.4% self-oriented
  - 24.4% physical aggression
  - 24% property damage
  - 9.8% sexually aggressive behavior
  - 4.9% of behaviors led to injury of the victim
  - few gender differences were observed
- often highly concerning for parents/caregivers and teachers, major contributor to caregiver burnout

Crocker 2006, Cooper 2007

Target Symptoms



Aberrant Behavioral Checklist

Percent item endorsement across age groups.

	≤2 (n = 28)	2 (n = 33)	3 (n = 20)	4 (n = 16)	Total (N = 97)
Irritability					
Injures self	**85.2**	**81.8**	**70.0**	62.5	**77.1**
Aggressive to others	63.0	**90.9**	**80.0**	68.8	**77.1**
Screams inappropriately	53.8	**71.9**	65.0	62.5	63.8
Temper tantrums	**96.4**	**93.8**	**95.0**	**81.3**	**92.7**
Irritable	60.7	**87.9**	65.0	**75.0**	**73.2**
Yells inappropriately	28.6	59.4	65.0	56.3	51.0
Depressed	**7.1**	27.3	26.3	**12.5**	**18.8**
Needs demands met quickly	**75.0**	**93.9**	**75.0**	**87.5**	**83.5**
Cries over minor things	42.9	69.7	45.0	43.8	52.6
Mood lability	42.9	**72.7**	**70.0**	56.3	60.8
Cries/screams inappropriately	42.9	**72.7**	50.0	56.3	56.7
Stomps feet/banging on objects	34.6	**75.8**	**70.0**	**75.0**	63.2
Deliberately hurts self	**71.4**	**72.7**	**75.0**	50.0	69.1
Does physical violence to self	67.9	69.7	**78.9**	**75.0**	**71.1**
Throws temper tantrums	**82.1**	**97.0**	**95.0**	**87.5**	**90.7**
Lethargy, Social Withdrawal					
Listless, sluggish	**0.0**	**9.1**	**15.0**	**18.8**	**9.3**
Seeks isolations	**14.3**	30.3	35.0	50.0	29.9
Preoccupied	25.0	40.6	30.0	43.8	34.4
Withdrawn	**14.3**	**12.1**	35.0	37.5	21.6
Fixed facial expression(s)	**7.1**	27.3	30.0	**18.8**	20.6
Sits and watches others	**3.6**	21.2	**10.0**	25.0	**14.4**
Resists physical contact	**3.6**	33.3	30.0	**18.8**	21.6
Isolates self	**10.7**	**15.2**	30.0	50.0	22.7
Sits/stands in one position	**14.3**	**12.1**	**10.0**	**6.3**	**11.3**
Unresponsive to structured activity	**17.9**	31.3	50.0	31.3	31.3
Difficult to reach/contact	39.3	60.6	55.0	75.0	55.7
Prefers to be alone	**7.4**	**15.2**	35.0	43.8	21.9
Communicates without words/gestures	21.4	30.3	50.0	56.3	36.1
Inactive	**3.6**	21.2	**5.0**	**0.0**	**9.3**
Responds negatively to affection	**7.1**	39.4	**15.8**	25.0	22.9
Shows few social reactions	**10.7**	33.3	47.4	56.3	33.3
Stereotypic Behavior					
Recurring body movements	32.1	43.8	40.0	68.8	43.8
Stereotypy	38.5	50.0	47.4	66.7	48.9
Odd/bizarre behavior	**14.3**	42.4	45.0	50.0	36.1
Moves or rolls head back and forth	21.4	28.1	**10.0**	31.3	22.9
Hand, body, or head stereotypy	32.1	50.0	35.0	62.5	43.8
Arm or leg stereotypy	23.1	28.1	31.6	53.3	31.5
Body rocking	25.0	21.2	20.0	25.0	22.7
Hyperactivity, Noncompliance					
Excessively active	24.0	**71.9**	68.4	**93.3**	61.5
Boisterous	40.7	**75.8**	63.2	62.5	61.1
Impulsive	29.6	66.7	**78.9**	**75.0**	60.0
Restless	50.0	**75.8**	**75.0**	**81.3**	69.1
Disobedient	57.1	**78.8**	**80.0**	**87.5**	**74.2**
Disturbs others	21.4	**81.8**	**80.0**	**75.0**	62.9
Uncooperative	46.4	**72.7**	**70.0**	81.3	66.0
Does not attend to instructions	51.9	**75.8**	**85.0**	**75.0**	**71.9**
Disrupts group activities	29.6	59.4	**85.0**	53.3	55.3
Does not stay in seat	40.7	**84.8**	**75.0**	**87.5**	**70.8**
Will not sit still	37.0	66.7	**70.0**	**93.8**	63.5
Easily distractible	44.4	**75.0**	**70.0**	**80.0**	66.0
Constantly runs or jumps	**17.9**	**72.7**	65.0	66.7	54.2
Pays no attention when spoken to	42.9	68.8	65.0	**86.7**	63.2
Excessively active	50.0	60.6	65.0	**86.7**	62.5
Deliberately ignores directions	46.4	69.7	**70.0**	**73.3**	63.5
Inappropriate Speech					
Talks excessively	**14.8**	36.4	30.0	26.7	27.4
Repetitive speech	**14.3**	46.9	25.0	26.7	29.5
Talks to self loudly	**14.3**	33.3	**10.0**	26.7	21.9
Repeats words/phrases	25.0	60.6	45.0	33.3	42.7

Note: Items in bold are either classified as "highly endorsed" (i.e., 70% or greater of the sample indicated the behavior occurred at some severity level) or "low endorsed" (i.e., 20% or less of the sample of the sample indicated the behavior occurred at some severity level).

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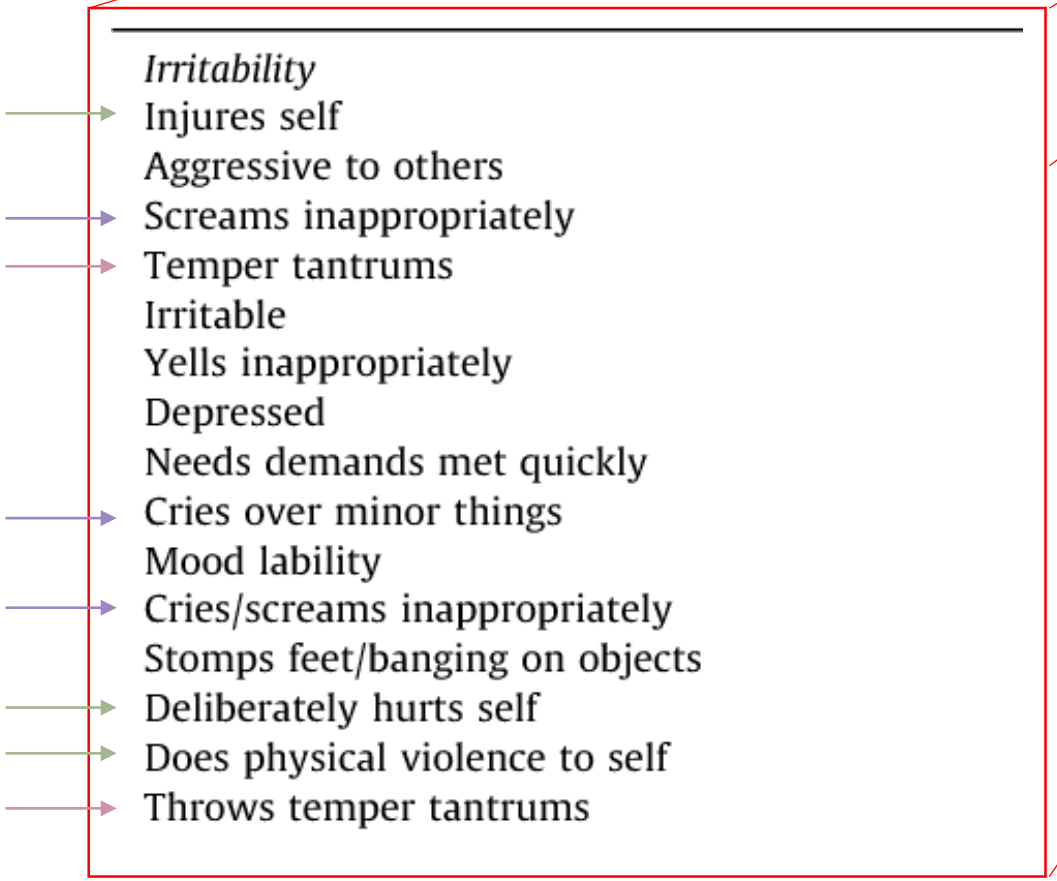

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Understanding Behaviors

Learning Theory

Behaviors are reinforced if they produce a desired outcome

Stress Threshold Theory

A lower capacity to cope with stress leads to problematic behaviors when stress levels surpass the capacity to cope

Unmet Needs Theory

Every child has a set of physical, social, and emotional needs but may not be able to communicate when these needs are not being met

MANAGEMENT | 04

General Approach

ASSESSMENT

TEAM

NON-PHARMACOLOGICAL

PHARMACOLOGICAL

FOLLOW-UP

General Approach

ASSESSMENT

TEAM

NON-PHARMACOLOGICAL

PHARMACOLOGICAL

FOLLOW-UP

- characterize the behaviour, onset/triggers, duration/frequency, alleviating factors, etc.
- consider medical issues:
  - pain/discomfort, sleep disorders, GI upset (constipation/diarrhea), other medical conditions
- consider comorbid psychiatric issues:
  - ADHD, anxiety, depression, psychosis, bipolar, OCD, etc.
- consider baseline measurements
- consider baseline investigations

General Approach

ASSESSMENT

TEAM

NON-PHARMACOLOGICAL

PHARMACOLOGICAL

FOLLOW-UP

- include the parents/caregivers!
  - psychoeducation
  - patient/parent educational resources
  - community resources
  - respite
- behavioural therapists
- social workers
- educational/occupational accommodations

General Approach

ASSESSMENT

TEAM

NON-PHARMACOLOGICAL

PHARMACOLOGICAL

FOLLOW-UP

Environmental Changes

- optimize familiarity – ensure routine and structure, ensure consistent with caregivers and support workers, anticipatory work with potential upcoming changes; reduce unpredictability when possible
- optimize the environment – reduce opportunity for overstimulation, use visual cues
- optimize physical health – ensure any issues with vision, hearing, pain/discomfort are managed

Applied Behaviour Analysis

- behavioural therapy and interventions
- learning new responses or making environmental changes to help child learn new behaviours
- positive reinforcement, frequent rewards

CBT

- comorbid anxiety/depressive symptoms
- sexual compulsions/behaviors that do not impact conventional sexual activity (paraphilia guidelines)

General Approach

ASSESSMENT

TEAM

NON-PHARMACOLOGICAL

PHARMACOLOGICAL

FOLLOW-UP

- Antipsychotics
- Anticonvulsants
- Antidepressants
- Psychostimulants
- Sleep Aids
- Opioid receptor antagonists

Autism Spectrum Disorder

5 Target Symptoms and their pharmacological choices:

- **Sleep**
  - Melatonin, Clonidine, low dose Quetiapine
- **ADHD** – **symptoms** (attention/focus)
  - Usual ADHD Meds Biphentin, Concerta, Vyvanse, Strattera
- **Anxiety** (Could include but not limited to: speech, behavior, food, play, routine, compulsion, worries, excessive need for reassurance)
  - SSRI medications; sometimes Benzodiazepines but be careful of paradoxical effect
- **Cognitive Rigidity** "stuckness" (eg. Difficulty switching from activity to a different activity)
  - Aripiprazole, Risperidone
- **Aggression** towards self or others (includes meltdowns)
  - The behaviour that is seen by people but it usually originates out of Anxiety or Cognitive Rigidity
    - Aripiprazole, Risperidone, Quetiapine, Olanzapine, Clonidine, Valproic Acid

We need to look at what of the above symptoms we want to <u>target</u>. Sometimes we use medications to treat target symptoms. Alternatively or in conjunction; education/information, parent supports and behavioral help (new skills) can be utilized.

History of Pharmacotherapy Research in Autism-Related Behavioral Problems

- 1970s-1980s: first generation antipsychotics (primarily haloperidol)
- 1980s-1990s: naltrexone
- 1990s: tricyclic antidepressants, clonidine
- **2000s onward: second generation antipsychotics (primarily risperidone and aripiprazole)**
  - SGAs>haloperidol, and lower discontinuation rates due to side effects

Antipsychotics: Risperidone

FDA Approved

- FDA approved in 2006 for autism-related irritability in 5-17-year-olds

Current Available Evidence	Numerous double-blind, placebo-controlled RCTs Multiple open-label studies Head-to-head studies with haloperidol and aripiprazole Studies with adjunctive NAC, topiramate, amantadine Studied in children 2-17yo (minimal evidence of efficacy in <5yo) with ASD, ID, treatment-resistant aggression in ADHD, Down's Syndrome, and Fragile X
Effective For	Irritability and hyperactivity (ABC scale) Stereotyped behaviors Social withdrawal, aggression, impulsivity
Suggested Doses	1 RDBPCT with n=96 of 5-17yo with ASD showed high dose (1.25mg-1.75mg) more effective than low dose (0.125-0.75mg) NICE guidelines: start at 0.25mg (if<20kg) – 0.5mg (if>20kg) and ↑at 0.25-0.5mg increments q2 weeks to a max of 3mg/d
Side Effects	Weight gain, increased appetite, metabolic side effects, hyperprolactinemia

Persico 2021, Lamy 2020, Sabus 2019, Koren, 2015, NICE Guidelines 2015

Antipsychotics: Aripiprazole

FDA Approved

- FDA approved in 2009 for autism-related irritability in 6-17-year-olds

Current Available Evidence	3 double-blind, placebo-controlled RCTs Multiple open-label studies Head-to-head studies with risperidone Studied in children 6-17yo with ASD
Effective For	Irritability and hyperactivity (ABC scale) Stereotyped behaviors
Side Effects	typically mild; weight gain, increased appetite, sedation, agitation

- switches from risperidone were tolerable and reduced med-induced sleep disturbance, hyperprolactinemia, and increased appetite
- relapse prevention: n=85 children 6-17yo with ASD followed x16wks after stabilization
  - no difference between aripiprazole and placebo in time to relapse, but post-hoc analysis showed NNT=6 to prevent one additional relapse

Persico 2021, Lamy 2020, Sabus 2019

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- 1990s: tricyclic antidepressants, clonidine
- 2000s onward: second generation antipsychotics (primarily risperidone and aripiprazole)
- **2000s-2010s: SSRIs/SNRIs, mood stabilizers, psychostimulants, sleep aids**
    - symptom-specific approaches (ie. ADHD-related symptoms, restricted repetitive behaviors, sleep disturbance, etc.)

Antidepressants: SSRIs and SNRIs

- RCTs of SSRIs (fluoxetine, fluvoxamine, citalopram, sertraline) and SNRI (venlafaxine) primarily examined repetitive behaviors in autism with mixed results

- no RCTs in children demonstrated improvements in irritability, aggression, hyperactivity, impulsivity
    - studies in adults demonstrate reduction in irritability with SSRIs and SNRIs

- many studies reported an increase in agitation, hyperactivity, and aggression with SSRIs

- no RCTs examining the effects of SSRIs/SNRIs in NDD youth with comorbid anxiety or depression
    - majority of treatment studies focus on CBT

Persico 2021, Lamy 2020, Sabus 2019

Mood Stabilizers and Anticonvulsants

- Valproate:
  - 1 RCT of n=30 with PDD-NOS demonstrated no difference between VPA and PLB in irritability or aggression
  - 2 subsequent RCTs of n=13 and n=27 children with ASD demonstrated significant difference in irritability
  - 1 RCT n=6 demonstrated that pre-treatment with valproate reduced fluoxetine-induced irritability
- Levetiracetam: 1 DB-RCT (n=20 children with ASD) found no improvement in irritability, impulsivity, or hyperactivity; significant adverse effect of increased aggressiveness
- Lamotrigine: 1 RCT, no impact on irritability
- Topiramate: 1 RCT limited benefits for irritability, hyperactivity in 2 out of 5 children
- Lithium: effective for bipolar-related irritability in children with comorbid ASD + BPAD

Persico 2021

Sleep Aids

- Melatonin – improves sleep (sleep duration, sleep onset latency, night-time awakenings)
  - Melatonin + behavioural interventions + parent education were most effective compared to other pharmacological alternatives
  - 6 studies report improvements in daytime behavior (irritability, temper tantrums, academic performance, social interaction) in children with ASD
  - 1 multisite, uncontrolled, open-label study, n=99 children 6-15yo with various developmental disorders (ASD, ADHD, ID, motor disorders, learning disorder, communication disorders) treated with melatonin (up to 4mg) for 26 weeks → reduction in irritability and hyperactivity

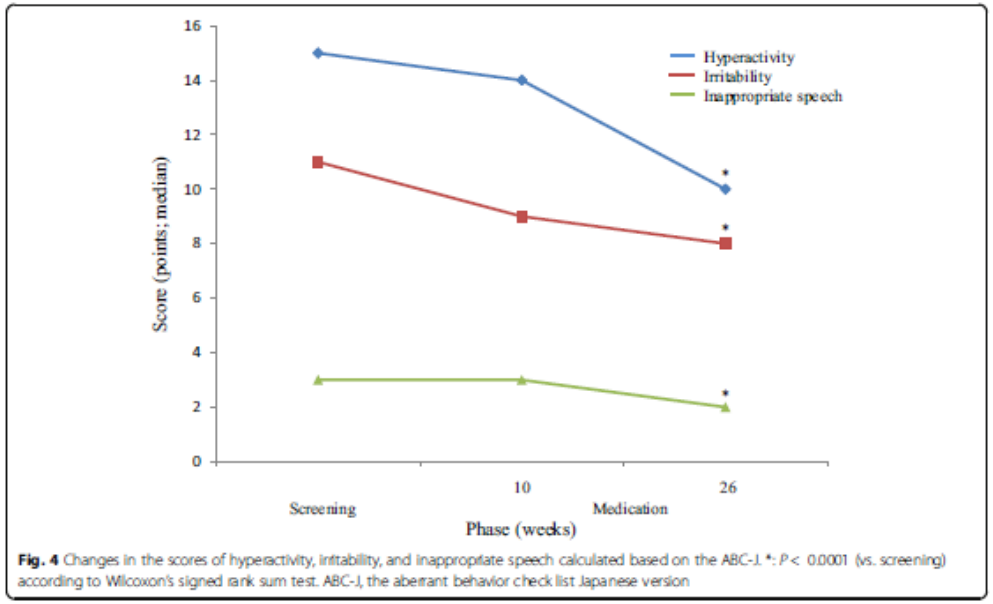

Fig. 4 Changes in the scores of hyperactivity, irritability, and inappropriate speech calculated based on the ABC-J. *: $P < 0.0001$ (vs. screening) according to Wilcoxon's signed rank sum test. ABC-J, the aberrant behavior check list Japanese version

- Trazodone: no specific studies in children with NDDs

Rossignol 2011, Yuge et al 2020

Stimulants

- Methylphenidate:
  - numerous RDBPCTs children with autism and ADHD-related symptoms
  - significant improvement in hyperactivity/impulsivity and inattention symptoms
  - most common adverse effects: irritability, appetite loss, insomnia, and emotional outbursts
  - lower response rate and less symptom reduction compared to children with ADHD and no comorbidities (50-60% vs. 75% response rate; 20-25% vs. 50% symptom reduction)
- Atomoxetine: 3 RCTs, several chart reviews and open label studies
  - improvements in hyperactivity/impulsivity, some improvement in inattention
  - ATX + parent training = lower doses of atomoxetine
- Guanfacine: 2 RCTs, 2 open label chart reviews, some case reports
  - Improvements in hyperactivity/impulsivity and inattention
  - ~45-50% response rates
  - non-responders or intolerance of MPH → 48% responded to guanfacine (open label study of 25 ASD children)

Persico 2021

Autism Spectrum Disorder

5 Target Symptoms and their pharmacological choices:

- **Sleep**
  - Melatonin, Clonidine, low dose Quetiapine
- **ADHD** – **symptoms** (attention/focus)
  - Usual ADHD Meds Biphentin, Concerta, Vyvanse, Strattera
- **Anxiety** (Could include but not limited to: speech, behavior, food, play, routine, compulsion, worries, excessive need for reassurance)
  - SSRI medications; sometimes Benzodiazepines but be careful of paradoxical effect
- **Cognitive Rigidity** "stuckness" (eg. Difficulty switching from activity to a different activity)
  - Aripiprazole, Risperidone
- **Aggression** towards self or others (includes meltdowns)
  - The behaviour that is seen by people but it usually originates out of Anxiety or Cognitive Rigidity
    - Aripiprazole, Risperidone, Quetiapine, Olanzapine, Clonidine, Valproic Acid

We need to look at what of the above symptoms we want to <u>target</u>. Sometimes we use medications to treat target symptoms. Alternatively or in conjunction; education/information, parent supports and behavioral help (new skills) can be utilized.

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