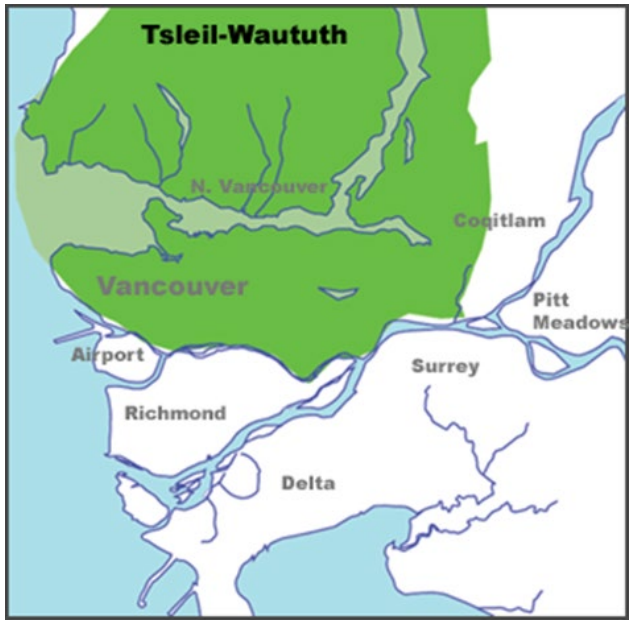
We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



Autism Spectrum Disorder

Andrea Saliba
Visiting Psychiatric Fellow
MD (Melit), MRCPsych (UK), CCT (psych)

Learning Objectives

- Define ASD
- Identify Comorbidities
- Understand Assessment Process
- Understand Irritability
- Evaluate Pharmacotherapy

Patient information

- 12 years old, male, 40Kg
- Chief Complaint & History of Present Illness
  - Low functioning ASD, requiring total care
  - Self injurious behavior (SIB)
- Reason for admission:
  - Blood work
  - Imagining
  - Physical examination
  - Second opinion

Diagnoses

- Psychiatric History
  - ASD (non-verbal)
  - Intellectual disability
  - ADHD
  - PTSD
  - Attachment Disorder
  - Self-Injurious Behaviors
- Medical History
  - Constipation
  - Dental caries
  - PICA

Admission medications

Drug	*Dose/Frequency*	Indication
guanfacine ER	2 mg HS	ADHD
Concerta	27 mg DAILY	ADHD
olanzapine	5mg BID and 2.5mg (1200)	Irritability of ASD
trazodone	25 mg (0800,1600) 50mg HS	Sedation
valproic acid	250 mg BID	Irritability of ASD
naproxen	500 mg PO BID	Dental pain
acetaminophen	650 mg PO Q6HR PRN	Pain
quetiapine	25mg PO TID PRN	Sedation
melatonin	3 mg SL HS PRN	Sleep
lorazepam	1-2 mg SL Q1H PRN	Sedation
polyethylene glycol	17 gm PO DAILY PRN	Constipation
ibuprofen	400 mg PO Q6HR PRN	Pain

Previous medication trials

Start Dates	*Drug*	*Dose/Route/Frequency*	*Comments*
27AUG24	clonidine	0.075mg AM, 0.05mg qNoon, 0.075mg HS	Worsened behavior at higher doses. Reported sedation, hypersalivation, aggression.
Oct 2020	risperidone	1.5 mg BID	Switched in Sept 2024
?? dates	lisdexamfetamine	?? dose	Behavioral activation reported; ?monotherapy trial
?? dates	sertraline	?? dose	Behavioral activation reported; ?monotherapy trial
May 2024	ferrous gluconate	300 mg (30 mg elemental iron) daily	Constipation

Family & Social History

- Birth – 6 yrs: living with mom, homeless, trauma.
  - Siblings – MCFD
  - Supervised visits once a week until 10 years old
- 6 yrs – 8 yrs: 6 different family homes
- 8 yrs – present: same care home
  - 1 year worsening behavior

Physical health

- Physical:
  - Bruising and bleeding from right cheekbone
  - Bloody gloves
  - Repetitive hitting R face
  - Vitals appropriate for age
  - Medically stable, no acute injury
  - Dental caries
  - ?Constipation.
  - Required sedation for physical examination and to draw labs

Physical health

- Imaging:
  - Sinus and facial bones X ray WNL
  - Head CT - WNL
- Blood work:
  - Valproate level 248(LL 350)
  - WBC 6.3, Hb 141 MCV 85.9, Lytes normal
  - CRP < 1, albumin 37
  - LFT all normal

Drug therapy problems identified

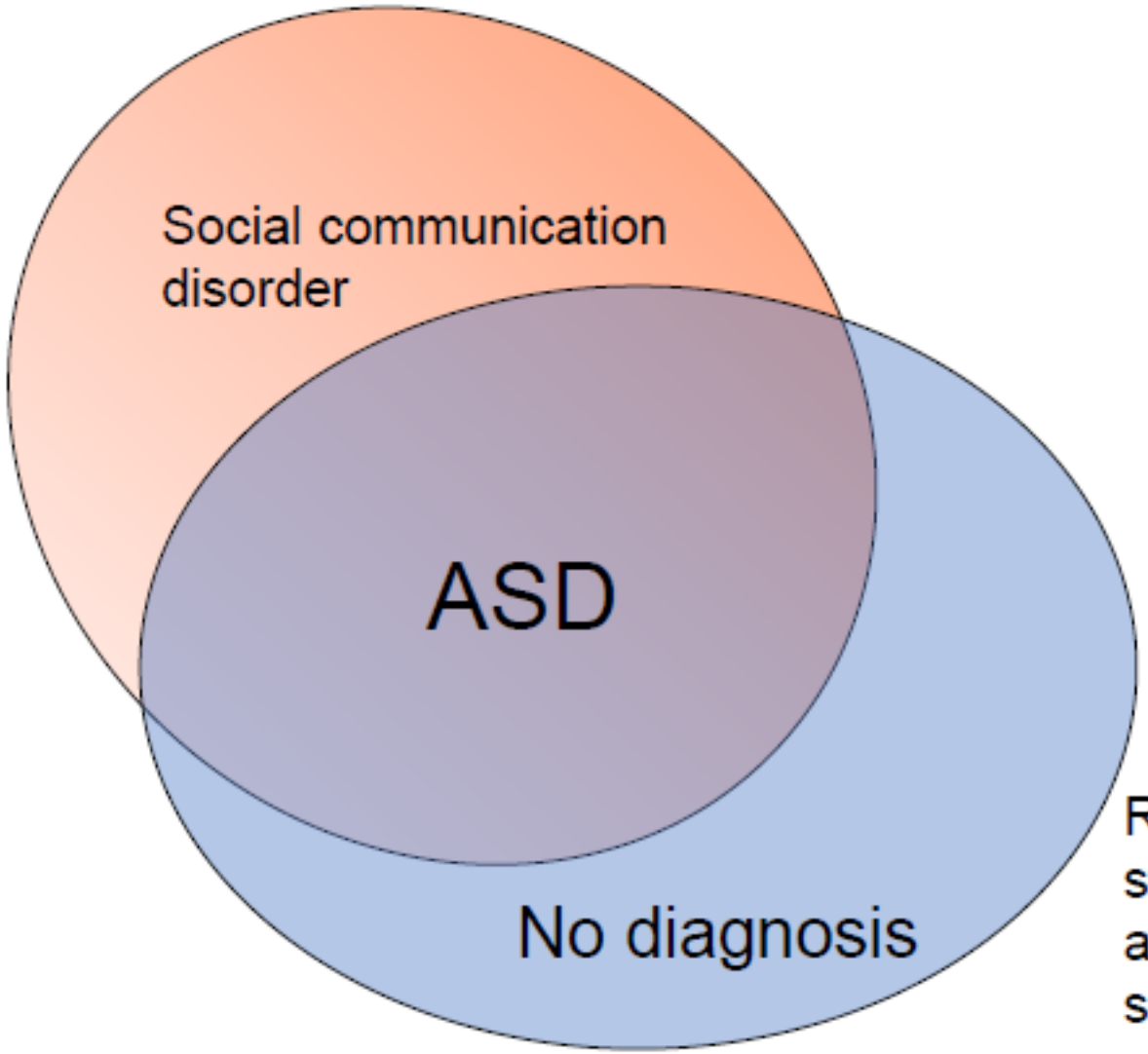
- Guanfacine ER: dose requires reassessment
- Olanzapine: for treatment of irritability in ASD and requires reassessment
- Valproate: level subtherapeutic and dose requires reassessment
- Concerta: dose requires reassessment
- Trazodone: experiencing adverse effect of sedation and timing requires reassessment
- Lorazepam: potentially experiencing an interaction with valproate and dose requires reassessment
- Melatonin: dose requires reassessment

History of diagnostic guidelines

- Autism entered the scientific literature in 1944, but it wasn't until DSM III, published in 1980, that it became a separate diagnostic category.
- DSM-IV, released in 1994 and revised in 2000, laid out six domains that define **autistic disorder** within a triad of impairments.
- DSM-5 released in 2013 revised diagnostic framework to reduce domains to just two – removing category of Asperger syndrome

DSM-5's conceptualization of the autism spectrum

Social – communication deficits



Repetitive, stereotyped interests and behaviours, sensory sensitivities

Skuse, 2012, JAACAP

DSM-5 criteria for ASD

- A: Persistent deficits in social communication and social interaction (ALL)
  - Deficits in social-emotional reciprocity
  - Deficits in nonverbal communicative behaviours used for social interaction
  - Deficits in developing, maintaining, and understanding relationships

American Psychiatric Association (2022)

DSM-5 criteria for ASD

- B: Restricted, repetitive patterns of behaviour, interests, or activities (≥ 2)
  - Stereotyped or repetitive motor movements, use of objects, or speech
  - Insistence on sameness, inflexible adherence to routines, or rituals
  - Highly restricted, fixated interests
  - Hyper-or hyporeactivity to sensory input or unusual

American Psychiatric Association (2022)

DSM-5 criteria for ASD

C. Symptoms must be present in the early developmental period

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

E: Disturbances are not better explained by ID or GGD

American Psychiatric Association (2022)

DSM-5 criteria for ASD

Specifiers

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

Severity levels

- Level 3 – requiring very substantial support
- Level 2 – requiring substantial support
- Level 1 – requiring support

American Psychiatric Association (2022)

Differential diagnosis

- Disorders of intellectual development
- Developmental language disorder (pragmatic language)
- Developmental Motor Coordination Disorder
- Attention Deficit Hyperactivity Disorder
- Stereotyped Movement Disorder
- Schizophrenia
- Schizotypal Disorder
- Social Anxiety Disorder
- Selective Mutism
- Obsessive-Compulsive Disorder
- Reactive Attachment Disorder
- Disinhibited Social Engagement Disorder
- Avoidant-Restrictive Food Intake Disorder
- Oppositional Defiant Disorder
- Personality Disorder
- Tic Disorders including Tourette syndrome
- Diseases of the Nervous System and other medical conditions
- Secondary to Neurodevelopmental Syndromes

ASD Assessment

- Standardized assessments
- Cultural biases & limitations of translation may affect performance
- Language proficiency must also be considered
- Where appropriately normed and standardized tests are not available, assessment requires greater reliance on clinical judgment based on appropriate evidence and assessment

Autism Diagnostic Observation Schedule - 2

The Autism Diagnostic Interview-Revised

- Provides categorical results for three domains:
  - Language/Communication
  - Reciprocal Social Interactions
  - Repetitive Behaviors/Interests
- Format: standardized interview and response coding
- Admin time: 90–150 minutes, including scoring
- Ages: children and adults with a mental age above 2 years

Rutter, M. (2003)

Benefits of diagnosing

- Connection to CYSN, access to resources
- Funding for therapies ($22k annual <6; $6k annual 6-18)
- School designation “G” (higher level of funding than “H”)
- A helpful lens through which to view a child’s challenges
- Connection to supportive community, parent networks, programs

ASD and Intellectual Ability

- Cognitive profile heterogeneous; strengths and weaknesses on specific subtests may differ in high and low-functioning ASD
- Intellectual profile may be associated with adaptive behaviour and not with core ASD features, as measured by ADI-R and ADOS (Mouga et al., 2016)
- On WISC, persons with ASD generally score higher in ‘‘Block design’’ and lower in ‘‘Comprehension’’.

Comorbidities

- Children with ASD can have other associated problems as well as skills
- 10% have special skill: music, art, memory, mathematical/ calculating
- Challenges:
  - Intellectual disability
  - Sensory abnormality
  - ADHD
  - OCD & SAD
  - Motor impairment
  - Epilepsy
- It is unclear to what extent these problems or skills are caused by the same process that leads to ASD.

Howlin et al (2009)
Romero et al (2016)

Irritability in ASD

- Irritability:
  - Abnormally sensitive
  - Tendency to easily exhibit uncontrolled anger or aggression
  - Catastrophic behavioral reactions in response to minor changes
- Common causes of aggression:
  - Impaired understanding of actions & consequences
  - Impaired ability to communicate and express wants & needs
  - Impaired coping skills
  - Conflict
  - Psychosocial dysfunction
  - Pain, constipation, seizures
  - Psychosis, mania, depression, suicidal or homicidal ideation
- Self injurious behavior in included in the ABC-irritability

Nazeer (2011)

Children and adolescents brain may…

- Be ‘damaged’ by therapeutic psychotropics (antidepressants, methylphenidate, dexamphetamine)
- Be ‘damaged’ by non-therapeutic substances (alcohol, nicotine, cannabis, amphetamines)
- Harm or be harmed by risky/impulsive behaviour (drinking, drug taking, violence, suicidality)
- Be ‘damaged’ if left undiagnosed and untreated

Psychopharmacology in ASD

- There is a growing number of pharmacological studies in ASD, often with methodological confounds:
  - Small sample size
  - Selection bias
  - Differing assessment methods
  - Often open label
  - No placebo, matching etc
- There are practice guidelines that we can use to guide management
- Ultimately, we need to be experts in interpreting the literature

Challenges in ASD

- More severe adverse effects
- Achieve an effective dose with minimum adverse effects
- Initiate in small doses and increased about every 5 half-lives
- Excluding any medical conditions
- Physical examination should be part of standard practice.
- Close monitoring for efficacy and adverse effects
- Use standardised behaviour ratings scales and adverse effect checklists

Polypharmacy is common

TABLE 1 Demographic and Clinical Composition of ASD Sample and Psychotropic Drug Use and Multiclass Polypharmacy by Demographic and Clinical Characteristics

Characteristic	Total ASD Subjects (n = 33 565) (N [%])	Proportion of ASD Subjects With Any Psychotropic Use (%)[a]	Proportion of ASD Subjects With Evidence of Multiclass Polypharmacy (%)[b]
Overall	33 565 (100)	21 334 (63.56)	11 598 (34.55)
Gender			
Male	27 479 (82)	63.55	34.36
Female	6086 (18)	63.60	35.41
Geographic region			
Northeast	5271 (16)	56.04	28.44
Midwest	11 561 (34)	67.79	39.35
South	12 090 (36)	65.96	34.99
West	4643 (14)	55.33	28.43
Race/ethnicity[c]			
White	17 796 (53)	67.33	38.03
African American/black	691 (2)	59.91	28.94
Asian	466 (1)	45.71	15.24
Hispanic	1366 (4)	55.93	25.99
Other	339 (1)	47.49	17.99
Unknown	12 907 (38)	60.43	32.10
Household income, $			
<50 000	3090 (9)	66.50	35.99
50 000–74 999	5149 (15)	67.37	36.71
75 000–99 999	4838 (14)	64.92	35.66
100 000–124 999	3596 (11)	63.01	34.43
≥125 000	2915 (9)	63.67	37.12
Unknown	13 977 (42)	61.15	32.56
Age group at index date[d]			
0–1 y	5609 (17)	33.77	9.89
2–10 y	19 987 (60)	63.51	32.33
11–17 y	7277 (22)	84.46	57.07
18–20 y	692 (2)	86.71	61.85
Co occurring conditions			
Epilepsy/seizure	2554 (8)	95.65	64.21
ADD	13 018 (39)	93.42	57.54
Anxiety	5507 (16)	86.73	59.32
Depression	4065 (12)	89.96	68.02
Bipolar disorder	3089 (9)	96.41	86.66
Psychiatrist visit	15 207 (45)	84.73	57.55

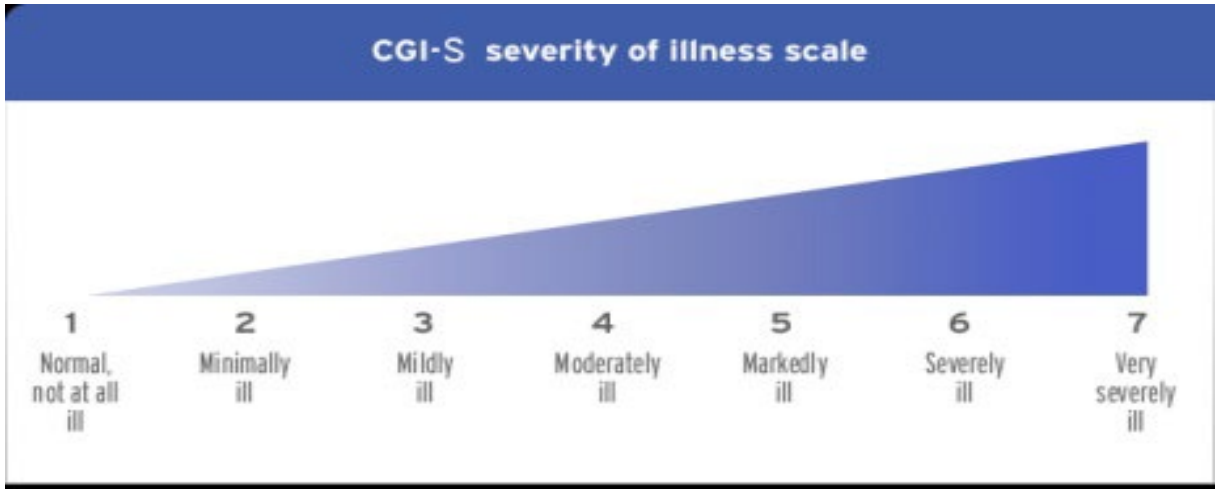
Spencer, D (2013)

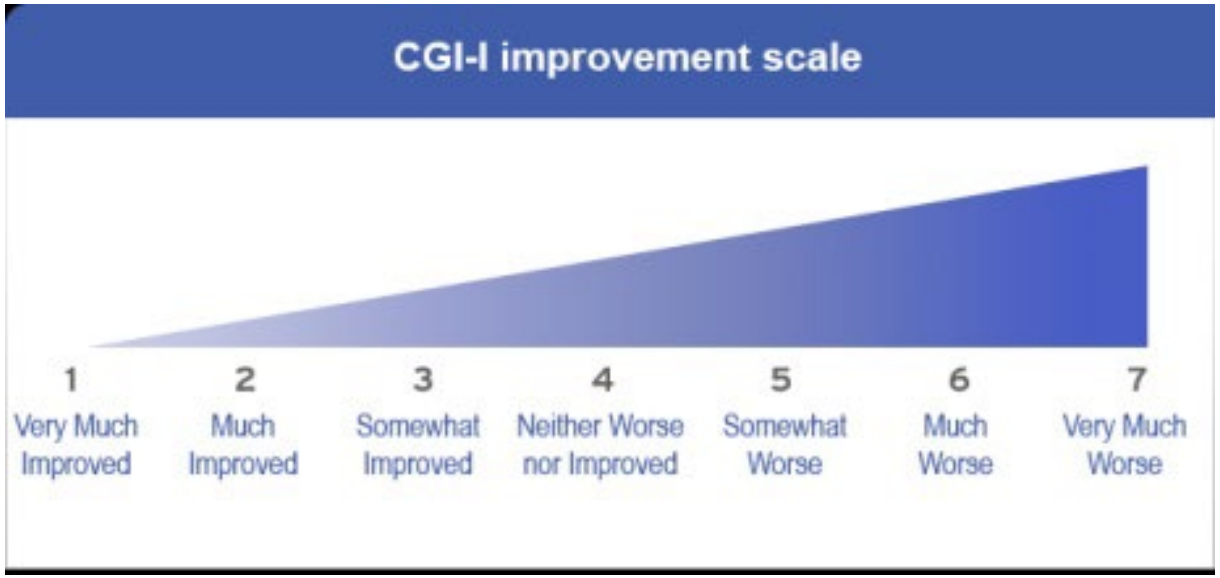
Aberrant Behavior Checklist - Irritability subscale

- Injures self
- Aggressive to others
- Temper tantrums
- Irritable
- Yells
- Depressed
- Demands
- Cries over minor annoyances
- Mood changes
- Cries and screams
- Stamps feet or bangs
- Deliberately hurts himself/herself
- Does physical violence
- Has temper outbursts

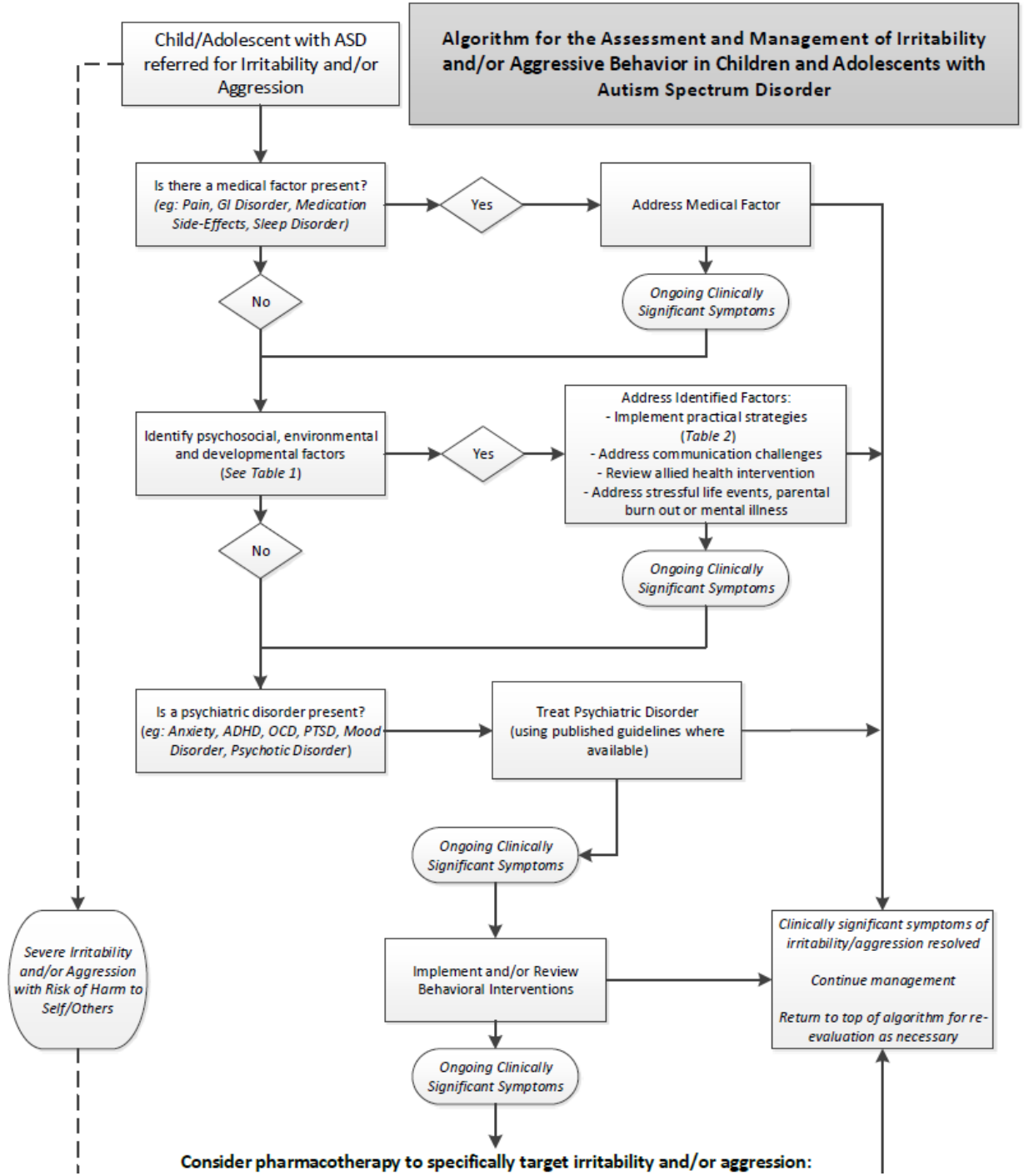
Aman, M. G. (1985)

Clinical Global Impressions

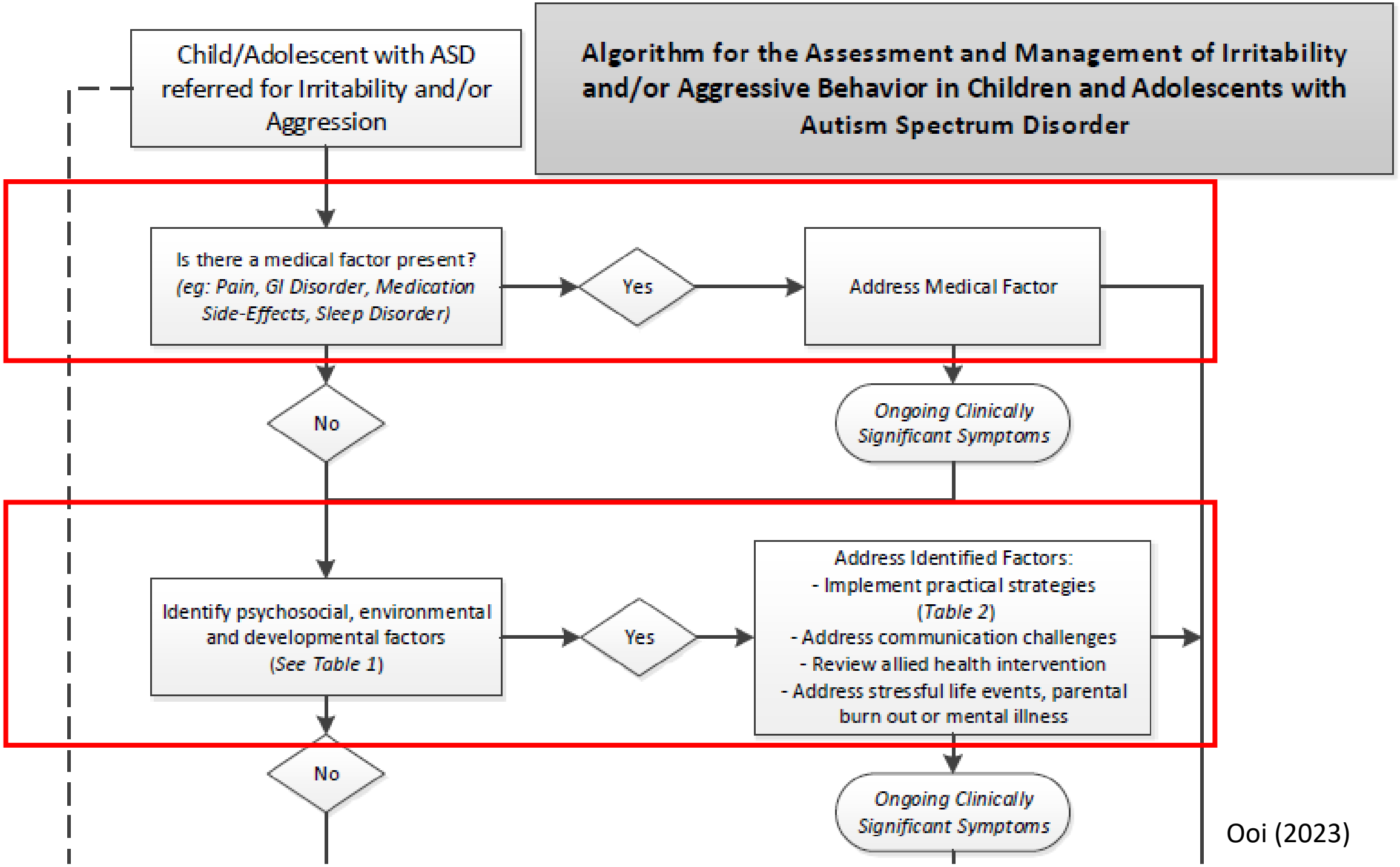




Toolan, C., (2022)


Child/Adolescent with ASD referred for Irritability and/or Aggression
Algorithm for the Assessment and Management of Irritability and/or Aggressive Behavior in Children and Adolescents with Autism Spectrum Disorder
Is there a medical factor present? (eg: Pain, GI Disorder, Medication Side-Effects, Sleep Disorder)
Yes
Address Medical Factor
No
Ongoing Clinically Significant Symptoms
Identify psychosocial, environmental and developmental factors (See Table 1)
Yes
Address Identified Factors:
- Implement practical strategies (Table 2)
- Address communication challenges
- Review allied health intervention
- Address stressful life events, parental burn out or mental illness
No
Ongoing Clinically Significant Symptoms
Is a psychiatric disorder present? (eg: Anxiety, ADHD, OCD, PTSD, Mood Disorder, Psychotic Disorder)
Treat Psychiatric Disorder (using published guidelines where available)
Ongoing Clinically Significant Symptoms
Severe Irritability and/or Aggression with Risk of Harm to Self/Others
Implement and/or Review Behavioral Interventions
Clinically significant symptoms of irritability/aggression resolved
Continue management
Return to top of algorithm for re-evaluation as necessary
Ongoing Clinically Significant Symptoms
Consider pharmacotherapy to specifically target irritability and/or aggression:

Ooi (2023)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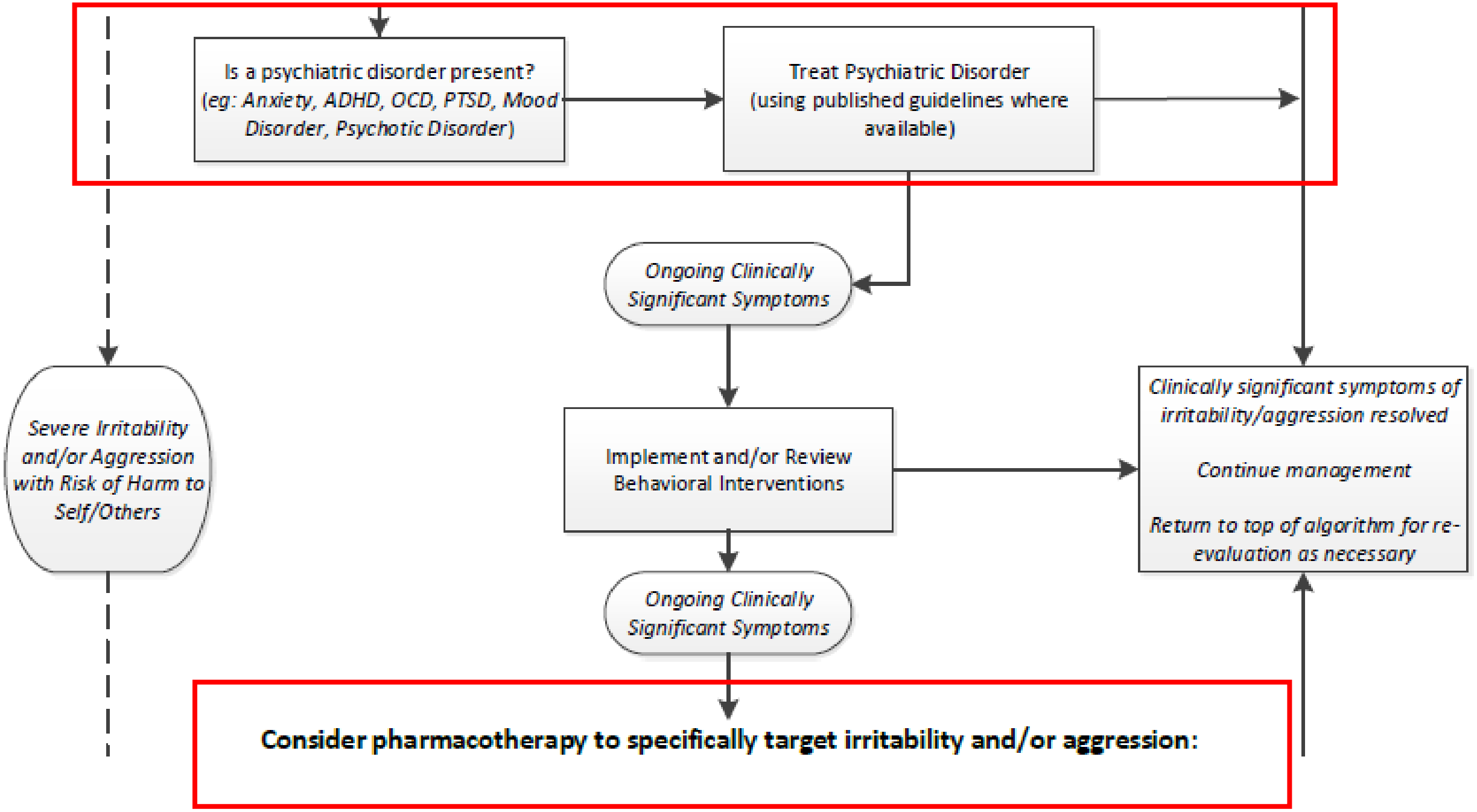
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Ongoing Clinically Significant Symptoms
Consider pharmacotherapy to specifically target irritability and/or aggression:

Ooi (2023)

Management

- Aggression towards others and the self are common problems in ASD.
- Behavioural and environment approaches should be first-line
- Severe and dangerous behaviours usually require pharmacotherapy
- Duration of recommended treatment is difficult to derive from published evidence, but treatment appears to be beneficial for up to 6–12 months.
- Efforts to reduce and possibly discontinue such treatment at the end of this period should be strongly considered.

Core ASD Treatment

- Currently there are no Health Canada approved pharmacological treatments that alleviate core ASD symptoms.
- Targeting problem behaviours and co-morbid psychiatric conditions with pharmacological interventions is, however, common practice.

Social and communication impairment

- No drug has been consistently shown to improve the core social and communication impairments
- **Risperidone and aripiprazole** may have a secondary effect through improvement in irritability.

Restricted repetitive behaviours and interests

- Risperidone and Aripiprazole have been shown effective in reducing repetitive behaviours in children who have high levels of irritability or aggression.
- SSRIs - fluoxetine, fluvoxamine, sertraline, citalopram and escitalopram.
  - Cochrane review published in 2013 found ‘no evidence of effect of SSRIs in children and emerging evidence of harm’.

Risperidone & aripiprazole

- 24 studies (n=1225) compared an atypical or typical antipsychotic to a placebo or other treatment
- Aripiprazole:
  - 8 studies: aripiprazole vs placebo or another atypical antipsychotic.
  - Most: once daily dose, fixed or flexibly-dosing, to a maximum of 15 mg/day.
  - Mean daily dose: 0.172 mg/kg/day - 0.354 mg/kg/day
- Risperidone:
  - 10 studies: risperidone vs placebo or other treatment.
  - Most: once daily dose.
  - Mean daily dosage for children <40 kg: 1.58 mg/day, >40kg: 2.27 mg/day
- **Risperidone** and **Aripiprazole** have been (relatively) reliably shown to help irritability, disruptive behaviours, aggression and hyperactivity. Both have been approved by the FDA to treat irritability associated with ASD.

Iffland, Cochrane review (2023)

Side Effects

- Weight gain and metabolic changes
- Increased appetite
- Somnolence (even with aripiprazole)
- Hyperprolactinemia with risperidone.
- Similar tolerability and efficacy profiles for risperidone and aripiprazole.

Iffland, Cochrane review (2023)

Guanfacine Vs Clonidine

Characteristic	Guanfacine	Clonidine
Absorption	Well absorbed, slow release in ER	Well absorbed
Half-life	17 hrs (ER)	6 hrs
Protein binding	70-80%	40-50%
Metabolism	3A4	2D6
Excretion	Renal and fecal excretion (~50% in urine)	Urinary excretion (40-60%)
Mechanism of action	Selective alpha-2A receptor agonist in CNS	Non-selective alpha-2 receptor agonist in CNS
CNS effects	Less sedating, improved focus and impulse control in ADHD	More sedating, reduces sympathetic activity, helpful for sleep or opioid withdrawal
Primary Use	ADHD, mild hypertension	ADHD, hypertension, insomnia, tic disorder

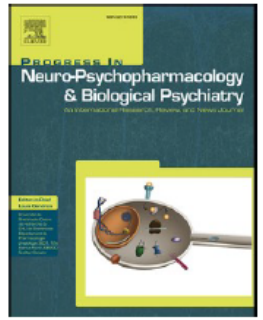
UpToDate 2024

Progress in Neuropsychopharmacology & Biological Psychiatry 110 (2021) 110326

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp



The pediatric psychopharmacology of autism spectrum disorder: A systematic review - Part I: The past and the present

Antonio M. Persico [a,*], Arianna Ricciardello [a], Marco Lamberti [b], Laura Turriziani [a], Francesca Cucinotta [a], Claudia Brogna [c,d], Benedetto Vitiello [e], Celso Arango [f]

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Persico, A. M., (2021)

Overall conclusion

Medication	References	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome Measures	Therapeutic effects	Side effects reported in the treated group
							hyperactivity	
Guanfacine	Handen et al. (2008)	RCT, crossover, 6 wks	11	5-9	1-3 mg/d	CGI-I, ABC-hyperactivity	Reduced hyperactivity. Responders: 5/11 (45%).	Sedation, irritability, enuresis,diarrhea, constipation, social withdrawal.
	RUPPAN Scahill et al. (2015)	RCT, 16 wks	62	5-14	1-4 mg/d ER (mode 3 mg/d)	ABC-hyperactivity, ADHDRS-IV, CGI-S/I, cognitive tests	Reduced hyperactivity and inattention, stereotypic behavior and inappropriate speech. Responders: 15/30 (50%).	Sedation, fatigue, decreased appetite, dry mouth, emotional/ tearful presentation, irritability, anxiety, hypotension.
	Politte et al. (2018)					HSQ-ASD, CASI, CSHQ, CYBOCS-ASD	Reduced opposition and repetitive behaviors. No change in anxiety and sleep.	

Persico, A. M., (2021)

Valproate

- 27 patients (84% male), mean 9.46 ± 2.65 years old
- valproate (divalproex) (titrated to effect & minimum level of 350 µmol/L)
- Monotherapy x 12 weeks
- Primary Endpoint Efficacy (ABC-I):
  - valproate: -7.5
  - placebo: -3.6
- Responders (CGI-I score < 2):
  - valproate: 63%
  - placebo: 9%
- moderate effect size (d=0.44)
- No differences in secondary measures (cY-BOCS, OAS-M)
- Adverse effects: Rash, polyuria, headache, severe agitation (1),
  - weight Increase:
    - valproate: 1.37 ± 2.91 kg
    - placebo: 1.34 ± 1.53 kg
  - No other metabolic tests

Hollander 2010

Recommendations

- Guanfacine ER
  - Dose titration by 1mg weekly
  - Target dose of 4mg/day (w/psychostimulant), i.e., 0.09mg/kg/day
  - If sleep is impacted, 4pm dosing instead of qHS (based on pharmacokinetics, off label)
  - Target ADHD symptoms, particularly hyperactivity.
  - May offer some reduction in irritability (SIB), unlike methylphenidate that can cause irritability (2% to 11%)
  - May offer some reduction in stereotypic behaviors, inappropriate speech, and opposition

UpToDate 2024

Recommendations

- Aripiprazole:
  - First line treatment for irritability of ASD
  - Particularly useful for hyperactivity (owing to it being a partial dopamine agonist)
  - Target dose 5mg/day; can ↑2.5mg/week, up to 15 mg/day if tolerated/required
  - Monitor for metabolic side effects, akathisia
- Olanzapine:
  - Taper off over 2 weeks after aripiprazole at target dose for 1 week

Recommendations

- Valproate:
  - Aim for serum valproate level in the 350-700 umol/L range; usually 15-20 mg/kg/day divided BID
  - Monitor levels and LFTs
- Concerta:
  - Dose optimisation to 36mg daily then 54mg daily can be considered
  - Usual max dose 54mg/day; may require 72 mg/day
- Naproxen: reassess since it was given for dental pain and extractions were completed
- Trazodone: consider slowly tapering as sedation may impact quality of life and sleep

Monitoring

System	Parameter	Frequency
Vitals	BMI and waist circumference. Weight BP, HR Height	Quarterly Baseline, 4 wks, 8 wks, 12 wks, then quarterly Every visit 6 monthly
Safety	Increased suicidal ideation and behavioral agitation	Each visit
CNS	Depression, anxiety, aggression, delusional thinking, hallucinations, mania, hostility, sleep SIB, ADHD symptoms	Each visit Each visit
CVS	Chest pain, unexplained syncope, ECG	Cardiology review if indicated
GI	S&S of pancreatitis	If clinically relevant
Derma	Signs of bruising/hemorrhage	If clinically relevant
Heme	CBC, LFTs, FBG, HbA1c, fasting insulin, lipids Valproate level TSH, total T4 Serum ammonia	Baseline, 3m, 6m, 1 year Baseline, 3m, 6m, 12m, then annually Every 5 days until levels stable, 3-6 months 3m, 6m, then yearly S&S of hyperammonemia
MSK	EPS, akathisia	Each outpatient visit

Follow-up

- Discharge meds:
  - Aripiprazole **2mg → 4mg HS**
  - Guanfacine **2mg → 3mg daily**
  - Valproate: **250mg → 500mg BID**
  - Olanzapine 5 mg BID + 2.5mg (1200hr)
  - Trazodone 25 mg (0800,1600) 50mg HS
  - Naproxen 500 mg PO BID
  - Concerta 27 mg daily
- Dental extractions
- Blood work and physical exam
- Follow up with neuropsychiatry

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Questions?