



Autism Guidelines

CMAJ 2014, AACAP 2014

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CMAJ Autism 2014

Epidemiology

- Canada → **1% (1 in 88)**
 - Higher in boys 4x
- Multifactorial causes (genetic, epigenetic, nongenetic)
 - Can be familial or inherited
 - Recurrence in families → 19-27%
- 10-30% cases have genetic cause
 - Copy number variants → 10% of idiopathic cases
 - 10% have known genetic conditions
 - **Fragile X** → 1%
 - **Tuberous sclerosis** → 1%
 - Rett syndrome → 0.5%



Epidemiology

- Incomplete concordance in monozygotic twins
 - Interaction of environmental + genetic factors
 - *In utero* exposures (only small number of cases)
 - Valproic acid, thalidomide, misoprostol, terbutaline, antidepressants, pesticides, congenital rubella
 - **Heritability only 37%! → stronger influence of environment**



Diagnosis

- 10-25% have associated medical disorder
 - E.g. Fragile X, tuberous sclerosis, teratogenic exposure, neurological
 - Thorough prenatal, perinatal, medical, family history
 - Physical exam, growth parameters, dysmorphic features
- Genetic testing
 - **Genome-wide microarray analysis** RECOMMENDED for ALL
 - Enhanced detection of chromosome abn (vs just karyotyping)
 - **Fragile X testing (FMR1)** RECOMMENDED for ALL
 - PTEN gene sequencing (if head circumference >3 stdev)
 - MECP2 gene rare (<2%) → only if comorbid intellectual disability
 - (esp if developmental regression, may be Rett syndrome)



Diagnosis

- EEG or metabolic testing (if clinically indicated)
- Routine neuroimaging **CONTROVERSIAL**
 - Recommend if substantial dysmorphology, microcephaly, seizures
- DSM criteria → good sensitivity + specificity
 - Difficulty if very young, mental age <2 yrs, severe IDD
- Autism Diagnostic Observation Schedule (**ADOS**)
- Childhood Autism Rating Scale 2 (**CARS-2**)
- Autism Diagnostic Interview-Revised (**ADIR**)



Table 1: Recommended clinical work-up for autism spectrum disorder at the centres represented by the authors*

Specialty	Indication for testing	Test
Genetics ^{9, 12, 22}	All	Genome-wide microarray, fragile X syndrome (<i>FMR1</i> gene)
	Head circumference > +3 SD	<i>PTEN</i> gene
	Concerns about other conditions	Tuberous sclerosis and others as indicated
	Consider for females with intellectual disability	<i>MECP2</i> gene
Neuroimaging ^{23,24}	Complex ASD (clinical focal findings, major dysmorphology, micro- or extreme (≥ 4 SD) macrocephaly, skin lesions, seizures, focal EEG abnormalities, motor regression)	Brain magnetic resonance imaging and/or spectroscopy†
Metabolic ²⁵	If clinically indicated (e.g., severe intellectual disability and seizures, developmental regression)	Levels of venous blood gas; serum ammonia; lactate, pyruvate and uric acid; plasma amino acid; total, free and acylcarnitine; urine organic acids, mucopolysaccharides
General medical	Should be considered, especially for developmental delay	T4, TSH, complete blood count, ferritin level
	If indicated (e.g., presence of lead in the area where the family lives, evidence of pica)	Lead level
	If neuroleptic therapy is considered	Fasting lipid profile, glucose, HbA1c, electrocardiogram



Table 1: Recommended clinical work-up for autism spectrum disorder at the centres represented by the authors*

Specialty	Indication for testing	Test
Gastroenterology ²⁶	Pain after meals, night awakening despite good sleep hygiene	Rule out gastroesophageal reflux disorder
	High eosinophil count	Rule out eosinophilic esophagitis
	Bloating (2 or 3 times per wk for more than 2 wk)	Tissue transglutaminase levels (to rule out celiac disorder)
	Failure to thrive, weight loss	Serum albumin, total protein, calcium, vitamin D levels
Neurology ²⁷	Suspected seizures, documented regression	EEG (ideally sleep record)
Psychology or psychiatry	Mental health concerns (e.g., anxiety, mood)	Comorbidity assessment
Psychology	Need to establish mental age	Cognitive and adaptive behaviour assessment†
	Learning concerns	Cognitive, academic assessment (may include evaluation of memory and executive functioning)
Speech-language pathology	Speech or language concerns	Speech-language assessment
Occupational and/or physiotherapy	Motor or sensory concerns	Motor and/or sensory assessment
Behaviour therapy	Behavioural concerns	Behavioural assessment



Detecting ASD Early

- Average age at diagnosis → **age 4**
 - 80% have **clear behavioral signs by age 2**
 - Earlier infancy → may have atypical regulatory functions
 - Sleep, eating, emotions
- Canadian Pediatric Society
 - **Developmental surveillance**, monitor parents' concerns
 - With or without standardized tools
 - Closer monitoring **if siblings with ASD**
 - (AACAP → universal screening at 18 + 24 mos, standardized tools)
- Screening
 - Modified Checklist for Autism in Toddlers (**M-CHAT**)
 - Infant-Toddler Checklist (**ITC**)



Red Flags for Autism in 12-18 month-olds

Social communication

- Reduced or atypical:
 - eye gaze and shared or joint attention
 - sharing of emotion (less positive and more negative affect)
 - social or reciprocal smiling
 - social interest and shared enjoyment
 - orienting when his or her name is called
 - coordination of different modes of communication (e.g., eye gaze, facial expression, gesture, vocalization)
- Regression or loss of social-emotional connectedness



Red Flags for Autism in 12-18 month-olds

Language

- Delayed or atypical:
 - babbling, particularly back-and-forth social babbling
 - language comprehension and production (e.g., delayed or odd first words or unusually repetitive)
 - unusual tone of voice (including crying)
 - development of gestures (e.g., pointing, waving)
- Regression or loss of communication skills (including words)



Red Flags for Autism in 12-18 month-olds

Play

- Reduced or atypical:
 - imitation of actions
 - functional and imaginative play
- Excessive or unusual manipulation or visual exploration of toys and other objects
- Repetitive actions with toys and other objects



Red Flags for Autism in 12-18 month-olds

Visual or other sensory and motor skills

- Atypical visual tracking, visual fixation (e.g., on lights)
- Under- or over-reaction to sounds or other forms of sensory stimulation
- Delayed fine and gross motor skills, atypical motor control (e.g., reduced muscle tone, reduced postural control for age)
- Repetitive motor behaviours, atypical posturing of limbs or digits



Comorbidities

- ADHD
- Anxiety disorders
- Mood disorders

Behavioral Interventions

- Focus on improving language, cognitive, adaptive skills
- Applied Behavior Analysis (ABA)
 - Empirically derived learning principles
 - **Antecedent-behavior-consequence contingency**
 - Discrete trial teaching → progresses to more naturalistic learning
 - Teach skills, reduce problem behavior
 - Can be provided in variety of settings
- Enhanced outcomes with **early intensive ABA-based treatment**
- For greatest gains in **verbal IQ + language communication IF:**
 - Stronger **pre-treatment skills**
 - Started **earlier**
 - **Greater intensity** or duration of intervention



Behavioral Interventions

- ABA
 - Efficacy in toddlers → **improved IQ, adaptive skills**
 - If ABA principles implemented in everyday contexts, child's interest
 - Greater generalization of learning
- Limited research on non-ABA treatments, limited efficacy
- Not as much research for older children to adults



Biomedical Interventions

- Irritability & impulsive aggression
 - **Risperidone & aripiprazole** (FDA approved, Cochrane review)
- Hyperactivity & inattention
 - **Stimulants, atomoxetine** → effective for ADHD sx in ASD
 - Smaller effect, more SE than when used in ADHD alone
 - **α 2-agonists (clonidine, guanfacine)** may have role
- Repetitive behaviors
 - **Risperidone & aripiprazole** → sig decr repetitive behaviors in ASD
 - Caution about SE
 - *NO effect with citalopram*



Biomedical Interventions

- Sleep disturbances
 - **Melatonin**
 - Improved sleep parameters, better daytime behavior, minimal SE
- Alternative medications
 - Lack of empirical support

Table 2: Medications used to treat autism spectrum disorder behaviours and symptoms

Medication	Target behaviour	Evidence	On- or off-label	Adverse events*
Atypical antipsychotic medications (i.e., aripiprazole, risperidone)	Irritability, aggression†	Multiple, well-designed RTCs supporting their use ^{69,75}	FDA indication	Weight gain, metabolic syndrome, gastrointestinal effects, sedation, akathisia, orthostatic hypotension, tachycardia, extrapyramidal syndrome, neuroleptic malignant syndrome (rare)
	Repetitive behaviours‡	≥ 2 large RCTs support efficacy (although not a primary outcome measure) ^{69,75}	Off-label	
Serotonin reuptake inhibitors	Repetitive behaviour§	1 unpublished and 1 published large RCT (fluoxetine, citalopram): no evidence for efficacy ⁷⁰	Off-label, unless comorbid obsessive-compulsive disorder	Gastrointestinal effects, insomnia, agitation, disinhibition, dry mouth, headache, sexual dysfunction
	Anxiety or depression	None in autism, but multiple studies for pediatric anxiety disorders and depression	On-label for anxiety disorders and depression	
Stimulants	ADHD-like symptoms¶	> 2 RCTs (methylphenidate) support its use ⁷⁶ ; smaller studies support longer-acting stimulants	On-label for ADHD	Poor appetite, weight loss, irritability, insomnia
Atomoxetine	ADHD-like symptoms**	1 large, 1 small RCT support effectiveness ^{77,78}	On-label for ADHD	Gastrointestinal effects, insomnia, orthostatic hypotension
α-agonists	ADHD-like symptoms	Several small RCT and open label studies in autism support efficacy ⁷⁹	Clonidine: off-label; guanfacine: FDA indication for ADHD††	Somnolence, hypotension, bradycardia, dry mouth, constipation, irritability
Melatonin	Initial insomnia‡‡	Cochrane meta-analysis, positive effect on initial insomnia compared to placebo ⁸⁰	Not regulated	Headache, dizziness and nausea (all rare outcomes)



Outcomes

- LOW to MODEST levels of independence + social inclusion
 - Among BOTH higher and lower-functioning individuals
- Core phenotypic features + challenging behaviors PERSIST
 - Some problems can improve over time
 - May be due to educational programs
 - Strongest predictor of outcomes
 - **Level of verbal communication & IQ before age 5**



AACAP Autism 2014

Clinical Presentation & Course

- Autism first described in 1943 by Kanner
 - Officially recognised in in DSM-III
- Variability in age of presentation
 - **Preschool children**
 - Marked lack on interest in others, failures in empathy
 - Absent/severely delayed speech + communication
 - Marked resistance to change, restricted interests
 - Stereotyped movements
 - **By school age**
 - Social + communication skills usually increase
 - Dealing with change, self-stimulation more prominent
 - **In adolescence**
 - Some make marked developmental gains, some deteriorate



Clinical Presentation & Course (2)

- Predictors of ultimate outcome
 - Communicative speech by age 5
 - Overall cognitive ability (IQ)
 - Earlier detection + services IMPROVES long-term prognosis
 - Incr risk of accidental death
- Rett's disorder
 - Girls with hand washing/wringing, stereotypies
 - Mutation in MeCP2
 - Normal head circumference + development at birth/infancy
 - Before age 4 → **head growth decelerates**
 - Purposeful hand movements lost → **characteristic stereotypies**
 - Boys may carry same mutations, but different clinical manifestations



DSM5 Differences

- Just 2 diagnostic domains now
 - Social communication + interaction deficits
 - Restricted, repetitive patterns of behavior + interests
 - Early developmental period (vs before age 3)
 - May no longer meet criteria through intervention/development



Etiology

- Neurobiology
 - **EEG abn + seizures disorders** → 20-25% of pts with autism
 - Limbic system abn (on post-mortem studies)
 - fMRI → social/affective judgement, facial/non-facial processing
 - MRI → INCREASED brain size, aberrations in WM tract development
 - **Incr peripheral serotonin**
- Neuropsychological correlates
 - Impaired **executive function**
 - Weak **central coherence** (integrating information)
 - Deficits in **theory-of-mind** (perspective of another person)



Etiology (2)

- Familial Pattern & Genetic Factors
 - High recurrence risk in **siblings** → 19%
 - Higher concordance in **identical twins**
- Risk factors for ASD
 - **Closer spacing of pregnancies**
 - **Advanced maternal/paternal age**
 - **Extremely premature birth** (<26 weeks GA)
- Contribution from multiple genes (common + rare)



Differential Diagnosis (1)

- Specific developmental disorders
 - Language disorders → pointing for interest, conventional gestures
 - Intellectual disability
 - Sensory impairments (esp deafness)
- If developmental regression → **Rett syndrome**
 - Also childhood-onset schizophrenia, degenerative CNS disorders
- Mild-mod developmental delay (Autism Diagnostic Interview)
 - 2 yrs → directing attention, attention to voice
 - 3 yrs → use of other's body, attention to voice, pointing, finger mannerisms
 - 6 yrs → if autism, more likely to have impaired nonverbal behavior to regulate social interaction (eye contact)



Differential Diagnosis (2)

- Reactive attachment disorder
 - Deficits in attachment + inappropriate social responsivity
 - BUT improve with adequate caretaking
- OCD
 - Later onset, not typically social/communication impairments
- Anxiety disorders
 - Both have anxiety/worry sx
 - But **no developed social insight** in autism
- Childhood-onset schizophrenia
 - Both have social impairment, odd patterns of thinking
 - Rarely florid delusions or hallucinations in autism
- Other organic conditions



Comorbidities

- Intellectual disability (NOT essential diagnostic feature)
 - 50% → severe to profound
 - 35% → mild to moderate
 - 20% → normal IQ range
 - Verbal skills typically more impaired (vs non-verbal)
- Range of behavioral + affective symptoms
 - Hyperactivity, obsessions/compulsions, tics, stereotypies
 - Self-injury, aggression
 - Inappropriate affective responses, anxiety, depression
 - Impaired emotion regulation processes
- Attentional difficulties frequent
 - Cognitive, language, social problems



Assessment Recommendations

- ***1) Developmental assessment of young children + psychiatric assessment of ALL children should routinely include questions about ASD symptomatology***
 - Social relatedness, repetitive or unusual behaviors
- ***2) If screening indicates significant ASD, a thorough diagnostic evaluation should be performed to determine the presence of ASD***
 - Interview child + family, review past records + historical info
 - Changes over course of development
 - Response to interventions (behavioral, educational)
 - Observation of child
 - Assessment instruments for ASD



Assessment Recommendations

- **3) Clinicians should coordinate an appropriate multidisciplinary assessment of children with ASD**
 - Medical assessment → physical exam, hearing screen
 - Wood's lamp exam → **tuberous sclerosis**
 - Genetic testing → karyotyping, fragile X testing
 - **Chromosomal microarray** → standard of care for initial eval
 - 15q11-13 maternal duplications
 - 16p11.2 duplications + deletions
 - Yield of genetic testing if clinical suspicion → 33% of cases
 - If unusual features → additional evals
 - Infectious (encephalitis, meningitis), endocrinologic (hypothyroidism), metabolic (homocystinuria), traumatic (head injury), toxic (fetal alcohol syndrome), genetic
 - Rule out **Landau-Kleffner syndrome**
 - Distinct EEG abn + marked aphasia



Assessment Recommendations

- ***3) Clinicians should coordinate an appropriate multidisciplinary assessment of children with ASD***
 - Psychological assessment
 - Cognitive ability + adaptive skills
 - May have unusual ability (“**splinter skills**”, “**savant skills**”)
 - If higher functioning → may have single-minded pursuit of special interests that interfere with ability to learn
 - Communication assessment
 - Receptive + expressive vocabulary
 - Language use (social + pragmatic)
 - Occupational + physical therapy eval
 - Sleep assessment



Treatment Recommendations

- ***4) The clinician should help the family obtain appropriate, evidence-based and structured educational + behavioral interventions for children with ASD***
 - Structured educational + behavioral interventions = EFFECTIVE
 - Assoc with better outcome
 - **Applied Behavioral Analysis (ABA)**
 - Informed by learning principles
 - Early Intensive Behavioral Intervention
 - Intensive, highly individualized → up to 40 hrs per week
 - Simple to more complex skills (e.g. verbal behavior)
 - Useful for interfering maladaptive behaviors
 - Effective for academic tasks, adaptive living skills, communication, social skills, vocational skills
 - Explicit focus on generalization important



Treatment Recommendations

- ***4) The clinician should help the family obtain appropriate, evidence-based and structured educational + behavioral interventions for children with ASD***
 - Communication
 - Addressed in **individualized educational plan** (with SLP)
 - Picture Exchange Communication System
 - Sign language, activity schedules
 - Voice output communication aids
 - Even if fluent speech → may have impaired pragmatic language
 - Programs to enhance social reciprocity



Treatment Recommendations

- ***4) The clinician should help the family obtain appropriate, evidence-based and structured educational + behavioral interventions for children with ASD***

- Educational

- Need structured educational approach with explicit teaching
- Planned, intensive, individualized
- Experienced, interdisciplinary team
- Family involvement (ensure generalization of skills)
- Younger children → parent-education, home component
- **Early Start Denver Model**
- **Treatment & Education of Autism and related Communication handicapped Children program**



Treatment Recommendations

- ***4) The clinician should help the family obtain appropriate, evidence-based and structured educational + behavioral interventions for children with ASD***
 - Other Interventions
 - **CBT** → efficacy for anxiety + anger mgmt in high functioning youth with ASD
 - Poor quality evidence for sensory integration interventions
 - Limited evidence for developmental, social-pragmatic models
 - Developmental-Individual Difference-Relationship Based/Floortime
 - Relationship Development Intervention
 - Social Communication Emotional Regulation & Transactional Support
 - Play & Language for Autistic Youths
 - Hospitalization higher in children with ASD, but unknown efficacy



Treatment Recommendations

- ***5) Pharmacotherapy may be offered to children with ASD when there is a specific target symptom or comorbid condition***
 - May incr ability to benefit from interventions, remain in less restrictive environments
 - Frequent targets
 - Assoc comorbid conditions (anxiety, depression)
 - Aggression, self-injurious behavior, hyperactivity, inattention
 - Compulsive-like behaviors, repetitive/stereotypic behaviors
 - Sleep disturbances
- **Risperidone + aripiprazole** → approved by FDA for **irritability**
 - (physical aggression + severe tantrum behavior)
- **Combined medication + parent training** → better than meds alone
- Use objective scales to monitor treatment response



Treatment Recommendations

- ***6) The clinician should maintain an active role in long-term treatment planning, family support & support of the individual***
 - Very young children → diagnosis, treatment programs
 - School-age children → psychopharmacological, behavioral issues
 - Adolescents → vocational, prevocational training
 - Planning for independence/self-sufficiency
 - Support for parents + siblings
 - Rates of parental separation/divorce NOT higher



Treatment Recommendations

- ***7) Clinicians should specifically inquire about the use of alternative/complementary treatments and be prepared to discuss their risk and potential benefits***
 - Commonly pursued by families (despite limited evidence)
 - Some may pose greater risk

